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PHARMACOLOGIC CONTROL OF TEMPERATURE REGULATION

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INTRODUCTION

During the past two decades the physiology and pharmacology of thermoregulation have been the subjects of a considerable volume of research and numerous books and reviews. The physiologic aspects have been reviewed in detail most recently by Cabanac (1). The effects of drugs on temperature regulation have been discussed at two symposia, which resulted in books containing the proceedings (2, 3), and a third symposium in this series was held in Banff in September 1976. In reviewing this prodigious development of knowledge of the subject, any demarcation of these reports into "pharmacologic" is somewhat arbitrary since in many cases drugs have been used as tools to elucidate physiologic mechanisms.

With respect to the actions of drugs on central thermoregulatory mechanisms, many of the compounds studied affect the CNS by modifying the activity of the several neuronal pathways that impinge on the central thermostats or that mediate the effector responses controlling body temperature. The role of the putative neurotransmitters involved constitutes perhaps the most debatable topic in thermoregulation (4). Because there has been no recent exhaustive review of this subject we restrict the present discussion to the role of these neuroamines and the effects of drugs on their activity in the CNS.

A convenient model on which to base a discussion of the role of amines in thermoregulation is the neural net described by Carlson (5). He divided the system into afferent, central, and efferent components. Of these three components there is little or no evidence for a role of amines in the afferent sensory division. Conversely there is good evidence for a role of amines in the peripheral effector part of the neural net; its pharmacology is easy to analyze and is well understood. The central compo-

nent is, perhaps predictably, not well understood and it is in this area that apparent inconsistencies exist and controversy abounds.

There are seven distinct efferent pathways in the neural net, of which six involve aminergic mechanisms and the seventh hormonal mechanisms. Of the aminergic systems four were described as sympathetic (5)—those to the skin blood vessels, sweat glands, adipose tissue (nonshivering thermogenesis), and adrenal medulla. The other two involve the somatic nervous system for the production of shivering and changes in respiration.

Pharmacologic manipulation of the effectors produces predictable thermoregulatory effects. For example, sympathomimetic drugs causing vasoconstriction will reduce heat loss, while drugs causing vasodilation (sympatholytics or cholinomimetics) will increase heat loss. Manipulation of these peripheral effectors can modify thermoregulatory behavior and affect heat loss or heat gain systems as well. The effects of a quaternary diphenhydramine derivative, which has ganglion blocking properties and does not pass the blood-brain barrier (6) will serve as an example. This drug, injected into rats, produced a fall in core temperature. However, if the rat was allowed access to a radiant heat source it used this source to maintain its temperature at the original set point (7). In the opposite situation, in which the rat had an elevated core temperature as a result of a 2-hr pretreatment with thyroxine, the rat avoided the heat source in an attempt to keep its temperature near the original set point.

Thus, the effect of drugs acting exclusively via the peripheral effectors are relatively easy to investigate and their actions can often be explained in terms of interactions with known neurotransmitter systems. When the central component of the neural net is considered, the situation is less clear and much of the experimental evidence is conflicting.

A number of models has been devised to explain the role of amines in the central component of the neural net. Problems in constructing such a model arise because of the wide species variations (8) and because of the differences in measured responses that occur after central monoamine injection depending on the route used and the ambient temperature of the study (9).

Typical models for the control of body temperature (10, 11) usually place the central thermostat in the preoptic anterior hypothalamus. This site receives information from peripheral cold and warm receptors. Stimulation of cold receptors is postulated to release 5-hydroxytryptamine (5-HT) in the preoptic anterior hypothalamus, which in turn activates a cholinergic pathway in the caudal hypothalamus to bring about heat conservation. Stimulation of warm receptors is thought to cause preoptic release of norepinephrine, which acts via caudal hypothalamic cholinergic mechanisms to activate heat loss processes. The validity and universality of this model have been subjected to a good deal of experimental study; this review summarizes some of the findings and discusses some of the apparent anomalies.

ACETYLCHOLINE

Central cholinergic mechanisms have been reported to mediate both hypo- and hyperthermic responses; this cannot be explained simply on the basis of either

species differences or the duality of the role proposed for acetylcholine in the model. Thus, intraventricular injection of cholinomimetics such as acetylcholine (alone or in combination with a cholinesterase inhibitor) or carbachol have been reported to increase the core temperature of primates (12) and rats (13). Systemic injection of the centrally active muscarinic agonist, oxotremorine, caused a fall in core temperature of rats (14), which occurred even when peripheral muscarinic receptors were blocked. One possible explanation for these divergent results was that different central sites were being activated by the different routes of injection. However, further experiments involving injection into brain tissue have not resolved the problem. When oxotremorine was injected directly into the rostral hypothalamus of the rat a hypothermia was reported (14). Injection into the surrounding tissue was without effect. In contrast, injection of carbachol into the preoptic anterior hypothalamus has been reported to produce a dose-dependent hyperthermia (15, 16). Support for a central hypothermic effect of cholinomimetics came from the work of Beckman & Carlisle (17) who noted that intrahypothalamic injection of acetylcholine led to an immediate fall in brain temperature accompanied by decreases in behavioral responses for heat gain. One reservation about comparing their results with others is that the experiments were carried out at −5°C. Other workers have observed falls in core temperature in rats after a variety of muscarinic agonists (oxotremorine, pilocarpine, nicotine, and acetylcholine) were injected centrally at normal ambient temperatures (15, 18, 19, 20).

In an interesting experiment in which a variety of variables were recorded simultaneously, Crawshaw (21) attempted to resolve the apparent anomalies. He measured hypothalamic and cutaneous tail temperature in lightly restrained rats and made bilateral injections of acetylcholine into the preoptic/anterior hypothalamic region. A coordinated set of heat loss responses occurred almost immediately after injection, which included postural changes and vasodilation. Crawshaw also noted that locomotor activity could prevent the hypothermia and suggested that the hyperthermia reported by other workers (13, 14, 16) was either related to an increase in locomotor activity or to measurements being made at a time (15 to 30 min) when a compensatory rise in temperature was taking place. An alternative view was put forward by Myers (22), who suggested that low doses of cholinomimetics produced hyperthermia and that high doses caused a "swamping of local receptors sites" and hypothermia, presumably as a result of depolarizing blockade. Work in the cat supported this hypothesis, where low doses of cholinomimetics injected into the rostral hypothalamus produced hyperthermia but where increasing the dose at the same site resulted in a hypothermia (23). However, a similar experiment in rats was reported to give exactly the opposite results (24). Which, if either, of these findings is correct remains to be resolved. Another possible view is that the differences are due to the activation of two subsets of cholinergic receptors (muscarinic and nicotinic?), but there are as yet insufficient data to allow analysis of such a suggestion.

Other approaches to the problem have involved the use of anticholinesterase or antimuscarinic drugs. Meeter & Wolthuis (25) found that systemic injection of tertiary nitrogen anticholinesterases lowered core temperature in rats, and in a similar experiment in mice, at least two thirds of the response to the anticholinesterases was shown to be due to an action in the CNS (R. Chitty and B. Cox, unpub-

lished). More recent studies have shown that intraventricular injection of the anticholinesterases caused hypothermia which was blocked by atropine (24). However, once again an alternative view has been presented: studies in the cat have shown that either intraventricular or intrahypothalamic injection of anticholinesterases can result in a hyperthermia (26).

In a detailed study of the effects of atropine on core temperature in the rat (27), systemic injection produced hypothermia but intrahypothalamic injection caused hyperthermia. Confirmation of these earlier studies have come recently from an investigation of cholinergic mechanisms in PGE_1 hyperthermia when central injection of atropine alone caused hyperthermia in the rat (28). Thus, the central injection of atropine gave results consistent with a hypothermia mediated by central cholinergic sites.

Clearly no unitary concept for a role of acetylcholine in thermoregulation can yet be advanced and it is only possible to echo the sentiments of Brimblecombe (29) who in 1973 said, "In view of the conflicting results it is remarkable that, in comparison with the monoamines, so little work has been done to elucidate the role of acetylcholine in central thermoregulation. This is clearly a fruitful field for further research."

NOREPINEPHRINE

The presence of norepinephrine in the hypothalamus, coupled with the known homeostatic function of this area, led in 1957 to a suggestion of a possible thermoregulatory role for this amine (30). Direct evidence of such a role came when it was shown that either intraventricular or intrahypothalamic injections of norepinephrine caused a fall in core temperature of the conscious cat (31, 32). Subsequently a great deal has been published concerning a thermoregulatory role for norepinephrine, but interpretation of these data is difficult. First, there is an apparently wide species variation (33). Second, in many studies, the precise site of injection is not well defined. Third, there are in the literature a number of reports of biphasic effects, which are particularly evident when the intraventricular route of injection is used (34, 35).

In the rat, the species most widely studied, low doses of norepinephrine injected into the hypothalamus are usually reported to increase core temperature (36–38), whereas high doses are reported to produce a fall (16, 36, 37, 39, 40). When the intraventricular route is used, the picture is less clear; in addition to the biphasic effect (35), there are also reports of hypo- or hyperthermia (13, 41, 42), which cannot be explained on the difference in dosage used. Satinoff & Cantor (43) attempted to resolve this problem by studying the effect of intraventricular norepinephrine on thermoregulatory behavior (the rats were trained to press a bar to obtain heat) and brain temperature. They recorded a fall in brain temperature accompanied by an increase in the animals' response to obtain heat. It was concluded that intraventricular injection of norepinephrine activated central heat loss pathways for which the rat attempted to compensate by behavioral responses for heat gain. The earlier investigations of Beckman (38) showed that intrahypothalamic norepinephrine also caused behavioral responses for heat gain but that these were associated with a rising

core temperature. The hypothesis resulting from these two findings was that low doses of norepinephrine injected directly into the hypothalamus caused a rise of the set point and an increase in temperature, while higher doses diffused out of the hypothalamus and activated more distant heat loss effectors. This latter site of action would be expected to override the former. Injection into the cerebral ventricles appears preferentially to act on these heat loss effectors, whose precise location is not yet defined. One possible location is in the ventrobasal thalamus, which has been suggested to be involved in behavioral thermoregulation (44).

Bruinvels (45) has also suggested that the hyper- and hypothermic responses in the rat result from activation of different thermosensitive sites in the brain. However, he could not demonstrate a hypothermic effect of high doses of norepinephrine and attributed the fall in core temperature reported by other workers to restraint of the animals. Another finding was that phentolamine, an α-adrenoceptor blocking drug, could modify the temperature changes. This work in the rat supports findings in other species (cats, rabbits, and mice) that the action of norepinephrine in thermoregulation is mediated via α-adrenoceptors (46–50). Recently, norepinephrine has been reported to produce hypothermia in various avian species including the chicken (51, 52) and the pigeon (53). The fall in core temperature in the pigeon was also blocked by phentolamine, but not propranolol, again confirming a role for α-adrenoreceptors. In the cat both norepinephrine and its α-methyl derivative produced hypothermia blocked by phentolamine (33). However, it was noted that although norepinephrine and α-methylnorepinephrine were almost equipotent in their central actions, norepinephrine was eight times more potent on peripheral α-adrenoceptors. Therefore it was concluded that although central thermoregulatory receptors for norepinephrine have some properties in common with α-adrenoceptors, they may not be identical. Further support for an involvement of central α-adrenoceptors came from studies with the drug clonidine (54), which is a centrally acting α-adrenoceptor agonist. This drug produced effects identical with those of norepinephrine when injected intraventricularly in sheep.

The use of other drugs has led to speculation that endogenous norepinephrine is indeed involved in thermoregulation. Imipramine, which prevents inactivation of endogenous norepinephrine by inhibiting neuronal uptake, produced changes analogous to those of injected norepinephrine (55). This finding held whether the response was hyperthermia (rabbit) or hypothermia (rat). Acute injection of 6-hydroxydopamine, which causes release of norepinephrine, has also been reported to produce hypothermia in the rat (56–58). More direct evidence for a role of endogenous norepinephrine comes from the work of Myers & Chinn (59). They showed that at raised ambient temperatures norepinephrine caused a decrease in core temperature of the monkey and that under these conditions there was selective increase in norepinephrine release from the rostral hypothalamus.

Finally, the effect of norepinephrine on electrical activity in the CNS needs to be considered to determine whether any neurophysiological correlates exist for norepinephrine and temperature control. The widespread distribution of thermosensitive cells in the CNS and the limited number of studies made allow few firm conclusions. The effects of norepinephrine on unit activity in the preoptic/anterior hypothalamic

area have been studied in rats (60), rabbits (61), and cats (62). In the rat and rabbit there was a correspondence of effects; norepinephrine decreased the rate of warm-sensitive neurons and increased the rate of cold-sensitive ones.

In conclusion, some tentative explanations have been advanced to explain the apparent anomalies in the thermoregulatory effects of norepinephrine, but the total picture is confused and more experiments under controlled conditions are required.

5-HYDROXYTRYPTAMINE

As with norepinephrine, the initial impetus for research into a possible role for 5-HT in temperature control came from the observations of Feldberg & Myers in 1964 (31), who noted that intraventricular injection of 5-HT in the cat increased core temperature. There is once more an apparent wide species variation. Initial reports showed that intraventricular 5-HT caused increased core temperature in the cat and dog (31, 63) and the opposite effect in the rabbit, sheep, rat, and mouse (35, 50, 64, 65). However, a later report of the effect of intrahypothalamic 5-HT in the rat claimed that hyperthermia rather than hypothermia occurred, particularly when low doses were employed (37, 66). 5-HT has also been implicated in the hyperthermia (which occurs in man, rabbit, and mouse) (67), resulting from injection of meperidine and a monoamineoxidase inhibitor. A possible solution to this problem of a hypo- or hyperthermic response has been presented with the finding that 5-hydroxytryptophol, a 5-HT metabolite, was hypothermic (68). It was postulated that 5-HT itself was hyperthermic, but that its metabolite was hypothermic. Some support for this idea came from the observation that monoamineoxidase inhibition, which prevented metabolite production, also prevented 5-hydroxytryptophan (5-HTP)-induced hypothermia. Further support for a hyperthermic role of 5-HT was the finding that stimulation of the midbrain raphe, which is the origin of most central 5-HT neurons, caused an increase in core temperature in the rat (69).

The role of 5-HT in the rabbit is also unclear in contrast to the hypothermia noted above (64); 5-HT has been suggested to mediate drug induced hyperthermia (70). To add to the confusion a biphasic effect has also been suggested, low doses decreasing and high doses increasing core temperature (71). Brimblecombe (72) has looked at 36 different tryptamine derivatives in the rabbit and found a hyperthermic response; in all cases the hyperthermia correlated with another measure of CNS activity.

Work in avian species has noted hyperthermia in the hen (52) and little or no effect in the pigeon (53). Therefore its role in this species requires elucidation.

Iontophoretic studies with 5-HT in the rat and rabbit (60, 61) have supported the original concept of Feldberg & Myers (31) for an opposite action of 5-HT and norepinephrine in these species. However, experiments in the cat, the species in which the hypothesis was first advanced, gave an equivocal result (62). In a more recent study (73) it was reported that 5-HT did not shift the sensitivity of medio-preoptic brain structures in the rat to thermal stimuli. Thus, although support for a neurotransmitter role has been published, the conflicting evidence makes a precise

statement about its function impossible. More evidence is likely to accrue from the use of drugs, analogous to 6-hydroxydopamine, which selectively destroy 5-HT neurons. Such a drug, 5,6-dihydroxytryptamine, has been injected into monkey hypothalamus. Acutely it acted like 5-HT to increase core temperature. Chronically the monkeys demonstrated a thermoregulatory deficit to a cold challenge, which supports the hypothesis of a 5-HT link in the pathway carrying information from cold receptors (74).

DOPAMINE

Compared to the other biogenic amines, dopamine was rather late in being considered for a role in thermoregulation. Before 1971, only slight or inconsistent hypothermic effects had been reported after intraventricular or intracisternal injection (13, 41, 50, 57). However, the use and introduction of two pharmacological tools significantly affected the work in this field. The first was apomorphine, a specific dopamine receptor agonist (75) and the specific antagonist, pimozide (76).

In the rat, intraventricular injection of apomorphine, amphetamine, or dopamine has been shown to produce hypothermia (77). Similar findings have been noted for the cat and the baboon (78, 79). In all cases the hypothermia was blocked by pimozide or other dopamine antagonists. The hypothermia in the cat was shown not only to be pimozide sensitive, but also to be located in the preoptic/anterior hypothalamic region (80) and not in the caudal hypothalamus (81). A wide variety of drugs which have in common an ability to stimulate central dopamine receptors consistently have been shown to produce hypothermia in commonly used laboratory animals (82–84). As with norepinephrine, however, the findings are not unanimous. Low doses (10 μg) of dopamine administered intraventricularly have been claimed to increase core temperature in the rat (85). Further studies are required to see whether an explanation similar to that advanced by Satinoff & Cantor (43) for norepinephrine applies in this case. An alternative hypothesis is that the hyperthermia results from the conversion of dopamine to norepinephrine (85). Barnett & Taber (86) postulated a differential role for brain dopamine in temperature control in mice based on experiments with diethyldithiocarbamic acid, which inhibits dopamine-β-oxidase, and *l*-dopa. They suggested that while dopamine was hypothermic in control mice, it would elevate core temperature in mice pretreated with reserpine. These experiments were subsequently confirmed and extended using a variety of dopamine agonists (82). This study also showed that for complete reserpine reversal a small, but significant, noradrenergic contribution was required.

The rabbit appears to be the only commonly used laboratory species in which injection of dopamine agonists consistently produces a rise in core temperature (87, 88) which is pimozide sensitive. More recent studies have indicated a 5-HT link in the hyperthermia (70); this may apply also to the fall in core temperature in the rat (89).

Evidence for a role of endogenous dopamine in temperature control comes mainly from indirect sources. Bilateral lesioning of the striatum in mice has been reported

to prevent apomorphine hypothermia (90), as did injections of scopolamine. This led the authors to postulate a role for dopamine receptors in the striatum, acting through cholinergic mechanisms in the hypothalamus. Other indirect evidence has suggested a role for endogenous dopamine in the rostral hypothalamus. Thus, morphine withdrawal hypothermia was blocked by injection of pimozide into the preoptic/anterior hypothalamic nuclei (91), which suggested that the hypothermia was mediated via endogenous dopamine at this site. Further studies, measuring thermoregulatory behavior in rats undergoing withdrawal, indicated that the effect of this dopamine was to lower the setting of the central thermostats (92).

In general there appears to be less controversy over the thermoregulatory actions of dopamine than for the other amines. However, it is quite possible that this merely reflects its late arrival on the scene.

HISTAMINE

As in the case of dopamine, histamine is a relative latecomer to the field of central control of temperature regulation. It has long been known that systemic administration of histamine can cause changes in body temperature in several species (see 93) but, since the amine does not readily penetrate the blood-brain barrier, these responses must be mediated peripherally. In 1970 Brezenoff & Lomax (94) reported a dose-dependent fall in core temperature after injection of histamine (1–5 μg) into the rostral hypothalamus of rats. This response was prevented by pretreatment of the animals with a histamine H_1-receptor antagonist (chlorcyclazine). Histamine also caused a fall in temperature when injected into the cerebral ventricles of mice but here the effect was not blocked by either systemic or intraventricular injection of chlorcyclazine (95).

An alternative to intracranial injection in the study of histamine as a neurotransmitter has been to increase central histamine concentrations by systemic loading with its precursor L-histidine (96, 97). Such systemic administration causes a fall in temperature of the rat maintained at an environmental temperature of 18°C (93). That this fall is indeed due to the enhancement of central histaminergic activity has been established (98, 99). Histamine H_1-receptor antagonists, injected systemically or centrally, had no effect on the histidine-induced hypothermia, whereas the response was blocked by H_2-receptor antagonists injected into the third ventricle (100).

The above data suggested at least two sites at which histamine affects the central thermoregulatory pathways: H_1-receptors in the rostral hypothalamic thermoregulatory centers and H_2-receptors in the pathways coursing close to the wall of the third ventricle. The responses evoked at these effectors were analyzed further using behavioral responses (7). These studies revealed that activation of H_1-receptors in the rostral hypothalamus lowers the set point of the thermostats causing heat loss mechanisms to be brought into play to lower the body temperature to the new set level. On the other hand, stimulation of the H_2-receptors activates the efferent heat loss pathways directly (101) and the set point is unchanged. A similar lowering of the set point mediated by H_1-receptors has been reported in the cat (102). The

data indicating that H_2-receptor stimulation activates heat loss mechanisms directly are supported by studies with 4-methylhistamine, a predominantly H_2-receptor agonist (103).

Whether or not the histamine H_1- and H_2-receptors in the thermoregulator pathways are on the same neuronal chain remains to be determined. However, using oxotremorine, which lowers the set point of the central thermostats after systemic injection (7), the fall in temperature was significantly reduced by an H_2-antagonist (cimetidine) injected into the third ventricle of the rat (unpublished data, M. D. Green and P. Lomax). Possibly, certain heat loss pathways contain this H_2-histaminergic link, and these are activated by any changes involving a lowering of the set temperature. The universality of histaminergic transmission in central temperature regulation has recently been illustrated by evidence that thermal environmental selection in fish can be modulated by histamine and H_1-antagonists (104).

CONCLUSIONS

Although it is not possible to establish rigorously all of the criteria necessary to implicate a specific transmitter function to any central neuroamines, the evidence is certainly compelling in the cases discussed above. The inherent difficulties in investigating neuronal pathways in the central nervous system do not allow, as yet, definitive statements as to the precise sites of action of these several transmitters; nor can one confidently predict whether the neurons involved represent long afferent or efferent pathways or short interneurons.

However, of the several neuroamines discussed it might be concluded that there is strong evidence for assigning a role in central thermoregulation to norepinephrine, 5-HT, and acetylcholine while dopamine and histamine, in the words of Feldberg (105) "although not yet admitted to the club, are knocking at the door." How many of the drug effects on thermoregulation will eventually be explained as due to modification of transmitter function remains the topic of some future review.

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