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CHOLECYSTOKININ: POSSIBLE MEDIATOR OF FEVER AND HYPOTHERMIA

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1. ABSTRACT

Thermoregulatory effects of cholecystokinin (CCK) peptides are reviewed with special emphasis on two types of responses, that is hyperthermia (fever) and hypothermia. Central microinjection of CCK in rats induces a thermogenic response that can be attenuated by CCK-B receptor antagonists, but some authors observed a hypothermia. By contrast to its central fever-inducing effect, in rodents exposed to cold CCK-8 elicits a dose-dependent hypothermia on peripheral injection probably acting on CCK-A receptors. It is suggested that neuronal CCK may have a specific role in the development of hyperthermia, and endogenous CCK-ergic mechanisms could contribute to the mediation of fever. The possible role of CCK-ergic mediation in endotoxin (LPS) fever has revealed that while CCK-B receptors seem to be involved in the development of fever, the role of CCK-A receptors could be more complex. In particular, while rats lacking functional CCK-A receptors show an exaggerated fever response, this phenomenon may be associated with a trait different from the absence of this receptor set. The relationship between the putative CCK-ergic febrile mechanism and the established central PGE mediation needs further study.

2. INTRODUCTION

Since the advent of the neuropeptide concept, there have been attempts to identify one or more regulatory peptides in the CNS playing roles as mediators or modulators in various autonomic functions. The first candidate peptides for such central regulatory roles were those having a distribution in CNS areas earlier shown to be important in the regulation of autonomic functions such as food and water intake, sleep, and thermoregulation, just to mention a few. Another criterion for ascribing a physiological role for any peptide has been its ability to be released on adequate functional stimuli, to imitate the purported response by external administration of that peptide under in vivo conditions and, more importantly, after application of specific antagonists of the putative peptide or of its receptor(s) the specific response observed on its administration should be reduced or abolished. In the latter case the evidence gained could speak for the role of an endogenous mechanism, thus supporting the existence of a physiological role for the substance in question.

One of the first hormones discovered, cholecystokinin (CCK) has been among the peptides originally found in the gastrointestinal tract but later shown to be present also in the CNS and up to now has proved to be the most abundant regulatory peptide there (1). In particular, a strong representation of CCK octapeptide (CCK-8) (2) and its binding sites (3) in the hypothalamus may indicate that hypothalamic regulatory functions connected to energetics such as food intake, metabolic rate or thermoregulation could be related to a modifying action, or even to a more significant regulatory role of that peptide. The first aspect of CCK's role in regulation of energetics has been its satiety inducing property (4) studied and confirmed in a number of species. Satiety role of neuronal CCK has been mainly inferred from studies applying peripheral injections supposing that the peptide could cross the blood-brain-barrier (BBB) to reach concentrations in the CNS neuropile needed for an action there or acting on CNS mechanisms via afferent nervous pathways such as the vagus. A neural afferent mechanism has indeed been found which under natural conditions could convey afferent signals induced by mechanical, chemical or other stimuli as local consequences of food ingestion in the gastrointestinal tract. In addition, central administration of CCK peptides reproduced the peripheral satiety inducing effects (5), so that complex peripheral and central sites of action could be envisaged.

A possible thermoregulatory role of this peptide has been inferred from studies in which a dose-dependent decrease in body core temperature was observed after its peripheral administration in rats exposed to cold ambient

Table 1. Changes of body core temperature induced by administration of CCK peptides (CCK-8S when not otherwise stated)

Species	Route of adm.	Dose (μg)	Temperatures (°C) Ambient	Core	Skin	MR	Remarks	Reference
Rat	icv	0.1-0.25	-	↓	-	-	CCK-8N had no effect	31
	icv	0.02-0.12	-	↓	-	-		28
	ihypoth	0.02-0.06	-	↓	↑	↓		32
	ihypoth	0.02-0.06	8-22	↓	↑	↓		45
	icv inf	0.06/hour	-	↑	-	-	for 5 days	12
	icv	10.0	18-28	↑	-	-	CCK-4, CC-8N had no effect	18
	icv	0.5	24-26	↑	↓	↑	LPS fever atten by B-antag	15
	icv	0.05-1.0	18-30	↑	↓	↑	Atten by B-antag only	14
	icv	0.06-0.1	24-26	↑	↓	↑	Ceruletide	14
	icv	0.02-0.9	21	↑	-	-		16
	icv	0.3	20	↑	-	-		17
	icv	1.6	24	↑	-	-		19
	icv inf	0.1-1.0/hour	26-28	↑	-	-	for 3 to 7 days, redu activity	*
	icv inf	1.0/hour	4-5	↑	-	-	for 7 days, „	*
	iv inf	18.0-50.0/hour	29.5	↓	↑	-	for 2 hours	24
	ip	4-50/kg	21	↓	-	-		6
	ip	5-50/kg	21	↓	-	-		7
	ip	4/kg	-	↓	-	-		54
	ip	100/kg	18	↓	-	↓	atten by A-antag only	14
	ip	10-250/kg	21	0	-	-	CCK-4, CCK-8N inject	44
	ip	100-150/kg	22	↓	-	-	LPS fever not atten by A-antag	23
	sc	50-250/kg	-	↓	-	-		39
Mouse	sc	36-210/kg	-	↓	-	-		33
Chick	icv	0.05	-	↑	-	-		10
	icv	0.1-0.2	-	↓	-	-		10
Guinea pig	icv	10-100	-	↑	-	-		9
Dog	icv	0.15	-	↑	-	-		11

* (Unpublished data of Z Szelényi, Z Hummel, M Székely, E Pétervári) Abbreviations and symbols: adm: administration, MR: metabolic rate, icv: intracerebroventricular, ihypoth: intrahypothalamic, iv: intravenous, ip: intraperitonal, sc: subcutaneous, inject: injected, inf: infusion, atten: attenuated, redu: reduced, antag: CCK receptor antagonist, CCK-8N: non-sulfated CCK-8, CCK-8S: sulfated CCK-8, -: not known or measured, ↑: increase, ↓: decrease, 0: no change

temperature (6,7). Thermoregulatory effect of CCK peptides proved to be indeed hypothermic when applied peripherally in a number of species (for details see Table 1). For the proper analysis of changes in body temperature induced by any substance thought to be involved in CNS control, the Koch's postulate-like criteria should be applied (8). Accordingly, a dose-dependent change in body temperature alone may not be sufficient to ascribe a specific thermoregulatory role to an endogenously produced substance on its exogenous administration, unless some additional criteria (such as demonstration of appropriate thermoregulatory response, and reduction of the response by blockers of production/effect of the putative mediator) are also fulfilled. In the following discussion an attempt is made to interpret various thermoregulatory responses observed in homeothermic species after application of CCK peptides.

3. FEVER

With the exception of the hyperthermia reported in guinea-pigs after central injection of 10 to 100 μg of CCK-8 (9), several orders of magnitude higher dose than those used for intracerebroventricular (icv) or hypothalamic injections by other authors, initially there were only sporadic data on a hyperthermic response to CCK in experiments on chicks (10) and dogs (11). This may have indicated a genuine species difference, still chronic icv infusion of CCK-8 in rats also tended to result in a slight hyperthermia, although the small number of experiments did not allow a definite conclusion (12). In experiments carried out on slightly restrained conscious female rats exposed to thermally controlled environments, CCK-8 was injected icv while core temperature, metabolic rate and tail-skin temperature were monitored (13,14). When injected icv into rats exposed to slightly cold to moderately warm ambient temperatures, CCK-8 induced a short-latency rise in core temperature accompanied by skin vasoconstriction when there was an initial vasodilatation or by a rise in heat production when there was an initial vasoconstriction (Figure 1). A similar injection of the CCK-derivative, ceruletide, induced a qualitatively similar coordinated hyperthermic response when given at doses corresponding to those applied for CCK-injections. In other words, a coordinated hyperthermia (i.e. fever-response) was observed in rats exposed to cool, thermoneutral or slightly warm ambient temperatures. The size of hyperthermic response was dose-dependent between 50 and 1000 ng

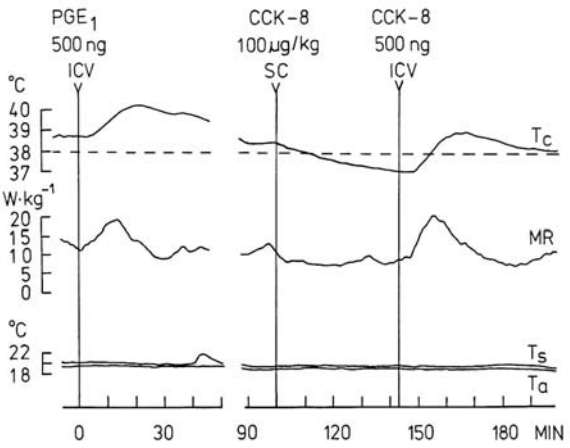

Figure 1. Thermogenic and hyperthermic effects of PGE1 or CCK-8 – both injected intracerebroventricularly (icv) – and hypothermic effect of subcutaneously (sc) injected CCK-8, the latter alteration in core temperature (Tc) being accompanied by a partial inhibition of metabolic rate (MR). Note that at the cool ambient temperature (Ta) of 19 oC tail skin temperature (Ts) of the rat remained low throughout, indicating vasoconstriction (Reprinted from ref 14, Figure 5., with permission from Elsevier).

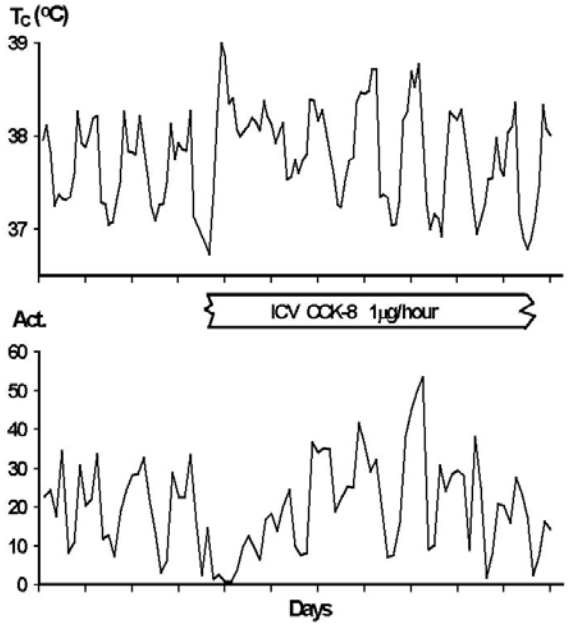

Figure 2. Effects of 7-day-long intracerebroventricular (icv) infusion of CCK-8 (1 μg per hour) on abdominal core temperature (Tc) and general activity (Act, in arbitrary units) in a freely-moving Wistar rat. Ambient temperature: 27-29 oC, 12 hours light/darkness schedule. Note that CCK-8 induced a slight rise in night maxima and greater rises of day minima of circadian Tb. These effect lasted for 4-5 days of infusion. Conversely, general activity, especially its night maxima decreased, with a gradual return of both parameters to pre-infusion values by the 6th day of infusion (from unpublished experiments of Z Szelényi, Z Hummel, M Székely, E Pétervári).

CCK-8 per rat. Moreover, icv injection of the established centrally acting pyrogen, prostaglandin E_1 (PGE_1) in a dose of 100 to 500 ng induced again a coordinated fever-response, which was even more expressed than that observed after administration of CCK-8 or ceruletide. The fever induced by either mediator was over within one hour of injection (Figure 1). These results seem to be compatible with the idea that central CCK-8 induced a fever-like response, although the initial evidence for that was insufficient.

The CCK-8-induced hyperthermia was attenuated by the CCK-B receptor (central receptor) antagonist L-365,260 but not by injection of the CCK-A receptor (peripheral receptor) antagonist L-364,718 (devazepide). Conversely, the CCK-A receptor antagonist significantly reduced the hypothermic response to peripheral injection of CCK-8 but failed to influence CCK-8-induced hyperthermia observed after icv injection of the peptide. The fever induced by PGE_1 in the same rats could not be influenced by pretreatment with the CCK-B receptor antagonist (14). Conversely, fever induced by icv injection of CCK-8 could not be influenced by pretreatment with the cyclooxygenase inhibitor, indomethacin in the same species (15). Hyperthermic effect of icv injected CCK-8 was supported in rat experiments carried out under various experimental conditions (16,17,18,19). More specifically, in male rats icv-administered CCK-8 induced hyperthermia accompanied by tail-skin vasoconstriction (19) and in male unrestrained rats a short-latency rise in brain temperature was observed together with a rise in metabolic rate (16). The threshold dose of icv-injected CCK-8 to induce hyperthermia was 20 ng, that is, in the same range as in earlier studies (14). In a more recent biotelemetric study carried out in unrestrained female rats, CCK-8 was infused icv for several days to see if – in addition to the expected rise in body core temperature – general activity, a behavioral parameter, could change in a way corresponding to fever. In fact, according to the expectations, an icv infusion of CCK-8 induced a rise in body core temperature during the day and with higher doses even night maxima were increased (unpublished from Z Szelényi, Z Hummel, M Székely, E Pétervári). Since along with rises of body temperature there was a reduction of general activity rather than a rise that could be expected if the peptide caused hyperthermia (Figure 2), it can be concluded that this increase in body temperature could have been a fever, in which according to the paradigm of ”sickness behavior” (20) inactivity could even indicate anorexia. In rodents there is a close parallel between consummatory behavior and general activity (21,22), so that the observed decrease in activity is at least not at variance with the phenomenology of fever. The temporary nature of increased core temperature and decreased activity while CCK-infusion was still on awaits an explanation.

The coordinated nature of CCK-induced hyperthermia (i.e. rise in metabolic rate together with tail-skin vasoconstriction) and the close similarity of this central hyperthermia to fever induced by icv injection of PGE_1 already made it plausible that this could be regarded as fever. The fever-like nature of icv CCK-induced

hyperthermia was further supported by the finding that it could only be attenuated by CCK-B receptor antagonist and not by the CCK-A receptor antagonist used (14). In another rat experiment the possibility was tested whether the generally used fever model, endotoxin (lipopolysaccharide, LPS)-fever could be influenced by CCK receptor antagonists. Pretreatment with the CCK-B receptor antagonist L-365,260 given either icv or intraperitoneally to rats, attenuated endotoxin LPS fever (15), while CCK-A receptor antagonist devazepide failed to influence fever (M Székely, M Balaskó & Z Szelényi, unpublished data). In another study it was shown that not only LPS fever but also interleukin-1 (IL-1)-induced fever was resistant to CCK-A receptor antagonism in the same species (23).

More recently the role of CCK-A receptor in fever genesis was analyzed using the CCK-A receptor deficient OLETF rat strain (24). Intravenous injection of LPS in normal rats induces a three-phasic fever, the first two of which remained intact in OLETF rats indicating that CCK-A receptors are not essential to these fever phases. Moreover, the third phase of LPS fever proved to be more robust in CCK-A receptor-deficient rats than in their normal counterparts. That late part of fever, however, could not be influenced by pharmacological manipulations of CCK-A receptor function in normal rats, which makes it highly likely that in OLETF rats a trait not directly related to the deficiency of CCK-A receptor could be behind this phenomenon. In fact neither CCK-fever (13,14), nor several behavioral aspects of fever (e.g. anorexia, or decreased exploratory behavior) could be influenced by CCK-A receptor antagonists in rats (25,26,27). The possibility of a prostaglandinergic mediation of CCK-hyperthermia appears to be unlikely since the prostaglandin-synthesis inhibitor indomethacin failed to influence CCK-induced fever (15).

4. HYPOTHERMIA

The first study reporting on the hypothermic action of CCK was published in 1981 (28) in which the peptide was injected icv in rats. The decrease of body temperature on central administration of CCK was reproduced by others in experiments on rats and mice (for earlier review see (29,30), but interpretation of centrally (28,31) or peripherally (6,7) induced CCK-hypothermia is difficult if absolute values of body temperature are not indicated and there is no information on other aspects of thermoregulation, such as heat production or heat loss (6,7,28,31). In fact, a fall in body temperature may either be caused by a general depression of CNS function without specific relation to central body temperature control, by interruption of afferent or efferent nervous pathways, or by a decrease of regulated level of body temperature (converse situation to fever). There is only one study that showed dose-dependent hypothermia in rats after a central (intrahypothalamic) injection of CCK-8 while monitoring thermoregulatory effectors (32). These authors recorded a fall in metabolic rate together with tail-skin vasodilatation accompanying hypothermia, indicating a coordinated thermoregulatory response. The long latency of the thermoregulatory response (more than one hour) observed in this study is otherwise unusual after central (28) or peripheral action of CCK experienced in other studies (6,7). Mediation of the CCK effect has also been unspecified in these studies since no receptor antagonists for that peptide were used, but in one study a serotonergic mediation of centrally induced CCK-hypothermia was suggested (32).

Hypothermia induced by any substance, such as CCK, could be dose-dependent, thus a pharmacological relevance of the thermoregulatory effect seems plausible. Still its specificity for normal thermoregulation may be questioned unless on application of the putative mediator metabolic rate does not fall below its resting value. An alternative explanation for the CCK-induced hypothermia on peripheral injection could be a direct skin-vasodilatation caused by the peptide as well as a fall in blood pressure. In fact, it has been shown that doses of CCK-8 used by some authors (6,24,33) can induce skin-flushing and a shock-like state (34) leading to an increased heat loss and to an inhibition of heat production, respectively, without the need to invoke a coordinated CNS-mechanism subserving temperature regulation.

As for the hypothermia induced by peripherally injected CCK peptides, the question of BBB permeability has been raised. For a genuine central action the peptide should be able to cross the BBB, but the older data on the difficulty or even inability to do so (35) are corroborated by more recent studies showing that both BBB (36), and blood-CSF barrier (37) are fully functional for CCK-8 in rats. It may be relevant to note here that even the ability of peripherally infused CCK-8 to partally anatgonize LPS-induced fever in rats could find explanation in a local vasodilatatory action (24).

The possible mechanism of action of CCK peptides after their peripheral administration may be clarified by using antagonists acting more or less specifically on peripheral or central type receptors. Similar to the satiety effects of CCK (38), the hypothermic action of the peptide in mammals seems to depend on CCK-A (peripheral type) receptors, since administration of CCK-A receptor antagonists attenuated this hypothermia, while the CCK-B (central type) receptor antagonist was without effect on this response (13,14). This is confirmed and extended by more recent data, in that CCK-8-induced hypothermia could be attenuated by the CCK-A receptor antagonist MK-329, but not the CCK-B receptor antagonist L-365,260 in rats (39). As opposed to the difficulty of CCK peptides to cross BBB, the non-peptide receptor antagonists used in studies on thermoregulatory role of endogenous CCK peptides are able to penetrate the brain freely (40,41). This means that data obtained on the use of either centrally or peripherally applied CCK receptor antagonist may be relevant to the role of these receptors in autonomic functions such as central regulation of body temperature.

All studies cited above indicated that hypothermia induced by peripheral (e.g. intraperitoneal) application of CCK peptides is mediated by CCK-A receptors as is the case for the satiety effects mentioned before. Theoretically a nervous afferent mechanism, such

as the vagal afferentation shown to be an important way of influencing central regulation of food intake (42) could also be relevant to act on specific thermoregulatory sites. However, no thermally sensitive peripheral site (abdominal or other) is known so far that utilizes a CCK-ergic mechanism and may convey this information to the CNS. As for the necessity of CCK-A receptor mediation in any thermoregulatory function rats lacking CCK-A receptors, the OLETF rats do not appear to have any deficiency in body temperature regulation (24,43). On the contrary, as for their ability to develop fever after an LPS challenge, these rats seemed to be "supernormal", in that their fever was even more expressed than rats possessing CCK-A receptors (24), as discussed earlier. Peripheral (systemic) injection of CCK-B receptor agonists failed to induce any change in body temperature of rats probably as a result of the inability of these agonists (CCK-4 and non-sulfated CCK-8) to cross the BBB in amounts needed for the stimulation of centrally localized CCK-B receptors (45). The possible role of these receptors in fever has already been dicussed in the first part of this review.

To sum up, the foregoing discussion seems to indicate that the CCK-induced hypothermic response either may not represent a specific thermoregulatory response, or could be utilized under special conditions such as the satiety induced by peripheral or central CCK-ergic mechanisms and hence could be looked upon as a fail-safe mechanism saving energy as a result of lowered body temperature. For a summary of thermoregulatory changes observed on central or peripheral administration of CCK-peptides see Table 1.

5. CCK-PEPTIDES AND CNS FUNCTION

Thermoregulatory effects of CCK peptides should be discussed in the context of neuronal CCK-ergic mechanisms known to affect various aspects of autonomic regulation. The most direct early in vivo information on central effects of CCK in rats revealed a hypothermic effect which was supported by single unit studies from the same laboratory indicating that local application of CCK-8 excited most warm-responsive hypothalamic neurons and inhibited some cold-responsive neurons (45). Since the possibility of some of the centrally injected small amount of CCK leaking out into the periphery – thus complicating the effect of intrahypothalamically applied peptide – is unlikely (46), centrally induced CCK-hypothermia seems to be a genuine CNS-mediated response, but support from other laboratories has been lacking so far.

Central thermoregulatory effects of CCK may be mediated by opioid receptors, since in rats μ-selective antagonists have been shown to block CCK-induced fever (6) and in man ACTH secretion induced by the CCK-like peptide ceruletide could be inhibited by another mu-receptor antagonist (47). It may be relevant to mention here that the endogenous pyrogen IL-1 has been shown to increase release of CCK from superfused rat hypothalamus linking CCK effect to fever (48). The mechanism of this release is still unclear, since in another study neither CCK-A nor CCK-B receptor antagonists influenced hypothalamo-pituitary response in vivo, although the CCK-A receptor antagonists inhibited CCK-release (49). Chronic stress other than cold-exposure was demonstrated to activate a cholecystokin-mediated pathway in the hypothalamus via CCK-B receptors (50) and CCK-release could also be induced in rat hypothalamus by acute stress (51). In the same study substance-P (SP) release remained unchanged on stress, although there is some evidence that central SP mediation could also contribute in thermoregulation and LPS-fever in the same species (52). The contribution of various afferent mechanisms on autonomic functions may be complex as shown by a recent study in which effects of CCK and LPS alone or in combination have been studied on various aspects of food intake of rats (53).

The two aspects of energetics are influenced by CCK-ergic mechanisms similarly, in that reductions of body temperature and food intake show strong positive correlation (54) when the peptide is administered peripherally. Centrally acting CCK, however, induces a rise of core temperature together with satiety and with a reduction in general activity, a combination favoring wastage of energy, but – as part of the sickness behavior – may allow short-term advantages for fighting invading microorganisms during infections. So, the question of usage of different putative mediators for the regulation of either food intake or body temperature appears to be even more complex than alluded to before. For example, CCK does not seem to mediate food-motivated behavior of LPS and IL-1 in mice (26), but in the same species short-term food intake is synergistically regulated by leptin and CCK (55) probably allowing magnification of the satiety response by increased utilization of these and by other mediators.

As for thermoregulation, CNS targets of CCK receptor activation could be quite different from the well-established central sites of body temperature control, such as the hypothalamus. At least in the case of peripheral adminstration of CCK, *c-fos* expression was found to be increased in rat brain, as expected, in nuclei of the solitary tract and in the paraventricular nuclei (56). Both in the hypothalamus and in the locus coeruleus/subcoeruleus complex, CCK-induced *c-fos* expression was dependent on A-receptor activation (57). The latter brainstem area has also been shown to be involved in thermogenic responses in guinea-pigs and it represents part of an ascending catecholaminergic system (58). CCK-B receptor related effects have been shown to contribute to cerebral excitation, in that peripheral CCK-injection led to glutamate release in some cortical and subcortical areas of rats studied by microdialysis technique (59). Also, CCK-8 induced excitatory effects were shown in hippocampal pyramidal neurons in slice preparation that could be attenuated by a CCK-B receptor antagonist but not by CCK-A receptor antagonist (60).

Possible involvement of CCK-B receptors in central hyperthermic and/or febrile mechanisms analysed in detail in the laboratories of the present authors and supported by others may necessitate the study of long-term

thermoregulation using CCK agonists or antagonists under different thermal conditions. In particular, it may be hypothesized that long-term antagonism of CCK-B receptors might lead to an attenuation of night-maxima of body temperature. Conversely, activation of the same receptor set could lead to steady-state fever either only during the day – the inactive period in rats – or causing a shift to higher body temperature around the clock. As observed in earlier studies in rats, icv infusion of PGE1 induced steady-state fever lasting for several hours, and this higher (febrile) core temperature was maintained in the face of both cold- and heat-challenge (61) when compared to core temperature measured without infusion of the pyrogen.

This could indicate that body temperature regulation was modified by this established central pyrogenic mediator in the sense of "increase in regulated body temperature" and not just a "regulated rise in body temperature" (62). In other words, a bolus injection of PGE icv results in a short-term rise in core temperature accompanied (or rather partially caused) by a rise in heat production (see also the first part of Figure 1), and – depending on ambient thermal conditions – signs of increased heat conservation that can be called a "regulated rise in body temperature", while regulation of core temperature at a high level during steady-state fever in the face of different thermal challenges (61) can be formulated as an "increase in regulated body temperature". It remains to be seen if a CCK-ergic central mechanism could modify body temperature regulation a similar fashion resembling the classical view of set-point control indicated above.

6. PERSPECTIVES

The foregoing discussion has been an attempt to collect available information on the possible mediator role of neuronal CCK-ergic mechanisms in thermoregulation, in general, and on the development of fever or hypothermia, in particular. Experimental evidence summarized above does not rule out at least a modulator role of this system as derived from results of in vivo studies, such as the effects of central or peripheral administration of CCK-peptides and/or their receptor blockers. Genetically modified rat or mouse strains have also contributed significantly to our understanding of the significance of this peptide system in normal and pathologic models of thermoregulation.

Clearly, more definite and conclusive evidence is still missing for the thorough understanding of the operation of this peptide system in thermal homeostasis. For example, data on central release of CCK peptides during physiological thermal challanges (cold- or heat-exposure, cold- or warm-adaptation) may shed light on the sensitivity and/or specificity of this system as part of physiological defense. Alternatively, it is concievable that CCK-ergic mechanisms are influenced only under extreme physiological loads or only during pathological situations (such as severe fever, hyperthermia or hypothermia) especially when energetics of the body are limited by restricted food intake and/or availability. Since the function analyzed in most detail so far in connection to central or peripheral manipulation of the CCK system has been the appetite/satiety complex and this consummatory behavioral modality has also been known to be closely connected to thermal balance, more complex experimental approach should be worked out in the hope of understanding body energetics as a whole.

7. ACKNOWLEDGMENTS

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