ELSEVIER

Autonomic Neuroscience: Basic and Clinical 85 (2000) 26–38

AUTONOMIC NEUROSCIENCE: Basic & Clinical

www.elsevier.com/locate/autneu

Review

The vagus nerve in thermoregulation and energy metabolism

Miklós Székely*

Department of Pathophysiology, University of Pécs, Faculty of Medicine, 12 Szigeti út, Pécs 7624, Hungary

Abstract

The vagus nerve may indirectly influence thermoregulation by modulation of energy balance: its afferent fibers convey signals that represent information on feeding state, resulting in either depression or stimulation of metabolic processes. A regulated metabolic depression can be detected in the background of fasting-induced hypometabolism and hypothermia. In its development (besides humoral signals) vagally transmitted neural signals of gastrointestinal and hepatoportal origin are important. These signals are related to hunger, to decrease of mechanical/chemical stimuli from the gut, to decline of blood glucose; they alter discharge rates of vagal afferents and activity of the nucleus of the solitary tract, eliciting inhibition of metabolic rate and enhancement of food intake. In this hunger-related metabolic inhibition the nucleus of the solitary tract is in interaction with hypothalamic nuclei, that contribute to neuropeptide changes characterized by high neuropeptide Y activity (with energy-conserving type of regulation) and depressed cholecystokinin and corticotropin releasing hormone activities (with depressed energy-expenditure). In postalimentary states the hypermetabolism and hyperthermia are due to opposite changes in metabolic regulation. Satiety-related stimulatory signals of abdominal origin, transmitted via hepatic vagal afferents to the nucleus of the solitary tract, contribute to enhancement of sympathetic activity and stress-responsiveness, leading to hypermetabolism and hyperthermia. Depressed neuropeptide Y release and enhanced cholecystokinin and corticotropin releasing hormone activities participate in the central regulatory changes, and in the high energy-expenditure. The biological role of these vagal functions is not directly the regulation of body temperature, rather the regulation of energy balance and energy content in the body.

Keywords: Fasting hypothermia; Diet-induced thermogenesis; Metabolic rate; Body temperature; Neuropeptides; Feeding behavior; Abdominal signals

1. Introduction

The past 5 years witnessed a remarkable development regarding our understanding of fever pathogenesis. It has become clear that the abdominal vagus may be involved in the genesis of experimental fevers (reviews: Blatteis et al., 1998; Romanovsky, this volume). Although fever itself is a pathological condition, it may also provide an opportunity to analyze more physiological variations of thermoregulation. Considering the concept that similar signals may participate in febrile and non-febrile thermoregulation (Székely and Romanovsky, 1998), the question arises, whether or not vagal fibers may also contribute to non-febrile regulation of metabolic rate and body temperature. The present paper makes an attempt to analyze the role the abdominal vagus might play in thermoregulatory and metabolic changes associated with nutritional state.

The vagus nerve is sensitive to various noxious and innocuous sensory modalities. It also contains a few thermosensitive afferent fibers (Adachi and Niijima, 1982), but it is not specialized to, and probably not even particularly important in, conveying *thermal* information from the periphery (Holzer, 1994). Similarly, the central vagal nuclei do not have specific or basic roles in the central thermoregulatory processes, although there is connection between the nucleus of the solitary tract (NTS) and brainstem, and the hypothalamic and other nuclei involved in thermoregulation and stress (Ciriello and Calaresu, 1980; Freie-Maia and Azevedo, 1990; Mönnikes et al., 1997). The main roles of efferent vagal fibers are also outside the field of temperature regulation. Therefore, a direct role of the vagus in thermoregulation does not appear to be important. There may, however, be overlap between vagal functions and the function of other regulatory circles that are responsible for, or involved in, thermal stability. Alternatively, the vagus may be involved primarily in the regulation of energy balance rather than directly in the regulation of body temperature.

The sensory part of the abdominal vagus is represented mainly by upper gastric-intestinal chemo- and mechanosensitive endings (that are sensitive to hormones,

*Tel./fax: +36-72-315-145.

E-mail address: mszekely@apacs.pote.hu (M. Székely).

1566-0702/00/$ – see front matter
PII: S1566-0702(00)00217-4

cytokines, nutrients, or to stretch, tension, stroking), besides different sensors in the hepatoportal system (Paintal, 1973; Mei, 1985). Altogether, these receptors are known to play a physiological role in the regulation of gastrointestinal motility and secretion, they may also influence homeostatic functions (e.g. glucoreceptors can modulate insulin secretion), and they may modify feeding behavior (Blessing, 1997). Under pathological conditions, vagal fibers may apparently participate also in the genesis of fever. It is possible that, apart from the mentioned physiological and pathological roles, various vagal fibers also play a role in feeding-related (non-febrile) thermoregulatory phenomena.

Feeding state has notable influence on body temperature. Chronic starvation or acute fasting is characteristically accompanied by hypometabolism and hypothermia, while both metabolic rate and body temperature are known to increase following food intake. The following basic questions need to be answered: firstly, are these variations of metabolic and thermal states consequences of regulatory changes or are they simply reflecting differences in the availability of metabolic substrates? Secondly, what sort of afferent signals participate in these changes? Is the afferent vagus involved? Thirdly, what are the characteristics of feeding-dependent changes in central regulatory functions? Fourthly, how can effector functions contribute to the metabolic and temperature changes in connection of altered food intake? Is there an efferent vagal participation?

2. Vagus and feeding-related metabolic/thermal changes

2.1. Fasting hypometabolism and hypothermia

2.1.1. Are they due to altered regulation?

Food deprivation results in decreased metabolic rate and body temperature. Hypometabolism and hypothermia have been observed in laboratory studies on fasting experimental animals, but history and medicine have also served with ample unfortunate examples of human starvation. The metabolic and thermal consequences were similar, irrespective of whether acute fasting or more prolonged starvation (chronic energy deficiency) was the cause. In medicine this state was regarded as 'vita parva', with life-functions continued on a low scale. It was not clear, whether simply the lack of metabolic substrates or rather a regulated depression can explain the phenomenon.

Common sense has suggested for a long time, that decreased fuel availability might be responsible for these changes. Indeed, some observations pointed to decreased substrate mobilization/utilization in the background of fasting hypometabolism, explained mainly by altered cAMP production/degradation (Jourdan et al., 1984), depressed sympathetic activity (Young and Landsberg, 1977), depressed thyroid functions (Hayashi and Nagasaka, 1983). In these cases the hypothermia could be regarded as only secondary. Although metabolic depression and hypothermia were observed at resting conditions at thermoneutrality, stronger stimuli were still able to induce some elevation of metabolic rate in all of these cases. From the finding that starving piglets established low resting temperatures and metabolic rates, despite being able to somewhat enhance their metabolism, McCance and Mount (1960) long ago concluded that rather well-organized regulatory changes had to be responsible for this hypothermia. On the basis of such earlier and more recent observations (Heim and Mestyán, 1964; Schwartz et al., 1995; Schwartz and Seeley, 1997), it seems likely that fasting-induced falls in metabolic rate and temperature are really manifestations of complex regulatory changes, elicited by the deficient food intake.

In cold-adapted rats fasting can quickly induce severe hypometabolism and hypothermia. Such rats were still demonstrated to maintain the 'overshoot' metabolic response to acute cold-exposure (Székely et al., 1997b), what was otherwise characteristic for cold-adapted rats (Székely and Mercer, 1999): upon acute cold-exposure their metabolic rate increased more than the actual need and body temperature exhibited a paradoxical rise. Fig. 1 shows a similar example: in cold-adapted fasting rats the reaction to centrally applied prostaglandin E (PGE) was greater than in similar rats without fasting. It may be concluded that, despite resting hypometabolism, the food-deprived animals still have some 'hidden' energy resources that they can mobilize. In these experiments the appropriate stimulus for mobilization was of thermoregulatory character: either cold-exposure or PGE. Similar conclusion can be drawn from the experiments of Hummel et al. (2000) and Yoda et al. (2000). These authors demonstrated that the circadian temperature changes not only were maintained, but were exaggerated in fasting rats: while the daytime resting temperature values (nadir) decreased, at night the peak values (acrometron) remained within about the normal range. In fasting pigeons the circadian temperature changes were also enhanced (Rashotte et al., 1998). In these rats and pigeons the circadian signal for the inactive–active transition provided a stimulus to switch on energy mobilization. Without such thermal or circadian stimuli, however, the animals failed to use their still-existing energy resources, and this probably cannot be explained by any other way than a *regulated* metabolic depression. This is primarily not a regulated temperature change in the sense used by Gordon (1983), but the altered metabolic regulation may secondarily lead to a decline in body temperature (already at thermoneutrality). Further support to the concept of regulatory character of the abnormality was lent by Yoda et al. (2000), who demonstrated incomplete behavioral compensation of hypothermia in fasting rats.

If so, what can explain this change in regulation? It seems plausible that feeding-related chemical or mechani-

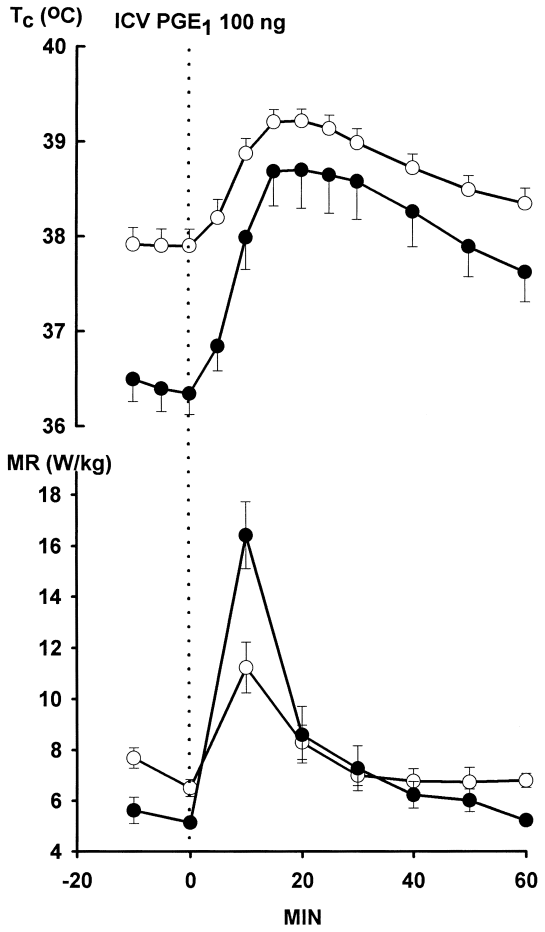

Fig. 1. Core temperature and metabolic rate in control (open circles) and 72-h fasted (closed circles) rats following intracerebroventricular injection of 100 ng PGE_1. Female Wistar rats ($n=7$ per group) were kept at a room temperature of 4°C for a period of over a month, the tests were performed at thermoneutrality (25°C). PGE abolished the resting hypometabolism and hypothermia of fasting rats, and in these rats the rises of metabolic rate and body temperature were even greater than in control animals (unpublished data of Székely and Balaskó).

cal signals (or their absence) from the gastrointestinal tract and/or the hepatoportal system may be responsible for, or contribute to, the regulatory depression. Since mainly the vagus nerve provides sensory innervation for the gastrointestinal tract (the role of the splanchnic nerve is smaller and more specific), it seems justified to assume that the neurally transmitted part of these signals is conveyed mostly by the vagus nerve.

In conclusion, the fasting-induced hypometabolism develops due to a regulated metabolic depression and results in hypothermia. Action of gastrointestinal factors (decreased gastrointestinal tension and chemical signals) can be hypothesized to contribute to this central regulatory change.

2.1.2. Afferent signals

From the previous data it is uncertain, however, what sort of gastrointestinal factors may explain the fasting-induced metabolic depression. Although neural signal transmission need not be the only information route (humorally transmitted signals may also play a role in influencing central regulatory processes), here emphasis is given to those gastrointestinal/hepatoportal factors, which induce neural signals.

It is not clear, whether the neural signals originate from (a) abdominal thermoreceptors, (b) gastrointestinal mechanoreceptors (e.g. lack of gastric/intestinal distension), or (c) chemoreceptors of the gastrointestinal tract (sensitive to gastrointestinal hormones and/or preabsorptive nutrients) and of the portal vein/liver (that may sense postabsorptive nutrients or products of altered metabolism). Nor is it clear whether (d) the depression is due simply to an absence of satiety-related signals that would normally stimulate metabolism, or rather to the presence of some hunger-related signals that could inhibit metabolic rate (i.e. that could induce energy-saving type of regulation).

(a) Peripheral cooling has previously been shown (Székely et al., 1997b) to overrule the metabolic depression, while central cold sensors (that are continuously excited due to the sustained hypothermia) do not seem to have such function. This is in accord with the finding that (at least in cold-adapted rats) peripheral cooling is more effective in activating cold defense than is internal cooling (Székely and Mercer, 1999). This also means that thermoregulatory factors, despite occurrence of thermosensitive fibers in the abdominal vagus, probably play no outstanding role in the development of the depression, the latter appears to result solely from non-thermal (gastrointestinal and liver) factors.

(b) The influence of gastrointestinal distension on temperature regulation has been nicely demonstrated in birds. Reinertsen and Bech (1994), as well as Geran and Rashotte (1997), observed that the nocturnal body temperature of pigeons was related to the volume rather than to the energy content of the food they had previously consumed. Decreasing the intake of non-nutritive pellets resulted in lower nocturnal body temperatures. Similarly, low nocturnal temperatures were found in young men when the amount of the evening meal was decreased (Driver et al., 1999).

(c) As regards chemosensors, the picture is less clear. There are no data available to demonstrate the accumulation of any hypothermia-inducing chemical substances in the gastrointestinal tract during fasting. In theory, out of the great number of intestinal chemoreceptors (Mei, 1985), some might have their activities altered with changing food availability, in a way to induce metabolic depression. Thus, e.g. gastrointestinal cholecystokinin (CCK) production decreases in fasting. *Positive* correlation will be demonstrated between peripheral/gut CCK levels and vagal activity (i.e. high CCK levels — high vagal discharge rates), coupled with depression of food intake, and activation of energy metabolism. By the

same token, low CCK levels may be expected to cause low vagal activity and low metabolic rate. Ichikawa et al. (1998) have indeed demonstrated that CCK-A-deficient rats have slightly low metabolic rates per body mass. Changes of other gastrointestinal peptides in the gut, as well as absence of preabsorptive nutrients, might also be presumed to provide signals for such energy-saving type of regulation.

Chemosensitive functions of the hepatoportal system (sensing postabsorptive nutrients) could also be important in this respect, but in a different way (indicating that possibly dissimilar vagal fibers or central cell populations are affected). Niijima and Meguid (1994) demonstrated an *inverse* relationship between nutrients in the portal vein and discharge rate of afferent vagal fibers that send information to the lateral hypothalamus. Accordingly, with low nutrient concentrations the discharge rate was high. Portal or intravenous infusions of nutrients were followed by enhanced brown fat activity (Sakaguchi and Yamazaki, 1988). Understandably, lack of such nutrient signals in fasting should be assumed to result in high vagal discharge rates and in hypometabolism with hypothermia. (This is different from the gastrointestinal CCK-type actions in which high vagal discharge is coupled with hyper- (and not hypo-) metabolism.) However, in contrast to the gut, only a small number of vagal sensory endings were found in the portal vein and none in the liver (Berthoud and Neuhuber, 1994).

Re-feeding of fasting rats either with normal chow or with calorie-free (saccharine-sweetened $CaCO_3$) tablets promptly normalized metabolic rate and body temperature (Székely et al., 1997b). Similarly, metabolic and thermal normalization followed when fasting rats were given food (or calorie-free X-ray contrast material) through a gastric cannula (Ember et al., 2000), to avoid oro-facial excitation. Thus, feeding-related chemical/mechanical gastrointestinal stimulatory signals that excite the vagus and cause 'satiety' were able to reverse the regulatory depression. It is likely, therefore, that the fasting depression was, at least partly, due to lack of these stimulatory signals, or to presence of other, 'hunger'-related (inhibitory) signals also from the gastrointestinal tract. Both types of signals are likely to be transmitted by branches of the abdominal vagus, since decreases in volume, CCK, or duodenal nutrients have all been suggested to attenuate (Schwartz et al., 1993; Schwartz and Moran, 1998), low blood glucose to elevate (Niijima and Meguid, 1994) vagal afferent activity. The role of the vagus in this transmission needs further analysis.

(d) Following subdiaphragmatic vagotomy the animals are in very poor condition (Kraly et al., 1986; Romanovsky et al., 1997a,b); they need special care for survival. Thus, vagotomy may not be a suitable model to study the role of vagus in metabolic/thermal balance, including food intake or body weight. Polymodal sensory nerves (e.g. afferent vagus) can, however, be selectively damaged by local capsaicin (Szolcsányi, 1982). In contrast to vagotomy, rats pretreated with intraperitoneal capsaicin are not in a bad shape, while the local damage to their afferent vagal fibers (Székely et al., 1997a) allows the analysis of vagal influence on metabolic regulation.

In more recent experiments (Székely, Balaskó, Pétervári, unpublished), food deprivation caused over 20% greater body weight fall in capsaicin-treated than in control rats (Fig. 2). In general, it is assumed that the greater the energy expenditure during fasting (or smaller the metabolic depression), the more severe the fall in body weight has to be. Thus, from their greater weight loss, capsaicin-treated rats might be concluded to have less expressed metabolic depression as compared with controls. The difference might be explained by changes of either satiety/metabolic-stimulatory or hunger/metabolic-inhibitory signals. During food-deprivation the satiety-signals were unavoidably reduced (which does not necessarily mean activation of hunger-induced inhibitory signals). Less expressed metabolic depression of capsaicin-treated animals could possibly be explained, if capsaicin lifted the depression by inducing satiety, or if capsaicin suppressed the assumed hunger-related inhibitory signals. However, no satiety was observed: upon re-feeding, capsaicin-desensitized rats ate more and regained more body weight than did control rats (Fig. 2). Accordingly, here hunger-signals (and not satiety-signals) had to be altered by capsaicin, and conversely, without capsaicin the fasting hypometabolism probably could not be explained simply by lacking satiety-signals, rather by presence of fasting-specific metabolic-inhibitory signals. These inhibitory-type hunger-signals might be attenuated by capsaicin-treatment, with a final result of lessening the metabolic depression.

The 'inhibitory-type' signals, whether neural or humoral, may possibly be qualitatively or quantitatively different from the 'stimulatory' signals seen in situations of satiety.

Presence of vagally carried inhibitory-type signals has also been demonstrated in the experiments of Yang et al. (1992): total parenteral nutrition suppressed oral food intake, and the suppression could be reduced by vagotomy, suggesting that some vagally-mediated inhibitory (hepatoportal?) influence was removed by transection of the vagus nerve. These studies referred to food intake regulation; metabolic rate was not measured. Niijima and Meguid (1994) reported similar observations.

In brief, in the fasting-induced central regulatory depression of metabolic rate (and in the consequent hypothermia) a role can be ascribed to vagally conveyed afferent signals

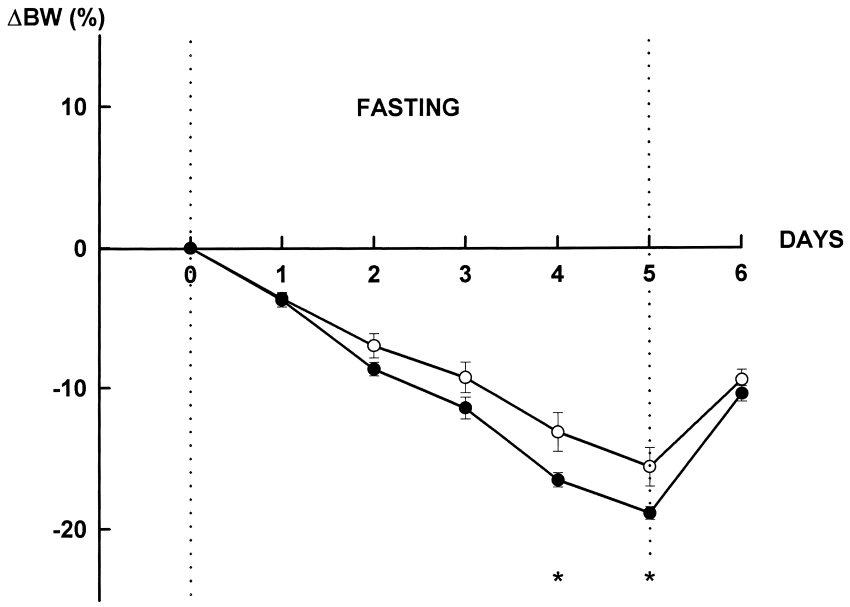

Fig. 2. In the course of 5 days food deprivation, the fasting-induced fall in body weight was 14.7% in control (open circles), and 19.0% in i.p. capsaicin-treated (closed circles) rats (unpublished data of Székely, Balaskó and Pétervári). Water was accessible, but its consumption was not measured. During re-feeding capsaicin-treated animals ate more than controls, and regained their body weights faster. Asterisks denote statistically significant differences.

of gastrointestinal (and hepatoportal) origin. These signals are related to hunger, and they inhibit metabolism. Peripheral or central thermoregulatory signals (PGE or cold exposure), or certain circadian signals may overrule the fasting-induced depression, just as gastrointestinal signals can do it in the course of feeding. Feeding-related signals may exert their actions by modulating the vagal afferentation, thereby inducing central regulatory changes. In contrast, the primary thermoregulatory and circadian signals, emotional or endocrine factors etc., originate from different sources, they are independent of the afferent vagus, and they may modulate (or even overrule) the central regulatory processes (including those derived from vagal afferent activity). Neither the development, nor the limitation of the metabolic and thermal changes to the latter signals and factors appears to be connected with afferent vagal function.

2.1.3. Central regulation in fasting hypometabolism and hypothermia

A great number of brain substances may be involved in regulation of food intake and energy metabolism, some of them being anabolic (enhancement of food intake and energy-conservation, with hypometabolism and hypothermia), others catabolic (with decreased food intake and high energy-expenditure, hypermetabolism and elevated body temperature). These include neurotransmitters like norepinephrine, dopamine, serotonin, acetylcholine; amino acids like glutamate, gamma-amino-butyric acid; and various peptides. The gastrointestinal peptide cholecystokinin (CCK) acts mainly, but not exclusively, at the periphery. Other peptides have more definite central points of action, among them the *anabolic* peptides neuropeptide Y (NPY), agouti-related protein, melanin-concentrating hormone, orexins, galanin, and the *catabolic* peptides like the products of the pro-opiomelanocortin (POMC) molecule (corticotropin-releasing hormone (CRH), α-melanocyte stimulating hormone (α-MSH) that act at melanocortin receptors), or thyrotropin-releasing hormone, cocain-amphetamine-regulated transcript (CART), amylin, etc. The present paper deals mainly with the proposed role of the neuropeptides CCK, NPY and the POMC group in fasting-induced changes of metabolic and temperature regulation, and also with their possible vagal connections.

Peripheral CCK is released mainly from the secretory cells of the gastrointestinal system. It modulates the function of gastric tension receptors (and perhaps that of hepatoportal receptors), and increases their activity (Raybould et al., 1985). Tension and CCK synergistically (Davison and Clarke, 1988; Schwartz et al., 1993) activate vagal fibers (Cox and Randich, 1997) and cause increased expression of *c-fos* in the NTS (the primary afferent projection area of the vagus) and in other interconnected nuclei (e.g. paraventricular nucleus). This indicates activation of these sites. Through the ventral noradrenergic bundle, NTS is connected to the preoptic area (Ricardo and Koh, 1978) where PGE is released, resulting in enhanced activity of catabolic effector pathways. NTS and the paraventricular nucleus are also connected with other sites (Freie-Maia and Azevedo, 1990), including the locus coeruleus that is related to the stress response (Valentino et al., 1993). In capsaicin-treated animals the effect of CCK

on NTS *c-fos* is suppressed (Fraser and Davison, 1992), and the effect of CCK to increase hindbrain neuronal discharge is attenuated (Ritter et al., 1989).

In these experiments, the described effects were related mainly to the action of CCK to cause anorexia. For comparison, it should be mentioned that similar *c-fos* expression in NTS and in the adjoining noradrenergic A_2 cell group has been described for pyrogenic lipopolysaccharide or interleukin-1 (IL-1) administration (Wan et al., 1994; Ericsson et al., 1994). Reportedly, the actions of these substances are vagally mediated (Fleshner et al., 1995). They include feeding depression, metabolic rise and fever (Blatteis et al., 1998). Capsaicin treatment of the caudal ventrolateral medulla, which is in connection with the NTS, also modifies endotoxin fever (Koulchitsky, 1998).

Thus, CCK may be one of the important peripheral signals for satiety and possibly for catabolic mechanisms. Data of Kapás et al. (1987) — showing hypothermia in response to CCK — do not appear to be fully in line with this idea, but the hypothermia might have been explained by heat loss effects of the high peripheral CCK doses used. Peripheral CCK acts by endocrine or paracrine pathways mainly at CCK-A receptors, but CCK is also a neurotransmitter in the brain, acting at CCK-B receptors. The two forms need not be related, but a relationship seems possible. The latter form is more important from the point of view of central regulations. Centrally applied CCK, besides eliciting depression of food intake (Della-Fera and Baile, 1979; Schick et al., 1994), induces sympathetic activation and enhanced brown fat thermogenesis (Yoshimatsu et al., 1992), and causes elevations in metabolic rate and body temperature (Szelényi et al., 1994).

Apparently, either peripheral CCK actions (through the vagus and NTS), or central CCK activity may be connected with satiety and may activate catabolic effector pathways. Obviously, suppressed peripheral and central CCK activities would be expected in fasting, but there are no data confirming such suppression. Earlier in this paper it was suggested that (apart from lack of stimulatory signals) vagally conveyed signals that inhibit metabolic rate and body temperature must play a role during fasting. However, the suppressing signals might easily have other targets (e.g. directly the vagus or hypothalamus), not necessarily the (vagal or central) actions of CCK. In fact, CCK-A deficiency in rats has been reported to leave body temperature unaffected (Sei et al., 1999), despite causing rather low resting metabolic rate (Ichikawa et al., 1998).

During fasting, those hypothalamic pathways that promote caloric intake and inhibit energy expenditure (‘anabolic effector pathways’) are activated, while the function of those that reduce food intake and energy storage (‘catabolic effector pathways’) is attenuated (Schwartz et al., 1995, 2000).

Insulin and leptin are known to depress anabolic NPY release in arcuate and paraventricular nuclei (Sahu et al., 1995; Schwartz et al., 1996), thus the known low leptin and insulin levels during food deprivation may be assumed to contribute to an elevation of NPY release. Schwartz and Seeley (1997) and Schwartz et al. (2000) have indeed demonstrated that during food deprivation the endogenous NPY release may be enhanced. Exogenous NPY injected into the hypothalamus or to the cerebral ventricle enhances food intake, and causes falls in metabolic rate, body temperature (Roscoe and Myers, 1991; Billington et al., 1991; Balaskó and Székely, 1999), and sympathetic activity (Egawa et al., 1991). Fasting-induced NPY release is coupled with hunger (or forebrain-to-hindbrain inhibition of NTS and incoming satiety signals of gastrointestinal origin) and also with decreased sympathetic activity and metabolic-thermal depression (through action within hypothalamic nuclei). NPY antagonists should cause hypermetabolism in fasting animals by depressing endogenous NPY or by counteracting its action, but no such antagonists have been found until now.

In rats, POMC is an important representative of the catabolic pathway (Schwartz et al., 1995; Schwartz and Seeley, 1997). CRH, either given centrally (Rothwell, 1989) or released endogenously due to IL-1 (Uehara et al., 1989), has opposite actions to NPY. Depression of hypothalamic CRH concentration during starvation (Suemaru et al., 1986) may promote the development of hypometabolism and hypothermia. Low leptin and insulin levels in fasting contribute to the depression of CRH synthesis in paraventricular nucleus (Schwartz et al., 1996; Seeley et al., 1996). However, the role of CRH seems to be more controversial, since in another species (rabbit) CRH is regarded as an endogenous antipyretic substance (Opp et al., 1989).

While one might assume a connection between peripheral (vagally transmitted) and central CCK activities in metabolic regulation, the connection with the vagus may be different for the other two peptides. NPY and CRH release may be, to a great extent, independent of the afferent vagus; their production may be regulated by other ways, mainly by the humoral action of insulin and leptin, or by the hypothalamo-pituitary axis. Only some insulin actions seem to be exerted not by the direct humoral route, but through vagal afferents (VanderWeele, 1998). The visceral afferent information conveyed by the vagus to the NTS may, however, be modulated by these peptides (Ergene et al., 1993; Ren et al., 1990), causing alterations in the relay function of the NTS and in the satiety state. At the same time, the hypothalamic nuclei are in reciprocal interaction with the NTS and are also influenced by NTS activity. Paraventricular NPY, for example, initiates anabolic signal to the NTS (and enhances food intake), while its hypothalamic effects causing hypometabolism and hypothermia are influenced by interconnection with the NTS. Paraventricular nucleus is also connected with other nuclei, like locus coeruleus. Locus coeruleus is another important site connected with NTS. This site may

have particular importance, as this is where CRH and catecholamine mediations of the stress response are integrated (Valentino et al., 1993) — increased activity in the locus coeruleus is coupled with enhanced stress response and thus, with a tendency for temperature rise.

Apparently, the abdominal vagus is an important contributor to the development of fasting-induced changes in central metabolic regulation. Vagotomy or capsaicin-treatment may attenuate the metabolic depression, i.e. vagal activity can definitely modify this regulatory function, although otherwise the central structures are capable of operating normally: the central regulation is completely responsive to extraabdominal challenges in vagotomized or capsaicin-treated animals. Thus, after vagotomy, cold exposure (Romanovsky et al., 1997b), intracerebroventricular injection of PGE (Milligan et al., 1997; Sugimoto et al., 1999), or emotions (Cabanac and Dardashti, 1999) can increase metabolic rate, but intraperitoneal (i.p.) IL-1β (that may use the abdominal vagus) is without effect (Watkins et al., 1995). Similarly, in vagotomized rats sleep deprivation is followed by normal sleep (Hansen and Krueger, 1998), but the cafeteria diet-induced sleep (with signals transmitted by the vagus) is prevented (Hansen et al., 1998). Following vagotomy anorexia to i.p. CCK is suppressed (Ritter and Ladenheim, 1985), but not to centrally acting IL-1α (Laviano et al., 1995). However, damage to the central endings of the vagus (NTS) has been reported to prevent such responses as the PGE-hyperthermia (Fyda et al., 1991).

2.1.4. Peripheral effector functions

Besides the regulatory changes, fasting hypometabolism is accompanied by metabolic abnormalities at the tissue level, e.g. the amount of brown adipose tissue decreases, the content of its mitochondrial protein and uncoupling protein is reduced (Muralidhara and Desautels, 1994). In vitro metabolic rate of brown fat from fasting rats is also low (Saha et al., 1999). Thermogenesis induced by a meal should involve activity of the sympathetic nervous system (Griggio et al., 1991), but during food deprivation the sympathetic activity is reduced (Young and Landsberg, 1977) and parasympathetic tone is enhanced. Reduced amount of thyroid hormones contributes to the low thermogenic response of brown fat to norepinephrine (Hayashi and Nagasaka, 1983), although the sympathetic depression is mainly due to enhanced NPY action in the paraventricular nucleus (Egawa et al., 1991). All these effects are independent of the efferent vagus.

2.2. Postalimentary thermogenesis

2.2.1. Is there a regulatory alteration involved?

Consumption of a single meal is followed by fast and short-lasting postalimentary elevation in metabolic rate and in body temperature, a phenomenon called the thermic effect of the food. Regular ‘hyperphagic’ food intake, depending on the composition and amount of the diet (e.g. cafeteria-diet), has more lasting influence on metabolic rate, usually named as diet-induced thermogenesis. Neither hypermetabolic state seems to depend directly on the increased availability of energy. Thermic effect of food can be demonstrated not only with normal meals, but also with meals containing no calories (Székely et al., 1997b). Conversely, in various animal models of obesity, diet-induced thermogenesis may be dissimilar in different animals even if their diets are similar (Rothwell and Stock, 1979). Apparently, postalimentary hypermetabolism and hyperthermia may be due to changes in metabolic regulation.

2.2.2. Afferent signals

Spontaneous food intake is usually preceded by a slight decline in blood glucose and the concurrent sympathetic activation already causes some temperature rise. The process of food intake is accompanied by further substantial elevation in metabolic rate and body temperature. Hepatic metabolism is particularly high, and in rats food consumption stops when liver temperature reaches a critical high (around 39°C) level (De Vries et al., 1993; Himms-Hagen, 1995). This means, on the one hand, that the process of food intake does participate in the development of hypermetabolism and hyperthermia, on the other hand, that ingestion-induced thermal signals influence ingestive behavior itself. Thermal signals from liver thermoreceptors are transmitted to the hypothalamus mainly through hepatic vagal fibers (Di Bella et al., 1981). According to Himms-Hagen (1995), in cold adaptation the meal size may be larger because, during feeding in the cold, liver temperature rises more slowly than at thermoneutrality. Liver temperature may, indeed, limit food intake and also the further rise in metabolic rate and body temperature (Baconnier et al., 1979; Di Bella et al., 1981; De Vries et al., 1993). This thermosensitivity, however, appears to counteract and not to promote the development of postalimentary hyperthermia.

Some data demonstrate a role played by mechanoreceptors in postprandial changes of metabolic regulation. In the experiments of Andrews et al. (1985) free-fed rats were additionally force-fed through a gastric tube. Such feeding with carbohydrate caused a rise in metabolic rate by 18% above the resting value, but the rise was only 8% in subdiaphragmatically vagotomized rats. Brown fat activation (that depends on sympathetic and not on vagal efferent activity) was also smaller after vagotomy, i.e. vagal afferents from the gastrointestinal tract (sensing satiety) must have participated in the induction of hypermetabolism.

To avoid the tube-feeding procedure, the thermic effect of food can be analyzed by other ways: e.g. by measuring metabolic rate and body temperature in the course of re-feeding previously food-deprived animals, or by using pre-implanted gastric cannula. Experiments cited earlier

(Székely et al., 1997b; Ember et al., 2000) have shown that when either conventional (calorie-containing) food or calorie-free substance was given to fasting rats, orally or through a gastric cannula, metabolic rate and body temperature were re-elevated. Regarding the role of the vagus in these volume-induced metabolic changes, there are no data available, as yet.

Data on parenteral feeding shows that, besides volume, the amount of introduced energy may also be an important factor in determining energy metabolism, suggesting a role for chemoreceptors. In rats with their total daily calorie requirement covered by venous infusions, the oral food intake was strongly depressed (Yang et al., 1992). This indicates antagonism against those gastrointestinal (hunger) signals, which would induce food intake (and which, according to the previous sections, would probably cause metabolic inhibition). Further, this shows that circulating nutrients (or insulin) can provide feedback signals for food intake and metabolic regulations (antagonize food intake and enhance metabolic rate). Interestingly, in vagotomized rats the oral intake was less antagonized, despite similar parenteral caloric infusion, emphasizing that some of these feedback signals were conveyed by the vagus nerve.

Both afferent vagal activity and food intake regulation are attenuated by portal infusion of glucose or amino acids (Schmitt, 1973; Sawchenko and Friedman, 1979; Niijima and Meguid, 1994; Niijima, 1996). In addition, portal infusion of glucose increased sympathetic discharge to brown adipose tissue in rats (Sakaguchi and Yamazaki, 1988). In human subjects intravenous injections of glucose or amino acids elevated metabolic rate (Green and Macdonald, 1981; Aksnes et al., 1995). These data indicate a significant chemoreceptor function for the hepatoportal system in metabolic regulations, through altered activity of hepatic afferent vagal fibers. This may be in line with the finding that hypermetabolism follows the infusion of endotoxin into the portal vein (Arita et al., 1988).

In other cases stimulation of the vagal fibers was connected with metabolic rise. Increased activity of afferent vagal fibers was observed in the course of IL-1β action (Niijima, 1996; Plata-Salamán, 1998) that involves hypermetabolism. Recent data also show that information conveyed by the hepatic vagal branch (Simons et al., 1998) participates in the initial part of experimental fevers, which part is coupled with high metabolic rate (Romanovsky et al., 2000b). Chemical factors from Kupffer cells (Husztik et al., 1980), by exciting the hepatic vagus, contribute to the initiation of febrile responses (Blatteis et al., 1998).

Presence of nutrients in the gut may provide important stimulatory signals for metabolic regulation. Apart from preabsorptive nutrients, other vagally transmitted chemical signals may be of even greater importance. Thus, gastrointestinal hormones are also altered in postalimentary states, e.g. CCK rises with postalimentary satiety, and CCK has been shown to stimulate the vagus nerve (Cox and Randich, 1997) and to influence central processes of metabolic regulation, to stimulate metabolism.

Besides neurally transmitted signals, humoral signals (e.g. rise of insulin, leptin) may also be important in the development of postalimentary hypermetabolism: they suppress NPY and enhance CRH release in the hypothalamus (Schwartz et al., 1995).

In the light of the above-mentioned data, it was rather intriguing to reconsider the interpretation of some old observations. The characteristic postnatal increase of minimum metabolic rate had been reported absent in newborn rabbits or lambs, in case where the neonates were not fed in the postnatal days (Andrews et al., 1975; Mercer et al., 1979). However, upon foster-feeding such rabbits, their metabolic rate immediately increased to the level observed in well-fed neonates of the same age (unpublished data of Andrews and Székely). Apparently, this might be explained by a suppressed fetal metabolism in utero (Laburn, 1996) presumably persisting after birth, until being abolished by alteration of the gastrointestinal signals at commencement of the normal feeding process. In other words, the metabolic suppression (and its abolition) seems to depend on gastrointestinal signals. This observation is very similar to those data according to which re-feeding normalized the low resting metabolic rate and body temperature of fasting rats (Székely et al., 1997b). Extreme caution is needed, however, with the interpretation of such re-feeding data, since in the course of oral feeding components of the ‘cephalic phase’ are intermingled with chemical and mechanical impulses of gastrointestinal origin.

In conclusion, satiety-related stimulatory signals of gastrointestinal mechanical, chemical/nutrient origin are transmitted through hepatic fibers of vagal afferents. Besides, postabsorptive nutrients may block the hunger-related inhibitory signals that are also carried by vagal fibers. Both processes are presumed to influence metabolic rate and body temperature, and both may contribute to the hypermetabolism and hyperthermia following food intake.

2.2.3. Central regulation in postalimentary hypermetabolism

Food intake induces enhanced secretion of CCK, as a satiety factor, in the gastrointestinal system. Insulin is also elevated and, at least in food intake regulation, it is reported to act synergistically with CCK (VanderWeele, 1998). The anorexigenic effect of peripheral CCK, although indirectly, may be connected with central CCK-B receptor activation. Centrally applied CCK causes sympathetic (and brown fat) activation, elevation in metabolic rate and hyperthermia (Yoshimatsu et al., 1992; Szelényi et al., 1994), besides leading to anorexia (Schick et al., 1994), and central CCK also contributes to fever (Székely et al., 1994). Peripherally applied CCK has been shown to activate hepatic vagal C-fiber afferents (Cox and Randich, 1997). This causes *c-fos* expression in NTS, dorsal vagal

complex, and other nuclei (like paraventricular nucleus, locus coeruleus) involved in the regulation of food intake, energy metabolism and body temperature (Fraser and Davison, 1992; Mönnikes et al., 1997). Food intake also elevates *c-fos* expression in NTS (Zittel et al., 1999). Similar *c-fos* expression was observed in NTS following endotoxin administration (Elmquist et al., 1996), together with increases in sympathetic tone, metabolic rate and body temperature (fever). Capsaicin pretreatment of the vagus nerve prevents *c-fos* expression to peripheral CCK (Fraser and Davison, 1992). Moreover, both capsaicin pretreatment (Ritter and Ladenheim, 1985) and abdominal vagotomy (Eberle-Wang et al., 1993) can prevent the anorexigenic effect of CCK, as well as the initial part of the febrile response to bacterial lipopolysaccharides (Romanovsky et al., 1997c, 2000b).

As demonstrated in the previous section, during starvation the hypothalamic NPY level increases (Schwartz et al., 1995; Schwartz and Seeley, 1997), contributing to fasting hypometabolism. By the same token, decreased hypothalamic NPY levels and hypermetabolism could be expected following feeding. However, in contrast to fasting, there has been no data showing that NPY levels or NPY release in the hypothalamus would change (decrease) simply in consequence of the well-fed state. Experimentally, small increases in insulin level (Sahu et al., 1995) or administration of leptin (Schwartz et al., 1995; Ahima et al., 1996) have been reported to suppress NPY release in the paraventricular nucleus. In fact, in well-fed states both plasma insulin and leptin levels are in the high-normal range. Portal insulin infusion causes fall in meal size (VanderWeele, 1998) in control, but not in vagotomized rats. Thus, various insulin actions are exerted through the vagus nerve, but insulin can also reach the brain directly. In both ways, the relative hyperinsulinemia leads to activation of the sympathetic system, and through this, to enhanced nonshivering thermogenesis. Understandably, this thermogenesis is not absolutely dependent on the vagus nerve: a vagal role is likely only if vagotomy or capsaicin-treatment can really influence thermogenesis. In fact, there is data showing such influence. Following systemic capsaicin-treatment, brown adipose tissue of rats exhibits signs of impaired thermogenic responsiveness to diet (Cui et al., 1990), but this may also be explained by other mechanisms.

A comparable situation occurs when, during cold exposure, the hypothalamic NPY levels (contrary to expectations) do not decrease, rather increase, as a result of depressed release and consequent accumulation in hypothalamic tissues (McCarthy et al., 1993; Bing et al., 1998). In this case the decreased release of NPY results in disinhibition of the sympathetic outflow to brown adipose tissue and the consequent elevation in heat production contributes to maintenance of thermal balance in the cold. The cold-induced (nonshivering) thermogenesis is not the same as, but in its mechanism is very similar to, diet-induced (nonshivering) thermogenesis (Champigny and Ricquier, 1990). The role of the vagus has not been compared in these cases.

Systemic injection of IL-1 induces a rise in hypothalamic CRH (Sapolsky et al., 1987), probably via a vagal mechanism, since vagotomy can prevent this rise (Gaykema et al., 1995) or the rise in corticosterone (Fleshner et al., 1995). Involuntary overfeeding and high levels of insulin (Seeley et al., 1996) also elicit elevation of CRH release. Acute stress (Dallman, 1993), or intracerebroventricular administration of leptin (Schwartz and Seeley, 1997) may stimulate the expression of CRH gene in the paraventricular nucleus, without apparent involvement of the vagus. Central administration of CRH activates the sympathetic system (Brown et al., 1982), elevates thermogenesis, and causes anorexia (Rothwell, 1989; Bray et al., 1990). CRH activity is certainly not controlled solely by vagal influences, but vagal signaling may have a role in feeding-related CRH activation.

Apparently, although vagal activity may influence both central NPY and CRH mechanisms, the production and release of NPY and CRH are regulated, to a large extent, by factors independent of the vagus. Central NPY is also known to enhance the activity of the hypothalamo-pituitary-adrenal axis (Schwartz and Seeley, 1997). Moreover, NPY can modulate the processing of vagus-mediated visceral information in the NTS (Ergene et al., 1993). Besides, through the connection between the NTS and paraventricular nucleus, locus coeruleus and/or other nuclei, vagally carried signals can modulate CRH and its role in the stress response (Valentino et al., 1993), including its effect to cause hypermetabolism. These indicate that, apart from their other actions, vagal afferent signals may have (an indirect) modifying effect on postalimentary temperature regulation also by changing CRH actions.

It can be concluded that stimulatory vagal afferent signals, through exciting NTS, may increase sympathetic activity, and may enhance stress-responsiveness, resulting in a tendency for hypermetabolism and hyperthermia. Suppression of the fasting-dependent inhibitory signals contributes to this tendency. The role of vagal afferents is additional to the humoral signals. Depressed NPY release, as well as enhanced CCK and CRH activities participate in the central regulatory changes.

2.2.4. Peripheral effector functions

Rothwell and Stock (1979) demonstrated that brown adipose tissue plays a pivotal role in diet-induced thermogenesis, primarily through sympathetic activation that accompanies feeding. The higher hypothalamic CCK and CRH, as well as the lower NPY activities, enhance sympathetic tone. Cui et al. (1990) demonstrated a role of tonic influence of sensory neuropeptides in maintenance of brown fat activity. Diet-induced (nonshivering) thermogenesis and cold-induced (also nonshivering) thermogenesis are different (Champigny and Ricquier, 1990),

although both involve contribution of the sympathetic system. Still, sympathetic activity may not account for the whole postalimentary hypermetabolism: Aksnes et al. (1995) demonstrated that in tetraplegic patients with complete cervical spinal cord lesion and low sympatho-adrenal activity the metabolic rise to parenteral feeding was similar to that seen in control subjects.

While in the development of the thermic effect of food and in diet-induced thermogenesis the afferent vagus may participate, these phenomena are independent of the efferent vagus, in contrast to the possible role the efferent vagus is suggested to play in febrile reactions (Romanovsky et al., 2000a). The efferent vagus can influence, however, the action of central NPY or CRH on production of pancreatic and gut hormones (including insulin, NPY, somatostatin, etc.), and thereby it can influence intermediary metabolism. This is, however, only very indirectly related to thermoregulation.

3. Concluding remarks

Chemical/mechanical hunger and satiety signals continuously influence the regulation of metabolic rate and body temperature, and their normal/altered levels may contribute to the normal/altered resting tone of these homeostatic functions. A part of the chemical signals (e.g. changes of plasma leptin, insulin) can be transmitted directly, by humoral means, to the central nervous system. Other chemical signals (gastrointestinal hormones, preabsorptive nutrients), along with mechanical ones, are thought to influence sensory nerve endings in the gastrointestinal tract, still others (insulin, postabsorptive nutrients) act in the hepatoportal system — the neural information is transmitted by branches of the afferent vagus.

On the basis of the available evidence a provocative model can be constructed, which is shown in Fig. 3. It demonstrates two types of vagal afferent fibers: one stimulating, the other inhibiting energy metabolism. The function of the first is based on satiety signals and conveys stimulatory information to NTS (causing *c-fos* expression), this is activated by gut/stomach wall-tension, local CCK, preabsorptive nutrients, possibly insulin, and also by endogenous pyrogens; the activated cell groups of NTS enhance metabolic rate and suppress food intake. The second fiber type, when excited, conveys inhibitory information to NTS, with consequent inhibition of energy metabolism and increase in food intake. The activity of these latter fibers is based on hunger signals, and low plasma glucose or low level of postabsorptive nutrients enhance it, while this activity is attenuated by abundance of nutrients (e.g. parenteral nutrition, high plasma glucose) or by high insulin level. It is possible that, in these processes, different cell groups of the NTS are involved. A balance of activities of the two fiber-types determines the final outcome, as regards food intake and energy metabolism. In central processing of the vagal information the roles of CCK, CRH and NPY are emphasized.

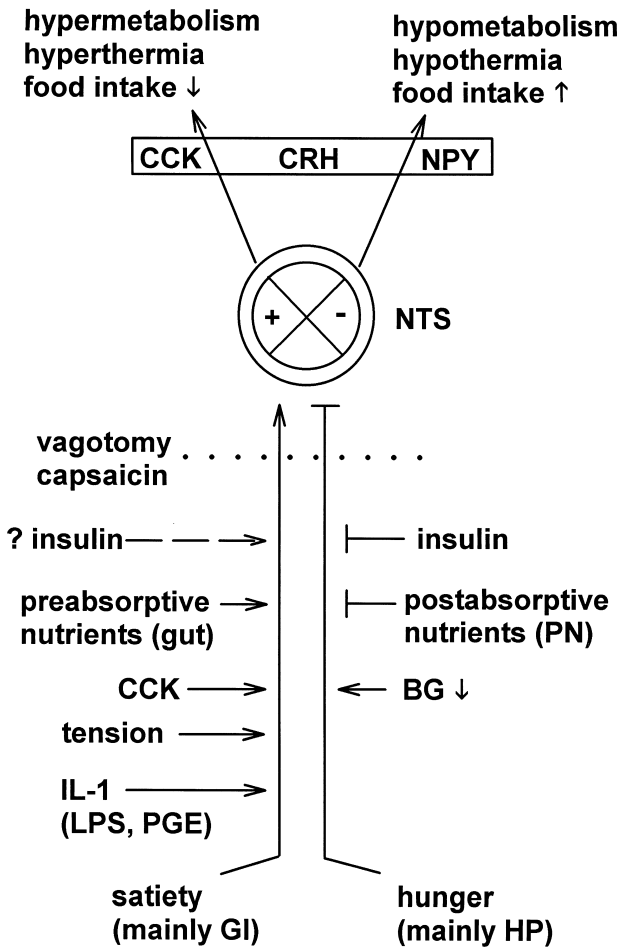

Fig. 3. The model depicts the proposed dual role of vagal afferents. Satiety-related signals (further activated by gut tension, CCK, preabsorptive nutrients in gut, pyrogens) stimulate NTS, and result in anorexia and increased energy metabolism (catabolic pathway, energy-expenditure). Hunger-related signals (further activated by low plasma glucose/nutrients in hepatoportal system, attenuated by insulin or postabsorptive nutrients) inhibit NTS, and evoke food intake and inhibit energy metabolism (anabolic pathway, energy-conservation). Vagotomy or capsaicin-treatment blocks both types of afferents. PN, parenteral nutrition; BG, blood glucose; GI, gastrointestinal; HP, hepatoportal; IL-1, interleukin-1; LPS, lipopolysaccharide; PGE, prostaglandin E; NTS, nucleus of the solitary tract; CCK, cholecystokinin; CRH, corticotropin releasing hormone; NPY, neuropeptide Y. Direct thermoregulatory effects (e.g. temperature, PGE), circadian signals and some other (e.g. emotional) factors influence the hypothalamic thermoregulatory mechanisms directly, not through the vagal system.

By fasting-induced (inhibitory) changes of the satiety/hunger signals an energy-saving (anabolic) type of regulation (i.e. a regulatory metabolic ‘depression’) could be initiated, resulting in hypometabolism and hypothermia. On the other hand, postalimentary changes of stimulatory satiety/hunger signals initiate energy-expending (catabolic) type of regulation with resultant hypermetabolism and hyperthermia. The role of the efferent vagal fibers in all these non-febrile changes of thermoregulation appears to

be much less important than the assumed role of the afferent fibers.

Energy balance, not body temperature, is the primary target of vagal action on homeostatic regulations. In the initiation of fever, probably the same or similar vagally transmitted signals play a transient role (eliciting temporary catabolic state by non-physiological stimulation of the vagal sensory endings), but they are unlikely to account for the whole fever course. The biological role of such vagal function is probably the regulation of energy content in the body. Fasting hypometabolism serves to decrease the severity of negative energy balance (and extends survival period), postalimentary hypermetabolism enhances energy loss (and prevents the development of obesity). Body temperature appears to be only secondarily affected by vagal activities.

Acknowledgements

While preparing this work, the author was fortunate to have the conscientious assistance of Drs. M. Balaskó and E. Pétervári who were of great help in searching the literature, preparing the figures and checking the manuscript. The author also wishes to express his sincere thanks to Prof. Z. Szelényi for his comments. A grant from the National Scientific Grant Agency of Hungary (OTKA T026511) is gratefully acknowledged.

References

Adachi, A., Niijima, A., 1982. Thermosensitive afferent fibers in the hepatic branch of the vagus nerve in the guinea pig. J. Auton. Nerv. Syst. 5, 101–109.

Ahima, R.S., Prabakaran, D., Mantzoros, C., Qu, M.D., Lowell, B., Maratos-Flier, E., Flier, J.S., 1996. Role of leptin in the neuroendocrine response to fasting. Nature 382, 250–252.

Aksnes, A.K., Brunbin, T., Hjeltnes, N., Wahren, J., 1995. Metabolic, thermal and circulatory effects of intravenous infusion of amino acids in tetraplegic patients. Clin. Physiol. 15, 377–396.

Andrews, J.F., Mercer, J.B., Ryan, E.M., Székely, M., 1975. The postnatal increase in minimum metabolic rate in the lamb. In: Jansky, L. (Ed.), Depressed Metabolism and Cold Thermogenesis. Charles University, Prague, pp. 15–18.

Andrews, P.L.R., Rothwell, N.J., Stock, M.J., 1985. Effects of subdiaphragmatic vagotomy on energy balance and thermogenesis in the rat. J. Physiol. 362, 1–12.

Arita, H., Ogle, C.K., Alexander, W., Warden, G.D., 1988. Induction of hypermetabolism in guinea pigs by endotoxin infused through the portal vein. Arch. Surg. 123, 1420–1424.

Baconnier, P., Benchetrit, G., Tanche, M., 1979. Liver heat production and temperature regulation in the anesthetized dog. Am. J. Physiol. 237, R334–R339.

Balaskó, M., Székely, M., 1999. The effects of centrally applied NPY on the regulation of body temperature and metabolic rate. Neurobiology 7, 277–278.

Berthoud, H.-R., Neuhuber, W.L., 1994. Distribution and morphology of vagal afferents and efferents supplying the digestive system. In: Taché, Y., Wingate, D.L., Burks, T.F. (Eds.), Innervation of the Gut: Pathophysiological Implications. CRC Press, Boca Raton, pp. 43–66.

Billington, C.J., Briggs, J.E., Grace, M., Levine, A.S., 1991. Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. Am. J. Physiol. 260, R321–R327.

Bing, C., Frankish, H.M., Pickavance, L., Wang, Q., Hopkins, D.F., Stock, M.J., Williams, G., 1998. Hyperphagia in cold-exposed rats is accompanied by decreased plasma leptin but unchanged hypothalamic NPY. Am. J. Physiol. 274, R62–R68.

Blatteis, C.M., Sehic, E., Li, S., 1998. Afferent pathways of pyrogen signaling. Ann. NY Acad. Sci. 856, 95–107.

Blessing, W.W., 1997. In: The Lower Brainstem and Bodily Homeostasis. Oxford University Press, New York, p. 575.

Bray, G.A., Fisler, J., York, D.A., 1990. Neuroendocrine control of the development of obesity: understanding gained from studies of experimental animal models. Front. Neuroendocrinol. 11, 128–181.

Brown, M.R., Fisher, C.A., Diver, J., Spiess, J., Rivier, C., Vale, W., 1982. Corticotropin-releasing factor: effects on the sympathetic nervous system and oxygen consumption. Life Sci. 30, 207–210.

Cabanac, M., Dardashti, M., 1999. Emotional fever in rats persists after vagotomy. Physiol. Behav. 67, 347–350.

Champigny, O., Ricquier, D., 1990. Effects of fasting and refeeding on the level of uncoupling protein mRNA in rat brown adipose tissue: evidence for diet-induced and cold-induced responses. J. Nutr. 120, 1730–1736.

Ciriello, J., Calaresu, F.R., 1980. Monosynaptic pathways from cardiovascular neurons in the nucleus tractus solitarii to the paraventricular nucleus in the cat. Brain Res. 193, 529–533.

Cox, J.E., Randich, A., 1997. CCK-8 activates hepatic vagal C-fiber afferents. Brain Res. 776, 189–194.

Cui, J., Zaror-Behrens, G., Himms-Hagen, J., 1990. Capsaicin desensitization induces atrophy of brown adipose tissue in rats. Am. J. Physiol. 259, R324–R332.

Dallman, M.F., 1993. Stress update: adaptation of the hypothalamic-pituitary-adrenal axis to chronic stress. Trends Endocrinol. Metab. 4, 62–69.

Davison, J.S., Clarke, G.D., 1988. Mechanical properties and sensitivity to CCK of vagal gastric slowly adapting mechanoreceptors. Am. J. Physiol. 255, G55–G61.

Della-Fera, M.A., Baile, C.A., 1979. Cholecystokinin-octapeptide: continuous picomole injections into the cerebral ventricles suppresses feeding. Science 206, 471–473.

De Vries, J., Strubbe, J.H., Wildering, W.C., Gorter, J.A., Prins, A.J.A., 1993. Patterns of body temperature during feeding in rats under varying ambient temperatures. Physiol. Behav. 53, 229–235.

Di Bella, L., Tarozzi, G., Rossi, M.T., Scalera, G., 1981. Behavioral patterns proceeding from liver thermoreceptors. Physiol. Behav. 26, 53–59.

Driver, H.S., Shulman, I., Baker, F.C., Buffenstein, R., 1999. Energy content of the evening meal alters nocturnal body temperature but not sleep. Physiol. Behav. 68, 17–23.

Eberle-Wang, K., Levitt, P., Simansky, K.J., 1993. Abdominal vagotomy dissociates the anorectic mechanisms for peripheral serotonin and cholecystokinin. Am. J. Physiol. 265, R602–R608.

Egawa, M., Yoshimatsu, H., Bray, G.A., 1991. Neuropeptide Y suppresses sympathetic activity to interscapular brown adipose tissue in rats. Am. J. Physiol. 260, R328–R334.

Elmquist, J.K., Scammel, T.E., Jacobson, C.D., Saper, C.B., 1996. Distribution of Fos-like immunoreactivity in the rat brain following intravenous lipopolysaccharide administration. J. Comp. Neurol. 371, 85–103.

Ember, Á., Göbel, Gy., Pétervári, E., Székely, M., 2000. Fasting hypometabolism and postalimentary hypermetabolism: neural signals from the gastrointestinal tract. J. Physiol. (Lond.) 526, 172–173.

Ergene, E., Dunbar, J.C., Barraco, R.A., 1993. Visceroendocrine responses elicited by neuropeptide Y in the nucleus tractus solitarius. Brain Res. Bull. 32, 461–465.

Ericsson, A., Kovács, K.J., Sawchenko, P.E., 1994. A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. J. Neurosci. 14, 897–913.

Fleshner, M., Goehler, L.E., Hermann, J., Relton, J.K., Maier, S.F., Watkins, L.R., 1995. Interleukin-1β induced corticosterone elevation and hypothalamic NE depletion is vagally mediated. Brain Res. Bull. 37, 605–610.

Fraser, K.A., Davison, J.S., 1992. Cholecystokinin-induced *c-fos* expression in the rat brain stem is influenced by vagal nerve integrity. Exp. Physiol. 77, 225–228.

Freie-Maia, L., Azevedo, A.D., 1990. The autonomic nervous system is not a purely efferent system. Med. Hypoth. 32, 91–99.

Fyda, D.M., Cooper, K.E., Veale, W.L., 1991. Nucleus tractus solitarii lesions alter the metabolic and hyperthermic response to central prostaglandin E_1 in the rat. J. Physiol. 442, 337–349.

Gaykema, R.P.A., Dijkstra, I., Tilders, F.J.H., 1995. Subdiaphragmatic vagotomy suppresses endotoxin-induced activation of hypothalamic corticotropin-releasing hormone neurons and ACTH secretion. Endocrinology 136, 4717–4720.

Geran, L.C., Rashotte, M.E., 1997. Participation of gastrointestinal-load volume in 'setting' the pigeon's nocturnal body temperature. Naturwissenschaften 84, 350–353.

Gordon, C.J., 1983. A review of terms for regulated vs. forced neurochemical-induced changes in body temperature. Life Sci. 32, 1285–1295.

Green, J.H., Macdonald, I.A., 1981. The influence of intravenous glucose on body temperature. Q. J. Exp. Physiol. 66, 465–473.

Griggio, M.A., Richard, D., LeBlanc, J., 1991. Involvement of the sympathetic nervous system in meal-induced thermogenesis in mice. Int. J. Obesity 15, 711–715.

Hansen, M.K., Kapás, L., Fang, J., Krueger, J.M., 1998. Cafeteria diet-induced sleep is blocked by subdiaphragmatic vagotomy in rats. Am. J. Physiol. 274, R168–R174.

Hansen, M.K., Krueger, J.M., 1998. Subdiaphragmatic vagotomy does not block sleep deprivation-induced sleep in rats. Physiol. Behav. 64, 361–365.

Hayashi, M., Nagasaka, T., 1983. Suppression of norepinephrine-induced thermogenesis in brown adipose tissue by fasting. Am. J. Physiol. 245, E582–E586.

Heim, T., Mestyán, J., 1964. Undernutrition and temperature regulation in adult rats. Acta Physiol. Hung. 24, 305–312.

Himms-Hagen, J., 1995. Role of brown adipose tissue thermogenesis in control of thermoregulatory feeding in rats: a new hypothesis that links thermostatic and glucostatic hypotheses for control of food intake. Proc. Soc. Biol. Exp. Med. 208, 159–169.

Holzer, P., 1994. Spinal afferent nerves: sensory, afferent, and effector functions. In: Taché, Y., Wingate, D.L., Burks, T.F. (Eds.), Innervation of the Gut: Pathophysiological Implications. CRC Press, Boca Raton, pp. 123–136.

Hummel, Z., Szelényi, Z., Székely, M., 2000. Effects of cold and/or fasting on circadian body temperature rhythms in rats. Neurobiology, Abstract; In press.

Husztik, E., Lázár, Gy., Párducz, A., 1980. Electron microscopic study of Kupffer cell phagocytosis blockade by gadolinium chloride. Br. J. Exp. Pathol. 61, 624–630.

Ichikawa, M., Miyasaka, K., Fujita, Y., Shimazoe, T., Funakoshi, A., 1998. Disappearance of diurnal rhythm of energy expenditure in genetically diabetic obese rats. Jpn. J. Physiol. 48, 211–214.

Jourdan, M.L., Wang, L.C.H., Christopherson, R.J., 1984. Effects of fasting and aminophylline on norepinephrine-stimulated non-shivering thermogenesis. Life Sci. 34, 1101–1109.

Kapás, L., Obál, Jr. F., Penke, B., Obál, F., 1987. Cholecystokinin-octapeptide-induced hypothermia in rats: dose–effect and structure–effect relationships, effect of ambient temperature, pharmacological interactions and tolerance. Neuropharmacology 26, 131–137.

Koulchitsky, S.V., 1998. Are the capsaicin-sensitive structures of ventral medulla involved in the temperature response to endotoxin fever in rats? Neurosci. Lett. 244, 112–114.

Kraly, F.S., Jerome, C., Smith, G.P., 1986. Specific postoperative syndromes after total and selective vagotomies in the rat. Appetite 7, 1–17.

Laburn, H.P., 1996. How does the fetus cope with thermal challenges? News Physiol. Sci. 11, 96–100.

Laviano, A., Yang, Z.J., Meguid, M.M., Koseki, M., Beverly, J.L., 1995. Hepatic vagus does not mediate IL-1 alpha induced anorexia. NeuroReport 6, 1394–1396.

McCance, R.A., Mount, L.E., 1960. Severe undernutrition in growing and adult animals. 5. Metabolic rate and body temperature in the pig. Br. J. Nutr. 14, 509–518.

McCarthy, H.D., Kilpatrick, A.P., Trayhurn, P., Williams, G., 1993. Widespread increases in regional hypothalamic neuropeptide Y levels in acute cold-exposed rats. Neuroscience 54, 127–132.

Mei, N., 1985. Intestinal chemosensitivity. Physiol. Rev. 65, 211–237.

Mercer, J.B., Andrews, J.F., Székely, M., 1979. Thermoregulatory responses in newborn lambs during the first thirty-six hours of life. J. Therm. Biol. 4, 239–245.

Milligan, E.D., McGorry, M.M., Fleshner, M., Gaykema, R.P., Goehler, L.E., Watkins, L.R., Maier, S.F., 1997. Subdiaphragmatic vagotomy does not prevent fever following intracerebroventricular prostaglandin E_2: further evidence for the importance of vagal afferents in immune-to-brain communication. Brain Res. 766, 240–243.

Mönnikes, H., Lauer, G., Arnold, R., 1997. Peripheral administration of cholecystokinin activates *c-fos* expression in the locus coeruleus/subcoeruleus nucleus, dorsal vagal complex and paraventricular nucleus via capsaicin-sensitive vagal afferents and CCK-A receptors in the rat. Brain Res. 770, 277–288.

Muralidhara, D.V., Desautels, M., 1994. Changes in brown adipose tissue composition during fasting and refeeding of diet-induced obese mice. Am. J. Physiol. 266, R1907–R1915.

Niijima, A., 1996. The afferent discharges from sensors for interleukin-1β in the hepatoportal system in the anaesthetized rat. J. Auton. Nerv. Syst. 61, 287–291.

Niijima, A., Meguid, M.M., 1994. Parenteral nutrients in rat suppresses hepatic vagal afferent signals from portal vein to hypothalamus. Surgery 116, 294–301.

Opp, M., Obál, Jr. F., Krueger, J.M., 1989. Corticotropin-releasing factor attenuates interleukin-1-induced sleep and fever in rabbits. Am. J. Physiol. 257, R528–R535.

Paintal, A.S., 1973. Vagal sensory receptors and their reflex effects. Physiol. Rev. 53, 159–227.

Plata-Salamán, C.R., 1998. Cytokine-induced anorexia. Behavioral, cellular, and molecular mechanisms. Ann. NY Acad. Sci. 856, 160–170.

Rashotte, M.E., Pastukhov, I.F., Poliakov, E.L., Henderson, R.P., 1998. Vigilance states and body temperature during the circadian cycle in fed and fasted pigeons (Columba livia). Am. J. Physiol. 275, R1690–R1702.

Raybould, H., Gayton, R.J., Dockray, G.J., 1985. CNS effects of circulating CCK8: involvement of brainstem neurones responding to gastric distension. Brain Res. 342, 187–190.

Reinertsen, R.E., Bech, C., 1994. Hypothermia in pigeons: relating body temperature regulation to the gastrointestinal system. Naturwissenschaften 81, 133–136.

Ren, K., Randich, A., Gebhart, G.F., 1990. Modulation of spinal nociceptive transmission from nuclei tractus solitarii: a relay for effects of vagal afferent stimulation. J. Neurophysiol. 63, 971–986.

Ricardo, J.A., Koh, E.T., 1978. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. Brain Res. 153, 1–26.

Ritter, R.C., Ladenheim, E.E., 1985. Capsaicin pretreatment attenuates suppression of food intake by cholecystokinin. Am. J. Physiol. 248, R501–R504.

Ritter, R.C., Ritter, S., Ewart, W.R., Wingate, D.L., 1989. Capsaicin attenuates hindbrain neuron responses to circulating cholecystokinin. Am. J. Physiol. 257, R1162–R1168.

Romanovsky, A.A., Kulchitsky, V.A., Simons, C.T., Sugimoto, N., Székely, M., 1997a. Febrile irresponsiveness of vagotomized rats is suppressed even in the absence of malnutrition. Am. J. Physiol. 273, R777–R783.

Romanovsky, A.A., Kulchitsky, V.A., Simons, C.T., Sugimoto, N., Székely, M., 1997b. Cold defense mechanisms in vagotomized rats. Am. J. Physiol. 273, R784–R789.

Romanovsky, A.A., Simons, C.T., Székely, M., Kulchitsky, V.A., 1997c. The vagus nerve in the thermoregulatory response to systemic inflammation. Am. J. Physiol. 273, R407–R413.

Romanovsky, A.A., Ivanov, A.I., Berthoud, H.-R., Kulchitsky, V.A., 2000a. Are vagal efferents involved in the fever response to intraperitoneal lipopolysaccharide? J. Therm. Biol. 25, 65–70.

Romanovsky, A.A., Simons, C.T., Kulchitsky, V.A., Balaskó, M., Székely, M., 2000b. Peripheral nerves in fever: multiple roles. FASEB J., 14A86 (97.7).

Roscoe, A.K., Myers, R.D., 1991. Hypothermia and feeding induced simultaneously in rats by perfusion of neuropeptide Y in preoptic area. Pharmacol. Biochem. Behav. 39, 1003–1009.

Rothwell, N., 1989. Central effects of CRF on metabolism and energy balance. Neurosci. Biobehav. Rev. 14, 263–271.

Rothwell, N.J., Stock, M.J., 1979. A role for brown adipose tissue in diet-induced thermogenesis. Nature 281, 31–35.

Saha, S.K., Ohno, T., Ohinata, H., Kuroshima, A., 1999. In vitro thermogenesis and phospholipid fatty acid composition of brown adipose tissue in fasted and refed rats. Jpn. J. Physiol. 49, 345–352.

Sahu, A., Dube, M.G., Phelps, C.P., Sninsky, C.A., Kalra, S.P., 1995. Insulin and insulin-like growth factor II suppress neuropeptide Y release from the nerve terminals in the paraventricular nucleus: a putative hypothalamic site for energy homeostasis. Endocrinology 136, 5718–5724.

Sakaguchi, T., Yamazaki, M., 1988. Hepatic portal injection of glucose elevates efferent sympathetic discharge of interscapular brown adipose tissue. Exp. Neurol. 101, 464–469.

Sapolsky, R., Rivier, C., Yamamoto, G., Plotsky, P., Vale, W., 1987. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 238, 522–524.

Sawchenko, P.E., Friedman, M.I., 1979. Sensory functions of the liver — a review. Am. J. Physiol. 236, R5–R20.

Schick, R.R., Schusdziarra, V., Yaksh, T.L., Go, V.L., 1994. Brain regions where cholecystokinin exerts its effect on satiety. Ann. NY Acad. Sci. 713, 242–254.

Schmitt, M., 1973. Influences of hepatic portal receptors on hypothalamic feeding and satiety centers. Am. J. Physiol. 225, 1089–1095.

Schwartz, G.J., Moran, T.H., 1998. Duodenal nutrient exposure elicits nutrient-specific gut motility and vagal afferent signals in rats. Am. J. Physiol. 274, R1236–R1242.

Schwartz, G.J., McHugh, P.R., Moran, T.H., 1993. Gastric loads and cholecystokinin synergistically stimulate rat gastric vagal afferents. Am. J. Physiol. 265, R872–R876.

Schwartz, M.W., Seeley, R.J., 1997. Neuroendocrine responses to starvation and weight loss. N. Engl. J. Med. 336, 1802–1811.

Schwartz, M.W., Dallman, M.F., Woods, S.C., 1995. Hypothalamic response to starvation: implications for the study of wasting disorders. Am. J. Physiol. 269, R949–R957.

Schwartz, M.W., Seeley, R.J., Campfield, L.A., Burn, P., Baskin, D.G., 1996. Identification of targets of leptin action in rat hypothalamus. J. Clin. Invest. 98, 1101–1106.

Schwartz, M.W., Woods, S.C., Porte, Jr. D., Seeley, R.J., Baskin, D.G., 2000. Central nervous system control of food intake. Nature 404, 661–671.

Seeley, R.J., Matson, C.A., Chavez, M., Woods, S.C., Dallman, M.F., Schwartz, M.W., 1996. Behavioral, endocrine, and hypothalamic responses to involuntary overfeeding. Am. J. Physiol. 271, R819–R823.

Sei, M., Sei, H., Shima, K., 1999. Spontaneous activity, sleep, and body temperature in rats lacking the CCK-A receptor. Physiol. Behav. 68, 25–29.

Simons, C.T., Kulchitsky, V.A., Sugimoto, N., Homer, L.D., Székely, M., Romanovsky, A.A., 1998. Signaling the brain in systemic inflammation: which vagal branch is involved in fever genesis? Am. J. Physiol. 275, R63–R68.

Suemaru, S., Hashimoto, K., Hattori, T., Inoue, H., Kageyama, J., Ota, Z., 1986. Starvation-induced changes in rat brain corticotropin-releasing factor (CRF) and pituitary-adrenocortical response. Life Sci. 39, 1161–1166.

Sugimoto, N., Simons, C.T., Romanovsky, A.A., 1999. Vagotomy does not affect thermal responsiveness to intrabrain prostaglandin E_2 and cholecystokinin octapeptide. Brain Res. 844, 157–163.

Székely, M., Mercer, J.B., 1999. Thermosensitivity changes in cold-adapted rats. J. Therm. Biol. 24, 369–371.

Székely, M., Romanovsky, A.A., 1998. Pyretic and antipyretic signals within and without fever: a possible interplay. Med. Hypoth. 50, 213–218.

Székely, M., Szelényi, Z., Balaskó, M., 1994. Cholecystokinin participates in the mediation of fever. Pflügers Arch. 428, 671–673.

Székely, M., Balaskó, M., Romanovsky, A.A., 1997a. Peripheral neural inputs: their role in fever. Ann. NY Acad. Sci. 813, 427–434.

Székely, M., Szelényi, Z., Kis, A., 1997b. Fasting and re-feeding: alterations in resting metabolic rate and body temperature. In: Nielsen Johannsen, B., Nielsen, R. (Eds.), Thermal Physiology 1997. August Krogh Institute, Copenhagen, pp. 235–238.

Szelényi, Z., Barthó, L., Székely, M., Romanovsky, A.A., 1994. Cholecystokinin octapeptide (CCK-8) injected into a cerebral ventricle induces a fever-like thermoregulatory response mediated by type B CCK-receptors in the rat. Brain Res. 638, 69–77.

Szolcsányi, J., 1982. Capsaicin type pungent agents producing pyrexia. Handb. Exp. Pharmacol. 60, 437–478.

Uehara, A., Sekiya, C., Takasugi, Y., Namiki, M., Arimura, A., 1989. Anorexia induced by interleukin 1: involvement of corticotropin releasing factor. Am. J. Physiol. 257, R613–R617.

Valentino, R.J., Foote, S.L., Page, M.E., 1993. The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. Ann. NY Acad. Sci. 697, 173–189.

VanderWeele, D.A., 1998. Insulin as a satiating signal. In: Smith, G.P. (Ed.), Satiation: From Gut to Brain. Oxford University Press, New York, pp. 198–216.

Wan, W.L., Wetmore, L., Sorensen, C.M., Greenberg, A.H., Vance, D.M., 1994. Neural and biochemical mediators of endotoxin and stress-induced *c-fos* expression in the rat brain. Brain Res. Bull. 34, 7–14.

Watkins, L.R., Goehler, L.E., Relton, J.K., Tartaglia, N., Silbert, L., Martin, D., Maier, F., 1995. Blockade of interleukin-1-induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune to brain communication. Neurosci. Lett. 183, 27–31.

Yang, Z.J., Ratto, C., Gleason, J.R., Bellantone, R., Crucitti, F., Meguid, M.M., 1992. Influence of anterior subdiaphragmatic vagotomy and TPN on rat feeding behavior. Physiol. Behav. 51, 919–926.

Yoda, T., Crawshaw, L.I., Yoshida, K., Su, L., Hosono, T., Shido, O., Sakurada, S., Fukuda, Y., Kanosue, K., 2000. Effects of food deprivation on daily changes in body temperature and behavioral thermoregulation in rats. Am. J. Physiol. 278, R134–R139.

Yoshimatsu, H., Egawa, M., Bray, G.A., 1992. Effects of cholecystokinin on sympathetic activity to interscapular brown adipose tissue. Brain Res. 597, 298–303.

Young, J.B., Landsberg, L., 1977. Suppression of sympathetic nervous system during fasting. Science 196, 1473–1475.

Zittel, T.T., Glatzle, J., Kreis, M.E., Starlinger, M., Eichner, M., Raybould, H.E., Becker, H.D., Jehle, E.C., 1999. *C-fos* protein expression in the nucleus of the solitary tract correlates with cholecystokinin dose injected and food intake in rats. Brain Res. 846, 1–11.