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Central nervous determination of food storage—a daily switch from conservation to expenditure: implications for the metabolic syndrome

Felix Kreier[a,b,c,*], Andries Kalsbeek[a], Marieke Ruiter[a], Ajda Yilmaz[a], Johannes A. Romijn[b], Hans P. Sauerwein[c], Eric Fliers[c], Ruud M. Buijs[a]

[a] Netherlands Institute for Brain Research, 1105 AZ Amsterdam, The Netherlands
[b] Department of Endocrinology and Metabolism, Leiden University Medical Center, 2300 RC Leiden, The Netherlands
[c] Department of Endocrinology and Metabolism, Academic Medical Center of the University of Amsterdam, 1100 DE Amsterdam, The Netherlands

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Abstract

Here, we present a neuroendocrine concept to review the circularly interacting energy homeostasis system between brain and body. Body–brain interaction is circular because the brain immediately integrates an input to an output, and because part of this response may be that the brain modulates the sensitivity of this perception. First, we describe how the brain senses the body through neurons and blood–borne factors. Direct neuronal connections report the state of various organs. In addition, humoral factors are perceived by the blood–brain barrier and circumventricular organs. We describe how circulating energy carriers are sensed and what signals reach the brain during food intake, exercise and an immune response. We describe that the brain regulates the homeostatic process at two fundamentally different levels during the active and inactive states. The unbalanced output of the brain in the metabolic syndrome is discussed in relation with such circadian rhythms and with regional activity of the autonomic nervous system. In line with the above, we suggest a new approach for the diagnosis and therapy of the metabolic syndrome.

Keywords: Autonomic nervous system; Hypothalamus; Circadian rhythm; Metabolic syndrome; Visceral obesity; Diabetes; Hypertension

1. Introduction: "new" concepts

Claude Bernard, a pioneer in the practice of modern medicine and scientific theory, proposed around the 1840s that nerves are either sensory or motor, that vasomotor nerves regulate blood supply by modulation of arterial tone, that the liver stores glucose, and that the pancreas secretes digestive enzymes. He assumed, now logically but at that time groundbreaking, that this important function had to be coordinated by the best protected organ of the body: the brain. To test his hypothesis, Claude Bernard punctured the fourth ventricle of rabbits and found them to develop diabetes (Bernard, 1850; Conti, 2001). His famous conclusion from these observations was that these body functions all serve one common objective: *keeping the internal environment stable*.

When Charles Darwin in the 1870s observed "a hungry man, if tempting food is placed in front of him, may not show his hunger by any outward gesture, but cannot control the secretion of glands (like saliva)", he assumed that the brain controls the body with will-dependent and will-independent nerves (Darwin, 1872).

When Harvey Cushing reviewed the data of William Raab in the 1920s that a fatty liver could be induced within 9 h after peripheral injection of pituitrin, he hypothesized a role for the brain and the autonomic nervous system in this effect. Raab injected pituitrin intracerebroventricularly, and subsequently the fatty liver developed already within 4 h after injection. Moreover, he could abolish this effect by lesions to either the central nervous or the peripheral autonomic nervous system (Cushing, 1932).

Interestingly, these three scientific pioneers shared the same concept to comprehend metabolism in mammals: they presumed a central role for the brain in the coordination of energy homeostasis. However, the interpretation of these experiments was extremely complex. After the discovery of

* Corresponding author. Netherlands Institute for Brain Research, 1105 AZ Amsterdam, The Netherlands. Tel.: +31-20-5665500; fax: +31-20-6961006.
E-mail address: f.kreier@nih.knaw.nl (F. Kreier).

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various powerful hormones in the first half of the 20th century, concepts changed. The interpretation of experiments with hormones seemed less complex and the direct measurable effect was much stronger, such as the results obtained with the intravenous injection of insulin. One could conduct an experiment easily by injecting a hormone. However, this experimental reduction was less feasible in the nervous system in vivo; a major obstacle appeared to be how to avoid uncontrolled counterregulatory mechanisms or major side effects.

In this period, a paradigm change occurred: endocrinology grew out to an independent area of research and specialization of medicine, focused on hormones and dissociating itself from the neurosciences. Extensive endocrinological research in the 20th century has yielded a staggering amount of data about the role of hormones in energy homeostasis. However, within the last decade, the open question of what coordinates body homeostasis has concerned more and more researchers. Today, the re-unification of neurosciences and endocrinology will allow us to see the ''big picture'', and the immense detailed knowledge will help us to test the viability of new hypotheses. Here, we will focus on the role of the brain as a coordinator of metabolism, and how the brain uses both neurons and hormones to communicate with the body. We will describe the coordinating function of the brain, and propose mechanisms that might be causing the metabolic syndrome and type 2 diabetes.

Forty-seven million Americans currently have the metabolic syndrome, which consists of abdominal obesity, hypertension, hyperinsulinemia, hyperglycemia and dyslipidemia (Virgin and Schmitke, 2003). The etiology of the metabolic syndrome, an emerging epidemic of wealthy countries, is unknown, but certainly multi-causal. We will point out potential targets for pharmacological intervention in the metabolic syndrome: (a) the input from the body to the brain by neurons and hormones, (b) the integration of this information in the brain and especially in the hypothalamus and (c) the output of the brain to the body by neurons and hormones.

To break into this circularly interacting homeostasis system, we choose the input to the brain as a starting point (Section 2). Here, we review how the brain is affected by a set of metabolic conditions of the body. However, the metabolic conditions that give feedback to the brain are under the control of the brain itself. Their integration in the brain is briefly reviewed in Section 3, and the resulting modulation of the output is reviewed in Section 4. In Section 3, we also introduce circadian rhythms as an example of a system that is able to anticipate and predict changes in the complex relationships between body and brain. The role of the unbalanced autonomic system in the metabolic syndrome is discussed in Section 4. Finally, while reviewing these aspects we have to be aware of the constant interaction between these three theoretically distinct systems.

2. Input: the brain gets affected by body conditions

2.1. Sensing circulating energy carriers

2.1.1. Glucose

Stable blood glucose levels are crucial for survival. The brain in particular is highly dependent on a steady access to this indispensable energy source. The brain therefore uses central and peripheral glucose-sensitive neurons to obtain information on the actual levels and the rate of consumption in different parts of the body.

In the portal vein, GLUT2-dependent vagal afferents sense glucose levels in the blood in the presence of the glucagon like peptide-1 receptor, a molecular pathway similar to that in the insulin secreting pancreatic beta-cells (Burcelin et al., 2000, 2001). The vagus may also conduct information from glucose sensors present in the splenic vein, in the renal tube, and in muscle and adipose tissue (Peters et al., 2002). The afferent vagus projects from the periphery to the nucleus of the solitary tract in the brainstem, a brain region situated in the dorsal vagal complex functioning as a port of entry for visceral information to the brain. Interestingly, the incoming peripheral signals about glucose levels can be modified by central glucose sensing neurons at nearly every level of the central nervous system (CNS). This also holds for the brainstem, where such neurons are present in the nucleus of the solitary tract, adjacent to the area postrema, a circumventricular organ for exchange of information between blood and brain (Grill and Kaplan, 2002; Zec and Kinney, 2003). The integrated signal is relayed directly to the hypothalamus, partly via the parabrachial nucleus of the brainstem, where it is collated with gustatory and sensory sympathetic signals (Davidson et al., 2000). The integrative function of the parabrachial nucleus is illustrated by the effect of estrogen microinjections into that area, leading to a decrease of sympathetic tonus and an increase in parasympathetic tonus (Saleh and Connell, 2003). This information is transported from the parabrachial nucleus to the hypothalamus and focuses on the ventromedial nucleus of the hypothalamus, which integrates neuronal feedback from outside the hypothalamus (Bray and York, 1998; Fulwiler and Saper, 1985). Again, neurons in the ventromedial nucleus have the ability to sense glucose (Routh, 2002). Thus, information about glucose levels is sensed in the periphery and is combined with other information in multiple brain regions. Strikingly, each integrative layer up to the cortex is able to sense glucose itself.

2.1.2. Fatty acids

Although heart and muscle use fatty acids as their primal source of energy, surprisingly little is known about how the brain senses fatty acids. However, circulating fatty acids are monitored by the brain, just like glucose. Intravenous infusion of lipid substrate decreases food intake. Recently, fatty acids have been shown to act directly on neurons of the arcuate nucleus of the hypothalamus, which is a hormonal

feedback center and also a circumventricular organ (Havel, 2001; Obici et al., 2002a, 2003). In view of the vital role of fatty acids, it seems logical that the monitoring and organization of fatty acids metabolism has similar characteristics and will be at least as sophisticated as the multi-level system monitoring of circulating glucose levels. Research in this field is therefore likely to increase in future.

2.1.3. Amino acids

Amino acids are extremely important as backbones for protein synthesis and as a source of energy. However, very little is known about the way the brain senses this third fuel type. Only indirect evidence indicates an effect of dietary and circulating amino acids on food intake (Bray, 1997; Gibson et al., 1995; Porrini et al., 1997). In addition, amino acids can act as a neurotransmitter (Bray, 1997). Thus, the role of amino acids as an afferent signal to the brain remains to be elucidated. However, we assume that similar mechanisms of control are present as described for glucose.

In summary, the brain monitors the energy levels in the internal environment in order to respond rapidly, precisely and adequately to changing nutrient levels. The measurement of acute energy requirements and stores is not sufficient for survival. To keep the internal environment safe and stable, the brain must avoid running behind the actualities and needs to be able to anticipate upcoming changes. Here, we describe three physiological conditions that affect the input to the brain.

2.2. Food intake

Food intake generates a broad range of signals to the brain. Even before a periodic meal, the stomach releases ghrelin, acting as an orexigenic growth hormone secretagogue in the hypothalamus (Cummings and Schwartz, 2003; Cummings et al., 2002).

Before and during a meal, olfactory and taste receptors detect glucose (and other sugars), fatty acids and possibly amino acids (Bray, 2000). Bitter and sour taste may signal harmful substances, and a salty taste signals the sodium content of the meal (Bray, 2000).

In the stomach, mechano-sensitive vagal afferents get activated by gastric load (Moran et al., 2001). After passing through the pyloric sphincter, vagal afferents in the duodenum respond to load volume and sense nutrient content, e.g., fatty acids (Cox et al., 2000, 2001; Lal et al., 2001; Moran et al., 2001; Randich et al., 2000). Vagal sensors also report the temperature of the ingested food from esophagus, stomach and duodenum to the brain (Berthoud and Neuhuber, 2000).

The proximal small intestines respond to feeding by releasing cholecystokinin (Havel, 2001; Herath et al., 1999; Keller and Layer, 2002). This hormone amplifies the signal of mechanoreceptive vagal afferents in stomach and duodenum through activation of their cholecystokinin type A receptor (Schwartz et al., 1993, 1995). Parenterally injected cholecystokinin produces a dose-related reduction of food intake in sham-fed animals, and activates vagal afferents projecting to the nucleus of the solitary tract and to neurons in the parabrachial nucleus and amygdala as shown by c-fos expression (Gibbs et al., 1973; Szewczyk and Laudeman, 2003). The anorectic effect of cholecystokinin can be blocked by vagotomy (Bray and York, 1979). However, to what extent such a major interference with homeostatic processes such as vagal de-afferentiation can be used to predict what happens in normal physiology is an open question.

Two other hormones entrained by food intake are gastrin-releasing peptide and bombesin, which are similar in their structure. The latter affects the brain, since it suppresses food intake after parenteral administration and lowers temperature in starved animals after central injection (Barton et al., 1995; Lieverse et al., 1993).

Glucagon and glucagon-like peptide-1, both derived from pro-glucagon and secreted by the pancreas and the small intestines, respectively, decrease food intake (Bray, 2000; Geary et al., 1997). Although the role of glucagon in food intake is not clear, it induces an increase in heart rate besides gastrointestinal and bronchoconstrictor relaxation (Ruiter et al., 2003; Sherwood et al., 2000). Thus, glucagon might indirectly activate the sympathetic nervous system or inhibit the parasympathetic branch under circumstances that are different from food intake. Glucagon-like peptide-1 is released under the influence of the vagus nerve and its receptor is present on vagal afferents in the liver (Anini and Brubaker, 2003; Burcelin et al., 2001). Centrally, glucagon-like peptide-1 receptors are found in the hypothalamus and in the nucleus of the solitary tract of the brainstem (Ur and Wilkinson, 2001). This hormone is also produced in hypothalamic neurons. Central glucagon-like peptide-1 contributes to insulin secretion and inhibits hunger, and conversely, intracerebroventricularly injected glucagon-like peptide-1 antagonists increase feeding in rodents (Havel, 2001).

The pancreas secretes insulin, glucagon and exocrine enzymes as soon as the food is captured and in the mouth (Herath et al., 1999; Strubbe, 1992). Although insulin is a very powerful regulator of food intake, it is still not completely understood to what extent peripheral insulin penetrates the CNS, or if insulin is produced in the brain itself. Intravenous injection of labeled insulin reaches the brain at regions with a less effective blood–brain barrier and through a delayed receptor-mediated mechanism that can be saturated with high insulin levels (Schwartz et al., 1991; Woods et al., 2003). Interestingly, after a carbohydrate-rich meal, the insulin content of the hypothalamus increases by twofold while it does not change in the cerebellum (Gerozissis et al., 1999). In contrast, a large amount (0.5 units) of exogenous insulin, administered via a jugular vein catheter, does not change the hypothalamic insulin content significantly (Gerozissis et al., 1993). Moreover, if a standard meal is repeated only once at the same time of the next day, hypothalamic insulin content increases by ca. 40% and after

2 days by ca. 100% within 30 min after the meal, without changing plasma insulin levels compared to basic levels (Orosco et al., 1995). In this particular example, in repeated meals, blood–brain barrier transport of insulin changes before the secretion of insulin itself. All these data indicate a major role for the blood–brain barrier in the modulation of blood-borne feedback signals to the brain. Alternatively, hypothalamic insulin could be of neuronal origin.

Central insulin infusions reduce food intake, counter-regulate hypoglycemia and modulate the autonomic nervous system (Davis et al., 1995; Liang et al., 1982; Woods et al., 1979). Recently, the arcuate nucleus has been shown to mediate 40% of the insulin-induced inhibition of the endogenous glucose production by the liver, as demonstrated by central infusion of insulin agonists and antagonists (Obici et al., 2002b). Yet, insulin receptors have been identified not only in the hypothalamus but also in the dorsal vagal complex and other caudal brainstem sites. Thus, similarly to glucose sensing in the brain, insulin levels are monitored at multiple layers of the system (Grill and Kaplan, 2002; Unger et al., 1991).

When glucose and fatty acids are taken up by fat tissue (the major energy store of the body) this tissue secretes a set of feedback hormones that are part of the cytokine family, such as leptin, tumor necrosis factor-alpha, interleukin-1beta and -6 (Ahima and Flier, 2000a; Coppack, 2001; Elmquist et al., 1999). Again, access to the brain is actively filtered by the blood–brain barrier. Recent studies on the penetration of these substances into the CNS provide an interesting insight in how information from the periphery can be gated. The blood–brain barrier transports leptin and tumor necrosis factor-alpha actively in a circadian fashion (Pan et al., 2002; Pan and Kastin, 2001). Moreover, the blood–brain barrier seems to be selectively active depending on the region: at a certain time point, tumor necrosis factor-alpha is transported into the cervical and lumbar spinal cord but not into the hypothalamic region, whereas interferon-gamma is transported faster into the cervical spinal cord (Pan et al., 2002; Pan and Kastin, 2003). Thus, the brain directs the site of humoral feedback depending on the time of the day, brain region and substrate (Kastin and Pan, 2000, 2003).

After reaching the brain, leptin acts on leptin receptors in the arcuate nucleus and activates the melanocortin system (Ahima and Flier, 2000b). Moreover, functional long isoform leptin receptors are present in the brainstem, e.g., in the dorsal vagal complex (Fei et al., 1997; Grill et al., 2002; Hay-Schmidt et al., 2001).

In summary, food intake induces a complex range of humoral and neuronal signals to the brain. Humoral and neuronal feedback signals cross-talk on all layers of the afferent nervous system; e.g., glucose can induce neuronal firing of the vagus nerve in the portal vein, but it can also modify the vagal signal entering in the nucleus of the solitary tract of the brainstem. Subsequently, higher order neurons, integrating the peripheral feedback, can also sense glucose themselves (Fig. 1). In turn, the brain can modulate

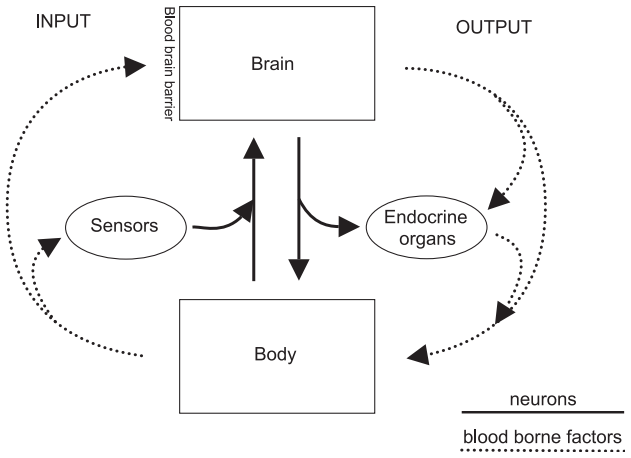

Fig. 1. Circularly interacting homeostasis system: brain–body communication by neurons and blood-borne factors. In Section 2 of this review, we highlight the way the brain senses the body (left part, "INPUT"). The brain generates an output depending on its input. At the same time, it modulates its sensitivity for metabolic substances. Direct neuronal connections report the state of various organs, while blood-borne factors are perceived by the blood–brain barrier and act on central neurons. In Section 3 we briefly review how the central clock in the brain modulates hypothalamic integration. In Section 4 (right part, "OUTPUT"), we describe how the brain controls the body by neurons and hormones. We put special emphasis on circadian rhythms and regional organization of the autonomic nervous system in the metabolic syndrome. In Section 5, we give suggestions for diagnosis and therapy of the metabolic syndrome.

the effect of humoral factors by modulating the activity of the blood–brain barrier, or by projections towards areas that integrate incoming afferents.

2.3. Exercise

Obviously, energy expenditure is a major challenge for the energy homeostasis system and should be monitored closely.

The feedback to the brain induced by exercise starts directly in the active muscle itself. Mechano- and chemosensory afferent nerves report movement and metabolic changes from the muscle to the brain, where the adaptation of the hemodynamic system can be coordinated (Rowell and O'Leary, 1990). This process is sensitive to ATP in muscle and can be blocked by epidural anesthesia, suggesting that sympathetic afferents are involved (Hanna and Kaufman, 2003; Smith et al., 2003). This information is relayed from spinal sensory neurons to the nucleus of the solitary tract, where cross-talk with the baroreflex signal from the carotid body and afferents from the heart take place. This results in modulation of heart rate, vascular and ventilatory control, as well as in renal sympathetic activity (Craig, 2002; DiCarlo et al., 1997; O'Leary, 1996; Piepoli et al., 1996; Potts et al., 1999; Potts and Li, 1998; Scott et al., 2002).

Energy consumption by muscle tissue changes the levels of circulating glucose, fat and protein, which is monitored centrally by the mechanisms described above. In view of the huge turnover of energy during exercise, it seems logical

that these homeostatic systems are the most active in counteracting the depletion of energy stores.

Moreover, not only the organs consuming fuel, but also the organs providing energy give feedback to the brain during exercise. The liver is the only organ that can produce glucose during exercise. Interestingly, a series of experiments demonstrates that the vagus nerve reports liver temperature and glycogen depletion directly to the brain (Berthoud and Neuhuber, 2000; Lavoie et al., 1987, 1988). Thus, here the vagus nerve is used to report at least two conditions: (a) metabolic parameters of passing blood through the portal vein and (b) glycogen levels in the liver (Lavoie, 2002).

Little is known about the way the major energy supplier, fat tissue, communicates to the brain during exercise (Romijn et al., 1993). However, a delayed reduction in leptin release has been reported after strenuous exercise (Friedman et al., 1997; Nindl et al., 2002). Interestingly, insulin levels significantly decrease with exercise due to reduced secretion of the pancreas, while insulin sensitivity of the muscle increases (Bjorntorp, 1983). Glucagon secretion increases with exercise and can induce an anorectic effect as described above (Wasserman et al., 1993). Plasma concentrations of cortisol depend on the time of the day in experiments with short-time exercise (Kanaley et al., 2001). Moreover, after exercise during the day, cortisol decreases during the following night (Hackney and Viru, 1999). In the brain, glucocorticoid receptor is present abundantly (Morimoto et al., 1996). Cortisol acts on the glucocorticoid receptor with different effects depending on the compartment: centrally, cortisol has an orexigenic effect, while intravenous or subcutaneous cortisol has an anorexic effect (Bjorntorp and Rosmond, 2000; Havel, 2001). How this action is connected to the presumed free passage of cortisol into the CNS is not known at present.

In summary, in contrast to a large amount of data on the effects of exercise on energy homeostasis in general, the intermediate step, the way in which exercise changes the input to the brain, has not been extensively studied.

2.4. Immune response

Energy homeostasis and the immune system interact extensively. Our body's defense system matches its activities to the available supplies. Therefore, both systems are strongly intertwined, illustrated by the fact that the largest energy store, fat tissue, uses proteins of the cytokine-family to report its metabolic state to the brain.

If pathogens break into the body, they induce hormonal and neuronal signals. Vagal afferents, e.g. in lymph nodes, are activated directly by the pathogens or indirectly by immune responsive cells (Goehler et al., 2000; Werner et al., 2003). Stimulation of an immune response activates the peripheral and central nervous systems by means of vagal afferents. Herein the nucleus of the solitary tract and the ventrolateral medulla in the brainstem as well as the central amygdala play a role in the mediation of the resulting hypotension (Engstrom et al., 2003; Ge et al., 2001; Mailman, 2002). After immune stimulation, the cytokine interleukin-1beta and the number of its receptors increase in the abdominal vagus but not in the cervical branch (Schwartz, 2002). Recent studies elucidate that the abdominal cavity is not the only region with the capacity to mount an immune response via the vagus. Researchers have shown that pulmonary sensory nerves of the vagus are activated by antigens (Berthoud and Neuhuber, 2000; Lai et al., 2002). Interestingly, fever develops differently after the induction of an immune response combined with capsaicin treatment, indicating a possible role for the sympathetic feedback, which has been given less attention by researchers (Szekely et al., 2000).

Immune-responsive cells in blood and organs release a range of cytokines, such as interleukin-1beta, -6 and tumor necrosis factor-alpha (Pittman and Mouihate, 2003). These cytokines induce the anorexia-cachexia syndrome, which is a prominent feature of a severe disease (Inui, 2002). Cytokines derived from the immune system are proposed to play a role in centrally mediated anorexia of cancer patients. They act on the brain not only via afferent nerves, but also by interaction with the cerebroventricular organs or directly on central neurons (Dantzer et al., 2000; Desson and Ferguson, 2003). At first glance, they bring an identical message to the brain as do adipose tissue-derived hormones in times of plenty, as illustrated by the fact that interleukin-6-deficient mice develop mature-onset obesity (Inui, 1999; Plata-Salaman, 2000, 2001; Wallenius et al., 2002).

2.5. Conclusion

Here we briefly review the data that show how the brain senses energy levels, food intake, exercise and antigen penetration. Although much less is known about the input to brain than is known about its output, it seems that the brain receives its information via neuronal afferents and humoral factors acting on the CNS via circumventricular organs or directly on neurons (Blessing, 1997).

While the brain gets affected by the conditions of the body, logically it has the capacity to change these conditions "online".

In summary, the complex communication between the periphery and the CNS has no beginning and no end. Infinite interaction of the brain with the body on all levels is the simplest description of it. To say anything meaningful about energy homeostasis, one needs to focus and cut out a starting point. In Section 2, we will choose circadian rhythms in energy homeostasis as a ruling principle related to function, since:

(a) anticipation by circadian rhythms is a critical factor for survival in an external environment oscillating between day and night,

(b) circadian rhythms produce detectable and significant changes of the homeostatic system within a physiological range, and
(c) disturbed circadian rhythms are a prominent feature of the metabolic syndrome.

3. The biological clock modulates hypothalamic integration

One basic principle of central nervous integration is the active filtering of noise. The brain decides which stimuli are relevant; e.g., the time of the day defines how a certain stimulus will affect the hypothalamus and consequently how it affects hypothalamic output. The time (the central clock) determines the level of response (Buijs and Kalsbeek, 2001). As mentioned earlier, the blood–brain barrier actively selects humoral factors that can pass to the hypothalamus; e.g. leptin and tumor necrosis factor-alpha get access to the brain depending on the time of the day (Pan et al., 2002; Pan and Kastin, 2001). This circadian filter can help us to order and direct the flood of information.

Evolution forced us to develop adaptive body functions to survive a hostile world. In the present review, we choose a functionally oriented approach to comprehend hypothalamic integration of energy homeostasis. The daily switch from light to dark as well as the outside temperature forced mammals to develop a circadian rhythm generator that saves energy and avoids predation by specialization to an active and an inactive period (Buijs and Kalsbeek, 2001). The central biological clock is situated in the suprachiasmatic nucleus (SCN) of the hypothalamus, adjacent to the optic chiasm, from where the SCN receives light information from the eyes through the retinohypothalamic tract (Buijs and Kalsbeek, 2001). Our biological clock causes our bodies to oscillate between an inactive phase for regeneration and preparation, and an active phase, in which energy is invested in physical activity (e.g., hunting) to assure survival in the future.

Here, we will focus on the modulation of the hypothalamic output by the SCN. The central clock receives information from the external environment about the time of the day by, e.g., light. Humoral input from the internal environment enables the SCN to read the internal synchronization message of the body, such as melatonin. In return, the SCN transports its time-of-the-day message throughout the body via various hormones, such as corticosterone and melatonin (Buijs et al., 2003b). The SCN communicates its phase-of-the-day message selectively through the sympathetic and parasympathetic branches of the autonomic nervous system (Buijs et al., 2003a). In addition, the SCN modulates the activity of neurons within the hypothalamus itself (Kalsbeek and Buijs, 1996).

SCN lesions in animals result in the disruption of circadian behavioral and metabolic rhythms, leading to flattened hormonal rhythms and an even distribution of locomotor activity during the day and the night. Since SCN transplants in a semi-permeable membrane, preventing neuronal sprouting, could restore locomotor activity in SCN-lesioned rats, one could reason that its message is broad and unspecific. However, this experiment also revealed that the transplants could not restore hormonal rhythmicity in cortisol and gonadal function, illustrating a more complex regulation of hormones by the SCN (Lehman et al., 1987; Meyer-Bernstein et al., 1999). Neuroanatomical and functional studies revealed that the SCN uses different sets of hypothalamic neurons to deliver selective messages to other brain regions (Buijs and Kalsbeek, 2001). The target areas can be divided into four functional groups of neurons:

(1) hypothalamic neurons projecting to the pituitary axes involved in the hormonal control of the body,
(2) hypothalamic neurons projecting to the autonomic nervous system involved in the neuronal control of the body. Note that the SCN can selectively affect the sympathetic and parasympathetic branch via separate projections (Buijs et al., 2003a),
(3) hypothalamic neurons of integrative centers involved in, e.g., energy homeostasis and temperature regulation, such as the dorsomedial nucleus and the medial preoptic area, putatively building an intermediate step between the SCN and the hormonal or neuronal output signal via the neurons of (1) and (2),
(4) thalamic neurons in the lateral geniculate nucleus and the paraventricular nucleus, synchronizing hypothalamic-induced behavior with locomotor activity.

4. Circadian output: the brain affects body functions

4.1. The adrenal—a model for the dual control of an organ

4.1.1. The central clock uses hormones as an output signal to the adrenal—sufficient to predict corticosterone levels?

Corticosterone and glucose peak in the beginning of the active phase, just 1 or 2 h before the central clock is planning to awaken us (Kalsbeek et al., 1996; la Fleur et al., 2001). This so-called dawn phenomenon prepares us to face the new day (Bolli et al., 1984). How is the rise in corticosterone accomplished? The SCN modulates the cascade of corticotrophin-releasing hormone-containing neurons stimulating the secretion of adrenocorticotropin hormone from the pituitary (ACTH), in turn resulting in corticosterone secretion from the adrenals, known as the hypothalamus-pituitary-adrenal axis (HPA-axis) (Kalsbeek et al., 1996). However, activity of the HPA-axis does not explain the pattern of corticosterone secretion as a whole: 24-h plotting of ACTH against corticosterone levels in plasma reveals that the sensitivity of the adrenal for ACTH is restricted to the active period (Kaneko et al., 1980).

4.1.2. The parallel output signal of the central clock: neuronal projections to the adrenal

The SCN talks to the body not only via the pituitary, but also via the autonomic nervous system. Neuroanatomical tools, such as retrograde tracers, are able to visualize central neurons controlling a particular organ. The retrograde transneuronal tracer pseudorabies virus travels against the direction of the neuronal signal and crosses synapses. Therefore, it can identify a chain of neurons in control of a particular organ. Using this technique, for the first time, a multisynaptic projection from the SCN to the adrenal by the autonomic nervous system was demonstrated (Buijs et al., 1999). Moreover, physiological experiments revealed that the function of this multisynaptic pathway from the SCN to the adrenal cortex is to modulate its sensitivity for ACTH (Buijs et al., 1999). In line with these results, a combination of neuroanatomical and physiological studies exhibited that the vagus nerve modulates the insulin sensitivity of fat tissue (Furness et al., 2001; Kreier et al., 2002). Therefore, we propose the dual hypothalamic control of organs by both hormones and neurons to be a principle of brain–body interactions.

4.2. The SCN and the oscillating body

Potentially, all cells of the body have clock genes, forming an intracellular clock. Here, we review data indicating that the central clock sets the time of the peripheral clocks by means of neurons and hormones (Buijs and Kalsbeek, 2001).

The neuroanatomical substrate for neuronal control was shown recently by experiments using pseudorabies virus. The SCN has specialized neurons that affect the sympathetic or the parasympathetic branch (Buijs et al., 2003a). Neuroanatomical tracer studies revealed a multisynaptic pathway from the SCN to various organs, e.g., heart, pancreas, liver, thyroid and pineal (Buijs et al., 2001; Kalsbeek et al., 2000; la Fleur et al., 2000; Scheer et al., 2003b). At present, the question that needs to be answered is, whether in addition to separate sympathetic and parasympathetic control by the SCN, also a separate control of the different organs is present.

The best-studied peripheral circadian oscillator is the pineal; here the SCN uses the autonomic nervous system to induce melatonin secretion (Kalsbeek and Buijs, 2002). Recently, the sympathetic nervous system has been demonstrated to affect clock gene expression in the liver (Terazono et al., 2003). Physiological studies on liver and pancreas revealed a circadian rhythm in glucose, insulin and glucagon secretion, induced by the SCN and in case of the latter also modulated by food intake (D'Alessio et al., 2001; Herath et al., 1999; La Fleur, 2003; la Fleur et al., 2001; Ruiter et al., 2003; Yamamoto et al., 1987). Also daily levels of the fat-derived hormone leptin are driven by the SCN (Kalsbeek et al., 2001). Within the cardiovascular system, heart rate, blood pressure, QT-interval length and K^+ channels show a circadian rhythm (Bonnemeier et al., 2003; Scheer et al., 2003b; Yamashita et al., 2003). These mechanisms might be the basis for the observation that body performance during exercise is best at the time of the day when training is regularly performed (Hill et al., 1998).

Another group of peripheral non-circadian oscillators is illustrative of the neuronal induction of organ rhythmicity. The sympathetic nervous system has been shown to induce 10 rapid oscillations per hour in lipolysis (Getty et al., 2000). In a series of studies on the endocrine pancreas, precise analysis of insulin and glucagon levels in the portal vein revealed a pulsatile secretion pattern (Porksen, 2002b). The individual beta-cell shows episodic beta-cell depolarizations in vitro (Santos et al., 1991). Here, the question arises how one million individual bursting islets could be orchestrated to create this coordinated rhythmic pattern. It was shown that application of a post-synaptic nicotinic receptor antagonist to the isolated perfused pancreas could impair the pulsatile release of insulin. Thus, the activity of the islets might be coordinated by an intra-pancreatic neuronal network (Stagner and Samols, 1985). In a next step, the correlation of pulsatile insulin secretion and re-innervation of islet transplants have been investigated in the rat in vivo (Porksen et al., 1994). Intra-portal injection of islets established a time-dependent re-entrainment of pulsatile insulin secretion within 28 days, suggesting that re-innervation of the islet causes the recovery of the ultradian rhythm.

4.3. The hypothalamus–autonomic nervous system–body axis: simply top-down?

The central role of the hypothalamus in the control of energy homeostasis was deduced from lesion studies. Stereotactic lesions in the region of the ventral medial hypothalamic nucleus cause overfeeding and obesity, whereas lesions in the lateral hypothalamic area result in an anorexia-cachexia syndrome (Stellar, 1954). These data suggest a simple one-way top-down control of the body by the hypothalamus in the control of energy homeostasis.

However, as the brain senses the body on all its integrative layers via humoral factors and afferent nerves, it also does so on the level of the autonomic motor neurons in brain stem and spinal cord. As reviewed by Grill and Kaplan, the decerebrate animal model with a hypothalamus disconnected from the brainstem sheds light on the autonomic integration of autonomic afferents and efferents (Grill and Kaplan, 2001, 2002). In the decerebrate animal model, the isolated autonomic nervous system is capable of coordinating oral movements and digestion, resulting in similar weight gain as compared to intact rats when meals are placed intraorally. Interestingly, the isolated autonomic nervous system is not capable to compensate for food deprivation, as demonstrated by intact rats increasing their

meal size, but not the decerebrate. Thus, while the autonomic nervous system can function autonomously in the short-term control of food intake, the hypothalamus is needed for the long-term coordination.

We propose that the hypothalamic–brainstem interaction is a model of the control of energy homeostasis, built up of nested autonomous units that are modulated by higher integrative layers.

4.4. The autonomic nervous system differentiates between functional body compartments

The purpose of the SCN is to anticipate fluctuations in the external environment in order to keep the internal environment stable. Therefore, the central clock needs to activate or silence tissues depending on their function at different time points of the day. For example, muscles work in the active phase when the digestive tract slows down. Therefore, an opposite autonomic tone on different parts of the circulation redirects the blood away from the abdominal compartment towards the movement compartment, whereas cerebral blood flow is kept constant. At night the SCN slows down heart function, resulting in a dip in blood pressure (Scheer et al., 2003b).

How can different regions of the body be controlled selectively? The brain has two avenues of communication: hormones and neurons. Hormones are present throughout the body and obtain their specificity by acting on receptors with a tissue-specific, fluctuating expression, whereas neurons deliver their message to a precisely targeted tissue in the body.

Both branches of the autonomic nervous system were shown to discriminate between different fat compartments throughout the body. Within the motor nuclei of both the sympathetic and the parasympathetic nervous systems, 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 (Kreier et al., 2002). This regional organization of the autonomic nervous system is the basis for an interesting observation in a study of autonomic function: here, the sympathetic tone on the heart and the pancreas seemed to be opposite, while a strong correlation between the heart and the vascular control of the arms and legs exists (LeBlanc and Mercier, 1992; Sundlof and Wallin, 1977).

Supported by these neuroanatomical and physiological 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 (Kreier et al., in press).

4.5. The regional unbalanced and arrhythmic autonomic nervous system induces the metabolic syndrome

A set of interesting hypotheses address the role of the central clock and the autonomic nervous system in the metabolic syndrome. In general, the ideas agree on the "thrifty genotype hypothesis" of Neel, stating that evolution prepared us very well for the storing of energy to survive periods of depletion, a quality that is highly conserved in mammals, virtually on all chromosomes. We are often incapable of adapting to our wealthy environment, since we keep storing energy until we get type 2 diabetes (Neel, 1962). In other words, our genes have no clue about cars, elevators and remote controls, as Bjorntorp points out (Bjorntorp, 1983). Interestingly, Bjorntorp adds that concerning genetic studies, genes correlated to obesity might be so ubiquitous that a search for them will result in the description of large parts of our genotype (Bjorntorp, 2001).

Meier and Cincotta observe that obesity in mammals fluctuates with season, most prominently so in hibernating animals (Meier and Cincotta, 1996). They therefore suggest that a failing SCN might not shift back to the "lean" season and thus induce type 2 diabetes.

Others point to an unbalanced autonomic nervous system in the development of type 2 diabetes. Peterson et al. (1988), studying autonomic function in obese subjects, conclude that both the sympathetic and the parasympathetic nervous systems are inhibited. Bray (1990) also observes a reduced sympathetic activity but highlights an enhanced adrenal activity. He also puts emphasis on the role of afferents in energy homeostasis regulation (Bray, 2000). Jeanrenaud et al. find an enhanced parasympathetic and reduced sympathetic tone in animal models of obesity (Jeanrenaud, 1985; Jeanrenaud and Rohner-Jeanrenaud, 2001; Jeanrenaud et al., 1992). Bjorntorp clearly showed that the regional distribution of body fat is crucial for the correlation to the metabolic syndrome (Bjorntorp, 1992). In a review on leptin resistance, the selective pressor and depressor effects of leptin in different regions of the body are described, concluding that leptin might enhance sympathetic tonus in the cardiovascular system but might miss an effect on metabolic actions (Mark et al., 2002).

How could these different ideas about the role of the SCN and the autonomic nervous system have developed? Recently, we proposed an unbalanced autonomic nervous system by means of region and rhythm as a cause for the metabolic syndrome (Kreier et al., in press). The different results concerning the role of the brain in the development of type 2 diabetes could be better understood if the region of the body and the time of the day were examined differentially. In our view, a shifted balance in favor of the parasympathetic nervous system in the abdominal compartment and, at the same time, a shifted balance in favor of the sympathetic nervous system in the thoracic and movement compartment could be the reason for the conflicting results.

It matters, *where* in the body and *when* the measurements take place (Bjorntorp, 1983).

Here, we will present the evidence for an unbalanced autonomic nervous system classified per symptom of the metabolic syndrome and related disorders. In addition, we will suggest possible therapeutic approaches to fight the epidemic.

4.5.1. Cardiovascular disease

In hypertensive humans, postmortem analysis of the SCN and its effector regions revealed pathological changes (Goncharuk et al., 2001, 2002; Scheer et al., 2001). In diabetic patients, the circadian modulation of the sympatho-vagal balance to the heart is impaired (Bernardi et al., 1992). Furthermore, the expression of circadian clock genes of the heart is irregular in animal models of diabetes and cardiac hypertrophy (Young et al., 2001, 2002).

A prospective study on 8000 patients revealed significant autonomic dysfunction already in the developmental stage of type 2 diabetes (Carnethon et al., 2003). In line with these findings, in normotensive, centrally obese subjects, blood pressure does not dip at night anymore and shows a prolonged QT-interval, already early in the development of the metabolic syndrome (Esposito et al., 2002, 2003). Also, normotensive, non-obese type 2 diabetes patients are prone to a reduced nocturnal fall in blood pressure (Nakano et al., 2002). In type 2 diabetes patients, a reversed circadian rhythm in blood pressure alone predicts renal failure (Nakano et al., 1999).

In another prospective study on adolescent subjects, it was shown that enhanced pain sensitivity of 14-year-old healthy boys is related to autonomic nervous system tonus to the heart and that it predicts high blood pressure 8 years later (Campbell et al., 2003). Some studies address the regional activity of the autonomic nervous system and show that cardiac and renal sympathetic tone can be differentially modulated by exercise or medication (Aggarwal et al., 2003; Esler et al., 2001; Meredith et al., 1991).

Not body mass index (BMI) but waist-to-hip ratio is strongly correlated to high sympathetic input to muscle and to the kidney, which can be decreased with weight loss (Egan, 2003; Jones et al., 1996, 1997).

A selective central leptin resistance is suggested since a high sympathetic tonus could explain cardiovascular disease but not the development of obesity (Mark et al., 2002).

4.5.2. Type 2 diabetes

The hypothalamic regulation of insulin sensitivity was recently demonstrated by brain-specific infusions of insulin and fatty acids, showing that humoral feedback can modulate suppression of endogenous glucose production by the liver (Obici et al., 2002a,b). Similarly, neuronal feedback changes the way the brain controls energy homeostasis. Manipulating vagal afferents results in insulin resistance, changes in fatty acids metabolism, increased sympathetic tonus to muscle and changed glucose metabolism in muscle (Galassetti et al., 1998; La Fleur et al., in press; Latour and Lautt, 2002; Lavoie et al., 1987, 1988; Moore et al., 2002). In line with these findings, the only animal model of the metabolic syndrome with specific visceral obesity, the OLETF-rat, lacks the vagal feedback from the abdomen due to a defect in the cholecystokinin-a receptor. Interestingly, this defect in vagal feedback also leads to a disturbed function of the SCN (Shimazoe et al., 1999, 2000).

The circadian and ultradian rhythm in insulin secretion and sensitivity is disturbed in obese as well as in type 2 diabetes patients and in their non-diabetic first degree relatives (Boden et al., 1996, 1999; Polonsky et al., 1988a,b). The aberrations of pulsatile insulin can be observed early in the development of type 2 diabetes and might serve as an early marker of the disease (Porksen, 2002a). The autonomic nervous system is disturbed in glucose-tolerant but insulin-resistant offspring of type 2 diabetes patients (Frontoni et al., 2003).

Interestingly, elderly people show a disruption of the ultradian pulsatile modes of glucose-stimulated insulin secretion (Meneilly et al., 1999). Although this study did not estimate the relative amount of visceral fat, the age-dependent impairment of SCN function is well described (Hofman and Swaab, 1994). The mechanism of aging in the SCN might contribute to the development of the metabolic syndrome, illustrated by the fact that type 2 diabetes used to be called the ‘‘diabetes of the elderly’’.

4.5.3. Visceral obesity

After hepatic vagotomy, the circadian rhythm of fat tissue substrate uptake disappears (Martin et al., 1990). Recently, the vagus nerve was shown to play a substantial role in substrate uptake by fat tissue, and separate sympathetic and parasympathetic motor neurons were shown to build a neuronal network for the regional control of intra-abdominal and subcutaneous fat (Kreier et al., 2002).

Sympathetic tonus to muscle tissue is enhanced already in the state of visceral obesity (Alvarez et al., 2002). BMI has a low predictive value for the development of the metabolic syndrome. Even normal-weight subjects can have metabolic dysfunction, depending on their body fat distribution. A large amount of visceral fat relative to total body fat can induce the ‘‘metabolically obese’’ state in normal weight combination (Ruderman et al., 1998).

In a large prospective study among 1200 middle aged men, high cardiovascular morbidity and mortality was developing in metabolic syndrome patients without manifest cardiovascular disease or diabetes (Lakka et al., 2002).

4.5.4. Immune response

There is a complementary geographical distribution in the incidence of infectious diseases and autoimmunity

(Lyon et al., 2003; Matarese et al., 2002). In countries with low energy intake people suffer from infections, whereas people in rich countries suffer from an overactive immune system. Recently, it has been shown that a leptin surge precedes an increased immune response in an animal model of multiple sclerosis (Sanna et al., 2003). Interestingly, bone growth is modulated by the sympathetic nervous system, which in turn gets activated by leptin (Takeda et al., 2002). Possibly, it is not only bone tissue but also bone marrow that receives input from the autonomic nervous system at the same time and changes immune response. Here, the familiarity of signaling in energy homeostasis and the immune system might interplay in the feedback to the brain. Vagal stimulation was shown to attenuate the immune response in systemic inflammation (Borovikova et al., 2000). Moreover, the nicotinic receptor plays a role in a response to inflammation (Wang et al., 2003).

HIV-infection, HIV-medication and autoimmune diseases like Crohn's disease are correlated to lipodystrophy syndromes. Pond (2003) addresses the close anatomical relationship between the lymph nodes and the fat pads affected in an interesting hypothesis on the paracrine interaction between cytokines derived from overactive lymph nodes and cytokines derived from fat tissue. Possibly, central regulation affects both the lymphnodes and their surrounding fat tissue due to a neuroanatomical relationship and contributes to this phenomenon.

4.5.5. Sleep apnea syndrome

Interestingly, in a study with vagal pacing for cardiac therapy, a significant improvement of the sleep apnea syndrome was found (Garrigue et al., 2002). Metabolic syndrome patients have an impaired swallowing reflex (Okada et al., 2000; Teramoto et al., 1999). The relationship between sleep apnea syndrome and the metabolic syndrome is not clear; however, these data suggest an involvement of the autonomic nervous system.

5. Diagnosis and therapy

Since the metabolic syndrome can be considered as being partly a brain disease, as indicated by a regionally and circadianally unbalanced autonomic nervous system, before starting therapy, the diagnosis should address autonomic nervous malfunction. In view of the differences in regional activity of the autonomic nervous system, it does not seem feasible anymore to translate an assessed local autonomic tone to be representative for the autonomic tone of the whole body. "It is important to look at the integrated organism at different times [...] and to examine the events in different tissues, because these events might not be similar or comparable" (Bjorntorp, 1983). We suppose that a catalog of autonomic function tests in different regions of the body, assessing the thoracic, the abdominal compartment and muscle tissue separately at different time points will be crucial for the early identification of those at risk. Circadian regional autonomic nervous system tests might give an important advantage in the prevention of the epidemic.

Since central obesity is a main feature of the metabolic syndrome, the therapeutic approach should interfere with energy homeostasis directed to change the autonomic balance of the central compartment from vagal to sympathetic tonus. However, energy stores are very well protected by the brain as the coordinator of metabolism. Evolution gave these skills some priority, as witnessed by hundreds of markers on all chromosomes except the x-chromosome (Cummings and Schwartz, 2003; Lev-Ran, 2001). Any negative change in energy intake or expenditure will be corrected by counter-regulatory mechanisms (Berthoud, 2002; Spiegelman and Flier, 2001).

To interfere with energy homeostasis, exercise is an obvious way to change energy expenditure. Again, the brain senses the metabolic needs of the body and might fight back to the correct metabolic time. If exercise is performed and muscle becomes active, mobilization and consumption of energy needs to be organized (Bjorntorp, 1983). This changed regional autonomic function might be reflected by the fat redistribution in an exercise study with type 2 diabetes patients. Visceral fat was reduced by 48% in this intervention and total body insulin sensitivity increased by 41%, although total body weight did not change (Mourier et al., 1997; Stewart, 2002). A program of three times weekly aerobic exercise for 12 weeks significantly improved autonomic nervous system function in type 2 diabetes patients (Amano et al., 2001). In another study involving a weight loss program, QT-intervals shortened significantly after a 1-year intervention (Corbi et al., 2002). Also, the nightly drop in blood pressure could be restored by caloric restriction (Nakano et al., 1999, 2001).

Another possible intervention at the level of the SCN is its re-entrainment 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 (O'Brien et al., 1986; Yaprak et al., 2003). Interestingly, melatonin suppletion re-entrains the SCN and restores the diurnal variation in blood pressure in hypertensive patients and lets blood pressure fall at night (Scheer et al., 2003a). In rats, administration of melatonin at night induces visceral fat loss and improves the metabolic syndrome (Wolden-Hanson et al., 2000).

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