Chapter 8

Histaminergic Modulation of Body Temperature and Energy Expenditure

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1. Introduction

The role of histamine signaling in the brain in thermoregulation has been unraveled in various organisms. The preoptic area/ anterior hypothalamus (PO/AH), region which contains thermoeregulatory neurons, is the main locus in which histamine affects body temperature. Histamine has a complex influence on thermoregulation and its circadian cycle and appears to be involved also in numerous pathological responses that involve changes in core body temperature. The neurotransmitter activates several signaling pathways involving H1, H2 and H3 subtype receptors and recruits distinct neuronal networks to modulate body temperature. In this review we describe the mechanism involved in the hypothalamic control of thermoregulation, the signaling mechanisms activated by histamine in the brain, the evidence for its role in thermoregulation as well as recent advances in the understanding of the cellular and neural network mechanisms involved.

2. Hypothalamic control of thermoregulation

Homeothermia is present in mammals and birds and enables them to maintain their deep-body temperature (Tcore) at stable levels. Tcore can physiologically deviate from its normal value (the value at rest in thermoneutral environment) under the influence of the day-night cycle, the menstrual cycle, or seasonal cycles, such as hibernation. Pathophysiological changes in Tcore include fever (a hyperthermic response to infections), dehydration hyperthermia, and starvation-induced hypothermia. The key role played by the preoptic area/anterior hypothalamus (PO/AH) in the regulation of Tcore was recognized more than a 100 years ago, based on experiments using experimental brain lesions, and selective hypothalamic cooling and heating with chronically implanted thermodes (reviewed in [1]). Sustained or alternating PO/AH cooling and heating induce thermoregulatory activities (physiological or behavioral), causing Tcore to change in the direction opposite to that of the

hypothalamic temperature (T_{hy}). Hammel and collegues proposed that a particular net thermoregulatory response was proportional to ($T_{hy} - T_{set}$), where T_{set} was conceived as a hypothetical set reference, a complex parameter representing the state of activity of thermosensitive neuronal populations [2].

Since the first extracellular single-unit study [3], which found that some PO/AH neurons, termed "warm-sensitive", increase their firing rates when T_{hy} increases, it has been considered that they represent the central thermoreceptors. The other PO/AH neurons, which display little temperature-dependent changes in firing rate, are considered temperature-insensitive. PO/AH thermosensitive neurons respond not only to changes in local and peripheral temperature, but also to hormones, osmolarity and glucose concentration (reviewed in [1]). These findings suggest that these neurons, or a subgroup of them, also play a role in the integration of thermoregulation with other homeostatic processes such as control of metabolic rate (glucose sensing). The thermosensitivity of PO/AH neurons is a plastic property both *in vivo* and *in vitro*. It has been found that the thermosensitivity can change rapidly in the presence of the pyrogens PGE2 [4] or IL-1 [5,6]. Slower changes are observed in some warm-sensitive PO/AH neurons which decrease their thermosensitivity during NREM sleep [7].

The mechanism of intrinsic thermosensitivity of PO/AH neurons is controversial. Boulant and colleagues consider that the increased firing rate is solely due to an increased rate of rise of the prepotential which precedes an action potential (reviewed in [8]. Other studies describe strong depolarizations (10 mV or larger) in response to heating which cause the increased firing rate in warm-sensitive neurons ([9]). In cultured PO/AH neurons both phenomena are present, however they occur also in temperature-insensitive neurons [10]. Finally, the warming-activated inward current was found to be tetrodotoxin (TTX)-insensitive in some studies [9,10,11] and TTX-sensitive (i.e. mediated by voltage-gated Na channels) in others [12]. The question remains open as to whether all warm-sensitive PO/AH neurons have some intrinsic thermosensitivity or if they can also display thermosensitive firing that is synaptically-driven [10]. We have shown that prostaglandin E2 (PGE2), a well established endogenous pyrogen, increases the thermosensitivity and firing rates of PO/AH neurons by decreasing the frequency of IPSPs [4]. In contrast, IL-1β hyperpolarizes a different set of PO/AH neurons and reduces their thermosensitivity by increasing the frequency of IPSPs and of miniature IPSPs [5,13].

3. Thermoregulatory neuronal networks comprising PO/AH thermosensitive neurons

The neuronal network controlling brow adipose tissue (BAT) thermogenesis and the fever response has been studied extensively. Thermal and chemical stimulation in the PO/AH combined with selective hypothalamic transections have shown that warm-sensitive PO/AH neurons send efferent signals to loci involved in the control of BAT thermogenesis) [14,15]. PO/AH warming or injection of glutamate suppressed BAT thermogenesis thus suggesting that it is controlled by warm-sensitive neurons ([14]). Studies using combined retrograde

labeling and immunocytochemistry revealed that EP3 prostanoid receptor-positive GABAergic PO/AH neurons project to the sympathetic premotor neurons in the rostral raphe pallidus (rRPA). The projections are either direct or via the dorsomedial hypothalamus (DMH) [16,17]. Bilateral microinjections of GABA-A receptor agonists or antagonists into the rRPa or DMH, blocked the fever induced by intra-PO/AH PGE2 applications. The central role of EP3-receptors in PO/AH neurons in the fever response was demonstrated also by local knockdown of its expression [18]. The role of the DMH in the control of BAT thermogenesis was proven also by direct chemical or electrical stimulation [19]. These studies clearly revealed a tonic GABAergic inhibition of the DMH and rRPA by the PO/AH as crucial for basal thermoregulation and hyperthermic responses.

Recent studies have established also the existence of direct glutamatergic projections from the PO/AH [20,21] as well as from the lateral hypothalamus [22] to the rRPA that control thermoregulation. Some glutamatergic PO/AH neurons projecting to rRPa are also peptidergic [20].

Shivering, a different mechanism of thermogenesis, is also controlled by the PO/AH.

Injections of excitatory amino acids as well as PO/AH warming inhibited cold-induced shivering suggesting that this mechanism, similar to BAT thermogenesis, is controlled by PO/AH warm-sensitive neurons [15]. In contrast, cooling of the PO/AH had little effect on cold-induced shivering. The efferent signals mediating shivering descend in the medial forebrain bundle [23].

Evaporative heat loss is also controlled by a network originating in the PO/AH since it is the only brain region that induces salivary secretion when warmed [23]. Preoptic warming, glutamate injections as well as electrical stimulation facilitate salivary secretion [5,13,15] as well as body extension [24], another aspect of evaporative heat loss.

The neuronal network controlling cutaneous blood flow also originates in the PO/AH.

Warming the PO/AH elicits skin vasodilation [25], by activation of warm-sensitive neurons [15]. The efferent pathway descends through the medial forebrain bundle [23]. It is believed that warm-sensitive neurons in PO/AH send excitatory signals to vasodilator neurons and inhibitory signals to vasoconstrictor neurons. PO/AH neurons controlling cutaneous blood flow project to the rostral medullary raphe region directly [26], suggesting that distinct populations of PO/AH neurons control thermogenesis and cutaneous vasomotion. This concept is supported by the observation that the two thermoregulatory mechanisms are activated at different threshold temperatures [27].

Little is known about the local networks comprising warm-sensitive and temperature-insensitive neurons. One study found little thermosensitivity in the frequency of spontaneous IPSPs and EPSPs recorded in either warm-sensitive or temperature-insensitive PO/AH neurons, suggesting that the former do not send local projections [28]. This study also compared the morphologies of w-s and t-i PO/AH neurons filled with Lucifer yellow or biocytin. The dendritic arbors were characterized, however the axonal projections could not be described. This finding may reflect technical limitations or the fact that PO/AH neurons

send few local projections [28]. Our studies in mice have not found evidence for local projections of PO/AH GABAergic neurons but have revealed reciprocal connections of PO/AH glutamatergic neurons [21].

4. Histamine signaling in the brain

Histamine is synthesized in the tuberomammilary nucleus (TMN) neurons from histidine by the specific enzyme histidine decarboxylase (HDC). After release histamine is methylated by histamine N-methyl-transferase (which is located postsynaptically and in glia). The turnover of neuronal histamine is high, with its half-life being ~ 30 min. The histaminergic TMN neurons project their axons throughout the brain and they control arousal, attention, energy expenditure, feeding, and thermoregulation. Histaminergic fibers are especially dense in the cortex, hypothalamus, amygdala and striatum (reviewed in [29]). In the hypothalamus the histaminergic fibers are particularly dense in the anterior part [30]. Another source of histamine in the brain is represented by resident mast cells [31].

Four histamine receptors, which are GPCRs, have been cloned (H1-H4R). The H1R, H2R and H3R are expressed in distinctive patterns in the brain [32] and all three receptor types are highly expressed in the hypothalamus. The H1Rs mediate excitatory actions on central neurons. At the cellular level, excitation is achieved by activation of $G_{q/11}$ and PLC, which leads to the formation of the two second messengers, diacylglycerol (DAG) and inositol-1,4,5-triphosphate (Ins(1,4,5)P3). Ins(1,4,5)P3 releases Ca^{2+} from internal stores, and this activates at least four Ca^{2+}-dependent processes. First, the opening of a cation channel, which causes depolarization [33]. Second, activation of the electrogenic Na-Ca exchanger in supraoptic neurons, which also causes depolarization [34]. Third, formation of nitric oxide and cyclic GMP [35]. And finally, opening of K^+ channels, resulting in hyperpolarization [36]. Furthermore, blocking a leak potassium conductance through direct G-protein action, or through PLC, DAG and PKC, can cause excitation in the thalamus [37], and in the striatum [38].

The H2Rs are coupled to G_s, adenylyl cyclase (AC) and PKA, which phosphorylates proteins and activates the transcription factor cyclic-AMP-response element (CRE)-binding protein (CREB). The direct action on neuronal membranes is usually excitatory or potentiates excitation. Like other transmitters that use this signaling pathway histamine blocks the small Ca^{2+}-dependent K^+ conductance ([39]). This conductance causes a long-lasting afterhyperpolarization and affects the accommodation of firing. A cortical neuron under active histaminergic input remains quiescent until it is reached by a sensory stimulus, which will then cause an enhanced and long-lasting response. Activation of H2Rs, by increasing cyclic AMP concentration, shifts the activation of the inwardly rectifying I_h towards a more positive voltage and contributes to a depolarization that modifies the thalamic relay of sensory input [37].

The H3Rs are located on histaminergic and other cell somata, dendrites and axons (varicosities), where they provide negative feedback to restrict histamine synthesis and release. They also provide negative feedback on the release of other transmitters, such as

glutamate [40], acetylcholine and noradrenaline [41]. H3Rs are coupled to $G_{i/o}$ and inhibit high voltage activated Ca^{2+} channels, a typical mechanism for the regulation of transmitter release. In rat, there are three functional splice variants of the H3R. In mouse, both RNase protection assay experiments and PCR results indicate that only one isoform of the H3R is present [42] which is coupled negatively to cAMP. H3Rs also activated the phospholipase A2 (PLA2) via the Gi/o proteins which results in production of arachidonic acid [43].

In summary, H1Rs and H2Rs have mostly excitatory actions on neurons or potentiate excitatory inputs. By contrast, H3-receptor activation causes autoinhibition of TMN neurons and inhibition of neurotransmitter release. Recent morphological and physiological studies suggest the presence of H3 receptors also postsynaptically [21,44,45].

5. Central histaminergic modulation of core body temperature

The role of CNS histamine in thermoregulation has been established in various organisms from invertebrates [46] to lower vertebrates [47] as well as mammals. Early studies in mammals have reported a role of hypothalamic histamine in the control of body temperature [48]. The preoptic area/ anterior hypothalamus (PO/AH), region which contains temperature-sensitive neurons and regulates the thermoregulation setpoint, is the main locus in which histamine affects body temperature [49]. Histamine injected in the medial preoptic nucleus (MPON) induces hyperthermia. Similarly, intra-MPON injection of a histamine-N-methyltransferase inhibitor (which results in a local increase of histamine concentration) also produces hyperthermia [50]. Behavioral temperature selection studies suggest that preoptic histamine signaling affects both the set point of the hypothalamic thermostat, as well as heat loss mechanisms [51]. Both H1 and H2 receptors have been implicated in these responses.

Some studies suggest a hyperthermic tone due to histamine signaling. Thus, premedication with a H2R antagonist before general anesthesia augments core hypothermia during this procedure [52]. In pathological conditions histamine appears to mediate hypothermic responses. Ionizing radiation induces hypothermia that can be blocked by H1R and H2R antagonists applied centrally [53]. Exposure of the head to ionizing radiation appers to stimulate histamine release from brain-resident mast-cells [53].

Peripherally, histamine is involved in the rise of skin blood flow during whole body heating [54]. Similarly, combined H1R and H2R antagonists diminish the alcohol-induced flushing in individuals of Oriental origin [55].

More recent observations using transgenic models further indicate a role of histamine signaling in thermoregulation are. Thus H3R-/- transgenic mice display a lowered core body temperature suggesting that these receptors mediate a tonic hyperthermic action [56]. Other studies point to a hypothermic action of histamine, mediated by H1 subtype receptors. Thus, anaphylaxis induced hypothermia is not observed in HDC(-/-) mice or in the presence of H1R antagonists [57]. Also, IL-1β-induced thermogenesis is potentiated by depletion of hypothalamic histamine [58].

Our studies have established that in mice histamine induces hyperthermia when administered in either the medial or the median preoptic nuclei [59]. Similarly, when the endogenous concentration of histamine was raised in either nucleus by local injection of histamine *N*-methyl transferase inhibitor a hyperthermia of similar amplitude was observed [59]. H1R and H3R specific agonists were equally potent in inducing a hyperthermia when infused in the median preoptic nucleus [21]. In contrast, H2R specific agonists mimicked the histamine effect when administered intra-MPON, while H1R specific agonists had little effect [60]. Surprisingly, H3R specific agonists were without effect in this nucleus [60].

Our experiments have also revealed that histamine modulation of the activity of GABAergic PO/AH neurons provides a mechanism for selective modulation of body temperature at the beginning of the active phase of the circadian cycle [61]. Thus, injection of a H3 antagonist in the MnPO induces a delay in the onset of the rise of the body temperature associated with the active phase of the circadian cycle [61].

6. Histaminergic control of energy expenditure

Maintenance of core body temperature represent a major energy expenditure of a homeothermic organism. Uncoupling proteins (UCPs) are inner mitochondrial membrane transporters of free fatty acids, which dissipate the proton gradient by releasing stored energy as heat, without coupling to other energy consuming processes [62]. UCP1 in brown adipose tissue (BAT) plays a crucial role in regulating energy expenditure and thermogenesis in rodents and neonates of larger mammalian species, including humans. UCP2 and UCP3 are not involved in adaptive thermogenesis, however their activation *in vivo* by physiological activators or pharmacological intervention has the capacity to be significantly thermogenic [63]. The hypothalamus controls UCP1 and UCP3 expression in BAT and white adipose tissue (WAT) via the sympathetic neuron system. Infusion of histamine in the third ventricle or in the preoptic area (POA) produces similar increases in BAT sympathetic nerve activity (SNA) and in the UCP1 mRNA expression [64]. By contrast injections of histamine in the lateral hypothalamus or the ventromedial hypothalamic nucleus were without effect ([64]), suggesting that the POA is the principal hypothalamic site which mediates the stimulatory effect of histamine of this efferent pathway. Histamine-deficient animals (HDC-/-) have an impaired ability to express UCP1 in BAT [65] further suggesting a role of histamine signaling in the control of energy expenditure. Similarly, the upregulation of UCP1 mRNA expression induced by central infusion of leptin is attenuated in H1R-/- mice [66] suggesting a role of this receptor subtype in mechanisms regulating energy expenditure. The role of the other histamine receptor subtypes also present in the PO/AH in this effect remains to be determined. Increased hypothalamic histamine also results in a decreased respiratory quotient, which indicates increased lipid oxidation [67].

In our study [59] we have determined the effects of activation of histamine receptors in the preoptic area by increasing the concentration of endogenous histamine or by local injection of specific agonists. Both approaches induce an elevation of core body temperature and

decreased respiratory exchange ratio (RER). The hyperthermic effect is associated with a rapid increase in mRNA expression of uncoupling proteins in thermogenic tissues, the most pronounced being that of uncoupling protein (UCP) 1 in brown adipose tissue and of UCP2 in white adipose tissue. In diet-induced obese mice histamine had much diminished hyperthermic effects as well as reduced effect on RER. Similarly, the ability of preoptic histamine signaling to increase the expression of uncoupling proteins was abolished. We also found that the expression of mRNA encoding the H1 receptor subtype in the preoptic area was significantly lower in obese animals [59].

Several H1R and H2R antagonists are clinically used in the treatment of several diseases. H1R antagonists (e.g. diphenhydramine hydrochloride, trade name Benadryl) are clinically used in the treatment of histamine-mediated allergic conditions. Clinically-relevant histamine H2R antagonists (e.g. ranitidine and cimetidine, trade names Zanatac and Tagamet, respectively) are used to reduce the secretion of gastric acid by acting on H2 receptors found principally in the parietal cells of the gastric mucosa. Interestingly, few side effects related to thermoregulation have been reported, due probably to the fact that these compounds cross the blood-brain barrier to a small extent. More recently, H3R antagonists have received a great interest from the pharmaceutical industry, with some drugs being in phase I or phase II of clinical trials [68]. Some projects have proposed H3R antagonists for the treatment of narcolepsy and/or cognitive disorders while others are trying H3R antagonists for the treatment of obesity and diabetes mellitus. All these drugs act at central H3Rs and produce increased levels of histamine in the brain, in particular in the hypothalamus. Since these compounds are designed to work centrally, the possibility of thermoregulatory side effects is significantly enhanced.

H1R antagonists have been reported to increase seizure susceptibility in patients with febrile seizures [69,70]. These observations strengthen the idea that these drugs can act centrally to influence body temperature and other centrally regulated functions. Thus, H1R antagonists in most cases should not be prescribed to patients, particularly young infants, with febrile seizures and epilepsy. Drug-induced fever due to H2R blockers was also encountered, however the effect appears to be mediated by an allergic reaction to the drugs, characterized by a marked increase in IgE [71].

7. Cellular mechanisms involved in histamine induced hyperthermia

An early extracellular recording study found that most rat PO/AH neurons, irrespective to their thermosensitivities were excited by histamine, effect which was blocked by a H1 antagonist in most neurons [72]. In few neurons the excitation was blocked also by an H2 antagonist [72]. Our recent studies have revealed that histamine acts differentially on neurons of the median and medial preoptic nuclei (MnPO and MPON respectively). The neurotransmitter reduced the spontaneous firing rate of thermoregulatory GABAergic MnPO neurons by activating H3 subtype histamine receptors [21]. This effect involved a decrease in the level of phosphorylation of the extracellular signal-regulated kinase

(ERK1/2) and was not dependent on synaptic activity. Single-cell reverse transcription-PCR analysis revealed expression of H3 receptors in the histamine responsive population of GABAergic MnPO neurons. Histamine applied in the MnPO nucleus induced a robust, long-lasting hyperthermia effect that was mimicked by H3 histamine receptor subtype-specific agonists [21]. We have also established that an increase in the A-type K^+ current in GABAergic MnPO neurons in response to activation of H3 histamine receptors results in decreased firing rate and hyperthermia in mice [61]. The Kv4.2 subunit is required for these actions since Kv4.2-/- preoptic GABAergic neurons are not affected by histamine or H3 agonists. Moreover, Kv4.2-/- mice develop much reduced hyperthermias in response to histamine or H3 agonists. Dynamic clamp experiments demonstrate that enhancement of the A-type current by a similar amount to that induced by histamine is sufficient to mimic its robust effect on firing rates. These experiments reveal a central role played by the Kv4.2 subunit in histamine regulation of body temperature and its interaction with pERK1/2 downstream of the H3 receptor.

Our studies have also established that a population of non-GABAergic MnPO preoptic neurons was depolarized, and their firing rate was enhanced by histamine acting at H1 subtype receptors [21]. In our experiments, activation of the H1R receptors was linked to the phospholipase C pathway and Ca^{2+} release from intracellular stores. This depolarization persisted in TTX or when fast synaptic potentials were blocked, indicating that it represents a postsynaptic effect. Single-cell reverse transcription-PCR analysis revealed the expression of H1 receptors in these putative glutamatergic cells. The inward current is activated in a Ca-dependent manner. At high histamine (20 μM) concentration the excitation elicited by histamine in glutamatergic MnPO neurons has also a persistent component that can last for at least 40 min after the removal of the bioamine. TRPC1 and TRPC5 channels appear to be the channels that contribute most to the inward current activated downstream of H1Rs. H1 agonists also induced long-lasting hyperthermia when injected intra-MnPO. These studies have shown that histamine modulates the core body temperature by acting at two distinct populations of preoptic neurons that express H1 and H3 receptor subtypes, respectively.

The mechanisms activated by histamine in the MPON are different. Histamine activates H2 subtype receptors in the MPON and induces hyperthermia [60]. We also found that a population of glutamatergic MPON neurons express H2Rs and are excited by H2R specific agonists. The agonists decreased the input resistance of the neuron and increased the depolarizing "sag" observed during hyperpolarizing current injections. Activation of H2Rs induced an inward current that was blocked by ZD7288, a specific blocker of the hyperpolarization activated cationic current (Ih). In voltage-clamp experiments, activation of H2R receptors resulted in increased Ih amplitude in response to hyperpolarizing voltage steps and a depolarizing shift in its voltage-dependent activation. The neurons excited by H2 specific agonism expressed the HCN1 and HCN2 channel subunits. Our data indicate that at the level of the MPON histamine influences thermoregulation by increasing the firing rate of glutamatergic neurons that express H2Rs [60].

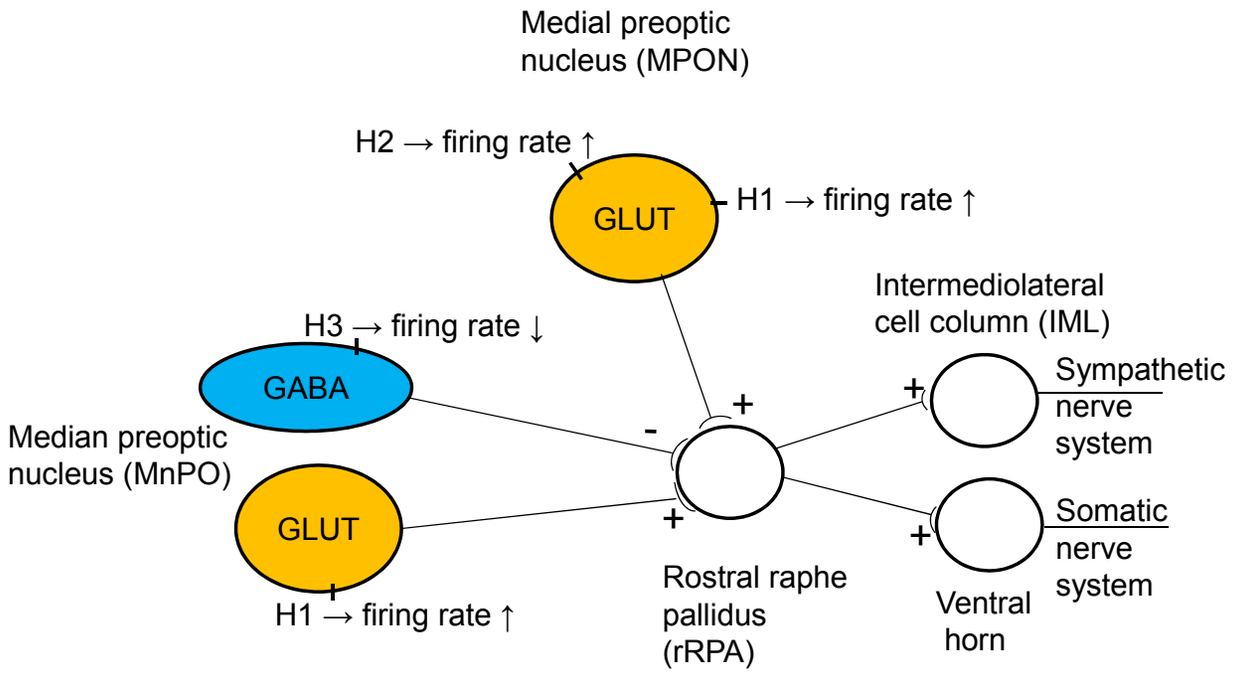

Figure 1. Simplified diagram of the neural pathways controlling thermoeffector mechanisms (Morrison and Nakamura, 2011). The diagram also illustrates the proposed cellular mechanisms activated by histamine. GABAergic neurons in the MnPOA tonically inhibit sympathetic premotor neurons in the rostral raphe pallidus. Histamine reduces the firing rates of GABAergic MnPO neurons. This results in stimulation of the sympathetic output system. Activation of H1 and H2 receptors expressed by MnPO and MPON neurons, respectively, increased firing rates and stimulates the sympathetic neuron system. The dashed lines indicate that the respective projections have been suggested by physiological studies but have not been demonstrated directly.

8. Conclusion

Histamine has a complex influence on thermoregulation and its circadian cycle and appears to be involved in numerous pathophysiological responses that involve changes in core body temperature. At the level of the MnPO and MPON histamine induces potent hyperthermia and an increase in energy expenditure by activating several signaling pathways and neuronal networks.

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