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OREXIGENIC VS. ANOREXIGENIC PEPTIDES AND FEEDING STATUS IN THE MODULATION OF FEVER AND HYPOTHERMIA

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1. ABSTRACT

Prevailing changes in the feeding status or the nutritional status, in general, can modify the expression of many orexigenic and anorexigenic peptides, which influence hypothalamic functions. These peptides usually adjust body temperature according to anabolic (increased appetite with suppressed metabolic rate and body temperature) or catabolic (anorexia with enhanced metabolism and temperature) patterns. It was plausible to presume that such peptides contribute to regulated changes of body temperature (either fever or hypothermia) in systemic inflammation, particularly since anorexia is a common feature in inflammatory processes. No consistent, common, or uniform way of action was, however, demonstrated, which could have described the effects of various peptides. With the exception of cholecystokinin (CCK), all investigated peptides were devoid of real thermoregulatory actions: they influenced the metabolic rate (and consequently body temperature), but not the mechanisms of heat loss. Central CCK is indeed catabolic and may participate in febrigenesis. Leptin may activate various cytokines, catabolic peptides and may inhibit anabolic peptides, but it probably has no direct febrigenic effect and it is not indispensable in fever. Melanocortins and corticotropin-releasing factor provide catabolic adaptive mechanisms to food intake (diet induced thermogenesis) and environmental stress, respectively, but they act rather as endogenous antipyretic substances during systemic inflammation, possibly contributing to the mechanisms of limitation of fever. Bacterial lipopolysaccharides enhance the expression of most of these catabolic peptides. In contrast, neuropeptide Y (NPY) expression may not be changed, only its release is decreased at specific nuclei – a defective NPY effect may also contribute to the febrile rise in body temperature. The data provide no clear-cut explanation for the mechanism of hypothermia seen in systemic inflammation. According to speculations, a presumed "overflow"-type release of NPY from the hypothalamic nuclei, as well as a suppression of the activity of catabolic peptides, could possibly cause hypothermia. There are no cues, however, referring to the identity of factors that could trigger such changes during systemic inflammation in order to induce hypothermia.

2. INTRODUCTION

In systemic inflammatory reactions – depending on species, environmental factors, or on the dose of infectious agents – either fever or hypothermia (1-5), or eventually bi-directional temperature excursions (with febrile and hypothermic phases) may develop. Both fever and hypothermia are centrally regulated phenomena and both can be viewed as adaptive mechanisms in the host defense against infection (2, 6, 7). Concurrently many other (centrally regulated) homeostatic mechanisms are affected, altogether forming the complex picture of sickness behavior (7-9), which includes suppression of feeding activity. This raises the possibility that body temperature and food intake regulations are at least partly interrelated or overlapping in the course of systemic inflammations: although infection-induced changes of neurotransmitters or modulators are not identical in the two regulations, they may participate in both of them, or may have an influence on both. Further support for this idea is provided by the finding that abnormal nutritional status (cachexia, obesity), which strongly alters various central neurotransmitter functions (10), can influence not only the metabolic/thermal status (11) but also the thermal response to pyrogens (12, 13). The prevailing feeding status (post-

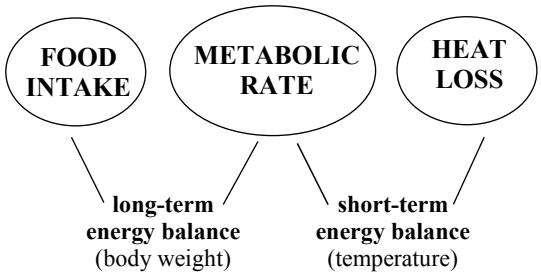

Figure 1. Schematic representation of basic components of long-term and short-term regulations of energy balance. Food intake, metabolic rate and heat loss may be influenced separately, or in combinations, according to certain anabolic or catabolic regulatory patterns.

meal, between-meals) may also influence central orexigenic and anorexigenic neuropeptides. Whereas these peptides are fundamental in the regulation of consummatory behavior and long-term energy balance (i.e. body weight regulation), they might also be assumed to play an additional short-term role in the thermoregulatory changes (whether fever or hypothermia) connected with systemic infections. This is in line with the idea that a dynamic balance of various opposing influences for and against elevating thermoregulatory set-point is responsible for the actual body temperature both in fever and under non-febrile conditions (14). Peripheral neural signals conveyed by the abdominal vagus have been suggested to participate in the regulation of consummatory behavior and at least in some parts of the febrile response to pyrogens (15-18), besides the humoral routes of signaling.

3. ENERGY BALANCE

Energy balance of the body consists of two intertwined homeostatic regulations. One of these regulations is aimed at maintaining long-term stability of energy reserves by regulating body weight, mainly through a balance between food intake and metabolic rate. (Food intake regulation itself has tonic components coming from the nutritional status vs. episodic components like hunger and postprandial satiety, the latter can be present independent of the actual body weight.) The other system is a short-term energy balance, which aims to defend caloric stability. This system relies on the balance between heat production and heat loss, the basic factors of thermoregulation. The two systems are interconnected in a complex way (Figure 1). Individual factors of the complex system might be influenced selectively, causing functional alteration in either system and invoking secondary alterations in the other one. The regulations of these systems often overlap and the central regulatory factors, neurotransmitter and modulator substances are many times identical or similar.

In systemic inflammation the whole complex system is affected. It seems plausible that common central regulatory mechanisms might (at least partly) explain the complex nature of energy balance changes. The most important orexigenic (mostly anabolic) and anorexigenic (mostly catabolic) neuropeptides possibly participate in such intricate energetic changes.

4. REGULATION OF BODY TEMPERATURE IN SYSTEMIC INFLAMMATION

In experimental analysis of host responses to infectious agents the most widely used inflammatory substance is the cell wall component of Gram-negative bacteria (endotoxin, lipopolysaccharide, LPS). Like many other pyrogenic substances (muramyl-dipeptide, various cytokines, etc.), LPS exerts characteristic effects on body temperature and food intake (9): body temperature is elevated to a febrile level, with a coincident suppression of appetite. In rats body temperature is influenced in a phasic manner, with sequential periods of rises and transient declines, finally resulting in biphasic or polyphasic fever (peaks ca one, two and often five hours after intravenous injection of moderate LPS doses), or in hypothermia if the declines prevail (1, 3, 4, 7). The suppression of food intake is usually sustained, without special phases.

Fever, as a basically thermoregulatory phenomenon, develops due to a regulated change in short-term energy balance: metabolic rate (heat production) increases and heat loss decreases (heat conservation increases) in a coordinated fashion, the complex effect causing a regulated elevation of body temperature, i.e. fever, as it is defined (19). Simultaneously, however, the long-term energy balance is also affected. When initiating fever, LPS appears to exert a coordinated catabolic effect on factors of long-term energy balance: it induces a negative energy balance by suppressing calorie intake (anorexia) and enhancing metabolic rate (8, 9). The factors responsible for the catabolic state and hypermetabolism might also contribute to the elevation of body temperature and the thermoregulatory changes. Thus, during fever changes in catabolic-anorexigenic and anabolic-orexigenic mechanisms and peptide actions (rise and fall, respectively) might have some, as yet unidentified role, either as endogenous pyretic or endogenous antipyretic factors. It is also possible, however, that in fever these peptides influence body temperature independent of their catabolic or anabolic properties.

Hypothermia following LPS administration may also involve regulatory components that affect body temperature as well as food intake and energy metabolism, but it is not inevitable that these regulatory changes form a pattern that is exactly opposite of what is observed in fever. Although LPS-hypothermia is often called anapyrexia, the term “anapyrexia” should be reserved for cases when the suppressed metabolic rate is coupled with enhanced heat loss, strengthening the tendency to establish a low body temperature (19). In contrast to fever (when heat loss is altered), in LPS-induced hypothermic responses this may not be the case and the hypometabolism may not be coupled with increased heat loss. Although animals have been reported to exhibit cold-seeking behavior in cases of regulated hypothermia (20), the autonomic mechanisms of heat loss (skin vasodilatation, panting, etc.) are usually not activated, particularly not in the regulated LPS-hypothermia. Accordingly, instead of a regulatory pattern just opposite of that seen in LPS-fever, so far poorly defined combinations of changes in the regulations of food

Table 1. Coordinated vs. uncoordinated peptide actions on energy balance

STATES	FI	MR/Tc	EXAMPLES
"Anabolic"	↑	↓	NPY, orexin-A, AGRP
"Catabolic"	↓	↑	CCK, POMC, CRF, leptin, CGRP, SP
"Hyperthyroid" "Cold-adapted"	↑	↑	?
"Hibernation"	↓	↓	neurotensin, bombesin

[FI = food intake, MR = metabolic rate, Tc = core temperature]. – Peptides of anabolic or catabolic character in table 1 might be considered fundamental in the pathogenesis of fever or hypothermia only in case they can also act on thermoregulation according to a coordinated pattern (e.g. increasing both heat production and heat conservation, or the other way round, decreasing both of them). Other anabolic or catabolic peptides, as well as those classified as non-anabolic/non-catabolic ones, may have some role at most as modulators.

intake, metabolic rate and heat loss may characterize the development of LPS-hypothermia, suggesting a special regulatory pattern. Presence or absence of some orexigenic or anorexigenic peptide actions (whether or not forming a catabolic or anabolic regulatory pattern) might still be assumed to contribute to the development of such hypothermia.

The question whether and how orexigenic and anorexigenic peptides participate in the coordinated regulatory changes of body temperature characteristic for fever or hypothermia in systemic infections cannot be readily answered. An integral role for any one of these peptides in infectious fever or hypothermia can be ascribed only if the given peptide can induce coordinated changes in thermoregulatory effector functions, i.e. if it causes a rise or fall in metabolic rate with a concurrent fall or rise in heat loss, respectively. Notwithstanding a possible lack of such coordinated thermoregulatory effect of a given orexigenic or anorexigenic neuropeptide, it remains a distinct possibility that this particular peptide still plays a modifying (although not fundamentally determinant) role in the development of fever or hypothermia during infections.

This review is an effort to analyze and summarize possible ways how some of the most important anabolic or catabolic neuropeptides that modulate consumption behavior may participate in or interfere with the thermoregulatory changes observed in the course of systemic inflammatory processes.

5. OREXIGENIC AND ANOREXIGENIC, ANABOLIC AND CATABOLIC NEUROPEPTIDES

Out of the multitude of neuropeptides influencing consummatory behavior either as orexigenic or as anorexigenic substances mainly those will be selected for thorough analysis, which are involved in coordinated anabolic or catabolic regulation of energy balance. It should be noted that some neuropeptides do not induce integrated anabolic (enhancement of energy intake with decrease in metabolic rate and energy expenditure) or catabolic (anorexia with high energy dissipation) actions, i.e. they do not exert such coordinated effects on consummatory behavior and metabolic rate. For example, bombesin (21) or neurotensin (22) suppresses both food intake and metabolic rate (i.e. they are anorectic, but not catabolic), unlike the catabolic melanocortin or leptin, both of which cause hypermetabolism simultaneously suppressing food intake (23, 24), or the anabolic neuropeptide Y, which suppresses metabolic rate concurrently enhancing food intake (24). Peptides not belonging clearly to the catabolic vs. anabolic groups may still modulate or separately influence some components (either food intake, or metabolic rate, or heat loss mechanisms) of certain integrative pathophysiological processes like the process of fever pathogenesis, but they are unlikely candidates for basic determination of such integrative phenomena.

6. OREXIGENIC AND ANOREXIGENIC PEPTIDES IN SYSTEMIC INFLAMMATION

On basis of their actions on metabolic rate and body temperature, the central melanocortin system [pro-opiomelanocortin (POMC) – adrenocorticotropin (ACTH) – melanotropins (alpha-, beta-, gamma-MSH) – melanocortin receptor group], corticotropin-releasing factor (CRF), leptin and cholecystokinin (CCK) are the main anorexigenic/catabolic peptides, which might be considered to participate in the pathogenesis of thermoregulatory changes in systemic inflammatory processes. Out of the orexigenic/anabolic group neuropeptide Y (NPY) is a possible candidate for participation. Apart from these, many other peptides (cocaine-amphetamine regulated transcript CART, arginine-vasopressin AVP, neurotensin NT, orexin-A, melanin concentrating hormone MCH, ghrelin, agouti-related peptide AGRP, glucagon-like peptide-1 GLP-1, galanin, thyrotropin-releasing hormone TRH, etc.) might play some, although probably less important role in interaction with the main catabolic and anabolic peptides (Table 1).

6.1. Melanocortin system

Pro-opiomelanocortin (POMC) is a common precursor molecule of ACTH, various MSH-s (melanocortin products) and of endorphins. POMC neurons are located in the arcuate nucleus and the melanocortins originating from this precursor molecule by post-translational cleavage can bind to specific melanocortin receptors at POMC projections in various areas of the hypothalamus like the paraventricular nucleus or the dorsolateral hypothalamic area (reviewed in 26). The central melanocortin system depends mainly on alpha-MSH (to a smaller extent possibly on gamma-MSH), on AGRP and on melanocortin type-3 and type-4 receptors (MC3R and MC4R) (27). Alpha-MSH and AGRP act as non-selective endogenous agonist and endogenous antagonist molecules, respectively, for the MC3/MC4 receptors. Gamma-MSH appears to be more selective for the MC3R

(28), but the MC4R may be more fundamental in the regulation of energy balance.

Centrally applied melanotan-II (MT-II), a non-selective agonist of MC3R and MC4R (29) suppressed spontaneous food intake in lean and obese rats (23, 30). Alpha-MSH (but not gamma-MSH) had similar effect (28). MT-II also enhanced metabolic rate (23) and elevated body temperature in nanogram doses (30), apparently eliciting a kind of coordinated catabolic response. In rats alpha-MSH, its analog [Nle4,D-Phe7]-alpha-MSH, or fragments of the analog induced dose-dependent rises in body temperature (31). No data is available, however, on the effects of any of these substances on heat loss effector systems, except for one report on alpha-MSH-induced slight hyperthermia without concurrent changes (fall) in skin temperature (32) (albeit, in the same report MSH was shown to influence skin vasomotor reaction to LPS). In rats a central infusion of MT-II for several days induced a rise in oxygen consumption and a fall in food intake at least during the first days of the infusion (33), while the MC4R antagonist HS024 caused hyperphagia with no change in oxygen uptake (it should be added that an expected decrease in metabolic rate might not be marked at near-thermoneutral environments). Chronic central infusion of SHU9119, a non-selective melanocortin receptor antagonist induced hyperphagia and a slight reduction in body temperature in rats, during their night-time active period (34). Forbes et al. (35) have demonstrated that in leptin-deficient ob/ob mice the low metabolic rate and deficient capacity to withstand a challenge of cold exposure were at least partly due to decreased MSH secretion in the hypothalamus: MSH administration to these mice was followed by reversal of both the low metabolic rate and the hyperphagia, together with an improved capacity to prevent hypothermia during cold exposure.

According to the above data a melanocortin-mediated coordinated catabolic mechanism could be visualized possibly contributing to a febrile rise in body temperature. Lack of coordination for thermoregulatory effector functions of MSH in control animals would not fully support the idea, but in fever (unlike in non-febrile conditions) the thermoregulatory effects of MSH appeared to be coordinated (32, 44). With or without such coordination, a tendency for rise in body temperature might be regarded a fever-promoting factor. Contrary to this, however, early data already suggested an opposite action during fever and indicated that MSH might be antipyretic (36) rather than febrigenic. An antipyretic role for the endogenous peptide was supported by the augmentation of LPS-fever by antiserum to alpha-MSH (37). Villar et al. (38) have found that centrally applied alpha-MSH was antipyretic already in doses that did not affect normal body temperature, showing a blockade of a febrigenic process rather than a fever antagonism by some hypothermia-inducing agent. Recent studies reinforced that MSH and melanocortin-receptor activation might inhibit (and not enhance) fever. Alpha-MSH inhibited the development of LPS-fever (39, 40), whereas a centrally applied non-selective melanocortin-receptor antagonist SHU9119 enhanced it, or prevented the antipyretic effect of MSH. The point of action seems to be central (40, 41), since central SHU9119 prevented the MSH antipyresis, irrespective of the route of MSH administration. Gamma-MSH injected into the septal region was also antipyretic (42). Nonspecific peripheral inflammations were also attenuated by central administration of alpha-MSH (43). Centrally (but not peripherally) injected MRLOB-0001, which is a specific agonist of MC4R, suppressed LPS-fever and also the simultaneous skin vasoconstriction in rats (i.e. during fever MC4R-activity induced an apparently coordinated thermoregulatory effect) (44). Inconsistent with these data was the finding that in MC4R-deficient mice the LPS-induced hypermetabolism was not greater (rather smaller) than in wild-type controls and the fever-height after LPS also remained unchanged (45, 46). Nevertheless, it can be safely stated that melanocortin receptors convey some antipyretic information. Since in non-febrile animals the activation of these receptors *per se* results primarily in elevation of metabolic rate and body temperature (see above) with hyperthermia and not hypothermia (32), the modification of fever can be regarded as a truly antipyretic and not simply a cryogenic action. Although in murine microglia alpha-MSH blocked the production of TNF-alpha, IL-6 and NO, the antipyretic action of melanocortins does not seem to involve cyclooxygenase (COX) inhibition, suppression of IL-6 production, or secretion of antipyretic corticosterone (47). No interaction was found between melanocortins and COX inhibitors. SHU9119 prevented the antipyretic but not the IL-6 suppressing effect of alpha-MSH. The ACTH-induced antipyresis was maintained after adrenalectomy, when a rise in cortisol level could not help the antipyresis. The LPS-induced rise in plasma cortisol was attenuated (not enhanced) during alpha-MSH-induced antipyresis (47).

Except for one report (48) describing an attenuation of IL-1-induced anorexia by alpha-MSH in fasting rats, other studies did not find such effect of the peptide. In contrast, alpha-MSH attenuated the fever induced by LPS, whereas it rather potentiated the concurrent anorexia (49). The melanocortin antagonist SHU9119 in turn alleviated the anorexia induced by LPS or IL-1-beta and either enhanced or did not affect fever (49, 50). In MC4R (but not MC3R) knockout mice the LPS-induced anorexia, but not the fever, was attenuated (32, 44). Accordingly, in contrast to the normal conditions, in systemic inflammatory processes the effects of melanocortins on regulations of food intake and body temperature do not appear to be parallel and do not form a consistent catabolic (or anabolic) regulatory pattern.

Whereas coordinated catabolic or anabolic patterns could not be demonstrated for melanocortins in the course of antipyresis, the thermoregulatory part of the actions of these peptides might have been still coordinated: a suppression of fever (and probably the LPS-induced hypermetabolism) by the selective MC4R agonist MRLOB-0001 was accompanied by a suppression of skin vasoconstriction that normally would have subserved a febrile rise in body temperature (32 ,44). This is particularly interesting, since in non-febrile animals the

alpha-MSH-induced hyperthermia did not involve skin vasomotor changes (32).

Out of the two main types of melanocortin receptors (MC3R or MC4R) supposedly involved in the regulation of energy balance MC4R appears to be more intimately connected with LPS actions and metabolic changes (51). The MC4R antagonist HS014, *per se*, had no effect on body temperature, but blocked the hyperthermia to alpha-MSH (32). The similar antagonist HS024 prevented the hypermetabolism to the treatment by non-selective agonist MT-II (33). Wild-type and MC3R-deficient mice increased their metabolic rate to a high-fat diet, in MC4R-deficient animals this response was missing (52).

In MC4R deficient obese mice MT-II did not cause anorexia (i.e. excitation of the persisting MC3R was either not sufficient for the development of anorexia or MC3R had some other effects), neither did leptin (which may rely on melanocortins for its anorectic effects), but CRF (which acts more independently of melanocortins) remained anorectic (28). The anorexia induced by LPS or tumor was absent in MC4R knockout mice but it was even enhanced in their MC3R knockout counterparts (45, 52), suggesting an autoinhibitory role for MC3R on POMC neurons. The MC4R agonist MRLOB-0001 suppressed LPS-induced fever in rats (44), which suppression was antagonized by the MC4R antagonist HS014. Although MSH had earlier been demonstrated to act as an antipyretic substance (36-38), the antagonist HS014 combined with alpha-MSH resulted in enhancement of fever, emphasizing a multiple character for melanocortin receptors participating in the MSH-action: only a part (the antipyretic part) of the MSH-action can be antagonized by the selective MC4R antagonist, other (hyperthermic) actions may remain unaffected and may enhance a rise in body temperature during fever. The non-selective antagonist SHU9119 prevented the MSH-antipyresis, but did not enhance fever (39) (it probably antagonized multiple melanocortin receptors and actions), in contrast to the effect of selective MC4R antagonist HS014, which caused enhancement by its virtue of blocking endogenous melanocortin effects (44). Since both the fever and the anorexia induced by LPS are reportedly unaltered in MC3R-deficient mice (45, 46), MC4R rather than MC3R activation may have a fundamental role as an endogenous antipyretic mechanism.

It is not clear whether or not melanocortins can contribute to a fall in body temperature. Selective MC4R antagonists did not cause hypothermia (44, 45, 47) and neither MC3R nor MC4R defective mice were hypothermic (45). The very mild reduction of body temperature upon chronic central infusion of SHU9119 (34) suggests that, if in the course of systemic inflammation the melanocortin actions were antagonized somehow, this could contribute to the development of temperature decline. It is rather unlikely, however, that a real hypothermia can be explained by melanocortin deficiency. Besides, the persisting anorexia would still need another explanation. The antipyretic effect cannot, either, explain a hypothermia. Further data might clarify a possible role of melanocortins in infection-induced hypothermia.

In summary, although on its own right – probably by activating MC4R (and perhaps MC3R) – MSH causes elevation in body temperature when injected into the central nervous system, during fever the melanocortin action may be different. The same MSH appears to be antipyretic when it is applied during LPS-fever and for this action particularly the MC4R of hypothalamic structures may be responsible. Experiments using selective MC4R antagonists suggest that endogenous melanocortins participate in the antipyretic effect. Since activation of these receptors, *per se*, does not cause hypothermia, the antipyretic effect cannot be explained as an assumed cryogenic action. The anorexigenic and hyperthermia-inducing actions of MSH point to a coordinated catabolic pattern of energy balance, but during LPS-action the anorexia is coupled with suppression of febrile body temperature, what does not fit a catabolic regulatory pattern. Thus, fever cannot be regarded simply as a consequence of a catabolic state due to activation of melanocortins. It is most likely that the multiplicity of melanocortin receptors (e.g. MC4R vs. MC3R) may explain the diversity of physiological actions. The hypothermia in systemic inflammation probably cannot be explained by melanocortins, at most their suppression could be assumed to have such role.

6.2. Corticotropin-releasing factor (CRF)-urocortin system

In endocrine systems corticotropin-releasing factor (CRF) functions as a regulator of the hypothalamo-pituitary-adrenal axis including central POMC derivatives ACTH, MSH and the peripheral cortisol. However, the distribution of CRF within the central nervous system (53) is suggestive of a neurotransmitter or neuromodulator role, which is independent of the peptide's participation in endocrine functions (54). In central actions of the peptide CRF1 and CRF2 receptors are involved, together with a CRF-binding protein and some endogenous receptor ligands such as various urocortins (55). Within the hypothalamus mainly the paraventricular nucleus contains CRF-producing cells and a part of the receptors is also located here, while further receptors are in the ventromedial nucleus (26). Neurons of the ventromedial nucleus function as a receptive field and – besides CRF, they may be sensitive to glucose and may have leptin receptors.

In rats a CRF injection into the third cerebral ventricle or the preoptic region was followed by suppression of food intake and enhancement of metabolic rate (increase in sympathetic activity), while during 7-day-long infusions the high sympathetic (and brown fat) activity and high metabolic rate prevailed and caused a fall in body weight without continued suppression of consumptive behavior (56, 57). In lean or obese Zucker rats intracerebroventricular CRF administrations had similarly catabolic effects: acute injections enhanced non-shivering thermogenesis by about 25-30%, chronic infusions elicited hyperthermia and fall in body weight (58, 59). No data are available on the effects of CRF on heat loss mechanisms.

Hypophagia was also observed in ob/ob mice following central injection of CRF or its fragments (60). Both CRF1 and CRF2 receptors may be involved in these actions (55), but the anorexigenic and metabolic actions are possibly connected to different receptors. Urocortin, which acts mainly on central CRF2 receptors, caused anorexia without actually enhancing metabolic rate in rats (61) or even with a concurrent fall of oxygen consumption in mice (62), although a urocortin-induced rise in metabolism and temperature has also been reported for Wistar rats (63). The CRF-induced hypermetabolism was not influenced by cyclooxygenase (COX) antagonist treatment (64), suggesting either that prostaglandin (PG) activity is not indispensable for the CRF effects or that CRF acts at a step beyond PG synthesis.

Rothwell et al. (65) have originally suggested that products of the POMC-MSH-melanocortin group may mediate the CRF-induced thermogenesis and fever, since anti-gamma-MSH prevented the CRF-induced hypermetabolism. According to what was described in the chapter on melanocortins, mainly the MC4-receptors could be assumed to contribute to these effects. However, the finding that HS014, a specific antagonist of MC4R was able to antagonize only the alpha-MSH-induced anorexia but not that induced by CRF (66) did not support a role for MC4R activation in mediation of CRF action. An earlier report (67) showing that alpha-MSH may participate in the CRF-induced anorexia in food-deprived rats has not been confirmed. Since gamma-MSH acts mainly at MC3R (28), it is possible that these receptors are necessary for the CRF actions. However, as shown in the previous chapter, out of the melanocortin receptor varieties MC4R rather than MC3R appears to be really important in the regulation of energy balance. CRF probably does not activate the PG system, either. On the contrary, PG-s were shown to activate the sympathetic nervous system normally through CRF: a COX-antagonist did not influence sympathetic activation by CRF, while alpha-helical-CRF suppressed sympathetic activation induced by PGE (68). The exact way of action CRF has on sympathetic activation, metabolic rate and body temperature has not been clarified.

Data on the role of CRF in febrigenesis are rather equivocal. Various reports demonstrated either enhancement or attenuation of febrile responses by CRF. On basis of its hyperthermic effect – independent of melanocortins – CRF could be expected to contribute somehow to the febrile elevation of body temperature. Such contribution would support the observation that both hyperthermia and hypophagia induced by stress were prevented by the CRF-receptor antagonist alpha-helical-CRF (69, 70). Indeed, fever induced by central IL-1-beta (but not peripheral IL-1 or central PGE) was attenuated by central injection of either alpha-helical-CRF (64, 71) or an antibody against CRF (72). Rothwell came to the conclusion that the cytokines IL-1 and IL-6 act as endogenous pyrogens in the brain and stimulate thermogenesis via synthesis of CRF in a step which follows local PG-synthesis (73). However, the febrigenic actions of intraperitoneal endotoxin are not dependent on CRF, neither are the actions of centrally applied TNF-alpha or exogenous PGE (64). The cited data of Katafuchi (68) confirm that CRF may have a role in conveying at least some effects of PGs. Data of Milton et al. (74) have provided further support for CRF contribution to fever: in rabbits poly(I):poly(C)-induced fever was shown to involve a propyretic role for peripheral CRF. Alpha-helical-CRF inhibited fevers induced by CRF, IL-8, or a preformed pyrogenic factor (PFPF), although not those fevers induced by TNF-alpha (75). In sharp contrast to these data, other experiments suggested no pyretic, rather an antipyretic role for CRF. Fevers induced by peripheral LPS, IL-1-alpha, TNF-alpha, or central PGE were not reduced by CRF-antagonist treatment (64, 76), demonstrating a lack of fever-enhancing CRF action. Furthermore, other investigators found that centrally applied CRF – instead of enhancing fever – caused antipyresis in LPS-treated rabbits (77) in doses, which did not cause any change in normal body temperature. Opp et al. (78) have reported on similar results in interleukin-treated rabbits. In rats with central CRF infusion a transient hyperthermia was followed by blunted febrile response to consecutive LPS administration (79).

Accordingly, some, but not all pyrogens may utilize central CRF mechanisms in febrigenesis (64), while CRF often functions as an endogenous antipyretic substance. However, both types of CRF effects seem to be coupled with anorexia, i.e. the catabolic pattern seen under non-febrile conditions is not observed during CRF-antipyresis, the anorectic and fever-modulating effects are not always parallel. In rats a CRF antagonist prevented the effects of chronic LPS treatment to suppress growth-hormone production and to slow down weight gain (80), the latter action being exerted through modifying appetite rather than through altering metabolic rate or fever.

An antipyretic role may also be conjectured from data showing enhanced CRF production upon fever development and suggesting a negative feedback role in the course of pyrogen action. LPS-administration caused an upregulation of the CRF gene-transcription in the paraventricular nucleus within 3-4 hours, prior to an upregulation for ACTH (81). Either IL-1-beta or PFPF stimulated the release of CRF in the hypothalamus (75), possibly contributing to the concurrent anorexia, since immuno-neutralization of CRF prevented the anorexia to IL-1 (82). In rabbits LPS-fever induced a rise in serum ACTH, which rise resisted indomethacin treatment, but was suppressed by alpha-helical-CRF (83). In rats the ACTH response to LPS-stress was associated to CRF1 receptor function (84).

The main target of urocortins is the CRF2 receptor and they induce anorexia only (without large increase in metabolic rate or sympathetic activity) and the selective CRF2 receptor antagonist antisauvagine-30 inhibits only the anorexia from the effects of CRF (61), while the non-selective antagonist alpha-helical-CRF abolishes all actions of the peptide (69-71). Therefore, it is likely that the metabolic effects are connected mostly with the CRF1 receptors. Interestingly, the CRF1 receptors are distributed mainly in the cerebral cortex and the pituitary gland

(both deeply involved in stress reactions), while CRF2 receptors are concentrated in the hypothalamus, principally in the paraventricular and ventromedial nuclei (85).

Whether fever is to be enhanced or attenuated by CRF appears to depend on the evoking factors. Fevers following stress (69), or exercise (72) (both elevating central interleukin levels) were enhanced, whereas the common fevers of systemic inflammatory processes (LPS, TNF-alpha, PGE) were inhibited by CRF (64, 73). CRF is usually viewed as a link between energy homeostasis and environmental factors (86). On basis of the distribution of the two types of receptors it might be speculated that in the "nonspecific" fevers CRF1 receptors are used in the adaptation to stressful, anxiogenic environmental factors (87), they induce a complex catabolic state with hypermetabolism and anorexia and contribute to fever development, simultaneously activating the hypothalamo-pituitary axis. In the more common fevers of systemic inflammation, however, the hypothalamic nuclei and CRF2 receptors function as targets of the pyrogenic mechanisms, their activation also evokes anorexia but it does not enhance fever, rather an antipyretic effect can be observed. In the latter forms, the hypothalamo-pituitary axis may or may not be activated. Further data might clarify the validity of such assumption.

In sum, CRF – like the melanocortins, but independent of them – often antagonizes the development of fever, although it enhances some fevers. Also, similar to melanocortins, the demonstrated primary catabolic CRF action on energy balance cannot be utilized in the antipyresis, although this action may participate in fever enhancement. Since the final catabolic effect of CRF *per se* is hyperthermia, any antipyretic effect of the peptide can be explained by a real antagonism of fever development and not simply by some cryogenic effect counteracting a febrile rise in body temperature. In those "nonspecific" fevers enhanced by CRF the high metabolic rate probably contributes to the febrile rise in body temperature.

A possible role for CRF in LPS-induced hypothermia has not been analyzed, but neither the direct CRF effects, nor the antipyretic action could explain a regulated hypothermia.

6.3. Leptin

Leptin was first described as a hormone from white adipose tissue cells, which provides tonic information about the nutritional state (i.e. energy reserves) for long-term regulation of energy balance. Leptin is a peptide, which – similarly to insulin – is accepted as an adiposity signal. The peptide has also been demonstrated in the stomach, its amount depending on the actual feeding state: together with CCK it integrates meal-related signals of gastrointestinal origin for short-term satiety (88). Between meals or during food deprivation the circulating leptin levels are low, while postprandially they increase (89). The peptide can bind to vagal receptors (88, 90) or can act directly in the brain at the nucleus of the solitary tract or at hypothalamic receptors (in the arcuate nucleus) (26, 91-93). Leptin-induced neural signals of the afferent vagus are mostly forwarded to the hypothalamus and act together with the locally bound leptin.

The most important target for leptin action is the arcuate nucleus. Leptin injections into this hypothalamic nucleus induced anorexia with a rise in metabolic rate, while in case of bilateral leptin transgene expression in the medial preoptic area (by recombinant adeno-associated virus vector-encoding leptin injections) only metabolic rate was increased (94). Mainly the anorectic effects were pronounced during times of plenty, mainly the metabolic ones (disinhibition of non-shivering thermogenesis, 95) during starvation or acute cold exposure (96-98). In leptin-deficient ob/ob mice leptin elevated (to normal) the abnormally low metabolic rate (99), caused larger loss of body weight than in pair-fed controls (i.e. apart form anorexia, it also enhanced energy expenditure), or reversed the fasting-induced torpor and hypothermia (100). In Wistar rats the leptin-induced hypermetabolism developed slowly and was coupled with tail skin vasoconstriction, i.e. the rise in body temperature was a coordinated thermoregulatory response (E. Pétervári, A. Garami & M. Székely, unpublished data).

Leptin exerts many of its effects via interactions with central neuropeptides. In ob/ob mice MSH normalized the low metabolic rate, the high food intake and restored cold responsiveness (35). Through distinct signaling pathways, leptin has been demonstrated to increase hypothalamic production of melanocortins and to suppress the production of NPY (101). Conversely, low leptin levels (or receptor deficiency) have been shown to enhance NPY mRNA and attenuate POMC mRNA expression in the hypothalamus (89). After intraperitoneal leptin infusions the suppression in NPY and AGRP were more pronounced than the elevation in POMC products (102, 103). The peptide interactions are not confined to the substances so far mentioned. In rats central leptin injections for 3 days induced not only a fall in body weight but also a decrease in hypothalamic gene expression of galanin, MCH and NPY, while in the pair-fed (practically semi-starving) controls the NPY gene expression increased (104). Both CART and POMC expressions were enhanced upon the influence of leptin (89, 102, 103). The excitatory (consummatory) orexins and AGRP were also downregulated (103), whereas the inhibitory neurotensin levels were rather enhanced (104).

The connection between leptin and CRF is not clear. Regarding the leptin-induced anorexia, Gardner et al. (105) suggested that CRF mediation might be important, since a CRF antagonist attenuated the anorectic effect of leptin. However, such mediation might not be valid for the thermoregulatory effects. Repeated stress – obviously involving CRF action – induced a fall in body weight and a rise in body temperature. These effects were not prevented by central leptin infusion, although the concomitant rise in corticosterone production was (106), suggesting that leptin did inhibit the CRF-hypothalamo-pituitary-adrenal axis. It is possible that leptin antagonized the CRF actions and at the same time it influenced food intake and body temperature similarly as CRF did, but independently of

CRF. Indeed, leptin administration was shown to prevent CRF synthesis in the paraventricular nucleus, particularly in food-deprived animals with low initial leptin levels (107), making it unlikely that all leptin effects on thermoregulation could be mediated by CRF. Whereas leptin decreased the synthesis of CRF, the transport of the CFR2 receptor agonist urocortin into the brain was enhanced by leptin (108). While some leptin actions were independent of CRF, some CRF actions in turn were independent of the actual leptin level: in Koletsky rats (complete absence of leptin receptors) CRF induced similar anorexia as in controls (109). In the experiments of Busbridge et al. (110) on obese Zucker (fa/fa) rats the fever induced by IL-1-beta was smaller than in controls, but the fever became more pronounced after adrenalectomy, possibly because the adrenal corticoids no longer suppressed CRF production and the rise in CRF contributed to the fever. If this was the case, it could be interpreted as a synergism between leptin and CRF (and antagonism with the circulating steroid hormones).

Short-term satiety, as observed postprandially, is often coupled with enhanced metabolic rate (111) and the afferent vagus has an important (although not exclusive) role in it (112). A vagal component has been suggested for the development of fever, as well (15-17). Thus, the afferent vagus might be a peripheral point of action for leptin to contribute to febrigenesis. Indeed, leptin excited vagal afferent fibers, or enhanced a CCK-induced excitation, but an IL-1-beta receptor antagonist (given into the local artery) inhibited these effects (90). Central leptin actions have also been implicated in febrigenesis: in rats, even after vagotomy, leptin induced rises both in central IL-1-beta levels and in body temperature (except in leptin-receptor defective fa/fa rats), which rises were inhibited by IL-1-receptor antagonist (92). In IL-1-receptor knockout mice leptin did not cause such changes (24). However, the reports on the role of leptin in febrigenesis are equivocal. In obese Zucker (fa/fa) rats the IL-1-induced fever was reported either low (110, 113) or high (114), while in other studies on similar rats the first part (2-3-h) of LPS fever appeared to be attenuated (115). Various cytokines brought widely different results (114): some caused much smaller, others much greater fevers in obese fa/fa rats than in lean controls. Under carefully controlled conditions, at thermoneutrality, the LPS fever of obese Zucker (fa/fa) rats did not differ from control fever (116).

Inconsistent results have been reported for the changes of leptin levels in LPS-induced fever. Following LPS administration – with or without antipyretics – the plasma levels of leptin were shown unchanged (117). In contrast, in other experiments decreased leptin expression was observed following LPS treatment (possibly not due to cytokines, but secondarily to the high metabolic rate) (118). Finally, LPS was reported to enhance the low leptin level of fasting mice to normal (119). Endotoxemia induced high leptin mRNA (and decreased beta-3-adrenergic receptor mRNA) expression in white adipose tissue (120). Apparently, LPS per se would increase the expression of leptin, but the LPS-induced elevation in metabolic rate might prevent this effect, resembling a feedback mechanism.

Despite all these data, a direct role for leptin in febrigenesis cannot be stated with certainty. Although various neuropeptide changes initiated by leptin (or accompaniments of leptin effects) may indirectly modify fever course, Ivanov and Romanovsky (116) have demonstrated that the basic regulatory mechanisms of LPS-fever are unchanged in obese Zucker rats, which lack effective leptin effects.

There are no convincing data to prove that leptin or its absence would be a direct causative factor in the development of hypothermia in systemic inflammatory processes, either. However, fasting mice (with presumably low leptin levels) were particularly susceptible to LPS shock (probably due to an extreme rise in plasma TNF-alpha level) and leptin replacement reduced the toxicity (119). Endogenous leptin acted as a protective agent against energetic and circulatory effects of TNF and exogenous leptin was also protective in ob/ob (but not in control) mice (121). Leptin-deficient ob/ob mice were similarly sensitive to LPS: they developed a massive temperature fall to large doses of LPS, which was reduced to less than half after leptin pretreatment (122). It is likely that the low leptin levels are coupled with low sympathetic (and brown fat) activity, rendering the subjects more susceptible to hypothermia or shock. Besides, in human monocytes leptin induced a 6- to 10-fold increase in IL-1-receptor antagonist secretion (123).

6.4. Cholecystokinin (CCK)

Since a recent review by Szelényi et al. (124) has extensively summarized the possible role of CCK in fever and hypothermia during systemic inflammation, a detailed analysis does not seem to be necessary, here only a brief survey of relevant data is given.

Primarily, CCK was shown to act within the gastrointestinal system and its role in energy metabolism was demonstrated as a satiety agent. Depending on the actual feeding status, the gastrointestinal stretch and released CCK send satiety signals through the afferent fibers of the abdominal vagus to the nucleus of the solitary tract and further to the hypothalamus (125). In this mechanism mainly vagal type-A CCK-receptors are involved. Within the regulation of food intake, this covers a short-term satiety mechanism not directly connected with the size of energy reserves or body weight, rather with the size of meal. Leptin (either derived from adipose tissue of from the stomach) acts synergistically with CCK on the vagus (126) to suppress food intake. Daily intraperitoneal CCK injections enhanced the fall in body weight induced by central leptin infusion in rats, although the chow consumption was not suppressed more than without CCK (127), suggesting that during combined treatment (in addition to anorexia) the metabolic rate also increased.

Apart from the peripheral CCK, neuronal CCK and type-B CCK receptors of the brain may also participate in the energy balance. Centrally applied CCK decreased food intake (128) and it induced a dose-dependent regulated (fever-like) rise in core temperature, involving appropriate skin vasoconstriction. While indomethacin did

not influence this CCK-fever, an antagonist of CCK-B receptors attenuated the first part of LPS-fever (129), suggesting that CCK may have a pyretic role, independent of PG-s. However, neither type-A nor type-B CCK receptor antagonists were able to antagonize the anorectic effect of LPS or IL-1-beta in mice (130). The LPS fever was not smaller in CCK-A receptor deficient OLETF rats than in wild-type ones (131).

Although peripheral CCK caused hypothermia in many experiments, in hypothermia of systemic inflammations no role has been proven for CCK-ergic mechanisms (124). Nevertheless, this possibility would deserve further analysis.

6.5. Neuropeptide Y (NPY)

The most potent orexigenic peptide known at present is NPY. It is produced in the arcuate nucleus (co-localized with AGRP, adjacent to POMC and CART), in which activation of leptin and insulin receptors inhibit NPY (and AGRP) production (26, 132). From the arcuate nucleus a dense projection runs mainly to the paraventricular nucleus and partly to the dorsomedial nucleus and dorsolateral hypothalamic area. NPY is released from the nerve terminals, to be bound to specific receptors (regarding energy balance, probably the Y1 and Y5 receptors are the most important). Leptin and insulin inhibit the release and receptorial binding of NPY at the paraventricular nucleus. NPY usually exerts its effects in concert with the co-localized AGRP, an endogenous MC3R/MC4R antagonist.

NPY injected into the paraventricular nucleus (133), the arcuate nucleus or preoptic region (25) induced a complex anabolic response: hyperphagia with falling body temperature. Intrahypothalamic injection of Y1 receptor antisense caused hypophagia and hyperthermia (134). However, the ingestive and thermal effects are not strictly parallel: small doses of naltrexone injected to the rostral part of the nucleus of the solitary tract blocked the feeding effect but not the inhibition of brown fat function following NPY injection to the paraventricular nucleus (135). Despite the coordinated anabolic character of the peptide, its thermal effects were not coordinated: the hypothermia was induced by hypometabolism only, without any change in heat loss (136, 137), i.e. the term “anapyrexia” cannot be used.

Since the NPY-hypothermia is not truly “regulated”, a role for NPY (or its lack) in the development of fever or hypothermia in the course of systemic inflammation was regarded as rather unlikely. Indeed, various cytokines were found to be without effect on NPY release from hypothalamic slices (138). Contrary to these, IL-1-beta induced a rise in NPY concentration in various hypothalamic nuclei *in vivo* (139, 140), including the medial preoptic, paraventricular, ventromedial nuclei, but not the arcuate nucleus (139, 141). Apparently, not the NPY production increased in the arcuate nucleus, rather the peptide’s release decreased in various nuclei, with consequent NPY accumulation in those nuclei. A decreased release, in turn, might contribute to a picture of defective NPY activity, like the one observed with Y1 receptor antisense administration (134). In fact, IL-1-beta treatment caused similar hypophagia and fever as those caused by the antisense substance. Indomethacin pretreatment prevented fever and anorexia as well as the rise in NPY level (139) in the hypothalamic nuclei, although it is not clear whether the production of NPY decreased or its release increased (from the antipyretic and anti-anorectic effects it is more likely that the release and not the production is influenced by local PG-s). In LPS-induced anorexia a downregulation of NPY-mediated mechanisms was suggested (142) and NPY administration restored the appetite. Central NPY injection also inhibited the PGE-hyperthermia (143). It would be interesting to know whether or not NPY agonists and antagonists can modify fever, but the experimental data are not sufficient for an answer.

Even if a defective NPY activity is assumed to play a role in some correlates of systemic inflammation, in fever itself this role is questionable, since the thermoregulatory effects of NPY are not coordinated. In this case a defective NPY activity only means that disinhibition of sympathetic activity and metabolic rate may promote a febrile elevation of body temperature, but it is not the primary cause of fever.

In the hypothermia seen in systemic inflammation a possible role for NPY may be even more intriguing, but this possibility has not been analyzed as yet. It is possible to speculate that in case the NPY is suddenly released (after accumulation in nerve endings in hypothalamic nuclei due to pyrogens), a hypothesized “overflow”-type release of the peptide from these overfilled hypothalamic nuclei could possibly cause hypothermia. There is no cue, however, as for the cause of a disinhibition of NPY release from these nerve endings.

6.6. Other peptides

From the previous chapters it must be obvious, that neither the marked anorexia, nor the temperature changes characteristic for systemic inflammation can be explained by isolated alterations of any single neuropeptide. Several peptides, functioning jointly with those detailed above are simultaneously affected and their changes are not necessarily confined to the already mentioned hypothalamic areas. The exact roles of these peptides have not been clarified, not to mention their possible roles in fever or hypothermia.

After an intraperitoneal dose of LPS levels of the anorexigenic POMC and CART but not the orexigenic NPY and MCH increased in the arcuate nucleus, while CART, MCH as well as the orexigenic galanin levels decreased in the lateral hypothalamus (141). LPS also enhanced the expression of CART and urocortin in mesencephalic vegetative nuclei (144). Plasma level of the orexigenic ghrelin of gastric origin was elevated in fasting rats and LPS suppressed the ghrelin level to the postprandial values (145). This suppression may obviously contribute to the loss of appetite.

In LPS-induced anorexia calcitonin gene-related peptide (CGRP) of the parabrachial nucleus and the

projections to the amygdala were shown to have a role (146). CGRP, amylin (147) or substance P (SP) injected into the cerebral ventricles induced satiety and hyperthermia and endogenous SP was shown to participate in fever mediation (148). Intracerebroventricular injection of the orexigenic galanin (149) or orexin-A (150) attenuated the endotoxin-induced fever, but they also decreased body temperature without LPS, showing a potentially cryogenic and not true antipyretic effect. While glucagon-like peptide-1 is known to act similarly as CCK-A receptor activity and to cause anorexia and hypothermia, its antagonist given centrally (in itself ineffective on body temperature) enhanced LPS-fever (151).

7. FEEDING STATUS, NUTRITIONAL STATUS AND SYSTEMIC INFLAMMATION

The ever-changing feeding status (post-meal vs. between-meals) can influence metabolic and thermoregulatory processes not simply through substrate availability, rather through central regulatory processes and altered neuropeptide actions. Satiety signals of neural, hormonal and nutrient origin (e.g. vagus, CCK and glucose, respectively), alone or in combinations can activate central catabolic peptides (e.g. melanocortins) and inhibit the anabolic ones (e.g. NPY, AGRP, MCH). Feeding-related and circadian patterns have been demonstrated for plasma leptin levels, with reciprocal changes in ghrelin (152) and with changes in those central peptides, which can influence both food intake and body temperature. Central MC4-receptors were regarded important in rapid adjustment of energy expenditure to energy intake (51). Both metabolic rate and body temperature was demonstrated to rise in the immediate postprandial period (111, 112) and the rise was, to a great extent, independent of the calorie content of the ingested food. The duration of postprandial hypermetabolism was further increased by central leptin administration (153), suggesting interaction of various signals. Heat loss is not suppressed simultaneously with the hypermetabolism, therefore this hyperthermia is caused exclusively by the hypermetabolism: in contrast to fever the process is not coordinated (as regards thermoregulation). Although vagus-mediated signals may also participate in the initiation of fever (15-17), it is not clear whether or not signals of the actual feeding status can modify the course of fever or hypothermia in systemic inflammations.

Nutritional status exerts a more tonic influence on energy balance than the actual feeding status. In starvation energy expenditure and body temperature are suppressed (154, 155) (without a rise in heat loss), whereas in obesity resulting from voluntary overfeeding the resting metabolic rate is elevated (156) (high heat loss prevents hyperthermia). Both alterations of energy balance develop on basis of changes in central regulatory processes, including changes in neuropeptide profiles. Signals for these changes do not originate from the gastrointestinal tract, rather from adipose tissue leptin together with other hormones (e.g. insulin) and various nutrients. During starvation plasma leptin levels fell (89), hypothalamic POMC and CRF expression decreased, whereas NPY expression increased (10, 157). In contrast to fed rats, in fasting animals LPS did not cause any further rise in hypothalamic NPY expression (140) thus, any possible febrile factor dependent on NPY-changes (e.g. altered release, see chapter 6.5.) was missing in the fasting state. Fasting hypometabolism was prevented by central leptin infusion in rats (158). In voluntarily obese humans (159) and rats (160) the leptin levels were high and correlated with fat content, although later on the leptin sensitivity decreased (161), the hypothalamic NPY levels were low (11). In ob/ob mice (also in Koletsky rats) the resting metabolic rate was low (99).

Despite a low resting metabolic rate in cold-adapted fasting rats, their responsiveness to acute cold exposure or central PGE injections was maintained (154), suggesting that the fasting-induced neuropeptide changes influenced basal metabolism, but not necessarily the thermal sensitivity, the thermoregulatory phenomena, or the extra heat production in cold. With similar central neuropeptide profile as in fasting rats, ob/ob mice could not normally withstand cold exposure (35) and leptin receptor-deficient db/db mice tended to give exaggerated hypothermic response to LPS at sub-thermoneutral ambient temperatures (122). Leptin receptor-deficient obese rats also had difficulties in defense against cold, but at a thermoneutral environment they were able to mount a normal fever to LPS (116).

Whether induced by voluntary overfeeding or genetic abnormality with high or low leptin levels, respectively, (and with corresponding other neuropeptide changes), obesity does not seem to influence the basic steps of fever pathogenesis (116). In contrast, fasting has been reported to modify the effects of pyrogens. In fasting newborn rabbits LPS induced hypothermia instead of the usual fever, even if the conditions were otherwise identical with those of controls (12). Fasting newborn rabbits could still develop a fever by behavioral means: by temperature selection in a thermal gradient (162), i.e. only the autonomic means of febrigenesis were restricted, the central regulatory steps were probably not different from those in well-fed controls. Starving rats exhibited blunted fever to pyrogen (13), but also a decreased ability to withstand cold. Accordingly, although the fever course may be modified in starvation, it may even be turned into hypothermia, these probably still do not reflect central regulatory alterations. Temperature changes (fevers) in turpentine-induced inflammation were practically identical in normal-weight, reduced-weight and overweight rats (163).

8. CONCLUSIONS AND PERSPECTIVES

Let it be fever or hypothermia, in systemic inflammation both should originate from coordinated changes in the regulation of body temperature: heat production and heat conservation should rise or fall in parallel. The direct action of orexigenic and anorexigenic neuropeptides in most cases (except for central CCK) is not coordinated in this sense, but they have other coordinated actions. The main target of these peptides is not the regulation of body temperature, rather the regulation of long-term energy

balance: according to their coordinated effects on food intake and metabolic rate they are either catabolic or anabolic. These substances may still influence body temperature and short-term energy balance, but their thermal effects are only secondary and depend entirely on how the metabolic rate is affected. No uniform way of action is valid for all these peptides.

Melanocortins and CRF are catabolic: besides anorexia they also induce hypermetabolism, the heat load causing an elevation of body temperature that is not (or not fully) counteracted by increased and not supported by decreased heat loss. Melanocortins link energy balance to consummatory behavior, i.e. they can participate in the fast adjustment of metabolism to food intake during diet-induced thermogenesis, but they are more important in the long-term balance of body weight. However, melanocortins do not seem to be principal participants in the elevation of body temperature during fever: melanocortin agonists do not enhance, rather attenuate fever. The catabolic CRF links energy balance to the environmental factors: it is involved in adaptation to stressful conditions, enhancing sympathetic activity and causing regulated elevation of body temperature not counteracted and not helped by heat loss changes. CRF may also be important in inducing a negative energy balance during chronic stress situations. Some, but not all febrigenic cytokines make use of CRF during their actions: mainly those, which can be connected with stress. In other cases CRF does not contribute to the elevation of body temperature.

It is interesting, however, that these two neuropeptides have a particular role in systemic inflammatory processes, independent of their primary catabolic character that could cause fever-like elevation in body temperature: both melanocortins and CRF are antipyretic. The antipyretic action cannot be explained simply as counteracting fever by a hypothermia-inducing "cryogenic" effect, rather as a specific inhibition of the action or the activity of some step in febrigenesis. At least for CRF, this step is probably beyond the production of PGE. The point of action of melanocortins needs to be clarified. It is difficult to reconcile the two types of actions seen with the application of these peptides: one is a catabolic the other is an antipyretic action. A possible (rather teleological) explanation is that too high fever would necessitate very large increase in metabolic rate and, consequently, a very serious negative energy balance on the long term, particularly since the whole process is unavoidably coupled with anorexia. This could be deleterious. One possibility to lessen the risk is to lessen the rise in metabolic rate and also the fever connected with the hypermetabolism. Endogenous antipyresis could be regarded as a break in the process of extreme metabolic rise and negative energy balance. The rise in body temperature during fever has been shown to have a limitation (164). Accordingly, those substances, which under normal circumstances result in a complex balance between the two regulatory mechanisms (i.e. body weight regulation and temperature regulation), during systemic inflammation exhibit a different pattern.

Directly or indirectly, leptin has catabolic effects. Although it can excite the afferent vagus (jointly with CCK), its effects are exerted mainly through secondary changes in other neuropeptides in the brain: rise in the catabolic, fall in the anabolic ones. Leptin may affect the short-term energy balance (including fast changes in metabolic rate and body temperature, occasionally in fever), but its main action is in the long-term balance and regulation of body weight. Leptin can induce IL-1 expression in the hypothalamus, but it is still not indispensable for fever development.

CCK is the only peptide, which – upon central application –induces coordinated thermoregulatory changes corresponding to fever. Besides, it is also catabolic. The peptide can also act on vagal afferent fibers. CCK is likely to be involved more intimately 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.

The only orexigenic-anabolic peptide analyzed here is NPY. It was shown that a decreased release in hypothalamic nuclei and a defective NPY activity possibly contributes to the catabolic state seen in fever: both anorexia and a rise in body temperature can find an explanation in defective NPY action. However, since the thermoregulatory actions of NPY (or its lack) are not coordinated, the effect of the peptide on fever depends entirely on how it modifies metabolic rate.

There is no convincing experimental proof showing that these peptides can in any way participate in the regulated hypothermia following LPS administration. None of the anorexigenic peptides or their antagonists can cause severe hypothermia, irrespective of the presence or absence of systemic inflammation. Lack of such peptides more easily renders the animal prone to cold or to LPS-hypothermia. Therefore, a possible direct role in the regulated hypothermia seems unlikely for these peptides, their defective activity, however might be considered as a factor for hypothermia, like in leptin-deficient animals. So far, however, no experimental data show that a systemic inflammation itself could induce significant suppression of anorexigenic peptides or that it could be coupled with suppression of anorexigenic peptides, on the contrary, the levels of these peptides usually rise in such cases. Some of them can be antipyretic, but even these do not turn fever into hypothermia. However, further detailed studies might provide some new data in this field. NPY, in turn, might easily be a candidate to have a role not only in a fever, but also in hypothermia. Although its release is inhibited in hypothalamic nuclei during inflammation, its amount in those nuclei is high. Anything promoting the release of the high amounts of NPY could therefore induce hypothermia, as it is seen in severe systemic inflammations. This possibility, however, would also need further analysis.

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Abbreviations: LPS: lipopolysaccharide, POMC: pro-opiomelanocortin, ACTH: adrenocorticotropin, MSH: melanotropin (melanocyte stimulating hormone), MC3R: melanocortin-3 receptor, MC4R: melanocortin-4 receptor, CRF: corticotropin-releasing factor, CCK: cholecystokinin, NPY: neuropeptide Y, CART: cocaine-amphetamine regulated transcript, MCH: melanin-concentrating hormone, AGRP: agouti-related peptide, GLP-1: glucagon-like peptide-1, MT-II: melanotan-II, TNF-alpha: tumor necrosis factor-alpha, IL-1 interleukin-1, IL-6: interleukin-6, NO: nitric oxide, COX: cyclooxygenase, PG: prostaglandin, PGE: prostaglandin E, mRNA: messenger ribonucleic acid, CGRP: calcitonin gene-related peptide, SP: substance P, FI: food intake, MR: metabolic rate, Tc: core temperature.

Key Words: Fever, hypothermia, endotoxin, anorexia, POMC, melanocortins, CRF, urocortin, leptin, CCK, NPY, orexigenic peptides, anorexigenic peptides, fasting, overfeeding, vagus, Review

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