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ENDOGENOUS ANTIPYRETICS: NEUROPEPTIDES AND GLUCOCORTICOIDS

Joachim Roth [1], Eugen Zeisberger [2], Stanislav Vybíral [3] and Ladislav Janský [2]

[1] Department of Veterinary Physiology, Justus-Liebig-Universität Giessen, Frankfurter Strasse 100, 35392-Giessen, Germany, [2] Faculty of Biology, University of South Bohemia, Budweis, Czech Republic, and [3] Faculty of Science, Charles University, Prague, Czech Republic

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1. ABSTRACT

Based on observations that fever is suppressed under several physiological circumstances the existence of endogenous antipyretically active molecules has been postulated. A large number of experimental and some clinical studies provided evidence that the neuropeptides arginine vasopressin (AVP), α- and γ-melanocyte stimulating hormones (α-MSH, γ-MSH) and adrenocorticotropic hormone (ACTH) as well as glucocorticoids are capable to antagonize febrile responses to pyrogens. Endogenous antipyresis is mediated by actions of these molecules within the central nervous system or, at least in some cases, by peripheral effects. Brain sites where endogenous antipyresis is activated include the septal area of the limbic system and the anterior hypothalamus. The precise neuronal mechanisms of how the aforementioned endogenous mediators cause a limitation or even suppression of fever are not known. There is, however, evidence that endogenous antipyretics cancel changes in neuronal activities which have been induced by endogenous pyrogens such as cytokines and prostaglandins. At the level of the hypothalamic controller of thermoregulation antipyretic peptides seem to cause a reversion of the pyrogen-induced upward shift of the threshold body core temperature for activation of metabolic heat production. Such a change in thermoregulatory characteristics is compatible with a limitation of fever in strength and duration.

2. INTRODUCTION

Fever is not the result of an inability to regulate body temperature appropriately. The febrile rise in core temperature is rather due to a change of the thermocontroller characteristics resulting in an elevation of the set-point of body temperature. The higher temperature is actively established and defended by the operation of heat-producing and heat-conserving thermoeffectors (1). This means, that in a plateau phase of fever thermoregulatory responses similar to those under normothermic conditions are evoked by attempts to lower or increase body temperature. A number of drugs or plant extracts are known to reduce febrile body temperature and such drugs are called antipyretics. According to the concept of fever as an upward shift of the set-point of the thermoregulatory system an antipyretic substance can be defined as a drug that reduces true febrile temperature but does not influence normal body temperature for example by inducing profound vasodilation under any circumstances (2). The most common synthetic antipyretic substances are drugs which inhibit pyrogen induced synthesis of prostaglandins (3). Administration of such drugs inhibits the febrile response when administered before or simultaneously with the respective pyrogen and produces defervescence when injected at any stage of fever, but does not reduce body temperature under non-febrile conditions (4, 5).

More than 50 years ago, DuBois (6) raised the question of why fever in humans rarely exceeds 106°F (corresponding to about 41°C). He postulated that there had to be a kind of emergency mechanism, that prevents febrile rises of body temperature to levels which threaten life due to a manifestation of brain damage. During the 1970s the search for this emergency mechanism started and it was investigated, if there might be true endogenous antipyretic molecules which could reduce or prevent fever under certain physiological conditions. In these years it was observed that the febrile response of newborn lambs to bacterial pyrogen is impaired (7, 8). In elegant studies it could be demonstrated that newborn and even fetal sheep respond to intravenous lipopolysaccharide (LPS) with a fall in the number of circulating white blood cells, but not with fever (2, 7). The observed transient leukopaenia, which belongs to the typical effects of LPS *in vivo*, clearly showed that newborn animals recognize and respond to the bacterial pyrogen. In addition, sheep are born with a fully developed thermoregulatory system and have the ability to regulate their body temperature against cold, meaning that they would potentially be capable to develop a fever. A similar phenomenon was observed in pregnant ewes (9) and

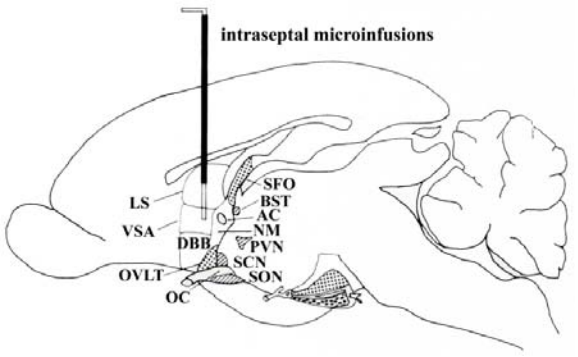

Figure 1. Mid-sagittal section of guinea pig brain showing the areas relevant for the regulation of fever and AVP-mediated antipyresis, and a cannula in the ventral septal area, through which solutions containing AVP or AVP antagonists were microinfused. AC = anterior commissure; BST = bed nucleus of the stria terminalis; DBB = dorsal band of Broca; LS = lateral septum; NM = nucleus medianus; OC = optic chiasm; OVLT = organum vasculosum laminae terminalis; PVN = paraventricular nucleus; SCN = suprachiasmatic nucleus; SFO = subfornical organ; SON = supraoptic nucleus; VSA = ventral septal area. Hatched areas denote brain nuclei containing vasopressinergic neurons, dotted areas indicate circumventricular organs with an incomplete blood-brain barrier. Modified from (30), with permission from Karger, Basel.

guinea pigs (10): during a period from several days pre-partum to a number of hours post-partum the animals failed to develop fever in response to injections of LPS. A possible adaptive value of a specific endogenous antipyretic mechanism which is activated during the late stage of pregnancy and in the newborn has been discussed (2) and nowadays this topic is still of basic and applied interest (11).

Based on this background the search for putative endogenous antipyretic mediators started. Predominantly, this search focussed on the nonapeptide arginine-vasopressin (AVP) and on the protein products of the pro-opiomelanocortin (POMC) gene such as the adrenocorticotropic hormone (ACTH) and α- or γ-melanocyte stimulating hormones (α-MSH, γ-MSH) (12, for review). The evidence for a role of these neuropeptides as endogenous antipyretic agents will be analyzed, followed by a look at the modulation of fever by glucocorticoids, the anti-inflammatory and immunomodulatory effects of which have already been known for decades (13, 14). As far as experimental data are available, special attention will be directed to the question, if a fever-reducing effect of a given endogenous antipyretic mediator is due to appropriate modifications of thermoregulatory effector responses.

3. ARGININE-VASOPRESSIN

The observation of a natural suppression of fever in pregnancy near term and in the neonate stimulated researchers to look for endogenous molecules which are produced and released in increased amounts in these states of fever resistance. The nonapeptide AVP, which has originally been recognized for ist antidiuretic and vasoactive effects, has been reported to circulate in increased concentrations during the late prepartum period (15, 16). However, an antipyretic activity could not be demonstrated for circulating AVP (17). Two areas in the brain that have been identified as sensitive loci for the antipyretic action of AVP are the ventral septal area and the medial amygdala (17, 18). In addition, there is some evidence for an influence of AVP on hypothalamic structures which control thermoeffector responses (see Chapter 5). Criteria for a given endogenous substance (here: AVP) to be legitimately categorized as an endogenous antipyretic or an endogeous cryogen have been listed and discussed by Kasting (19) and Kluger (20). According to both of these excellent reviews, AVP fulfils most of the criteria to be accepted as a true endogenous antipyretic peptide. A number of studies which have characterized the antipyretic properties of AVP and demonstrated the locations of its actions in the brain can be summarized as follows.

Perfusions of the ventral septal area with AVP at doses, which had no effect on normal body temperature, significantly depressed fever in sheep (17), rabbits (21), and rats (22). Microinfusions of AVP in rather small amounts into the ventral septal area of guinea pigs also resulted in a strong attenuation of the febrile response to bacterial LPS (23). The brain site where microinfusions of AVP reduces fever in guinea pigs is shown in Figure 1. The ventral septal area is innervated by vasopressinergic neurons. In rats, the major source of the AVP-innervation of the ventral septal area is the bed nucleus of the stria terminalis (24). In guinea pigs, vasopressinergic pathways to the septal area of the limbic system mainly originate from parvocellular neurons within the hypothalamic paraventricular nucleus (25). Thus, in guinea pigs an increased AVP-immunoreactivity can be observed in the parvocellular neurons of the paraventricular nucleus as well as in nerve fibers and terminals in the ventral septal area and in the amygdala in situations when endogenous antipyresis is activated (10, 26, 27, 28, 29). The relevant brain areas which are involved in AVP-mediated antipyresis are schematically illustrated in Figure 1.

According to the species-specific origin of vasopressinergic projections to the ventral septal area, an electrical stimulation of the bed nucleus of the stria terminalis suppresses fever in rats (31), while the febrile response of guinea pigs can effectively be attenuated by electrical stimulation of the hypothalamic paraventricular nucleus (29, 32). Physiological or pathophysiological situations in which peripheral and central release of AVP is enhanced, such as hemorrhage, infusions of hypertonic saline, or dehydration are frequently accompanied by an attenuation of fever (33, 34).

The precise mechanism by which AVP released into the ventral septal area acts to prevent a febrile increase of body temperature is not known. It has been suggested (35) that AVP stimulates septal neurons, the excitation of

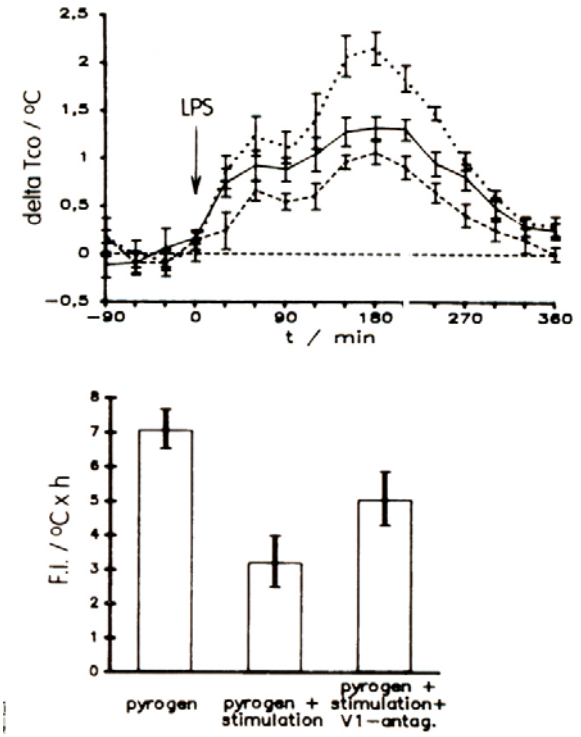

Figure 2. Febrile responses to bacterial endotoxin (LPS) in three groups of guinea pigs under the influence of elecrical stimulation of the paraventricular nucleus (PVN; dashed line) and electrical stimulation of the PVN combined with intraseptal microinfusions of a V1 antagonist (solid line) and in animals given endotoxin alone. The integrated fever response (fever index, F.I., lower panel) is significantly different between all three groups [from (32), with permission of The American Physiological Society].

which is then transmitted via septofugal fibers to hypothalamic thermoregulatory relevant structures (36). By this kind of AVP-induced excitation of hypothalamic thermoregulatory networks pyrogen-induced changes of neuronal activities may be canceled. In addition, electrophysiological studies demonstrated numerous connections between limbic and hypothalamic structures (37, 38). These findings implicated the ventral septal area in thermoregulatory pathways by the identification of neurons in this area which respond to peripheral thermal stimulation (38). In the same study it was shown that the activity of these thermoresponsive septal neurons can be modified by afferent inputs from different hypothalamic and limbic structures. This population of neurons may play a role in the AVP-mediated attenuation or even suppression of fever. As a possible cellular mechanism in the ventral septal area a reduction of activity of glutamate excited neurons by AVP has been suggested (39).

There is evidence (40, 41) that AVP stimulates septal neurons via the V_1-receptor (vasopressor subtype of peripheral AVP receptors) rather that the V_2 receptor (antidiuretic subtype of peripheral AVP receptors). It is thus not surprising that the antipyretic effect of AVP in the ventral septal area can be pharmacologically antagonized by specific V_1-receptor antagonists. Cooper *et al.* (22) injected a specific V_1-receptor antagonist into the ventral septal area and observed a dose-related exacerbation of fever evoked by administration of interleukin-1 into the lateral cerebral ventricle. Fever induced by intracerebroventricular injection of prostaglandins is also enhanced by intraseptal application of the V_1-receptor antagonist (42). Further evidence for a role of septal V_1 receptors in endogenous antipyresis derives from experiments which aimed to stimulate vasopressinergic projections to the ventral septal area electrically. For this purpose stimulating electrodes were implanted into the bed nucleus of the stria terminalis in rats (31) or into the hypothalamic PVN in guinea pigs (32). In both studies an electrical stimulation of the respective brain area had antipyretic effects, and in both studies these antipyretic effects could be antagonized (31) or partly reversed (32) by administration of a V_1-receptor antagonists into the ventral septal area. These actions were site sprecific in that the attenuation of fever was observed only when the electrode tips were located in the area of the bed nucleus of the stria terminalis or in the hypothalamic PVN. Similarly, the V_1-receptor antagonists only blocked or attenuated the effect of electrical stimulation when administered into the ventral septal area. One example for such an experiment is shown in Figure 2.

LPS-induced fever in guinea pigs is reduced by more than 50 % by electrical stimulation of the hypothalamic PVN. This reduction of fever is partly reversed by intraseptal microinfusion of the vasopressinergic V_1-receptor antagonist. This result clearly demonstrates a participation of septal V_1 receptors in endogenous antipyresis. However, the failure of the V_1 antagonist to restore completely the febrile response in the experiments shown in Figure 2 shows that there must be additional antipyretic mechanisms which are activated by electrical stimulation of the hypothalamic PVN. The parvocellular neurons of the PVN produce a mixture of peptidergic transmitters, mainly corticotropin-releasing hormone (CRH) and AVP (43). CRH stimulates the secretion of products of the proopio-melanocortin (POMC) from the corticotrophs of the anterior lobe of the pituitary (see Chapter 4). It is thus likely that electrical stimulation of the hypothalamic PVN causes the activation of more than one antipyretic mechanism.

A few critical arguments concerning an obligatory role of AVP as a centrally acting antipyretic mediator should be introduced and discussed briefly. Firstly, it has been reported that the attenuation of fever near term of pregnancy is mediated by AVP only when prostaglandin E, but not when IL-1β is used as fever-inducing agent (44, 45). The exclusive role for endogenous AVP as the endogenous antipyretic mediator in this specific physiological situation seems thus to be equivocal. Secondly, during fever and especially in some situations when endogenous antipyresis is activated prior to a challenge with a pyrogen, AVP is constantly released in increased amounts not only into the ventral septal area but also into the systemic circulation (34, 42, 46, 47). This means that the central (for example into the septum) and

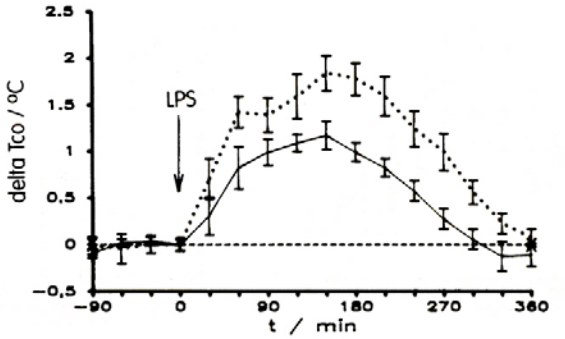

Figure 3. Influence of intra-arterial infusion of γ-MSH (0.261 μmol within 6 hours, solid line) or solvent (0.9 % saline, dotted line) on the febrile response to bacterial endotoxin (LPS) in guinea pigs [from (32), with permission of The American Physiological Society].

the peripheral (into the neurohypophysis) vasopressinergic projections are activated during fever concomitantly. Is it possible that the rise in circulating AVP influences thermoregulation and fever ? Indeed, it has been reported that peripheral administration of a vasopressinergic V_1-receptor antagonist modulates fever in rabbits (48). In addition, intravenous injections of AVP cause hypothermia in rats (49). However, it should be noted that circulating concentrations of AVP under physiological and even under stimulated conditions (with the exception of severe hemorrhage) never exceed the range of picograms per ml plasma, while hypothermia develops in response to a substantially higher dose of 2 μg/kg AVP (49). Thus, the original observation by Cooper *et al.* (17), that intravenous administration of AVP in physiological doses *per se* has no influence on body temperature and that the antipyretic mechanism of AVP is due to its central effects, is not challenged by this study. Finally, the most equivocal results concerning the role of AVP in endogenous antipyresis derive from experiments with the Brattleboro rat. This rat strain possesses a recessive autosomal allele which results, when present in the homozygous condition, in a profound AVP deficiency. This animal was therefore used as a model to investigate the role of AVP as a regulator of the febrile response. However, in contrast to the hypothesis that animals deficient in AVP would get very high fevers, the Brattleboro rat failed to develop fever to endotoxin in one study (50), but developed fever in another study in response to a dose of intravenously administered LPS that caused hypothermia in control rats (51). The main reason for the conflicting results of these studies may be the existence of redundant antipyretic systems in the brain which are able to compensate the missing mediator for the regulation and limitation of the febrile response.

4. PRODUCTS OF THE PROOPIOMELANOCORTIN GENE

Arround the same time, when the intensive research on the role of AVP in natural suppression and regulation of fever started, it was reported that intracerebroventricular injections of α-melanocyte stimulating hormone (α-MSH) or adrenocorticotropic hormone (ACTH) cause antipyresis in rabbits (52). The lateral septum was identified as one putative central site for the manifestation of the antipyretic effect of α-MSH (53). In accordance with this finding a pulsatile release of of α-MSH into the lateral septum was observed during IL-1-induced fever (54). More recently it was shown that intraseptal microinfusion of γ-MSH, which is another product of the proopiomelanocortin (POMC) gene, also has a fever reducing effect (32). Due to the prolonged microinfusion of γ-MSH into the septal area we can, however, not exclude the possibility that the microinfused neuropeptide diffused to adjacent brain areas and thus acted at sites remote from the site of infusion. Additional brain sites where endogenous melanocortins have antipyretic activity are the preoptic region (55) and the anterior hypothalamus located caudally to the preoptic area (see Chapter 5). The suggested brain regions for the antipyretic effects of α-MSH or γ-MSH are consistent with the high density of melanocortin receptors expressed in the septal and preoptic areas (12, for review). Further evidence for a role of endogenous α-MSH as an antipyretic peptide derived from studies, in which intracerebroventricular administration of an antiserum against α-MSH markedly prolonged fever (56), or in which chemical depletion of the central α-MSH sources strongly enhanced fever (57).

In contrast to AVP, it has been reported for all antipyretically active products of the POMC (ACTH, α-MSH, γ-MSH) that not only their central but also their peripheral administration recuces fever (32, 58, 59, 60, 61). An example for the antipyretic effect of intra-arterial infusions of γ-MSH in guinea pigs is shown in Figure 3.

The exact mechanisms of antipyretic actions of peripherally administered endogenous melanocortins are not clear. Circulating ACTH causes the release of glucocorticoids from the adrenal glands, the antipyretic properties of which have been known for decades (see Chapter 6). It has not yet been demonstrated under *in vivo* conditions that circulating α-MSH or γ-MSH have the potency to stimulate glucocorticoid secretion. There is just one *in vitro* study showing that γ-MSH significantly potentiates ACTH-induced corticosterone secretion of isolated perfused rat zona glomerulosa cells (62). Provided that such an effect of γ-MSH also manifests itself under *in vivo* conditions, this could explain, in part, the result shown in Figure 3. A stimulation of tissue from the adrenal glands by α-MSH has not yet been reported. The antipyretic activity of peripherally administered α-MSH seems rather to be due to a direct influence of this peptide on the central nervous system (61). Based on the observation that the antipyretic effect of peripheral α-MSH could effectively be antagonized by blocking central melanocortin receptors, the authors of this study (61) suggested that systemic α-MSH exerts its antipyretic capacity at the level of melanocortin receptors expressed in certain circumventricular organs and adjacent brain areas. Remarkably, this hypothesis implicates that circumventricular organs, structures which lack a tight blood-brain barrier, play a role as sensors for circulating pyrogenic (63) as well as antipyretic signal molecules. In this context, it should be noted that the antipyretic effect of peripherally injected ACTH manifests

itself in intact and in adrenalectomized animals (64). This finding indicates that the fever-reducing effect of ACTH is not necessarily dependent on glucocoticoids and might also be caused by a direct action of this neuropeptide on the brain. Finally, one study should be mentioned in which another effect of intravenous injections of α-MSH was detected in rabbits (60). In this study fever and concomitant increases in plasma levels of prostaglandin E2 (PGE2) were induced by treatment with bacterial LPS or pyrogenic cytokines. Interestingly, both effects were inhibited by systemic injections of α-MSH. The authors suggested the prevention of PGE2 synthesis as a possible mechanism which might contribute to the antipyretic effect of circulating α-MSH.

As already mentioned above, POMC-derived peptides exert antipyretic effects by actions within the central nervous system, for example in the limbic septal area. The projections to the septum which use α-MSH or γ-MSH as neurotransmitters originate from neurons located in the hypothalamic arcuate nucleus (65, 66). There are five types of melanocortin receptors (MCRs) which are all coupled to adenylate cyclase and differentiated into the subtypes MCR1-MCR5 (67). MCR1 is expressed in melanoma cells. The primarily location of MCR2 is the adrenal cortex; this receptor is activated by ACTH, but not by MSH peptides. MCR3 and MCR4 are of special interest for the topic of this paper, because they are expressed in the brain. MCR3 is the only melanocortin receptor subtype which is sensitive to γ-MSH but also responsive to other MSH forms, while the most potent natural agonist of MCR4 is α-MSH. Finally, MCR5 is widely expressed within peripheral tissues including lung, skeletal muscle and lymphoid organs (67, for review). Due to the emerging role of α-MSH in the central nervous control of food intake (68, 69) specific agonists and antagonists for the central MCRs have been constructed and used for *in vivo* experiments. Using an antagonist against both, MCR3 and MCR4, Huang *et al.* (61, 70) reported that the antipyretic effect of α-MSH can be antagonized by central administration of this substance and that LPS-fever is significantly enhanced by central injection of the MCR3 / MCR4 antagonist. More recently, selective MCR4 agonists or antagonists have been used to investigate the influence of activation or inhibition of this receptor on the febrile response (71). The main result of this study was that an activation of central MCR4 suppresses LPS-fever in rats. It should, however, be noted that central administration of the MCR3 / MCR4 antagonist had profound influence on anorexia but not on fever induced by intracerebral injection of IL-1 in another study (69). This discrepancy might be due to to the distinct fever models used in both studies (systemic injection of LPS versus central administration of IL-1). Up to date, nothing is known about the precise mechanism by which α-MSH or γ-MSH exert their central effects on fever. It has been speculated that central melanocortins influence descending neuronal pathways which activate an inhibitory influence from brainstem sites on spinal cord, dorsal root ganglia and the sympathetic chain to reduce several centrally mediated signs of inflammation including pain (66). By the influence on such descending CNS projections, MSH peptides possibly could inhibit descending thermoeffector pathways (71).

5. THERMOREGULATORY CHARACTERISTICS AND EFFECTOR RESPONSES

The antipyretic effect of neuropeptides has been known for several decades (72). However, the detailed mode of action of neuropeptides on thermoregulatory functions of febrile homeotherms has not been satisfactorily explained yet. There is ample evidence that the aforementioned neuropeptides (see Chapters 3 and 4) exert an antipyretic effect when administered centrally or peripherally. These antipyretic properties are judged from the ability of these peptides to eliminate or reduce an increase in body temperature induced by pyrogens.

Simple measurements of core temperature changes to central injection of a given neuropeptide in a thermoneutral environment provides only limited information about the mode of action of the substance on the thermoregulatory controller and especially on individual thermoeffector responses. Such thermoeffector responses include cold-induced thermogenesis (CT), peripheral vasomotor tone (PVMT) and respiratory evaporative heat loss (REHL) or sweating. All these responses can be measured in relation to experimentally induced changes of body core temperature. One method to manipulate body core temperature is the technique of intestinal cooling or warming. This method has been introduced into the experimental research on thermoregulation more than 20 years ago (73). Briefly, activation of thermoeffector responses is stimulated by heating or cooling the body core with intestinal thermodes which are introduced deeply into the colon of rabbits and perfused with water of 5°C or 45°C. This method enables manipulations of core temperature (measured in the hypothalamus) while leaving the peripheral body temperature relatively unaffected (for further details see 73, 74). During intestinal cooling or warming and thereby during experimentally induced changes of hypothalamic temperature the intensity of individual thermoregulatory outputs can be monitored in response to microinjections of neuropeptides into the brain (75, 76). Thus, thermoregulatory responses are induced which are almost exclusively due to stimulation of the central temperature input. This approach allows to express activity of individual thermoregulatory effectors as a simple function of the central body temperature.

Figure 4A schematically shows that in the normal (nonfebrile) rabbit deviation of the central temperature from a threshold (38.8°C) represents a signal for activation of thermoregulatory effectors and that the intensity of activation of these effectors increases proportionally to the temperature change, the temperature operational range being about 2.5°C. By this approach thermoregulatory thresholds and also the magnitude of thermoregulatory outputs at respective body temperatures can be estimated. The slope of the relation between hypothalamic temperature changes and the strength of the

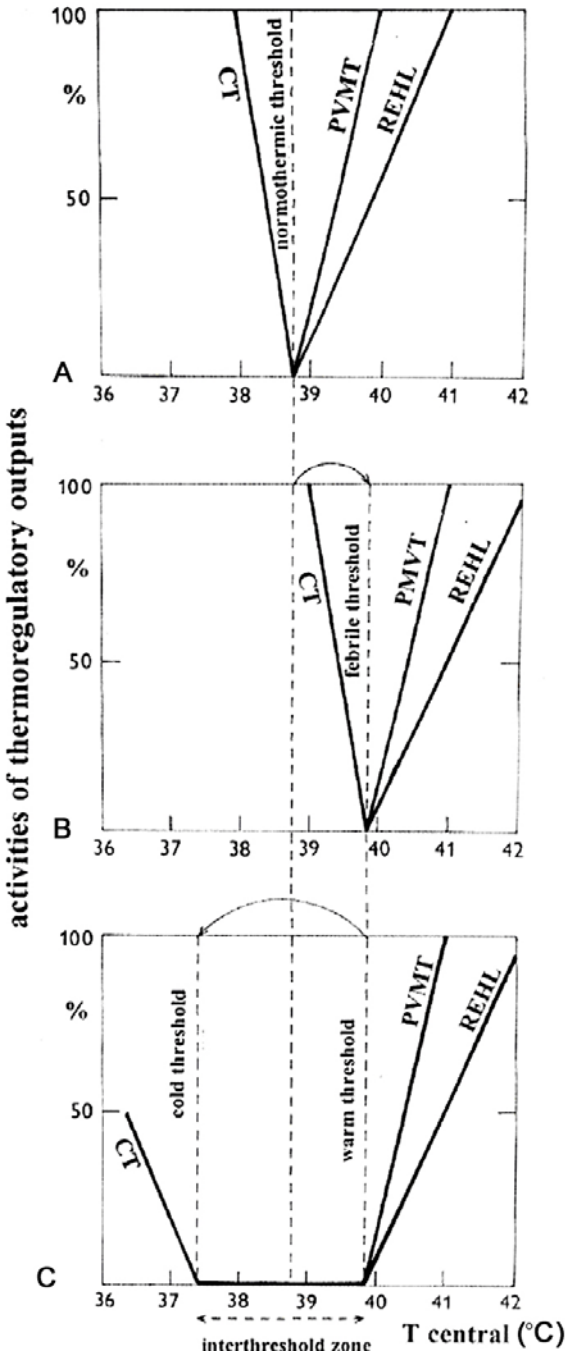

Figure 4. Activation of thermoregulatory effectors (CT = cold thermogenesis; PVMT = peripheral vasomotor tone; REHL = respiratory evaporative heat loss) due to changes in central body temperature (measured with a thermocouple introduced into the anterior hypothalamus) during intestinal cooling or warming of nonfebrile rabbits (A), in febrile rabbits during the early phase of fever (B) and in febrile rabbits during the late phase of fever (C).

thermoregulatory outputs represents a measure for *in vivo* thermosensitivity (73, 74, 75, 76).

Figure 4B/C indicates changes in thermoregulatory functions during the early (B) and late (C) phase of fever (based on data from 77, 78, 79). Thermoeffector responses to intestinal cooling or heating were recorded 20 min (early or rising phase of fever) and 120 min (late phase or plateau phase of fever) after intravenous injection 1 µg/kg bacterial LPS. Evidently, the threshold temperature for all thermoregulatory outputs is shifted upwards by 1°C to a hypothalamic temperature of 39.9°C in the rising phase of fever, while the thermosensitivity of the controller and the magnitude of thermoregulatory outputs are not affected. Thus, the increase in body temperature during the early phase of fever is due to activation of CT and not due to inhibition of heat loss mechanisms. During the late phase of fever (two hours after administration of bacterial endotoxin) a dissociation of the thresholds for the cold and warm defence mechanisms occurs. The threshold for CT is shifted downwards below the prefebrile level, while the thresholds for PVMT and REHL remain temporarily increased. As a result of these modifications the interthreshold zone is enlarged. The magnitude of CT is depressed, while the thermosensitivity of the thermoregulatory controller is not changed. Thus, during the late phase of fever animals become insensitive to relatively large changes in their body temperature. The body temperature within this range of temperatures is therefore a consequence of the passive heat exchange between body and environment. Hypothalamic cytokines (80) might be involved in induction of the early phase of fever, because intrahypothalamic microinjections of IL-1, IL-6 or TNF induce a similar shift of thermoregulatory thresholds as peripherally applied pyrogens (81). Their effects might be mediated by opiods and prostaglandins (82).

The aforementioned neuropeptides (AVP, ACTH, α-MSH) exert a specific antipyretic effect when injected into the septum or the anterior hypothalamus of rabbits during the early phase of fever. As shown in Figure 5, intrahypothalamic administration of 5 µg ACTH lowers the threshold for the induction of CT during the early phase of fever even below the the threshold of nonfebrile animals. Thresholds for PVMT and REHL are not influenced by ACTH. Thermosensitivity of the body temperature controller is slightly lowered and the magnitude of CT is depressed, similarly as during the late phase of fever (see Figure 4). Thus, ACTH seems to convert the first phase of fever into the late phase and thereby to shorten the time course of the entire febrile process.

In contrast, intrahypothalamic administration of α-MSH or AVP at a dose of 20 µg not only lowered the threshold for cold thermogenesis, but also lowered the thresholds for the warm defence mechanims PVMT and REHL (83). It was further found that dopaminergic pathways in the brain may play a role in this phenomenon, since intraperitoneal injections of the dopamine antagonist haloperidol induce similar effects on thermoeffector responses during fever as antipyretic neuropeptides (84). It should, however, be noted that intraperitoneal injections of

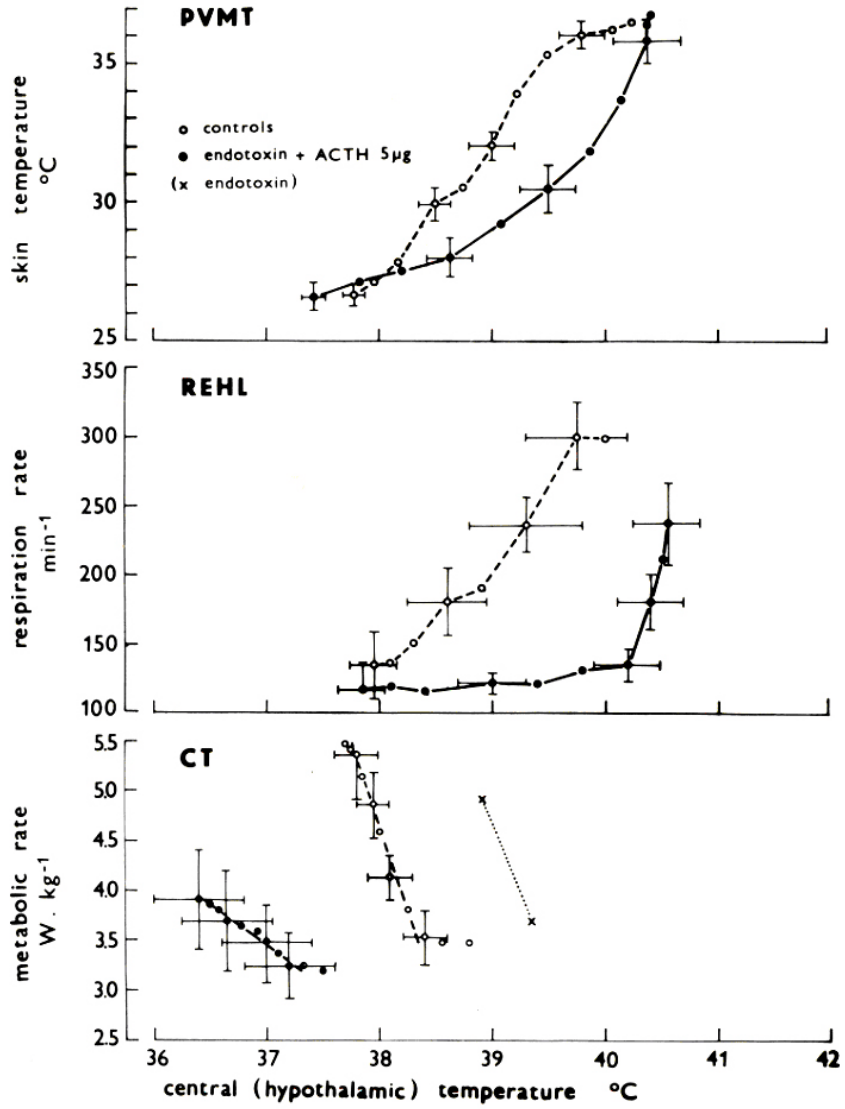

Figure 5. Relationship between hypothalamic temperature and the intensity of individual thermoregulatory effectors during intestinal cooling of nonfebrile rabbits (empty symbols) and in rabbits made febrile by an i.v. injection of endotoxin and injected with ACTH immediately afterwards (5 µg into the anterior hypothalamus at the level of the supraoptic nucleus). Dotted line and crosses show the upward shift of the temperature threshold for induction of cold thermogenesis in the early phase of fever induced by endotoxin in rabbits which were not treated with ACTH [from (78) with permission of Pergamon Press].

haloperidol lower thermoregulatory thresholds also in normothermic (nonfebrile) animals, while intrahypothalamic injections of this drug are without effect (85).

The detailed mode of action of neuropeptides on hypothalamic neurons participating in body temperature control remains to be explained. It has been reported that pyrogens, namely cytokines, when added to hypothalamic slices from guinea pigs, depress the firing rate of warm sensitive neurons and excite cold sensitive neurons (86). Moravec and Pierau (87) working with hypothalamic slices from nonfebrile rats observed that AVP has multiple neuronal effects. AVP seems to decrease the cold sensitivity in most cold sensitive neurons, increases the temperature coefficient in warm sensitive neurons, and increases the tonic activity of warm sensitive neurons with low firing rates. These changes were interpreted as that those neurons may activate thermoregulatory heat loss responses. During fever AVP could thus, at the level of the hypothalamus, preferentially increase the firing rate of those warm sensitive neurons which were previously depressed by pyrogens.

6. GLUCOCORTICOIDS

In 1958 it has been reported that glucocorticoids (GCs) have an antipyretic action on natural fevers in man

(88). Since then numerous studies have been performed to identify the site and mechanism of action of GC-induced antipyresis. In rabbits, intravenous infusions of synthetic GCs failed to reduce fever when administered simultaneously with bacterial LPS or „endogenous pyrogen" while systemic pretreatment with GCs for three days or acute microinjection of GCs into the anterior hypothalamus caused an attenuation of the febrile response (89). The authors of this study concluded that the antipyretic effect of GCs was the result not of a peripheral inhibition of endogenous pyrogen production, but rather of an action on the central nervous system. It should be noted that cytokines, which are regarded as obligatory mediators of fever (20), had not yet been cloned and characterized when this study in rabbits was published. By the use of cellular and molecular techniques it has, however, clearly been demonstrated that there are interactions between GCs and fever-inducing cytokines. Thus, GCs exert a strong inhibitory influence on the transcription of proinflammatory cytokine genes, the promoters of which contain GC response elements. GCs are further involved in the blockade of nuclear transcription factors such as NF□B which are involved in the positive control of the transcription of cytokine genes. Finally, GCs affect the translation of proinflammatory cytokine mRNAs by reducing the stability of cytokine mRNAs (14, 90). As a consequence of these effects a depressed production of proinflammatory cytokines has been observed under the influence of treatment with GCs in experimental and clinical studies (91, 92, 93).

Treatment with GCs is frequently accompanied by reduced fever under experimental or clinical conditions (92, 94, 95). Another body of evidence for a role of GCs as endogenous antipyretics derives from experiments in adrenalectomized animals. Injection of LPS into adrenalectomized rats leeds to higher fevers than in sham-operated controls (94) and treatment with GC-replacement pellets normalizes the febrile response of adrenalectomized animals (93). In spite of the effects of GCs on endogenous formation of cytokines, the anterior hypothalamus has repeatedly been identified as a site where GCs exert antipyretic properties. Thus, microinjection of the GC-receptor antagonist RU-38486 into the anterior hypothalamus results in a marked exarcerbation of LPS-fever in intact animals (96) and intrahypothalamic microinjection of GCs reduce fever in adrenalectomized rats (97).

The central antipyretic effect of GCs could be mediated by lipocortin-1, a GC-inducible protein which is a potent inhibitor of phospholipase A2. This idea is supported by the observations that central injections of lipocortin-1 reduce fever (98) and that lipocortin-1 down-regulates the LPS-induced expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in microglial cells (99). As it has been discussed above for neuropeptides, the antipyretic effects of GCs seem to be mediated by multiple mechanisms.

7. FINAL CONCLUSIONS

The search for mediators of endogenous antipyresis started with the observation that fever is depressed in newborn animals and in pregnancy near term. For several decades this phenomenon has been ascribed to the action of endogenous AVP in the brain. Recently, it has been reported that pyrogen-induced expression of cyclooxygenase (COX)-2 in thermoregulatory relevant areas of the brain is strongly reduced near term (100, 101). Since central induction of COX-2 is regarded as a critical step for the manifestation of fever, the hypothesis for an exclusive role of AVP in natural suppression of fever at term of pregnancy is challenged. This novel finding tells us that the regulation of fever and endogenous antipyresis is a complex process which clearly involves more than one mediator and more than one mechanism. The fact that there are redundant endogenous antipyretic systems indicates that endogenous antipyresis, like fever, has an adaptive value. One component of the adpative value of endogenous antipyretic mechanisms might be the determination of an upper limit of fever. However, the fact that several antipyretic pathways are already activated short time after the induction of fever (102) indicates that there must be a rather complex regulation of fever in strength and duration. These complex interactions between endogenous pyrogens on the one hand and endogenous cryogens on the other hand will require further investigations, especially in situations which are accompanied by a natural suppression of fever.

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Send correspondence to: Joachim Roth, Department of Veterinary-Physiology, Faculty of Veterinary-Medicine, University of Giessen, Frankfurter Strasse 100, D-35392 Giessen, Germany, Tel: (49) 641-99-38850, Fax: (49) 99-38159, E-mail: joachim.roth@vetmed.uni-giessen.de