Neuro-endocrinology BRIEFINGS

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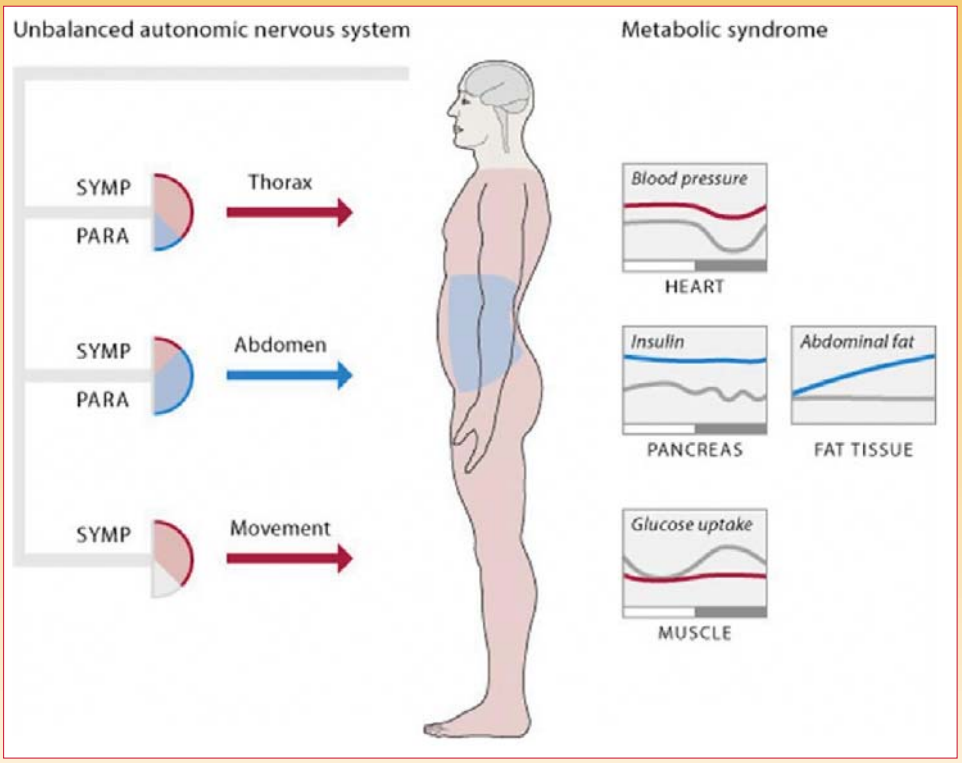
THE METABOLIC SYNDROME: A BRAIN DISEASE?

SUMMARY

The incidence of obesity with, as consequence, a rise in associated diseases such as diabetes, hypertension and dyslipidemia – "the metabolic syndrome" – is reaching epidemic proportions in industrialized countries. Here we provide a hypothesis that the biological clock which normally prepares us each morning for the coming activity period is altered due to a modern life style of low activity during the day and late-night food intake. Furthermore we review the anatomical evidence supporting the proposal that an unbalanced autonomic nervous system output may lead to the simultaneous occurrence of diabetes type 2, dyslipidemia, hypertension and visceral obesity.

The biological clock times us

The background of the mechanisms causing the metabolic syndrome is incompletely understood. In general there is agreement that the cause for this obesity outbreak has to be found in the abundance of food in modern societies and the fact that evolution has shaped us for periods of scarcity rather than surplus. In addition our homeostatic systems shaped by evolution have "learned" to adapt to the ever changing light-dark cycle such that the body anticipates the coming sleep and activity period. In all organisms, mechanisms have been developed that can predict when the day ends or starts; these mechanisms are known as the "circadian system". In all cells of the body,



Lifestyle may result in disturbed output of the biological clock affecting the selective balance of the autonomic nervous system in different parts of the body. In the intra-abdominal compartment, the autonomic nervous system output is shifted in favour of the parasympathetic branch, resulting in high insulin secretion, growth of intra-abdominal fat tissue and fatty liver. In contrast, in the thorax and movement compartment the sympathetic branch prevails, leading to high blood pressure and impaired glucose uptake by the muscle. In this model, the symptoms of the metabolic syndrome are the result and not the cause of the disease.

clocks have evolved that in one way or another can keep track of time, however the brain, and more precisely the ventral hypothalamus at its base, is the location where the only autonomous biological clock, the suprachiasmatic nucleus (SCN), is located. By distributing its message via hormones and the autonomic nervous system, the SCN transmits its daily signal to all tissues of the body. By these signals the homeostatic mechanisms of the tissues are prepared for activity or sleep. This additional bequest of evolution has developed to allow us to predict changes in our environment that would be favourable for activity or sleep. The advantage of such prediction is that our body can anticipate these changes and store or free-up metabolites for fuel consumption necessary for the hard labour of the day.

An environmental "mutation"?

During the last century, life has changed dramatically in industrialized countries. Food has become abundant, snacking frequency increased and feeding has shifted towards the end of the day; simultaneously, the necessity for physical effort has become considerably reduced. Moreover, physical activity does not need to coincide with the light period anymore. We hypothesize that in such conditions the susceptible brain loses its "feeling" for internal and external rhythm. As a result, the environment sensed by the brain has become metabolically flattened and arrhythmic. From the perspective of longstanding evolutionary development, this can be seen as an abrupt environmental "mutation". Since the brain uses the autonomic nervous system to implement the internal rhythmicity we propose an unbalanced and arrhythmic autonomic nervous system as a major cause of the metabolic syndrome.

". . . the susceptible brain loses its 'feeling' for internal and external rhythm"

The balance of life

The basis for this proposal stems from the organization of the output of the SCN via the autonomic nervous system. Although the SCN, via the output of hypothalamus, translates its rhythm onto the body by means of pituitary hormones, only recently have we started to appreciate the contribution of the autonomic nervous system. Obviously the advantage of the autonomic nervous system is that delivery of the message of the SCN can be achieved with much more spatial resolution.

Fat tissue was for a long time assumed to be targeted by hormones or to be innervated by the sympathetic nervous system only. We recently demonstrated that parasympathetic input from the vagal motor nucleus to fat tissue clearly modulates its insulin sensitivity and glucose and fat metabolism in an anabolic way. This allows the brain to stimulate either the burning of fat (sympathetic) or the accumulation of fat (parasympathetic). Moreover, we demonstrated that in the brain an astonishing capacity exists with respect to the specialization of neurons in the hypothalamus and SCN. For example preautonomic neurons are present in the SCN and other hypothalamic areas that project either to the intra-abdominal or the subcutaneous body compartment. The significance of this is that the intra-abdominal organs, such as visceral fat, liver, and pancreas, receive input from the same neurons. Since consuming a meal stimulates the parasympathetic output to the pancreas and results in insulin secretion, the consequence of this hard wiring of the autonomic nervous system is that the same stimulus will increase insulin sensitivity of the liver and also of the visceral fat. Since meals consumed in the evening are known to give an enhanced insulin secretion, a more efficient uptake of glucose in visceral fat will accordingly result in easier accumulation of intra-abdominal fat.

Taken together, we can see that as a consequence of the changed life style in industrialized countries the metabolic syndrome is on the rise, not necessarily through consuming too much food, but by eating it at the wrong time!

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