

# NEUROENDOCRINOLOGY SYMPOSIUM & WORKSHOP

## “Experimental Models for Studying Neuroendocrine Disorders”



23-25 April 2009  
Yeditepe University, Istanbul

# FINAL PROGRAM & BOOK of ABSTRACTS

Neuroendocrinology Society

[www.tned.org](http://www.tned.org)

## **TABLE of CONTENTS**

<b>GREETINGS .....</b>	<b>P 03</b>
<b>PROGRAM .....</b>	<b>P 04</b>
<b>ABSTRACTS AT A GLANCE .....</b>	<b>P 07</b>
<b>CONFERENCE ABSTRACTS .....</b>	<b>P 09</b>
<b>ORAL COMMUNICATIONS .....</b>	<b>P 21</b>
<b>WORKSHOPS.....</b>	<b>P 25</b>
<b>POSTER COMMUNICATIONS.....</b>	<b>P 33</b>
<b>INDEX.....</b>	<b>P 41</b>



## GREETINGS

Dear Colleagues,

On behalf of the Symposium & Workshop Organizing Committee, it is my pleasure to invite you to the first Neuroendocrinology Symposium & Workshop that will be held at Yeditepe University, İstanbul, on 23–25 April 2009.

Neuroendocrinology Society (TNED) was founded on April 22, 2008 in İstanbul. It is a multidisciplinary organization involving clinical and pre-clinical departments and committed to see promotion of the discipline of neuroendocrinology in Turkey. TNED has very recently been granted with full membership to the International Neuroendocrine Federation. Neuroendocrinology Symposium & Workshop will coincide with the first anniversary of TNED. At this first event of the Society, the symposium will include a variety of topics and conference speakers and be followed by six different workshops on in vivo and in vitro experimental models for studying clinical neuroendocrine disorders.

In addition to an intensive scientific program, the participants will also enjoy a social program and have the opportunity to visit beautiful Bosphorus and several cultural and historical attractions in İstanbul. We are looking forward to welcoming you to İstanbul and Yeditepe University and making this symposium & workshop a special and successful scientific event.

Prof. Bayram Yılmaz  
President of the Neuroendocrinology Society

## COMMITTEES

### ORGANISING COMMITTEE

Bayram Yılmaz (President)  
Haluk Keleştimur  
Canan Aykut Bingöl  
Ertuğrul Kılıç  
Mustafa Özen  
Ertan Tezcan  
Uğur Türe  
Ramis Çolak  
Sedat Yıldız  
Kürşad Ünlühızarıcı

**Contact:** Prof. Dr. Bayram Yılmaz  
Yeditepe Üniversitesi Tıp Fakültesi Fizyoloji Anabilim Dalı 34755, Kayışdağı Cad. İSTANBUL  
**Tel:** 0 (216) 578 0675  
**Fax:** 0 (216) 578 0575  
**E-mail:** [byilmaz@yeditepe.edu.tr](mailto:byilmaz@yeditepe.edu.tr)  
**Web:** [www.tned.org](http://www.tned.org)

### Symposium Secretariat:



Meet the Expert Congress & Event Services  
Ergenekon Mah. Halaskargazi Cad. Hülya Apt. No.57 K.7 D.7 Harbiye Şişli – İSTANBUL  
**Tel:** 0 (212) 241 46 56 ext. 16  
**Fax:** 0 (212) 241 67 46  
**E-mail:** [neuroendocrine@meethexpert.com](mailto:neuroendocrine@meethexpert.com)  
**Web:** [www.meethexpert.com](http://www.meethexpert.com)

## PROGRAM

### 23 April 2009, Thursday (Mavi Salon/Blue Hall)

---

17.30 - 18.15	Registration
18.15 - 19.00	Opening Ceremony
19.00 - 21.00	Opening Reception (Yeditepe University)

### 24 April 2009, Friday (Mavi Salon/Blue Hall)

---

8.30 - 9.00 Registration

*Chairs: Fahrettin Keleştimur & Bayram Yılmaz*

9.00 - 9.45 **Conference 1**  
Neuroendocrine Mechanisms Controlling the Timing of Puberty in Primates (*Tony Plant*)

9.45 - 10.30 **Conference 2**  
Stress, the GnRH Pulse Generator and Infertility (*Kevin T. O'Byrne*)

10.30 - 10.45 **Oral Communication 1**  
Chronic Leptin Infusion Advances Puberty Onset in Sham and Pinealectomized Normally Fed Female Rats (*Haluk Keleştimur*)

10.45 - 11.15 **COFFEE BREAK**

*Chairs: Vedat Bulut & Ece Genç*

11.15 - 11.55 **Conference 3**  
Neurokinin B: A Novel Regulator of Reproductive Functions (*Ali Kemal Topaloğlu*)

11.55 - 12.40 **Conference 4**  
From Biomarkers to Drug Targets: Genetic Animal Models of Stress and Psychiatric Disorders (*Eva Redei*)

12.40 - 12.55 **Oral Communication 2**  
Leptin and Ghrelin Differentially Modulate Noradrenaline Release in the Paraventricular Nucleus and Plasma Oxytocin Levels in Female Rats: A Microdialysis Study (*Selim Kutlu*)

13.00 - 14.00 **LUNCH**

## PROGRAM

(continued)

**Chairs: Uğur Türe & Kemal Sarıca**

- 14.00 – 14.45**      **Conference 5**  
Effects of Somatostatin Analogs on Normal and Tumoral Growth Hormone Secretion: In vitro and In vivo Studies (*Leo J. Hofland*)
- 14.45 – 15.30**      **Conference 6**  
Aneuploidy, Stem Cells and Cancer (*Sen Pathak*)
- 15.30 – 16.00**      **Conference 7**  
Disruption of FGF Signaling as an Approach to Prostate Cancer Gene Therapy (*Mustafa Özen*)
- 16.00 – 16.30**      **COFFEE BREAK**

**Chairs: Canan Aykut Bingöl & Oğuz Tanrıdağ**

- 16.30 – 17.15**      **Conference 8**  
Beyond Estrogen: The Role of Gonadotropins on Cognition and Alzheimer's Disease (*Gemma Casadesus & Mark Smith*)
- 17.15 – 17.35**      **Oral Communication 3**  
Metabolically-Induced Paradoxical Cell Cycle Activities in Astrocyte and Neuron Linked to Neurodegeneration (*Adnan Erol*)
- 17.35 – 18.10**      **Conference 9**  
Neuroprotective Therapy Strategies After Stroke: Drug Delivery, Estrogen and VEGF (*Ertuğrul Kılıç*)
- 18.10 – 18.25**      **Closing Session**
- 19.30 – 23.00**      **Symposium Dinner**              **(İSTEK Balmumcu Tesisleri)**

## 25 April 2009, Saturday

---

- 9.00 – 11.30**      **Workshop I**                      **(Physiology LAB, 448)**  
A) Non-human Primate Models of Human Reproduction: Advantages and Disadvantages (*Tony Plant*)  
B) Models of Stress and Reproductive Dysfunction (*Kevin O'Byrne*)  
C) Cellular Models for GnRH Neurobiology and Neuropathic Pain (*Ahmet Ayar*)



## ABSTRACTS AT A GLANCE

- C 01 Neuroendocrine Mechanisms Controlling the Timing of Puberty in Primates**  
Tony M. Plant
- C 02 Stress, the GnRH pulse generator and infertility**  
Kevin T O'Byrne
- C 03 Neurokinin B: A Novel Regulator of Reproductive Functions**  
A. Kemal Topaloğlu
- C 04 From Biomarkers to Drug Targets: Genetic Animal Models of Stress and Psychiatric Disorders**  
Eva Redei
- C 05 Effects of Somatostatin Analogs on Normal and Tumoral Growth Hormone Secretion: In Vitro and In Vivo Studies**  
Leo J. Hofland
- C 06 Telomere Dynamics in Aneuploidy and Cancer: A Translational Research**  
Sen Pathak
- C 07 Disruption of FGF Signaling as an Approach to Prostate Cancer Gene Therapy**  
Mustafa Özen
- C 08 Beyond Estrogen: The Role of Gonadotropins on Cognition and Alzheimer Disease**  
Gemma Casadesus<sup>1</sup>, Mark A Smith<sup>2</sup>, Jennifer Reeves<sup>1</sup>, Joseph Mudd<sup>1</sup>, Hyoung-gon Lee<sup>2</sup>, Kathryn Bryan<sup>1</sup>
- C 09 Neuroprotective Therapy Strategies After Stroke: Drug Delivery, Estrogen and VEGF**  
Ertuğrul Kılıç
- C 10 Physiopathology and Clinical Evaluation of Endometriosis**  
Erkut Attar
- C 11 Animal Models in Endometriosis Research**  
Narter Yeşildağlar
- OC 01 Chronic Leptin Infusion Advances Puberty Onset in Sham and Pinealectomized Normally Fed Female Rats**  
Haluk Keleştimur<sup>1</sup>, Bayram Yılmaz<sup>2</sup>, Ahmet Ayar<sup>3</sup>, Ertuğrul Kılıç<sup>2</sup>, Mete Özcan<sup>4</sup>, Ergül Alçin<sup>1</sup>, Ülkan Kılıç<sup>2</sup>, Ramis Çolak<sup>5</sup>
- OC 02 Leptin and Ghrelin Differentially Modulate Noradrenaline Release in the Paraventricular Nucleus and Plasma Oxytocin Levels in Female Rats: A Microdialysis Study**  
Selim Kutlu<sup>1</sup>, Mehmet Aydın<sup>1</sup>, Ergül Alçin<sup>1</sup>, Mete Özcan<sup>2</sup>, Jan Bakos<sup>3</sup>, Daniela Jezova<sup>3</sup>, Bayram Yılmaz<sup>4</sup>
- OC 03 Metabolically-Induced Paradoxical Cell Cycle Activities in Astrocyte and Neuron Linked to Neurodegeneration**  
Adnan Erol
- W 1 (A) Non-human Primate Models of Human Reproduction: Advantages and Disadvantages**  
Tony M. Plant

## ABSTRACTS AT A GLANCE

(continued)

- W 1 (B) Models of Stress and Reproductive Dysfunction**  
Kevin T O'Byrne
- W 1 (C) Cellular Models for GnRH Neurobiology and Neuropathic Pain**  
Ahmet AYAR
- W 2 (A) Detection of aneuploidy and telomeres in prostate cancer cell lines by conventional cytogenetics**
- W 2 (B) Determination of stem cell markers in prostate cancer cells by real time PCR assays**  
Sen Pathak<sup>1</sup> and Mustafa Özen<sup>2</sup>
- W 3 Animal Models of Alzheimer's Disease: Challenges and Considerations**  
Gemma Casadesus<sup>1</sup>, Mark A Smith<sup>2</sup>, Kathryn Bryan<sup>1</sup>, Jennifer Reeves<sup>1</sup>, Joseph Mudd<sup>1</sup>, Xiongwei Zhu<sup>2</sup> and Hyoung-gon Lee<sup>2</sup>
- W 4 Characterization of Somatostatin Receptors in Neuroendocrine Tumors**  
Leo J. Hofland
- W 5 Neurobehavioral and Psychiatric Disorder Models Workshop**  
Eva Redei<sup>1</sup> & Ertuğrul Kılıç<sup>2</sup>
- W 6 Experimental Models for Endometriosis**  
Erkut Attar<sup>1</sup> & Narter Yeşildağlar<sup>2</sup>
- PC 1 Influences of Hypertonic and Hypovolemic Treatments on Vasopressin Response in Propylthiouracil (PTU) -Induced Hypothyroid Rat and Effects of Supplementation with L- Thyroxine**  
Aydın L, Moğulkoç R, Baltacı AK
- PC 2 Effect of Melatonin Supplementation on Plasma Vasopressin Response to Different Conditions in Rats with Hyperthyroidism Induced by L-Thyroxine**  
Moğulkoç R & Baltacı AK
- PC 3 Effect of Testosterone Supplementation on Leptin Release in Rats which Underwent Castration and Unilateral Srenalectomy**  
Kul A, Baltacı AK, Moğulkoç R
- PC 4 Pinealectomy Inhibits Antioxidant System in Rats with Hyperthyroidism**  
Moğulkoç R, Baltacı AK, Aydın L, Öztekin E and Sivrikaya A
- PC 5 Post-Injury Administration of Erythropoietin Promotes Neuronal Survival and Motor Recovery After Mild Focal Cerebral Ischemia in Mice**  
Ülkan Kılıç<sup>1</sup>, Max Gassmann<sup>2</sup> and Ertuğrul Kılıç<sup>3</sup>
- PC 6 Effect of High Fat Intake on Behavior and Monoamine Metabolite Levels in Striatum and Cortex of Rats exposed to Stress**  
Deniz Kırac<sup>1</sup>, İnci Özden<sup>1</sup>, Alper Yıldırım<sup>2</sup> and Ece Genç<sup>3</sup>

# **CONFERENCE ABSTRACTS**

**C 01**

**Neuroendocrine Mechanisms Controlling the Timing of Puberty in Primates**

Tony M. Plant

University of Pittsburgh, School of Medicine, Pittsburgh, USA.

Although puberty in primates is delayed for several years after birth, GnRH pulsatility during infancy is robust and the endocrine activity of the infant pituitary-testicular axis is similar to adults. Within a few months, GnRH release is restrained and thereby the quiescence of the prepubertal gonad is guaranteed. This “up-down-up” pattern of GnRH during postnatal development unfolds in the absence of the gonad, and may be viewed to result from application of a neurobiological brake that restrains GnRH neuron activity during the intervening childhood/juvenile phase of development. Expression of *GnRH1* does not appear to be subjected to major developmental regulation, and an adult pattern of pulsatile GnRH release may easily be induced from the juvenile hypothalamus by application of an intermittent neurochemical stimulus. Kisspeptin expression in the mediobasal hypothalamus (MBH) changes in parallel with that of GnRH release from birth to puberty, and repetitive stimulation of GPR54 in the juvenile hypothalamus induces a sustained precocious pubertal pattern of GnRH release. Kisspeptin perikarya in the primate brain are located primarily in the region of the arcuate nucleus, while GnRH cell bodies are more lateral. Although kisspeptin neurons appear to communicate with GnRH neurons via axo-somatic and axo-dendritic contacts, extensive and intimate association between kisspeptin and GnRH axonal projections in the internal layer of the monkey median eminence raises the possibility that regulation of GnRH release by kisspeptin may be exerted at the median eminence. It remains to be determined, however, whether kisspeptin neurons of the arcuate nucleus are a component of a pubertal clock or growth tracking device, or simply serve as a link that relays information from such a puberty control center to the GnRH network. Similarly, there is an urgent need to integrate kisspeptin signaling with that of other pathways implicated in the developmental regulation of GnRH release in primates.

Supported by NIH grants HD 013254 and HD 001860.

**C 02**

**Stress, the GnRH pulse generator and infertility**

Kevin T O'Byrne

King's College London, Division of Reproduction & Endocrinology, London, UK

The central importance of the GnRH pulse generator as a limiting component of the control system that governs reproductive processes is unequivocal. Deviations from the normal physiological frequency range of this pulse generator are commonly associated with major disruptions in follicular development and ovulation resulting in infertility. Additionally, there is growing evidence that adverse early environments can permanently modify the hypothalamo-pituitary-adrenocortical axis and stress responsiveness of the GnRH pulse generator. Our research is focused on understanding how the GnRH pulse generator responds to acute and chronic stress and how these responses are altered by early life events in the rat.

Considerable progress has been made concerning the role of corticotrophin-releasing hormone (CRH), the classical stress neuropeptide, in control of GnRH pulse generator activity. We identified a novel site of action for CRH within the locus coeruleus and have shown a differential role for this principal noradrenergic brainstem nucleus, with its strong limbic (emotional) connections, in the aetiology of psychological stress responses, but not systemic responses such as metabolic perturbations. We have also shown a differential involvement of CRH receptor type 1 and 2 in stress-induced suppression of the GnRH pulse generator. The novel role for the type 2 CRH receptors affords further research on the function of the urocortin family of peptides, some of which are highly selective endogenous ligands for type 2 CRH receptors.

Recent identification of kisspeptin and its receptor (Kiss1r) as essential for controlling gonadotrophic hormone secretion and puberty has raised the possibility that they play a role in the transduction of stress-induced suppression of reproduction. Indeed, we have observed a stress-induced down regulation of kisspeptin-Kiss1r expression in hypothalamic regions critical to the control of LH secretion. Furthermore, a delay in puberty consequent to exposure to the endotoxin, lipopolysaccharide, in early neonatal life was associated with a concomitant decrease in kisspeptin expression in the hypothalamic preoptic area of female rats.

**C 03**

**Neurokinin B: A Novel Regulator of Reproductive Functions**

A. Kemal Topaloğlu

Çukurova University, Faculty of Medicine, Department of Pediatric Endocrinology and Metabolism, Adana, Turkey

The production of LH and FSH from pituitary gonadotrope cells is largely controlled by the pulsatile delivery of gonadotropin releasing hormone from a functionally interconnected group of secretory neurons in the hypothalamus. The gonadal endocrine system is active in utero and for the first few months of life before entering a state of quiescence. The mechanism of reactivation of the GnRH pulse generating system at puberty is an enduring enigma of human biology.

Nine multiplex consanguineous families from Turkey affected by normosmic idiopathic hypogonadotropic hypogonadism (nIHH) were subjected to genome-wide SNP analysis, and within each family regions of homozygosity common to all affected individuals were identified. In three families, homozygosity at a locus on chromosome 4 segregated with nIHH. Alignment of all six affected members of the three families refined a 2.74 MB genomic region encompassing 20 known or predicted genes. Of those genes, we selected TACR3 for further analysis. TACR3 encodes NK3R, the receptor for Neurokinin B, a tachykinin peptide known to be highly expressed in hypothalamic neurons. And, on sequencing we found homozygous nonsynonymous mutations (G93D and P353S) in the coding sequence of TACR3. In yet another multiplex family in which TACR3 mutations had been excluded, we identified two autozygous regions that were common to the two affected family members but not to their unaffected sister. Although these regions encompassed around 120 genes, TAC3, on chromosome 12 encoding Neurokinin B, the preferred ligand for the neurokinin-3 receptor was the most biologically plausible candidate. On sequencing TAC3, we identified a homozygous missense mutation (M90T). Deleterious nature of the mutations in both genes were confirmed by demonstrating impaired calcium signaling in a heterologous expression system.

In summary, we have identified loss-of-function mutations in either neurokinin B or its receptor in four multiplex families affected by normosmic idiopathic hypogonadotropic hypogonadism. These findings establish that neurokinin B action via the NK3R is necessary for the central neuroendocrine control of human reproduction. These families represent the first examples of inherited defects of tachykinin signaling in any human disorder and our results suggest that the NKB/NK3R system may provide a new avenue for the pharmacological manipulation of human fertility and the treatment of sex steroid-related diseases.

**C 04**

**From Biomarkers to Drug Targets: Genetic Animal Models of Stress and Psychiatric Disorders**

Eva Redei

Northwestern University, Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, Chicago, IL, USA

Evidence is accumulating in the literature demonstrating that genetic susceptibility plays a very similar role in complex disease pathogenesis in humans and rodent models in spite of interspecies differences.

Animal models of depression can mirror endophenotypes such as psychomotor retardation and anhedonia, which are within the animal's behavioral repertoire. Biomarker candidate genes were identified from a validated and generally well-accepted genetic animal model of depression, the Wistar Kyoto (WKY) rat strain whose depressive behavior can be alleviated by chronic administration of antidepressants. Within this strain, we conducted selective breeding using depressive behavior as a functional selector (Will et al., 2003). Two sub-strains of WKYs were created, currently at their 20<sup>th</sup> generation, that consistently show high (WMI) and low (WLI) levels of depressive behavior. Affymetrix microarray profiling of gene expression patterns were carried out in the frontal cortex, amygdala, hippocampus and blood of WMI and WLI rats.

Analysis of the data compiled through the brain and blood microarrays identified genes whose expression difference was the same in the brain regions and blood between the two substrains. The expression of these genes in the blood can serve as biomarkers of depressive behavior, while they are also potential targets for drug discovery efforts.

Animals also present consistent stress coping strategies similar to human coping strategies. We have previously identified three quantitative trait loci (QTL) on rat chromosome X that contribute to behavioral variation in coping characteristics. To determine the contribution of gene(s) mapped within one of these QTL regions to DB behavior, congenic strains were generated. Microarray analysis of brain regions identified candidate genes in the amygdala, hippocampus, and frontal cortex, allowing further analysis of these positional candidate genes. The behavioral characterization of the congenic strain containing a passive coping locus, combined with our microarray analysis, is a promising approach for elucidating specific genetic factors contributing to stress coping behaviors. These candidate genes can present novel treatment alternatives of stress-related illnesses.

## C 05

### Effects of Somatostatin Analogs on Normal and Tumoral Growth Hormone Secretion: In Vitro and In Vivo Studies

Leo J. Hofland

Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center,  
Rotterdam, The Netherlands

Somatostatin (SS) receptors (sst) play a key role in the regulation of pituitary growth hormone (GH) hormone secretion. In the anterior pituitary gland 4 of the 5 known sst subtypes are expressed (sst<sub>1</sub>, sst<sub>2</sub>, sst<sub>3</sub> and sst<sub>5</sub>). Sst<sub>2</sub> and sst<sub>5</sub> are the most important sst subtypes in the regulation of GH secretion. Chronic exposure of normal somatotroph cells to sst<sub>2</sub> preferring SS analogs, such as octreotide and lanreotide, results in desensitization of their inhibitory effects on GH secretion *in vitro* and on GH and IGF-I serum concentrations *in vivo*. Mechanisms such as receptor uncoupling from the signalling cascade, as well as receptor internalization and/or downregulation are involved. SS analogs with different sst receptor binding profiles can have enhanced inhibitory effects on normal GH and IGF-I secretion.

In acromegalic patients treatment with octreotide or lanreotide (targeting mainly sst<sub>2</sub>) results in biochemical control in approximately two-thirds of patients. Significant tumor shrinkage is observed in more than one-third of patients when given as first line treatment. In GH secreting pituitary adenomas, sst<sub>2</sub> and sst<sub>5</sub>, and to a lesser extent sst<sub>1</sub>, are the main expressed sst subtypes. Sst<sub>2</sub> and sst<sub>5</sub> and seem primarily involved in the regulation of tumoral GH secretion *in vitro*. Evidence suggests that sst<sub>1</sub> and sst<sub>2</sub> may influence tumor growth via reducing cell viability and by inducing apoptosis of GH-secreting pituitary adenoma cells, respectively. An enhanced inhibition of GH secretion by GH-secreting pituitary adenoma cells has been shown using recently developed SS-analogs and SS-dopamine chimeric compounds that target both sst<sub>2</sub> and sst<sub>5</sub> receptors, and sst<sub>2</sub> and dopamine D2 receptors, respectively. The efficacy of novel SS analogs with a more universal binding affinity to sst subtypes is under clinical investigation.

**C 06**

**Telomere Dynamics in Aneuploidy and Cancer: A Translational Research**

Sen Pathak

University of Texas, M.D. Anderson Cancer Center, Department of Genetics, Houston, Texas  
77030, USA

Recently discovered cellular mechanisms of normal and tumor cell growth and differentiation have begun to have an impact on our understanding of the biological forces that significantly contribute to the development and progression of cancer. Cancer is a group of genetic diseases of altered organ- and tissue-specific stem cells. Normal stem cells and cancer stem cells share, in addition to many, three most important characteristics: (a) self renewal, (b) migration (metastasis), and (c) differentiation. Most human cancers spring from a conspiracy between the genetic profile of a person and the life style (environment). The gross chromosomal alterations and/or gene mutations, hall-marks of tumor cells, are caused by telomere attrition. Telomeres which protect chromosomes from end-to-end fusion and maintain the genomic integrity during cell proliferations play a crucial role in aneuploidy and cellular aging. We provide evidence in support of the hypothesis that telomere dysfunction is the earliest genetic alteration responsible for the induction of genetic instability and aneuploidy. Dysfunctional telomeres are highly recombinogenic leading to the formation of dicentric and ring chromosomes. During cell divisions, such complex chromosome alterations will follow breakage-fusion-bridge-cycles which may lead to LOH (loss of heterozygosity), gene amplification and/or differential methylation of DNA. Furthermore, we have provided evidence in support of the hypothesis that all human cancers originate in the organ- or tissue-specific stem cells. A small population of metaphases present in the lymphocytes of cancer patients and in some of their asymptomatic first degree relatives may have been derived from the organ-specific stem cells. Successful treatment of cancer patients, therefore, will require intense research towards the elimination of these cancer stem cells.

(E-mail: [spathak@mdanderson.org](mailto:spathak@mdanderson.org))

**C 07**

**Disruption of FGF Signaling as an Approach to Prostate Cancer Gene Therapy**

Mustafa Özen

Yeditepe University, Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey

Prostate cancer cells express multiple types of FGF receptor and increased expression of FGF receptor-1 (FGFR-1) is present in poorly differentiated human prostate cancers *in vivo*. We have proposed to evaluate biological affects of DN FGFR expression in human primary prostate epithelial cells and prostate cancer cell lines. The findings in this report support that prostate cancer cells are dependent upon FGFR signaling for survival and cells treated with DN FGFR are arrested G2/M phase of cell cycle followed by cell death. FGF signaling modulated *CDC25C* activity in prostate cancer, and in this manner can promote progression through the G2/M checkpoint. *CDC25C* protein is up-regulated in comparison to normal prostate tissue and is present almost exclusively in its active dephosphorylated form. The cell cycle inhibitor p21 also plays a role in the G2/M checkpoint. We have found that there is a strong induction of p21 protein following DN FGFR expression. Cells infected with both the antisense p21 adenovirus (AS p21) and DN FGFR had significantly higher cell numbers at 48 hours compared to cells infected with DN FGFR only ( $p=0.03$ ). Thus AS p21 was able to substantially block the effect of DN FGFR. Therefore, p21 induction does play an important role in the effects of DN FGFR expression. To directly explore the utility of disruption of FGF receptor signaling using dominant negative receptors, we have used xenograft models. Adeno-DN FGFR was highly effective in inhibiting tumor growth in both subcutaneous ( $p<0.001$ ) and orthotopic models ( $p=0.042$ ).

In summary, our data shows that disruption of FGFR signaling pathway can be potentially used as a therapeutic approach for prostate cancer. Determining other molecules involved in this pathway contributing tumor growth and survival will facilitate the development of new cancer therapies to target FGF signaling pathway. Drugs that inhibit FGF receptor signaling are already undergoing Phase I clinical trials as cancer therapy. Our data will help to determine the potential for these agents as well as DN FGFR expressing adenovirus as treatments for prostate cancer especially as adjuvant to radiotherapy, the mechanism of cell death by FGF receptor signaling antagonists and new targets in this pathway to design novel therapeutic strategies for prostate cancer. Our *in vivo* experiments showed that AdDN FGFR can be used as therapeutic agent in prostate cancers in nude mice. More studies need to be done to show the validity of this approach in humans.

**C 08**

**Beyond Estrogen: The Role of Gonadotropins on Cognition and Alzheimer Disease**

Gemma Casadesus<sup>1</sup>, Mark A Smith<sup>2</sup>, Jennifer Reeves<sup>1</sup>, Joseph Mudd<sup>1</sup>, Hyoung-gon Lee<sup>2</sup>,  
Kathryn Bryan<sup>1</sup>

Departments of Neurosciences<sup>1</sup> and Pathology<sup>2</sup>, Case Western Reserve University,  
Cleveland, Ohio, USA

Estrogen is thought to play an important role in age-related cognitive decline, neuronal plasticity, as well as the pathogenesis of Alzheimer disease (AD). Epidemiological evidence links a decreased incidence of AD and cognitive decline in women previously exposed to hormone (estrogen) replacement therapy (HRT). Further, clinical data correlates estrogen deficiency to the etiology of AD. However, initiating HRT in elderly (age 65 and over) post-menopausal women failed to improve cognitive performance. These latter findings have led many in the field, including us, to re-examine the role of estrogen in cognition and AD and to look beyond the direct effects of estrogen to more indirect, though perhaps no less important, effects. To this end, declining levels of sex steroids in women, and men albeit to a lesser degree, result in increases in gonadotropins such as luteinizing hormone (LH) through loss of feedback inhibition. LH, like estrogen, is modulated by HRT and serum levels of LH are higher in AD patients compared to aged-matched controls. Recent published including our own studies, show that LH is capable of modulating cognitive behavior and associated neuronal plasticity markers, is present in the brain, has the highest levels of receptors in the hippocampus, is increased in the AD brain, and is capable of altering amyloid- $\beta$  protein precursor processing. Our ongoing studies involve dissecting the hormonal contributions and interactions of estrogen and LH on cognition, synaptic plasticity, and AD pathogenesis using animal models of menopause and AD. This systematic analysis will not only address the importance of hormonal action in cognition but will also begin to dissect the individual contributions of estrogen and LH and how these aspects are affected by the post-menopausal timing of HRT.

**C 09**

**Neuroprotective Therapy Strategies After Stroke: Drug Delivery, Estrogen and VEGF**

Ertuğrul Kılıç

Yeditepe University, Faculty of Medicine, Department of Physiology, İstanbul, Turkey

Neuroprotection therapies have made limited progress in recent years. Several compounds shown to be efficacious in animals were tested in humans in cost-expensive trials. Unfortunately none of these studies were able to demonstrate efficacy under clinical conditions in patients. In order to establish treatments that are of benefit not only in animals but also humans, new strategies are clearly needed, comprising (i) new factors mimicking intrinsic mechanisms that the brain itself makes use of, (ii) novel delivery techniques allowing drugs to pass the blood-brain barrier more efficaciously than before, (iii) better, functionally relevant readouts of brain recovery and (iv) strategies that are of usefulness not only in the acute, but also post-acute stroke phase. In this presentation, our recent studies will be reviewed.

**C 10**

**Physiopathology and Clinical Evaluation of Endometriosis**

Erkut Attar

Istanbul University, School of Medicine, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Istanbul, Turkey

Endometriosis was known for almost 300 years. In the late 17<sup>th</sup> century it was recognised as peritoneal ulcers in the abdomen. Its association between pelvic pain, tissue damage and scarring was recognized in 18<sup>th</sup> century by Rokitsansky (1). With the improvements in microscopy, Sampson first described the disease formally in 1921. In the last century various theories were proposed to explain the pathogenesis of endometriosis. Despite the extensive investigation of disease, the pathogenesis of this enigmatic disease is still poorly understood and remains controversial. Classical theories for the pathogenesis of endometriosis can be divided into three main concepts: 1) coelomic metaplasia (in situ development), 2) the induction theory, 3) the transplantation or implantation theory. These theories have been met with considerable opposition over the years and largely abandoned. Sampson proposed the hypothesis that the origin of peritoneal endometrial implants was tissue delivered by the retrograde menstruation. Current clinical observations and research on endometriosis revealed a new concept on the pathogenesis of the disease. In endometriosis, at least three different forms must be defined. It is seems that peritoneal, ovarian and recto-vaginal endometriosis are different forms of the disease. Therefore, with the current knowledge and understanding of the disease, pathogenesis of endometriosis can be explained by a combination of possible causes rather than a certain theory. Research on the pathogenesis of endometriosis currently interfaces with five areas of basic research: 1) Hormonal factors and steroidogenesis, 2) Genetics, 3) Environmental Science, 4) Immunology, 5) Cancer Biology. Investigations about the role of genetics, environment, immune system, and estradiol in the pathogenesis of this disorder, as well as postgenomic study of intrinsic abnormalities in eutopic (ie, within the uterus) and ectopic (ie, endometriotic lesions) endometrium in women with the disease are providing insights into the pathophysiology and treatment of endometriosis associated pain and infertility.

**C 11**

**Animal Models in Endometriosis Research**

Narter Yeşildağlar

Yeditepe University, Faculty of Medicine, Department of Obstetrics and Gynecology,  
Istanbul, Turkey

Endometriosis is a common gynecological disease, defined as the presence of endometrial tissue outside the uterus, causing pelvic pain and sub-fertility in ~10% of women of reproductive age. Current therapies lead to pain relief, however, do not address the causes and entail severe side effects. Still little is known about the pathogenic processes leading to the development and maintenance of endometriosis. Because endometriosis occurs spontaneously only in humans and some non-human primates, animal models of induced endometriosis have been developed and are of high value for the evaluation of pathophysiological mechanisms underlying the development of this disease. These experimental models include the autotransplantation of uterine fragments into the peritoneal cavity of rodents and non-human primates or the hetero-transplantation of human endometrial or endometriotic tissue to immunodeficient mice. This presentation describes the animal models for endometriosis and assesses their different potentials and limitations in regard to endometriosis research, with the aim of improved strategies for the treatment of endometriosis in women.

# **ORAL COMMUNICATIONS**

## OC 01

### **Chronic Leptin Infusion Advances Puberty Onset in Sham and Pinealectomized Normally Fed Female Rats**

Haluk Keleştimur<sup>1</sup>, Bayram Yılmaz<sup>2</sup>, Ahmet Ayar<sup>3</sup>, Ertuğrul Kılıç<sup>2</sup>, Mete Özcan<sup>4</sup>, Ergül Alçin<sup>1</sup>, Ülkan Kılıç<sup>2</sup>, Ramis Çolak<sup>5</sup>

<sup>1</sup>Firat University, Faculty of Medicine, Department of Physiology, Elazığ,

<sup>2</sup>Yeditepe University, Faculty of Medicine, Departments of Physiology and Medical Biology, İstanbul

<sup>3</sup>Karadeniz Technical University, Faculty of Medicine, Department of Physiology, Trabzon  
Firat University, Faculty of Medicine, Departments of Biophysics<sup>4</sup> and Endocrinology and Metabolism<sup>5</sup>, Elazığ, Turkey

It is proposed that leptin provides information to the brain that there are enough energy stores for reproductive functions, and may be a major determinant or only a permissive factor of the timing of puberty. It is suggested that centrally infused leptin advances puberty onset in normally fed female rats while peripherally infused leptin accelerates puberty onset in only feed restricted rats. In several reports investigating the effect of leptin on puberty onset, leptin administration was started after weaning. However, it is also suggested that pre-weaning leptin infusion may programme adult energy metabolism. Therefore, we investigated whether chronic peripheral administration of leptin to immature female rats, beginning before weaning, affects also pubertal maturation. There is evidence that the pineal gland may be also involved in puberty onset because melatonin secretion declines near puberty. Thus, it was also checked whether there was an interaction between leptin and melatonin in timing of puberty onset. Prepubertal female rats were chronically infused with leptin, by using osmotic pump implanted subcutaneously on day 15. The rats were weaned on day 21 and surgically pinealectomized. Puberty onset was monitored by examination of vaginal opening (VO). Leptin (1µg/day) advanced VO in sham-operated (SHAM) and pinealectomized (PNX) rats compared to sham-vehicle rats ((29 and 30 days versus 33 days, respectively). Pubertal weight was also much lower in leptin-treated SHAM and PNX rats compared with sham-vehicle ones, being 63,9 ± 3,5 g and 61,1 ± 2,1 g versus 82,5 ± 4,1 g, respectively. Pinealectomy did not significantly alter the effect of leptin on pubertal age and weight. We conclude that peripheral leptin can advance puberty onset in normally fed rats if it is administered before weaning in immature female rats.

Acknowledgement: This study was supported by TUBITAK project # 107T825.

OC 02

**Leptin and Ghrelin Differentially Modulate Noradrenaline Release in the Paraventricular Nucleus and Plasma Oxytocin Levels in Female Rats: A Microdialysis Study**

Selim Kutlu<sup>1</sup>, Mehmet Aydın<sup>1</sup>, Ergül Alçın<sup>1</sup>, Mete Özcan<sup>2</sup>, Jan Bakos<sup>3</sup>, Daniela Jezova<sup>3</sup>, Bayram Yılmaz<sup>4</sup>

Firat University, Faculty of Medicine, Departments of Physiology<sup>1</sup> and Biophysics<sup>2</sup>, Elazig, Turkey; <sup>3</sup>Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia; <sup>4</sup>Yeditepe University, Faculty of Medicine, Department of Physiology, Istanbul, Turkey.

The neural control and mutual interrelationships among individual factors involved in the regulation of food intake and simultaneously related to reproduction are far from being understood. We have suggested that at least some of the effects of orexigenic and anorexigenic peptides might be mediated via noradrenaline release in the paraventricular nucleus (PVN). The main hypothesis was that leptin has an inhibitory while ghrelin a stimulatory action on oxytocin secretion and hypothalamic release of noradrenaline. Non-pregnant female rats in their diestrus were subjected to cannulation of the carotid artery and a microdialysis procedure with the probes in the hypothalamic PVN. Peripheral administration of cholecystokinin-8 (CCK) was used to induce oxytocin and noradrenaline release. CCK plus leptin (10µg/5µl) and ghrelin alone (1µg/5µl) were injected intracerebroventricularly. Blood and microdialysis samples were collected at 20 min intervals for 80 min. In the second interval (20-40 min), NA content of PVN was significantly elevated in the CCK group ( $p<0.001$ ). Leptin decreased this CCK-induced rise in NA content for second and third intervals respectively ( $p<0.001$ ,  $p<0.01$ ). CCK increased oxytocin levels in second and third samples ( $p<0.05$ ). Treatment with ghrelin induced a mild increase in plasma oxytocin levels at 60 min ( $p<0.05$ ) but it failed to alter noradrenaline concentrations in microdialysis samples collected from the PVN. In conclusion, leptin may inhibit oxytocin secretion by lowering noradrenergic neurotransmission in the PVN. The modulator effect of leptin on noradrenaline release in the PVN may be related to feeding behavior. As for ghrelin, we have shown that it may stimulate oxytocin secretion without affecting noradrenaline concentrations in the PVN.

**OC 03**

**Metabolically-Induced Paradoxical Cell Cycle Activities in Astrocyte and Neuron Linked to Neurodegeneration**

Adnan Erol

Namık Kemal University, Faculty of Medicine, Department of Internal Medicine, Tekirdağ - Turkey

Progression and outcome of neurological diseases are determined by the balance between destruction, neuroprotection and regeneration. In this context, astroglial cells are invariably involved in every kind of neuropathology. Mitotically active astrocytes provide metabolic support to active neurons, contribute to coupling between synaptic activity and local blood flow, protect against oxidative stress. Disturbances of the complex neuron –astrocyte interrelation are recognized increasingly as potentially important pathophysiological mechanism in a wide of neurological disorders including neurodegeneration. Peripheral insulin resistance related increased oxidative stress in astrocytes reason in DNA damage response induced senescence in astrocytes. Senescence-associated secretory phenotype developed in astroglial cells causes the development of an inflammatory tissue milieu. The immune mediators released by senescent (activated) astroglial cells are considered to be neurotoxic, increasing oxidant loads of neuron. The neuron is the prototypical post-mitotic, fully differentiated and nonreplicating to its death. Some subsets of neurons, however, are known to reactivate cell-cycle activity in response to certain triggers of neuronal apoptosis including genotoxic stress generated by redox changes due to pathological alterations in supporting astroglial cells. Thus, paradoxical cell cycle block in astrocyte and re-entry in neurons due to cellular redox alterations created by peripheral insulin resistance-induced neuroendocrine signaling changes may cause neurodegeneration, including Alzheimer's disease.

# **WORKSHOPS**

## W 1 (A)

### Non-human Primate Models of Human Reproduction: Advantages and Disadvantages

Tony M. Plant

University of Pittsburgh, School of Medicine, Pittsburgh, USA.

The rhesus and cynomolgus monkey (*Macaca mulatta* and *fasicularis*, respectively) are commonly used non-human primates in research on reproduction. These macaque are Old World primates with extensive development of the neocortex and neocortical mechanisms and provide ideal models to examine many aspects of human reproduction. Puberty in the monkey, as in man, is initiated after a protracted phase of juvenile development. Similarly, the female monkey exhibits a menstrual cycle with a duration of 28 days on average, and in the male monkey the cell biology and endocrine control of spermatogenesis resembles that in man. On the other hand, non-human primates provide special challenges to the investigator: they are extremely expensive to obtain and maintain, they are difficult to handle and in most countries their use in biomedical research is governed by extensive governmental regulations. In this talk, emphasis will be placed on the value of the monkey in studies of the control of ovarian and testicular function in the adult.

## W 1 (B)

### Models of Stress and Reproductive Dysfunction

Kevin T O'Byrne

King's College London, Division of Reproduction & Endocrinology, London, UK

Many strategies have been used to monitor GnRH pulse generator activity *in vivo*, including the detection of LH pulses in the peripheral blood, the measurement of pulsatile GnRH in pituitary portal blood, in cerebrospinal fluid and in hypothalamic extracellular fluid sampled by microperfusion, and the monitoring of its electrophysiological manifestation pioneered by Knobil. *In vitro* strategies are equally impressive, including recordings of electrical activity or calcium oscillations from single GFP-identified GnRH neurones in situ in brain slices or cultured GnRH neurones, and the measurement of pulsatile GnRH from primary GnRH neuronal cell cultures or immortalised GnRH cell lines, such as the GT1-7 cells. Collectively these models span a wide range of species from mice to Old World primates.

To examine the neural mechanism underlying stress-induced suppression of the reproductive neuroendocrine axis, all of the above strategies to monitor GnRH pulse generator activity are available. The nature of the stressors available is equally diverse; some of which the animal rapidly habituate to (e.g. restraint) whilst others show no evidence of habituation (e.g. insulin-induced hypoglycaemia). Activation of stressor specific neurocircuitry or stressor specific neurochemical phenotypes and cognate receptors adds to the complexity. Further, the use of telemetric monitoring of blood pressure and heart rate, for example, gives a dramatic realisation of the hitherto occult nature of the impact of our manipulation on the physiological stress response. There is also increasing appreciation or realisation that subthreshold stressors, which alone have little or no impact on the GnRH pulse generator, summate or synergise to significantly compromise normal reproductive function. Moreover, individuals vary substantially in their vulnerability to stressors and although the underlying mechanisms are poorly understood genetic factors, polymorphisms and early life events play their part.

## W 1 (C)

### Cellular Models for GnRH Neurobiology and Neuropathic Pain

Ahmet AYAR

Karadeniz Technical University, Faculty of Medicine, Department of Physiology, Trabzon-Turkey

Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and transported through the portal system to the anterior pituitary gland where it controls secretion of gonadotropic hormones which regulates reproductive functions, behavior and some other physiological functions. Study of neurobiology of these hypothalamic neuroendocrine cells is somewhat difficult in *in vivo* systems and exact mechanism(s) by which GnRH secretion is modulated remain to be fully elucidated. Possibility of easy manipulations (not feasible for *in vivo* systems) is advantageous for cellular models to be employed in neuroendocrine research where one would wish to study the regulatory mechanism of a cell by multiple stimulatory and inhibitory factors. GT1-7 neuronal cells are well-characterized cell line as a model for GnRH-secretion. Cultures of these hypothalamic neurons are prepared and used for calcium imaging experiments in our laboratory.

Cultured rat dorsal root ganglion (DRG) neurons functionally express a variety of ion channels and receptors for several agents including those involved in pain transmission, they have been successfully used as an *in vitro* model for studying cellular mechanisms of nociception including diabetic neuropathy. Calcium is a ubiquitous second messenger mediating broad range of cellular functions including gene expression, muscle contraction, neurotransmitter release and modulation of pain. Our recent research design employs ratiometric fluorescence calcium imaging to study the effects of various novel pharmacological agents and hypothalamic peptides like orexin A and B in *in vitro* cellular models for GnRH secretion and diabetic neuropathic pain.

## W 2 (A) & (B)

### A) Detection of aneuploidy and telomeres in prostate cancer cell lines by conventional cytogenetics

### B) Determination of stem cell markers in prostate cancer cells by real time PCR assays

Sen Pathak<sup>1</sup> and Mustafa Özen<sup>2</sup>

<sup>1</sup>Department of Genetics UT MD Anderson Cancer Center, Houston, TX, USA and

<sup>2</sup>Department of Medical Genetics Yeditepe University Medical School, Istanbul, Turkey.

Cancer cells are known to have chromosomal alterations. In order to detect these alterations, chromosomal preparations will be made on the most commonly used prostate cancer cell lines, DU145, PC3, LAPC4, LNCaP and an immortalized prostate cell line PNT1a. After G-banding, these chromosomal preparations will be evaluated and a karyotype will be made for each cell line and compared to a karyotype of a normal cell.

In the second part of this workshop, RNA will be isolated from the prostate cancer cell lines mentioned above. After cDNA synthesis, a real time RT-PCR analysis will be carried out to determine the expression levels of stem cell markers including *klf4*, *nanog*, *nestin*, *oct4*, *cd90*, *cd24* and *cd133*. Expression levels of these genes will be compared to normal cells.

After completing this workshop an attendee should be able to differentiate prostate cancer cell from a normal cell by chromosome analysis. s/he should also be able to determine prostate cancer stem cells by analyzing gene expression levels of selected stem cell markers.

### **W 3**

#### **Animal Models of Alzheimer's Disease: Challenges and Considerations**

Gemma Casadesus<sup>1</sup>, Mark A Smith<sup>2</sup>, Kathryn Bryan<sup>1</sup>, Jennifer Reeves<sup>1</sup>, Joseph Mudd<sup>1</sup>,  
Xiongwei Zhu<sup>2</sup> and Hyoung-gon Lee<sup>2</sup>

Departments of Neurosciences and Pathology, Case Western Reserve University, Cleveland, Ohio, USA

Transgenic mouse models allow us to examine the mechanisms involved in the development of diseases such as Alzheimer's disease, one of the best studied diseases with the largest number of available transgenic models. However, because of the large discrepancy in the behavioral findings and its chronology with respect to the appearance of pathological entities such as amyloid- $\beta$  and tau hyper-phosphorylation amongst these models, a simple question that arises is whether animal models that are based on the over-expression of human pathological mutations will bring us closer to elucidating the mechanisms associated with this disease. While seemingly obvious, it is important to remember that the validity of a mouse model of disease is tightly linked to the ability of the animal to mimic the signs of the disease - in the case of AD - cognitive decline, pathology and neurodegeneration. The aim of this workshop is to critically evaluate the validity of AD models and discuss the advantages and challenges associated with using these models to study AD.

**W 4**

**Characterization of Somatostatin Receptors in Neuroendocrine Tumors**

Leo J. Hofland

Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center,  
Rotterdam, The Netherlands

Since the cloning and characterization of the five human somatostatin (SS) receptor subtypes (sst), our understanding of the expression and functional significance of sst subtypes in human (neuro-)endocrine tumors has increased significantly. The majority of (neuro-)endocrine tumors express multiple sst subtypes. The characterization of sst in human neuroendocrine tumors has important clinical consequences. Sst expressed on growth hormone secreting pituitary adenomas and gastroenteropancreatic neuroendocrine tumors (GEP-NET) form the molecular basis for treatment with SS analogs (SSA) to control hormonal hypersecretion syndromes. In GEP-NET, sst expressed on the tumor cell surface are also used to specifically target the tumors with radiolabeled SSA, thereby enabling the *in vivo* localization of tumors and their distant metastases by gamma camera scintigraphy (Octreoscan). Moreover, sst targeted radionuclide therapy with radiolabeled SSA has shown promising results in GEP-NET. Recently, novel SSAs have been developed with sst subtype binding profiles that are different from the currently clinically used sst<sub>2</sub>-preferring SSAs octreotide and lanreotide. Therefore, a detailed knowledge of the sst subtypes that are expressed in tumors may have significant impact on the possibilities to treat patients harboring these tumors. In this workshop different methods for the characterization and quantification of sst in human tumors at the mRNA and protein level will be discussed, including their specific advantages and limitations. Finally, some functional aspects of sst subtypes that may influence the efficacy of SSAs on tumor cells will be addressed.

## **W 5**

### **Neurobehavioral and Psychiatric Disorder Models Workshop**

Eva Redei<sup>1</sup> & Ertuğrul Kılıç<sup>2</sup>

<sup>1</sup>Northwestern University, Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, Chicago, IL, USA

<sup>2</sup>Yeditepe University, Faculty of Medicine, Department of Physiology, İstanbul, Turkey

In the first part of this workshop, the definition of a good animal model, particularly genetic animal models will be introduced. Behaviors, such as defensive burying, forced swim test and elevated plus maze test and their interpretation in affective disorder models will be reviewed and discussed with the participants. Brief information about microarray experiments, their design, data mining and confirmation will also be covered.

In the second part of the workshop, open field test, grip strength test, rota rod test, dark-light test, elevated O maze and hemi-neglect tests will be introduced. Their use in various experiments, especially in stroke, will be reviewed and discussed with the participants.

## **W 6**

### **Experimental Models for Endometriosis**

Erkut Attar<sup>1</sup> & Narter Yeşildağlar<sup>2</sup>

<sup>1</sup>Istanbul University, School of Medicine, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, İstanbul, Turkey

<sup>2</sup>Yeditepe University, Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey

Please refer to the abstracts presented as Conferences 10 & 11.

# **POSTER COMMUNICATIONS**

**PC 1**

**Influences of Hypertonic and Hypovolemic Treatments on Vasopressin Response in Propylthiouracil (PTU) -Induced Hypothyroid Rat and Effects of Supplementation with L-Thyroxine**

Aydın L, Moğulkoç R, Baltacı AK

Department of Physiology, Meram Medical School, Selçuk University, Konya- Turkey

Regulations of fluid-electrolyte balance are very complex. Arginine vasopressin (AVP), angiotensin II, natriuretic peptides, vasoactive intestinal peptide, urotensin II and corticosteroid have roles in the control of water and maintaining salt balance. This study was performed to investigate the effects of L-thyroxine treatment on plasma vasopressin (AVP) levels in rats with hypothyroidism induced by propylthiouracil (PTU). Animals were separated into three groups each having 6 rats: control, PTU, PTU+L-thyroxine groups. Then, the groups were further divided into 3 sub-groups including 6 rats (a; basal, b; hypertonic stimulated and c; hypovolemic stimulated). At the end of the experiments all rats were decapitated in order to obtain plasma samples for analysis in terms of Hct, osmolality,  $TT_3$ ,  $TT_4$  and vasopressin. Haematocrit (Hct) levels were the highest in hypovolemic stimulated sub-group ( $P<0.001$ ). Osmolality levels were higher in hypertonic stimulated sub-groups ( $P<0.001$ ). Total  $T_3$  and  $T_4$  values were the lowest in the PTU group and the highest in the L-thyroxine treated group ( $P<0.001$ ). Plasma AVP levels were reduced by hypothyroidism. However, L-thyroxine treatment after the hypothyroidism prevented this reduction ( $P<0.001$ ). Vasopressin responses to basal, hypovolemic and hypertonic stimulations were the lowest in the PTU group ( $P<0.001$ ). The results of the present study show that basal and stimulated plasma vasopressin levels are reduced in PTU-induced hypothyroidism. However, L-thyroxine treatment following hypothyroidism prevents this reduction.

**PC 2**

**Effect of Melatonin Supplementation on Plasma Vasopressin Response to Different Conditions in Rats with Hyperthyroidism Induced by L-Thyroxine**

Moğulkoç R & Baltacı AK

Department of Physiology, Meram Medical School, Selçuk University, Konya - Turkey

The present study was performed to determine how basal, isotonic, hypertonic and hypovolemic treatments affect fluid-electrolyte balance and plasma (arginine vasopressin) AVP levels in rats with hyperthyroidism and hyperthyroidism plus melatonin supplementation. The animals were initially separated into 4 groups: 1-control, 2- L-thyroxine treatment, 3- L-thyroxine treatment + sham-melatonin, 4- L-thyroxine treatment + melatonin. L-thyroxine was supplemented for 4 weeks. At the end of week 4 each group was further divided into four sub-groups as unstimulated/basal, isotonic, hypertonic and hypovolemic stimulations. Plasma AVP, total triiodothyronine (TT<sub>3</sub>), total thyroxine (TT<sub>4</sub>) and melatonin levels were measured in plasma by Phoenix Pharmaceutical RIA test kit. Hematocrit and osmolalities levels were determined. It was found that total T<sub>3</sub> and T<sub>4</sub> levels showed significant increases in L-thyroxine treatment groups (P<0.001). Plasma melatonin levels increased in L-thyroxine plus melatonin supplemented group (P<0.001). It was seen that plasma AVP levels increased in L-thyroxine treatment groups (groups 2 and 3). However, this increase was reduced by melatonin supplementation (P<0.001). The results of the present study indicate that L-thyroxine treatment increases unstimulated and stimulated AVP release. However, increased AVP release was inhibited by melatonin supplementation. Secondly, AVP response to hypertonic and hypovolemic stimulations are not affected by L-thyroxine treatment and/or L-thyroxine +melatonin treatment.

**PC 3**

**Effect of Testosterone Supplementation on Leptin Release in Rats which Underwent Castration and Unilateral Surrenalectomy**

Kul A, Baltacı AK, Moğulkoç R

Selcuk University Meram Medical School Department of Physiology, Konya - Turkey

The objective of this study is to examine the effect of testosterone supplementation on leptin release in rats which underwent castration and unilateral surrenalectomy. Wistar Albino rats, which were equally divided into eight groups: Group 1, Control. Group 2, Testosterone. Group 3, Castration. Group 4, Surrenalectomy, Group 5, Castration-Surrenalectomy. Group 6, Castration-Testosterone. Group 7, Surrenalectomy-Testosterone. Group 8, Castration-Surrenalectomy-Testosterone. The animals in Groups 2, 6, 7 and 8 were administered 5 mg/kg/day intramuscular testosterone propionate for 4 weeks. Plasma leptin, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and free and total testosterone levels were determined. Groups 3 and 5 had higher leptin and LH levels than all other groups ( $p<0.01$ ). Leptin and LH levels in groups 1 and 4 were higher than those in Groups 2, 6, 7 and 8 ( $p<0.01$ ). Plasma FSH levels significantly higher in groups 3 and 5, than in the other groups ( $p<0.01$ ). FSH levels in Groups 1 and 4 were lower than those in all other groups ( $p<0.01$ ). The highest free and total testosterone levels were obtained in Groups 2, 6, 7 and 8 ( $p<0.01$ ). Free and total testosterone levels in Groups 1 and 4 were higher than those in groups 3 and 5 ( $p<0.01$ ). The results of this study demonstrate that unilateral surrenalectomy in rats does not have a significant effect on leptin release, while plasma LH levels, rather than testosterone, may be more effective on plasma leptin.

**PC 4**

**Pinealectomy Inhibits Antioxidant System in Rats with Hyperthyroidism**

Moğulkoç R, Baltacı AK, Aydın L, Öztekin E and Sivrikaya A

Department of Physiology, Meram Medical School, Selcuk University, Konya - Turkey

Thyroid hormones regulate energy metabolism and act on the mitochondria, which is an important source of free radicals in the cell. Reactive oxygen types play a significant role in physiological mechanisms, but in excessive amounts they can cause oxidative damage in molecules. The aim of the present study was to determine levels of lipid peroxidation caused by induced hyperthyroidism in cerebral, hepatic and cardiac tissues of pinealectomized rats. Experimental animals used in the study were allocated to three groups as general control group, hyperthyroidism-sham pinealectomy group and hyperthyroidism-pinealectomy group. GSH and MDA levels in cerebral, hepatic and cardiac tissues were evaluated at the end of the 3-week study period. It was found that MDA levels in cerebral, hepatic and cardiac tissues were the highest in hyperthyroidism and pinealectomy group and that these values were higher in hyperthyroidism-sham pinealectomy group than in the control group ( $p<0.001$ ). It was seen that tissue GSH levels significantly increased in hyperthyroidism-sham pinealectomy group ( $p<0.001$ ) and that the increase in hyperthyroidism and pinealectomy group was higher than the increase in the control group only ( $p<0.001$ ). Results of our study show that MDA and GSH levels in cerebral, hepatic and cardiac tissues increased due to hyperthyroidism and that the increase in MDA levels became more evident and GSH levels were significantly suppressed after pinealectomy.

PC 5

**Post-Injury Administration of Erythropoietin Promotes Neuronal Survival and Motor Recovery After Mild Focal Cerebral Ischemia in Mice**

Ülkan Kılıç<sup>1</sup>, Max Gassmann<sup>2</sup> and Ertuğrul Kılıç<sup>3</sup>

Yeditepe University, Faculty of Medicine, Departments of Medical Biology<sup>1</sup> and Physiology<sup>3</sup>,  
Istanbul – Turkey

<sup>2</sup>Zurich University, Vetsuisse Faculty, Institute of Veterinary Physiology, Switzerland

Erythropoietin (EPO), a hematopoietic growth-factor, is produced by the kidney in response to hypoxia. EPO exerts its actions via EPO receptors (EPO-R) which are members of the cytokine type 1 receptor subfamily. Diverse cell types have been demonstrated to produce EPO and many cells express the EPO-R, including the neurons. Besides its hematopoietic function, EPO exerts neuroprotective activity upon reduced oxygenation or ischemia of brain, retina, and spinal cord. We have recently evaluated neuroprotective effects of EPO after focal cerebral ischemia and optic nerve axotomy in mice. In this study our aim is to assess post-acute effects of EPO on brain plasticity and functional behavioural recovery. Adult male C57Bl6/j mice weighing 23-25 g were submitted to transient focal cerebral ischemia and were treated either with vehicle, 1 or 10 U/ day EPO starting 3 days after ischemia. Focal cerebral ischemia was induced using an intraluminal filament technique. Vehicle or EPO were administrated intracerebroventricularly by using a mini-osmotic pump (Alzet, 2004/ 0.25 µl/ hr for 4 weeks). Six weeks after transient MCA occlusion, animals were deeply anesthetized (1 % halothane) and decapitated. Brains were removed and frozen on dry ice. Brain sections were used for NeuN, CD31 and Iba1 immunohistochemistry. For assessment of functional neurologic deficits, grip strength, RotaRod, and Elevated 0 Maze tests were used prior to stroke as well as at defined time points thereafter.

To investigate EPO's effects on neuronal survival, NeuN stainings, that identifies neuron-specific nuclear protein in most neuronal cell types, were analyzed. Thirty minutes of MCA occlusion resulted in disseminated neuronal injury in the striatum, but not in the overlying cortex. Interestingly, the number of surviving neurons in the striatum, assessed by NeuN, was significantly higher in animals treated with high EPO dose than in low dose EPO or vehicle-treated animals, indicating that high doses of EPO exerted structural rescue effects even when applied 72-hr after injury. To evaluate capillary density in the ischemic brain, CD31 expression was also examined by immunohistochemistry. CD31 stainings revealed that EPO stimulated angiogenesis in the ischemic striatum. No significant angiogenesis was observed in cortex and corpus callosum. To determine EPO's influence on brain activation of microglia, immunohistochemistry for the specific Iba1 marker was performed. EPO-treatment increased the density of Iba1-positive ramified microglia in the ischemic tissue. To elucidate how EPO influences motor recovery, grip strength, and RotaRod tests were evaluated. Grip strength tests performed at 7 or 14 days after stroke revealed a mild paresis

of the right forelimb that was associated with coordination deficits in RotaRod tests. High doses of EPO significantly enhanced the animals' motor performances as compared with low dose or non-treated animals 42 days after reperfusion. However, it has no effect on anxiety of ischemic mice. Besides neuroprotective effects of EPO, we have also evaluated the effects of EPO on functional recovery after stroke. Our study provides evidence that EPO induces functionally relevant neurologic improvements in mice suffering from stroke. Furthermore EPO exerted a delayed neuroprotective action and also stimulated angiogenesis. In view of the fact that EPO is a well known drug with little to no side effects future studies in patients to evaluate time windows and dose–response relationships of EPO are obvious.

**PC 6**

**Effect of High Fat Intake on Behavior and Monoamine Metabolite Levels  
in Striatum and Cortex of Rats exposed to Stress**

Deniz Kıracı<sup>1</sup>, İnci Özden<sup>1</sup>, Alper Yıldırım<sup>2</sup> and Ece Genç<sup>3</sup>

Yeditepe University, Faculty of Medicine, Departments of Biochemistry<sup>1</sup>, Anatomy<sup>2</sup> and  
Pharmacology<sup>3</sup>, İstanbul - Turkey

Brain monoaminergic systems in behavioral and neurochemical stress responses and effect of high fat diets on these have been extensively researched (1,2,3,4). In the present study we investigated whether high fat consumption changes the effects of stress on both motor activity performance, striatal and cortical dopamine and serotonin metabolites in rats. Male Wistar rats weighing 180-250 g were used and divided into four groups: Control (C), Stress (S), Lipid (L) and Stress + Lipid (S+L). C and S groups received 25 g of standard feeding pellets; and L and S+L groups received 25 g of high fat containing pellets daily for 4 weeks. Restraint stress lasting for 15 minutes at +4° C was applied daily to stress exposed groups. By using motor activity monitoring systems, locomotor activity performance was weekly measured. At the end of the study, animals were sacrificed; Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) levels of the striatum and cerebral cortex were measured by using High Performance Liquid Chromatography with Electrochemical Detector (HPLC-EC). The study showed that stress application increased locomotor activity and high fat diet prevented this effect. Stress and high fat intake had an additive decreasing effect on striatal HVA levels. 5-HIAA levels, on the other hand, were lower in both high fat and high fat + stress groups compared to the stress group. These results suggested that high fat intake differentially affected the stress response on striatal dopaminergic and serotonergic neurons in rat brain and this may be related to the effects observed in locomotor activity performance.

References:

1. Buwalda B et al. Behavioral and physiological responses to stress are effected by high-fat feeding in male rats. *Physiol Behav* 2001; 73: 371-377.
2. Del Arco A et al. Stress, prefrontal cortex and environmental enrichment: Studies on dopamine and acetylcholine release and working memory performance in rats. *Behav Brain Res* 2007; 176: 267-273.
3. Kamara K et al. High-fat diets and stress responsivity. *Physiol Behav* 1998; 64: 1-6.
4. Prasad A & Prasad C. Short-term consumption of a diet rich in fat decreases anxiety response in adult male rats. *Physiol Behav* 1996; 60: 1039-1042.

## AUTHOR INDEX

ALÇİN, E.	OC 01 , OC 02
ATTAR, E.	C 10, W 6
AYAR, A.	OC 01, W 1C
AYDIN, L.	PC 1, PC 2, PC 3, PC 4
AYDIN, M.	OC 02
BAKOS, J.	OC 02
BALTACI, AK	PC 1, PC 2, PC 3, PC 4
BRYAN, K.	C 08, W 3
CASADESUS, G.	C 08, W 3
ÇOLAK, R.	OC 01
EROL, A.	OC 03
GASSMANN, M.	PC 5
GENÇ, E.	PC 6
HOFLAND, L.J.	C 05, W 4
JEZOVA, D.	OC 02
KELEŞTİMUR, H.	OC 01
KILIÇ, E.	C 09, OC 01, W 5, PC 5
KILIÇ, Ü.	PC 5
KILIÇ, Ü.	OC 01
KIRAÇ, D.	PC 6
KUL, A.	PC 3
KUTLU, S.	OC 02
LEE, H.	C 08, W 3
MOĞULKOÇ, R.	PC 1, PC 2, PC 3, PC 4
MUDD, J.	C 08, W 3
O'BYRNE, K.T.	C 02, W 1B
ÖZCAN, M.	OC 01 , OC 02
ÖZDEN, İ.	PC 6
ÖZEN, M.	C 07, W 2A&B
ÖZTEKİN, E.	PC 4
PATHAK, S.	C 06, W 2A&B
PLANT, T.M.	C 01, W 1A
REDEJ, E.	C 04, W 6
REEVES, J.	C 08, W 3
SİVRİKAYA, A.	PC 4
SMİTH, M.A.	C 08, W 3
TOPALOĞLU, A.K.	C 03
YEŞİLDAĞLAR, N.	C 11, W 6
YILDIRIM, A.	PC 6
YILMAZ, B.	OC 01 , OC 02
ZHU, X.	W 3

# NEUROENDOCRINOLOGY SYMPOSIUM & WORKSHOP

## “Experimental Models for Studying Neuroendocrine Disorders”



WITH KIND CONTRIBUTIONS OF



**MedSanTek®**  
LABORATUVAR MALZEMELERİ SAN. VE TİC. LTD. ŞTİ.



RADON LTD. ŞTİ.