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Thermoregulation, energy balance, regulatory peptides: recent developments

Miklos Szekely, Erika Petervari, Marta Balasko

Department of Pathophysiology and Gerontology, Medical School, University of Pecs, Hungary

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1. ABSTRACT

Energy balance of the body is determined mainly by the function of various hypothalamic and brainstem nuclei, according to a complex interaction between the regulation of body temperature (actual metabolic rate *vs.* heat loss) and regulation of body weight (metabolic rate *vs.* food intake). The direct effect of central anabolic

neuropeptides (neuropeptide Y, orexins, melanin concentrating hormone, *etc.*) is to enhance food intake and suppress metabolic rate with a tendency to cause hypothermia, while central catabolic neuropeptides (melanocortins, corticotropin releasing factor, cocaine-amphetamine regulated peptide, *etc.*) suppress food intake and enhance energy expenditure with a tendency to induce hyperthermia. Many other neuropeptides are neither clearly anabolic, nor clearly catabolic, but still influence these complex hypothalamic/brainstem functions. Some peripheral peptides (*e.g.* leptin, insulin, ghrelin) acting at either peripheral or cerebral sites also contribute to the regulation of energy balance. The prevailing thermoregulatory status, the substances or neural signals representing actual feeding *vs.* established nutritional states, and the aging process may modify the expression and/or activity of peripheral and central peptides and peptide receptors.

2. INTRODUCTION: REGULATION OF BODY TEMPERATURE AND ENERGY BALANCE – A ROLE FOR PEPTIDERGIC MECHANISMS

Amongst the prerequisites of optimal function of various cells, tissues, organs and organ systems, the standard temperature is as important as the standard osmotic pressure, pH, or the adequate blood perfusion for continuous supply of nutrients and oxygen with concurrent removal of waste-products. This is why a relatively standard body temperature, secured by a regulated balance between heat production (metabolic rate) and heat loss is of outstanding importance (for reviews see: 1, 2). However, this is only one part of the overall energy balance.

Energy balance is a more complex function of the body. It means an overall balance between energy intake and energy expenditure, *i.e.* the energy dissipated from the body in form of heat. In other words, it involves food intake and energy storage as well as thermal equilibrium. An organism can secure the permanent energy need of its tissues by continuous production of molecules with an high energy bond. This necessitates adequate intake and utilization of nutrients. Some of the ingested/absorbed nutrients may be readily available and used immediately, some others may be stored to be mobilized and utilized later, altogether securing a continuous nutrient supply for the tissues. In addition, removal of the heat originating from these processes is also indispensable – were there a complete absence of heat loss, in humans even the minimal heat originating from resting metabolic rate (about 80-100 kcal/h), would cause a rise in body temperature exceeding 1ºC/h. Accordingly, the energy equilibrium of the body refers to a regulated balance of energy contained in different forms in the body (calorie-containing nutrients, which are either carried by the plasma or stored for later mobilization, and also heat calories distributed in the body). Changes in nutrient supply will evoke thermoregulatory reactions (*e.g.* postprandial hypermetabolism and hyperthermia, or fasting hypometabolism and decline in body temperature), while changes in thermoregulation lead to alterations in feeding behavior (*e.g.* cold-induced hyperphagia). Still, with very few exceptions (3), even in excellent reviews, energy balance is often reduced to an analysis of the relationship of food intake and body weight, without addressing energy expenditure and the thermal components – in many papers even environmental temperature (at which the authors performed the experiments) is not well-specified. Other papers deal strictly with thermoregulation. In reality, in its full complexity, energy balance is established on the one hand by the regulation of food intake, metabolic rate and body weight, and on the other hand by the regulation of body temperature (metabolic rate *vs.* heat loss). The first part is a complex balance which consists of slow mechanisms to provide sufficient amounts of mobile or stored nutrient calories, while thermoregulation means a fast energetic adjustment to secure a relative thermal stability of the body. Each of these functions (characteristics and regulation of food intake, regulation of body temperature, *etc.*) may be investigated separately, but the relationship and interaction of these functions should be kept in mind, particularly because these functions are often influenced by common regulatory factors and mechanisms. The present review analyzes the role of peptidergic mechanisms in the regulation of this complex energy balance.

Besides many other factors (monoamines, nutrients, neural influences, *etc.*), various peptides from the periphery or neuropeptides of the central nervous system (regulatory peptides) have eminent roles in the regulation of overall energy balance, including the regulation of body temperature, as described in an earlier review by Clark and Fregly (4). However, tremendous amounts of data have accumulated since this review. Most regulatory peptides were shown to have an apparently coordinated influence on food intake and metabolic rate: the anabolic peptides are orexigenic and suppress metabolic rate, the catabolic ones are anorexigenic and enhance metabolic rate (5, 6). Those peptides, which suppress metabolic rate, tend to lead to a fall in body temperature (passive hypothermia, observed at sub-thermoneutral environments), while the ones which elevate metabolic rate easily lead to elevation of body temperature (hyperthermia). Some peptides do not fit the anabolic/catabolic pattern (*e.g.* bombesin suppresses food intake and induces hypothermia; 7). The primary sites of action of some important anabolic and catabolic peptides are shown in Table 1, together with those without such type of coordinated effect. It is still to be clarified whether or not the peripheral/central peptides (or which ones, and how) can participate in development of fever (elevated metabolic rate plus a decrease in heat loss), in endogenous antipyresis (prevention of febrile temperature rise), or in anapyrexia (suppressed metabolism and/or increased heat loss, causing sustained low body temperature). In other cases the thermoregulatory part of the complex energy balance may be different: as regards thermoregulation, some neuropeptide effects appear to be "uncoordinated" (even if their anabolic or catabolic features are coordinated), *e.g.* a certain neuropeptide (as later shown for alpha-MSH) may induce a rise in metabolic rate together with a practically simultaneous increase in heat loss, thereby it may result in no change in core temperature or may induce a rise in some cases and a fall in other ones, depending on the balance of the counteracting effector activities.

Table 1. Main or primary sites of action of the most important anabolic, and catabolic peptides along with those without an apparently coordinated effect

Type of effects on energy metabolism	FI	MR/Tc	Primary site of action	
			Vagus /brainstem	Hypothalamus
Anabolic	↑	↓	Ghrelin Cannabinoids (MCH)	NPY AgRP Orexin MCH (Ghrelin)
Catabolic	↓	↑	(Melanocortins) (CART) (Leptin) (Insulin)	CCK (2R) Melanocortins CART CRF Leptin Insulin
Unco-ordinated			CCK (1R)	Neurotensin Bombesin

FI = food intake, MR = metabolic rate, Tc = core temperature

Some peptides of this regulatory system may be derived from the periphery and may send information via the afferent vagus to the brainstem, NTS and further to hypothalamic and other CNS structures, or they may reach the brain (hypothalamus, brainstem) by the circulation via the circumventricular organs or through the blood-brain-barrier (8, 9). Others are produced within hypothalamic/brainstem nuclei – there is a complex interaction between these neuropeptides and those peptides of peripheral origin. Interactions between the NTS and the preoptic/anteroventral hypothalamus in fever and other processes have been thoroughly described in earlier reviews (9, 10). The vagus conveys peripheral information by CCK, cannabinoids (CB-1), MCH, ghrelin, *etc.,* thereby it influences the expression of several central substances and receptors (*e.g.* MCH, CART, NPY receptors) (11).

Each of the individual factors of this regulatory complex (food intake, metabolic rate including different ways of heat production, or various forms of heat loss) may be affected independently, or may be separate targets for the action of some peptides or other substances – the primarily uncoordinated effects and influences may ignite different compensatory mechanisms.

Disorders of the overall energy balance – including those disorders, which reflect primarily altered neuropeptide functions – may be manifested as abnormalities of body weight and composition, or as abnormalities of body temperature.

3. PERIPHERAL PEPTIDES WITH PERIPHERAL OR CENTRAL ACTIONS

3.1. Leptin

The polypeptide leptin is derived mainly from the adipose tissue, but smaller amounts are produced by the epithelial cells of the stomach and also by some other tissues (12). Although leptin is better known for its effects on body weight, it also influences energy expenditure and the thermoregulatory status. The peptide, as a cytokine, can enter the CNS by receptor-mediated transport system, binds to its receptors, mainly to the long receptor (named LRb or Ob-Rb), which is a classical transmembrane cytokine receptor with intracellular domains (13). Upon leptin binding in the arcuate nucleus of the hypothalamus (some in the lateral hypothalamus and the PVN), via JAK2-STAT3 signaling (14) it modifies the expression/activity of hypothalamic neuropeptides (15), thereby suppressing food intake and enhancing energy expenditure. Leptin also binds to the afferent vagus nerve (16) and to neurons of the brainstem, mainly to the NTS, partly to the parabrachial and supragenual nuclei (17). Binding to the NTS is of particular importance, since here leptin acts in concert with the humoral and neural (afferent vagal) information reaching the NTS from the gastrointestinal system to suppress food intake (18, 19). The role of vagal binding of leptin may, however, be questioned, because in vagotomized and control rats leptin caused similar induction of *fos* expression and STAT3 changes in the NTS, where the vagal fibers terminate, rejecting an exclusive role for vagal afferent leptin-dependent information (20). Finally, vagotomy itself also induced *fos* expression in the NTS along with changes in AgRP and POMC mRNA in the hypothalamus, at least partly explaining the severe anorexia seen after vagotomy.

Mice that lack the gene for producing leptin (*ob/ob* strain) are hyperphagic, obese, hypometabolic and exhibit cold intolerance (21, 22, 23, 24). These *ob/ob* mice have high NPY, AgRP, but low POMC and CART expression in the arcuate nucleus, and low UCP expression in the brown fat. Unlike the leptin-deficient mice, the *db/db* mice have leptin, but lack the LRb, and display hyperphagia, decreased energy expenditure, obesity, hyperglycemia, decreased linear growth, infertility and thermoregulatory abnormalities (tendency for hypothermia; 25). Similarly, mice null for STAT3 in the brain are hyperphagic and obese, with failure of somatic and neuroendocrine development (26). In *db/db* mice the POMC mRNA is decreased and the AgRP and NPY mRNA levels are increased in the arcuate nucleus. In mice with mutant LRb (*s/s* strain) the glycemic control is normal, suggesting a role for some STAT3-independent signaling (27). In such mice the linear growth, somatic development and the hypothalamic NPY expression are also normal, although they develop hyperphagia, decreased energy expenditure and obesity just as *db/db* animals do. Interestingly, leptin overexpressing transgenic mice are also sensitive to cold, since they accumulate adipose tissue (substrate of heat production) only poorly, at a later age (28). Some rat strains either have a mutation of the leptin gene and thereby a dysfunctional form of leptin-peptide (Zucker *fa/fa* fatty rat) or lack the normal LRb (due to mutation, Koletsky *f/f* strain), these are also obese and have a tendency for hypothermia in a cool environment (29).

Rats receiving leptin either peripherally (using vagal afferentation or reaching the brain via the circumventricular organs; 30) or centrally (31) eat less than the controls and lose body weight, but they do not decrease their resting metabolic rate as pair-fed (*i.e.* food-restricted) animals do, showing that this peptide somehow enhances energy expenditure (32). Central infusion also enhances the peripheral fat and glucose utilization (12). Most of these leptin effects on food intake and metabolic rate are not exerted directly, rather via neuropeptides

and second order neurons of the hypothalamus: leptin administration enhances the expression of POMC and CART in the arcuate nucleus (31). Leptin binding influences other important neuropeptides as well: it suppresses the expression of NPY and AgRP, and through neural connections from the arcuate to the PVN, it enhances the expression of CRF. The sensitivity and activity of the most important anabolic and catabolic peptides at these second order neurons may be maintained even in the absence of active leptin or in cases of severe leptin resistance (33), showing that they are not completely dependent on leptin action, although normally it is usually leptin that determines their activity.

Upon binding to the LRb on the surface of the cells of the arcuate nucleus and NTS, leptin enhances the POMC gene expression in these cells and activates the anorexigenic POMC neurons (34), simultaneously suppressing the NPY expression. Conversely, in leptin-deficient *ob/ob* mice, in *db/db* mice with LRb mutation, as well as in Zucker rats with dysfunctional leptin or in Koletsky rats with LRb mutation, the hypothalamic POMC gene expression is decreased. All these mouse and rat strains are obese and show most symptoms of the metabolic syndrome. Transgenic neural expression of POMC in *ob/ob* mice attenuates the consequences of leptin deficiency (35). In MC4R knockout obese mice neither leptin nor MTII can act, but other peptides like CRF, CNTF, NPY can (36). All the above data support the opinion that the melanocortin system lies downstream of leptin signaling, and this system serves as probably the most important – although not exclusive (37) – immediate mediator of leptin actions. However, not all POMC neurons have LRb receptors, and there are also leptin-independent ways of activating the melanocortin system (38). Besides, leptin may have other, melanocortin-independent effects, *e.g.* it can increase the sympathetic tone and elevate blood pressure (39).

During chronic starvation the leptin level decreases, resulting in increased appetite (disinhibition of orexigenic mechanisms), suppression of energy expenditure, lowering core temperature, and exaggerating hypothermia or increasing lethality in systemic infection (14, 40). However, in such cases, the sensitivity to exogenous leptin may even increase. In starvation and fasting-induced hypothermia, leptin administration cannot suppress food intake but due to the maintained (or even enhanced) leptin sensitivity it can exert the anti-hypothermic thermoregulatory effects (14). In well-fed animals the anorexic rather than the thermoregulatory effect dominates. Apparently, leptin seems to control thermoregulatory energy expenditure when food supplies are scarce, while it alters food intake, rather than energy expenditure, when food is abundant (41). In fed subjects leptin elevates both metabolic rate and heat loss, only supraphysiological doses cause hyperthermia (14).

In contrast to starvation, with increasingly severe obesity (*e.g.* in rats/mice kept on high-fat diet, in human dietary obesity, *etc.*) the amount of leptin increases, but progressive leptin resistance develops (15, 42, 43, 44). Aging itself leads to leptin resistance both in the presence (45) and in the absence of obesity (46). Leptin resistance does not necessarily affect all leptin-effects simultaneously: in chronic primary (induced) hyperleptinemia the anorexic effect was attenuated after 25 days due to developing resistance, while the elevation of energy expenditure dissolved only after 83 days (47). Leptin resistance in animals as well as in humans promotes the symptomatic manifestation of metabolic syndrome. An ICV infusion of leptin first suppressed food intake and POMC expression in the hypothalamus, but by the time leptin resistance developed and food intake was normalized, the POMC level was also normalized (48). Similar results were reported regarding the changes of NPY expression in the course of development of leptin resistance (49). Thus, any additional rise in fat content remains without signaling to the hypothalamus, opening possibility for further obesity.

Leptin upregulates the uncoupling protein-1 (UCP-1) transcription in brown adipose tissue and UCP-1 and other UCP forms in other tissues (50). The peptide is also required for UCP-1-independent thermogenesis during cold stress (51). It activates the sympathetic system (52) and besides thermogenesis, it also contributes to development of hypertension (53). A 7-day-long ICV infusion of leptin antagonist in rats enhanced food intake and body weight, prevented the UCP activation by high-fat diet feeding (54), and prevented the spontaneous reversion of transient increase in caloric intake when switched to a high-fat diet.

Lack of leptin signaling impairs activation of thermogenesis in a cool environment. As a result, *ob/ob* mice, *db/db* mice, Koletsky *f/f* rats, and Zucker *fa/fa* rats are hypothermic in a usual laboratory environment, which is often cool for small rodents. In a thermoneutral environment body temperature is regulated not by activation or inactivation of thermogenesis, but by vasomotor changes of skin vessels. Accordingly, in thermoneutral environments the lack of leptin signaling does not result in hypothermia (29, 55, 56, 57). At thermoneutrality, the febrile response to lipopolysaccharide (LPS) is normal in Zucker fatty rats and in Koletsky *f/f* rats. However, the hypothermic response to the endotoxin in a cool environment is significantly prolonged in leptin receptor-deficient Koletsky rats, while in mutant Zucker rats an attenuated fever was reported, likely as a result of prolongation of an obvious or hidden hypothermic component (58) of the overall thermoregulatory response to LPS or cytokines (29, 56, 59).

LPS and pro-inflammatory pyrogenic cytokines increase the expression of the leptin gene and the concentration of leptin in the blood (60) – this might contribute to the febrile anorexia (61, 62), but according to recent data (63) probably not to the febrile rise in body temperature. Leptin actions on food intake and body temperature were reported to be mediated by IL-1 in earlier studies (64), but a more recent study demonstrated that in free-feeding rats kept at either cool or thermoneutral temperature, leptin failed to elevate the levels of febrigenic

cytokines (TNF-alpha, IL-6) or to elevate body temperature, although IL-1-beta was able to cause fever and elevation of these cytokines (63). Antibody against leptin did not influence the production of enzymes involved in prostaglandin synthesis upon LPS administration (65). However, persistently high leptin levels have been shown to stimulate leukocytes to produce pro-inflammatory cytokines, thereby leading to a chronic, low-grade inflammatory process (66), as observed in human obesity (67).

Inhibition of phosphatidylinositol-3-OH kinase (PI3K) blocks the suppression of feeding by leptin (but not by melanocortin agonists), suggesting that insulin-receptor substrate-protein (IRS-2) → PI3K signaling contributes to the regulation of energy balance by leptin (68). PI3K but not the STAT3 pathway of leptin signaling is impaired during the development of diet-induced obesity in mice kept on high-fat diet for 19 weeks (69). Thus, a defective PI3K pathway of leptin signaling in the hypothalamus may be one of the mechanisms of central leptin resistance and diet-induced obesity.

In summary, adipose tissue-derived leptin acts mainly in the hypothalamus. It activates the POMC-melanocortin pathway and suppresses the NPY/AgRP activity. In the consequent metabolic imbalance food intake decreases and the metabolic rate (thermogenesis) increases. Defective leptin activity results in obesity. In the course of aging and in diet-induced obesity leptin resistance develops and plasma leptin levels are elevated. Leptin also functions as a pro-inflammatory substance, which may participate in the pathogenesis of fever and chronic low-grade inflammatory processes.

3.2. Insulin

For a long time, the peptide hormone insulin of the pancreatic B-cells was known only for its role in the regulation of glucose homeostasis. Defective insulin activity leads to diabetes, while overly strong insulin effects induce hypoglycemia and sympathetic activation. However, more recent data have proved that insulin has many other roles (70). In particular, it can enter the brain by a specific receptor-facilitated transport and can bind to receptors (71) in the arcuate nucleus since POMC-expressing neurons co-express leptin and insulin receptors (72). Thereby insulin can influence anabolic and catabolic mechanisms in a way similar to that of leptin (73, 74, 75, 76). Accordingly, the level and efficacy of circulating insulin may be of importance not only in the short-term regulation of glucose homeostasis, but also in the long-term regulation of energy balance. Over the short term, plasma insulin levels change with the feeding status (basal, postprandial, glucose-stimulated insulin levels), while over the long term the plasma level of insulin varies with the nutritional state (higher in obese, lower in lean individuals).

A decrease in hypothalamic insulin receptors leads to rapid onset hyperphagia, increased fat mass and insulin resistance (77).

There are several overlaps between the insulin and leptin signaling pathways in hypothalamic neurons (13, 78). Both leptin and insulin have classical transmembrane receptors with intracellular domains, and they have many similarities. The mechanisms of the short-term (feeding-related) changes of energy balance and leptin level appear to involve insulin, as evidenced by the positive correlation between the plasma levels of leptin and insulin, and by the ability of insulin treatment to increase fat cell metabolism and leptin production (79). While the leptin receptor (tyrosine residue of JAK2-kinase) Tyr1138 → STAT3 pathway is central to the adiposity-dependent regulation of insulin sensitivity, this pathway is dispensable for the adiposity-independent regulation of glucose homeostasis by leptin (80). Thus, although such pathways (that may be dispensable for some neuroendocrine functions of leptin) are required for the normal regulation of POMC and AgRP expression in the hypothalamus and thus for the control of feeding and energy expenditure by leptin, still another signal, such as the insulin-receptor substrate (IRS)-protein → PI3K pathway, must mediate the adiposity-independent regulation of glucose homeostasis by leptin (81). Peripheral as well as central insulin (or leptin) can modify peripheral substrate utilization.

Similar to leptin's effects, the catabolic effects of insulin are mediated mainly (although not exclusively) by the melanocortin system (82, 83). Other neuropeptides are also involved. ICV infusion of NPY acutely induces insulin resistance and glucose intolerance via activation of sympathetic output to the liver (84).

An interaction with leptin is demonstrated by the finding that ICV insulin infusion was without effect on food intake or body weight of the obese Zucker rats (85). Insulin modulates the signal transduction pathway of leptin, and may provide a molecular basis for the coordinated effects of insulin and leptin in feeding behavior and weight control: insulin increased the leptin-induced phosphorylation of STAT3 and its activation (86).

In conclusion, insulin in the brain appears to be an important catabolic substance. It acts in concert with leptin mainly by activating the melanocortin system. Obesity and aging are accompanied by central and peripheral insulin resistance.

3.3. Cholecystokinin (CCK)

A postprandial release of gastrointestinal CCK is the key in activating the intestinal feedback control of gastrointestinal function, comprising short term inhibition of gastric emptying and acid secretion, stimulation of the exocrine pancreas and gallbladder, and inhibition of food intake. In this way, CCK plays a fundamental role in coordinating the entry of nutrients into the small intestine of high digestive and absorptive capacity (87). There are two major receptors, the predominantly peripheral CCK-1 (CCK-A) and predominantly central CCK-2 (CCK-B). They are likely to be involved in the short-term changes of energy balance, including thermoregulation and modification of feeding pattern (satiety) – less so in the regulation of long-term balance. Depending on the actual feeding status, the gastrointestinal stretch and released CCK send satiety signals mainly through capsaicin-

sensitive afferent fibers of the abdominal vagus to the NTS (88) and further to the hypothalamus. In this mechanism vagal CCK-1 receptors are involved. However, on the afferent vagus CCK acts in interaction with many other peptides: *e.g.* peripherally applied CCK enhances the firing rate of this nerve in fasting animals, which in turn may be suppressed again by administration of ghrelin (89). PYY, PP, orexin, GLP-1, cannabinoid and leptin receptors are also present (see later), while MCH and CART are also expressed (89) on the afferent vagus – many of these depend on the peripheral CCK-1 receptor activity. CCK8 (the most common active form of the peptide) has also been shown to increase the permeability of the blood-brain-barrier for leptin, thereby also contributing to the catabolic status (90). Leptin activates vagal afferent nerves in cooperation with CCK (91).

In humans, plasma concentrations of CCK increase after the age of 70-75 years (92) – this may be important in the anorexia of aging (see Ch. 7).

Interestingly, the peripherally applied CCK induces hypothermia via CCK-1 receptors (probably acting at the periphery, increasing heat loss through the skin), while – except from sporadic contradictory results – the central application of the peptide is widely accepted to lead to fever-like hyperthermia (for review see: 93). Upon warming and cooling, CCK-1 receptor deficient mice showed larger hysteresis (*i.e.* decreased homeostatic stability) than their wild-type counterparts (94).

In sum, peripheral CCK – in conjunction with a number of other gastrointestinal peptides – acts mainly on the afferent vagus. The information reaches the NTS and induces anorexia. Peripheral (but not central; Ch. 4.2.4.) CCK causes hypothermia probably by increasing heat loss.

3.4. Ghrelin

Ghrelin is the first peripheral orexigenic hormone identified. It is produced predominantly in the stomach, but small quantities have been found in other tissues including the brain (95). Most ghrelin-containing neuronal cell bodies are located in the ventrolateral part of the arcuate nucleus (96). Ghrelin secretion is increased by fasting, weight loss, insulin-induced hypoglycemia, while it is inhibited by intake of food or glucose (97). The circulating baseline ghrelin level and its fall upon nutrient intake was not affected by (efferent) vagotomy (98), but the fasting-induced elevation in ghrelin level was prevented. Ghrelin interacts with other neuropeptides. It enhances the spontaneous activity of NPY neurons and inhibits POMC neurons. Inhibition of endogenous NPY and AgRP by anti-NPY and anti-AgRP antibodies or antagonists for Y1 and Y5 receptors abolished ghrelin-induced feeding (99). In NPY- or AgRP-null mice, ghrelin-induced feeding is weakly attenuated, but completely abolished in mice lacking both NPY and AgRP (100). Ablation of the NPY/AgRP neurons completely suppressed the feeding response to ghrelin in mice (101). Very low doses of α-MSH or MTII administered ICV significantly reduced ghrelin-dependent hyperphagia (102). Ghrelin also activates PVN and lateral hypothalamic neurons expressing orexins, but not MCH (103, 104, 105). Additionally, ghrelin was shown to inhibit CART expression *in vitro* (89).

Chronic administration of ghrelin increased body weight by promoting adipogenesis, and it decreased energy expenditure (106). Ablation of ghrelin improved the diabetic (though not the obese) phenotype of *ob/ob* mice (22). Knockdown of ghrelin receptors in the PVN did not affect the daily food intake but significantly reduced body weight and blood ghrelin levels, suggesting that the central ghrelin system might selectively regulate body weight without affecting energy intake (107). The vagus nerve may transmit ghrelin signal from the stomach to the NTS and further to other sites of the brain (108). Ghrelin receptors were synthesized in vagal afferent neurons and transported to the afferent terminals. Ghrelin suppressed firing of the vagal afferent nerve, whereas CCK stimulated it. The gastric vagal afferent is the major pathway conveying ghrelin-signals for starvation and growth hormone secretion to the brain. Vagotomy prevents the effect of peripheral ghrelin on the hypothalamus, suggesting that the direct effect of ghrelin on the brain may be of intrinsic origin (109).

Administration of ghrelin or its synthetic analogues into the cerebral ventricles transiently reduced the core temperature in rats (105). In mice kept at a cool environment, torpor is induced by fasting, coincident with an elevation of circulating ghrelin levels (110). Ghrelin suppresses brown fat activity (111). Both motor activity and energy expenditure were reported to increase following simultaneous deletion of ghrelin and its receptor (112). However, large dose of ghrelin has also been described to induce hyperthermic responses, mainly by activating CRF and the HPA axis (113).

Summarizing the data, ghrelin was shown to be the first known orexigenic hormone of peripheral origin. Apparently, it also suppresses metabolic activity. It may act through the afferent vagus in the brainstem, but a hypothalamic action cannot be excluded.

3.5. Other peptides of peripheral origin

3.5.1. Adiponectin

As leptin, adiponectin is also derived from the adipose tissue. It can be demonstrated in the cerebrospinal fluid. Central administration of adiponectin is catabolic even in *ob/ob* mice, but there may also be some interactions with leptin. The main action of this peptide is not so much hypophagia, rather the enhancement of thermogenesis and utilization of peripheral substrates (glucose, lipids), altogether resulting in a catabolic state. Adiponectin enhances the expression of hypothalamic CRF but no other leptin-dependent peptides. The melanocortin pathway may, however, participate in conveying the actions of this peptide, since agouti-mice do not respond to adiponectin (114, 115).

3.5.2. Peptide YY

Peptide YY (PYY) is synthesized in the gut. PYY satiety-signals are transmitted via the afferent vagus (116) and act mainly on rostral medullary neurons, with most

PYY fibers in the NTS and the dorsal motor nucleus of the vagus (117). Traditionally, the peptide was thought to suppress food intake, but it also decreases respiratory quotient – suggesting enhanced peripheral fat utilization (118, 119). Recent data emphasize that a rise in postprandial energy expenditure by PYY rather than hypophagia is important in maintenance of normal energy balance (120). In transgenic mice, PYY over-expression protected against diet-induced obesity, increased the body temperature and maintained a high TRH release (121).

3.5.3. Pancreatic polypeptide

The pancreatic polypeptide (PP) acts partly on the vagus through hindbrain structures and it has similar effects as PYY: it suppresses food intake and increases energy expenditure (122, 123). PP overexpressing mice are thin and at this level (not in the gastrointestinal functions) show synergism with CCK. However, the direct central action of PP through hypothalamic neuropeptides is the opposite: it induces hyperphagia, probably in connection with activation of orexins (reviewed by 124).

3.5.4. Amylin

Amylin is similarly a catabolic peptide derived from the pancreas (secreted together with insulin) and acting in the brainstem. Upon peripheral or central administration it inhibits food intake (125), increases metabolic rate (126, 127) and body temperature (Székely *et al.,* unpublished). NTS lesions prevent the effects of amylin (128). Its inhibition by a specific antagonist induces hyperphagia, increased body adiposity (not lean body mass) and plasma insulin level (129).

3.5.5. GLP-1 and oxyntomodulin.

The pancreas, gut and NTS contain preproglucagon, which (besides glucagon) produces glucagon-like peptide-1 (GLP-1) and oxyntomodulin. GLP-1 agonist exendin was demonstrated to have both anorexic and hypometabolic effects (130) via the NTS (131). In humans, plasma GLP-1 was shown to elevate energy expenditure and promote satiety (132).

3.5.6. Galanin

Galanin enhances feeding (133), particularly the fat and alcohol consumption (134), and it reduces energy expenditure upon administration into brain structures (135, 136) thus may be regarded as an anabolic substance. Transgenic mice with 10-fold higher than normal circulating galanin level were obese mainly due to a decrease in energy expenditure (137). An antipyretic effect was also described for ICV applied galanin (138).

3.5.7. Cannabinoids

Cannabinoids are not peptides, but they are anabolic and act, at least partly, via modification of central orexigenic and anorexigenic peptides. Rimonabant (SR141716), a cannabinoid antagonist, decreased the expression of NPY and increased that of CART and alpha-MSH in the hypothalamus (139). The antagonist reversed the diet-induced obesity mainly by enhancing energy expenditure (140).

4. CENTRAL NEUROPEPTIDES

Apart from those peripheral peptides that – in addition to a peripheral action – may get into the brain or may bind to the afferent vagus and act on nuclei of the hypothalamus or the brainstem to influence energy balance (*e.g.* CCK has effects in the gastrointestinal system but also binds to the vagus to induce satiety), there are several neuropeptides produced in these nuclei. Such central peptides regulate food intake and body weight as well as energy expenditure. There is no strict distinction regarding the classification of these substances. For example, NPY is also produced at the periphery (it exerts mainly vasomotor actions), but NPY is probably more important as a central anabolic neuropeptide. CCK is regarded a peripheral hormone, but it is also produced in the brain. MSH has several effects, some in the periphery, but its most important role is probably the central catabolic function. Moreover, most of these central neuropeptides are involved in other functions, which functions are independent of or only loosely connected with the role of the given peptide in energy balance (*e.g.* orexin-A is important in the regulation of sleep, CRF in stress reactions, *etc.*, barely connected with their anabolic or catabolic roles).

4.1. Anabolic peptides

4.1.1. Neuropeptide Y (NPY)

Neuropeptide Y (NPY) is widely accepted as the most potent orexigenic peptide (3, 141). It is produced mainly in the arcuate nucleus, to be released primarily at nerve projections in the paraventricular, perifornical, dorsomedial and ventromedial nuclei of the hypothalamus, and also in the lateral hypothalamic and median preoptic area. The PVN also receives projections from the NPY-synthesizing neurons in the brain stem. It is important mainly in normal eating and in genetic and diet-induced obesity (142). Although it is effective throughout the day, in nocturnal animals the most pronounced effects are seen at the beginning of the dark period. It also influences the sympathetic system (143). NPY may, however, be more than just an orexigenic peptide. It has also been shown to suppress metabolic rate and/or body temperature, to act presumably as a rather complex regulator of energy balance and as such, it is better referred to as an anabolic substance (5, 6). Central administration of NPY induces food intake and hypothermia by suppressing brown fat metabolism (144), its antisense (145) or high-fat diet that suppresses the NPY level (146) causes opposite effects. Altogether, NPY exhibits a complex anabolic pattern (147), mainly via its receptors, Y1R and Y5R. The importance of NPY in the regulation of food intake is further emphasized by its interaction with leptin (141): leptin decreases NPY expression in the arcuate nucleus, while in food deprivation (with low leptin levels) the NPY expression is enhanced (148), similarly as in *ob/ob* mice. Central NPY administration induces sympathetic activation of the liver, together with insulin resistance and abnormal glucose tolerance (84), *i.e.* NPY can influence peripheral substrate utilization.

NPY works in interaction with other neuropeptides. In fasting, hypothalamic NPY/AgRP

expression quickly increases (148). Co-administration of NPY and AgRP additively increased food intake compared with either peptide alone (149). NPY suppressed the proTRH expression in the PVN (150). GLP-1 inhibited the NPY-induced food intake (151). The action of orexins may be connected with NPY activity (see Ch. 4.1.2.). In the arcuate nucleus there is a delicate balance between NPY and the melanocortin system: NPY expression is inhibited, while that of melanocortins is enhanced by leptin or insulin.

Recently mainly knockout strains of mice are used in analyzing the role of NPY and its receptors. Originally, NPY knockout mice were reported to have a normal feeding pattern (152) and a normal responsiveness to fasting, to exogenous NPY or leptin, but not to CRF or melanocortins (153). NPY deficient mice had higher oxygen consumption and UCP-1 expression during fasting than the control mice (154). Knockout of various NPY-receptors brought new results. Interestingly, the Y1-receptor (Y1R) knockout mice were found to be mildly obese, although not hyperphagic and had upregulation of UCP1 in brown fat with downregulation of UCP2 in white adipose tissue (155). Similarly to Y1R deleted animals, Y5R knockout mice show an obese phenotype. This is, however, probably simply a result of overeating, since upon food deprivation their body weights fell by the same rate as that of their wild-type counterparts, suggesting that the energy expenditure was not altered (156). Deletion of Y2R in *ob/ob* mice (with high NPY, AgRP and low POMC and CART expressions in the arcuate nucleus) significantly increased the hypothalamic POMC mRNA expression, with no effect on the expression of the other peptides, and upregulation of UCP1 – the adiposity of these mice was smaller as compared with the simple ob/ob animals (157). The diet-induced obesity in Y1R knockout as well as in Y1Y2 or Y1Y4 receptor double knockout mice was exacerbated, while in Y2Y4 double knockout animals the body weight was maintained: the rise in food intake was counteracted by increased metabolic rate (158). Similar ablation of Y2 and Y4 receptors protected against diet-induced obesity (159).

Apparently, as regards thermoregulation, Y1R may be more important than Y5R (145), but the other receptor types might also participate in thermoregulatory reactions. Both Y4R knockout and control mice have higher fever responses to lipopolysaccharide than the Y2R knockout animals, but the sickness behavior is more pronounced in the Y2R knockout group (160).

It can be concluded that hypothalamic NPY is the most potent orexigenic peptide, which also suppresses metabolic rate (brown fat thermogenesis) and body temperature, altogether exhibiting an anabolic pattern. The production of NPY is inhibited mainly by peripheral leptin and insulin, but enhanced by fasting states and information from brainstem structures. It can also influence peripheral substrate utilization. NPY exerts these actions mainly via hypothalamic Y1 and Y5 receptors. AgRP, the endogenous antagonist of the melanocortins has a similar regulation and similar (although more prolonged) effects.

4.1.2. Orexins (A and B, hypocretins)

Orexins have first been described as peptides regulating feeding behavior and as neuroexcitatory substances setting the threshold for arousal (review 161).

Orexins are produced mainly by neurons of the lateral hypothalamic and perifornical area that project to the entire brain except the cerebellum (162). Peripheral ghrelin contributes to the activation of orexin-containing neurons. Peripheral metabolic cues, such as glucose, leptin, cholecystokinin, ghrelin, might also influence the activity of orexin neurons via vagal afferents and the NTS, because it was reported that orexin neurons are stimulated by hypoglycemia at least partly via the NTS (103, 163). Orexin expression of normal and *ob/ob* mice is negatively correlated with changes in blood glucose, leptin, and food intake (164). Insulin exerted no direct effect on orexin neurons.

Some investigators report on short-lasting enhancement of food intake and suppression of energy balance upon central orexin-A administration (provided that the cool environment allows to observe this suppression; 165), which are later followed by increased metabolic activity and (postprandial?) hyperthermia. Others emphasize that the orexin A-induced hyperphagia is accompanied by concurrent hypermetabolism and hyperthermia (3, 166). Centrally applied orexin A seems to induce a short feeding-period first, then an enhancement of spontaneous activity (167). In addition to effects on the arousal state, orexin-A simultaneously increases energy expenditure by increasing the firing rate of sympathetic nerves to brown fat (166). Orexin knockout mice have higher core temperatures in the active (dark) period than their wild-type counterparts, and also higher core temperature values during sleep (168), indicating an overall hypothermic effect for orexins. An intraperitoneal dose of the orexin-1 receptor antagonist reduced orexin-A-induced feeding and spontaneous food intake, and it also increased the metabolic rate in rats. Chronic peripheral administration of the antagonist diminished cumulative food intake and body weight gain over 14 days: the total fat mass gain was reduced, while the gain in fat-free mass was not changed. Brown fat that expresses orexin-1 receptor mRNA, increases UCP-1 mRNA expression in response to chronic orexin-1 receptor antagonist administration, suggesting a stimulation of thermogenesis by the antagonist (169).

Orexin neuron-deficient mice also exhibit late-onset obesity, despite the reduction of food intake and on high-fat diet they gain more weight than the wild-type mice (170). Insulin-induced metabolism of glucose, a major source of energy, is finely tuned by the hypothalamic orexin system (171). The ability of orexin administered into the PVN to increase spontaneous locomotor activity and oxygen consumption is diminished in diet-induced obese (DIO) rats compared with diet resistant (DR) animals (172).

As many other peptides, orexins also act in concert with other neuropeptides. Orexin-positive axons are in contact with NPY neurons in the arcuate nucleus, which

neurons express orexin receptors (173). Administration of orexin in doses that elicit a feeding response also increased the NPY mRNA levels in the hypothalamus (174). Besides, pretreatment with an NPY antagonist abolished the feeding response to orexin (175). According to new data POMC neurons are also activated by hypocretins (176). Furthermore, ICV administered orexin-A reverses the inhibitory effect of intraperitoneal CCK on food intake in mice (177). CCK may inhibit orexin neurons in the posterior brainstem and this may be related to the CCK-induced inhibition of food intake after 48-h food deprivation (178).

Altogether, the higher arousal levels induced by orexins are possibly connected with a food-searching behavior and increased appetite. The effect of orexins on metabolic rate has not been completely clarified.

4.1.3. Melanin concentrating hormone (MCH)

Melanin-concentrating hormone (MCH) is a 19-amino-acid cyclic peptide exerting its actions through two G-protein coupled receptors, MCHR1 and MCHR2. MCH is implicated in the regulation of different physiological functions, including energy homeostasis and mood (179). Within the central nervous system, the expression of MCH is most abundant in the lateral hypothalamus, but it may also be detected in the amygdala and the magnocellular neurons of the zona incerta (180). Perifornical and lateral hypothalamic MCH neurons project to the dorsal vagal complex, they interact with (inhibit) pre-synaptic mechanisms reaching the NTS (181). It has been shown that MCH-containing neurons often coexpress another orexigenic peptide, orexin (182). MCHR1 mRNA has moderate expression in the VMN, the arculate nucleus and the zona incerta. In the periphery it is expressed in the beta cells of the pancreatic islets (183): it enhances insulin secretion.

MCH administration into the lateral ventricle of rats causes an acute and rapid increase in feeding (184, 185). Chronic infusions of MCH were shown to produce hyperphagia and obesity in mice (186, 187) and rats (188). A two-fold MCH overexpression in transgenic mice leads to obesity and insulin resistance (189). Fourth ventricular administration of MCH in freely moving rats decreased core temperature but did not change locomotor activity and food or water intake (181) – in the brainstem MCH affects mainly the metabolic rate. ICV infusion of MCH decreased the rectal temperature in rats, due to a down-regulation of the expression of UCP-1 in brown fat, and that of key enzymes of fatty acid oxidation (187). In rats the hypothalamic MCH expression is enhanced by cold exposure, and this contributes to the metabolic rearrangement (substrate intake and utilization) in the thermoregulatory adaptation (190).

MCH- and MCHR1-knockout animals show a lean phenotype with hypophagia and increased resting energy expenditure, high locomotor activity (191, 192, 193) and a varying degree of protection against diet-induced obesity depending on the mouse strain (194). Deleting the MCH gene in the *ob/ob* mouse improved their obesity, diabetes, and hepatic steatosis (195). MCHR1 gene deletion on the *ob/ob* background had no effect on body weight, food intake, or energy expenditure. However, the *ob/ob* MCHR1 knockout animals had lower blood glucose response and insulin levels compared to their *ob/ob* littermates. The double knockouts demonstrated higher locomotor activity, higher lean body mass, lower fat mass and better temperature regulation in a cold environment than the ob/ob mice. The latter findings suggested that MCH and leptin exert opposing effects on sympathetic nervous system thermogenic regulation (196, 197). The physiological functions of the MCHR2 remain to be determined. MCHR1 knockout mice had even higher temperature than the wild animals (198).

Vagal afferent neurons showing MCH and MCHR1 expression also express CCK-1 receptors (199) in a feeding-dependent way. Refed or CCK treated rats exhibited down-regulation of MCH and MCHR1 expression. ICV administration of anorexigenic peptides (alpha-MSH, glucagon-like peptide-1 /GLP-1/, neurotensin) effectively inhibits the orexigenic action of a centrally injected MCH (151). In MCH deficiency the POMC expression of the arcuate nucleus is markedly decreased (196).

Pharmacological studies using different classes of selective MCHR1 antagonists also point towards the role of MCHR1 in the regulation of food intake and metabolic rate. High-affinity MCHR1 antagonists reduce food intake and body weight gain in several animal models (200, 201). The effects of MCHR1 antagonists were centrally mediated since only MCHR1 antagonists that crossed the blood–brain barrier were able to exert an anorectic effect, whereas another antagonist that had poor brain penetration was without effect (202).

4.1.4. Other anabolic peptides

4.1.4.1. Nociceptin/orphanin FQ

Among other functions, nociceptin/orphanin FQ, an endogenous ligand for opioid receptor-like-1 structures, has anabolic properties, too: its chronic ICV infusion caused hyperphagia, suppression of energy expenditure and consequent obesity in mice (203).

4.1.4.2. QRFP

QRFP is an RFamide peptide, which is an endogenous ligand of the orphan G protein-coupled receptor, GPR103. In mice, a 13 day-long ICV infusion of this peptide induced hyperphagia and obesity (particularly in those on high-fat diet), along with a decrease in core temperature and decreased expression of UCP-1 in brown fat (204).

4.2. Catabolic peptides

4.2.1. The POMC-melanocortin system

Under normal circumstances, this system appears to be the most important anorexigenic-catabolic system of the body. It has many interactions with other anorexigenic substances and mechanisms (*e.g.* leptin, insulin), it has not only endogenous agonist (alpha-MSH) but also endogenous antagonist (AgRP) peptides, and it has several abnormalities.

Pro-opiomelanocortin (POMC) has been demonstrated in the hypothalamic arcuate nucleus and, in smaller amounts, in the NTS (181, 205, 206). It is a big molecule complex and precursor of many polypeptides (207, 208), which encompass a wide spectrum of activity (ACTH /adrenocorticotropic hormone/, beta-lipotropin, various forms of melanocyte-stimulating hormone /alpha- beta- or gamma-MSH/, beta-endorphin, etc.). POMC production in the arcuate nucleus is enhanced mainly by the circulating leptin and insulin, also by nutrients (*e.g.* glucose; 15) or nutrient derivatives (*e.g.* malonyl-CoA; 209), but CRH (210) and glucocorticoids also have an influence. Some of the most important MSH forms bind to melanocortin receptors (211) in the hypothalamus and brainstem, mainly to types MC3R and MC4R (alpha-MSH to both, gamma-MSH to MC3R: the two receptors exhibit similarities as well as differences; 212, 213). Their endogenous antagonist (214) or inverse agonist (215) is agouti-related peptide (AgRP), which is produced in the arcuate nucleus (but not in the NTS).

In studies of energy balance, the alpha-MSH peptide – as an ACTH-related molecule – was first regarded as a functional antagonist of proinflammatory cytokines and, from the early nineteen eighties, it was investigated as an endogenous antipyretic and anti-inflammatory peptide in the rabbit and other large animals (216, 217). Central administration of the peptide in a dose, which had no influence on normal resting body temperature practically abolished the fevers induced by endotoxin or various cytokines (218). In contrast, centrally applied alpha-MSH-antiserum augmented the febrile reactions (219). Besides, it was further assumed that alpha-MSH attenuates at least some components of the acute-phase response, sickness behavior and inflammatory reactions (220). The basic findings were confirmed several times, but there were widely different theories to explain how these antipyretic and other effects might be elicited (221, 222, 223).

Not much later further investigations made the picture more complicated: melanocortins were shown to exhibit strong anorexigenic and catabolic effects (224, 225, 226). Since fever itself is an anorexigenic and catabolic process, this finding was obviously difficult to reconcile with the described antipyretic effects of the peptide. The investigations went on in two directions: (i) to specify the role of alpha-MSH and melanocortins in the overall energy balance (including feeding behavior and body weight) and (ii) to characterize the roles these peptides may play in thermoregulation, fever and fever-associated phenomena.

4.2.1.1. Melanocortin effects on food intake and body weight

While it had soon become clear that leptin-activated melanocortins influence both food intake and metabolic rate, it was described (227, 228) that at least 10-times smaller dose of MTII (melanotan, nonspecific agonist of MC3R and MC4R) was needed to evoke anorexia than to cause hyperthermia. The conclusion that the anorexigenic and thermogenic effects can be dissociated was confirmed in another way by Balthasar *et al.* (229), who found that food intake is influenced mainly through the PVN and the amygdala, in contrast to the energy expenditure, which they found to be influenced through some non-defined structures (*e.g.* dorsomedial hypothalamus; 230). Apparently, the negative influence on food intake is more pronounced, but regarding also the concurrent enhancement of energy expenditure, these effects act together in the direction of loss of body weight, *i.e.* they exhibit a full catabolic pattern.

Corticosterone supplemented POMC null mice are obese, but alpha-MSH decreases both their fat mass and lean body mass (231), suggesting that the melanocortin receptors and downstream pathways to the paraventricular nucleus, lateral hypothalamic area and brainstem are still functional and can still be activated.

The specific melanocortin receptors of the hypothalamus (MC3R and MC4R) have somewhat different roles (211). MC4R of the paraventricular nucleus and amygdala (and perhaps the lateral hypothalamic area) are probably responsible for the post-ingestion satiety and suppression of food intake, and similar receptors simultaneously activate the raphe pallidus and the sympathetic preganglionic neurons of the intermediolateral nucleus of the spinal cord, thereby providing an adaptive hypermetabolic response to excess calorie consumption and inducing a negative energy balance (229). MC4R knockout mice are hyperphagic and obese and they are resistant to cachexia induced by tumor growth or pyrogens (229, 232) – partly due to a hyperphagia, which (in the absence of MC4R) compensates the tumor/pyrogen-induced rise in energy expenditure, partly due to absence of melanocortin-induced excess in metabolic rate. Not only centrally (232) but also a peripherally administered MC4R-antagonist prevented the cancer-induced cachexia in mice (233). In contrast, MC3R is likely to be less important in the suppression of food intake: MTII exerted its anorexigenic effect even in MC3R knockout mice (211, 212) probably through MC4R mechanisms. Nevertheless, AgRP evoked a moderate increase in food intake in MC4R knockout animals (36, 234), suggesting some role for MC3R in the regulation of food intake (or a melanocortin-receptor independent role for AgRP). MC3R knockout mice are not particularly hyperphagic, not much heavier than the wild-type controls, but they are obese and their lean body mass is low (212). On a high-fat diet they gain excess weight not so much due to overfeeding, but rather to different fat utilization: their respiratory quotient slightly exceeds that seen in control mice, suggesting a diminished ability to burn fat (211). In case of tumors such mice quickly become cachectic (232, 235).

Extrahypothalamic (mainly brainstem, NTS) melanocortin activity has basically similar effects, but there are some remarkable differences. Melanocortin receptor agonists and antagonists injected into the brainstem region exert long-lasting effects on body weight (236) and body temperature (237). The melanocortin activity transiently increases upon injection of recombinant adeno-associated viral vector encoding the POMC gene into the arcuate nucleus (the tachyphylaxis is explained by enhancement of AgRP expression in the same nucleus, which counteracts

the high melanocortin activity). No similar tachyphylaxis but a lasting suppression of food intake and decrease in body weight was observed upon administrating the vector into the NTS where no AgRP production was found (238). Whereas fasting (*i.e.* suppression of leptin level) caused decrease of POMC mRNA and of the levels of POMC derivatives in the arcuate nucleus, in the NTS only the POMC mRNA but not the peptide levels decreased, and leptin prevented the changes exclusively in the arcuate nucleus (239). This is an important difference: the afferent vagal signals (conveying mainly short-term information about the actual feeding state) influence the NTS directly, not the arcuate nucleus. Accordingly, the possible melanocortin-linked anorexic neural or humoral signals of gastrointestinal origin (*e.g.* CCK; 240) may be able to activate the melanocortin system without any local counteracting mechanisms that could limit their actions, thereby they may influence short-term food intake (and only less the body weight) (241, 242), and may also modify the sympathetic tone and energy expenditure (243), which in these cases are more important determinants of body weight. The dorsal vagal complex (including the NTS) seems to be appropriate place to receive a variety of afferent vagal information, to process it and – through vago-vagal reflexes – to give appropriate short-term answers (206, 244, 245).

4.2.1.2. Melanocortin effects on thermoregulation

An 8-day-long ICV infusion of MTII (246) caused transient increase of oxygen consumption in rats, but – contrary to expectations – no decrease in energy expenditure was noticed upon ICV infusion of the relatively specific MC4R antagonist HS024 (although it induced hyperphagia). A possible explanation is that due to hypothalamic compensatory steps, ICV infused substances (like MTII in the present case) often induce only transient changes (147, 247). On the other hand, an expected suppression of energy expenditure by the antagonist might only be observed at temperatures well below thermoneutrality. In other studies (248) MTII infusion elevated the oxygen consumption and decreased the respiratory quotient of lean Zucker rats, suggesting enhanced fat utilization. Large-dose central injections of MTII induced hyperthermia in rats (228). In contrast, MC4R antagonist treatment (in addition to increasing food intake) suppressed the metabolic rate of cancer-bearing mice – this seems to be an important factor in the prevention of cancer-induced cachexia (233). Activation of either the hypothalamic (249) or the brainstem (250) melanocortin receptors also increased the expression of UCP-1 mRNA in brown adipose tissue of rats. All these support the notion that melanocortins enhance thermogenesis (243). Although in these studies body temperature was measured only occasionally, some earlier (251) and more recent reports (252) demonstrated development of hyperthermia upon administration of melanocortin agonists. Administration of [Nle^4,D-Phe^7]-alpha-MSH, a strong melanocortin agonist, induced a sustained elevation of metabolic rate (without any change in food intake) in both wild-type and *ob/ob* mice (253), and activation of the caudal brainstem MC3/4R caused hyperthermia through sympathetic effector activation (237). In contrast, in rats an ICV infusion of SHU9119, a non-specific antagonist of MC3/4R suppressed body temperature and induced obesity without any change in the hypothalamic expression of neuropeptides (254). SHU9119 also enhanced food intake, and it inhibited the MTII-induced activation of brown fat (255), although not the sympathetic activation normally induced (39) by leptin. As compared with the wild type animals, the intake of either low-fat or high-fat containing food was not altered in mice with transgenic MSH overexpression, but the body fat content decreased, particularly in the group consuming high-fat diet – the high oxygen consumption and low RQ suggested continuous enhancement of metabolic rate and fat utilization in these mice (256). The fasting insulin levels were also decreased, the glucose tolerance improved, and the hepatic fat accumulation attenuated.

There were only very few trials for *lege artis* analysis of the complex thermoregulatory effects of alpha-MSH or other melanocortin agonists *vs.* antagonists. In most of the above studies the environmental temperature was not specified. This was less critical in the early experiments on rabbits, since rabbits have a very wide range of thermoneutrality and practically all experiments were performed at a thermoneutral environment. However, the environmental temperature may influence the thermoregulatory responses in small-size species like rats and mice, with narrower range of thermoneutrality. For example, in rats endotoxin induces fever at thermoneutrality, but results in hypothermia at cold temperatures (257). Likewise ICV noradrenaline elevates core temperature in a warm environment, but decreases it at cold temperatures in sheep (1). In rats alpha-MSH is known to enhance brown fat thermogenesis through activation of the neurons of the rostral raphe pallidus (258), as well as to stimulate brain-derived neurotrophic factor (BDNF) release to increase body temperature (252), but until recently the entire scale of efferent mechanisms (heat production, heat loss, resultant core temperature changes) and their interactions has not been thoroughly analyzed. Sinha *et al.* (259) described some hyperthermia upon alpha-MSH administration, but they did not observe any regular change in skin temperature (in case of a fever-like temperature rise, skin vasoconstriction should be expected, what they did demonstrate in the same report using a pyrogen). Apparently, pyrogenic substances and MSH influenced body temperature by dissimilar mechanisms. When analyzing the effects of central alpha-MSH administration on heat production, heat loss and body temperature in Wistar rats at different ambient temperatures, we (260) found that at cool (15-20ºC) environments the ICV injection of alpha-MSH caused a marked elevation of metabolic rate and body temperature, which were accompanied – due to the cold – by a continuous tail-skin vasoconstriction (*i.e.* no change in the already maximally inhibited heat loss activity). However, at warmer environments (which in some cases also elevated the initial body temperature) the rise in metabolic rate was minimal or completely absent and minute or practically no rises of body temperature or metabolic rate were accompanied by a pronounced skin vasodilatation (*i.e.* a rise in heat loss). Eventually, if the initial body temperature was high enough, the ICV alpha-MSH injection was followed by

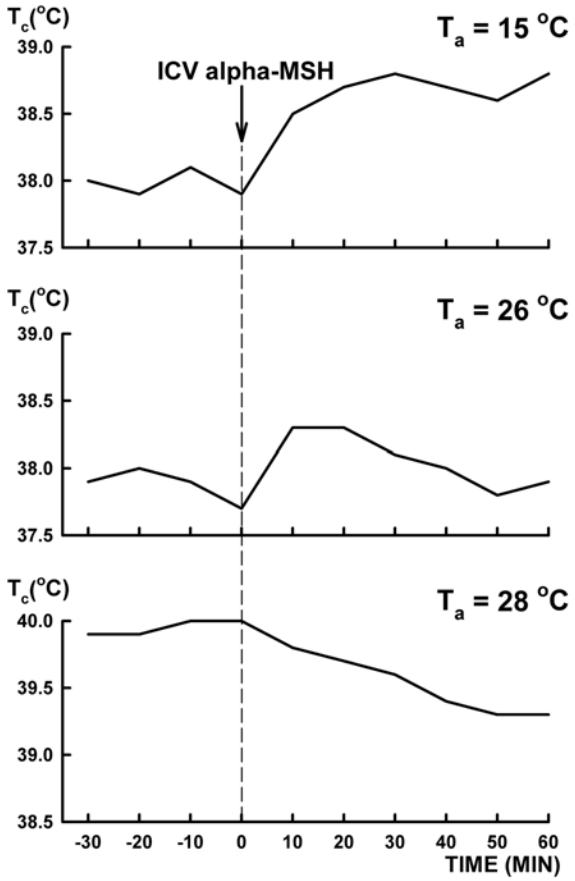

Figure 1. Effects of 5 microgram ICV alpha-MSH on core temperature (Tc) in rats exhibiting various initial body temperatures (individual experiments). At cool ambient temperature (Ta) there was no vasodilatation, at around thermoneutrality a late-onset, while in a warm environment an immediate vasodilatation was observed (not shown), resulting in core temperature changes depending on the initial values (Garami *et al.*, unpublished).

immediate vasodilatation only, resulting in a fall of body temperature (Figure 1). Accordingly, in contrast to the coordinated anorexigenic features of alpha-MSH effects, which are similar as those in fever, the thermoregulatory effects of this peptide are different from the coordinated pattern seen in fever: heat production is enhanced practically simultaneously with a tendency to increase heat loss – the circumstances (*i.e.* the environmental and initial body temperatures) seem to determine which one prevails.

Such changes of skin vasomotor tone induced by alpha-MSH might contribute to the explanation why a rising body temperature following administration of endotoxin or cytokines was halted by alpha-MSH pretreatment (Figure 2) or was enhanced by melanocortin antagonists (261, 262). Others (259, 263) have come to a similar conclusion: an MC4R agonist inhibited the endotoxin-induced heat conservation mechanisms (*viz.,* it inhibited tail skin vasoconstriction that normally follows endotoxin administration), but they observed only moderate skin-temperature changes and did not experience vasodilatation upon alpha-MSH administration. Nevertheless – in contrast to the assumed antipyretic actions – the melanocortin system may have some role in the pathogenesis of fever or fever-related phenomena: interleukins can bind to receptors of the arcuate nucleus (less to the NTS), stimulate the POMC neurons and enhance the release of alpha-MSH (264). In other studies the anorexigenic (although not the pyrogenic) effects of a pyrogenic cytokine were modulated by a MC3/4R antagonist in the rat (265), and AgRP prevented the endotoxin-induced anorexia in sheep (266). All these add further emphasis to the earlier data regarding the antipyretic features of alpha-MSH, and extend them with the observations that other components of the sickness behavior, like anorexia, are rather enhanced by the melanocortins. Clearly, the anorexigenic and thermoregulatory effects of melanocortins can be dissociated.

Main conclusions: (i) the anorexigenic and thermoregulatory effects of melanocortins can be dissociated (229), (ii) leptin may be regulator of most, but not all melanocortin activities (33, 38), (iii) leptin/obesity may have melanocortin-independent effects in this system or other systems (39).

4.2.2. Corticotropin-releasing factor (CRF) – urocortins

The distribution of CRF in the central nervous system suggests that it does not function simply as a regulator of the hypothalamo-pituitary-adrenal (HPA) axis, but has some neurotransmitter or modulator roles as well (267). In these functions CRF1 and CRF2 receptors are involved, together with a CRF-binding protein and various urocortins as endogenous ligands (CRF itself is a less effective ligand) of the receptors. The CRF-containing cells are located in the PVN (and in VMN).

On basis of experiments performed on rabbits, CRF – also an ACTH- and stress-related molecule – was first regarded a functional antagonist of proinflammatory cytokines and an endogenous antipyretic peptide (268), similarly as it was described for MSH. Despite some confirming data, other investigators came to an opposite conclusion, *viz.* that most effects of the various pyrogens checked were rather mediated and not antagonized by CRF (269). Obviously, an analysis of the effects of CRF in various mechanisms of energy balance was again necessary.

The gene expression of CRF is lower in states of negative energy balance or high energy need (pregnancy; fasting, 270; cold exposure, 271), while it is higher in states of positive energy balance (overfeeding, 272; hyperglycemia, 273). The VMN serves mainly as receptive field with neurons, which contain many CRF-receptors (and some leptin-receptors), and which are also sensitive to glucose, orexin and CCK. While CRF1 receptors show widespread appearance and seem to be responsible mainly for the activity of the HPA-axis and for the stress-reaction, the CRF2 receptors are more concentrated in the VMN and PVN, they have a more definite connection with the energy homeostasis and they probably dampen stress sensitivity

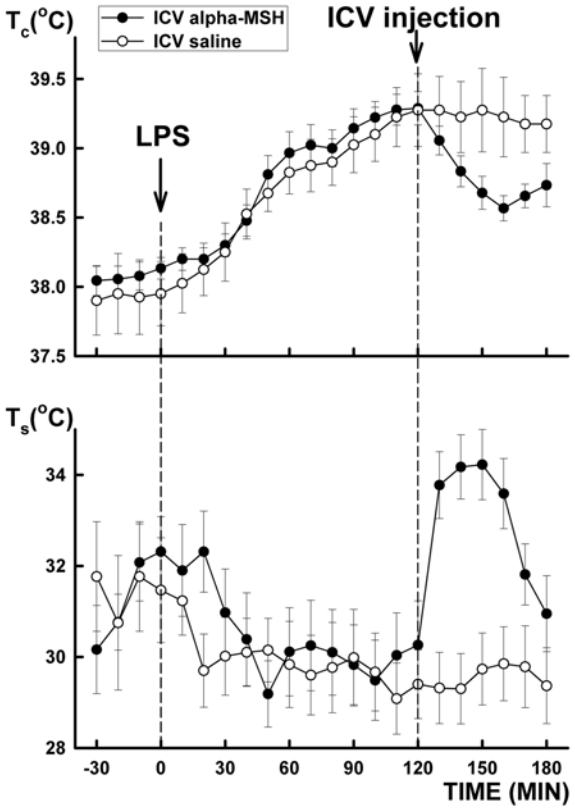

Figure 2. Effects of ICV 5 microgram alpha-MSH or 0.9% saline on core (Tc) and tail skin (Ts) temperatures in rats receiving 10 microgram/kg LPS intravenously 120-min prior to the ICV injection. Alpha-MSH accelerated defervescence by causing skin vasodilatation (Petervari *et al.*, unpublished).

(274). CRF2 receptor-deficient mice were shown to have elevated brown fat thermogenesis, but also exhibited warm preference suggesting that brown fat was activated primarily by enhanced heat loss (275). Urocortin I has a high affinity for CRF1 receptors, whereas urocortin II and III are the main ligands of CRF2 receptors.

In the complex picture of energy balance both CRF1 and CRF2 receptors have certain roles, even if these roles are not precisely defined as yet. ICV injection/infusion of CRF or urocortin, as well as stress suppressed food intake, enhanced sympathetic and brown fat activity, increased fat utilization (decreased the respiratory quotient, 276) and decreased body weight (277, 278, 279). Most effects were antagonized by the non-specific antagonist alpha-helical-CRF (280, 281). The anorexic effects were antagonized by antisauvagine-30, a selective CRF2 receptor antagonist, but this substance did not influence the metabolic (and thermoregulatory) effects (282). Apparently, the latter effects may depend on CRF1 receptor activation. However, in Zucker obese rats a CRF1 receptor antagonist (*i.e.* inactivation of CRF1 receptors) also enhanced fat metabolism, metabolic rate, decreased the plasma levels of both triglycerides and leptin, improved insulin resistance (210).

The anorexic effects are possibly connected (downstream) with the melanocortin system: in CRF knockout mice a melanocortin agonist did not suppress food intake for a *ca.* 4-h period, implying that CRF has a mediating role in the anorexic effect of melanocortins (283). CRF-antibodies also prevented the leptin-anorexia (37). Since urocortins can activate the intracellular leptin-signaling pathways, they may have a compensatory role in leptin resistant states (279).

Central injection of urocortins results in elevation of sympathetic activity with adjoining elevation of oxygen consumption and body temperature (284, 285), mainly by urocortin I acting at CRF1 receptors (but urocortin II and III, which act at CRF2 receptors were also reported to cause hyperthermia; 286). Leptin blunts the exercise-evoked induction of CRF1-receptors and enhances the induction of the CRF2-receptors in the PVN and VMN, respectively, suggesting inhibition of HPA-axis and the concurrent metabolic and thermoregulatory responses, but it enhances the anorexic effects (287).

Main conclusions: Apart from the role of CRF in the HPA and stress responses, CRF and urocortins suppress food intake and enhance metabolic rate, i.e. they are catabolic substances. At least some of the leptin and melanocortin effects are exerted via CRF mediation. The role of CRF in fever and antipyresis has not been clarified.

4.2.3. Cocaine-amphetamine regulated transcript (CART)

In rodents CART is expressed mainly in POMC neurons of the arcuate nucleus, although it has also been demonstrated in the paraventricular, periventricular, perifornical, supraoptic, lateral and dorsomedial nuclei (288, 289), but not in neurons expressing orexigenic neuropeptides like NPY or AgRP. CART neurons may coexpress mRNA of TRH, MCH, neurotensin, dynorphin, *etc.* In the PVN, CART mRNA is co-localized with vasopressin and CRF-containing neurons (289). Typically, CART neurons have LRb receptors that can be activated by leptin, although in the absence of CART (unlike in the absence of MC3/4R) leptin retains its full activity (290). Insulin (75) and glucocorticoids (291) also activate these neurons, just as dietary fat does (273). Low leptin levels (*e.g.* fasting or *ob/ob* mice) are accompanied by downregulation, high leptin levels (*e.g.* in dietary obesity) by upregulation of hypothalamic CART mRNA expression. In vagal afferent fibers CART expression is enhanced by CCK-1 agonist and inhibited by ghrelin (89).

The ICV injection of CART suppressed food intake induced by fasting or central NPY administration, the chronic ICV infusion of the peptide caused sustained falls in food intake and body weight (review: 6). Fasting also caused downregulation of CART expression in monkeys (292). All these seem to suggest an anorexigenic, catabolic role for CART. Indeed, a missense mutation of CART gene was reportedly associated with obesity (293) in a family.

However, in the human hypothalamus the CART distribution is different (294): co-localization of CART in about one third of orexigenic NPY and AgRP neurons in

the infundibular nucleus and in MCH neurons of the PVN was demonstrated, but not in alpha-MSH containing neurons, allowing also for an orexigenic role of the CART peptide. Data for the orexigenic effects of CART have already been published for rodents as well (295): in rats an overexpression of CART in the arcuate nucleus enhanced the spontaneous daytime food intake and the re-feeding upon food deprivation.

Besides food intake, CART also influences metabolic rate and some thermoregulatory processes. The leptin-activated CART-containing neurons project from the retrochiasmatic area and lateral arcuate nucleus to the spinal cord, innervate the sympathetic preganglionic neurons, enhance thermogenesis and energy expenditure (296). A significant activation of brown fat UCP-1 mRNA might have explained in the experiments of Kong *et al.* (295) that upon repeated administration or overexpression of CART body weight did not change in rats, despite an enhanced food intake – this may be a possible mechanism in the adaptation to cold. A low respiratory quotient upon CART administration also suggests enhanced lipid metabolism (297). The obesity in a family of missense mutation of CART gene is likely explained by suppression of resting metabolic rate in the absence of CART activity (293). CART knockout mice were obese, despite lack of hyperphagia, and they also had impaired insulin secretion and glucose intolerance (298).

Taken together, under normal circumstances CART probably participates not so much in tonic changes of energy balance, it may rather be important in short-term energy imbalances. By enhancing energy expenditure, it seems to participate in the acute energetic response to high-fat diet. Besides, upon cold exposure (which elevates the level of adrenal gland hormones) a high CART activity possibly contributes to the thermoregulatory adaptation by enhancing both food intake and brown fat thermogenesis.

4.2.4. Cholecystokinin (CCK)

One of the first known catabolic neuropeptides is CCK. Whether applied peripherally (299) or centrally (300), CCK induced satiety and decreased food intake. Brain CCK receptors (CCK-2) may be involved in satiety induced by gastric distension, but peripheral CCK-1 receptors may be responsible for the satiety induced by nutrient administration to the small bowel (301). The peripheral actions have been mentioned earlier (Ch. 3.3).

An ICV injection of CCK8 resulted in hyperthermia (302) with fever-like characteristics (for review see 93), altogether presenting a catabolic pattern. In fact, CCK has been reported to participate at least in the first part of LPS-induced fever via the activation of central CCK-2 (but not CCK-1) receptors (303) – this action was independent of the role of central prostaglandins in the pathogenesis of fever. In mice lacking functional CCK-2 receptors several parameters of sickness behavior (decreased activity, body weight and food intake), as well as the febrile rise in core temperature were attenuated in the response to IP LPS injection (304), while CCK-1 deficient rats developed normal fever to LPS (305).

It is concluded that – in contrast to the peripheral actions (Ch. 3.3.) – the central actions of CCK exhibit a coordinated catabolic pattern.

4.2.5. Other catabolic peptides

4.2.5.1. Nesfatin-1

The newly discovered nesfatin-1 of the paraventricular and supraoptic nuclei is produced in larger amounts upon re-feeding after a fasting period (306). It is coexpressed with several peptides, some (but not all) of which are definitely catabolic. Peripheral administration of nesfatin-1 enhances the POMC and CART mRNA expression in the NTS (but not in the arcuate nucleus) (307).

4.2.5.2. GALP, PrRP, BDNF, SP, CGRP, CNTF

Several recently discovered hypothalamic peptides have catabolic roles in energy balance. In contrast to galanin, the galanin-like peptide (GALP) is one of those catabolic peptides that mediate leptin effects (308). Its chronic administration decreases food intake and body weight even in ob/ob mice, and GALP also increases brown fat activity (308) and body temperature (309). Since the POMC expression simultaneously decreases, these effects seem to be independent of melanocortins (308). The prolactin-releasing peptide (PrRP) is also anorectic and it increases metabolic rate – the effects seem to be mediated by CRF receptors (310). Another similar substance is the brain-derived neurotrophic factor (BDNF) of the ventromedial hypothalamus, which exerts its complex catabolic effects, including hypophagia and enhanced thermogenesis (311) downstream of the melanocortin system (312). Substance P (SP) shows catabolic properties: it attenuates consumptive behavior (313) and enhances metabolic rate, causes fever-like dose-related hyperthermia (314, 315). Hypothalamic injection of calcitonin gene-related peptide (CGRP) activated heat production (316) and suppressed food intake (317). Complex catabolic effects were reported for the calcitonin receptor-stimulating peptide-1 (155): it slightly suppressed food intake, but caused a great rise in body temperature (318). Coordinated catabolic effects were described for the ciliary neurotrophic factor (CNTF), as well (319).

4.2.5.3. NPB, NPW, NMU

In an effort to find new ways of therapy for obesity, further peptides are being analyzed. Neuropeptide B (NPB) and neuropeptide W (NPW) are novel hypothalamic peptides that activate the previously described orphan G protein-coupled receptors, GPR7 and GPR8. ICV infusion of NPW suppressed feeding and body weight gain, increased heat production and body temperature (320). GPR7 knockout mice are hyperphagic and show decreased energy expenditure (321). In *GPR7−/−ob/ob* double null mice, as compared with *ob/ob* ones, an increased weight gain was demonstrated, suggesting that the NPB/NPW system and leptin influence energy balance similarly, but via different pathways (321). Neuromedin U (NMU) and neuromedin S (NMS) act at the type-2 NMU-receptors (NMU2R), which are predominantly expressed in the brain (NMU1R in peripheral tissues). Upon intrahypothalamic injection, these peptides suppressed food intake and increased non-exercise activity thermogenesis (322). NMU-deficient mice are obese with low

energy expenditure, transgenic mice with overexpression of NMU are hypophagic and thin. In CRF deficient mice NMU administration has no effect on energy balance suggesting that NMU acts via CRF pathway (323). Leptin seems to stimulate the NMU expression (review in: 324). CCK has also been shown to stimulate NMU-containing neurons in the NTS (325).

4.3. Other peptides

4.3.1. Vasopressin

Vasopressin is known to be involved primarily in water balance. However, a possible role for arginine vasopressin (AVP) as an endogenous antipyretic peptide was suggested about two decades ago (326). Apparently, activation of the AVP V1 receptors in the ventral septal area attenuates the febrigenic function of the adjacent preoptic/anterior hypothalamic region (327). AVP released during fever may act as an endogenous break to the temperature rise during fever (328). More recent data reveal not only endogenous antipyretic properties, but more complex effects of AVP on energy balance. Female spiny mice repeatedly treated with vasopressin exhibited a loss of body weight and some rise in energy expenditure, but this was explained not as a direct action of the peptide, rather as a consequence of increased salinity (329). A more direct role for the peptide was demonstrated in V(1B) receptor knockout mice, which had a low oxygen consumption and body temperature (330) and altered metabolism at the periphery (331): higher adiponectin and lower leptin levels were found as well as increased insulin sensitivity, low lipolysis, high lipogenesis, resulting in larger proportion of fat tissue.

4.3.2. Angiotensin II

Centrally applied angiotensin II has been shown to decrease food intake and to increase energy expenditure by enhancing the mRNA expression of uncoupling protein in the brown adipose tissue in rats (332). The catabolic effects were independent of the dypsogenic effect of the peptide. Our unpublished observations confirm the catabolic nature of angiotensin II. However, antagonist of type-1 angiotensin receptor (ATR1) was also shown to have hypophagic effects in rats (333). In mice, angiotensin II and III suppress food intake via the type-2 receptor (ATR2) (334). Angiotensin converting enzyme inhibitors have long been used as antihypertensive drugs. Recently, however, they have been shown to decrease body weight and adiposity in rats. Moreover they decrease it at a disproportionally greater degree than expected from the suppression of food intake (335), suggesting simultaneous enhancement of energy expenditure. In mice lacking ATR1a the increased energy expenditure attenuated the diet-induced obesity (336). The role of angiotensin in temperature regulation is also more controversial (337) than thought originally: exogenous and endogenous angiotensin appear to behave differently, *viz.* exogenous angiotensin II was found to induce hypothermia, while the endogenous form to be involved in heat loss or heat production responses according to the environmental temperature. Besides, ATR1 and ATR2 may be involved in various fever-reactions and may also contribute to the production of cytokines (like TNF), which participate in the hypothermia of systemic inflammation.

4.3.3. Hypothermic/hypometabolic peptides

4.3.3.1. Neurotensin

The effects of neurotensin depend on the hypothalamic site the peptide is applied. Injections to the preoptic area caused hyperthermia (338), while ICV injections or neurotensin (247) or its analogue (339, 340) were followed by hypothermia. Neurotensin is also anorectic (341). Chronic leptin administration enhances the hypothalamic neurotensin gene expression (48), it also increases neurotensin content and its inhibitory effect on food intake (342), *i.e.* some of leptin actions may be exerted via neurotensin pathways. In neurotensin-1 receptor deficient mice the anorectic effect of leptin is impaired (343). The hypothermic effects of neurotensin seem to be connected to NT2 receptors (344). Neurotensin may also be related to CRF: it acts in the PVN to activate CRF and the HPA (345).

4.3.3.2. Bombesin

Bombesin or bombesin-like peptides injected ICV (346) or into the amygdala (347) inhibited feeding, while in other studies central injections of the peptide induced hypothermia (7).

4.3.3.3. PACAP/VIP

The ICV injection of pituitary adenylate cyclase-activating polypeptide 38 (PACAP) or vasoactive intestinal peptide (VIP) inhibits food intake probably via CRF (348) or melanocortin (349) mediation. ICV injection of large dose VIP caused hyperthermia (295). Alas, mice deficient in PACAP/VIP receptor-2 have slightly elevated basal metabolic rate and growth retardation (350), indicating a primary hypometabolic effect for the peptide(s). Contrary to these observations, PACAP null mice were extremely cold sensitive, they could not increase the sympathetic tone, brown fat thermogenesis and blood glucose/lipid regulation, a situation that often resulted in early postnatal death (351, 352).

4.3.4. Hyperthermic/hypermetabolic peptides

4.3.4.1. Somatostatin

Central administration of somatostatin results in elevation of body temperature at lower doses (353), but causes hypothermia at a higher (supraphysiological) dose (354), in interaction with opioids. Somatostatin also reduces postprandial satiety and serves as a permissive factor in the development of obesity (355). By decreasing ghrelin secretion (356) and gastrointestinal motility (357), peripheral somatostatin also attenuates food intake. In other studies somatostatin was shown to reduce leptin responsiveness (358). Somatostatin has also been suggested as one of the factors contributing to the development of fever (359).

4.3.4.2. TRH

Over two decades ago centrally applied TRH and its analogues were reported to be thermogenic in the rat by increasing sympathetic outflow to the brown fat, and the

body weight of these animals also decreased (360). The immediate thermal effect was independent of the slow activation of thyroid hormone production. In anesthetized rats similar injections decreased brown fat thermogenesis and suppressed body temperature (361). Later it was recognized that ICV or intrahypothalamic TRH also attenuates food intake (362, 363). However, TRH applied to the brainstem did not suppress, rather enhanced food intake (by cholinergic stimulation of ghrelin secretion; 364). Apart from its direct effects on components of energy balance, TRH neurons of the PVN (which neurons have inputs from leptin-sensitive neurons of the arcuate nucleus) also influence gene expressions in the hypothalamus and this appears to orchestrate the expression and activity of anabolic and/or catabolic peptides (365). For example, during fasting the low TRH mRNA finally leads to decreased expression of melanocortins and CART peptides with increased expression of NPY and AgRP, contrary to the situation seen during satiety. Upon refeeding first the melanocortins, then the (NPY/AgRP-stimulated) TRH is activated (366) as a regulator of the expression of other peptides. In other cases endotoxin enhances the local T_3 level (by deiodinase activation in glial tanycytes), thereby suppresses TRH mRNA, while the leptin, melanocortin and CART expressions all increase. Other brain regions as well as body temperature may also influence the TRH neurons. Mice mutant for TRH conversion from pro-TRH are obese and cold-sensitive (367).

4.3.4.3. TLQP-21

A VGF-derived peptide (TLQP-21) prevents diet-induced obesity mainly by increasing energy expenditure (368). The data are controversial: VGF knockout mice are thin, small and hypermetabolic (369).

5. THERMAL FACTORS AND THE PEPTIDERGIC REGULATION

Temperature of the environment or the body may influence neuropeptide functions. Although there is no uniform way for such influence, there are several examples, which demonstrate the importance of environmental factors in the regulation of energy balance.

Results of chronic intraperitoneal leptin treatment on energy balance of mice maintained on low-fat or high-fat diet at three different ambient temperatures were analyzed (42): only those mice lost body fat that were kept on low-fat diet in a cold but not at warmer environments, high-fat fed mice were leptin resistant and in the warmest environment their adiposity even increased.

Acute exposure of chickens to cold (4ºC) or 10 day-long exposure to heat (32ºC) upregulates hepatic leptin and muscle UCP gene expression without any change in plasma glucose or insulin (370), *i.e.* the increase in leptin and UCP mRNA seems to be connected with thermoregulatory rather than metabolic processes. High-fat diet or low environmental temperature enhance the production various forms of UCP in brown fat and other tissues (371), obviously influenced by the regulatory peptides. Although it cannot be disputed that brown fat thermogenesis participates in the overall energy balance, its function may be more important in cold defence than in prevention of obesity (372).

Short-term cold-exposure may decrease hypothalamic NPY in rats (373). In the course of chronic cold exposure plasma leptin levels of rats decreased, the hypothalamic NPY remained unchanged (374). In rats, cold exposure elevated the hypothalamic MCH expression and contributed to the thermoregulatory adaptation (190). Cold exposure increases, warm one decreases the hypothalamic somatostatin level (353). Since somatostatin is a general inhibitor of neuropeptide actions, the temperature may interfere with hypothalamic neuropeptide activities. Although there are some data regarding the possible role of CART and CRF (271) in the metabolic adaptation to cold, the results are not yet convincing.

In rats, the activity-based anorexia is a model of anorexia nervosa. Such rats have high expression of MC4R and (as an adaptation) also AgRP with a decreased expression of POMC. At an ambient temperature of 21ºC these rats lost body weight. However, at 32ºC both the neuropeptide abnormalities and body weight were normalized (375). No changes were seen in control animals.

Heat stress, which is known to elicit anorexia, enhanced the activity of some anorexigenic peptides, such as CRF or neurotensin, but the thermal activation of (hepatic) afferent vagal fibers may also participate in a more complex adjustment of neuropeptide activities resulting in suppression of food intake (reviewed in: 6).

In other cases not the amount, rather the effect of the peptide changes with the temperature: ICV injected NPY caused more pronounced hypothermia in a cold than in warmer environments (147, 376), while orexin-A appeared to induce hypothermia in a cool environment (particularly in food-deprived animals), but hyperthermia in warm environments (165).

6. REGULATORY ALTERATIONS IN ENERGY BALANCE, THERMAL BALANCE – A ROLE FOR PEPTIDES

The most general abnormalities of overall energy balance are connected with regulation of body weight and adiposity. Based on the previous descriptions regarding the effects of the peripheral and central neuropeptides, it is obvious that either an overactivity of anabolic or – more often – a defective activity of catabolic peptides leads to obesity. Neuropeptide abnormalities may also result in or contribute to severe anorexia (*e.g. anx/anx* mice: 377; anorectic girls: 378, 379). The limits of this review do not allow a detailed analysis of such deviations of body weight.

However, the role of neuropeptides in connection to body weight changes adjoining thermal adaptation, chronic diseases, nutritional anomalies as well as in connection to fever and fever-related phenomena needs mentioning. Peripheral or central peptides may participate in adaptive changes or disorders of the regulation of body temperature.

During chronic cold exposure both thermoregulatory adaptation and enhancement of food intake are indispensable. The role of neuropeptides in this process has not been completely clarified. Anabolic substances might increase food intake, but they should be expected to cause concurrent hypometabolism and potentially life-threatening hypothermia in this environment. In the cold, hyperphagia develops within 24-48-hrs, this cannot be explained by activation of NPY or any other orexigenic peptide, neither by suppression of anorectic-catabolic peptides. However, when cold-adaptation is completed (in rats a period of *ca.* 3-weeks), the refeeding hyperphagia following a fasting period is greater in cold-adapted than in non-adapted animals, suggesting a higher tone for orexigenic peptides. ICV injection of NPY induces greater food intake in cold-adapted than in non-adapted rats. An increased sensitivity for orexigenic peptides could be supported by the finding that NPY antagonists caused greater reduction of hyperphagia induced by NPY-injection in cold-adapted than in non-adapted rats. However, this conclusion is not supported by the finding that the same antagonists influenced the refeeding hyperphagia only in non-adapted, but not in cold-adapted rats, despite that they reversed the fasting hypothermia in both groups (380). Apparently, an elevated orexigenic tone developing with cold adaptation cannot be explained simply by a higher NPY activity. In cold adaptation the role of NPY or other neuropeptides is still to be defined. A role for CART (295) and TRH (365) in cold adaptation is, however, possible.

Melanocortins, in particular MC3 rather than MC4 receptors, have been implicated in the development of cancer-related cachexia (213, 235).

The hypothermia accompanying starvation or food restriction involves the enhanced activity of several central neuropeptides (NPY, AgRP and other orexigenic peptides) or decreased activity of leptin and anorexigenic neuropeptides (*e.g.* melanocortins) (381): these effects suppress the sympathetic activity and brown fat function. Primary defect of brown fat UCP activity causes cold-sensitivity, but does not necessarily lead to obesity, except in cases when excess ingested calories should be transformed to heat (382). Neuropeptides participate in the diet-induced thermogenesis, as well. MC4R null obese mice have low basal metabolic rate and cannot adapt with hypermetabolism to high-fat diet (172, 383), the brown fat does not adapt to acute cold exposure, either, in contrast to diet-resistant animals in which high-fat diet reduces the hypothalamic NPY mRNA expression and enhances UCP1 expression in the brown fat (146).

In genetically obese rats the interleukin-induced fever was found attenuated (59). Zucker fatty rats deficient of normal leptin were able to mount a fever response to endotoxin at a thermoneutral temperature, but they developed exaggerated hypothermia in a cool environment (56). Leptin also participates in the recovery of body temperature after a LPS-induced hypothermia (29).

Over two decades ago the central MSH and/or CRF were suggested to behave as endogenous antipyretic agents (216, 221, 268, 326). More recently, central administration of a MC4R receptor agonist was shown to be antipyretic (259, 263) and melanocortin agonist attenuated fever and the fever-related anorexia (259, 263, 384), while the attenuation was prevented by exogenous melanocortin antagonists or fasting/AgRP (266). Further, centrally applied HS024, a melanocortin antagonist, attenuated the metabolic and locomotor responses adjoining the cytokine-induced fever (385). Interleukins have been reported to increase the central melanocortin signaling (264). Another cytokine, TNF-alpha – itself causing anorexia and rise in core temperature (at least in high dose) – activates some but not all signaling pathways of leptin and insulin, thereby partially attenuates the effects of insulin and leptin (386). However, while the early data pointed to a possible endogenous antipyretic role of CRF (268), other data suggested a pro-pyretic role for this peptide (269, 387). The possible antipyretic roles of melanocortins and CRF have been dealt with in earlier chapters (Ch. 4.2.1.; 4.2.2.).

Similarly, intraseptally applied vasopressin was shown to inhibit fever, via V1 receptors (326, 328), although the functions of AVP have not yet been completely clarified (see Ch. 4.3.1.). Electrical stimulation of ventral septal area has recently been shown to influence firing rates of pyrogen-treated thermosensitive neurons in the preoptic anterior hypothalamus of rabbits and to influence fever responses (327).

Other peptides may also contribute to the development of fever. Endotoxins enhance the production of leptin, and leptin probably contributes to the anorexia of infection (60). Both CCK (303) and substance P (314, 315) have been demonstrated to participate in the mediation of endotoxin-induced fever. In other studies, somatostatin was suggested to participate in the pathogenesis of endotoxin-induced fever (353, 359). The anorexic and febrigenic actions of GALP seem to be mediated by IL-1 (388).

Lipopolysaccharides have been shown to bring high fasting plasma ghrelin back to postprandial levels (389). In rats a single LPS injection activated the HPA-axis (CRF, ACTH, cortisol), TNF-alpha, expression of CRF in PVN, expression of CART in the arcuate nucleus and it decreased the appetite. In the case of repeated LPS injections (*i.e.* causing desensitization) neither these activations nor anorexia was found, but there was a decline in plasma leptin level (390).

7. AGING: CHANGES IN THE FUNCTION OF PEPTIDES INVOLVED IN ENERGY BALANCE

Aging is accompanied by characteristic changes in energy balance (391). Various peripheral or central peptides (leptin, NPY, melanocortins, CRF, CCK, PYY, *etc.*) may be involved, which influence appetite, gastric motility (392) and/or thermoregulation. As regards the energy stores of the body in animals, the changes resemble those seen in humans: most investigators confirm that experimental rodents follow the common human observation according to which body weight (particularly the fat content of the body) increases in the middle-aged

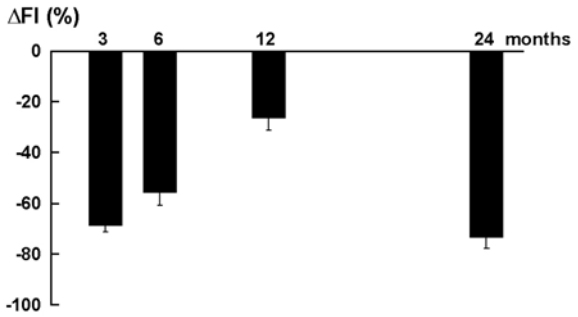

Figure 3. Differences of food intake (DFI) following ICV injection of 5 microgram alpha-MSH or ICV 0.9% saline in the first hour of refeeding after 24-h food deprivation in rats aged 3, 6, 12 or 24 months (1 young adult, 2 middle-aged or 1 old groups, respectively). The gradually decreasing inhibitory effect of alpha-MSH became excessive in the old group (Balasko *et al.*, unpublished).

persons (age-related obesity; 393), but beyond the age of 65-75 years the body weight starts decreasing and the sarcopenia (loss of muscle mass) becomes pronounced (anorexia of aging or senile cachexia; 394, 395, 396), occasionally in the presence of large fat stores (fat may also be deposited in various organs, causing lipotoxicity). In the main changes, altered neuropeptide functions may have an important role. Similarly, the thermoregulatory reactions to cold, warm, pyrogens, *etc.* are modified in the course of aging – these may also involve neuropeptide alterations, but may as well be consequences of the changes in body weight and composition.

Leptin resistance develops with aging even in the absence of obesity (46, 397), although it is more pronounced in cases of concurrent obesity (45, 393). Glucocorticoids have been suggested to play a role in leptin resistance (398), but it is questionable, whether or not this role changes with age (46). It is more likely that the signal transducing pathways are altered with age (399), contributing to leptin (and insulin) resistance. Leptin resistance, in turn, enhances fat accumulation. However, resistance to leptin does not necessarily mean that LRb-presenting neurons and neuropeptides downstream of leptin action cannot act, *e.g.* strong responses to melanocortin agonists and antagonists have been demonstrated in aged-obese rats (33), which are resistant to the anorexigenic and thermogenic effects of leptin (400). Nevertheless, age-related changes possibly affect the production and/or activity of downstream peptides as well. In our experiments (401) the suppression of food intake by ICV alpha-MSH administration was smaller in middle-aged, but more pronounced in old rats than in young adults (Figure 3).

Very old male rats were unresponsive to the behavioral effects of ICV administered ACTH (402). Obese (quasi middle-aged) Zucker rats (*vs.* lean ones) were found to have reduced endogenous melanocortin tone (248). In the arcuate nucleus the POMC gene expression was shown to decrease with age (403). A 30-40% decline in the POMC mRNA producing cells was demonstrated in the periarcuate region of 12 months *vs.* 3 months-old rats and the total POMC mRNA also exhibited a significant fall by aging (404), although no continuation of the decline was detected with further aging. By POMC gene delivery to aged-obese rats (405) the aging obesity was attenuated, and the brown fat uncoupling protein-1 production enhanced, despite low MC3R and MC4R expression; the MTII sensitivity was also pronounced (406) in similar aged-obese rats.

It is known that food restriction increases longevity. AgRP-deficient mice have moderate changes in response to feeding challenges like fasting or melanocortins: they are lean, with increased metabolic rate, high locomotor activity and increased UCP expression in brown fat (407) – this phenotype predisposes for longer life-span.

Fasting resulted in a relatively smaller hypothalamic NPY gene expression in old rats as compared with young ones (408). Besides, the orexigenic responsiveness to NPY, orexin, and ghrelin exhibited a gradual decrease with age in rats (409). In other studies (410), the fasting-induced AgRP gene expression decreased with aging in the arcuate nucleus, the CART gene expression increased concurrently, while in these studies no changes in POMC expression were found – at the same time the feeding responses to exogenous AgRP were rather enhanced and those to NPY decreased in old rats.

The number of CRF-containing neurons in the human PVN was reported to increase with age (411), and the CRF level in the rat PVN of old rats was shown to give a disproportional rise upon stress (412). CRF was presumed to provide some protection against the pathogenesis of Alzheimer disease (413). On the other hand, fasting induced a greater fall in the PVN CRF levels in old than in young rats (414).

Jeon *et al.* (415) found that MCH knockout animals have beneficial metabolic alterations at older ages. During a 19-month period, the MCH knockout mice had a leaner body mass, lower body weight, better glucose tolerance, and greater insulin sensitivity than the wild-type animals. The aging-associated reduction in locomotor activity was also attenuated. This study indicated that lack of MCH could prolong life and improve the age-related decline in metabolic activity.

Apparently, it may be difficult to find any single mechanism, which could possibly explain both the age-related obesity and the anorexia of aging. The developing resistance to leptin (and insulin; 416) may act in the direction of weight gain and increased adiposity, but cannot explain the late-developing sarcopenia. Conversely, the gradual reduction in the activity of orexigenic peptides might explain anorexia and the late-appearing sarcopenia, but not the earlier age-related obesity. CCK synthesis and release was reported to decrease from brain synaptosomes and from peripheral tissues of old rats (417), but other reports (392, 396) suggest that overactivity of postprandial anorexigenic signals (like CCK, PYY) may contribute to the anorexia of aging. According to still other reports, the

age-related malnutrition rather than age itself may be responsible for high CCK levels (418). In humans advanced age and frailty were shown to be coupled with low fasting ghrelin levels and no changes of ghrelin upon feeding, while the postprandial insulin release was exaggerated (419). A decline in orexin neuronal activity (420) and receptor signaling during aging may contribute to the explanation of reduction in spontaneous locomotor activity and increased propensity for obesity observed during aging.

A more detailed analysis of the efficacy of centrally applied alpha-MSH has demonstrated bidirectional variations in the anorexic effect of the peptide, depending on age (401). As compared with young (3 months-old) adults, in middle-aged (6-12 months-old) rats the centrally applied alpha-MSH was much less anorexic, while in old (24 months) animals the efficacy of the peptide was outstanding (the suppression of re-feeding food intake after 24-h food withdrawal was *ca.* 68%, 46%, 22% and 78%, respectively; Fig.3). Such pattern of efficacy possibly offers some explanation to both the age-related obesity and the anorexia of aging.

In the late phase of aging the postprandial CCK release becomes enhanced, probably contributing to the aging anorexia (418). In human studies the plasma CCK concentration increased with age and its suppressive effect became more pronounced (92). Unfortunately, the thermoregulatory responses to CCK have not been investigated in the context of aging. In case of CCK overactivity, enhanced fevers could be expected in aging animals. This does not seem to be the case. Old and young rats were able to mount similar fevers in response to LPS or IL-1 at warm (31ºC) environmental temperature, but at a cool (21ºC) temperature only the young animals developed fever (421). This was explained by the low resting metabolic rate of old animals and by a limited capacity of further enhancement of their metabolic rate by pyrogens in addition to the cold-induced hypermetabolism. However, both the resting metabolic rate and the capacity to elevate it, depend to a great extent on neuropeptide activities. Cerebral glucose utilization was lower in old than in young rats, but TRH treatment promptly abolished the difference, suggesting that TRH activity is decreased in the old animals (422). Since THR was suggested to influence or coordinate the expression and activity of various anabolic and catabolic peptides (365), it may be justified to assume that these peptide functions also change with aging. Apparently, a more detailed analysis of the age-dependence of neuropeptide activities is becoming more and more indispensable.

As many other functions (*e.g.* HPA-axis; 412), the thermoregulatory reactions are also altered with age. This is partly due to defects in the effector mechanisms: both heat producing (metabolic rate) and heat loss pathways (*e.g.* skin vasomotor changes in cases of a compromised circulation) may be limited, but the central regulatory mechanisms may also be affected, including the neuropeptide effects. Alpha-MSH overactivity was suggested to contribute to the suppression of fever response to endotoxin in aged rabbits (423) – this is in line with the observation that in suppression of feeding the melanocortin sensitivity increases in aged rats (401). The leptin resistance, which develops with aging (45, 46, 393), may interfere with the febrile or fever-related reactions to various pyrogens. Leptin resistance is manifested by its failure to inhibit food intake, to deplete fat stores, to downregulate its own expression in adipose tissue, and to increase thermogenesis (400) – all pointing to reinforcement of obesity (397, 416), but some consequences of resistance may manifest even in the absence of obesity. Besides, both leptin and insulin signaling is decreased in the hypothalamus of aged rats. Furthermore, persistently high peripheral leptin levels result in production of pro-inflammatory cytokines, thereby lead to chronic, low-grade inflammatory process (66). With aging, particularly in age-related obesity, such chronic inflammatory processes possibly contribute to the manifestation of various diseases. Age-related leptin resistance does not necessarily mean simultaneous resistance to other peptides: for example the melanocortin sensitivity is maintained (33), or even enhanced (Figure 3).

8. CONCLUSIONS AND PERSPECTIVES

Thermoregulation is an inseparable component of the complex energy balance. This balance also involves the regulation of food intake and body weight. Peptides originating from the periphery and acting at the afferent vagus and hindbrain (and sending information to further brain structures) as well as hypothalamic neuropeptides acting at central nervous structures have diverse effects and important influence on the whole process. Orexigenic peptides increase food intake, simultaneously suppress metabolic rate and they tend to lead to hypothermia as a primary effect. In contrast, anorexigenic peptides suppress food intake, enhance metabolic rate and tend to cause elevation of body temperature. A number of peptides do not show clearly coordinated orexigenic or anorexigenic features, but they may still be involved in the overall energy balance and may influence body temperature in a seemingly coordinated way. In other cases there is an obvious absence of any coordination.

A better understanding of the complex actions of peripheral and central regulatory peptides influencing basic structures of hypothalamic components is of great importance as well as the understanding of the basic processes of energy balance. Apparently, some of these complex mechanisms may lay behind the increasingly common, population-wide abnormalities and present-day trends in body weight regulation. In particular these may lay behind the high prevalence of obesity, whether it is induced by diet or developed while aging. Moreover, since the regulatory peptides influence peripheral substrate utilization, they may contribute to the regulation of blood glucose and lipid levels or the sympathetic tone. Apart from this, chronically high leptin levels that are often found in leptin resistant states – with or without obesity – may lead to production of pro-inflammatory cytokines. These cytokines may participate in various chronic, low-grade inflammatory processes affecting several systems.

Altogether, the neuropeptides may be important not only in thermoregulation, but they may also be important in the overall energetic regulation and its abnormalities, *e.g.* in the metabolic syndrome (obesity, hyperlipidemia, diabetes, hypertension) and chronic inflammatory or degenerative diseases. It is crucial to gain more information about both the normal regulation and the complex abnormalities of energy balance. It is also of similar importance to analyze the effects of the regulatory peptides and the ways of their action. Information derived from these studies may enable researchers to clarify the ways in which abnormalities of energy equilibrium develop. Future application of this knowledge may lead to an improvement of intervention methods and even to the prevention of these disorders themselves.

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Abbreviations: ACTH (adrenocorticotropic hormone), AgRP (agouti-related peptide), AVP (arginine vasopressin), BDNF (brain-derived neurotrophic factor), CART (cocaine-amphetamine regulated transcript), CCK (cholecystokinin), CGRP (calcitonin gene-related peptide), CNS (central nervous system), CNTF (ciliary neurotrophic factor), CRF (corticotropin releasing factor), DIO (diet-induced obese), DR (diet-resistant), FI (food intake), GALP (galanin-like peptide), GLP-1 (glucagon-like peptide-1), GPR (G-protein-coupled receptor), HPA-axis (hypothalamo-pituitary-adrenal axis), ICV (intracerebroventricular), IL-1 (interleukin-1), IP (intraperitoneal), IRS (insulin-receptor substrate), JAK2 (Janus-kinase-2), LRb (leptin receptor, long form), LPS (lipopolysaccharide), LH (luteinizing hormone), MCH (melanin concentrating hormone), MC3R or MC4R (melanocortin 3 or 4 receptor), MR (metabolic rate), MSH (melanocyte-stimulating hormone), MTII (melanotan = MC3/4R agonist), NMU (neuromedin U), NPW (neuropeptide W), NPY (neuropeptide Y), NTS (nucleus of the solitary tract), PACAP (pituitary adenylate cyclase-activating polypeptide 38), PI3K (phosphatidylinositol-3-OH kinase), POMC (pro-opiomelanocortin), PVN

(paraventricular nucleus), PP (pancreatic polypeptide), PrRP (prolactin-releasing peptide), PVN (paraventricular nucleus), PYY (peptide YY), RQ (respiratory quotient), SP (substance P), STAT3 (signal transducer and activator of transcription 3), Tc (core temperature), TNF (tumor necrosis factor), TRH (thyrotropin releasing hormone), UCP (uncoupling protein), VIP (vasoactive intestinal peptide), VMN (ventromedial nucleus), Y1R or Y5R (NPY Y1 or NPY Y5 receptor)

Key Words: Neuropeptides, Peripheral Peptides, Body Temperature, Energy Expenditure, Fever, Hypothermia, Energy Balance, Vagus, Body Weight, Obesity, Food Intake, Anorexia, Aging, Review

Send correspondence to: Miklos Szekely, Department of Pathophysiology and Gerontology, Medical School, University of Pecs, 12 Szigeti str., Pecs, H-7624, P.O.B.: 99, Hungary, Tel: 36-72-536-246, Fax: 36-72-536-247, E-mail: miklos.szekely@aok.pte.hu

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