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Abstract Book

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Work Shop

WS-01

How to publish your research?

Robert P Millar

University of Pretoria, Centre for Neuroendocrinology, Departments of Immunology and Physiology, Pretoria, South Africa

University of Cape Town, Institute for Infectious Diseases, Cape Town, South Africa

Professor Bob Millar is editor in chief of the journal, Neuroendocrinology. In this talk he will draw on this experience to discuss the 'dos' and 'donts' for ensuring success in getting your research published.



Conferences

C-01

Traumatic brain injury-induced neuroendocrine changes

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Traumatic brain injury which is a growing public health problem worldwide has recently been recognized as one of the most common causes of hypopituitarism. The causes of TBI-induced pituitary dysfunction are car accidents, falls, violence and war accidents including blast-related brain injuries. Neuroendocrine abnormalities were also reported in athletes dealing with contact sports including boxing and kickboxing. Boxing and kickboxing are characterized by chronic repetitive head trauma and they are accepted as mild traumatic brain injury. The prevalence of hypopituitarism after TBI is about 30%. GH is the most common hormone lost. The mechanisms underlying the hypopituitarism are still unclear; however, recent studies have demonstrated that genetic predisposition, neuroinflammation and autoimmunity may be responsible for the development pituitary dysfunction. The frequency of hypopituitarism is significantly lower in TBI victims with APO E3/E3 than in victims without APO E3/E3 genotype. The positivity of anti-pituitary and anti-hypothalamic antibodies is also a significant risk factor. Altered expression of miR-126-3p and miR-3610 may play an important role in the occurrence of hypopituitarism after TBI. Treatment of hypopituitarism with appropriate replacement therapies is beneficial in the improvement of manifestations caused by insufficient hormones.

A body weight homeostat that regulates fat mass in rats and mice

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Subjects spending much time sitting have increased risk of obesity but the mechanism for the antiobesity effect of standing is unknown. It is known that osteocytes can sense changes in bone strain, opening for the possibility that osteocytes of the weight bearing bones could sense changes in the body weight as well. We hypothesized that there is a homeostatic regulation of body weight, which can be influenced by posture.

To test this hypothesis, we implanted capsules that weighed 15% of the body weight into the abdomen of adult Sprague-Dawley rats and C57BL6 mice with diet induced obesity (Load). Control animals were implanted with an empty capsule of equal size (3% of the body weight). The body weight was recorded throughout the experiment and at the end fat pads and skeletal muscle was dissected and weighed. The glucose tolerance and leptin levels were checked in mice. We also unloaded some animals by exchanging the heavy capsule to light capsule after a couple of weeks.

We demonstrated that increased loading of rodents, reversibly decreases the biological body weight via reduced food intake. Importantly, loading relieved diet induced obesity and improved glucose tolerance. However, the body weight-reducing effect of increased loading was lost in mice depleted of osteocytes. We propose that increased body weight activates a sensor dependent on osteocytes of the weight bearing bones. This induces an afferent signal, which reduces body weight. These findings demonstrate a novel leptin-independent body weight homeostat ("gravitostat") that regulates fat mass.

Hypothalamic appetite pathways examined in a PWS mouse model

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Prader-Willi Syndrome (PWS) is a neurodevelopmental disorder characterized by childhood obesity and social deficits. Several genes including, MAGEL2 have been described to be inactivated in PWS. MAGEL2 is also abundantly expressed in hypothalamic appetite regulating neurons. We hypothesized that loss of MAGEL2 in key hypothalamic circuits may underlie or contribute to some of the metabolic phenotypes seen in PWS. Using cell type specific approach, we characterized impact ofMagel2 deletion on AGRP and POMC-neuron activity and behavioural function focusing on appetite. We observed alteration in POMC neuron activity as well as behavioural function whereas AGRP neurons appear to function relatively normal.

Neuroendocrin regulation of energy homeostasis and Hypothalamic obesity in children

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Energy balance in humans is regulated by a complex neuroendocrine system centred in the hypothalamus. The key hypothalamic areas of energy regulation are the ARC (arcuate nucleus), the VMH (ventromedial hypothalamus), the PVN (paraventriculer nuclei) and the LHA (lateral hypothalamic area). The mechanical or functional disruption of the hypothalamic network that regulates energy homeostasis causes intractable weight gain, which is named "Hypothalamic Obesity (HyOb)". Although, understanding of mechanisms for the role of hypothalamus in energy homeostasis took many years, especially recent studies shed light on how the hypothalamus regulates appetite and satiety. The disruptions causing HyOb can result from brain tumours, neurosurgery, cranial radiotherapy, and genetic defects. Rapid weight gain and severe obesity are the most striking features of HyOb and caused by hyperphagia, reduced basal metabolic rate (BMR) and decreased physical activity. Currently, attempts at controlling of HyOb through diet, exercise or pharmacological treatment are not satisfactory. However, new treatment opportunities in genetic obesity and the application of bariatric surgery hold promise for the treatment of HyOb. This talk will summarize hypothalamic appetite regulation, and the pathophysiology, metabolic features, etiology, clinical characteristics, and treatment modalities for hypothalamic obesity in children and adolescents.

A time to feast and a time to fast: The influence of feeding patterns on endocrine, growth and metabolic outcomes

Timothy Wells

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The physiological impact of temporal feeding patterns remains a major unanswered question in nutritional science. We used a CLAMS-based automated feeding station with automated blood sampling to assess the impact of contemporary feeding patterns on growth and hormone profiles.

Grazing (GR; 1/24th of the daily consumption of *ad libitum* (AL)-fed rats provided every 30 mins during the dark phase), or meal-feeding (MF; 3x 1hr AL meals at the beginning, middle and end of the dark phase) with a standard rodent chow (StRC) reduced caloric intake in male rats by 20% (vs AL-fed controls). GR reduced weight gain by 14%, nose-anus length and femoral length by 3% and tibial epiphyseal plate width (tEPW) by 15%, all of which were unaffected in MF rats. When fed a high fat (AFE 45% Fat) diet, abdominal fat storage efficiency was elevated in GR and MF rats by 52% and 37% respectively.

Although these feeding patterns had no effect on growth in StRC-fed male wild type (WT) mice, MF reduced tEPW by 15-16% in ghrelin^{-/-} littermates.

Rats receiving StRC in either GR or MF patterns displayed a large pre-prandial ghrelin surge with a sharp feeding-induced decline. Despite continued feeding, circulating ghrelin increased progressively across the dark phase in GR rats, while MF rats produced a large surge in ghrelin before the last dark phase meal. GR aligned individual growth hormone (GH) profiles without altering total secretion or pulse parameters. In contrast, MF induced a 166% increase in overall GH secretion due principally to the appearance of two additional GH pulses per day.

Despite reducing caloric intake, meal feeding preserved skeletal growth by a ghrelin-dependent augmentation of pulsatile GH secretion, while grazing promoted fat storage. Thus, the contemporary shift from regular meals to more continuous feeding may switch nutrient partitioning from skeletal growth to fat storage.

The potential role of neuronal structure and function underlying cognitive brain aging

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Normal aging is accompanied by a range of biological changes that diminish the quality of life. Understanding the alterations contributing to memory decline is important for developing strategies to prevent or lessen cognitive problems. What are the specific changes that take place during aging which lead to decrements in neural function? What are the intrinsic biological determinants of those changes? What factors can ameliorate these changes? I will present data from the laboratory examining the neural consequences of aging on the brain and behaviour. Specifically, I will present data that covers some of the neurobiological changes that occur in the aging brain and how these relate to declines in higher cognitive functions such as learning and memory. Additionally, I will discuss possible interventions, ranging from hormonal to dietary manipulations, which could alter the course of these changes. Finally, throughout the seminar I will present a variety of different models that have been used in my laboratory to examine the consequences of normal aging and their possible interventions. Take together these data have the potential to increase our understanding of the neurobiological alterations that occur in the aging brain in the absence of disease and provide potential therapeutic targets that could be modulated to improve the quality of life for aged individuals.

Restoring function to inactivating GPCR mutations in the HPG axis

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Inactivating mutations in G-protein coupled receptors (GPCRs) at all levels of the HPG axis give rise to incomplete reproductive development and adult infertility. The majority of the mutations in GPCRs cause misfolding of the receptor and a failure to traffic to the cell surface. We have therefore sought for cell permeant small molecules which can bind orthosterically or allosterically to stabilize the nascent GPCR in the endoplasmic reticulum and chaperone the mutant GPCR to the cell membrane.

We have successfully 'rescued' many GnRH mutant receptors using small molecule antagonists which bind orthosterically. After removal of the antagonists the mutant GnRH receptors demonstrate good cell surface expression. Michael Conn's laboratory has since demonstrated that such receptor rescue can restore reproductive competence in mice harbouring an inactivating GnRH receptor mutation.

We have also demonstrated rescue of cell surface expression and signalling in a substantial number of LH receptor mutations causing infertility in humans using a cell permeant allosteric agonist.

Most recently we have rescued function of NKB receptor inactivating mutations with cell permeant small molecules.

These discoveries represent an advance towards personalized medicine for GPCR deficiencies in the human HPG axis.

Role of amygdala kisspeptin in reproduction and behaviour

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The neuropeptide kisspeptin is a potent stimulator of gonadotropin-releasing hormone (GnRH) secretion and essential regulator of reproduction. Mutations in the genes for kisspeptin or its receptor results in hypogonadotropic hypogonadism and failure to enter puberty. In addition to the well-studied kisspeptin neurones located in the hypothalamic arcuate nucleus and preoptic area, that are key to GnRH pulse and surge generation, they are present in several extra-hypothalamic loci, most notably the posterodorsal subnucleus of the medial amygdala (MePD). Although the medial amygdala has a long history of involvement in gonadotrophic hormone secretion, puberty and behaviour, we have recently shown using neuropharmacological techniques, and selective optogenetic and chemogenetic activation of MePD kisspeptin, their involvement in the regulation of hypothalamic GnRH pulse generator frequency, pubertal timing and behaviours including social and sexual behaviour, and anxiety.

Neuroprotective and Restorative Effects of Melatonin: In Molecular Aspect

<u>Ülkan Kılıç</u>

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Melatonin is a powerful free radical scavenger with the desirable characteristics of a clinically-reliable antioxidant. So far, the neuroprotective effect of melatonin has been linked mainly to its direct free radical scavenging and indirect antioxidant activities. In recent years, we have focused on the signal transduction mechanisms of melatonin's neuroprotective, therapeutic and plasticity-promoting effects against acute and post-acute brain injury. Melatonin regulates cellular signaling pathways through receptor-dependent and independent mechanisms. We have provided evidence that the neuroprotective effects of melatonin appear to be mediated through a mechanism independent of Gi protein-coupled metabotropic membrane receptors MT1, MT2. Our observations suggest that melatonin acts through the PI3K/Akt pathway to inhibit p53 phosphorylation which results in increased neuronal survival. Molecular and proteomics analysis indicate that nighttime Ischemic/Reperfusion injury results in less severe neuronal damage, with increased neuronal survival, increased levels of survival kinases and circadian clock proteins, and also alters the circadian-related proteins.

Besides its neuroprotective activity, post acute administration of melatonin coordinates both ipsilesional and contralesional recovery processes on stroke-damaged brain tissue reflected by increased neurogenesis and decreased reactive astrogliosis that resulted in reduced scar formation. Moreover, melatonin improves motor coordination and exploration behavior and changes expression of plasticity-and angiogenesis-related genes and proteins suggesting an improvement in neurogenesis and angiogenesis in both hemispheres in a different manner. Melatonin triggers considerable changes in the expression of inflammation-related genes, many with distinct temporal and spatial patterns in different phases of poststroke recovery.

In the aspect of our previous- and present studies, the neurohormon melatonin, being well tolerated and having minimal side effects, is a promising candidate by its neuroprotective and restorative effect for the treatment of stroke patients either as a monotherapy or an add-on to the thrombolytic therapy.



Oral Communications

OC-001

The role of physiological and pharmacological concentration of melatonin on protection of remote preconditioning in myocardial ischemia reperfusion induced inflammatory mediator nuclear factor-kappa B

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Ischemic heart disease is the leading cause of morbidity and mortality in developed nations. In recently, it has been found that remote organ/limb temporary ischemia that renamed remote ischemic conditioning (RIC) can provide protection as an obstacle to the formation of lethal ischemic outcomes. The finding of this phenomenon can remove the requirement for direct cardiac intervention in cardiac protection. It has been shown that the cardioprotective effects of conditioning in aging and comorbidities are impaired. With aging, decreased melatonin synthesis in the pineal gland suggests that it is important in the pathogenesis of aging and aged-related cardiovascular diseases. In this study, effects of remote ischemic preconditioning (RIPerC) and melatonin on the inflammatory mediator nuclear factor-kappa B (NfkB) were investigated using an *in vivo* model of myocardial ischemia/reperfusion (I/R) injury.

Sprague-Dawley rats were divided into first two groups as non-pinealectomized (Non-Px) and pinealectomized (Px) groups, and then (i) Control; (ii) I/R (30 min ischemia, 120 min reperfusion caused by left coronary artery ligation); (iii) I/R+RIPerC (when myocardial ischemia initiated, 3 cycles of 5 min occlusion followed by 5 min reperfusion); (iv) I/R+Mel (10 days 10 mg/kg); (v) Px; (vi) Px+I/R; (vii) Px+I/R+RIPerC; (viii) Px+I/R+RIPerC+Mel groups. Hemodynamic parameters including ECG, blood pressure, heart rate were evaluated. NfkB was analyzed by qRT-PCR.

NfkB level was increased in the Non-Px+I/R group (2,2±0,3; 1,0±0,3; respectively) when compared with control. However, it was decreased with RIPerC and melatonin (0,4±0,2; 0,5±0,2; respectively). Compared with Px, NfkB level was increased in the Px+I/R group (1,2±0,2; 2,3±0,3; respectively). RIPerC applied to Px group was decreased NfkB level (1,1±0,4), but its expression was reduced more when melatonin was administered before RIPerC (0,5±0,1).

The physiological and pharmacological concentrations of melatonin may be important in I/R-induced inflammation. These results suggest that myocardial conditionings and melatonin are protective with similar so melatonin may be an agent which leads to pharmacological conditioning.

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Novel methods for three-dimensional microscopic imaging of neuroendocrine tissues: Whole organ clearing and light sheet microscopy

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To visualize neuroendocrine tissues microscopically uninterrupted at high resolution, novel sampling and microscopy techniques are being developed. The aim of this study is clearing of various neuroendocrine tissues by CLARITY and 3DISCO, observe tissues in 3D to compare with conventional methods in terms of visualization of morphological and functional properties.

C57 adult mice (n=10) were used to obtain tissues (brain, cerebellum, hypophysis, adrenal gland, pancreas, ovary, testis) of varying thickness (10, 40, 400, 1000µm).

For thin sections, tissues were perfused with 4% PFA, removed, post-fixed with PFA; followed by sucrose-processing, cryo-sectioning, immunofluorescent labelling.

For CLARITY, mice were perfused with hydrogel monomer(HM) solution. Tissues were then incubated with HM, placed in clearing solution, primary/secondary antibodies were administered for 2 days.

For 3DISCO, tissues were perfused with 4% PFA with fluorescent-conjugated antibodies. Following post-fixation in PFA; tetrahydrofuran and dibenzylether were administered. As primary/primary conjugated antibodies, beta-III tubulin, MAP2 Neu-N, FITC-dextran, ASMA, 3bhydroxysteroid dehydrogenase, cytokeratin were used, and Alexa 488-594 were used as secondary antibodies. Tissues were imaged under Leica dmi8-SP8 confocal/LS and Leica dm6 MP microscope, with 488 nm, 552 nm and titanium-sapphire laser (920 nm).

CLARITY samples were successful for 1000 μ m z-depth imaging. 3DISCO is faster for preparation, and gave good results at 400-600 μ m with MP. 3DISCO samples were effective with conventional confocal microscope at 200 μ m z-depth. 10-40 μ m sections showed a resolution of 100-150nm at x-y, structural integrity was not good for z.

CLARITY and 3DISCO methods can effectively be used for imaging of neuroendocrine tissues at z-axis with high resolution.

Acknowledgement: This study has been conducted at KUTTAM.

Acute REM sleep deprivation induced learning and memory impairments amoleriated by long term mild treadmill exercise

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It is clearly explained from the molecular to the phenomenological levels that sleep greatly contributes to the processes of memory and learning. Sleep problems are very common from infancy to adolescence and frequently elicit learning and memory impairment. Environmental enrichments like social interactions and exercise can adverse the diminished effects of stress on learning/memory and behavior. Therefore, we aimed to investigate the effects of chronic mild treadmill exercise on learning and memory on sleep deprivated rats.

Male Wistar rats (n=28) 3 weeks old were randomly divided into; control (C), control + exercise (CE), sleep deprivation (SD), sleep deprivation + exercise (SE). Rats were deprived from sleep by placing into Plexiglas tanks. Animals for the SD, exercise / SD groups were remained on the tank for 48 hours after the exercise protocol. The running time in exercise groups were increased progressively through 4 weeks (15 min, 30 min, 45 min, 60 min and speed 10 m/min respectively). For define learning and memory of rats, we used Morris Water Maze test (MWMT). Results were analysed by SPSS 11.5 statistic software.

In MWMT, compare to the C (32, 33 ± 6 ,13), CE (35, 14 ± 6 ,65), SD+E (43, 52 ± 8 ,77) groups; sleep deprived rats spent less time in the target quadrant (21, 86 ± 6 ,21) (p<0.05).

According to the MWMT, long-term mild treadmill exercise ameliorated the diminished learning and memory that caused from acute sleep deprivation. In Rajizahed study, they demonstrated the voluntary exercise impacts on learning and memory and found that exercise ameliorated the SD-induced learning and memory impairments. A recent review from the literature suggests that forced exercise and voluntary exercise have different effects on brain neurochemistry and behaviour. Taken together, both types of exercise can be powerful application to rehabilitate the various stress conditions like sleep deprivation.

Effects of noopept on hippocampal NGF and BDNF levels and cognitive functions of prepubertal rats with streptozotocin-induced diabetes

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Insulin resistance and long-term hyperinsulinemia impair blood-brain barrier functions and insulin activity in pubertal type 1 diabetes mellitus (T1DM) patients. Hyperinsulinemia causes neuronal degeneration leading to non-reversible cognitive disorders. NGF and BDNF are important proteins in neuronal regeneration, their tissue levels have been shown to decrease in diabetes and cognitive impairment. Noopept is a nootropic dipeptide that is used as a cognitive regulator. Noopept studies have suggested it to have anti-neuronal degeneration and anti-diabetic properties. In our study, we tried to determine the effects of noopept on hippocampal NGF & BDNF levels and cognitive functions in prepubertal DM rats.

In this study 60 prepubertal, posnatal 28th-day, male Sprague Dawley rats were divided into 6 randomized groups. i) control, ii) DM control, iii) noopept control, iv) DM-noopept, v) DM-insulin, vi) DM-insulin-noopept. On postnatal 28th day diabetes model was created by applying 50 mg / kg streptozotocin. 0,5 mg / kg noopept, one unit insulin was intraperitoneally administered for 14 days in the required groups. Cognitive assessment was done with Morris Water Maze test in postnatal 41-45th days. The research ended on postnatal 46th day. NGF and BDNF were assessed by ELISA test from hippocampal homogenate.

There was no statistically significant difference between NGF and BDNF values (p>0.05). There was no statistically significant difference in Morris Water Maze test (p>0.05).

By looking at references, we think that our research's time limitation of two weeks, has affected the results. Measuring the levels of NGF and BDNF at the pro-protein and mRNA levels may provide more comprehensive results.

Acknowledgement: This study is supported by TUBITAK (Project no: 215S629).

Galectin-3 expression in brain tissue in the rats administered with Adriamycin

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Experimental studies have shown that adriamycin (ADR) affects lipid peroxidation in the neurons, thereby causing sensory neuropathy. Galectin-3 is novel marker with a potential role in inflammation and fibrosis as well as tumour progression. In this study, we aimed to investigate the effects of ADR on galectin-3 expression in brain tissue in rats administered with ADR.

A total of 14 adult male Wistar Albino rats were used for the experiment. The rats were divided into two groups as (I) experimental and (II) control groups. The experimental group was administered single-dose intraperitoneal ADR 10 mg/kg and the control group received no treatment. The experiment was performed over a period of 14 days. After the experiment, all the rats were decapitated under anaesthesia and the brain tissues were removed promptly. The tissues were embedded into paraffin blocks for histological analysis. Indirect immunohistochemical staining was performed with paraffin-embedded sections to determine galectin-3 immunoreactivity. In the evaluation of immunohistochemical staining, a histoscore was calculated based on the diffuseness and intensity of staining.

The results indicated that the galectin-3 expression in rat brain was significantly increased in the rats administered with ADR compared to control rats (p<0,05).

The increase in galectin-3 immunoreactivity induced by ADR suggests that galectin-3 may have a role in the pathophysiology of the neurotoxicity caused by ADR.

Anaesthesia management of a morbid obese woman undergoing transsphenoidal hypophysectomy

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Anterior pituitary tumours account for nearly 18% of all intracranial tumours. Pituitary adenomas that cause hypersecretion of hormones lead to some diseases in patients. We present a surgical case under general anaesthesia of a woman suffering from visual disturbance caused by pituitary adenoma.

A 56-year-old, 129 kg, 161 cm, body mass index: 50 kg/m2, ASA physical status III, presented 8 months after suffering a head injury, severe fatigue and defect of vision. Macroadenoma (pituiter hypophysis adenoma) revealed in the suprasellar region as a dimension of 26x22 cm extending into the sfenoid sinus, and causing stalk left deviation was diagnosed on MR imaging. His medical history was diabetus mellitus, hypertension, asthma, hypothyroidism and phthisis. His past surgical history included cataract surgery 2 years before and it was learned that the problem was not encountered. His medications included metformin, levothyroxine and valsartan + hydrochlorothiazide. The rest of the physical examination was notable for oedema and puckers in the feet. Free T4: 0,85 ng/dl, TSH:0,59 µIU/ml, FSH:4.82 mIU/ml, prolactin:13,7 ng/ml and HbA1C: %5,6 were in her laboratory review. His vital signs were heart rate, 90; blood pressure, 160/70; and respiratory rate, 18. The patient was pretreated with 2 mg midazolam iv. On arrival to the operating room, routine monitors were placed, and invasive arterial cannulation additionally. Anaesthesia induction was performed with propofol, fentanyl and rocuronium, and intubation was completed intraorally, successfully. Transsphenoidal hypophysectomy surgery took nearly 3 hours, and patient was extubated uneventfully. Bleeding 100 cc occurred during surgery and no blood transfusion was applied. After 3 days the patient was discharged without any problems.

Consequently, various comorbidities may develop depending on the changes in the hormones in patients with pituitary adenoma. These may also impair anaesthesia management. Anaesthesia management should be planned considering the physiological characteristics of the patient.

Effects of two boron containing compounds and melatonin in $A\beta_{1-42}$ toxicity

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Boron is a very important micronutrient for plant, animal and human health and metabolism. Melatonin has well-known neuroprotective effects. The presence of amyloid beta plaques is one of the neuropathological hallmarks of neurodegeneration. The aim of this study is to investigate the possible effects of two boron containing compounds, borax and boric acid, and melatonin in amyloid beta $(A\beta)$ toxicity model.

In this study, SH-S5Y5 cells were used. Cells are seeded into 6-well plates for 250,000 cells/well, 10 μ M A β 1-42 was used as a most effective toxic dose. Borax, boric acid (200 μ g/ml) and melatonin (100 μ M) were used before and after A β 1-42 application Lactate dehydrogenase (LDH), Total Antioxidant (TAS) and Total Oxidant (TOS) levels were measured colorimetrically from cell culture media. Total protein isolation was done and the changes in the expression levels of pro-survival proteins (SIRT1, GSK-3 β and Akt) were investigated by western blotting technique. All data were statistically evaluated by one-way ANOVA test.

LDH analysis showed that cellular toxicity increased in 10 μ M A β 1-42 (p<0.001). A β 1-42 toxicity decreased when borax, boric acid and melatonin were added before and after A β 1-42 application (p<0.001). Melatonin increased TAS levels whereas it decreased TOS levels (p<0.001). Western blotting exhibited that levels of SIRT1 and p-GSK-3 β increased when boric acid was applied after A β 1-42. The level of p-Akt elevated when borax was used after A β 1-42 (p<0.05). Melatonin increased SIRT1, p-GSK-3 β and p-Akt when it was added before and after A β 1-42 application (p<0.05)

Our data indicated for the first time that the expression of SIRT1was increased by boron containing compounds. These compounds decreased A β 1-42 toxicity by elevating p-Akt ve p-GSK-3 β levels. In conclusion, boron as a strategic mineral has been shown to have positive effects which are similar with melatonin on cell metabolism.

Impaired melanocortin pathway function in Prader-Willi Syndrome gene-Magel2 deficient mice

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‡: equal contribution

Prader-Willi Syndrome (PWS) is a neurodevelopmental disorder causing social and learning deficits, impaired satiety and severe childhood obesity. Genetic underpinning of PWS involves deletion of a chromosomal region with several genes, including Magel2, which is abundantly expressed in the hypothalamus of appetite regulating hypothalamic cell types, both AGRP and POMC-expressing neurons contain Magel2 transcripts but the functional impact of its deletion on these cells has not been fully characterized. Here, we investigated these key neurons in Magel2-null mice in terms of the activity levels at different energy states as well as their behavioural function.

Using cell type specific ex vivo electrophysiological recordings and in vivo chemogenetic activation approaches, we evaluated impact of Magel2 deletion on AGRP and POMC-neuron induced changes in appetite. To achieve this, *Agrp-cre, Agrp-cre::Magel2*^{+m/-p}, *Pomc-cre* and *Pomc-cre::Magel2*^{+m/-p} mice were transduced with rAAV2/8-FLEX-GFP virus for ex vivo electrophysiological recordings or rAAV2/1-EF1a-DIO-hM3D(Gq)-mCherry virus for food intake study. Florescence guided loose-seal recordings were performed from both sated and food deprived *Agrp-cre* and *Agrp-cre::Magel2*^{+m/-p} mice.

We found that under *ad libitum* and food deprived feeding conditions, baseline firing rates of AGRP neurons were similar in *Agrp-cre* or *Agrp-cre::Magel2*^{+m/-p} mice. We then compared POMC neuron firing rates under fed state, which was significantly lower in *Pomc-cre::Magel2*^{+m/-p} mice compared to *Pomc-cre* littermates. A closer examination of firing patterns showed that, POMC neurons from *Magel2* null mice had significantly lower instantaneous firing rates. Chemogenetic activation approaches revealed that food intake and body weight changes were comparable in *Agrp-cre* or *Agrp-cre::Magel2*^{+m/-p} mice. However, the extent of appetite suppression was much weaker in *Pomc-cre::Magel2*^{+m/-p} mice compared to *Pomc-cre* littermates.

Our results suggest that POMC neuron activity profile as well as its communication with downstream targets is significantly compromised while AGRP neuron function is relatively unaffected in Magel2 deficiency.

The effect of captopril on pentylenetetrazole-induced epileptic seizure and post seizure hippocampal neuronal damage in mice

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Recent studies show that angiotensin converting enzyme (ACE) inhibitors have positive effects on nervous system. The aim of this study was to investigate the effect of captopril, an ACE inhibitor, on pentylenetetrazole (PTZ)-induced seizures and post seizure hippocampal damage.

In our study, we used 35 male 30-33 g Balb-c mice. Animals were divided into five groups as control, saline (PTZ; 1 ml/kg serum physiologic), positive control (200 mg/kg valproic acid), captopril (25 mg/kg/day for 7 days) and captopril (50 mg/kg/day for 7 days). Thirty min after drugs administration at the indicated doses, PTZ was administered 60 mg/kg to induce epileptic seizure. The animals were observed for 20 min. Seizure stages (according to the Racine Scale), first myoclonic jerk times (FMJ) and first generalized tonic-clonic seizure (GTCS) times were recorded. Four hours after PTZ injection, brain tissues were removed. After routine histological process, serial sections from brain tissues were stained with toluidine blue to determine neuronal damage. The hippocampal Cornu ammonis (CA) 1, CA2, CA3 and dentate gyrus regions were evaluated histopathologically. Statistical evaluation of the data was performed by one-way ANOVA and multiple comparisons were determined by the Tukey test. Statistical significance was defined at p<0,05.

Obtained data suggest that in terms of epileptic evaluation, 25mg/kg captopril decreased seizure stages and increased FMJ and GTCS compared to PTZ group (p<0,05). However, 50 mg/kg captopril did not change seizure stages, FMJ and GTCS compared to PTZ group (p>0,05). In terms of histopathology, both 25 mg/kg captopril and 50 mg/kg captopril reduced neuronal damage in hippocampal CA1, CA2, CA3 and DG regions compared to PTZ group (p<0,05).

In conclusion, we suggest that captopril has positive effects on epileptic seizure and post seizure hippocampal neuronal damage.

Potential effect of 2-isopropyl-5-methylphenol (thymol) alone and in combination with selenium on apoptosis, intracellular calcium, caspase 3 and 9 levels through activation of TRPV1 channel.

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In the current study, we investigated the protective effects of Selenium (Sel) on apoptosis and oxidative stress through Thymol induced TRPV1 channels activation in SHSY-5Y neuroblastoma cell line.

The cells were divided into 7 groups as control, Thymol, Thymol+Capsazepine, Thymol+Sel, Thymol+Sel+ Capsazepine, Sel, Sel+ Capsazepine and all groups were stimulated by TRPV1 Channel agonist which is Capsaicin before or during related analysis.

Results of the study demonstrated that thymol efficiently increased free cytosolic Ca²⁺ concentration and reactive oxygen species, caspase 3 and Caspase 9, mitochondrial depolariation and apoptosis levels through induction of TRPV1 Channels. However, increased apoptosis and other values in the cells were decreased by Sel treatments in Thymol+Sel group but, apoptosis, ROS, mitochondrial depolarization, caspase 3 & 9 values were increased in the Selenium group compared with the control group.

In conclusion, thymol could be used as a potent drug against several cancers types such as neuroblastoma through the regulation effect of Sel on Thymol induced-excessive TRPV1 channel activation.

Melanin concentrating hormone neurons regulate reward seeking independent of post-ingestive actions

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Evolutionarily, our brains drive great enthusiasm towards palatable nutrients. Craving and consuming palatable foods with high fat or sugar content often overcome homeostatic feeding. Even though certain brain regions are known to control physiological fed and fasted states along with hedonic and homeostatic feeding, neural populations that regulate hedonic feeding through predominating physiological needs remain unidentified. Earlier genetic studies have implicated a role for melanin concentrating hormone (MCH) neurons of lateral hypothalamic area (LHA) in food reward.

In this study, we aimed to use acute neuronal activity manipulation tools to functionally characterize MCH neurons in terms of appetite and reward. For this purpose, using DREADD technology, we remotely and reversibly manipulated MCH neurons to reveal their involvement in acute and chronic food intake control as well as glucose and insulin sensitivity. We also investigated rewarding capacity of MCH neuronal stimulation alone by optogenetic activation. We conducted nose poke assay, lever press assay and real time place preference assay to assess reward value of MCH neurons.

Our results suggest that MCH neurons are neither necessary nor sufficient to acutely change food intake but can alter blood glucose levels. Chemogenetic or optogenetic activation of MCH neurons does not regulate homeostatic feeding. Surprisingly, close loop self-stimulation experiments, along with nose poke and lever press assays have shown that MCH-neuron activation alone was sufficient to drive reward seeking.

Collectively, these experiments show a connection between MCH neurons and reward seeking, which takes place independent of homeostatic post-ingestive actions.

The effects of sitagliptin on anxiety-like behaviour and GLP-1 in streptozotocin-induced diabetic rats

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Glucagon-like peptide-1 (GLP-1) is an incretin that is secreted mostly in the terminal ileum and increases glucose-induced insulin synthesis and secretion, decreases glucagon secretion and blocks beta-cell apoptosis. GLP-1 is inactivated by the dipeptidyl-peptidase 4 (DPP-4) enzyme in the plasma. GLP-1 receptor agonists and DPP-4 enzyme inhibitors have been widely used in the treatment of diabetes. It is known that diabetics have higher anxiety levels. The effect of GLP-1 on anxiety is unclear. The aim of this study was to investigate the effects of sitagliptin on anxiety-like behavior and GLP-1 in diabetic rats.

There were four groups in the study; control, control+sitagliptin (a DPP-4 enzyme inhibitor), diabetes and diabetes+sitagliptin. Diabetes was induced by streptozotocin (single 40mg/kg, intraperitoneally). After 48 hours rats with blood glucose levels higher than 250mg/dL were considered as diabetic. Sitagliptin was given 20mg/kg (PO) for 21 days. Anxiety levels were evaluated with open field and elevated plus maze tests. GLP-1 and GLP-1 receptor levels in ileum, prefrontal cortex (PFC) tissues and plasma were measured with ELISA.

Diabetic rats exhibited greater anxiety-like behavior in the elevated plus maze test (p<0.05). GLP-1 receptor levels in PFC were decreased in diabetic rats (p<0.05). Both GLP-1 and GLP-1 receptor levels in ileum were decreased in diabetic rats (p<0.05). Sitagliptin didn't affect anxiety-like behavior, didn't change ileum and PFC GLP-1 receptor levels; but decreased ileum GLP-1 levels and failed to lower blood glucose levels in diabetic rats (p<0.05). In non-diabetic animals, sitagliptin increased anxiety levels, decreased both GLP-1 and GLP-1 receptor levels in PFC and decreased plasma GLP-1 levels (p<0.05). Also, there was a moderate positive correlation between anxiety and PFC GLP-1 receptor levels (r=0.63, p<0.01).

These results indicate that GLP-1 was related with anxiety, whereas our sitagliptin dose may not be enough for the change of anxiety, GLP-1 and GLP-1 receptor levels in diabetic rats.

Investigation of a catecholaminergic circuit for feeding between hindbrain and hypothalamus

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Nucleus of solitary tract (NTS) is a structure that plays a critical role in homeostasis. It contains a variety of neuronal subtypes, each playing important roles in diverse aspects of physiology such as stress, blood sugar, energy expenditure. Ascending appetite related signals to hypothalamus have been poorly investigated. We have studied the role of NTS to paraventricular hypothalamus (PVH) connection in feeding behavior with an emphasis on catecholaminergic [tyrosine hydroxylase (TH+)] neurons.

We used optogenetics and patch clamp electrophysiology to selectively activate NTSTH axons over PVH and evaluated cellular response. For this, we transduced NTS region of *Th-cre* mice with rAAV-Flex-ChR2 viral vectors and performed patch clamp recordings from acutely prepared PVH slices.

Nearly half of the cells did not respond to the NTSTH axonal stimulation and the remaining neurons responded equally with increasing or decreasing activity.

Our results suggest a heterogeneous response profile among PVH neurons upon optogenetic stimulation of NTS^{TH} axons.

Chronic manipulation of arcuate kisspeptin neurons in $A\beta_{1\text{-}42}$ induced mouse model of Alzheimer's disease

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease which begins with insidious deterioration of cognitive functions and progresses to severe dementia, confusion, behavioural and personality changes. AD is microscopically characterized by several neuropathological lesions including formation of β -amyloid plaques and neurofibrillary tangles. Kisspeptin receptor GPR54 is expressed in extra-hypothalamic tissues like hippocampus and cortex. In this study, possible role of kisspeptin-GPR54 system in AD mouse model and effects on catecholamine levels were investigated.

In this study, the AH mouse model was generated by injection of $A\beta_{1-42}$ into the Dentate Gyrus (DG) region of Kiss1-CreGFP tansgenic mice. Hypothalamic injection of CRE-dependent virus (AAV-Flex-hM3D (Gq) -mCherry / -hM3D (Gq) -mCherry) was performed by stereotaxic surgery into the hypothalamic Arcuate (ARC) region for pharmacogenetic manipulations of the kisspeptin neurons. The AH model was behaviorally evaluated using the Morris Water Maze (MWM) test. Experimental groups were given intraperitoneal clozapine-N-oxide (CNO) injection for 1 month to enable chronic activation/inhibition of the kisspeptin neurons. MWM test was performed again after chronic manipulation. Brain fluid from cerebral ventricles were collected using brain microdialysis perfusion probe. Seven samples were collected at intervals of 20 min and CNO injection was performed after the second sample. Catecholamine levels (noradrenaline, dihydroxyphenylglycol, dopamine, dihydroxyphenyl acetic acid) were determined by HPLC method from collected samples. LH serum levels were determined by ELISA method in blood samples collected after decapitation. Coronal cross sections of 50 µm were taken with vibratome to determine the injection sites by confocal microscopy.

A significant difference was found when the escape latencies were compared in the MWM test (Oneway ANOVA, p<0.05). As a result of the MWM test performed after chronic manipulation, it was seen that the activation group was significantly different from the other groups (p<0.05). Catecholamine levels were altered after CNO injection. There was no significant difference in serum levels of LH.

In the MWM test after chronic activation of the Kisspeptin neurons of the AH mouse model, the finding of the platform earlier shows a positive effect of the kisspeptin on learning and memory despite the hippocampal injury.

Synaptic pharmacology of orexigenic ARC^{AGRP} → PVN connection

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Agouti related peptide (AGRP) expressing neurons in the arcuate nucleus of hypothalamus (ARC), has a central role in regulating appetite and metabolism. It has been shown that activity changes in these neurons are necessary and sufficient to acutely regulate feeding behaviour. AGRP neurons send dense intrahypothalamic axonal projections and make synaptic connections to paraventricular nucleus (PVH), which have been shown to be the key downstream target region.

Since $ARC^{AGRP} \rightarrow PVN$ synaptic connection play a pivotal role in feeding, neuromodulators controlling the strength of this connection are also likely to be critical for appetite regulation. In this study we aimed to test the pharmacological properties of the $ARC^{AGRP} \rightarrow PVN$ connection. For this purpose, we tested the effect of norepinephrine, serotonin and other key appetite regulating neuromodulators on the synaptic properties of this connection.

We used a combination of optogenetic and electrophysiology to study $ARC^{AGRP} \rightarrow PVN$ synapses. For this we used channel rhodopsin assisted circuit mapping approach to isolate AGRP axon evoked synaptic currents from PVH neurons and evaluated impact of various neuromodulators.

Our preliminary results suggest that application of antagonists for norepinephrine and serotonin receptors work in opposite fashion to potentiate and inhibit $ARC^{AGRP} \rightarrow PVN$ synapses respectively. We also showed that ghrelin and NPY have limited impact on this connection.

Endoscopic endonasal transsphenoidal surgical resection for microadenomas: clinical experience and surgical results of 30 pituitary microadenomas treated in a single centre

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Microadenomas are a privileged group of hypophyseal tumours and pose significant surgical difficulties. The recent advances in endoscopic systems and surgical techniques, understanding the sellar anatomy facilitate endoscopic surgeries and improved surgical outcomes. However, there is still lack of adequate information about surgical results of microadenomas depending on case series. The aim of this retrospective study is to evaluate the results of pure transsphenoidal endoscopic surgery in a series of patients with microadenomas.

Thirty-one patients with hormone secreting microadenoma who underwent pure transsphenoidal endoscopic surgery at the Department of Neurosurgery of Ankara University in Turkey, between January 2014- March 2018 were retrospectively analysed in our study. Tumours were classified according to the types of hormone they secreted. All patients were followed up for at least 1 year. The disease control was analysed for each patient clinically and radiologically.

During the study period, 30 patients underwent pure endoscopic transsphenoidal surgery for treatment of microadenomas. There were 19 growth hormone-secreting, 1 prolactin-secreting, 8 adrenocorticotropin hormone secreting, 1 FSH-LH secreting and 1 thyroid-stimulating hormone-secreting adenomas. Gross total removal was achieved in 96.6% of the cases after a median follow-up of 15.6 months. The remission results for patients with secreting microadenomas was 83% and for functioning microadenomas, 89.47% for GH hormone-secreting, 100% for prolactin hormone-secreting, 75% for ACTH hormone-secreting, 100% for FSH-LH hormone-secreting and 100% for TSH hormone-secreting.

Endoscopic transsphenoidal surgery is an effective treatment option for patients with hypophyseal microadenomas. Although a small number of complications and unsuccessful interventions are some of the disadvantages of this approach and reported in recent literature, high disease control rates can be achieved even in this small size and deep-located tumours. Given the results of transsphenoidal approaches in literature, endoscopic approach is significantly superior to microsurgery in terms of introducing wide operative field and surgical freedom. Simultaneous use of navigation systems with endoscopic instruments will improve the patient outcomes.

TRPM2 immunreactivity in cerebellar Purkinje cell of ovariectomised rats

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It is known that sex steroids affect neurological functions in normal and pathophysiological conditions. Purkinje cells are large neuronal cells in the cortex of the cerebellum that play a fundamental role in motor control. In this study we aimed to investigate the immunoreactivity of Transient Receptor Potential Melastatin2 (TRPM2) in cerebellar Purkinje cells of experimental ovariectomized rats.

In our study, 14 female Wistar albino rats with regular cycles were divided into 2 equal groups, control and ovariectomy. For the control group, no procedure was performed during the experiment period of 30 days. The rats in the ovariectomy group were admitted to the operation table in the supine position and the abdomen was inserted with midline incision. Both ovaries were ligated from the mesothelium region and the cornu-uterine junctions, and the ovaries were excised and taken out.

At the end of the experiment, cerebellum tissues of decapitated rats were rapidly removed. Cerebellar tissues were embedded in paraffin blocks after routine histologic follow-up. The sections from paraffin blocks were treated with avidin-biotin-peroxidase method for TRPM2 immunoreactivity. In the evaluation of immunohistochemical staining; based on the prevalence and severity of immunoreactivity, histoscor was established.

At the end of the evaluation of the prepared immunohistochemical staining under the light microscopy, in the ovariectomized group the TRPM2 immunoreactivity in Purkinje cells was increased statistically significantly compared with the control group.

It has been concluded that TRPM2 may play a role in the development of neuronal changings that may occur due to experimental menopause.

Visfatin immunoreactivity in rat brain tissues of experimental ischemia-reperfusion

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In ischemia, the brain does not hide glucose for itself as a primary energy source and is exposed to anaerobic metabolism. Recently, the views on the hormonal regulation of metabolism have changed markedly. Adipokines have been described as the result of studies on adipose tissue, which provides the relationship between adipose tissue and brain. Visfatin was found when searching for new cytokine-like molecules released from lymphocytes. Studies have shown that visfatin levels may be associated with endothelial dysfunction and increased inflammation. In this study, it was aimed to investigate visfatin expression which is known to be related to energy metabolism in brain tissue of rats with brain ischemia-reperfusion model.

In our study, 14 adult male Wistar albino rats were used. Experimental animals were divided into two groups as control and ischemia-reperfusion (IR) group. Nothing was done to the control group during the experiment. For the IR group, surgical bilateral carotid communis arteries were uncovered, followed by clipping with aneurysm clips for 60 minutes followed by opening of the clips and reperfusion for 120 minutes. At the end of the experiment, rats were decapitated under anaesthesia and brain tissues were rapidly removed. Brain tissues were embedded in paraffin blocks after histological procedures. Sections taken from paraffin blocks were subjected to avidin-biotin-peroxidase method for visfatin immunoreactivity. In the evaluation of immunohistochemical staining; a histoscore was established based on the prevalence and severity of immunoreactivity,

As a result of immunohistochemical staining, visfatin immunoreactivity was found to be statistically significant in the IR group when compared to control group (p<0,05).

It has been concluded that visfatin may play a role in the pathogenesis of central nervous system changes that may occur due to ischemia-reperfusion

Adropin and immune-reactivity of NUCB2/Nesfatin-1 in brain tissue of the rats with experimentallyinduced diabetes mellitus

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Diabetes mellitus (DM) has an impact on each organ or system including the nervous system and brain. NUCB2/Nesfatin-1 first discovered in the hypothalamus, as well as adropin, a modulator of glucose homeostasis has not been previously assessed with regards to the change in their expression in the brain tissue during diabetes. Here it was aimed to evaluate the immune reactivity of NUCB2/ Nesfatin-1 and adropin in the brain tissue of the rats with experimentally induced diabetes.

In this study 14 male Wistar albino rats were either assigned to control or diabetic groups. During the study no intervention was performed for the rats in the control group. To induce diabetes, 60 mg/kg of streptozotocin was intraperitoneally injected to the rats. At the end of the study, rats were rapidly decapitated. Brain tissues were embedded into paraffin blocks following a routine histological screening. Avidin-biotin-peroxidase method was performed for the layers of paraffin blocks in order to obtain NUCB2/ Nesfatin-1 and adropin immunoreactivity. While evaluating the degree of staining with immunohistochemical stains, histoscores were measured with regards to the extent and severity of immune-reactivity.

The staining of adropin and NUCB2 / Nesfatin-1 immunoreactivity in rat brain tissue was evaluated under the light microscopy. The values obtained with adropin and NUCB2 / Nesfatin-1 immunoreactivities were found to be increased both (p < 0.001).

It has been demonstrated that adropin and NUCB2 / Nesfatin-1 molecules may play a role in the pathophysiology of structural, electrophysiological and cognitive dysfunctions that may occur in the central nervous system due to chronic hyperglycaemia and increased in the diabetic rat brain compared with the control group. It has been concluded that more extensive and detailed studies should be done in the future in order to find out whether adropin and NUCB2 / nesfatin-1 can be used in central nervous system problems caused by clinically prolonged hyperglycaemia.

N-Cadherin expression in Cushing's disease: is it a prognostic marker?

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Cadherins are Ca2+-dependent adhesion molecules. During tumour progression, the expression profile of them change resulting in a highly motile and invasive phenotype. N- (neural) cadherin (NCAD) promotes tumour cell survival, migration and invasion, and is associated with poor prognosis. Cushing's disease (CD) is associated with significant morbidity and however the markers to predict the prognosis and recurrence are limited. NCAD was found to be expressed in growth hormone and prolactin secreting pituitary adenomas. Therefore, we aimed to evaluate NCAD expression in pituitary adenoma tissues of the patients with CD and the relationship with prognosis.

This retrospective evaluation included 72 patients with the diagnosis of CD. All patients had complete confirmatory data for CD and appropriate pathologic sections. NCAD were evaluated by immunohistochemical method, pituitary tumour size, invasiveness and histopathology features such as p53 and Ki-67 staining and postoperative disease activity were noted.

NCAD was expressed in 29 (32%) patients, gender distribution and the mean age were similar in NCAD+ and NCAD- patients. The tumour size and preoperative cortisol levels were higher in NCAD+ patients (p: 0,022 and p: 0,023) also p53 positivity and higher Ki67 expression were correlated with higher NCAD staining grade (p: 0,001 and p: 0,048). However, disease remission and recurrence rate were not different among NCAD+ and NCAD- groups. Also radiologic tumour invasion was similar between groups.

NCAD was expressed in 32% of CD adenoma but this rate is lower than anticipated in growth hormone and prolactin secreting pituitary adenomas. NCAD expression was related with higher tumour size but other radiologic features were similar with NCAD- cases. Also atypical adenomas (p53+ and >2% Ki-67 staining) had higher grade of NCAD staining then non atypical adenomas, that might be attributable as a prognostic role. However, more evidence is needed to confirm this hypothesis.

Effects of alpha lipoic acid on oxidative damage in central nervous system in experimentally induced diabetic rats

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Diabetes mellitus (DM) is a metabolic disease characterized by developing hyperglycaemia related with the disruption in insulin secretion or activity. Recent studies revealed that DM is generating functional disruption in CNS. Alpha lipoic acid (ALA) is a cofactor for mitochondrial enzymes which have a role in energy production and metabolism and can be naturally synthesized in the body. Malondialdehyde (MDA) is an end product of lipid peroxidation and used for demonstration of the level of oxidative damage. Superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) are antioxidant enzymes. While glutathione (GSH) resists damaging caused by radicals, it has a role as a substrate for antioxidant enzymes and acts as a radical holder.

In this experiment we used a total of 28 rats. 14 rats were given 180mg/kg streptozotocin (STZ) dissolved by single intraperitoneal (i.p.) injection. According to measurement results, the ones with blood glucose >250 mg/dL are considered as diabetics. Rats are divided into 4 groups; Control (group I), DM (group II), ALA (group III) and DM+ALA (group IV). MDA, SOD, CAT, GSH-Px and GSH values were measured in each group.

Our study suggested that ALA causes a decrease in MDA level while causing an increase in CAT, GPx, and SOD level and prevents the disturbances caused by oxidative stress. This study suggests that ALA has a neuroprotective effect, which prevents oxidative damage thereby decreasing oxidative stress in brain tissues.

Investigation of the protective effects of vitamin e on changes in tacrolimus applied to the rat brain

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Tacrolimus is an immunosuppressive agent and is used to prevent tissue rejection after kidney, liver and heart transplantations. Tacrolimus is known to cause harmful effects on myocardium, kidney, bowel and liver. It has also been reported to have side effects such as neurotoxicity, hypertension, impaired glucose metabolism, gastrointestinal disturbances and a tendency to infection, increasing oxidative stress and reducing antioxidant status. Vitamin E forms the first line of defense against lipid peroxidation by protecting the free radical scavenger activity in the biomembrane from the free radical effect of polyunsaturated fatty acids present in the resulting cell membrane phospholipids. The aim of this study was to investigate the protective effects of vitamin E on changes in rat brain tissue induced by administration of tacrolimus.

Twenty-one male Wistar Albino rats were used in our study; Control, tacrolimus and tacrolimus + vitamin E. 0.8 mg / kg / day for tacrolimus group, 0.8 mg / kg / day for tacrolimus, 0.8 mg / kg / day for tacrolimus + vitamin E Group Vitamin E together with tacrolimus was orally administered at 500 mg / kg / day. At the end of 3 weeks of experiment, all groups were decapitated, Bax immunoreactivity was assessed by TUNEL staining and avidin-biotin peroxidase method on sections taken from paraffin blocks.

When compared with the control group, Bax immunoreactivity and TUNEL positive cells were significantly increased in the tacrolimus group. Compared with the tacrolimus group, Bax immunoreactivity and TUNEL positive cells in the tacrolimus + vitamin E group were significantly decreased.

Depending on the application of tacrolimus, apoptosis has increased in rat brain tissue. Therefore, it has been concluded that the application of antioxidants with tacrolimus would be beneficial.

Response of vagal afferent neurons to macronutrients

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The aim of this study is to investigate the responses of the vagal afferent endings to nutrients. Vagal afferents are the longest central nerves that innervate many visceral organs including intestines. They transmit information from the intestines to the brain and vice versa providing a two-way communication. The cell bodies of vagal afferents are within the nodose ganglia. Vagal afferents extend to the intestinal epithelium; but though they go into the villi they do not penetrate them they have no contact with the luminal content. In this study, neurons of nodose ganglia were cultured and the electrical response of neurons to various nutrients was analysed.

Nodose ganglia of young adult mice were removed and neuron culture was performed. The culture is kept in Hank's salt solution. Also this solution was used for control group. The cells were loaded with voltage-sensitive dye Dibac-4. Spinning disc microscopy recorded the changing fluorescent brightness for 3 minutes while adding nutrients. Changing brightness was measured with Image J programme. One-way ANOVA and Posthoc Tukey tests were performed for statistical analysis. Nutrients were lipid mix, alanine, phenilalanine, glutamine, histidine, leucine, methionine, cysteine, threonine, galactose and glucose.

The neurons responded to nutrients differently. Seven amino acids out of eight responded electrically and this was usually depolarization. There was no response to glucose while galactose caused hyperpolarisation in general it led to depolarization in a subset of neurons. The response of nodose ganglia cells to lipids was inhibition.

This study indicates that vagal afferent neurons are influenced directly by numerous varied nutrients, which may be excitation or inhibition. These results challenge the currently accepted model suggesting that these afferents respond only indirectly to a few neuromediators released from intestinal epithelial cells.
The effect of pinealectomy and melatonin application on metallothionin, ZnT3 and ZIP2 levels in rat brain tissue

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The aim of this project was to investigate the relation among the metallothionin, ZnT3 and ZIP2 levels which is the basic mechanism in the regulation of zinc pool in the brain tissue parts of rats with pinealectomized and melatonin treatment.

Study was performed on total 36 male rats:

Group 1. (n:6) Control: The group with no intervention and fed with normal diet

Group 2. (n=10) Melatonin: The group with subcutaneous melatonin application with a dose of 5 mg/kg for four weeks.

Group 3. (n=10) Pinealecomy: The group with pinealectomy and fed with normal diet.

Group 4. (n=10) Pinealectomy+ Melatonin: The group with pinealectomy and subcutaneouos melatonin application with a dose of 5 mg/kg for four weeks after pinealectomy.

Brain cortex, hippocampus and hypothalamus samples were analysed for ZnT3, ZIP2, and metallothionein by immunohistochemistry.

Pinealectomy caused significant decreases in metallothionin, ZnT3 levels in brain cortex and hippocampus (p<0.05). Melatonin supplementation increased mentioned parameters in groups 2 and 3 (p<0.05). Although pinealectomy did not cause any significant difference in ZIP2 levels in brain cortex and hipothalamus compared with the control group; melatonin application caused significant difference in ZIP2 levels in brain cortex, hypothalamus and hippocampus (p<0.05).

The results of present study show that pineal gland is closely related with the regulation of ZnT3 and metallothionins in brain tissue. We can conclude that our findings especially indicating the relation between pineal gland and ZnT3 regulation in brain cortex, hypothalamus and hippocampus are the first and original findings when considering medline scanning.

The effect of pinealectomy and melatonin supplementation on serum melatonin, nesfatin-1 and ghrelin levels in rats

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There is scarcely any study examining the relationship between the pineal gland and ghrelin and nesfatin-1 hormones, which are significantly involved in the regulation of diet. A few animal studies, although they have contradictory results, point out that there may be a relation between the pineal gland, and ghrelin and nesfatin-1. The present study aims was to explore how ghrelin and nesfatin-1 hormones are affected in pinealectomized and melatonin-supplemented rats.

The study was conducted at the Experimental Medicine Research and Application Centre of Selcuk University and approved by local ethic committee. 36 Wistar male rats were used for experiments. Grouped designed as Group 1, Control group; Group 2, Melatonin-supplemented group; Group 3, Pinealectomized group; Group 4, Pinealectomized and melatonin-supplemented group. Blood samples collected from the animals which were decapitated at the end of the 4-weeks procedures were analysed by rat kits to determine melatonin (pg/ml), Nesfatin-1 (ng/ml) and ghrelin (pg/ml) levels according to ELISA method.

The lowest serum melatonin levels were found in the pinealectomized group 2, and the highest in the melatonin-supplemented group (group 4) (p<0.01). A comparison of serum ghrelin levels between groups revealed that group 1 (control) and group 4 (melatonin supplementation) had the lowest, while Px group (group 2) had the highest levels (p<0.01). As for nesfatin-1 levels, the lowest serum nesfatin-1 levels were established in the pinealectomized group 2, and the highest levels were found in the melatonin-supplemented group (group 4) (p<0.01).

An overall evaluation of study results suggests that the pineal gland and melatonin may have a substantial effect on the blood levels of ghrelin and nesfatin-1 hormones, which play critical roles in dietary behaviours. Melatonin supplementation has inhibitory effects on ghrelin levels and stimulatory effects on nesfatin-1 levels.

Determination of effective mechanism of melatonin in hyperthermic febrile convulsion in rats

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Melatonin is a neurohormone that has anticonvulsant effects in neuroprotective and different experimental seizure models. In our previous study, melatonin has been shown to be anticonvulsant in the hyperthermic febrile seizure model. However, the mechanism of this effect at the receptor level is not clear. Our aim in this study is to investigate which melatonin receptors / receptors the anticonvulsant effect of melatonin shows in the hyperthermic febrile seizure model.

In our study, we used male Wistar Albino rats of 22 to 30 days, corresponding to 1.5-2 years of age in children. Groups were performed as Control; Etanol/salin; DMSO; Melatonin; Melatonin + Luzindole; Melatonin + K-185; Melatonin + Prazosin. The hyperthermic febrile seizure pattern was established by keeping the rats in 45°C water, and the latency, duration and severity of seizures were determined.

In our study, it was observed that melatonin shortened the duration of seizure, weakened the severity and did not affect latency (p<0.001, p<0.001 and p>0.05, respectively) and that these effects were not completely blocked by receptor antagonists when compared to ethanol/saline group and DMSO groups.

In conclusion, the fact that the anticonvulsant effect of melatonin is not completely blocked by melatonin receptor antagonists in the present study suggests that a multimodal mechanism may be responsible for the effect of melatonin receptors alone on the anticonvulsant effect of melatonin. It will be useful to design new pharmacological studies to make the subject clear.

Acetaminophen (paracetamol): "Empathy-killer" in a dose-response relationship in rats

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Empathy is the ability to understand and share someone else's feelings, thoughts and behaviors; this is an important ability to survive and live together. Acetaminophen is affected cannabinoid 1 receptor that is located on empathy-related neuron's presynaptic membrane such as oxytocin and vasopressin. The aim of this study is to investigate the effects of acetaminophen on empathy and empathy related neurohormones, oxytocin and vasopressin.

Twenty-eight adult outbred male Sprague Dawley rats were used in this study. Rats were harbored in the same environment 14 days, then all rats were trained for 12 days via Helping Behavior Test Equipment to rescue cagemate. After that all rats were divided into: (1) Control group (n=7), (2) 100-mg/kg (n=7), (3) 200-mg/kg (n=7) and (4) 400-mg/kg acetaminophen group (n=7). Each acetaminophen administration was one-time daily and given orally, empathy behavior evaluated 30 minutes later. A single dose and repeated dose of acetaminophen effect on empathy and anxiety was evaluated. Motor functions were assessed by Rotarod performance and open field tests. Blood samples were obtained. Brain tissues, thymus and adrenal glands were removed; amygdala and prefrontal cortex tissues were separated.

In Helping Behaviour Test Equipment, the mean opening door latency was found to be decreased in all animals (28=19.912, p<0.0001). After single dose acetaminophen door opening time was found to be increased in only 400-mg/kg-acetaminophen group (p<0.001). Repeated acetaminophen increased door opening time in both 200-mg/kg and 400mg/kg-acetaminophen groups (p<0.001). In Open field test; there was not any difference between all groups (p>0.05). There was not any difference about ambulation in open arms of elevated test equipment (p>0.05). There was not difference between the groups in the performance of the rotarod test (p>0.05). Prefrontal cortex oxytocin levels decreased in all acetaminophen-taking groups (p<0.0001 for all). Prefrontal cortex vasopressin level decreased in only 200-mg/kg acetaminophen group (p<0.0007). Oxytocin in amygdalae tissue decreased in both 100-mg/kg and 200-mg/kg-acetaminophen group (both of p<0.05). Amygdala vasopressin levels decreased in all acetaminophen -taking groups (all of, p<0.05).

These findings suggest that, acetaminophen decreased prefrontal cortex and amygdala oxytocin and vasopressin levels; reduces empathy both single high dose and repeated lower dose.

Lipid profile and atherogenic indices and their association with coronary flow reserve in acromegaly patients

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In this study, we aimed to investigate the atherogenic indices used in the detection of coronary microvascular disease in patients with acromegaly.

This prospective study included 54 patients with acromegaly and 31 healthy subjects. Patients consisted of patients active and remissioned according to GH (growth hormone) and IGF-I (insulin-like growth factor-1) levels. Lipid parameters (total cholesterol, triglyceride, low density lipoprotein cholesterol) levels of all patients and control groups were recorded. We also calculated atherogenic indices (plasma atherogenic index (PAI: logarithmTG / HDL), atherogenic coefficient (EC): nonHDL / HDL, Castalle risk indexes I: TG / HDL and II: LDL / HDL lipid parameters. Coronary flow reserve was measured using dipyridamole on the left anterior descending coronary artery using transthoracic Doppler echocardiography (TTDE).

There was no difference in biochemical parameters including lipid profile in patient and control group. Serum hs-CRP levels were high in the patient group but not statistically significant. The baseline diastolic flow rate measured from the left anterior descending coronary artery by the echocardiographic method was significantly higher in the patient group and the coronary flow reserve, expressed as the ratio of peak flow rate to basal flow rate, was significantly lower. In the correlation analysis; coronary flow reserve, Castelli index II, plasma atherogenic index, atherogenic coefficient were found to be negative correlations IGF-I, and age in the patients group. HDL cholesterol was positively correlated.

The use of plasma atherogenic indexes besides IGF-1 may be useful in the detection of coronary microvascular disease risk in patients with acromegaly.

The effect of hexarelin on pentylenetetrazole-induced epileptic seizure and hippocampal neuronal damage in rat

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Recent studies have demonstrated that ghrelin receptors have antiepileptic effects. The aim of this study was to investigate the effect of ghrelin receptor agonist hexarelin on pentylenetetrazole (PTZ)-induced seizures and post seizure hippocampal damage.

In our study, we used 42 male 230-250 g Wistar Albino rats. Animals were divided into seven groups as control, saline (PTZ; 1 ml/kg serum physiologic), positive control (5 mg/kg diazepam), 50 µg/kg, 100 µg/kg, 200 µg/kg and 400 µg/kg hexarelin. 30 min after drugs administration at the indicated doses, PTZ was administered 45 mg/kg to induce epileptic seizure. The animals were observed for 30 min. Seizure stages (according to the Racine Scale) and first myoclonic jerk times (FMJ). 24 hours after PTZ injection, passive avoidance test was performed and then brain tissues were removed. After routine histological process, serial sections from brain tissues were stained with toluidine blue to determine neuronal damage. The hippocampal Cornu ammonis (CA)1, CA3 and dentate gyrus regions were evaluated histopathologically. Statistical evaluation of the data was performed by one way ANOVA and multiple comparisons were determined by the Tukey test. Statistical significance was defined at p<0.05.

Obtained data suggest that 200 μ g/kg and 400 μ g/kg hexarelin decreased seizure stages and increased FMJ compared to PTZ group (p<0,05). In addition, 200 μ g/kg and 400 μ g/kg hexarelin improved retention time in passive avoidance compared to PTZ group (p<0,05). Furthermore, 200 μ g/kg and 400 μ g/kg hexarelin reduced neuronal damage in hippocampal CA1, CA3 and DG regions compared to PTZ group (p<0,05). However, all these effects of hexarelin were not observed at 50 μ g/kg and 100 μ g/kg (p>0,05).

In conclusion, we suggest that hexarelin has protective effects on epileptic seizures and neuronal damage after PTZ dose-dependently.

The role of orexin1 and orexin2 receptors in morphine analgesia and tolerance in rats

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Tolerance mechanism against morphine analgesia has not been clarified yet. The aim of this study was to investigate role of orexin₁ and orexin₂ receptor on morphine analgesia and tolerance in rats.

In our study, 90 Wistar Albino 230-250 g male rats were used. The animals were divided into fiveteen groups as saline (serum physiologic 1ml/kg; n=6), orexin_A (orexin₁ receptor agonist;10µg/kg; n=6), SB-334867 (orexin₁ receptor antagonist 1mg/kg; n=6), orexin_B (orexin₂ receptor agonist;15µg/kg; n=6), TCS-OX229 (orexin₂ receptor antagonist 0,5mg/kg;n=6), morphine (5mg/kg;n=6), orexin_A+morphine (n=6), SB-334867+morphine (n=6), orexin_B+morphine (n=6), TCS-OX229+morphine (n=6), morphine tolerance(n=6), morphine tolerance+orexin_A (n=6), morphine tolerance+SB-334867 (n=6), morphine tolerance, 10mg/kg morphine was injected daily in the morning and evening for five days and tolerance was evaluated sixth days single dose of morphine. Analgesic effects were assessed by hot plate and tail flick analgesia tests. The resulting analgesic effect was measured and recorded at 0th, 30th, 60th, 90th and 120th minutes. Assessment of analgesic effect was formulated as % analgesia (MPE) (% analgesia=100x[postdrug latancy-basal latancy]/[cut off time-basal latancy]). Statistical evaluation of the data was performed by two-way ANOVA and multiple comparisons were determined by the Tukey test. Statistical significance was defined at p<0.05 level.

Obtained data suggest that orexin_A and SB-334867 did not change morphine analgesia (p>0,05). SB-334867 decreased tolerance development to morhine (p<0,05).Orexin_B reduced morphine analgesia (p<0,05) but TCS-OX229 did not change morphine analgesia (p>0,05).Orexin_B decreased tolerance development to morhine (p<0,05).

In conclusion, we suggest orexin receptors may role in morphine analgesia and tolerance.

The review of thyroid hormones levels in lithium therapy patients

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Lithium toxicity or long-term lithium therapy have potential side effects for the thyroid. The aim of this study was to determine the effect of lithium on thyroid functions in euthymic patients with bipolar affective disorder, who have been on lithium monotherapy.

We collected laboratory data from the Clinical Chemistry department of the Turgut Ozal Medical Centre. Our study population included all patients who had at least one serum lithium measurement from November 1st 2000 to April 30th 2018. When the files were scanned, the results of sociodemographic data and thyroid function tests were recorded of the in patients diagnosed with bipolar affective disorder taking lithium-monotherapy.

A total of sixty-three patients were included in this study and 34.9 % of the patients (n=22) were male and 65.1 % (n=41) were female. All patients were diagnosed with bipolar affective disorder. The mean age of the patients was 42±13; 40± 12 years for females versus 42± 13 years for males. Free T4 (f T4) values of 76.2% (n=48), free T3 (f T3) values of 93,1% (n=54), TSH values of 95,2% (n=59) of the patients were within the reference range.

According to the results of a study of patients using lithium, the ratio of the patients is in the reference range given as 95.3%, 95.3% and 84.4% respectively. These results were similar to the results of our study. The thyroid functions of the most patients were not affected by this drug. It is important to monitor the side effects of this drug, which has common endocrinological and haematological side effects, to evaluate the effectiveness of the treatment. More extensive studies are needed for better evaluation of the side effects of the disease.

The effect of the application of melatonin and zinc in dmba-induced mammary carcinoma in rats on lipid peroxidation and element metabolism

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In this study, it was aimed to investigate the effects of application of melatonin and zinc on lipid peroxidation and elemental metabolism in female rats with DMBA-induced mammary carcinoma. The study groups were composed of control, DMBA control and treatment (DMBA+ zinc, DMBA + melatonin and DMBA + zinc+melatonin) groups. Female rats (except the control group) were given a strong carcinogen DMBA. After tumour formation, zinc and melatonin were administered to the treatment groups at a dose of 5 mg/kg/day for 4 weeks. MDA as an indicator of tissue damage and GSH levels as an indicator of antioxidant activity in blood and breast tissue samples were determined by spectrophotometric method. Besides, some serum element levels (iron, magnesium, zinc and copper) were calculated.

The highest level of MDA found in plasma and breast tissue was obtained in the DMBA control group. Plasma MDA levels of the breast tissue were lower in the zinc group than in the melatonin group and significantly decreased in the zinc + melatonin group. Plasma MDA levels showed a significant decrease in the zinc + melatonin group, although there was no difference in the zinc and melatonin groups. The lowest GSH level found in erythrocytes and breast tissue was obtained in the DMBA control group. When zinc and melatonin groups were compared in the breast tissue, GSH level of zinc group was found to be higher than GSH level of melatonin group. Furthermore, the highest increase was found in the zinc + melatonin group. The highest levels of iron, magnesium and zinc were found in the zinc + melatonin group, and the highest level of copper was obtained in the DMBA control group.

The findings showed that the antioxidant activity suppressed by increased oxidative damage in rat mammary carcinoma was improved, but the administration of zinc + melatonin gave better results.

Effects of melatonin on hepatic and aortic tissue stat-3 levels in hypercholesteraemic rats

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Hypercholesterolemia is recognized as a major risk factor for cardiovascular disease and has been reported that increase all-cause mortality in different epidemiological studies. It is characterized by nitric oxide bioavailability, lipid profile and oxidative stres changes. STAT-3 is an important transcription factor that upregulates a number of pro-inflammatory genes in endothelial cells, including cytokines, chemokines and adhesion molecules. In this study, it was aimed to investigate the effects of melatonin on hypercholesterolemia, STAT-3 levels in liver and aortic tissue.

Rats were divided into 5 groups (n:7). While control group was fed with normal diet, other groups were fed with 2% cholesterol and 0.5% cholic acid diet to develop hypercholesterolemia for 8 weeks. Melatonin was administrated by i.p. injection both concurrently with cholesterol and only last 2 weeks. The tissue STAT-3 levels were detected by Western-Blot.

STAT-3 levels were increased with hypercholesteraemic diet and decreased with melatonin administrations compared to hypercholesterolemia group. There was more reduction with the prophylactic melatonin administration than in the last two weeks.

Melatonin may protect against hepatic and vascular injury due to hypercholesterolemia via reduce the level of proinflammatory STAT-3. Life style changes such as protecting the level of endogenous melatonin may protect people from hypercholesterolemia-induced disorders.

The effect of dopamin₂ receptor on oxytocin-induced analgesia in rats

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Recent studies have shown that oxytocin has analgesic activity. However, it has not yet been clarified by which way it has performed this analgesic activity. The aim of this study was to investigate the effect of dopamine₂ on the oxytocin-induced analgesia.

In our study, 48 male 230-250 gr Wistar Albino rats were used. First, dose studies were performed with 100 μ g/kg, 200 μ g/kg and 400 μ g/kg to determine the optimal analgesic effect of oxytocin. Optimal dose was found at 200 μ g/kg and then animals were divided into nine groups as Saline, Cabergoline (D2 agonist;0,5 mg/kg), Sulpride (D2 antagonist;10 mg/kg), Cabergoline + Oxytocin and Sulpride + Oxytocin. Serum physiologic was given to the saline group and other drugs were administered intraperitoneally at the indicated doses. Tail-flick and Hot-plate tests were used to measure analgesic effects. Analgesic tests were measured at 30 min-intervals (at 30th, 60th, 90th, and 120th minutes) and recorded in seconds. In order to evaluate the percentages of maximum antinociceptive effect (% MPE), the tail-flick and hot-plate latencies were converted to the percentage of anti-nociceptive effect veness using this equation: % MPE = [(Post drug latency–Baseline latency)/(Cutoff value–Baseline latency)]×100. Statistical evaluation of the data was performed by two-way ANOVA and multiple comparisons were determined by the Tukey test. Statistical significance was defined at p<0.05 level.

Obtained data suggest that the cabergoline produced analgesic activity alone (p<0.05) and the combination with oxytocin increased the analgesic activity of oxytocin (p<0.05). Sulpride did not produce analgesic activity alone (p>0.05), but the combination with oxytocin reduced the analgesic activity of oxytocin (p<0.05).

In conclusion, we suggest that oxytocin may performs its analgesic activity with dopamine 2 receptors.

Levels of plasma NPY, leptin and nesfatin-1, and their relation to zinc in children with obese and metabolic syndrome

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The aim of the present study was to investigate the relation between zinc, a major trace element, and nesfatin-1, leptin, and NPY hormones, which are significantly involved in the regulation of food intake, in children diagnosed with metabolic syndrome and obesity.

The study registered 60 cases, of whom, 20 were boys and girls who presented at the Paediatric Endocrinology Polyclinic of Konya Education and Research Hospital with obesity and were diagnosed with metabolic syndrome [MeS(+) obese], 20 were obese patients without metabolic syndrome criteria, and 20 were healthy control individuals. The sixty cases included in the study were allocated to six groups with an equal number of cases in each: Group 1, Boys with Metabolic Syndrome; Group 2, Girls with Metabolic Syndrome; Group 3, Obese Boys; Group 4, Obese Girls; Group 5, Control Boys; and Group 6, Control Girls. Plasma samples were analyses for NPY (ng/ml), Leptin (pg/ml) and Nesfatin-1 (ng/ml) levels using ELISA method and serum zinc (μ g/dl) levels determined after a minimum of 10 to 12 hours of fasting by atomic absorption method.

Leptin levels in boys and girls with metabolic syndrome were found significantly higher than those in obese and control boys and girls (p<0.05). Nesfatin-1 and NPY levels in both control boys and girls, on the other hand, were higher than those in obese boys and girls (p<0.05). Serum zinc levels were found higher in boys and girls with metabolic syndrome, in comparison to obese and control boys and girls (p<0.05).

The results of the study demonstrate that metabolic syndrome and obesity alter the levels of leptin, nesfatin-1 and NPY, hormones which are involved in the regulation of food intake. These alterations may be associated with zinc levels, which are elevated in the metabolic syndrome.

Effect of white tea consumption on serum leptin, TNF- α and body weight in menopausal model rats

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The postmenopausal period is associated with body weight gain in women. Body weight gain is also a common phenomenon in ovariectomized (Ovx) rats. In clinical and experimental studies, tea polyphenols have been reported to cause weight loss through thermogenesis and lipid peroxidation. However, the effect of white tea on Ovx-induced body weight changes is unknown. For this purpose, the role of long-term consumption of white tea (WT) on body weight gain in the menopausal model rats in the present study was examined.

In the study, 32 female rats were used in the range of 250-300 gr. Bilateral ovariectomy procedures were performed to sixteen rats. Then, the rats were grouped into sham, Ovx, white tea (WT) and Ovx+WT, respectively, as 8 in each group. WT was administered for 12 weeks with 0.5% drinking water. As a result of the experiment, body weight changes of rats, serum estradiol (E2), leptin and TNF- α levels were evaluated. Statistical analysis of body weights of groups used variance analysis in repeated measures. Data were analysed with one-way ANOVA.

There was significant difference between the body weights of Ovx and Ovx+WT group (p<0.001). Body weight of the Ovx + WT group is lower than Ovx group. Serum E2 levels in Ovx group was found low compared to control group. Serum leptin levels in Ovx and WT groups were significantly decreased compared to control group (p<0.01, p<0.05, respectively). Serum TNF- α levels in Ovx group was significantly increased compared to control group (p<0.01), but there was no significant in serum TNF- α between control and WT groups (p>0.05).

The increase in body weight due to menopause can be limited by the addition of white tea to the diet. This effect can be regulated by both hormone and proinflammatory cytokine levels.

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The effects of angiotensin II receptor blocker on brain oxidative stress and neurobehavioural alterations in ovariectomized rats

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It is known that women are more susceptible to anxiety and depression in menopause. These disorders may occur due to increased oxidative stress. The renin-angiotensin system (RAS) components are produced within the CNS and related to mood disorders such as depression. Valsartan, a synthetic angiotensin II type 1 receptor antagonist, is a hypertensive agent. It was shown that valsartan (val) prevents Amiloid- β -related memory deficits in the Alzheimer disease model and anxiety/depressive-like behaviour in chronic mild stress model. The aim of this study was to investigate the effects of valsartan anxiety/depressive-like behaviour and oxidative stress in ovariectomized (ovx) female rats.

Thirty-two female rats were assigned to one of the following groups (n:8): control; control+val; Ovx and Ovx+val. Ovariectomy surgery was performed to remove both ovaries from the rats. Two weeks after surgery valsartan (40 mg/kg) administered orally by gavage for 14 days. Forced swimming test (FST) and open field test (OFT) was used to assess anxiety/depressive-like behaviour. The levels of malondialdehyde (MDA), a marker of lipid peroxidation, and reduced glutathione (GSH) was evaluated by spectrophotometrically in hippocampus and prefrontal cortex tissues. Arterial blood pressure was also measured. Differences between groups were evaluated with Kruskal-Wallis followed by a posthoc Bonferroni test to evaluate the differences with in the groups.

Our results have shown that ovariectomy significantly increased the immobility time in the FST and anxiety like behaviour in OFT. Ovariectomy also caused elevation of oxidative stress in hippocampus. Valsartan treatment significantly restored GSH levels and reduced MDA levels in hippocampus indicating attenuation of oxidative stress. In the prefrontal cortex, ovariectomy did not have any effect on oxidative stress parameters. Arterial blood pressure did not show any significant difference between groups.

The results of this study show that valsartan treatment diminish anxiety/depressive-like behaviour by reducing oxidative stress in hippocampal region in Ovx rat brain.

ACTH and amlodipine effects on neuroblastoma and cortical neurons

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Neuroblastoma (NB) is a type of cancer that occurs in certain types of nerve tissue. Cortex neuron have important role in central nervous system. Ectopic adrenocorticotropic hormone (ACTH) sedation is the cause of 10% -18% of Cushing's syndrome cases. Ca²⁺ signalling is important for regulation of vital events for the cell such as contraction, motility, apoptosis, transmitter oscillation. Studies have shown that voltage-gated calcium channels are involved in many of the cancer features such as avoiding growth suppressors, resisting cell death, providing replicative immortality, stimulating angiogenesis and activating invasion and metastases and activating more.

In this study, it was aimed to determine the effects of amlodipine, a calcium channel blocker, and ACTH on human neuroblastomas and cortex cells by using different doses. The cytotoxicity assays were performed using the 3-(4,5-dimetiltiyazol2-yl)-2,5-difeniltetrazolyum-bromür (MTT) method depending on time and concentration. After obtaining the confluence (up to 85% for SH-SY5Y) and sufficient branches (rat cortex neurons), the cells were treated with amlodipine (10 μ M) and ACTH (25, 50 and 75 μ g) at different concentrations for 24 hours. MTT assay, propidium iodide (PI) and Annexin V test were done according to the manufacturer's protocol.

When the data were analysed, cell death was more than only ACTH application when amlodipine alone was applied. However, doses of amlodipine and ACTH co-administered neuroblastoma deaths were much higher (P<0,05) than control group. Early apoptosis ratio in cortex neuron cell is the lowest in 25 μ g dose of ACTH. These and similar studies are promising in the treatment of cancer.

Relationship between maximum standardized uptake value obtained with Ga68-DOTATATE positron emission tomography-computerized tomography (PET-CT) and tumour grade in neuroendocrine tumours

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Neuroendocrine tumours (NETs) are neoplasms that arise from cells of endocrine and nervous systems. The most common clinically encountered NETs are gastroenteropancreatic tumours, lung carcinoids, pheochromocytoma and medullary thyroid carcinoma. Ga-68 DOTATATE Positron Emission Tomography-Computerized Tomography(PET-CT) is more common gallium analogues used in the evaluation of NETs. Their mechanism of uptake in neuroendocrine cells is due to the increased expression of somatostatin receptor (SSTr) and is also the basis of imaging with somatostatin receptor scintigraphy. The maximum standardized uptake value (SUVmax) is a parameter used for the semi-quantitative analysis of tumour metabolism. In our study, we investigated the association of SUVmax values obtained with PET-CT images with Ga68 DOTATATE with NETs diagnosis or, of course, tumour grade.

The data of 16 patients with definite histologic diagnosis of NETS were selected. 68Ga-DOTA-NOC PET-CT was performed on a dedicated dual modality PET-CT. A dose of 132 to 222 MBq of 68Ga-DOTATATE was injected intravenously. After 60-minute uptake period, the patients were taken for PET-CT. The tumour grade and SUVmax values of 16 patients with NETs were retrospectively compared.

An inverse relationship was found between SUVmax values obtained from tumour grade and Ga68 DOTATATE PET-CT images. The SUVmax values are decreasing as the number of mitoses and Ki67 score, which determine the Grade of tumours, increase.

According to the results obtained from Ga-68-DOTA PET-CT images, the expression of SSTr decreases as the NETS grade increases (poor differentiation). The results we obtained are similar to those of the literature.

Very unknown neuroendocrine features of Rubinstein-Taybi syndrome in the context of a novel identified mutation

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Rubinstein–Taybi syndrome (RSTS) is a rare, congenital, and neurodevelopmental disorder. One of the over 8,000 known rare diseases, RSTS affects males and females equally with a birth prevalence of 1:100,000 to 1:125,000. In addition to genetic polyclinic applications, these patients may sometimes perform their first application to the neurology, endocrine and psychiatry polyclinic. Neuroendocrine abnormalities seen in these patients; Arnold-Chiari malformation, cerebellar hypoplasia, syringomyelia, hypothyroidism, hypoplasia, growth hormone deficiency, pituitary hypoplasia, pituiatery adenoma, parathyroid adenoma, pheochromocytoma and neuroendocrine tumours. Common behaviour problems in RSTS patients; short attention span, decreased tolerance for noise and crowds, autistic behaviours, impulsivity, and moodiness are frequently observed. Other abnormal behaviours included attention problems, hyperactivity, self-injurious behaviours, and aggressive behaviours.

We report the novel mutation in cAMP response elements binding protein (CREBBP) gene in two years old boy from Turkey who presented with developmental delay, intellectual disability, cerebellar hypoplasia, self-injurious behaviours, endocrine abnormalities and dysmorphic facial features. CREBBP sequencing analysis showed a novel mutation c.3233 C>T. It should be kept in mind that this disease, which is easily recognized by clinical geneticists with phenotypic characteristics, can be observed in any outpatient clinic with different findings.

Comparison of Ga-68-DOTATATE PET-CT and F-18 FDG PET-CT in neuroendocrine tumours; Pamukkale University's first 3 months of experience

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A group of neuroendocrine tumours (NETs) includes the somatostatin receptors (SSRs). In the evaluation of NET, Ga-68-DOTA PET-CT is frequently used and shows the SSR expression. In our study, we wanted to exhibit the Ga-68-DOTA PET-CT data.

In the study, F-18-FDG and Ga-68-DOTA PET-CT examinations of 12 patients with NET (7M;5F) were retrospectively investigated. After fasting for 6 h (blood glucose level was<200 mg/dL), the patients received 259–407 MBq of F-18-FDG intravenously; on a different day, they received 148-296 MBq of Ga-68-DOTA intravenously. The patients were examined using a same dedicated PET/CT scanner (Gemini TF-TOF PET-CT).

Ga-68-DOTA and F-18-FDG uptake were concordant in 3 of 12 patients and discordant in 9 of 12 patients. Ga-68-DOTA and F-18-FDG uptake was positive in one patient (TSHoma). In 2 patients, Ga-68 DOTA and F-18-FDG uptake were not detected (colonNET, thyroid papillary cancer). In 3 of 9 patients, Ga-68-DOTA uptake was observed in the lesions, while F-18-FDG uptake was not detected (two lung NET, one stomach NET (grade 1-2)). In 2 patients, F-18-FDG uptake was observed, while Ga-68-DOTA uptake was not observed (oesophagusNET+squamouscell carcinoma (grade 3), lung squamous cell carcinoma). Although Ga-68-DOTA and F-18-FDG uptake was observed in 2 patients, Ga-68-DOTA uptake was higher than F-18-FDG (paraganglioma, lung typical carcinoid tumour (grade 1)). In 2 patients, Ga-68-DOTA and F-18-FDG uptake showed heterogeneity (thyroid medullar cancer, lung atypical carcinoid tumour (grade 2)).

In our first 3-month Ga-68-DOTA PET-CT experience, it has been noticed that Ga-68-DOTA PET-CT in grade 1-2 tumours and F-18-FDG PET-CT in grade 3 tumours give more accurate results. Some of the grade 2 tumours showed heterogeneity due to the uptake of Ga-68-DOTA and F-18-FDG. These findings are consistent with the literature.

Clinical features and risk factors of diabetic polyneuropathy

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Diabetes mellitus is a serious chronic disease characterized by hyperglycaemia that results from insulin deficiency. Diabetic neuropathies manifest in several different forms, including sensory, motor, focal/multifocal and autonomic neuropathies. The most common type is diabetic distal symmetric polyneuropathy (DPN).

In this study, it was aimed to determine the polyneuropathy characteristics and risk factors in diabetic patients with neuropathic symptoms

Thirty-five patients with diabetes who were referred to our clinic for neuropathy symptoms between 2016 and 2017 were included in the study. Detailed ophthalmological, physical and neurological examinations of all patients were performed. Total neuropathy scores of patients are calculated. Age, sex, duration of diabetes, duration of neuropathic symptoms, antidiabetic drugs used, additional diseases, haemoglobin A1c (HbA1c) levels were recorded.

The mean age of the patients was 61.6 ± 13.6 (range 37-78, for females 66.3 ± 11.3 , for males 57.7 ± 14.5 , p<0.05) years. The mean duration of diabetes was 19.6 ± 14.0 (range 2-40) years. The mean duration of neuropathic symptoms was 6.6 ± 5.3 (range 1-15) years. The mean neuropathic symptoms duration was 9.6 ± 5.1 years for females and 4.1 ± 4.1 years for males (p<0.05). The mean HbA1c level was 9.1 ± 1.8 and the mean total neuropathy score was 11.6 ± 6.7 . The mean total neuropathy score was 16.0 ± 3.8 for females and 8.0 ± 6.6 for males (p<0.05). The mean duration of neuropathic symptoms was 1.3 ± 0.5 years in patients without additional disease, and it was 8.5 ± 6.8 years in patients without additional disease, and it was 8.5 ± 6.8 years in patients without additional disease, and it was 10.7 ± 7.7 in patients with additional disease (p<0.05). Age, total neuropathy score, HbA1c level, duration of diabetes and duration of neuropathic symptoms were higher in the patients who were diagnosed as polyneuropathy during the neurological examination (p<0.05).

DPN is diagnosed by the combination of neuropathic symptoms and abnormal electrophysiological findings and the total neuropathy score used in this study includes these parameters. In our study, total neuropathy score was higher in female patients, patients with comorbid diseases, and patients with polyneuropathy. In literature, it was reported that diabetic neuropathy is more common in males. In some studies, it was revealed that there was no difference in terms of sex. Unlike the literature, we found a significant relationship between female gender and total neuropathy score. HbA1c value, duration of diabetes and duration of neuropathic symptoms were higher in patients with polyneuropathy. As a result, duration of diabetes, duration of neuropathic symptoms, elevated HbA1c levels, additional diseases and female gender may be specified as risk factors for the development of DPN.

Effects of tacrolimus on endothelin-1, melatonin and heat shock protein levels in experimental brain ischemia

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The aim of the present experiment to investigate the effects of tacrolimus on plasma endothelin-1, melatonin and brain Hsp-70 levels in experimental ischemic stroke.

Twenty-one male Wistar-Albino male rats were randomly divided into three groups which included seven rats. Animals in group 2 and group 3 were anesthetized and bilateral common carotid arteries were clamped with aneurysm clips for 10 minutes. Animals in group 1 were not clamped and were not given any treatment. Rats in group 2 received 1 ml saline and those in group 3 received 1 mg/kg tacrolimus intraperitoneally. Injections were applied 1st hour before ischemia and at 6th, 24th, 48th and 72nd hours post ischemia. All the animals were decapitated on the 4th day and plasma samples were obtained and brains were excised. Plasma endothelin-1 and melatonin levels were measured. Brain Hsp-70 immunostaining and neuronal cell death were scored semiquantitatively.

The plasma endothelin-1 levels in group 3 were higher than group 2 and group 1, but were similar in group 1 and group 2. In group 1 plasma melatonin levels were lesser than group 2 and group 3. In group 2 plasma melatonin levels were higher than group 3. The mean neuronal death in group 3 was lesser than in group 2. The mean Hsp-70 immunostaining intensity in group 2 was greater than group 3 and group 1. In group 1 the mean Hsp-70 immunostaining intensity was lesser than group 3.

Tacrolimus administration in ischemic stroke reduces plasma melatonin and brain Hsp-70 levels and increases plasma endothelin-1 levels and has neuroprotective effect.

Gastroenteropancreatic neuroendocrine grade 2 neoplasms: Can we define stricter criteria

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Gastroenteropancreatic neuroendocrine tumours (GEP-NET) are a heterogeneous group of neoplasms derived from the gastrointestinal tract and the neuroendocrine section of the pancreas. The aim of this study was to evaluate Ki 67 proliferation index by histopathological analysis of GEP-NET G2 patients. Between 2011 and 2017, 15 patients with grade 2 neuroendocrine tumours originating from the gastroenteropancreatic system were studied retrospectively from the reports of Inonu University Medical Faculty Department of Pathology.

Histopathological and prognostic markers were compared with Ki-67 proliferation index. The median age at diagnosis was 51.55 (28-76) years. Seven of the patients (46.6%) were female and 8 (53.3%) were male. The most common localization was small bowel (36.7%). 2 of the patients (13.3%) had stomach, 5 (33.3%) had small intestine and 2 (13.3%) had colon NET. Pancreas-induced NET was present in four patients (26.6%). The mean tumour size was 4.5 cm (0.4-10 cm). The mean number of mitosis was 3.3 (1-10 number / 10BBA). Tumour necrosis was seen in 2 of the cases. Lymphovascular invasion was present in 7. Both had perineural invasion. Lymph node metastasis was present in 5 cases. The mean number of metastatic lymph nodes was 3,6 (1-7). The mean proliferation index with Ki67 was 6.9% (2% -20%). The metastasis was observed in two cases. We evaluated the histopathologic prognostic criteria differences, in the mitotic index range, and marked variability in Ki 67 ratios in the NETG2-diagnosed cases.

Regular swimming exercise in rats alleviates gastric ulcer-induced oxidative stress by an oxytocinmediated mechanism

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Oxytocin, a neuropeptide of the paraventricular nucleus, has anti-inflammatory actions. Regular exercise is known to reduce inflammation and exert protection on the gastrointestinal system. The aim was to investigate the role of endogenous oxytocin in potential anti-inflammatory effects of exercise on gastric ulcer healing.

Wistar albino rats (n=56) were divided randomly as exercise (30 min/day swimming, 5 days/week for 6 weeks) or sedentary groups. On the 7th week, acetic acid (80%; ulcer) or saline (control) was applied on gastric serosa under anaesthesia. Starting at 4 days before ulcer induction and the following postsurgical 3 days, rats were injected intraperitoneally with oxytocin antagonist atosiban (0.1 mg/kg/day) or saline. On the 4th day of ulcer, following the measurement of gastric serosal blood flow, gastric tissue samples were obtained for the determination of 8-hydroxy-2'-deoxyguanosine (80HDG) levels (ELISA); IL-6, IL-8, TNF-alpha levels, caspase-3 activity (Western Blot); myeloperoxidase activity, malondialdehyde, glutathione levels (spectrophotometric), luminol (chemiluminescence) and histopathologic analysis (hemotoxylin&eosin). Statistical analyses were made using ANOVA and Student's t-test.

When compared with sedentary control groups, myeloperoxidase and caspase-3 activities, malondialdehyde, IL-6, IL-8, TNF-alpha, luminol and 8-OHDG levels showed significant increases in the sedentary ulcer groups, whilst glutathione levels and serosal blood flow were significantly decreased (p<0.05-0.001). Compared with sedentary ulcer groups, regular exercise elevated serosal blood flow, reduced myeloperoxidase and malondialdehyde levels, and attenuated ulcer-induced gastric damage. Atosiban treatment in exercised ulcer groups reversed exercise-induced alleviation of gastric damage and the reduction in malondialdehyde levels. Regular swimming exercise training accomplished prior to ulcer induction facilitated ulcer healing via alleviating ulcer-induced oxidative stress.

This anti-inflammatory effect of exercise appears to be mediated by an oxytocin-mediated mechanism.

Effects of tobacco and alpha lipoic acid treatment on puberty parameters in male rats

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In a wide range of countries, tobacco usage has become more common among adolescents. In the literature, several clinical and experimental studies investigated effects of tobacco on puberty, but alpha lipoic acid effects with tobacco using on puberty are not exactly known. Alpha lipoic acid (ALA) is a strong antioxidant and anti-inflammatory agent and important for gonadotrophin biosynthesis. In this study, we investigated ALA effects on puberty development on maternally tobacco-exposed female rats' male offspring.

For the experimental studies, totally 28 female Sprague Dawley rats were used. All animals were randomly divided into four groups [control (I), tobacco (II), tobacco+alpha lipoic acid (III) and alpha lipoic acid (IV)] and each group comprised of 7 rats. Female rats in group II and III were exposed to tobacco smoke (20 g/per day) twice a day for an hour during the experiment. Group III and group IV rats were received ALA (20 mg/kg) dissolved in saline by oral gavage in every other day. At the end of the eighth week, female rats in all groups were mated with male rats. Tobacco smoke and alpha lipoic acid administration were continued throughout pregnancy. New-born male rats were selected for each group (n=7). Then, puberty was determined by preputial separation. There was significantly delayed on puberty onset day group-III (57.44 \pm 0.60) compared to control (51.87 \pm 0.95), (p<0.001). There was significantly increased difference in pubertal weight between control (153.3 \pm 3.73, g) and group-IV (182.63 \pm 4.24 g, p<0.01). There was no any significant change in serum FSH levels. There was significant increase in serum LH level in all groups (II, III and IV) compared to control group (3.12 \pm 0.05a, 3.00 \pm 0.084b, 3.51 \pm 0.104c and 2.60 \pm 0.089, IU/mL, respectively, p<0.01, p<0.05, p<0.001).

As a result, it was concluded that alpha lipoic acid and tobacco delayed puberty with together and LH increase was independent from alpha lipoic acid treatment.

The role of bilateral inferior petrosal sinus sampling in differential diagnosis of Cushing syndrome

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Bilateral inferior petrosal sinus sampling (IPSS) is the gold standard method in the differential diagnosis of Cushing Syndrome (CS) and has also been used in tumour lateralization. In this study, we aimed to evaluate the value of IPSS in differential diagnosis of CS, and diagnostic accuracy of IPSS in lateralizing the pituitary mass.

Twenty consecutive patients with CS and normal or suspicious magnetic resonance imaging (MRI) were assessed in the study. Four patients were not included in the study due to missing data. After selective catheterization of petrosal sinuses, the ratio of inferior petrosal sinus ACTH to peripheral blood ACTH (IPS:P), and the ratio of bilateral petrosal sinus ACTH levels to each other were measured at basal status and after intravenous (iv) corticotrophin releasing hormone (CRH) administration. Demographic, biochemical and clinical findings were retrospectively evaluated for each patient.

Of these patients, 14 were female (87.5%), and mean age were 38.19 (±11.095). Mean cortisol and ACTH levels were 24 ± 26 (range 1-89 µg / L) and 74.6 ± 123 (range 11.5-520 pg/L) respectively. After IPSS with CRH, the diagnosis of Cushing's disease was confirmed by IPS:P ratio of \geq 2.0 at basal state and/or \geq 3.0 after CRH administration in 11 of 16 patients (68.7%). Of these, the pituitary mass was lateralized to the right in 7 patients and to the left part of pituitary gland in 3 patients. The mass could not be lateralized in one patient. Except one (she refused surgery), all patients subsequently underwent to transsphenoidal exploration to evacuate the pituitary adenoma. Likewise; results of IPSS indicated peripheral location of tumors in 5 patients. Further evaluation of these patients pointed out adrenal Cushing syndrome in two patients (one had adrenal adenoma with co-secretion of catecholamine, the other bilateral adrenal hyperplasia). One patient was diagnosed as bronchial carcinoma located to the mediastinum. Tumours could not have been localized in other two patients. Of these five cases, two underwent to surrenalectomy and in one case bronchial carcinoma was successfully resected.

IPSS using iv CRH is very helpful for differential diagnosis of CS and lateralization of tumour mases.

RF9 increases intracellular calcium concentration by protein kinase C activation in rHypoE-8 cells

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RF9 is an antagonist of the RFamide-related peptide-3 (RFRP-3) receptor. RFRP-3 is accepted as the mammalian orthologue of avian gonadotropin-inhibitory hormone (GnIH). There are several studies that indicate a potential interaction between RF9 and kisspeptin neurons. However, mechanism of action of the RF9 as a kisspeptin agonist remains to be elucidated. Intracellular calcium $[Ca^{2+}]i$ signalling is an important mechanism involved in hormone secretion. For this aim, the role of RF9 on $[Ca^{2+}]i$ concentrations in rHypoE-8 cells, a model of kisspeptin neurons, were investigated by using in vitro calcium imaging system.

rHypoE-8 cells were plated on glass coverslip and loaded with 1µM Fura-2 AM. RF9 was prepared at different doses (1-10 µM). Calpostin C was used as a protein kinase C (PKC) inhibitor. $[Ca^{2+}]i$ analyses were performed in both normal and extracellular calcium-free conditions. Using the fura-2-based calcium imaging technique, $[Ca^{2+}]i$ responses were quantified by the changes in 340/380 ratio.

RF9 caused a significant increase in basal levels of $[Ca^{2+}]i$ after application at doses of 1 μ M (n=15, p<0.05) and 10 μ M (n=15, p<0.01). The stimulatory effect of RF9 (10 μ M) on $[Ca^{2+}]i$ was persistent in extracellular Ca²⁺ free conditions (n=15, p<0.01). The changes in $[Ca^{2+}]i$ were significantly attenuated by pre-treatment with the PKC inhibitor.

Our results indicate that RF9 activates [Ca²⁺]i signaling through PKC mediated mechanism in the kisspeptin neurons.

Effect of different doses of corticosterone administration on brain monoamine levels in male and female rats

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Stress causes various psychopathologies by acting on brain monoamine levels. However, relationship between glucocorticoids and monoamines is not well understood. The aim of this study was to investigate effect of chronic corticosterone administration on norepinephrine and dopamine levels and turnover rates in critical brain regions at different doses and its differences according to gender.

Female and male rats were injected with vehicle or 10, 20, 40 mg/kg corticosterone for 21 days. Norepinephrine, dopamine and their metabolites in hippocampus and striatum were analysed by HPLC. In male, hippocampus norepinephrine concentration was higher in the 40mg group (16.34±1.51) than control, 10mg, 20mg groups (7.95±0.90;6.33±0.51;10.61±0.98, p<0.05). Dopamine concentration (10.22±1.28) in 40mg group is higher than control (4.94±0.58, p<0.05). Norepinephrine turnover rate in 40mg was lower than all other groups; DA turnover rate was lower in 20mg (0.23±0.02) and 40mg (0.27±0.02) groups compared to control (0.43±0.06, p<0.05). In female rats, hippocampus norepinephrine level was lower in 20mg and 40mg (1.77±0.22;1.18±0.13) compared to the control and 10mg (5.77±0.91;7.38±0.55, p<0.05). Dopamine concentrations were decreased in the 20mg (3.97±0.44) compared with control and 10mg (6.25±0.90;6.18±0.30, p<0.05). Norepinephrine turnover rate was increased in 20mg and 40mg compared to the control and 10mg. Dopamine turnover rate was higher in 20mg than control and 10mg (p<0.05). In the 20mg and 40mg groups, the females had a lower concentration of norepinephrine and dopamine than the males (p<0.001). In male, striatum norepinephrine and dopamine levels were lower in all corticosterone administration groups than control (p<0.05). In female, norepinephrine, dopamine concentration and turnover rate didn't differ between groups.

In conclusion, corticosterone administration caused opposite effects on norepinephrine and dopamine in the male and female hippocampus, but it affects only male in the striatum. Chronic corticosterone results in changes in norepinephrine, dopamine levels and turnover rates in the hippocampus and striatum in dose-dependent manner and these changes are quite different in males and females.

Effects of intracerebroventricular administration of salusin- β on food intake, water consumption and body weight in male rats

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Salusin- β is an endogenous parasympathomimetic peptide. This peptide is predominantly localized to the hypothalamus and posterior pituitary. Hypothalamus is controlling of feeding and drinking behaviour in a delicate balance. This study intends to clarify possible effects of the salusin- β on feeding and water intake behaviour in rats.

In this study, 250-270 g in weight of 40 male *Wistar-Albino* rats were used. Rats were evenly separated into four groups (n=10). Osmotic mini-pumps were implanted to lateral ventricle and artificial cerebrospinal fluid (vehicle; sham group), 2 and 20 nmol/kg concentrations of salusin- β were infused for 7 days (10 µl/hour) to rats. Throughout the experimental period, the rats were kept in individual cages, and body weight, food and water consumption of the animals were daily recorded.

At the end of the seven-day infusion, all concentrations of salusin- β (2 and 20 nmol/kg) increased the daily food intake and body weight of the rats (p<0.05). On the other hand, icv infusion of salusin- β decreased the daily water intake of the rats (p<0.05).

All these findings indicated that salusin- β increased the appetite in rats. Additionally, salusin- β increased body weight but decreased water consumption in rats. It is well known that many hormones such as leptin, neuropeptide Y (NPY), agouti-related peptide (AGRP), proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) take active roles in the interaction of the hypothalamic controlling of feeding behaviour in a delicate balance. The effects of salusin- β on hypothalamic orexigenic or an-orexigenic peptides should be investigated.

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Effect of pregnancy and lactation period on depression like behaviour in depressive rats

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Sertraline is an antidepressant agent used for depression therapy in depressive patient. There is quite limited study with regards to effect of sertraline in experimental depression model in rats. Additionally, there is no detailed data regarding pregnancy and lactation period on behavioural status in depressive and sertraline treated rats. We aimed to investigate the effect of perinatal processes on depressive behaviour in animal model of depressive like behaviour.

Adult female pregnant Wistar rats were included in this study. Chronic light stress procedure was applied to animals in order to constitute depression model for 21 days of pregnancy. Forced Swim Test was used for evaluate depression like behaviour condition of rats in 8th day of gestation. Sertraline was subcutaneously administered to the depressive and non-depressive groups at 10mg/kg for 15 days through osmotic minipumps. Controls and depressive groups received saline via osmotic minipumps. Climbing time, swimming time, immobility time and mobility percent were determined by using animal behaviour monitoring and recording system. After weaning at 30th day of lactation, forced swimming test was applied to all animals for determining the behavioural condition.

Before antidepressant and vehicle treatments, depressive like behaviours were observed in depressive groups by analysing immobility, active swimming and climbing behaviours compared to control (p<0.01, all). Although there is slightly decrease in climbing and swimming time and slightly increase in immobility in depressive rat, there is no significant difference in depressive behaviours at 30th day of lactation.

Data from this study revealed that pregnancy and lactation period may decrease depressive like behaviours in female rats. Antidepressant treatment in gestation period may be additive curative effect on depression.

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Investigation of the effects of mitochondrial-derived peptide (MOTS-c) on the control of feeding in obese rats

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Obesity is a condition that is associated with having an excess of body fat, defined by genetic and environmental factors that are difficult to control when dieting. Many individuals are affected by obesity and are not aware of it. A novel bioactive peptide, mitochondrial-derived peptide (MOTS-c), has recently attracted attention as a potential prevention or therapeutic option for obesity and type 2 diabetes mellitus. MOTS-c is a potential regulator of metabolic homeostasis under conditions of high-energy supply. However, the effect of insulin resistance and obesity on plasma MOTS-c concentration in humans or rats is unknown. We hypothesize that MOTS-c may regulate the hypothalamic control of feeding system.

40 Wistar Albino male rats were used in the study. The rats were separated into 4 groups as the control, sham, 10 μ M MOTS-c and 100 μ M MOTS-c infusion (n=10). The rats were fed with high-fat diet food as of the 21th day of birth for 12 weeks. After 12 weeks, it was determined that obesity occurred in the rats by scoring according to the Lee Index. Then, the rats were anesthetized (except for the control group), and osmotic mini pumps were placed in the lateral ventricle. With the help of the osmotic mini pumps, infusion of artificial cerebrospinal fluid (solvent) was performed to the sham group at a 120 μ l volume (5 μ l/hour) daily; and the infusion of 10 and 100 μ M MOTS-c were performed to the study groups. Throughout the experimental period, the rats were kept in individual cages, and food consumption and body weight of the animals were daily recorded. After infusion period (14 day), the rats were decapitated, and the blood and brain tissue samples were collected. Serum ghrelin levels were measured by ELISA method in blood tissue. The NPY levels were determined using Western Blot method in hypothalamus tissue.

Chronic infusion of the MOTS-c caused to significantly increases in food consumption (p <0.05), but in the body weights of obese rats were not found any significantly difference. On the other hand, intracerebroventricular infusion of MOTS-c resulted in significant increases ghrelin and NPY levels (p<0.05).

Our results show that MOTS-c may change feeding behaviour by affecting hypothalamic process in obese rats.

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MOTS-c increases food consumption of rats but does not alter body weight

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Obesity is one of the medical condition defined with an excessive increase of the amount of body fat that causes a number of metabolic illnesses. Obesity adversely influences the individuals of health status, quality of life and reduces the lifetime. In accordance with the data of World Health Organization (WHO), obesity influences more than 300 million people worldwide and almost 1 billion individuals are overweight. The Mitochondrial-Derived Peptide (MOTS-c) is one of the new hormones discovered in 2015. The first findings of the preliminary studies on the physiological roles of MOTS-c suggest that it prevents the formation of insulin resistance. The study was designed to evaluate effects of chronic central infusion of MOTS-c on food intake and body weight in the rats.

In this study 40 male Wistar-Albino rats were used. Rats were evenly separated into four groups (n=10). Osmotic mini-pumps were implanted to lateral ventricule and artificial cerebrospinal fluid (vehicle; sham group), 10 and 100 μ M concentrations of MOTS-c were infused for 14 days. Throughout the experimental period, the rats were kept in individual cages, and food consumption and body weight of the animals were daily recorded. At the end of the study, chronic infusion of both concentrations of the MOTS-c caused to significantly increases in food consumption (p <0.05), but in the body weights of rats were not found any significantly difference.

The study results support that MOTS-c can play important roles in hypothalamus on regulation of feeding behavior and control of energy metabolism.

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Cannabinoid type 2 receptors activation improves cognitive dysfunction in a okadaic acid induced Alzheimer rat model

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The Alzheimer's disease (AD) is a neurodegenerative disease accompanied by changes in behaviours and neuropsychiatric symptoms and characterized by degeneration in cognitive skills and decrease in daily life activities. It has been shown in many experimental studies that tau hyperphosphorylation occurred in AD and memory formation was impaired. Neuroinflammation occurred in the brain and oxidative stress developed after intracerebroventricular (ICV) administration of okadaic acid (OKA). Expression of cannabinoid type 2 (KB2) receptors, which are found in many regions of the brain, are also found in the hippocampus. JWH-133 is a selective KB2 receptor agonist. In this study we investigated the role of JWH-133 on learning and memory in ICV OKA model of AD in rats.

In the present study, fourty male Sprague-Dawley rats were randomly divided into four groups. Control, Sham: Rats were injected ICV with artificial cerebrospinal fluid (aCSF) and treated vehicle for 13 days, OKA: OKA was dissolved in aCSF and injected ICV (200 ng) in a volume of 5 μ l bilaterally. OKA+JWH-133: Rats injected ICV with OKA and treated with JWH-133 intraperitoneally 0,2 mg/kg/day for 13 days. After 14 days of surgical operations and injections, Morris water maze test was performed. The parameters of latency to platform, distance moved to reach the platform and time spent in the target quadrant were evaluated.

The latency to platform and distance moved of OKA injected rats were increased in comparison to control, sham and OKA+JWH-133 groups. In the OKA+JWH-133 group, time latency to platform and distance moved were shorter than OKA group. In the OKA+JWH-133 group, time spent on target quadrant was more than OKA group.

OKA-treated rats showed significant impairments of spatial memory in Morris water maze test, which were largely reversed by administration of JWH-133.

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The effect of curcumin on brain trpm2 channel gene mRNA expression level in experimental Alzheimer's rat model induced by application of intracerebroventricular streptozotocin

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TRPM2 channel protein has a negative effect on Alzheimer pathology with intrinsic calcium influx into the neurons. It has been reported in recent studies that curcumin could inhibit induced TRPM2 channel protein in vitro. The aim of this study is to investigate the effect of curcumin on TRPM2 gene and Alzheimer pathology in in vivo Alzheimer rat model.

This study was carried out with 50 Wistar albino male rats. Analysis of experimental Alzheimer rat model performed by Morris water maze. Biochemical analyses including SOD, MDA, GSH in rat brain tissue accomplished by spectrophotometric methods. TRPM2 and MAPT gene expression levels performed by RT-PCR in rat hippocampus tissue. Hematoxylin-eosin staining was performed on brain tissues for histopathological analysis.

MDA levels increased in STZ group compared to STZ+curcumin. It was found that GSH levels decreased in STZ group while it increased STZ+curcumin group (P < 0.05). SOD activities were higher in STZ group than in STZ+curcumin group (P< 0.05). TRPM2 mRNA levels increased in STZ rats, but they were lower in STZ+curcumin group. Histopathologically, STZ group had neurodegeneration and STZ+curcumin had attenuated damage.

Oxidative stres, neurodegeneration and increased TRPM2 mRNA levels were shown in STZ induced Alzheimer rats. Curcumin caused a reduction in TRPM2 mRNA levels with positive effect on neurodegeneration.

Effects of paroxetine, bupropion or agomelatine on ovarian tissue and anti-mullerian hormone levels in female rats

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There is no almost study in the literature about the effects of antidepressants on gonads in female rats. Serum levels of anti-mullerian hormone (AMH) may represent both the amount and property of the ovarian follicle pool and so could be a useful marker of ovarian reserve. The purpose of the present study is to evaluate the effects of paroxetine, bupropion and agomelatine; having different mechanism of action and used as antidepressant drugs, on histopathology of ovarian and AMH levels.

Female Sprague-Dawley rats (n=40) were used. All animals were randomly divided into four groups (control, paroxetine, bupropion and agomelatine) and each group consisted of 10 rats. The animals started to receive daily oral paroxetine (3,6 mg/kg), bupropion (17 mg/kg) or agomelatine (10 mg/kg) from postnatal day 21 to minimum 90 days. The control group received only vehicle. The rats were decapitated under general anaesthesia on the first diestrus phase following 90th day. Afterwards, ovarian tissues were prepared for histological studies, and histopathological scores were performed. The changes were evaluated as non-existent (0), mild (1), moderate (2) or severe (3) according to histopathological status. Mean scores were calculated for each group. Also, serum AMH levels were measured by using ELISA method.

There was a significant difference in extreme vascular dilatation and congestion between control and paroxetine or agomelatine groups (p<0.01). Agomelatine treatment significantly increased follicular degeneration (p<0.001) and disruption of zone pellucida (p<0.05) compared to control group. AMH levels were lower in the paroxetine and agomelatine groups compared to control group, but there was no statistical difference. However, there was a significant decrease in bupropion group (p<0.001).

Our results showed that chronic peripheral treatment of paroxetine, bupropion or agomelatine adversely affected ovarian tissue and AMH levels. Thus, these antidepressants may cause reproductive system disruptions in females.

Paroxetine, bupropion, agomelatine, ovarian tissue, anti-Mullerian hormone, female rats.

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Role of TSH, FT3 and anti-thyroid antibodies on neurodegeneration of streptozotocin-induced diabetic rats

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Diabetes Mellitus (DM) disrupts the pituitary-thyroid axis and leads to a higher prevalence of thyroid disease. Type 1 Diabetes Mellitus (DM1) and the dysfunction of thyroid are the most common endocrine diseases, which are interrelated with each other. The aim of this work was to carry out a comparative study on the thyroid functional state in streptozotocin (STZ)-induced diabetic rats.

Eight-weeks-old male Wistar albino rats were used in this experiment. Twenty rats were divided into two groups: control group and STZ group. A single ip injection of 50 mg/kg of STZ was given to the diabetic rats. Three days after the STZ injection, the animals that showed a fasting blood glucose level above 200mg/dl were considered to have diabetes and were used in this study. The models of acute DM1 induced by high doses of STZ were used. After 6 months, all animals were decapitated and their blood samples were collected. Their brains were rapidly removed. After the serum was separated, it was immediately frosted and stored at -80°C. The levels of the serum thyroid-stimulating hormone (TSH), free triiodothyronine (fT3) and anti-thyroid antibodies (anti-TPO) were quantified by using ELISA. Transmission electron microscopy was used to examine the ultrastructural features of the neurons in the brains.

According to the results obtained from the diabetic rats with STZ, the levels of TSH (n: 10, in each; p<0.005) and fT3 (n: 10, in each; p<0.001) decreased significantly, while the TPO levels were the same with the control group. According to the histological findings, there was a significant difference in the degeneration of myelin between the STZ group and Control group.

These findings suggest that the decrease of the thyroid status and TSH levels in diabetic rats lead to neurodegeneration.

Examining the effects of agomelatine on uterine activity of rats in which agomelatine is used during, before and in various stages of pregnancy

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Agomelatine is a new anti-depressant shown as the best synthetic melatonergic medicine defined so far. It has agonist effects on MT1 and MT2 receptors, and antagonist effects on 5-HT2c receptors. Agomelatine is included in B Category for use during pregnancy. Melatonin, on the other hand, is a hormone known to have inhibitory effects on rat uterus, whether pregnant or not. In the light of these data, the possible effects of Agomelatine on rat uterine contractions were investigated in our study.

Seven Wistar Albino female rats were used in each of the 4 groups in the study. 1^{st} Group: Diestrus; 2^{nd} Group: Pregnant; 3^{rd} Group: diestrus used chronic Agomelatine; 4^{th} Group: pregnant group in which Agomelatine was used during all pregnancy stages as of the onset of the pregnancy. The uterine sections obtained from each group were placed in glass containers in isolated organ bath and Agomelatine was applied in non-cumulative dosage with 50, 100 and 200µM doses; and isometric contractions were recorded. For the purpose of questioning the effect mechanism of Agomelatine, 2μ M dose luzindole was used.

When we compared each group within itself, was observed that Agomelatine caused inhibition in all groups at 200 μ M; and caused 100% inhibition at 100 μ M dose in Group 4. Statistically significant inhibition was detected at100 μ M dose in all groups in p-p, frequency and area values. In 50 μ M dose, statistically significant inhibition was detected in the area values of all groups, and significant inhibition was detected in p-p values in Group 1 and 4. Also, significant inhibition was detected in frequency in Group 1, 3 and 4. When all groups were compared with the 1st Group, 200 μ M, %100 inhibition was detected in all groups, and no statistically significant results were detected in all groups in 50 μ M dose. In 100 μ M dose, on the other hand, statistically significant inhibition was detected in Group 4 in p-p, frequency and area values, and there was no significance in other groups.

As a result, it was concluded that Agomelatine has an inhibitory effect on uterine contractions in rats, whether pregnant or not. However, the inhibition that was observed in the rats in which Agomelatine was used during pregnancy was at lower concentrations when compared with other groups. This effect being returned with luzindole, which is a melatonin MT1 and MT2 receptor antagonist, makes us consider that Agomelatine shows this effect through the mediation of melatonin MT1 and MT2 receptor.

Effects of central infusion of irisin on the energy metabolism and glucose uptake in rats

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Irisin is a myokine/adipokine mainly released by skeletal muscles during the exercise and it encourages browning of the white adipose tissue. It has been suggested that irisin regulates glucose and lipid homeostasis. The aim of this study was to investigate the possible changes in serum glucose and lipid levels and gene expression/protein levels of uncoupling proteins (UCPs) in muscle, white and brown adipose tissues after intracerebroventricularly irisin infusion

The Wistar-albino male rats weighing 150-200 g were used in this study. The rats were divided into groups (n=9 in each group). Two different doses of irisin were infused to all animals (except control and sham groups) as centrally for 14 days. The mRNA gene expression/protein levels of UCP1(in brown and white adipose tissue), UCP3 (in skeletal muscle) and serum glucose levels and lipid profiles were determined.

The centrally infusion of irisin caused significant elevations in the UCP1 protein levels of white and brown adipose tissues (p<0.05), but no significant alterations were determined UCP1 gene expression. The significant decreases were seen gene expression levels of UCP3 in muscle tissue (p<0.05), but no significant changes were revealed in the UCP3 protein levels. It was demonstrated that irisin did not cause significant alterations in serum HDL, LDL, triglyceride, total cholesterol and serum glucose levels.

We found relationship between irisin infusion and the UCP1 and 3 in white and brown adipose tissues and we conclude that irisin may have effects on energy metabolism by affecting the UCPs.

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Investigation of the relation between high fructose corn syrup consumption and stress-induced behavioural changes

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High fructose corn syrup (HFCS) is extensively used in a variety of commercial foods and soft drinks as a sweetener due to its low cost, high relative sweetness and long shelf life. In recent studies show that increasing in the consumption of HFCS has been linked to increasing in the risk of diabetes, obesity and cardiovascular diseases. As fructose containing beverages cause slight increase in insulin levels and less satiating than glucose or other saccharides, people consume more food than normal and get more calories than needed and hence, cause obesity and similar metabolic diseases. Aim of the study was to investigate possible effects of different amounts HFCS consumption on depression- and anxiety-like behaviours besides known metabolic diseases.

32 Wistar male rats were randomly divided into four groups: control group receiving only drinking water, Fructose 20 (F20) and Fructose 40 (F40) groups were given water sweetened with 20% and 40% HFCS solution, respectively. Stress group were exposed to stress. Following 14 consecutive days administration, animals were subjected to tail suspension test (TST), light/dark test (LDT) and open field test (OFT). After the behaviour tests, blood samples were collected.

There was no significant difference between groups in TST. LDT revealed that significant increase in the time spent in dark compartment in F20 (238.08±8.38sec), F40 (209.66±11.35sec) and stress (233.39±8.94sec) groups compared to control group (112.38±12.99sec; p<0.01). The number of crossings were found significantly lower in stress group (167.64±5.68) when compared to control (188.66±9.64), F20 (173.66±8.22) and F40 (180.40±6.73) groups in OFT (p<0.01). There was no significant difference in corticosterone levels of control (286.17±18.20ng/mL) and F20 (354.27±17.91ng/mL) groups, while F40 group (504.29±40.96ng/mL) had significantly higher corticosterone levels compared to stress group (412.51±20.60ng/mL; p<0.01).

In conclusion, especially when the results of LDT and corticosterone levels were considered, our results supported the idea that different amounts of HFCS consumption may cause the anxiety- and depression-like behaviours like stress in rats.

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Sitagliptin alleviates high blood pressure, oxidative stress related endothelial dysfunction and inflammation in experimental hypertension

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Hypertension (HT), Diabetes Mellitus (DM) and their complications are major public health problems worldwide due to their association with high cardiovascular morbidity and mortality. The prevalence of hypertension among patients with diabetes are well documented in various populations. Both in these pathologies, the disruption of the balance between vasodilator and vasoconstrictor actions of endothelium is considered as a crucial event in the initiation of the cardiovascular problems. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, is used for the treatment of type-2 DM, enhances phosphorylation of eNOS. This may ensure vasodilatation and reduction in blood pressure. This study was designed to investigate the effect of sitagliptin on blood pressure (BP), body weight and levels of ADMA known as oxidative stress indicator and also NOS inhibitor, ICAM-1 that participates inflammation and an adipokine resistin, on nondiabetic hypertensive rats.

Rats were divided into four groups (control, sitagliptin, hypertension and hypertension + sitagliptin). L-NAME was administered in order to induce hypertension, for 4 weeks. Sitagliptin was given by oral gavage for last 14 days. Blood pressure was measured by using tail-cuff method and ADMA, ICAM-1 and resistin analysed by ELISA.

L-NAME led to a significant increase in blood pressure. Sitagliptin administration (80mg/kg) to L-NAME treated rats significantly reduced blood pressure. Body weights were not different between groups. But while control and hypertensive groups gained weight significantly from 14 to 28th days, weights in sitagliptin administrated groups didn't change significantly. ADMA and ICAM-1 levels increased significantly in hypertension but sitagliptin administration decreased the values significantly. Resistin levels were not different between the groups.

Although further studies are needed to determine its effectiveness; these findings indicate that sitagliptin may have a protective role in hypertension via mechanisms targeting inflammation and oxidative stress related endothelial dysfunction.

Hypothyroidism and anaesthesia management

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Hypothyroidism has negative effects on the cardiovascular and respiratory system, which is particularly important in anaesthesia. The most common clinical features are weight gain, cold intolerance, muscle weakness, lethargy, hypoactive reflexes, pleural and pericardial effusion. In this report, we aimed to emphasize the importance of hypothyroidism for preoperative management.

A fifty-eight years old male patient was planned for surgery due to an intracranial mass. Hypothyroidism and anaemia were examined in the preoperative evaluation. The case was consulted to endocrinology for thyroid hormone therapy and then elective surgery was scheduled.

Although patients are considered as euthyroid clinic, mild and moderate hypothyroidism are a relative contraindication for surgery. Untreated severe hypothyroidism or myxoedema coma is a serious life-threatening complication. This disease should not perform as an elective surgery. If the patients planned to undergo emergency surgery, they should be treated with iv T3 hormone before anaesthesia. Hypothyroid patients are more susceptible to hypotensive effect of anaesthetic agents in respect to reduced heart rate, deactivated baroreceptor reflexes and reduced intravascular volumes. Hypothyroidism may accompany with hypoglycaemia, anaemia and hyponatremia. Bigger tongue leads to difficult intubation. As gastric drainage is delayed, we have to avoid from premedication for sedation and perform aspiration prophylaxis.

The patients have to be induced with ketamine or etomidate. The doses of muscle relaxants should be reduced and its effects should be monitored by train of four. Total intravenous anaesthesia is an ideal strategy for a rapid recovery. Close hemodynamic monitoring, intermittent electrolyte and blood sugar analysis are necessary for intraoperative management.

Mechanical ventilation support may be needed because of the respiratory depression and extended recovery time. Also multimodal analgesia has to be preferred.

Investigation of prohormone vitamin D in diabetic foot population

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Vitamin D is a steroidal prohormone produced mainly by skin the action of ultraviolet light from skin with the 7-dehydrocholesterol. The name of the form vitamin D synthesized on the skin is cholecalciferol (vitamin D3), the form taken with food is ergocalciferol (vitamin D2). Vitamin D deficiency is quite common with distal symmetric polyneuropathic in diabetic patients. There are many publications reporting the relationship between vitamin D deficiency and peripheral neuropathy. D vitamins also play an important role in the pathogenesis of vascular diseases. Endothelial cells are the target cells for vitamin D. In previous study, vitamin D has been shown to reduce peripheral neuropathy by increasing the production and repair of nociceptors.

In this study, we aimed to examine the effect of vitamin D levels in diabetic foot formation. Between March 1, 2016 and May 22, 2018, 25-hydroxy vitamin D (25-OHD) results were evaluated in patients admitted to our hyperbaric polyclinic with diabetic foot wound diagnosis. Thirteen patients were included in the study. Eight of the patients were male and five were male. The mean 25-OHD values of our patients were found to be 21.76 ± 17.58 . This mean value was assessed as vitamin D deficiency. When we evaluated the values of the patients individually, severe deficiency (<10 ng / ml) was found in 3 of 13 patients and D vitamin levels were found to be sufficient (> 25 ng / ml) in only 2 patients. Vitamin D levels are associated with glucose metabolism, vascular endothelial cells and most importantly neuropathy. We can think of this as a neurotropic effect of vitamin D.

As a result, vitamin D, known as a neuroendocrine prohormone, is responsible for the development of diabetes and its complications. Therefore, in diabetic patients, vitamin D level control is recommended at certain periods.

Major vascular pathologies in a young male patient with diabetic foot: case report

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A 53-year-old male patient was diagnosed with type 2 diabetes mellitus approximately 10 years ago. He's been on insulin therapy for the last 6 years. He was followed and treated at the external centre for diabetic foot 1 year ago but amputation of the right foot was applied. When we applied to our clinic, there was complaints of coldness, paleness and colour change from the right ankle. On physical examination, bilateral lower extremity distal pulses were detected with Doppler ++ and ankle-brachial index (ABI) 0.5 on the left and 0.3 on the right. Computed tomography angiography (BTA) revealed a 70-80% stenosis in the right iliac artery, extensive calcifications in the distal bed, and plaques that allow streaming. A 60% stenosis in the left iliac artery and a malformed vascular structure with calcification at the distal side were seen. With these findings, the patient underwent aorto-bifemoral bypass operation with dacron graft. Ischemia was resolved in the postoperative period, distal pulses with Doppler (++) and with ABI levels of 0.7. Acetylsalicylic acid 150 mg. and Cilostazol 100 mg. treatment was started and the patient was discharged. 8 months later, popliteal and distal pulses were not detected in the patient with dysplasia, paleness and colour change in the lower right extremity. CT angiography performed and the absence of blood flow from the right popliteal artery level was detected. The patient was undergone right femoral embolectomy and clinically resolved. When it reached the dischargeable stage, sudden coldness and pallor and lack of distal pulse were detected in the ankle area. Patient without popliteal pulse with Doppler were subjected to right femoro-popliteal infragenital safen vein bypass at emergency conditions. At the end of the procedure, the patient's distal pulses, whose ABI values rose again to around 0.7, could be strongly picked up by the Doppler. He discharged with cilostazol 2x100 mg, acetylsalicylic acid 150 mg, clopidogrel 75 mg doses treatment. There is no standing ischemia in the outpatient clinic for approximately 3 years, the distance of the claudication is about 300 meters and the final ABI is 0.6.

Major vascular pathology should not be overlooked, especially when blood glucose regulation and diabetic foot treatment are applied after diabetic foot diagnosis is made especially in diabetic young male patients. For this reason, even if distal pulses can be taken, we believe that the patients with normal urea and creatinine values should undergo CT angiography in order to screen for diabetic vascular pathologies. If peripheral bypass is necessary, it should not be avoided because of diabetes, and if high open rates are to be achieved, saphein vein must be preferred for peripheral bypass to artificial vascular grafts.

Challenges for haemodialysis in type I diabetic patients: case report

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A 49-year-old man has been diagnosed with type I diabetes for about 13 years and is receiving insulin treatment. 8 years ago, we present our first case to our clinic for the purpose of opening the arteria venous fistula (AVF) for haemodialysis with chronic renal failure. Blood glucose values are measured from time to time around 500-600 mg/dl and there is an uncontrolled diabetes. Patient underwent right jugular permanent haemodialysis catheter. The dialysis process was provided by this way three days a week for four hours. The patient was underwent for left radiocephalic fistula (RCF). After 1 month there was not enough blood flow in the fistula and fistula revision was applied 2 times between 3 weeks. Upon insufficient fistula flow, a proximal RCF was opened to the patient. After 2 months of follow-up, sufficient AVF flow was not available. Left brachiocephalic fistula (BCF) was opened after 1 year. The patient was able to dialyse for 2 years by this fistula. He was subjected to fistula revision for this fistula two times for two weeks. Six months later, a right jugular permanent haemodialysis catheter was applied to the patient. The patient dialysed by this way for about 3 years then opened the right RCF. The radial artery was calcific and sclerotic. Despite 2 months of follow-up, insufficient fistula flow was achieved. One more revision of the fistula was performed. After 1 year, the right proximal RCF was opened. During the follow-up period of 2 months there was no sufficient blood flow. The right BCF was opened 1 month before. Thrill can be felt on the fistula and the control blood flow is around 350 ml/min. The haemodialysis is performing to the patient by the right jugular permanent dialysis catheter now.

AVFs for haemodialysis in patients with uncontrolled diabetes mellitus are often problematic due to arterial defects. Opened AVFs are not enough for long-term dialysis. More proximal high flow AVFs are considered to be more durable in terms of usability. We believe that unnecessary waiting time should not be wasted for distal AVFs in patients with advanced vascular complications of diabetes, AVF opening in the proximal major artery as soon as possible, and continued dialysis of the patient with central jugular permanent haemodialysis catheter if appropriate.

Anaesthetic management in hypertensive neuroblastoma: A case report

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Neuroblastoma (NB) is the most common extracranial solid tumor in childhood deriving from neural crest cells. In this report, we present our experience in the anaesthetic management of a child with hypertensive neuroblastoma.

A 21 year-old, 8.5 kg, male child, ASA score III was taken into operation due to an abdominal mass and a prediagnosis of neuroblastoma and for bone marrow and lymph node biopsy. Intranasal midazolam 0.5 mg/kg was administered preoperatively. Baseline values for routine monitoring were as follows: pulse rate: 135 beats/min, non-invasive blood pressure: 140/85 mmHg, and SpO2: 94%. Anaesthesia was induced with 1 mg.kg-1 lidocaine, 2 mg.kg-1 propofol, 1 mcg.kg-1 fentanyl, and 0.6 mg.kg-1 rocuronium. Sellick's manoeuvre was administered and intubation was achieved with a cuffed endotracheal tube. Maintenance of anaesthesia was achieved with 2.5% sevoflurane in 50% O2 and 50% air and the remifentanil infusion was initiated at 1-2 mcg.kg-1.min-1. After the initiation of the surgery, the patient developed tachycardia and hypertension. Although the remifentanil dose was increased, hypertension and tachycardia persisted. After the administration of esmolol 0.5 mg/kg, nitroglycerin 0.5-10 μ g/kg/min was initiated at an infusion rate of 0.05 mg/kg/min. After controlling tachycardia and hypertension, the patient remained intubated and was transferred to the intensive care unit with continuous nitroglycerin infusion.

Hypertension and tachycardia are significant factors that complicate the anaesthetic management in cases of neuroblastoma. Preoperative control of hypertension is of prime importance for reducing perioperative morbidity and mortality. To avoid aspiration in such cases, Sellick's manoeuvre should be considered during the intubation process. Therefore, pre- and peri-operative measures should be taken to prevent these conditions.

Effects of the calcium MALIC ACID complex against hydrogen peroxide induced oxidative stress in human retinal pigment epithelium cells

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Oxidative stress plays an important role in cell damage associated with the onset and progression of many diseases. Reactive oxygen species play an important role in pathological processes such as aging, hypertension, atherosclerosis, cancer, ischemia, neurodegenerative diseases and diabetes.

This study aimed to evaluate the protective effects of calcium malic acid complex against oxidative stress induced by hydrogen peroxide (H_2O_2) in human retinal pigment epithelium.

ARPE-19 cells were pretreated with 0.00001-1000 μ M calcium malic acid complex alone for 4 h, then exposed to H₂O₂ for 16 h. Cell viability was evaluated with the 3-(4,5- dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) assay. Pretreatment of ARPE-19 cells with calcium malic acid complex reduced H₂O₂ mediated cell death. calcium malic acid complex has a protective effect on ARPE-19 cells against oxidative stress.

Incubation with 400 μ M H₂O₂ alone for 16 h decreased cell viability by 55%. When the statistical results of calcium malic acid complex were evaluated, it was found that the difference between control group and at a maximum of 10 μ M was statistically significant. In addition, the cell viability rate of 10 μ M was determined to be 98%. However, further studies are required to evaluate the effects of malic acid complex and its metabolites in animal models of age related macular degeneration.

Necrobiosis lipoidica: A case report

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Necrobiosis lipoidica (NL) is a chronic granulomatous inflammatory skin disease of unknown origin. It's associated with diabetes mellitus and glucose intolerance. 25% of the patients may have ulcerated lesions. It usually begins in the third or fourth decade of life. There are few reported paediatric cases of ulcerated necrobiosis lipoidica associated with type-1 diabetes mellitus (DM). Here in this case, an 8 years old girl who had been diagnosed with NL before she was diagnosed with diabetes mellitus has been presented.

An 8 years old girl has been consulted to our clinic due to an ulcerative lesion on her ankle for 6 months. There was a 9x9 cm sized, ulcerated and haemorrhagic-crusted plaque on an erythematous basis on her right ankle. The histopathologic assessment revealed necrobiotic collagen, mucin accumulation and histiocytic cell proliferation around. After 2 months of treatment with a cicatrisant magistral and topical tacrolimus 0.1 % twice a day, the lesion has shown regression.

There are few paediatric case reports of NL, some of these are as follows: a 16 years old girl, a 14 years old boy and a 17 years old girl who have had underlying DM, respectively for 15 years, 9 years and 2,5 years. Considering these cases, all of them have had underlying type-1 DM for years. Our case was diagnosed with NL before the diagnosis of DM and to our knowledge, she is the youngest paediatric case reported in the literature. NL is typically seen on the lower extremity as erythematous plaques and it slowly turns into yellowish atrophic plaques. Without a treatment, it may show ulceration over the time and rarely squamous cell carcinoma development may be encountered on the lesion. There are two main theories of NL etiopathogenesis including microangiopathy and immunologic vasculitis. Degeneration of collagenous tissue due to microangiopathy may lead to granulomatous reaction in the dermis. Although there are various agents for the treatment of NL, our knowledge on treatment is limited to the reported case series. Tacrolimus prevents granulomatous reaction and ulceration by inhibiting the fusion of monocytes to form multinucleated giant cells. NL mostly develops in the patients who are in their middle ages and have DM for a long time. Especially in patients who have a familial history of DM, it must be kept in mind that ulcerated NL lesions may be seen even in early childhood.

Anaesthesia management of laparoscopic pheochromocytoma excision – case report

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Pheochromocytoma is a neuroendocrine tumour of the adrenal medulla chromaffin cells. It has some variable clinical symptoms such as hypertension, headache, sweating, palpitations and anxiety. Anesthesia induction and surgical manipulations usually lead to release of catecholamines. The aim of this case report is to present the intraoperative anaesthesia management of a patient with successful resection of a pheochromocytoma.

A 42-year-old man weighing 98 kg was presented with a 3-year history of uncontrolled hypertension, headaches and palpitations. Patient was using doxazosin and carvedilol for the hypertension. Biochemical evaluation; vanillylmandelic acid: 9,65 mg/24h, nor-metanephrine: 4256 µg/24h and other tests were normal. The patient was taken to the operating room after premedication of midazolam. Standard monitoring was performed. ECG was sinus rhythm, Blood Pressure (BP): 140/84 mmHg, heart rate: 96 beats.min-1, SpO2: 97%. Following the preoxygenation, anaesthesia was induced with propofol, fentanyl and rocuronium. Anaesthesia was maintained by desflurane in oxygen air mixture. Invasive arterial cannulation was performed to monitor BP. Surgery was performed in a left lateral decubitus position. After the pneumoperitoneum, general surgeons began to dissection. Especially following manipulation of the tumour, we observed episodes of arrhythmias and hypertension. BP was 210/110 mmHg. Glyceryl trinitrate and esmolol infusions were administered but BP was still high. Then, phentolamine was intermittently applied and BP reached normal limits (125/75 mmHg). We provided the hemodynamic stabilization after the resection of tumour. Laparoscopic pheochromocytoma excision was completed in 120 minutes. Patient was extubated and transferred to the intensive care unit and recovery remained uneventful. Catecholamines can worsen the hemodynamic parameters.

This case report highlights an accurate preoperative pharmacological preparation and rapid perioperative intervention to control hemodynamic stabilization in patients with pheochromocytoma.

Investigation of cytotoxic effects of KAl(SO $_4$) $_2$.12H $_2$ O salt in HT-29 human colorectal adenocarcinoma cells

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 $KAl(SO_4)_2.12H_2O$, potassium alum is potassium double sulphate of aluminium. It has astringent, styptic and antiseptic effect. Physicians used alum in mouth washing, as a pessary for menorrhagia, as treatment for itchy scabs, gonorrhoea and purulent ophthalmia, in ancient times. Alum also induced a stronger antibody production when injected into guinea pigs than soluble toxoid alone. In this study, it was aimed to investigate the cytotoxic and oxidative effects of $KAl(SO_4)_2.12H_2O$ in HT-29 human colorectal adenocarcinoma cells.

Human colorectal cancer cells were cultured in appropriate medium and waited until 100 % confluence achieved. After that different concentrations of KAI $(SO_4)_2.12H_2O$ (final concentrations in the well to be 10⁻² to 10⁻⁹ M) were added into the medium. After 24 hours, MTT was used to observe acute toxicity, and also total antioxidant status (TAS) and total oxidant status (TOS) kits were used to evaluate reactive oxygen species generation. Obtained data were analysed statistically by using One-Way ANOVA test.

According to MTT assay, it was determined that cell viability decreased following KAl(SO₄)₂.12H₂O administration and observed that 10^{-2} to 10^{-8} M had an anti-proliferative effect on cell viability compared to control (p<0.05). The IC₅₀ of KAl (SO₄)₂.12H₂O was found as 10^{-6} M in HT-29 cells at 24th hour. TAS assay results demonstrated that 10^{-2} to 10^{-6} M of KAl (SO₄)₂.12H₂O increased the antioxidant level in cells (p<0.05). These analysis results showed a correlation with MTT results.

In this study, it was determined that $KAl(SO_4)_2.12H_2O$ has significant anti-proliferative and antioxidant effects in HT-29 cells in a dose-dependent manner. These results suggest that low-dose KAl(SO4)2.12H2O may be an effective agent in the treatment of colorectal adenocarcinoma. However, prospective studies are needed to further clarify the mechanism of action.

Management of Tuberculosis Lymphadenitis in A Poorly Controlled Diabetic Man

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Fifty-two years old man applied with right cervical pain, purulan flux and weakness over than 2 months. Poorly controlled Type 2 diabetes mellitus over five years was learned from his medical history. Only operational scare was found in his physical examination and other systemical examination finding were normal.

In the first visit, the laboratory values were normal except glucose and HgA1C. Glucose was 220 mg/dl and HgA1C was 10.7%. PPD was detected as 12 mm (no vaccine scare). Lung graphy was negative for any cavitation. The neck USG was reported as '41x19 mm, lymphadenomegaly in the right anterior cervical triangle. 'The Cervical Tomography was reported as 'LAP? With contrast and necrotic areas'.

The conglomerate lymph nodes which include chronical caseified granulomatouse inflammation were reported in the pathological examination of the excisional biopsy materials.

The results and treatment regimens (H/R/E/P [rifampicin (R) and isoniazid (H), pyrazinamide (P) and ethambutol (E)] over two months and H/R over four months) was discussed with patient. The necessary of switching his oral antidiabetic drugs (OAD)'s to insulin was mentioned to patient but, he didn't want to change his OAD's to insulin. Then Isoniaside 300 mg tb 1x1, Rifampicin 300 mg tb 1x2, Pyrazinamid 500 mg 1x3, Etambutol 500 mg tb 1x3 and pridoxin 50mg/day added to his OADs (Metformin 1000 mg tb 2x1 and Glicazide 60 mg tb 2x1).

In the first week of therapy, all of the examinations were normal. Antimicrobial treatment was continued. The patient didn't come for second week's control. But, in the day 18, he applied with compliants such as nausea, vomiting, weakness and plenty sweating. The results were observed as following; AST:123 U/L, ALT:141U/L, ALP: 92U/L, GGT: 134 U/L, LDH 247U/L, Glucose: 288 mg/dl HgA1C%: 10.7 CRP: 16.8 mg/dl,

The patient was accepted drug induced hepatotoxicity and hospitalized. All drugs were stopped. The infusion solutions were started. The blood glucose regulation was provided with 3x12 unit of crystalized insulin and 1x14 unit of NPH insulin. After two weeks of treatment break, the liver tests came back to normal and drugs started all together again. The follow up and treatment are still continuing.

Insulin therapy is recommended and it should be initiated at the onset of the antituberculouse therapy. Minor drug interaction among R-H and metformin-glicaside has been reported previously. More intense monitoring of liver and kidney functions was recommended. In the case of both tuberculose and diabetes, it is necessary to switch OADs to insulin both to achieve glucose regulation and to decrease the drug burden and hepatotoxicity risk.

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Poster communications

PC-001

The effect of vitamin D3 on thioacetamide-induced acute liver injury and encephalopathy in rats

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Thioacetamide (TAA) undergoes metabolism to reactive metabolites resulting in hepatic necrosis, hyperammonemia and oxidative stress. Vitamin D3 (vitD3) regulates calcium homeostasis by influencing bone turnover and has extraosseous effects (e.g. regulatory effects on cells of the adaptive and innate immune system). This study investigates the putative protective effect of vitD3 on TAA-induced hepatic injury and encephalopathy in rats.

Female Sprague-Dawley rats (250-300 g) were allocated into control, TAA, TAA+vitD3, and VitD3 groups (n=8/group). VitD3 (0.3 ug/kg) or olive oil (1 ml) was given orogastrically for 15 days prior to intraperitoneal TAA (200 mg/kg) or saline (0.2 ml/100 g) injections for the last 3 days. Open field and new object recognition tests were performed on day-15. After decapitation, blood was collected for ALT, AST and calcium assays. Liver and brain (hippocampus and prefrontal cortex) were excised, weighed and stored for malondialdehyde (MDA), glutathione, myeloperoxidase (MPO) and chemiluminescence (CL) assays. Tissues were also scored microscopically. Data were compared using Mann-Whitney U or ANOVA test followed by Tukey-Kramer. Statistical significance level was p<0.05.

ALT (p<0.05), AST (p<0.001) in serum, weight (p<0.001), microscopic score (p<0.001), MPO (p<0.001), CL (p<0.001) in liver, and microscopic score in both liver and brain (p<0.001) increased in TAA group compared to control. TAA group had lower locomotor activity compared to control. VitD3 attenuated microscopic score of liver (p<0.001), brain (p<0.01), and also MPO (p<0.05) and CL (p<0.001) in liver. Restoration of the locomotor activity by vitD3 was not significant. VitD3 pre-treatment decreased the extent of liver and brain injury and showed protection via suppressing neutrophil infiltration, and oxidant production.

Our data may suggest additional value of using vitD3 as a therapy in patients with hepatic failure in clinical settings.

Effects of bee bread on apoptosis in hypothalamus in obese rats

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Obesity, which is defined as the "New World Syndrome", is one of the most important problems of the modern age. The treatment options, which are developed to cope with this disease that threatens the entire world including our country, substantially relate to dietary supplements. During this project, we examined the usability of bee bread, which is gaining importance each day with its rich nutrient content, as a dietary supplement.

The aim of this study was the determination of the effect of bee bread supplement in diets on apoptosis in obese rats.

In this study, 40 Sprague Dawley adult female rats, weighing 200-250 g was used. Rats were randomly divided into 5 separate groups (n= 8 for each group). For this study, the first step was to separate rats as the control group (n= 8) and the obesity group (n= 32). The rats, on which obesity formed, (n= 32) was fed with high fat content diet. The rats, on which obesity formed, was fed with this supplement for 4 weeks. Rats in the control group was fed with standard rat supplement during this period (n= 8). The rats, on which obesity formed, were separated into experiment groups with 8 members in each group (group 2, 3, 4, 5).

1st Group: Control: Group fed with standard rat supplement (n=8)

2nd Group: Group fed with high fat diet (n=8)

3nd Group: Group fed with 100 mg/kg/day bee bread (n=8)

4rd Group: Group fed with 200 mg/kg/day bee bread (n=8)

5th Group: Group administered with Metformin 300 mg/kg/day as positive control (n=8).

When the experiment protocol is complete at the end of the four week feeding period, the rats were decapitated under ketamine+xylazine anaesthesia following collection hypothalamus tissues. Hypothalamus were fixed in formaldehyde and buried into paraffin blocks with the application of routine histologic tissue tracking methods. Apoptotic cell death with TUNEL is evaluated.

TUNEL assays showed that the increase in the apoptotic cell number was statistically significant in fed with high fat diet group compared to control group (p<0.05). The decrease in the apoptotic cell number was statistically significant in group 3,4 and 5 compared to high fat diet group (p<0.05). Group 3, 4 and 5 showed close results when compared with the control group.

Our results have been shown that bee bread against obesity with a high-fat diet reduces and prevents apoptosis in the hypothalamus.

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Effects of melatonin and metabolites on hydrogen peroxide damage on retinal pigment epithelium (arpe-19)

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Melatonin, an endogenous neurohormone produced by the pineal gland and retina, is known to be a powerful antioxidant and free radical scavenger. Recently, circulating melatonin levels were significantly lower in Age-related macular degeneration (AMD) patients than age-matched controls. It is not known whether reduced melatonin levels play a role in the development of the disease in AMD patients. To determine the relationship between melatonin deficiency and RPE cell damage, it is important to investigate the protective effects of melatonin and its metabolites (N-acetyl serotonin and 6-Hydroxy melatonin) on RPE cells against oxidative stress.

This study aimed to evaluate the effects of melatonin and its metabolites in human retinal pigment epithelium cell (ARPE-19) culture model of oxidative stress. Control cells were cultured in the hydrogen peroxide (H2O2)-free medium. In H2O2 group ARPE-19 cells were exposed to 500 μ M H2O2 alone for 16 h. In study groups, cells were preincubated with melatonin and its metabolites (0.000001-100 μ M) for 4 h before H2O2 exposure. Cell viability was evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide).

Incubation with 500 μ M H2O2 alone for 16 h decreased cell viability by 33%. When the statistical results of melatonin were evaluated, it was found that the difference between control group and low concentration 0.000001 μ M was statistically significant. In addition, the cell viability rate of 0.000001 μ M was determined to be 47% (33% to 47%). However, further studies are required to evaluate the effects of melatonin and its metabolites in animal models of AMD

Investigation of adropin levels in experimental myoglobinuric acute kidney injury

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Myoglobinuric acute kidney injury (MAKI) is a uremic syndrome caused by intracellular elements getting into the circulation (rhabdomyolysis) due to traumatic or non-traumatic injury to striated muscle cells. It is reported that adropin expressed in brain, liver and kidney tissues is the regulator of energy homeostasis and metabolism in humans. However, the role of adropin in MAKI is still uncertain. The aim of this study is to evaluate serum and urine adropin levels, their relationship with urine microalbumin levels and their usefulness as biomarkers.

In our study, male Sprague-Dawley rats weighing 180-200 grams were divided into 2 groups (n = 8) as Control and MAKI. Both groups of rats which are anhydrous 24 hours before the procedure were injected in hind limb muscles. The rats in the control group were injected with saline whereas the rats in the MAKI group were injected with 50% glycerol solution at a dose of 8 ml/kg to induce MAKI. Rats were taken in metabolic cages 24 hours after the injections. After collecting the 24-hour urine, blood was taken under anaesthesia at 48 hours and the rats were euthanized.

Urine microalbuminuria and adropin levels were significantly higher in the MAKI group compared to the control group (p<0.01). However, there is no significant difference in serum adropin levels between the groups. Urine adropin levels and microalbumin levels were positively correlated with a high correlation coefficient (r=0.747, p=0.001).

Adropin may potentially have a variety of metabolic effects in the pathophysiology of kidney injury. It can be considered as a new biomarker for kidney injury. Adropin should be investigated as a possible marker in assessing the time-dependent change in kidney injury.

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The effect of ghrelin receptor on morphine analgesia and tolerance in rats

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The tolerance mechanism against morphine analgesia has not yet been elucidated. The aim of this study was to investigate effects of ghrelin receptor on morphine analgesia and tolerance in rats. In our study, 54 Wistar Albino 230-250 g male rats were used.

The animals were divided into nine groups as saline (serum physiologic 1 ml/kg; n=6), hexarelin (ghrelin receptor agonist 200 μ g/kg; n=6), GHRP-6 (ghrelin receptor antagonist 0,2 mg/kg; n=6), morphine (5mg/kg; n=6), hexarelin+morphine (n=6), GHRP-6+morphine (n=6), morphine tolerance (n=6), morphine tolerance+hexarelin (n=6) and morphine tolerance+GHRP-6 (n=6). Serum physiologic and GHRP-6 were administered intraperitoneally while hexarelin and morphine were administered subcutaneously at the indicated doses. In order to develop morphine tolerance, 10mg/kg morphine was injected daily in the morning and evening for five days and tolerance was evaluated on sixth days single dose of morphine. Analgesic effects were assessed by hot plate and tail flick analgesia tests. The resulting analgesic effect was measured and recorded at 0th, 30th, 60th, 90th and 120th minutes. Assessment of analgesic effect was formulated as % analgesia (MPE) (% analgesia=100 x [postdrug latancy-basal latancy]/[cut off time-basal latancy]). Statistical evaluation of the data was performed by two-way ANOVA and multiple comparisons were determined by the Tukey test. Statistical significance was defined at p<0.05 level.

Obtained data suggest that hexarelin increased morphine analgesic effect (p<0,05) but GHRP-6 did not change morphine analgesic effect (p>0,05) in analgesia tests. On the other hand, hexarelin decreased tolerance development to morphine (p<0,05) but GHRP-6 did not change tolerance development to morphine (p>0,05) but GHRP-6 did not change tolerance development to morphine (p>0,05) in analgesia tests.

In conclusion, we suggest that ghrelin receptor may have important roles on morphine analgesia and tolerance.

Investigation of the relation of nesfatin-1 and adropin with blood pressure in experimental hypertension model

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Hypertension is the most common cardiovascular disease in terms of mortality, which increases the risk of developing myocardial infarction, stroke, heart failure and renal failure. Adropin and nesfatin-1 are peptides associated with energy homeostasis and metabolism. It is reported that the decrease in plasma adropin level may be associated with high blood pressure and brain nesfatin-1 signal plays a role in the regulation of cardiovascular response under stress. In our study, we aimed to investigate the relationship of nesfatin-1 and adropin with blood pressure levels in an experimental hypertension model induced by angiotensin II.

In our study, Sprague-Dawley rats weighing 240-260 grams were divided into control and hypertension groups (n=8). With the osmotic mini-pump, angiotensin II solvent (0.01N acetic acid in saline) was administered to the control group and angiotensin II was given to the hypertension group for 7 days at a dose of 0.7 mg/kg/day. For both groups, blood pressures were measured by tail cuff plethysmography on days 1, 3, 5 and 7. After 24-hour urine collection, blood and tissue samples were taken under anaesthesia and the rats were euthanized.

There was no significant difference between renal tissue, serum and urine nesfatin-1 and adropin levels in control and hypertension groups. In the hypertension group; systolic, diastolic and mean blood pressure increased from the 1st day of the experiment, compared to the control group (p<0.05).

We suggest that experimental hypertension models have a potential to investigate the relationship of nesfatin-1 and adropin levels with hypertension in molecular level at different time intervals and new studies are needed.

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Effects of maternal tobacco smoke or alpha lipoic acid on puberty onset, estrous cycle and gonadotropin levels in female rats

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Various environmental factors are known to affect puberty onset. However, there are few studies in literature about how maternal tobacco smoke (ts) or alpha lipoic acid (ala) affect the hypothalamuspituitary-gonadal axis at peripheral or central levels in rats. This study aimed to investigate effects of maternal tobacco smoke or alpha lipoic acid on puberty onset, estrous cycle and serum gonadotropin levels in female rats.

Adult female spraque-dawley rats were used. All animals were randomly divided into 4 groups (control, ts, ts+ala and ala) and each group consisted of 7 rats. All ts rats were exposed to ts (20 gram\day, for one hour twice a day) and all ala rats received daily oral ala (20 mg/kg) during 8 week. Afterwards all rats were impregnated, ts or ala treatments continued during pregnancy. All treatments ended with birth and later newborn female rats were selected for each group (n=7). Puberty onset was monitored by examination of vaginal opening in female rat pups. Subsequently, estrous cycle was conducted daily for 15 days and determined by examination of the vaginal smear cytology. Also, serum fsh and lh levels were measured using elisa method at the end of the experiment.

There was significantly advanced on puberty onset day for ts group (p<0.05). There was a significantly increase in pubertal weight in ala group compared to control group (p<0.001). The mean total number of estrous cycles and average duration of metestrus, diestrus, proestrus or estrus phases were not significantly different in all treatments groups compared to control group. There was no any significant change in serum fsh levels, but serum Ih levels were significantly increased in all treatment groups compared to control group (p<0.05).

Present study showed that maternal tobacco smoke or alpha lipoic acid may affect hypothalamuspituitary-gonadal axis differently in rats.

Changes in UCP2 and microRNA-139 Levels due to myocardial ischemic postconditioning and melatonin administration

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Ischemic postconditioning (PostC) is a strong endogenous cardioprotective phenomenon, which targets the increased tolerance of the myocardium against ischemia-reperfusion (I/R). It has been reported that protective effects of PostC decrease/disappear with age and chronic heart disease. Similarly, low serum melatonin levels have been reported in the same risk groups. UCP2 is a mitochondrial inner membrane protein which reduces mitochondrial reactive oxygen species formation. MicroRNAs have emerged as a group of important regulators via degradation or translational inhibition of their target mRNAs. Increasing evidences indicate that microRNAs are involved in the regulation of I/R injury. The aim of this study was to investigate the effects of PostC and physiological and pharmacological concentration of melatonin on I/R induced change of UCP2 and microRNA-139 levels using an *in vivo* model of myocardial I/R injury.

Rats were pinealectomized (Px) or sham-operated (non-Px) (control) 2 months before the I/R studies. 30 minutes of ischemia and 120 minutes of reperfusion were produced. PostC was induced by 3 cycles of R/I (10 s each) after the ischemia. Melatonin was administrated by ip injection last 10 days (10 mg/kg). UCP2 and microRNA-139 levels were analysed by using both qRT-PCR.

UCP2 decreased with I/R and Px, increased by PostC and melatonin. PostC does not create significant effect in Px but protection was provided with melatonin. microRNA-139 decreased with Px and I/R, these changes have prevented with the treatment

These results suggest that physiologic and pharmacological melatonin may be important in the protective effects of PostC. The protective effect of PostC disappeared when physiological melatonin decreased and this effect was seen to reverse with melatonin replacement. UCP2 and microRNA-139 may play an important role in cardioprotective mechanism of melatonin and PostC.

Functional evaluation of oxytocin neuron circuits in Magel2 deficient mice

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Prader-Willi syndrome (PWS) is a genetic disorder caused by disruption of a well-defined region on chromosome 15, which contains several paternally active genes including Magel2. PWS is associated with several physiological and behavioural problems including hyperphagia and social deficits. The chromosomal abnormalities that underlie PWS leads to inactivation of several genes, that is thought to cause hypothalamic dysfunction. Oxytocin is an important hypothalamic neuropeptide that has been implicated in both social and feeding behaviours. Since Magel2 is highly expressed in hypothalamus, we hypothesized that its deletion may cause oxytocinergic circuit defects that may contribute to PWS phenotype.

To understand full scope of oxytocinergic circuitry defects, we examined circuit properties of oxytocin neurons in normal and Magel2-deficient PWS mouse model. For this, we used patch-clamp electrophysiology technique to identify physiological properties of oxytocinergic information processing.

Electrophysiology results show that synaptic inputs to oxytocin neurons are dramatically altered, driving reduced activity in Magel2-deficient oxytocin neurons. Loss of Magel2 changes physiological properties of these neurons including the spontaneous activity, cell autonomous mechanism and synaptic input properties.

Our results suggest that Magel2 deletion leads to the disruption of oxytocin neurons circuits. Defects in satiety-circuits defined by oxytocin neurons may underlie the veracious appetite seen in PWS patients.

The effect of melatonin on depressive like behaviour, age and s100b levels in diabetic rats

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In both human and animal models, diabetes is associated with pathological changes in the brain that lead to cognitive and affective deficits, and to an increased risk of depression and anxiety. Hyperglycaemia accompanied by an accelerated rate of advanced glycation end product (AGE) formation and accumulation. AGEs play a role in diabetes-related depression and cognitive decline. The aim of the present study is to investigate the effects of melatonin on anxiety and depression-like behaviour and AGE and S100B, a calcium-binding protein secreted by astrocytes, levels in hippocampus and prefrontal cortex (PFC) in diabetic rats.

40 Wistar albino rats (6 months old) were divided in four experimental groups of 10 rats each: Normoglycemic control, Normoglycemic+melatonin treated group, diabetic control and Diabetic+melatonin treated group. Experimental diabetes was induced by a single intraperitoneal injection of streptozotocin(STZ) at the dose of 60 mg/kg. Melatonin (10 mg/kg, i.p) was administered once a day for 28 days. Anxiety and depression like behaviour was evaluated by Elevated plus maze (EPM) and Forced swimming test (FST), respectively. The concentrations of AGE and S100 B in hippocampus and PFC were measured by ELISA. Differences between groups were evaluated with Kruskal-Wallis followed by a post-hoc Bonferroni test to evaluate the differences with in the groups.

The results showed that diabetic rats exhibited a significant behavioural deficit, including depressionlike behaviour in FST and anxiety-like behaviour in EPM, along with a significant increase in AGE levels and decreased in S100B levels in hippocampus and PFC. Melatonin treatment prevented these behavioural abnormalities, decreased AGE levels and normalized S100B levels in these brain areas.

In conclusion, the present study revealed that melatonin exerts antidepressant like and anxiolytic like effects in STZ induced diabetic rats, at least in part, through reducing AGE levels and preserving S100B levels in the hippocampus and PFC.

The interaction of SIRT1, TLR4 and IL7 in human dementia

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The growing association between neurodegeneration and inflammation has led researchers to investigate interaction of sirtuins with inflammation markers in neurodegenerative diseases. Herein, we analysed the contribution of SIRT1 to chronic inflammation associated with dementia through Tolllike receptor 4 (TLR4) and Interleukin-7 (IL7), for the first time. Furthermore, we investigated the association of three single nucleotide polymorphisms of SIRT1 gene including (rs7895833, rs7069102, rs2273773) with levels of SIRT1, TLR4 and IL7 expressions, as well as total antioxidant status (TAS), total oxidant status (TOS) with dementia in Turkish population.

We observed a significant increase in the SIRT1 level in dementia including Alzheimer's Disease (AD). Interestingly, the level of TLR4 protein was significantly lower only in AD patients. There was a decrease in the level of IL7 between diseased- and healthy elderly subjects, however, it did not reach the accepted significance level. In the Pearson's correlation test, we found a significant positive correlation between SIRT1 level and age in healthy elderly subjects whereas this correlation was disappeared in dementia patients. Also the positive correlation between IL7 and TLR4 in healthy elderly subjects was absent in dementia patients. However, there was no direct association between studied SNPs and dementia. According to logistic regression analysis, the superiority of AD risk 1.16 times increases due to an increase in the SIRT1 level and 24.23 times increases due to a decrease in the TLR4 level. Interestingly, a high level in the TAS increases the risk of AD approximately 33.32 times.

Taken together, the current study being the first for a much better molecular understanding of the interaction of the decreasing TLR4 levels and increasing SIRT1 levels in dementia and AD points the importance of epigenetics in several age-related diseases to provide a healthy aging by developing novel therapies to prevent or slow down the progression of AD.

The effects of thymoquinone against cisplatin-induced neurotoxic rat model

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Cisplatin (CIS) is an effective broad-spectrum chemotherapeutic agent that is often associated with side effects such as neurotoxicity. Thymoquinone (TQ), one of the main components of *Nigella sativa*, exhibits various bioactive properties such as anti-inflammatory and antioxidant. We evaluated the neuroprotective effects of TQ in CIS-induced neurotoxicity by using biochemical and histopathological methods.

Rats were randomly assigned into four groups (n=8). Control group; only solvent intraperitoneally. TQ group; 5 mg/kg on three consecutive days. CIS group; 7 mg/kg single dose of CIS. CIS+TQ group; 5 mg/kg TQ on three consecutive days after 7 mg/kg single dose of CIS. On day 4 of the study, the rats under anaesthesia were sacrificed. Brain tissue was assessed in all groups by histological, immunohistochemical (Image j) and biochemical means.

In the histological and immunohistochemical evaluations; the cerebral cortex was normal appereance in the control and TQ groups. In these groups, caspase-3 immunoreactivity was observed slightly. The CIS group exhibited histological changes such as congestion and neurondegeneration. It was found that the caspase-3 immunoreactivity significantly increased in the CIS group when compared with control group (p=0.002). There was a marked attenuation in histological changes in the CIS+TQ group according to the CIS group. Additionally, caspase-3 immunoreactivity was detected to be milder in the CIS+TQ group compared with CIS group (p=0.041). On the other hand, tau and neurofilament immunoreactivity were similar in all groups (p>0.05).

In the biochemical evaluations; malondialdehyde (MDA) level of CIS group was significantly higher than that of the control group (p=0.017). But, MDA level of CIS+TQ group was similar to CIS group (p>0.05). Glutathione (GSH) level and Superoxide dismutase (SOD) activity were similar in all groups (p>0.05). All groups were similar in terms of SOD activity and MDA level (p>0.05).

Consequently, it is our thought that ISO has a therapeutic role against CIS-induced neurotoxicity.

Weight gain and metabolic changes due to olanzapine treatment in psychotic patients

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It is known that olanzapine, an atypical antipsychotic, causes higher weight gain, blood glucose, lipid profile and adverse effects on liver enzymes. In this study, we aimed to determine the effect of olanzapine on body weight, serum lipid profile and liver enzymes in in psychotic patients.

30 patients, male or female, between the ages of 18-65 who the onset of olanzapine treatment with the cause of psychotic symptoms in psychiatric clinic. At the beginning of the study (baseline), 2nd week (treatment day 15) and 8th week (treatment day 60) were measured AST, ALT, LDL, HDL, TG, Total Cholesterol values from the height, weight and waist circumference.

It was determined that values of the weight and waist circumference of patients sustained increased. While waist circumference increase was statistically significant (p<0.01) between baseline and day 15 of treatment values, but there was a decrease in the increase ratio afterwards, besides the increase in the value of every three weight was statistically significant (p<0.01). SGOT and SGPT as liver enzymes were elevated at a statistically significant (p<0.01) level between baseline and day 15 of treatment, but they reduced between day 15 of treatment and day 60 of treatment. There was a significant increase in the lipid profile, LDL, triglyceride, total cholesterol values in both treatment groups compared to baseline (p<0.01).

Olanzapine-induced liver enzyme elevation was evident in the early stages of treatment, but tended to decline as it progressed. This situation can be interpreted as the treatment should not be interrupted, even if the liver enzyme is elevated in the early period of treatment. Because elevation of olanzapine-induced blood lipid levels may cause in long-term serious consequences, it is important to take the necessary precautions in this regard and to regulate the treatment.

Central salusin- β infusion increase serum testosterone levels in male rats

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Salusin- β , which is derived from preprosalusin, is a multifunctional bioactive peptide-based hormone. Salusin- β is predominantly localized to the hypothalamus. Hypothalamus is controlling of reproduction and drinking behaviour. The effects of this peptide on the reproductive system are not known. This study was undertaken to determine whether there is a relationship between salusin- β and serum testosterone level.

In this study, adult 40 male adult Wistar-Albino rats were used. The rats were separated into 4 groups as the control, sham, 2 nmol Salusin- β and 20 nmol Salusin- β (n=10). All rats were anesthetized (except for the control group), and osmotic mini pumps (Alzet 2ML1) were placed in the right lateral ventricle. With the help of the osmotic mini pumps, infusion of artificial cerebrospinal fluid (solvent) was performed to the sham group at a 240 µl volume (10 µl/hour) daily; and the infusion of 20 and 20 nmol Salusin- β were performed to the study groups. After infusion period (7 day), the rats were decapitated, and the blood tissue samples were collected. Serum testosterone levels were measured by ELISA method in blood tissue.

Chronic intracerebroventricular infusion of the Salusin- β resulted in significant increases serum testosterone levels (p<0.05). Our results have shown that Salusin- β can play an active role in regulating reproductive behaviour in a peripheral manner by increasing testosterone release.

These results show that the Salusin- β may be beneficial in the treatment of infertility.

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Neuroprotective effects of leucomicine sesquiterpene on differentiated SH-SY5Y neuroblastoma cell line

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Alzheimer's disease (AD) generally covers 60% of mental disorders and is one of the most important neurodegenerative diseases. In our study, the human neuroblastoma cell line (SH-SY5Y) was transformed into neuron-like cells via introducing retinoic acid.

In the transformed cells, β -amyloid protein (200-0 μ M) was applied for 24/48 hours at wide dose intervals to establish the Alzheimer's environment and IC50 values were determined. Next, neuroprotective effect against toxicity generated by administration of leucomicine sesquiterpene in a wide spectrum doses (100-0 μ g/ml) to β -amyloid administered cell culture was examined for 24 and 48 hours. 3-(4,5-dimethyl-thiazol-2-yl) 2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) release tests were performed to determine cell viability rates in the in vitro Alzheimer model. Subsequently, the Annexin-V/PI study flow cytometry method was used to determine the type of death caused by toxicity in the cells. Apoptosis and nucleus integrities of the cells were examined under the microscope using the Hoechst 33258 fluorescence staining method. Furthermore, leucomicine effects on acetylcholinesterase (AChE) activity, total antioxidant capacity (TAC) and total oxidative status (TOS) levels were determined.

According to the results, the protective effect of leucomicine concentrations against β -amyloid for 24 hours and 48 hours was determined by cell viability tests. Flow-cytometry findings revealed that leucomicine caused significant decrease in necrosis deaths in cells. It was further analyzed that the AchE activity, the TOS level and the TAC level decreased after leucomicine application.

Investigation the effectiveness of chronic agomelatine on foetal number in before and different periods of pregnancy in rats

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Agomelatine, an analogue of melatonin, is a new antidepressant approved by the European Union Pharmaceutical Agency in 2009 under the trade name valdoxan. Agomelatine has with high affinity melatonergic (MT1 and MT2) receptor agonist and serotoninergic 5-HT2C receptor antagonist property at low sensitivity. Melatonin is an important molecule that regulates female reproductive cycle and has been detected at high concentration in preovulatory follicular fluid. Agomelatine is a derivative drug of melatonin and included in B category for use during pregnancy. For these reasons in our study we aimed to investigate the change of foetal number in rats using agomelatine at different periods of gestation.

In the study, 42 female Wistar-Albino rats were divided into 6 groups with 7 animals in each group: Group 1: Pregnant.

Group 2: Pregnant group in which chronic agomelatine was used before pregnancy.

Group 3: Pregnant group in which chronic agomelatine was used before and during the first 2 trimester of pregnancy.

Group 4: Pregnant group in which agomelatine was used during the first two trimester of pregnancy. Group 5: Pregnant group in which agomelatine was used during all pregnancy stages.

Group 6: Pregnant group in which chronic agomelatine was used before and during all pregnancy stages.

One-way analysis of variance (ANOVA) test were used to assess the data and differences between groups.

As a result, mean foetal number values of the groups were calculated as 9.1, 10.7, 12, 11.7, 11.4 and 12.8 respectively. There was statistically significant difference between control and group 3 (p=0.001), group 4 (p=0.002), group 5 (p=0.01), group 6 (p<0.001), except group 2.

According to the information obtained as a result of the other researches carried out, it is noticed that there is not enough study on this topic. In this study showed that agomelatine has foetal count enhancing activity in rats.

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Bipolar affective disorders related to vitamin B12 and folic acid levels

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Vitamin B12 and folic acid are vitamins that are necessary for the central nervous system function. Deficiency of these vitamins contributes to pathogenesis of several neuropsychiatric disorders such as mood disorders, cognitive changes and paranoid disorders. In this study, we investigated the levels of vitamin B12 and folic acid in patients with bipolar affective disorder who applied to our clinic.

We collected laboratory data from the clinical chemistry department of the Turgut Özal Medical Center incorporating Malatya. Our study population included all patients who had at least one serum lithium measurement from November 1st 2000 to April 30th 2014 inclusive. When files were scanned, sociodemographic data including the patient's identity and the results of B12 and folic acid tests were recorded.

In this study, a total of 222 patients were retrospectively screened. Although vitamin b12 levels results of all the patients could be reached, folic acid levels result of only 210 patients could be reached. Vitamin B12 levels of the % 72.5 (n=161) patients were between the reference range, % 0.5 (n=58) of patients were below the reference range, % 1.4 (n=3) of patients were on the reference range. Folic acid levels of the % 96.2 (n=202) of patient were between the reference range, % 0.5 (n=1) of patient were below the reference range, % 3.3 (n=7) of patient were on the reference range.

In our study, most of the patients' vitamin B12 and folic acid levels were evaluated as normal. This retrospective study had significant limitations. First, this study was a retrospective patient file screening study. The second was drug use, frequency of exacerbations, and treatment response rates of patients with low levels of vitamin B12 and folic acid could not be evaluated. There is a need for more extensive work to address these limitations.

Protective effect of Fe_3O_4 -Sio₂-NH₂ nanocomposite functionalized with boronophenylalanine on glutamate excitotoxicity in primary cortical neuron cell culture

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Boron, an essential element, is involved in metabolic events such as cell membrane function, central nervous system function, hormonal metabolism and enzyme reactions. Boronophenylalanine (BPA) as boron compounds is preferred in the clinical treatment. Glutamate, the major stimulant neurotransmitter in the central nervous system, has functions in physiological events such as learning and perception. The aim of study was to investigate the neuroprotective effect of magnetic Fe_3O_4 -SiO₂-NH₂ -BPA nanocomposite on glutamate toxicity in primer cortical neuron cultures.

In accordance with this purpose, firstly, the magnetic Fe_3O_4 -SiO₂-NH₂ nanocomposite functionalized with BPA have been synthesized. While, the structure of the nanocomposite and chemical composition have been confirmed by TEM and FTIR methods, the boron content of Fe_3O_4 -SiO₂-NH₂-BPA was determined as 1.47 % by ICP/MS method. Afterwards, primary cortical neuron culture was prepared using new born Sprague-Dawley rats and glutamate excitotoxicity was induced by exposure to $6x10^{-5}$ M glutamate. The cells were incubated for 24 hours using different concentrations of BPA, Fe_3O_4 -SiO₂-NH₂-BPA (final concentrations in the well to be 10-250 μ M). The proliferation-inducing effect on cell viability was determined by using MTT assay.

According to MTT assay, it was determined that cell viability was increased following BPA administration and observed that at 10-100 μ M concentration of BPA, Fe₃O₄-SiO₂-NH₂ and Fe₃O₄-SiO₂-NH₂ and Fe₃O₄-SiO₂-NH₂-BPA had a statistically significant protective effect on cell viability compared to glutamate control (p<0.01). The most significant increase was observed following 10 μ M BPA and Fe₃O₄-SiO₂-NH₂-BPA (equivalent to 10 μ M BPA) administration (p<0.001).

In this study, BPA and Fe_3O_4 -SiO₂-NH₂–BPA at the low doses showed high neuroprotective effects in primary rat cortical neurons cultures against glutamate excitotoxicity. These results suggest that BPA and Fe_3O_4 -SiO₂-NH₂–BPA can be used as a therapeutic agent against glutamate excitotoxicity, however, further studies are need clarify the mechanism of action of BPA.

The role of cholinergic neurons in arcuate nucleus on anxiety behaviour

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Acetylcholine (Ach), which is known as a modulator in the central nervous system by affecting the presynaptic release of neurotransmitters has a relationship with anxiety and depression through basolateral amygdala and dorsal hippocampus. Arcuate nucleus (ARC) is the centre of appetite and regulates energy metabolism through its postsynaptic targets. The physiologic roles of newfound cholinergic (ChAT) population in the ARC are unknown. This new population has a possible relation between anxiety and eating habits. Here we intend that the ChAT in ARC have an anxiolytic effect on anxiety. This study aimed to reveal the anxiety relation of ARC^{ChAT} neurons.

To determine whether cholinergic signalling through the arcuate nucleus of the hypothalamus is associated with anxiety behaviour, we used ChAT-Cre transgenic mice expressing the Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) which are G-coupled channels to selectively stimulate ChAT neurons. Behavioural tests include elevated plus maze (EPM), open field (OF) and light-dark box tests.

Pharmacogenetic activation group has a significant increase (independent Student T-test, p<0,05) of the open arm duration in EPM compared to the control group. In contrast, results of OF and light dark box tests have no significance.

We have shown that the cholinergic neurons in ARC have an anxiolytic effect on anxiety in elevated plus maze.

Investigation of the effects of isorhamnetin on motor function, sedation and analgesia in the diabetic rats with streptozotocin

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Flavonoids are phenolic compounds used in traditional Chinese medicine due to their high content of nutrients and their therapeutic effects. We aimed to investigate the effects of isorhamnetin (ISO), a compound in the flavonoid structure, on motor function, sedation, and analgesia in diabetic rats.

For this aim, 32 Wistar albino rats were divided into 4 groups (n=8 in each group); Control group: We administered only 0.5 ml saline (SF) intraperitoneally (i.p.). STZ Group: 50 mg/kg streptozotocin (STZ) was dissolved in citrate buffer solution (pH: 4.5) to give single dose i.p. STZ + ISO Group: 50 mg / kg STZ i.p. 3 days after administration, 5 mg / kg ISO for 7 days single dose daily i.p. ISO + STZ Group: 5 mg / kg ISO for 7 days single dose 50 mg / kg STZ i.p.

The rats with a blood glucose level above 200 mg/dL at baseline 72 h after administrating a single dose of 50 mg/kg STZ were diabetic. All the rats were tested for rotarod and accelerod balance-to-motor coordination performance measurements, hot plate and tail-flick analgesimetry tests, and the effects of ISO on the nervous system and functions.

There were no significant results between the groups in the accelerod and tail flick tests. Nevertheless; In the rotarod test, it was tested that the starting time of 20 rpm was significantly lower in the control group than in the other groups. In the hot plate test, the end-of-test period of the STZ + ISO group was measured to be significantly reduced compared to the STZ and ISO + STZ groups.

In conclusion, the results of the present study demonstrated that ISO application after STZ injection lowered the pain threshold in the rats and also ISO application had a positive effect on motor functions.

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Investigation of the effects of thalidomide against global cerebral ischemia-reperfusion injury in rats

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Stroke is the second most common cause of death worldwide and a common cause of morbidity in developing countries. Ischemia and subsequent reperfusion (I/R) causes severe damage to tissues and organs. Thalidomide (Th) reduces the destruction of inflammatory cascades on tissue cells by suppressing the production of Tumour Necrosis Factor- α , interleukins (IL-6, IL-10 and IL-12) and cytokines. Th has shown protective effects in different models of I/R damage. We aimed to investigate the effects of Th in global cerebral I/R injury in rats.

Rats were divided into 4 groups (n=8). 1) Sham group: Only midline incision was performed. 2) I/R group: Twenty-four hours of reperfusion after 15 minutes cerebral ischemia after bilateral carotid artery occlusion. 3) Th+I/R group: 20 mg/kg Th was given 1 hour before the 15 minutes of ischemia then 24 hours of reperfusion 4) I/R+Th group: 20 mg/kg Th was given 1 hour after the 15 minutes of ischemia then 24 hours of reperfusion. At the end of the experimental procedure all rats were sacrificed and histological and biochemical analyses were run in the cerebral and cerebellar tissues.

Th also lowered the caspase-3 immunoreactivity in Th+I/R and I/R+Th groups by comparison to I/R group in the cerebrum. In the I/R+Th group, there was a significant decrease in the intensity of immunoreactivity compared to the I/R group (p = 0.008). Also, cerebellar cortex of I/R+Th group was observed in normal appearance. Superoxide dismutase and total glutathione levels in the cerebrum and cerebellum were found as increased whereas malondialdehyde production was found as decreased due to Th treatment when compared to the I/R group.

These findings have showed us Th has anti-apoptotic, anti-oxidant, and anti-inflammatory effects on neural tissues.

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Comparison of expression levels of MiRNAs between serum and tumour tissues of colorectal cancer patients

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MiRNAs are known to take part in important cellular events, such as cell proliferation, apoptosis and cancer development. It is known that a large number of miRNAs play a role in the pathogenesis of colorectal cancer and studies are conducted to clarify the role of new miRNAs in this disease. The aim of this study was to examine the expression levels of miRNAs known to be associated with the regulation of the expression levels of the APC and K-Ras, which are important in the development of CRC.

Forty-seven colorectal cancer patients were included in this study and the tumour tissue and adjacent normal tissue were collected from these patients during the surgical operation. MiR-27, miR-663, miR-217, miR-181d expression levels were detected by qRT-PCR in the tumour and adjacent normal tissues of colorectal cancer patients.

Expression levels of miR-217, mR-181d, miR-663, miR-27 and K-Ras were found higher in the CRC tissues than the normal tissues of the patients. On the other hand, the APC gene expression was higher in the normal tissues (p=0.007; % 95 CI=0.47-2.95).

We think that increased expression levels of miR-27 and miR-663 in the tumor tissue are also related to the decreased APC gene expression in the tumor tissue. It can be said that miR-27 and miR-663, which suppress the expression of APC, the tumor suppressor gene, can function as oncogenic miRNAs in the development of CRC. Also, the expression levels of miR-181d and miR-217 are related to increased expression of K-Ras gene in tumour tissues and that expression of K-Ras gene, which plays an oncogenic role in colorectal cancer development, is regulated by these miRNAs.

Anaesthesia management of a child with mucopolysaccharidosis 1 undergoing tonsillectomy

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Mucopolysaccharidosis I (MPS I) is a rare metabolic disorder that is associated with a high degree of anesthetic risk. We describe the anesthetic and airway management in a 9-year-old patient with Hurler syndrome who required tonsillectomy.

A 9-year-old, 90 cm, 18 kg, child with a history of MPS I was scheduled for tonsillectomy. His medical history was significant for sleep apnea and mitral valve failure. His past surgical history included congenital cataract surgery 3 years before and it was learned that the problem was not encountered. His medications included enzyme replacement therapy with a-l-iduronidase once weekly. The rest of the physical examination was notable for a short neck with limited mobility, an inability to open his mouth fully and a Mallampati IV airway, and flexed wrists and elbows. His vital signs were heart rate, 110; blood pressure, 90/70; and respiratory rate, 20. Pulmonary function tests showed a restrictive pattern with the forced vital capacity of 44% of the reference value. From the preoperative assessment, a difficult intubation was anticipated and an awake fiber-optic intubation was planned. The patient was pretreated with 5 mg midazolam intranasally. On arrival to the operating room, routine monitors were placed, and oxygen was administered via nasal canula. Dexmedetomidine infusion was administered by IV route as bolus of 0.5 mcg.kg-1 dose for 10 min. After bolus administration, dexmedetomidine infusion was continued for maintenance dose as 0.6 mg.kg-1.h-1. Dexmedetomidine infusion was continued for 20 min throughout the procedure. Airway topicalization was accomplished with 5 mL of lidocaine 4% and nebulization, and lidocaine 2% gel was applied to the pyriformis fossa to block the superior laryngeal nerve. Intubation was completed successfully. General anesthesia was induced with propofol, fentanyl, and rocuronium. The surgery took nearly 35 minutes, and patient was extubated uneventfully.

The combined of Na⁺ channel blockers and cisplatine effect on neuroblastoma cancer viability: in vitro study

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Neuroblastoma (SH-SY5Y) is a type of cancer with aggressive and resistant features and is one of the most common solid tumors in children. The neuroblastoma (NB) stems from the precursor cells of the sympathetic nervous system. Only 20-35% of children with metastatic neuroblastoma disease survive with standard therapy. Cisplatin or cis-diamminedichloroplatinum (CDDP) is one of the most commonly used drugs in the treatment of NB. Cisplatin causes cytotoxic cell death mediated by death receptor-mediated apoptotic signaling mechanisms as well as activation of mitochondrial pathways. Valproic acid (VPA) is histone deacetylase inhibitor (HDAC). VPA is used for long-term treatment of epilepsy in both adults and children. But VPA is also thought to have antitumoral activity. In this study, the effects of VPA and cisplatin combination therapy on neuroblastoma in vitro were investigation.

For this purpose, three different application groups were chosen. Our application groups compose of VPA (5mM), Cisplatin (5, 10, 15 μ g) and combination of VPA (5mM) and Cisplatin (5, 10, 15 μ g). We applied this groups on SH-SY5Y cancer cell lines for 24 hours. MTT cell viability test, flow cytometry, Anexin-V-FITC apoptosis test and lactate dehydrogenase test were performed 24 hours after the application.

As a result of the MTT test, it was determined that both cisplatin 15 μ g and the combination of Cisplatin 15 μ g + VPA reduced cell proliferation by approximately 25% compared to the control but according to Cisplatin (5,10 μ g), the other groups (VPA+ Cisplatin 5,10 μ g) a little more reduce proliferation. It appears that adding VPA to Cisplatin does not make a striking difference. That is, sodium channel blockers have no synergistic effect with the cisplatin.
Intraoperatively diagnosed paraganglioma

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Paragonangioma is a rare tumour caused by the neuroendocrine cells of the autonomic nervous system. Paragonangiomas can be seen everywhere that the chromophone cells exist. The most common localization sites are carotid communis artery bifurcation, jugular foramen, aortic arch and retroperitoneum. Retroperitoneal paragangliomas usually develop in childhood and have slow progression and usually functioning. The most common symptoms are headache, sweating, abdominal pain and palpitation. Asymptomatic paragangliomas is not common. We aimed to present a retroperitoneal paraganglioma case without symptoms except abdominal pain.

A 50 years old male patient with no previous known disease is referred to our general surgery clinic for abdominal pain. Abdominal pain is continuous. The patient told that the abdominal pain has persisted for 3 months, accompanied by constipation complaints occasionally. Colonoscopy was performed previously due to constipation and no pathology was detected. There was no significant finding in the physical examination. Abdominal computed tomography was performed. An abdominal mass structure with 4 cm in diameter in the inferior part of the pancreas tail segment has been detected. However, during the mass removal operation, the operation is terminated because the systolic artery pressure exceeds 250 mm Hg. The patient who does not have a previous history of tension illness is referred to us for further examination. Paraganlioma was suspected, and 24-hour urine catecholamines levels were 1685 μ g of normetanephrine (88-444 μ g) and homograhinic acid of 6.3 UG / 24 h (0.5-6.2 UG). The patient underwent Ga-68 DOTATATE PET imaging and was told that the lesion seen on CT may be compatible with NET. With preoperative preparations, the patient was reoperated for mass excision. In the postoperative pathology examination, $5 \times 4 \times 3$ cm irregularly redbrown excisional material was observed. On microscopic examination mass had S100 and chromogranin painting positive and which did not react with amyloid, glial fibrillar acidic protein (GFAP), vimentin and pancytokeratin was compatible with paraganglioma. Catecholamine levels are monitored regularly for a year and they were normal and the patient has no symptoms for now.

It is important that the retroperitoneal paragangliomas can be detected at an early stage and prepared appropriately for surgical treatment. False diagnoses and inappropriate operations may lead to further intraoperative complications, possibly with hypertensive crisis. For this reason, the diagnosis should be made using preoperative catecholamine level and advanced imaging studies, even if there is no symptom in the patient in cases where the paraganglioma is suspected.

Na⁺ channel blockers and vincristine effect on neuroblastoma cell viability: cell culture test

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Neuroblastoma originating from undifferentiated cells of the sympathetic nervous system is the most common solid tumour in children and is the main cause of neoplastic death in infancy. Neuroblastoma behaviour can range from low-risk cancers with a tendency toward spontaneous regression or maturation, to high-risk ones with extensive growth, early metastasis and a poor prognosis. Valproic acid (VPA) is thought to inhibit the proliferation of neuroectodermal cells and to increase immunogenicity in neuroblastoma and glioma cells and to diminish their ability to metastasize. Vincristine is used in many cancer type treatments. The aim of the study is to assess the antiproliferative effect of known Vincristine, VPA and their combinations on the cell viability of the neuroblastoma cancer line.

In this relation, the SH-SY5Y cell line was grown in normal cell culture medium. Different dose of Vincristine (0.5, 1 and 2 ng), VPA (5mM), Vincristine (0.5, 1 and 2 ng) + VPA (5 mM) was applied on SH-SY5Y cancer cell lines for 24 hours. MTT cell viability test, Anexin-V-FITC apoptosis test and lactate dehydrogenase test were performed 24 hours after the application.

As a result of the MTT test, it was determined that the combination of 2 ng Vincristine and Vincristine + VPA (2 ng + 5mM) reduced cell proliferation by approximately 23 and 28%, respectively, compared to the control.

It appears that the vincristin combination with VPA does not make a sense in compare to pure Vincristine.

ACTH on HT29 cell line can be tolerate by nifedipine: in vitro study

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In present study we evaluate Ca⁺² channel blockers and metformin effects on neuroendocrine relation with HT29 cell culture model. For this aim we used MTT assay and annexin-V (flowcytom study apoptosis marker).

We obtained HT29 cells form Department of Medical Pharmacology, Ataturk University (Erzurum, Turkey). When the cells reach %90 confluent, different doses of ACTH (25, 50 and 75 μ g) and nifedipine (10 μ g) were added to each wells (n=6). The MTT and apoptosis marker were measured. All data were analysed by using One Way ANOVA method.

Our result shows ACTH increased cell viability in HT29 culture up to %15. But the L type Ca⁺² channel blockers reduced cell viability of both cancer lines. By increasing dose of ACTH to 75 μ g viability of clone carcinoma increased rapidly in 24 h. Combination of neuroendocrine hormones with nifedipine bringing back cells to near equal with control group. According to our results we conclude that L Type Ca⁺² channel blocker can eliminate cancer cells population minimum to normal levels. We suggest amlodipine can be used as adjuvant to cancer therapy of patient suffering from Cushing syndrome.

Lethal effect of amlodipine and metformin on neuroblastoma cell line

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Neuroblastoma (SH-SY5Y) is a tumour seen in adrenal medulla and sympathetic ganglions, originating from primitive neural crest cells and seen in children under 10 years of age. The cause of neuroblastoma is not known exactly. It is the most common extracranial solid tumour. Amlodipine is one of calcium channel blockers and dilates blood vessels and improves blood flow. There are new studies on Ca⁺² channel blockers that prevent cancer cells from migrating and multiplying. Metformin is an oral antidiabetic drug used for control high blood glucose. In the literature, there is no study on the use of amlodipine and metformin on neuroblastoma cancer cell line. The aim of this study was to examine the effects of amlodipine, metformin and combinations of these drugs on neuroblastoma cancer cell line viability.

In this study, the SH-SY5Y cell line was grown in the appropriate cell culture medium. Doses of Metformin (10 μ M, 20 μ M, 40 μ M), Amlodipine (10 μ l), Metformin + Amlodipine (10 μ M, 20 μ M, 40 μ M) was applied on SH-SY5Y cancer cell lines for 24 hours. MTT cell viability test, flow cytometry, Anexin-V-FITC apoptosis test and lactate dehydrogenase test were performed 24 hours after the application.

As a result of the MTT test, it was determined that the combination of Metformin 40 μ M + Amlodipine reduced cell proliferation by approximately 29% compared to the control and single application of Metformin and Amlodipine. It was observed that amlodipine + metformin combination therapy is more effective than single drug administration.

Vincristin combination with calcium channel blocker increase antitumor effects

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Neuroblastoma, ganglioneuroblastoma and ganglioneuroma are neuroblastic tumours and derived from primordial neural crest cells. It is derived from neural crest cells forming the sempatho-adrenal system and is located in the adrenal chromaffin cells or spinal sympathetic ganglion cells where the sympathetic nervous system is located. Calcium (Ca²⁺) signalling is an important factor in the regulation of events such as contraction, motility, apoptosis, transmitter oscillation, exocytosis and endocytosis. Studies have shown that voltage-gated calcium channels are involved in many of the cancer features such as sustaining proliferative signalling, avoiding growth suppressors, resisting cell death, providing replicative immortality, stimulating angiogenesis and activating invasion and metastases and activating more.

In this study, it was aimed to determine the effects of amlodipine, a calcium channel blocker, and vincristine, an antineoplastic, on human neuroblastomas using different doses. The cytotoxicity assays of the study were performed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method depending on time and concentration. After obtaining the mixture (up to 85% for SH-SY5Y) and sufficient branches (cortex neurons), the cells were treated with amlodipine (10 μ M) and vincristine (0.5, 1 and 2 μ g) at different concentrations for 24 hours. MTT assay was performed by the commercially available kit. Cells were harvested, washed and stained with propidium iodide (PI) and Annexin V, respectively, according to the manufacturer's protocol. Than analyses were carried out.

Results were quite impressive. When amlodipine (10 μ M) was administered alone there was little change compared to the control. However, all doses of amlodipine (10 μ M) and vincristine (0.5, 1 and 2 μ g) were greater than the deaths in the doses alone (0.5, 1 and 2 μ g) of vinkristin alone (P<0,05).

In conclusion, the use of calcium channel blockers in combination with antineoplastics is expected to be a promising new approach in treatment.

Na⁺ channel blocker enhances metformin effects on neuroblastoma cell line

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Neuroblastoma is solid tumour of the postganglionic sympathetic nervous system and arises in the adrenal glands and spreads to various organs such as liver, bone, lymph nodes, neck and chest. Metformin is widely used in the treatment of type 2 diabetes. In recent years, oncologists are paying considerable attention to metformin anticancer effects and low cancer incidence among diabetic patients. Valproic acid acts as inhibitor of histone deacetylase and antitumor activities is a well-known antiepileptic drug. Hydroxamic acid-based (HDAC) inhibitors have come to the forefront in the treatment of various disease groups such as cancer, spinal musculoskeletal atrophy, Alzheimer's disease, diabetes and etc.

In this study, it was aimed to determine the effects of valproic acid and metformin, an antidiabetic, on human neuroblastomas by using different doses and combination of both. After obtaining the mixture (up to 85% for SH-SY5Y) and sufficient branches (cortex neurons), the cells were treated with valproic acid (5 mM) and metformin (10, 20 and 40 μ M) at different concentrations for 24 hours. The cytotoxicity assays of the study were performed by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and flowcytometry (PI and Annexin V staining) respectively.

Pure valproic acid and metformin only showed low efficacy when the results were examined (P>0,05). However, 10-18 µgr doses of valproic acid and metformin co-administered increased neuroblastoma mortality (P<0,05). These and similar studies are expected to shed light on cancer research.

Anaesthesia management of a patient with Duchenne muscular dystrophy undergoing rhinoplasty

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Duchene's muscular dystrophy (DMD) is the most common and severe form of myopathy occurring in patients. Sensitivity of patients with DMD to sedative, anaesthetic and neuromuscular blocking agents may result in intraoperative and early postoperative cardiovascular and respiratory complications, as well as prolonged recovery from anaesthesia. Anaesthetic management of these patients is challenging and may cause serious problems to the anaesthesiologists. We present anaesthesia management of a woman with Duchene muscular dystrophy undergoing rhinoplasty.

A 26-year-old woman, 55 kg, 165 cm, ASA physical status III, applied to our institution with complaining of difficulty breathing, and was scheduled for rhinoplasty. In preoperative evaluation, it was learned that DMD was diagnosed 16 years ago and difficulty in swallowing solid foods, fatigue when climbing stairs, and difficulty sitting and getting up were recently increased. His vital signs were heart rate, 60; blood pressure, 110/60. 18. The patient was pre-treated with 2 mg midazolam iv. On arrival to the operating room, routine monitors were placed, General anaesthesia induction was induced with target controlled infusion of propofol (3.0 microg x ml(-1)) and 0.4 microg x kg(-1) of min(-1) of remifentanil without muscle relaxant. Anaesthesia was maintained by intravenous infusion of propofol and remifentanil with a total intravenous anaesthesia technique (TIVA). Oro-tracheal intubation was successfully done with good conditions. No neuromuscular blockers were administered and no perioperative complications emerged. The intraoperative course of patient was uneventful. The duration of surgery was 90 min. Controlled hypotension, rapid recovery and uneventful postoperative period were achieved with this technique. Consequently, we report the use of TIVA with remifentanil and propofol without muscle relaxants in patient undergoing rhinoplasty surgery. Total intravenous anaesthesia seems the best way to provide general anaesthesia for a patient with DMD.

Effect of ADH and amlodipin on HT29 cell line: in vitro study

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HT-29 is a human colorectal adenocarcinoma cell line with epithelial morphology. Colon cancer can be seen in 1 out of every 20 people throughout life. ADH is also called arginine vasopressin and have important role in neuroendocrine system.

Previously it was proofed vasopressin is able to impair tumour aggressiveness and distant spread on colorectal cancer. Ca⁺⁺ signalling is an important factor in the regulation of events such as contraction, motility, apoptosis, transmitter oscillation, exocytosis and endocytosis. In this study we aimed to study ADH combination with Ca⁺⁺ against HT29 cancer cells and also anti metastatic effect of ADH can be increased by amlodipine or not?

The cytotoxicity assays of the study were performed using the 3-[4,5-dimethylthiazole-2-yl]-2,5diphenyltetrazolium bromide (MTT) and total antioxidant and oxidant status depending on time and concentration. HT29 obtained from medical pharmacology department (Ataturk Univ, Erzurum, Turkey). After reaching 85% confluency for HT29 cells were treated with amlodipine (10 μ M) and ADH (12.5, 25 and 50 μ g) at different concentrations for 24 hours.

Than analyses were carried out by SPSS 21.0 program and one-way ANOVA method. Results were quite impressive. When ADH was administered dose dependently decreased HT29 cell viability ratio and antioxidant status but it does not have significant difference in compare to control group (P>0,05). In addition, amlodipine (10 μ M) alone also did not have any positive effect (P>0,05) but the combination of amlodipine and ADH effectively killed cancer cells in compare to control group (P<0,05).

Neuroendocrine hormones have antitumor effects. In future study we have plan to investigate molecular mechanisms of ADH effects on colon cancer.

Primary hyperaldosteronism and anaesthesia management

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Hypertension and hypokalemia are the results of uncontrolled hormone secretion from adrenal gland as named primary hyperaldosteronism (PHA) or Conn Syndrome (1). In this case report, we aimed to present anesthesia management of PHA.

A thirty-nine years old female patient with PHA was operated for laparoscopic surrenal mass excision. There were no abnormal laboratory findings. The patient had regular hypertension (165/102 mm / Hg) in preoperative evaluation. IV midazolam was given as premedication for sedation. bispectral index monitoring for depth of anesthesia and invasive arterial monitoring were performed in addition to routine anesthetic monitoring. The patient was induced with fentanyl, lidocaine, propofol and rocuronium. After induction, the invasive blood pressure was 126/85 mmHg. Anesthesia was maintained with sevoflurane and remifentanil, Nitro-glycerine infusion was administered to control blood pressure. The duration of operation was 120 minutes. The patient was extubated with nitroglycerine infusion. For postoperative analgesia, multimodal analgesia was administered. The patient transferred intensive care unit for postoperative hemodynamic stability.

PHA cases require treatment of hypertension and hypokalemia in preoperative period. In the preoperative preparation; the blood pressure should be regulated at normal limits and the side effects of antihypertensive drugs should be considered. The patients have to take the preoperative anxiolytics. Antihypertensive drugs should be given till the morning of operation.

Other anesthetics except ketamine can be safely used in induction of anesthesia. Depth of anesthesia should be monitored with bispectral index. In addition to administering intraoperative anesthesia, beta-blockers, nitro-glycerine, and sodium nitroprusside infusions should be added as needed. Close hemodynamic monitoring is essential specifically for hypokalemia. Multimodal analgesia is important. Anesthesia management can be provided by close monitoring of PHA case.

Investigation of effects of fagopyrum *esculentum* methanol extract in HT-29 human colorectal adenocarcinoma cells

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Fagopyrum esculentum is a kind of plant which contained alkaloids, amino acids, anthraquinones, carbohydrates, flavonoids and tannins. Fagopyrum esculentum has anticancer, antidiabetic, antigenotoxic, anti-inflammatory, antimicrobial, antioxidant, wound healing and antistress effects. In this study, it is aimed to investigate the cytotoxic and apoptotic effects of methanol extract in HT-29 human colorectal adenocarcinoma cells of buckwheat (Fagopyrum esculentum) flour, produced in Gölpazarı, Bilecik.

Human colorectal cancer cells were cultured in appropriate medium and were kept until 100% confluence achieved. After that different concentrations of Fagopyrum *esculentum* methanol extract (final concentrations in the well to be 125-1000 μ M) were added into the medium and left to incubate for 24 hours. The cytotoxic effect on cell viability was determined by using MTT assay. Caspase-3 activity was measured by using a colorimetric protease assay kit.

According to MTT assay, methanol extract of Fagopyrum *esculentum* exhibited significant antiproliferative effect on cell viability at 24 hours dose range of 500-1000 μ M in a dose- and timedependent manner. According to Caspase-3 colorimetric protease assay, we reported that methanol extract from Fagopyrum esculentum at high doses have ability to trigger caspase-3 induced apoptosis in HT-29 human colorectal adenocarcinoma cells.

It was shown that methanol extract of Fagopyrum *esculentum* has anti-proliferative effect and induce apoptosis via caspase 3 activation in a dose-dependent manner in this study. The results of the study show that methanol extract from Fagopyrum *esculentum* alone or in combination with other drugs may be useful in the treatment of colon adenocarcinoma. However, further studies are needed to clarify the mechanisms of action.