[Frontiers in Bioscience 8, s1398-1408, September 1, 2003]

FEVER AND ANAPYREXIA IN SYSTEMIC INFLAMMATION: INTRACELLULAR SIGNALING BY CYCLIC NUCLEOTIDES

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1. ABSTRACT

During systemic inflammation, body temperature is either increased (fever) or decreased (anapyrexia). Either response depends on the dose of the inflammatory agent, *e.g.*, lipopolysaccharide (LPS), and on the ambient temperature. Under thermoneutrality, LPS always produces fever; under subthermoneutral conditions, LPS evokes fever at lower doses and anapyrexia at higher doses. Because of the diagnostic and adaptive values of these responses, understanding their mechanisms is of interest. Recently, the intracellular mechanisms that occur in the preoptic region (PO), the thermointegrative site of the brain, to produce fever and anapyrexia have begun to be clarified. In response to febrigenic doses of LPS, an increased production of prostaglandin E_2 and an inhibition of nitric oxide synthesis produce fever respectively by decreasing the intracellular content of cyclic AMP (cAMP) and cyclic GMP (cGMP) in the PO. Although the role of preoptic cAMP and cGMP has not been directly assessed in the anapyrexia induced by LPS, it has been studied in that induced by hypoxia. The likeness between the thermoregulatory responses to hypoxia and to a high dose of LPS suggests that they may have similar mechanisms. In contrast to fever, hypoxia-induced anapyrexia seems to be mediated by a simultaneous increase in the levels of cAMP and cGMP in the PO as the result of an enhanced production and/or release of serotonin and nitric oxide, respectively. This article reviews the recent advances in the understanding of the role of preoptic cAMP and cGMP signaling cascades in fever and anapyrexia.

2. INTRODUCTION

The term sepsis defines the occurrence of systemic inflammation in the setting of a documented infection (1). Among the four criteria that define the systemic inflammatory response syndrome is an "abnormal" (outside the normothermic range) body core temperature (T_c): 90% of the patients with severe sepsis have an elevated T_c (>38ºC), whereas a reduced T_c (<36ºC) is observed in the remainder (1-2). In experimental animals, intravenous or intraperitoneal administration of lipopolysaccharide (LPS), a constituent of the outer membrane of Gram-negative bacteria, has been used widely to induce systemic inflammation. The accumulated data indicate that both the increase and decrease in T_c induced by LPS are brought about by shifts in the thermal balance as the result of changes in the temperature thresholds for activation of thermoeffectors and in the behavioral component of thermoregulation (3-7). A shift in the thermal balance to a higher level is named fever; a shift in the thermal balance to a lower level is named anapyrexia (8). In rats, the occurrence of fever or anapyrexia is dependent on the dose of LPS and on the ambient temperature. In a thermoneutral environment, fever prevails irrespective of the LPS dose. Under subthermoneutral conditions, LPS evokes fever at lower doses and anapyrexia at higher doses (5,9). Aside of their diagnostic value, fever and anapyrexia are two different strategies for survival during systemic inflammation (10). Therefore, understanding their underlying mechanisms is clearly of interest.

The preoptic region (PO) plays a pivotal role in thermoregulation. It is not only a thermosensitive site, but also receives afferent projections from peripheral and core thermosensors, and sends efferent projections to brain regions involved in the control of thermoeffector activity (11-12). Not surprisingly, this region plays an important role in fever (11) and anapyrexia (13). Three neuronal types exist in the PO (11,14): warm-sensitive, cold-sensitive, and temperature-insensitive neurons. Among them, warm-sensitive neurons, which represent ~30% of the neuronal population, have been shown to be involved in thermoregulation: their activation inhibits thermogenesis and triggers heat loss mechanisms (12). Accordingly, whereas the electrical activity of warm-sensitive neurons is

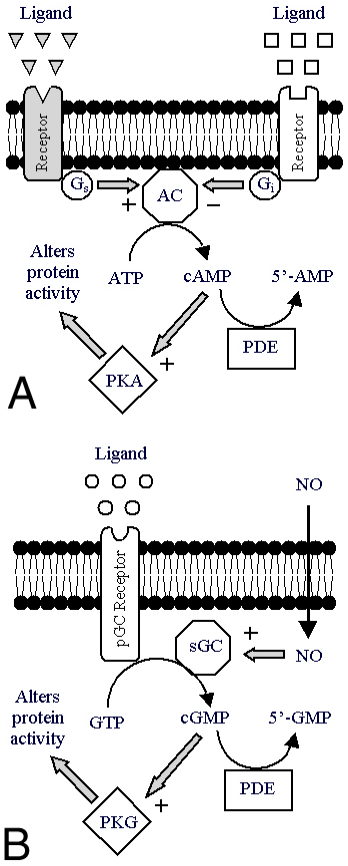

Figure 1. Basic molecular steps of cAMP (panel A) and cGMP (panel B) signaling cascades. See text for explanation. Abbreviations: G_s, stimulatory G protein; G_i, inhibitory G protein; AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic 3',5'-adenosine monophosphate; 5'-AMP, 5'-adenosine monophosphate; PKA, protein kinase A; pGC Receptor; receptor displaying particulate guanylate cyclase activity; NO, nitric oxide; sGC, soluble guanylate cyclase; GTP, guanosine triphosphate; cGMP; cyclic 3',5'-guanosine monophosphate; 5'-GMP, 5'-guanosine monophosphate; PKG, protein kinase G; PDE, phosphodiesterase.

reduced by febrigenic mediators, such as interleukin (IL)-1 (15-16), IL-6 (17), and prostaglandin (PG) E_2 (18-20), it is enhanced by agents that elicit anapyrexia, such as histamine (21), opioids (22), bombesin (23), and γ-aminobutyric acid (24).

Although several neurotransmitters and/or neuromodulators are known to act on the PO to produce fever and anapyrexia, little is known about the intracellular signaling pathways responsible for the expression of their effects. Many of these neurotransmitters produce their effects by affecting the intracellular levels of cyclic nucleotides. However, only recently have the thermoregulatory role of the cyclic nucleotides, cyclic 3',5'-adenosine monophosphate (cAMP) and cyclic 3',5'-guanosine monophosphate (cGMP), begun to be clarified. This review considers the recent advances in defining the role of preoptic cAMP and cGMP signaling cascades in fever and anapyrexia.

3. MOLECULAR ASPECTS OF cAMP- AND cGMP-DEPENDENT SIGNALING

Signal transduction involving cAMP starts when a neurotransmitter or neuromodulator binds to a surface receptor that is coupled via a G protein to the membrane-bound enzyme adenylate cyclase (AC). Depending on the subtype of G protein involved, AC may be either activated (in the case of a stimulatory G protein, G_s) or inhibited (in the case of an inhibitory G protein, G_i). Once AC is activated by G_s, it catalyzes the conversion of ATP to cAMP. The resulting cAMP acts as a second messenger, *i.e.*, it conveys the neurotransmitter signal to its intracellular targets. Many effects of cAMP are mediated by activation of protein kinase A (PKA). By phosphorylating serine/threonine residues of enzymes, ion channels, and/or transcription factors, PKA may affect several cellular processes, including electrical activity, neurotransmitter release, metabolism, and contractility. When AC is inactivated by a G_i, the whole signaling cascade is inhibited, opposing the cellular effects triggered by G_s-induced activation of AC (for review, see Refs. 25-26).

Unlike cAMP, the synthesis of cGMP is independent of G protein-coupled receptors. Guanylate cyclase (GC) is the enzyme that catalyses the conversion of GTP to cGMP. It exists in two major forms, one of them is dissolved in the cytosol [soluble GC (sGC)] and the other is attached to the plasma membrane [particulate GC (pGC)]. Nitric oxide (NO) is the main activator of sGC. Due to its lipophilicity, NO easily diffuses across cell membranes of nearby cells to reach its intracellular target. Natriuretic peptides are the main activators of pGC. In fact, pGC activity exists in the natriuretic peptide receptors themselves when the ligand is present. By activating a serine/threonine kinase named protein kinase G (PKG), cGMP produces most of its cellular effects (for review, see Refs. 27-28).

In both cAMP- and cGMP-dependent cascades, phosphodiesterases catalyze the hydrolysis of cAMP and cGMP to their inactive metabolites, 5'-AMP and 5'-GMP, respectively. At present, phosphodiesterases have been classified into 11 different families based on their substrate, inhibitor profile, and structural characteristics. Some of these enzymes display preference for hydrolysing cAMP (*e.g.*, phosphodiesterase-4), others for cGMP (*e.g.*, phosphodiesterase-5), and others for both nucleotides (*e.g.*, phosphodiesterase-11). These enzymes are not only important for signaling termination, but also may have a broader role in promoting cyclic nucleotide signaling (for review, see Refs. 29-30). For example, a dramatic decrease in the content of cGMP in the retina caused by activation of phosphodiesterase-6 is associated with light perception (31).

The basic steps of cAMP and cGMP signaling cascades are schematically presented in Figure 1. Although

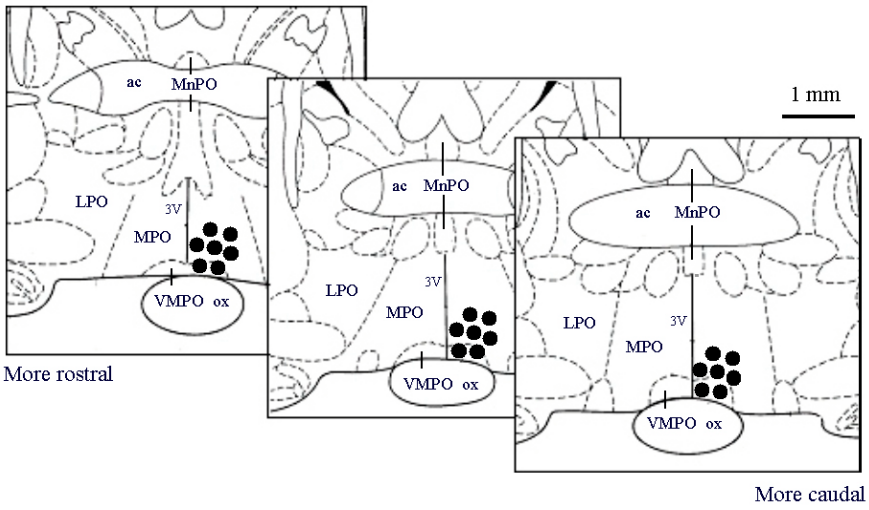

Figure 2. Serial diagrams of coronal sections of the rat brain containing the anteroventral preoptic region (AVPO). The region occupied by the filled circles corresponds to the AVPO. Abbreviations: MPO, medial preoptic region; LPO, lateral preoptic region; VMPO, ventromedial preoptic region; MnPO, median preoptic nucleus; ac, anterior commissure; 3V, third ventricle; ox, optic chiasm. Adapted with permission from Ref. 87.

numerous interactions between these signaling pathways have already been described, they are not included in this schema. When appropriate, they will be mentioned during the discussion of the role of preoptic cyclic nucleotides in fever and anapyrexia.

4. THERMOREGULATORY EFFECTS OF EXOGENOUS cAMP AND cGMP IN THE PO

The thermoregulatory effects of exogenously administered cAMP and cGMP have been determined by using membrane-permeable, phosphodiesterase hydrolysis-resistant cyclic nucleotide analogs that, like cAMP and cGMP, activate PKA and PKG, respectively. These agents have been named cyclic nucleotide agonists (32).

The first studies (33-34) suggesting that cyclic nucleotides have a thermoregulatory effect published in the 1970s found that microinjections of cAMP agonists into the PO increased T_c. In 1984, these studies were contested when Dascombe (35) showed that intra-PO cAMP and cGMP agonists produce a brief transient decrease followed by a prolonged increase in the T_c of rabbits. Interestingly, the late increase, but not the early decrease in T_c, was abolished by treatment with the nonsteroidal anti-inflammatory drug, acetaminophen. The finding suggested that the previously reported increase in T_c in response to intra-PO cyclic nucleotide agonists may have resulted from a local inflammatory reaction, probably produced by the microinjection procedure. Accordingly, microinjection-induced tissue injury and consequent inflammation in the PO have been shown to increase the T_c of rats (36-37), cats (38), guinea pigs (39), and rabbits (35). Because cAMP may enhance the production of some inflammatory mediators with a febrigenic property, *e.g.*, PGE_2 (40), it also may potentiate the microinjection-induced increase in T_c. This effect is, however, only an experimental artifact.

To minimize the microinjection-induced increase in T_c, recent studies (41-42) have performed intra-PO microinjections in a small volume (100 nl). It was observed that activation of cAMP-PKA and cGMP-PKG signaling pathways by intra-PO microinjection of the cyclic nucleotide agonists, dibutyryl-cAMP and 8-Br-cGMP, actually reduces the T_c of rats. Consistent with this finding, cAMP agonists, like many anapyrexia-inducing agents, increase the firing rate of warm-sensitive preoptic neurons (14, 43). This is not a nonselective effect of cAMP in neurons because cAMP agonists may even reduce the firing rate of other neuronal populations, such as neostriatal neurons (44). The use of small-volume microinjections also allowed the identification of the anteroventral PO (AVPO) as the preoptic site most sensitive to the thermoregulatory effects of cyclic nucleotides (41-42). Furthermore, the AVPO is the site of the PO that contains the highest density of cAMP- and cGMP-producing cells (13). The AVPO is constituted by the ventromedial PO and part of the surrounding medial PO (Figure 2), brain regions that are known for their major role in fever (45-47) and anapyrexia (13).

5. ROLE OF PREOPTIC cAMP AND cGMP IN FEVER

Not only did the early studies on the thermoregulatory role of cyclic nucleotides suggest that cAMP agonists increase T_c, but they also hypothesized that preoptic cAMP mediates fever. The following results were used to support this hypothesis: 1) the levels of cAMP are increased in the cerebrospinal fluid of rabbits during fevers of diverse etiology (33, 48-51), and 2) intra-hypothalamic administration of a *Bacillus thuringiensis* exotoxin with an AC-inhibiting property attenuates PGE_1-induced fever (34). Given the more recent finding that preoptic cAMP actually reduces T_c, this hypothesis had to be rejected, and

alternative interpretations were suggested. First, the level of cAMP in the cerebrospinal fluid may not reflect that in the PO. Second, that the *Bacillus thuringiensis* exotoxin was not restrictedly delivered to the PO raises the possibility that it attenuated fever by inhibiting cAMP production in other hypothalamic regions. For example, an increased level of cAMP in the paraventricular nucleus seems to be associated with LPS-evoked events (52).

To verify whether the level of cAMP in the PO is changed in the course of fever, a recent study (41) determined the content of cAMP in the anteroventral third ventricular region (AV3V) of rats. Besides including the PO, the dissected AV3V also included another structure possibly involved in the febrile response, *i.e.*, the *organum vasculosum laminae terminalis* (OVLT). Albeit inclusion of the OVLT may represent a limitation for these experiments, it also may have the advantage of ensuring the presence of the AVPO, which surrounds the OVLT, in the AV3V samples. By using this approach, no change in the content of cAMP was observed after intraperitoneal LPS, either before (1 h postinjection) or after (4 h postinjection) the onset of fever (41). Another study similarly reported that the content of cAMP in the PO did not change during yeast-induced fever in rats (37). These results would a priori rule out the involvement of preoptic cAMP in fever. However, considering that a cascade of events occurs upstream from PGE_2 [the proximal mediator of fever (53)] in the PO during systemic inflammation, this assumption may be premature. Different patterns of changes in cAMP levels could occur in distinct neuronal groups driven by different neurotransmitters, even though the overall content of cAMP in the AV3V is unaffected. For example, by raising cAMP in first-order neurons (54-56), norepinephrine might increase the production and release of PGE_2 (40,57), which, in turn, could reduce the level of cAMP in second-order neurons to produce fever.

Regardless of whether cAMP mediates and/or modulates the cellular events upstream from PGE_2, intracerebroventricular PGE_2-induced fever is accompanied by a decrease in the level of cAMP in the AV3V (41). Demonstrating the physiological relevance of this response is the observation that intracerebroventricular aminophylline, which enhances the intracellular content of cAMP by inhibiting phosphodiesterase activity, attenuates PGE_2 fever (41). Although aminophylline also acts as an antagonist of adenosine receptors (58), this action is unlikely to have accounted for the attenuation of PGE_2 fever because adenosine has no febrigenic property in the brain. In fact, intracerebroventricular adenosine evokes pronounced decreases in T_c (59-60). That PGE_2 produces fever by reducing the level of cAMP in the PO is consistent with the idea that fever is mediated by the prostaglandin EP3 receptor (61). This receptor couples preferentially via G_i to AC and exerts most of its physiological effects by reducing the intracellular level of cAMP (62-63), even though some of its splicing variants may be positively coupled to AC via G_s (64-65). Indeed, the soma of neurons expressing the EP3 receptor are found in the medial PO (66-68), one of the most sensitive sites to the thermal effects of PGE_2 (45,47) and cAMP (13,41). These neurons project to thermogenesis-controlling sites in the brain stem (47). Fever production also may depend on the EP1 receptor for PGE_2 (69-70), activation of which affects inositol triphosphate turnover and calcium mobilization (63). Interestingly, some studies have shown that extracellular calcium in the brain is involved in thermoregulation (71-73), but the thermoregulatory role of calcium-dependent signaling pathways in the PO remains unknown.

Although preoptic cAMP seems to be involved in fever, its isolated action is unlikely to affect T_c. Corroborating this idea is the finding that treatments that selectively increase or decrease the level of cAMP within the physiological range produce no thermal effect (13,34,41,74-76). Therefore, it has been proposed that the thermoregulatory effect of preoptic cAMP depends on the presence of a synergistic agent. A putative candidate is cGMP. In support, a synergistic action of cAMP and cGMP has already been reported for other physiological processes, *e.g.*, calcium mobilization (77) and relaxation (78) in smooth muscle cells. The synergistic action of cAMP and cGMP in fever has been shown by using Rp-adenosine-3',5'-monophosphorothionate (Rp-cAMPS) and Rp-guanosine-3',5'-monophosphorothionate (Rp-cGMPS), which are inhibitors of PKA and PKG, respectively, and have been named cAMP and cGMP antagonists (32,79). Their co-administration into the PO, mimicking a simultaneous inactivation of cAMP-PKA and cGMP-PKG signaling cascades, produces an increase (~1ºC) in T_c. When administered separately, these same agents produce no thermal effect (41).

It was then hypothesized that a decreased level of cGMP in the PO contributes to the genesis of LPS fever. That intraperitoneal LPS-induced fever in rats is accompanied by a reduction in the level of cGMP in the AV3V supports this hypothesis (42). This drop in the level of cGMP is likely to result from a diminished production of NO [a potent activator of cGMP synthesis (27,80-81)] because the levels of the NO metabolites, nitrite and nitrate, in the AV3V parallel those of cGMP in the course of LPS fever (42). The constitutive, calcium-dependent isoforms of NO synthase (NOS) are highly expressed in the PO (82-83), and a reduction of their activity can easily account for the diminished NO production. There is a misconception that LPS-treated animals present a systemic overexpression of the inducible NOS isoform, which produces high amounts of NO. In reality, low to moderate febrigenic doses of LPS cause no expression of inducible NOS in the PO (84). They may even inhibit NO production at a systemic level (85). Only high doses of LPS, which evoke septic shock and anapyrexia (5), have consistently caused the overexpression of inducible NOS in both peripheral tissues and brain (86).

Directly showing that an inactivation of the NO-cGMP pathway in the PO contributes to the genesis of LPS fever is the finding that intra-PO N^G-monomethyl-L-arginine (L-NMMA; a NOS inhibitor) reduces the latency to the onset of LPS fever in unanesthetized rats (42). A similar effect is produced by intra-PO methylene blue, a

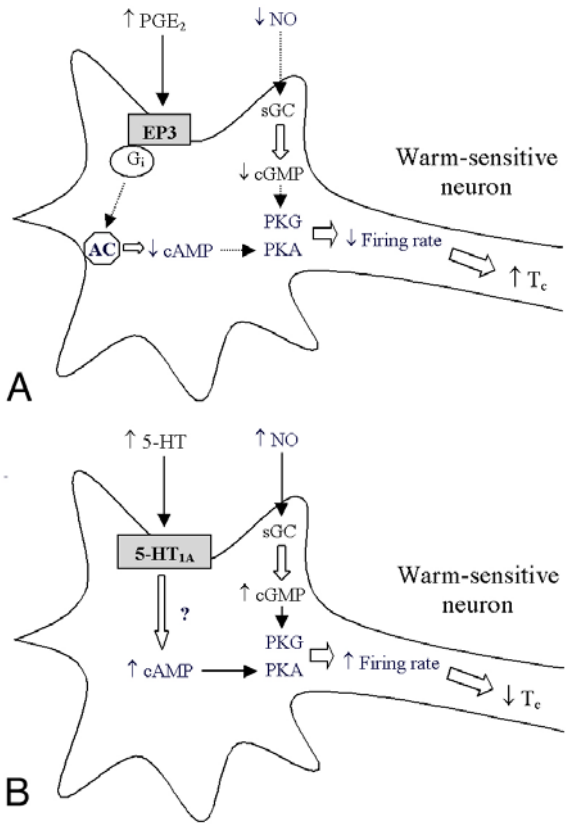

Figure 3. Possible intracellular events that occur in the preoptic region to produce fever (panel A) or anapyrexia (panel B). See text for explanation. Abbreviations: PGE_2, prostaglandin E_2; EP3, EP3 receptor; G_i, inhibitory G protein; AC, adenylate cyclase; 5-HT, 5-hydroxytryptamine (serotonin); 5-HT_{1A}, 5-HT_{1A} receptor; NO, nitric oxide; sGC, soluble guanylate cyclase; cAMP, cyclic 3',5'-adenosine monophosphate; cGMP; cyclic 3',5'-guanosine monophosphate; PKA, protein kinase A; PKG, protein kinase G; T_c, body core temperature. Arrows: ↑, increase in; ↓, decrease in; ⟶, activates; ⇢, inhibits; ⇨, causes. ?, unknown mechanism. Adapted with permission from Refs. 13 and 34.

drug that reduces cGMP production by inhibiting not only NOS, but also sGC (87). In contrast, Amir *et al.* (88) have reported that intra-PO L-NMMA attenuates PGE_2 fever in anesthetized rats. However, this result may be unrelated to a thermoregulatory effect of cGMP. Because L-NMMA and PGE_2 were co-injected into the PO, L-NMMA-induced vasoconstriction (81) could have limited the diffusion of PGE_2, resulting in an attenuated fever. Additionally, that thermoregulation is disrupted during anesthesia (89) also may have contributed to this conflicting result.

Albeit not in a model of fever, the interplay between PGE_2-cAMP and NO-cGMP pathways has been shown experimentally. The phosphorylation of a serine by PKA enhances the activity of NOS in vessels (90). If the same occurs in the PO, PGE_2-induced inhibition of the cAMP-PKA signaling cascade might contribute to the inactivation of the NO-cGMP pathway. NO also might affect the production of PGE_2. Because free NO seems to inhibit cyclooxygenase (91), an enzyme involved in PGE_2 biosynthesis, diminished levels of NO may have a permissive role on the production of PGE_2.

Based on the reviewed data, the following neurochemical model (Figure 3A) has been proposed for the genesis of fever. 1) Administration of exogenous pyrogens, by means of several steps, leads to an increased level of PGE_2 in the PO (53). 2) PGE_2, possibly through the interaction with EP3 G_i-coupled receptors that inhibit AC (62-63), reduces the intracellular level of cAMP and consequently the activity of PKA (41). Such mechanism seems to be an important intracellular event to trigger fever (41). 3) We speculate that inactivation of the cAMP-PKA pathway evokes fever by diminishing the firing rate of warm-sensitive preoptic neurons. The reason for this speculation is twofold. First, because activation of the cAMP-PKA pathway by cAMP agonists increases the firing rate of warm-sensitive preoptic neurons (14,43), it is conceivable that inactivation of the same pathway produces the opposite effect. Second, inhibition of the firing rate of warm-sensitive preoptic neurons is associated with the development of fever (11,14-20). 4) In parallel, exogenous pyrogens lead to an inactivation of the NO-sGC-cGMP-PKG pathway in the PO (42). This mechanism contributes to the genesis of fever (42). Although there is evidence that cAMP affects the firing rate of warm-sensitive neurons (14,43), the effect of cGMP on the neuronal activity in the PO remains unknown. However, for the sake of simplicity, Figure 3A shows cGMP affecting the firing rate of warm-sensitive preoptic neurons. 5) The simultaneous inactivation of cAMP and cGMP signaling cascades acts synergistically to produce fever (41).

6. ROLE OF PREOPTIC cAMP AND cGMP IN ANAPYREXIA

To date, the role of preoptic cAMP and cGMP signaling cascades has only been studied in the anapyrexia induced by hypoxia (13). However, the likeness between the thermoregulatory responses to hypoxia and to a high dose of LPS suggests that they may have similar mechanisms. Both hypoxia- and LPS-induced anapyrexia are brought about by inhibition of thermogenesis in concert with a cold-seeking behavior (5,92). In addition, because circulatory shock precedes the T_c decline in rats treated with a high dose of LPS (5), it is tempting to propose that LPS-induced anapyrexia occurs in response to circulatory hypoxia. Indeed, hypoxia increases the plasma levels of tumor necrosis factor-alpha (93), an established mediator of LPS-induced anapyrexia (94).

It has been hypothesized that anapyrexia is mediated by a simultaneous increase in the levels of cAMP and cGMP in the PO. In support of this hypothesis, hypoxia-induced anapyrexia is accompanied by an increase in the levels of both cAMP and cGMP in the AV3V, and is attenuated by intra-PO cAMP and cGMP antagonists (13). Importantly, cAMP and cGMP may act synergistically to produce anapyrexia, as evidenced by the observation that intra-PO 8-Br-cGMP (a cGMP agonist), at a dose that does

Table 1. Effects of some neurotransmitters on body temperature and on the levels of cAMP and cGMP

NEUROTRANSMITTER	BODY TEMPERATURE			CYCLIC AMP			CYCLIC GMP		
	Effect	**Receptor**	**Ref.**	**Effect**	**Receptor**	**Ref.**	**Effect**	**Receptor**	**Ref.**
Adenosine	↓	A_1	59,60	↓	A_1	102	↑	A_1	103
	↓	A_{2A}	59,60	↑	A_{2A}	102			
Dopamine	↓	D_1	104	↑	D_1	106	↑	D_1	108
	↓	D_3	105	↑ / ↓	D_3	107			
Endogenous Opioids	↑	μ	109	↑ / ↓	μ	110	↑ / ↓	?	111
	↓	δ, κ	109	↑ / ↓	δ, κ	110			
Histamine	↓	H_1	112	↑	H_2	113	↑	H_1	114
	↓	H_2	112						
MIP-1	↑	?	115	↓	CCR5	116	?	?	–
Prostaglandin D_2	↓	?	117	↑	DP	118	↑	?	119

MIP-1; macrophage inflammatory protein-1; ↑, increase; ↓, decrease; ↑ / ↓, increase or decrease; ?, unknown; Ref., reference; –, no study.

not affect T_c by itself, prolongs the decrease in T_c evoked by intra-PO microinjection of the cAMP agonist, dibutyryl-cAMP (41).

Consistent with propranolol preventing the enhanced production of cAMP in anoxic rats (95-96), its intra-PO administration attenuates hypoxia-induced anapyrexia (13). Because propranolol is a mixed beta-adrenergic and 5-HT_{1A}-serotonergic antagonist (97), this result indicates that either a catecholamine- or a serotonin-cAMP pathway is involved in the genesis of anapyrexia. The involvement of a catecholamine-cAMP pathway is unlikely because the drop in T_c evoked by intra-PO epinephrine is not blocked by the cAMP antagonist, Rp-cAMPS (13). In contrast, the involvement of a serotonin-cAMP pathway is confirmed by the finding that Rp-cAMPS completely abolishes the reduction in T_c produced by intra-PO serotonin (13). In agreement, it has been reported that activation of the 5-HT_{1A} receptor increases cAMP formation in rat hippocampal neurons, even though the transduction mechanism remains uncertain (98). Activation of this receptor also causes dose-dependent decreases in the T_c of several species, including humans (99). As for cGMP, its increased production seems to be driven by NO for the following three reasons: 1) hypoxic rats present an increased production of NO in several brain regions, including the hypothalamus (100); 2) the attenuation of hypoxia-induced anapyrexia caused by intra-PO L-NMMA (a NOS inhibitor) is similar to that produced by the cGMP antagonist, Rp-cGMPS (13); and 3) the drop in T_c evoked by intra-PO sodium nitroprusside (a NO donor) is abolished by Rp-cGMPS (13).

Based on the reviewed data, the following neurochemical model (Figure 3B) has been proposed for the genesis of anapyrexia. 1) Hypoxia (and perhaps other anapyrexia-inducing stimuli) increases the levels of serotonin in the PO (101). 2) By acting probably on the 5-HT_{1A} receptor, serotonin enhances the production of cAMP (13,98), which, in turn, activates PKA. 3) The increased activity of the cAMP-PKA pathway is a key mechanism to produce anapyrexia (13). 4) This mechanism is known to enhance the firing rate of warm-sensitive preoptic neurons (14,43), a response that is associated with the occurrence of anapyrexia (21-24). 4) In parallel, activation of the NO-sGC-cGMP-PKG cascade in the PO contributes to decrease T_c (13), but the effect of cGMP on the neuronal activity in the PO remains unknown. For simplicity, however, Figure 3B shows cGMP affecting the firing rate of warm-sensitive neurons. 5) The simultaneous activation of cAMP and cGMP signaling cascades acts synergistically to produce anapyrexia (13,41).

7. CONCLUDING REMARKS AND PERSPECTIVES

In the 1970s and 1980s, the first studies aiming at understanding the intracellular mechanisms involved in thermoregulation were performed, but the results obtained were controversial. More recently, the use of more precise microinjection, electrophysiological, and analytical techniques and the availability of an arsenal of well-characterized pharmacological tools have improved the understanding of such mechanisms. The accumulated data indicate that cAMP and cGMP in the PO play a major role in thermoregulation: their reduced levels mediate fever; their increased levels mediate anapyrexia. We believe that these cyclic nucleotide signaling cascades are not only involved in the thermal effects of PGE_2, serotonin, and NO but are likely to be a common final thermoregulatory pathway. Accordingly, like PGE_2, cold exposure increases heat production, decreases heat loss, triggers a warm-seeking behavior, and diminishes cAMP production in the PO (95). Moreover, because activation of their receptors either increases or decreases the levels of cAMP and/or cGMP, it is conceivable that several other neurotransmitters exert their thermoregulatory effects in the PO by cyclic nucleotide-dependent pathways (Table 1).

Although it seems clear that cAMP and cGMP play an important role in thermoregulation, which thermoeffector neuronal pathways are controlled by the action of these intracellular messengers in the PO are unknown. Contrary to the concept of a single thermoregulatory set point, which has been widely accepted for many years, it is now known that thermoeffector mechanisms are under the influence of multiple controllers (120-121). As a result, they may be affected independently of each other. Consistent with this notion is the finding that

distinct neurons project from the PO to independent neuronal circuits, each responsible for the control of a specific thermoeffector (12). Future studies are needed to embrace cAMP and cGMP in this new scenario. The interaction of preoptic cAMP and cGMP signaling cascades with other signaling pathways in the mediation of fever and anapyrexia is also an interesting topic for future studies. Indeed, a cross talk between cyclic nucleotide and calcium signaling cascades is known to play a major role in the control of smooth muscle contraction (122). This topic becomes particularly interesting considering the studies showing the involvement of hypothalamic calcium in thermoregulation (71-73).

8. ACKNOWLEDGMENTS

We thank Dr. S. A. Kick and Ms. M. Milovancevic for editorial assistance. The authors' research reviewed in this paper was supported by grants (L.G.S. Branco) from "Fundacao de Amparo a Pesquisa do Estado de Sao Paulo" (FAPESP, Brazil), "Conselho Nacional de Desenvolvimento Cientifico e Tecnologico" (CNPq, Brazil), and "Programa Nacional de Desenvolvimento de Nucleos de Excelencia" (PRONEX, Brazil).

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Key Words: Body temperature, thermoregulation, hypothermia, lipopolysaccharide, LPS, hypoxia, preoptic region, cyclic nucleotides, cAMP, cGMP, Review

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