Hypothesis: Shifting the Equilibrium From Activity to Food Leads to Autonomic Unbalance and the Metabolic Syndrome

Felix Kreier,[1,2,3] Ajda Yilmaz,[1] Andries Kalsbeek,[1] Johannes A. Romijn,[2] Hans P. Sauerwein,[3] Eric Fliers,[3] and Ruud M. Buijs[1]

"*The stability of the internal environment is the condition that life should be free and independent. . . So, far from the higher animal being indifferent to the external world, it is on the contrary in a precise and informed relation with it, in such a way that its equilibrium results from a continuous and delicate compensation, established as by the most sensitive of balances.*"
Claude Bernard (1865)

The incidence of the metabolic syndrome, the most threatening epidemic in industrialized countries, is rapidly rising. Nonetheless, the mechanisms causing visceral obesity and its associated comorbidity of type 2 diabetes, cardiovascular disease, and dyslipidemia are incompletely understood. Extensive endocrine research has identified important players in the metabolic syndrome but has failed to present a unifying hypothesis regarding its pathogenesis.

Evolution created powerful tools to keep our internal environment stable, mainly by forecasting the conditions of the external environment by synchronizing activity and rest to the day/night cycle by means of biological clock mechanisms.

During the last century, life has changed dramatically in industrialized countries. Food has become abundant, snacking frequency increased and shifted toward the end of the day, and simultaneously, the necessity for physical effort became considerably reduced (1–6). Moreover, physical activity does not need to coincide with the light period anymore. As a result, the environment sensed by the brain has become metabolically flattened and arrhythmic. From the perspective of a longstanding evolutionary development, this has been an abrupt "environmental mutation." We hypothesize that in such conditions the susceptible brain loses its feeling for internal and external rhythm. 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 AUTONOMIC NERVOUS SYSTEM AND NEUROENDOCRINE CIRCUITS MAINTAIN HARMONY BETWEEN INTERNAL AND EXTERNAL ENVIRONMENT

To maintain homeostasis, the brain has two avenues of communication: hormones and neurons. Hormones present themselves broadly throughout the body and obtain their specificity by acting on their receptors expressed in specific tissues, whereas neurons deliver their message to a precisely targeted tissue in the body.

This communication network coordinates the transition of the body from the inactive to the active period and vice versa. For instance, in the preparation for an upcoming active period, cortisol and glucose blood levels rise just before awakening, known as the "dawn phenomenon." The autonomic nervous system (ANS) coordinates the "dawn phenomenon," by modulating the adrenocorticotropic hormone sensitivity of the adrenal glands and the glucose output of the liver (7–11). The autonomic nervous system commands the organs through two antagonistic branches: the sympathetic nervous system, predominant in the active period ("fight, fright, and flight"), whereas the parasympathetic nervous system rules the body in the inactive period ("rest and digest"). For instance, in the active period the sympathetic tone to the heart is enhanced, in contrast, in the inactive period the parasympathetic input prevails and heart rate and blood pressure decrease.

Still, the brain needs to translate this general message to different parts of the body in a selective manner. The sympathetic nervous system directs blood to certain parts of the body by selectively constricting blood vessels. With physical activity in the active period, the movement apparatus requires blood, while the digestive apparatus slows down; the opposite holds for the inactive period (12). Thus, blood vessels in these different regions must receive different autonomic signals depending on the time of the day.

A neuroanatomical network for distinct regional control

From the [1]Netherlands Institute for Brain Research, Amsterdam, the Netherlands, the [2]Department of Endocrinology and Metabolism, Academic Medical Center of the University of Amsterdam, Amsterdam, the Netherlands; and the [3]Department of Endocrinology and Metabolism, Leiden University Medical Center, Leiden, the Netherlands.

Address correspondence and reprint requests to Felix Kreier, Meibergdreef 33, 1105 AZ Amsterdam. E-mail: f.kreier@nih.knaw.nl.

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ANS, autonomic nervous system; SCN, suprachiasmatic nucleus.

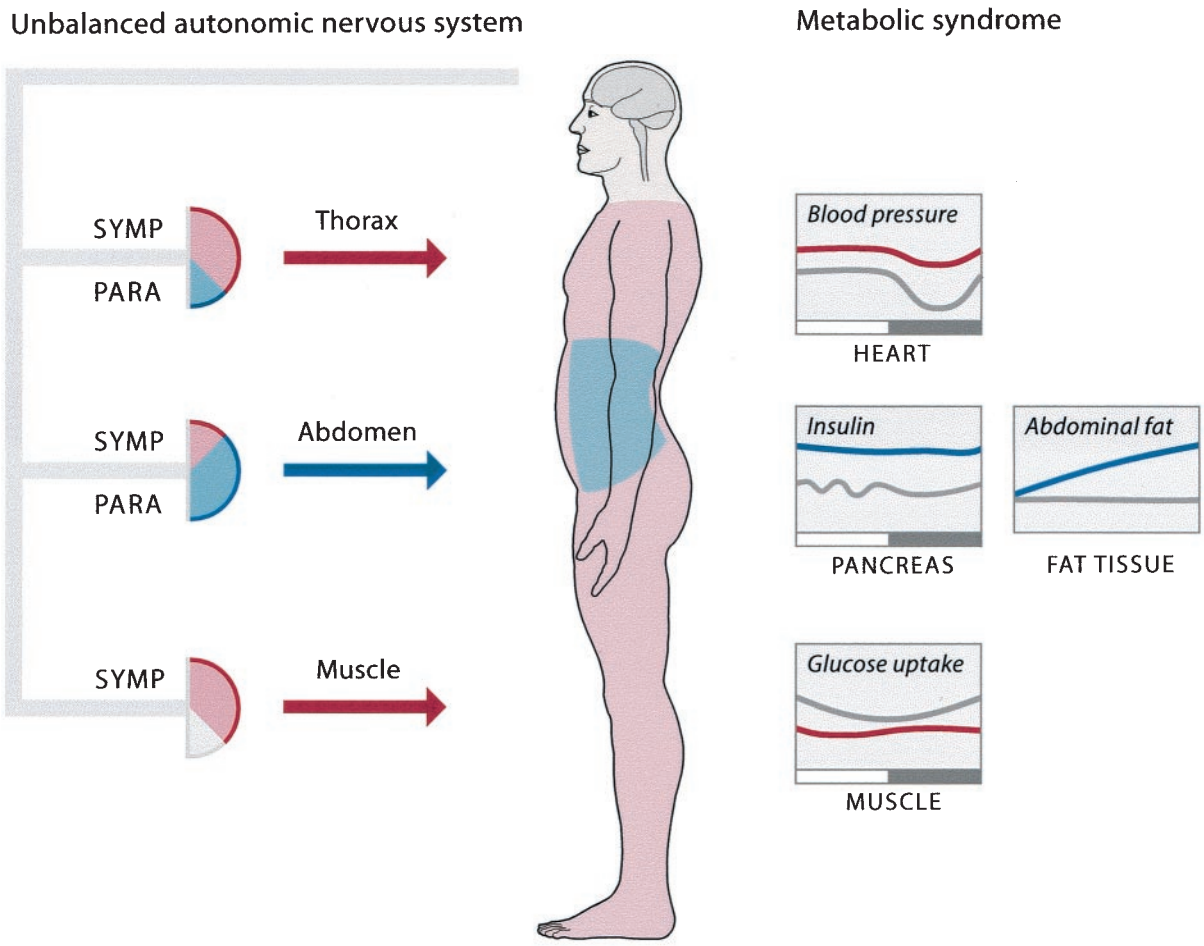

FIG. 1. Model of the metabolic syndrome caused by a central nervous deregulation. The disturbed output of the biological clock effects the selective balance of the ANS in different parts of the body. In the intra-abdominal compartment, the ANS is shifted in favor of the parasympathetic branch (blue), resulting in increased insulin secretion and growth of intra-abdominal fat tissue compared with normal values (grey). Contrarily, in the thorax and movement compartment the sympathetic branch (red) prevails, leading to high blood pressure and impaired glucose uptake by the muscle compared with normal values. In this model, the symptoms of the metabolic syndrome are the result and not the cause of the disease.

has been described recently. Both branches of the ANS were shown to discriminate between different fat compartments throughout the body. Within the motor nuclei of both the sympathetic and the parasympathetic nervous system the intra-abdominal and the subcutaneous fat compartment is represented by specific neurons. This compartmentalization of autonomic motor neurons provides the neuroanatomical basis for selective changes of the sympatho-parasympathetic balance in different compartments of the body (13).

Supported by these anatomical data, we propose that the body can be divided into different functional autonomic compartments and that at least a thoracic and movement compartment and a visceral compartment should exist. In this setting, a balanced and flexible autonomic nervous system can oscillate the activities of the organs within the compartments according to the actual needs of the body.

THE BRAIN ANTICIPATES THE DIURNAL RHYTHM OF THE INTERNAL AND EXTERNAL ENVIRONMENT

The central biological clock in the hypothalamus (suprachiasmatic nucleus [SCN]) uses both this differentiated autonomic network and hormonal signals to generate and organize metabolic rhythms (10,14). The crucial role of the SCN has been demonstrated by lesion studies. Without a functioning SCN, cortisol and glucose do not rise before the beginning of the active period and blood pressure does not dip anymore in the inactive period.

The central clock requires information from the environment to keep running on time. Light information from the eyes reaches directly into the SCN via the retinohypothalamic tract (15). The sensory organs inform the brain about the external environment (16). The state of the internal environment is reported to spinal cord and brain stem through feedback from virtually all organs (16,17). In addition, the brain integrates information about circulating hormone and substrate availability through receptors located in areas where the blood-brain barrier allows this information to be passed to the brain (18–20).

In the active period, the movement compartment uses glucose and free fatty acids. As a reaction, the brain facilitates liberation of energy substrate from storage organs, such as liver and fat tissue. If physical activity is being repeated on a daily basis, the SCN will be programmed to facilitate performance at the entrained time point (10,21,22). In contrast, in the inactive period the brain shifts the body toward an anabolic state of recovery. In summary, information from the internal and external environment sets the central clock to run on time and

prepares the body for the upcoming (inner and outer) tasks.

A METABOLICALLY SHIFTED ENVIRONMENT

We hypothesize that the brain needs repeated metabolic clues from both the external and the internal environment to maintain endogenous physiological rhythms in autonomic output. The western lifestyle is characterized by increased energy intake and decreased energy expenditure; in fact, evolution prepared us to use this anabolic state very efficiently, referred to as the "thrifty genotype" hypothesis (1–6,23,24). The precisely timed seasonal development of obesity in animals might be an expression of the thrifty genotype induced by the biological clock (24). The effects of lifestyle on a population can develop very rapidly, as shown by the increase of the BMI in children within 10 years in Eastern Germany after reunification and westernization (25). Due to our current sedentary lifestyle, the brain no longer senses the urge to oscillate the body between the anabolic and catabolic states. The fact that such information is crucial can be inferred from the effect of absent hepatic feedback to the brain: after hepatic vagotomy, food intake in the inactive phase of rats increases, leading to weight gain, while insulin resistance develops in muscle (26,27).

The central clock might also be affected by the changed environment (24). In humans, the circadian rhythm in insulin secretion and sensitivity is disturbed and flattened in diabetic patients, and their nondiabetic offspring has reduced diurnal blood pressure variation (28,29). An impaired functioning of the SCN would explain early changes in the metabolic syndrome, such as the absence of a physiological dip in blood pressure at night caused by a impaired circadian rhythm in sympatho-vagal balance (30–35). In hypertensive patients, postmortem neuroanatomical assessment revealed indeed a disturbed SCN structure (36). The impairment of the central clock function in the elderly might relate to the high incidence of the metabolic syndrome in this population (37). Epidemiological analysis of a 6-year survey among 2,000 workers revealed a correlation between irregular eating and snacking habits and insufficient hours of sleep, while smoking or alcohol drinking did not affect sleep (38). Nocturnal eating leads to an abnormal endocrine response (39). Interestingly, other studies showed that overeaters tend to consume a larger part of their daily energy in the evening (40). In OLETF rats (a model of type 2 diabetes and selective visceral obesity), induced by a lack of the cholecystokinin-a receptor-mediated vagal feedback to the brainstem, spontaneous activity, sleep, and temperature rhythms are also disturbed (41). In general, it should be noted that although a certain metabolic value is physiological at one time point, it might be pathophysiological at a different time point of the day.

HYPOTHESIS: THE UNBALANCED AUTONOMIC NERVOUS SYSTEM CAUSES THE SYMPTOMS OF THE METABOLIC SYNDROME.

The metabolic syndrome consists of visceral obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and cardiovascular diseases. A common pathophysiological denominator underlying these epidemiological correlations has not been identified. However, the autonomic nervous system was shown to play a role in the metabolic syndrome. Recently, a prospective cohort study in 8,000 patients from 1987–1998 revealed a high relative risk to develop type 2 diabetes if autonomic dysfunction is present in healthy subjects independent from other risk factors, such as body weight (42). However, if the status of the autonomic nervous system in a certain compartment is understood as an indicator of autonomic balance of the whole body, the picture becomes confusing. As a result, the finding of reduced plasma catecholamines, increased heart rate, decreased parasympathetic activity measured by R-R interval after β-adrenergic blockade, and increased pupil latency period before but not after muscarinic blockade is summarized as an overall decreased sympathetic and parasympathetic tone in the development of obesity (43). In rat models of hypothalamic obesity, a reduction in sympathetic tonus to the pancreas, white and brown fat tissue was shown to play a role in fat growth (44). Others show evidence for a high parasympathetic activity in obesity, leading to high insulin and fat storage (45,46). Contrarily, an overactive sympathetic nervous system is described in type 2 diabetes, resulting in increased heart rate, vascular resistance, and sodium retention (47). Consequently, we propose that the picture has become confusing because autonomic parameters are measured in different compartments (Fig. 1).

The metabolic syndrome is associated with enhanced insulin secretion and fat accumulation in the abdomen. Interestingly, parasympathetic input to fat tissue has been shown to enhance insulin sensitivity and fat accumulation (13). Moreover, insulin secretion by the pancreas is parasympathetically driven, and parasympathetic input to the liver has been shown to increase insulin sensitivity and glucose uptake (26,48). Less pulsatile insulin secretion in type 2 diabetic patients indicates a more rigid autonomic tonus to the abdomen and might be used as a marker, since profound defects of pulsatile secretion are already present in glucose-intolerant individuals (49,50). These data indicate that all organs receiving an enhanced parasympathetic tone are situated in the visceral compartment. Interestingly, in apparent contrast at the same time, in the metabolic syndrome the balance is shifted to a sympathetic overweight to the heart, resulting in increased blood pressure and insulin-resistant muscles (51,52). Thus, organs in the thoracic and movement compartment act metabolically opposite to the visceral compartment (53). While in healthy subjects the autonomic balance of the compartments oscillates, these findings indicate that an unbalanced autonomic output develops in the metabolic syndrome with increased parasympathetic dominance in the visceral compartment and increased sympathetic tone in the thoracic and movement compartment.

CAN THIS VICIOUS CYCLE BE BROKEN?

If our hypothesis is correct, interventions on the level of feedback to the autonomic centers or to the central clock should be beneficial in the metabolic syndrome.

During exercise, energy is consumed, which is sensed by the brain. As a reflex, the autonomic input to the visceral compartment shifts to sympathetic dominance and visceral fat decreases (54–57), and at the same time the

sympathetic outflow to the heart and arteries decrease in order to facilitate blood flow to the muscles, resulting in lower blood pressure and an improvement of insulin sensitivity of the muscle (58–60). Consequently, daily exercise and weight loss reestablishes the counteracting metabolic balance between the anabolic and catabolic state such that the autonomic outflow becomes rhythmic again (60,61).

Another possible intervention at the level of the SCN is its reentrainment by melatonin, which is expressed in the pineal gland in a circadian fashion as the signal of the night. Diabetic patients with autonomic disturbances and patients with coronary artery disease have a flattened melatonin rhythm (62,63). Interestingly, melatonin supplementation reentrains the SCN and restores the diurnal variation in blood pressure in hypertensive patients and allows blood pressure to fall at night (64). In rats, administration of melatonin at night induces visceral fat loss and improves the metabolic syndrome (65).

In conclusion, the reversal of the metabolic syndrome by these entrainment procedures of the SCN argues for a possible treatment aimed at restoring a physiological daily rhythm in energy balance.

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