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Commentary

Histamine in the brain: Beyond sleep and memory

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ABSTRACT

A few decades elapsed between the attribution of unwanted side effects of classic antihistamine compounds to the blockade of central H_1 receptors, and the acceptance of the concept that the histaminergic system commands general states of metabolism and consciousness. In the early 80s, two laboratories discovered independently that histaminergic neurons are located in the posterior hypothalamus and project to the whole CNS [Panula P, Yang HY, Costa E. Histamine-containing neurons in the rat hypothalamus. Proc Natl Acad Sci 1984;81:2572–76, Watanabe T, Taguchi Y, Hayashi H, Tanaka J, Shiosaka S, Tohyama M, Kubota H, Terano Y, Wada H. Evidence for the presence of a histaminergic neuron system in the rat brain: an immunohistochemical analysis. Neurosci Lett 1983;39:249–54], suggesting a global nature of histamine regulatory effects. Recently, functional studies demonstrated that activation of the central histaminergic system alters CNS functions in both behavioral and homeostatic contexts, which include sleep and wakefulness, learning and memory, anxiety, locomotion, feeding and drinking, and neuroendocrine regulation. These actions are achieved through interactions with other neurotransmitter systems, and the interplay between histaminergic neurons and other neurotransmitter systems are becoming clear. Hence, numerous laboratories are pursuing novel compounds targeting the three known histamine receptors found in the brain for various therapeutic indications. Preclinical studies are focusing on three major areas of interest and intense research is mainly oriented towards providing drugs for the treatment of sleep, cognitive and feeding disorders. This commentary is intended to summarize some of the latest findings that suggest functional roles for the interplay between histamine and other neurotransmitter systems, and to propose novel interactions as physiological substrates that may partially underlie some of the behavioral changes observed following manipulation of the histaminergic system.

1. Interactions among histaminergic and other neurotransmitter systems regulate the sleep–wake cycle

Several experimental observations support the hypothesis that the histaminergic system constitutes a major wake-promoting system, as its terminals influence neuronal excitability in several brain areas [1,2]. Direct electrophysiological recordings from freely moving cats showed that the activity of histaminergic neurons is high during waking and low or absent during sleep [3], and their firing rate changes with the behavioral state [4]. The importance of histaminergic

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neurons in maintaining the brain in an awake state when challenged by environmental demands was demonstrated in mice lacking either histidine decarboxylase (HDC, the histamine synthesizing enzyme) [5], or the histamine H_1 receptor [6]. Indeed, the abolition of histamine synthesis or one of its effector mechanisms impairs the cortical electroencephalogram (EEG) and deteriorates both sleep and waking quality, thus causing somnolence and behavioral deficits.

Wakefulness is maintained by the interactions among, or coordinated action of different chemical neurotransmitters, such as the histaminergic, cholinergic, serotonergic, adrenergic, and orexinergic cells (Fig. 1). Collectively, these wake promoting neurons are named the ascending arousal system [7], and each contributes in a unique way to the onset or maintenance of wakefulness [8]. The histaminergic effects on arousal are likely mediated by stimulation of cholinergic nuclei. Acetylcholine-containing neurons discharge during waking, decrease firing during slow-wave sleep (SWS) and fire at high rates during paradoxical sleep (PS) in association with fast cortical activity. The histaminergic system achieves cortical activation through excitatory interactions with the cholinergic corticopetal neurons originating in the basal forebrain [9], as well as with the cholinergic mesopontine tegmentum projecting to the thalamus and hypothalamus which in turn affect cortical excitability [10]. Activation of H_1 receptors is responsible for the wake promoting effect of histamine in cats [10]; furthermore, H_1 receptor agonists cause excitation of cholinergic neurons in the nucleus basalis magnocellularis (NBM) that project to the cortex [11]. Close partners of the histaminergic system in the regulation of wakefulness are the noradrenergic and serotonergic neurons, which together with the histaminergic neurons are minimally

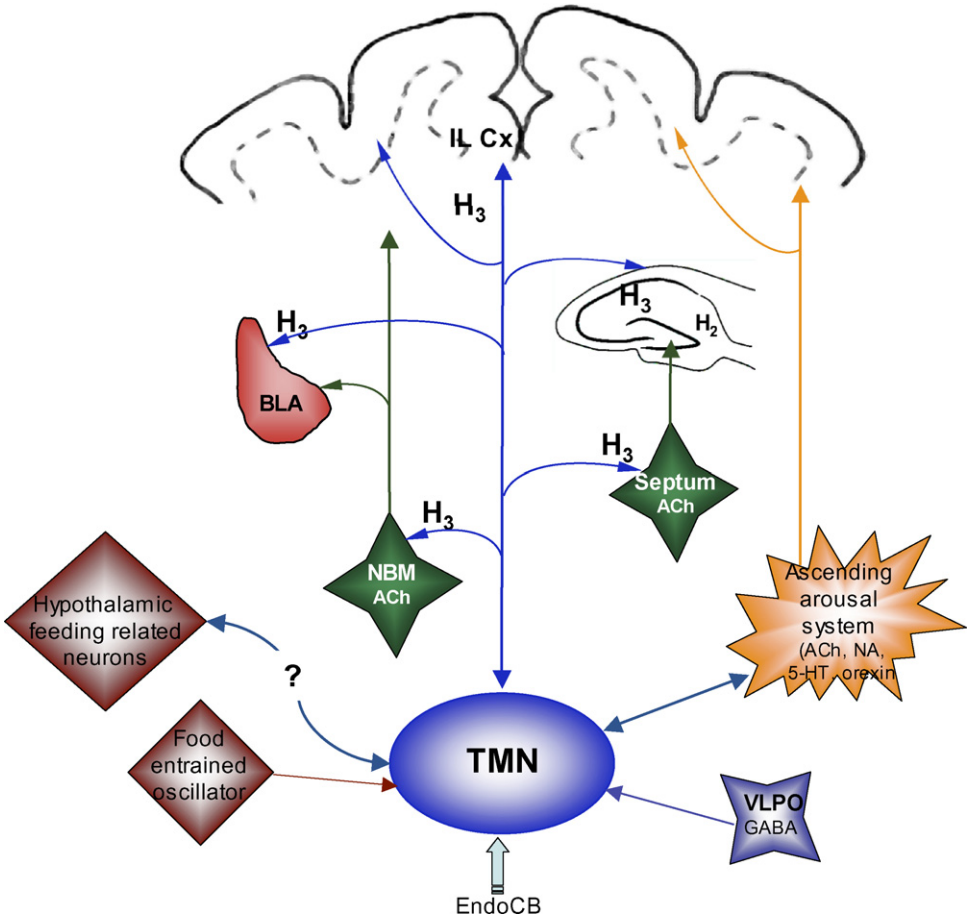

Fig. 1 – Simplified circuitry representing the hypothetical wiring of histaminergic neurons and their impact on the sleep–wake cycle, cognition and feeding behavior. Multiple interactions between histamine-containing neurons in the tuberomamillary nucleus (TMN) and the other components of the ascending arousal system have a major role in neocortical activation during wakefulness. Histaminergic neurons can also activate the cortex directly by diffuse hypothalamo–cortical projections. The TMN is under the inhibitory control of GABAergic projections from the ventrolateral preoptic area (VLPO). H_3 receptor ligands influence learning and memory by modulating ACh release in the basolateral amygdala (BLA), a region that receives cholinergic projections from the nucleus basalis magnocellularis (NBM). Blockade of H_3 autoreceptors in the BLA, septum and NBM increases histamine release locally. In the hippocampus, H_2 and H_3 receptors activation triggers erk-2 phosphorylation and improves the expression of fear memory. The TMN is engaged by circadian signals entrained during scheduled feeding, and by infralimbic (ILCx) inputs during the appetitive behavior. The interactions between TMN and hypothalamic, feeding related nuclei are not clear. Endocannabinoids (EndoCB) activate TMN neurons, but the functional role is not known.

active during PS [12,13]. Noradrenaline-, serotonin- and histamine-containing neurons are active during waking with behavioral arousal, decrease firing during SWS and cease firing during PS (reviewed in Ref. [8]). However, very little is known on the interplay between histaminergic neurons and the other aminergic cells in the regulation of wakefulness. Noteworthy, a striking difference among the activity of these monoaminergic systems was reported in genetically narcoleptic Doberman dogs during cataplexy, a state in which muscle tone is suddenly lost, but awareness continues as in alert waking. Whereas noradrenergic cells of the locus coeruleus and serotonergic cells cease or reduce discharge during cataplexy [14,15], histaminergic cells maintain waking levels of activity [16], reinforcing the concept of brain histamine being tightly linked to forebrain arousal, whereas serotonergic and noradrenergic cells controlling muscle tone during waking. Histamine is also involved in regulating the maintenance of the circadian rhythm; indeed, histamine deficiency leads to a lowered activity level, disrupted circadian rhythm of the clock genes *mPer1* and *mPer2* expression in the neocortex and striatum, but not in the circadian pacemaker suprachiasmatic nucleus, suggesting that histamine modulates the output behavior of the circadian pacemaker [17].

Hypocretin/orexin neurons integrate circadian-photic and nutritional-metabolic influences and coordinate the activity of the aminergic nuclei [18]. They fire maximally during active waking and are quiescent during PS, like the histaminergic cells [8]. One of the major outputs of the orexinergic system that likely promotes wakefulness is the direct activation of histaminergic neurons in the tuberomamillary nucleus (TMN) where all histaminergic cell bodies are located [19]. The first demonstration of a functional interaction between the histaminergic and orexin systems was provided by Huang and collaborators. They showed that i.c.v. administration of orexin causes increased wakefulness in rats, and this effect is dampened when histamine neurotransmission is blocked [20]. A further proof of the tight link between the two systems in controlling wakefulness is the altered histamine content in the brain of orexin receptor-deficient, narcoleptic dogs [21] and in the cerebrospinal fluid of orexin-deficient narcoleptic patients [22].

Histamine-containing neurons, therefore, participate to a complex neuronal network that promotes wakefulness. The histaminergic system participate in the generation and maintenance of wakefulness, and recent data indicate that the activity of histaminergic neurons is mostly linked to behavioral arousal, for instance, in food anticipating arousal (see below).

2. Interactions among histaminergic and other neurotransmitter systems affect cognition

It is known that manipulation of the histaminergic central system during several learning paradigms modifies animal behavior; however, the results are often contradictory, as both facilitatory and inhibitory effects of histamine on memory have been described (see review [23]). This is not too surprising, as memory is a complex process that consists of related but dissociable events, involving, in the elaboration of disparate learning situations, distinct brain regions activated to different degrees and at different times. The specificity of action of histamine depends on the localization of histaminergic receptor subtypes, the brain region and the nature of the cognitive task involved, and the activation of specific intracellular pathways. Furthermore, intracerebral pharmacological manipulations may help elucidate the role of small brain regions in certain behavioral responses, but do not necessarily predict general conclusions on the effect of the same compounds when administered systemically.

We proposed that the controversial role of histamine can be partially reconciled with the observation that histamine modulates the cholinergic function differently in discrete brain regions that are known to be devoted to the acquisition and/or expression of specific behaviors [23,24]. In our laboratory, we are interested in emotional memory, which we study using an adversely motivated training task, contextual fear conditioning. In this test, the experimental animal learns to associate a mild electrical foot-shock with the environment where it receives the punishment. Re-exposure to the same environment will induce, even in the absence of the punishment, a stereotyped behavior named freezing that is characterized by the complete absence of voluntary movements. The time spent freezing during recall is correlated with animal memory ability, since an amnesic animal will spend less time freezing during recall, than a normal one. Fear memories become stabilized through a time-dependent process known as consolidation, during which they are labile and can be disrupted by a number of interfering events, including electroconvulsive shock, trauma and several drugs, such as protein synthesis inhibitors or receptor blockers. A critical event for emotional memory consolidation is the stimulation of muscarinic receptors within the basolateral amygdala (BLA) [25–27]. Also, administration of H_3 receptor ligands into the BLA modifies the expression of fear memories in a bimodal fashion, and modulates the cholinergic tone within the amygdala accordingly. Local perfusion with H_3-antagonists/inverse agonists moderates acetylcholine (ACh) release from the BLA, as measured with microdialysis, and decreases the freezing time of trained rats compared to saline injected controls [26], thus causing an amnesic effect (Fig. 2A). Conversely, intra-BLA administration of H_3 receptor agonists augments the freezing time, which is an indication of procognitive effects, and increases ACh release from the BLA [27].

Moreover, systemic administration of ABT-239, a selective H_3-receptor antagonist, improves social memory and the acquisition of a five trial, inhibitory avoidance test, and increases ACh release from the hippocampus and the cortex [28]. This effect may be relevant for the observed behavioral changes. Since local administration of histamine in the hippocampus does not modify ACh release [29], likely, H_3 receptor antagonists facilitate ACh release in the hippocampus interacting with histaminergic H_3 autoreceptors in the septum where the cholinergic cell bodies that project to the hippocampus are located (see Fig. 1). Indeed, using the dual-probe microdialysis technique, it was shown that the blockade of H_3 receptors in the septum with selective antagonists/inverse agonists, such as thioperamide or ciproxifan, increases ACh release from the hippocampus [29]. However,

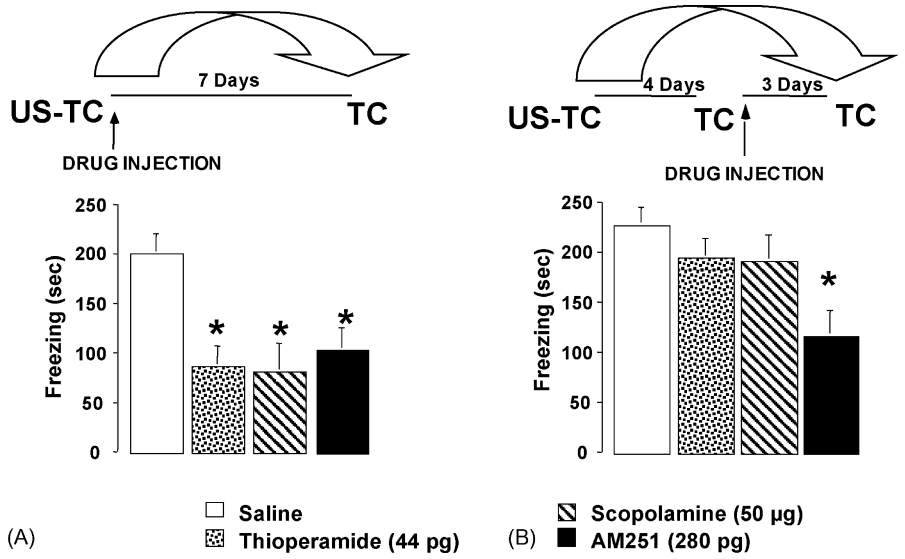

Fig. 2 – Antagonists of CB1-r, muscarinic and histamine H_3 receptors have different effects on consolidation and reconsolidation of contextual fear memory. (A) Effects on contextual fear conditioning of immediate post-training bilateral injection of AM251, scopolamine, or thioperamide into the amygdala. (B) Effects on contextual fear conditioning of bilateral injection of AM251, scopolamine, or thioperamide into the amygdala administered 4 days after training and immediately after re-exposure to TC. In both paradigms, freezing was measured seven days after training during the 6 min test period in saline-injected controls ($n = 9$), rats injected with 280 pg AM251 ($n = 9$), 50 μg scopolamine ($n = 8$) or 44 pg thioperamide ($n = 9$). Means ± S.E.M. are shown. $^{*}P < 0.05$ vs. saline (ANOVA and post hoc "All Pairs Tukey–Kramer" test). US: unconditioned stimulus; TC: training context. Data were obtained from Ref. [35].

hippocampal histamine may influence cognition also independently of ACh modulation. For instance, local administration of histamine in the hippocampus improves the expression of fear memory through activation of H_2 and H_3 receptors [30]. This effect is a direct consequence of the H_2 and H_3 receptor-elicited activation of erk-2 in hippocampal CA3 pyramidal neurons [30].

Consolidation of fear memory is affected by other systems as well [31]. We have begun to explore the possibility that endocannabinoids and histamine modulate the behavior associated with fear memory in a concerted manner in the amygdala. Endocannabinoids are unorthodox neuromodulators, as supposedly they are produced and travel from a postsynaptic to a presynaptic site. A well-established physiological role of the endocannabinoid system is the regulation of neurotransmitter release at a wide variety of synapses throughout the CNS [32]. Endocannabinoids underlie associative plasticity in the amygdala [33] and cannabinoid CB1 receptors are involved in long-term depression of GABA-mediated inhibitory currents in the amygdala [34]. We recently showed that blockade of the CB1 receptor immediately after training, impairs consolidation of fear memory in a manner similar to H_3 receptor antagonists and scopolamine (Fig. 2A), suggesting that after contextual fear conditioning endocannabinoids are produced in the amygdala and participate in the consolidation of emotional memories [35].

Evidence suggests that a consolidated memory is not permanent, because retrieval renders a consolidated memory susceptible to amnesic treatments [36]. Retrieval may be induced by briefly re-exposing the experimental animal to one of the elements (e.g. context) initially associated with the punishment (footshock). Another consolidation process, named 'reconsolidation', has been hypothesized to keep the original memory persistent [37]. Results, though, appear conflicting, as some authors failed to demonstrate 'reconsolidation'. Indeed, although the protein synthesis inhibitor anisomycin impairs memory when given after retrieval [36], this amnesia reverses with time [38–40]. Thus, a temporary deficit argues against the 'reconsolidation' hypothesis. To unravel this controversy, much effort has focused on determining whether reconsolidation and consolidation share the same mechanisms. The question is not of merely academic interest, since erasing stubborn memories reactivated with neutral stimuli may have promising clinical applications in the treatment of mood disorders, for instance post-traumatic stress disorders. In clinical practice, one way to overcome inappropriate panic is to expose the patient to an element of the disturbing situation. Then, one might envisage the association of exposure with drug treatment to disrupt the reactivated memory. Similarly, the treatment of drug abuse may benefit from disrupting reconsolidation of memory associated drugs of abuse to reduce drug seeking behavior, as demonstrated in rats [41]. We recently showed that in the amygdala, the neuronal systems engaged in consolidation and reconsolidation, do not completely overlap [35]. As shown in Fig. 2B, the endocannabinoid system appears to participate in both memory-consolidation and -maintenance after reactivation, as the intra-amygdala administration of the selective CB1 receptor antagonist AM251 (used at a concentration that do not block Na^+ conductance [42]) has detrimental effects on both. Conversely, cholinergic and histaminergic neurotransmission

appears involved only in consolidation [35]. Conceivably, these findings fit well with the 'reconsolidation' hypothesis, and it appears that in the amygdala the neuronal circuitries engaged during 'reconsolidation' partially recapitulate the activity during consolidation. This is presumably a more reliable and economic way to maintain fear-associated memories after reactivation. A caveat is, however, appropriate: a 3-day interval might be too short to rule out that the observed amnesia is temporary. Nevertheless, further investigation is required to elucidate whether the endocannabinoid and histaminergic systems modulate these processes in a concerted manner within the amygdala. Furthermore, systemic administrations of compounds should clarify the potential clinical application of cannabinoid and histaminergic ligands. In fact, one cautionary note should be drawn from these studies. Intracerebral administration of compounds is an important protocol to elucidate specific mechanisms underlying biological events such as learning and memory and to pinpoint possible unwanted side effects. Caution should be used when making general conclusions on the effect of systemic administrations of the same compounds.

One concluding remark should be spent addressing the issue of the difficulty in dissociating the arousal from the cognitive effects of histaminergic compounds. It is known that the level of arousal affects retention and consolidation of memories [43]. Thus, it is conceivable that neuronal histamine affects cognitive processes by modulating neuronal functions throughout the brain, according to the animal state. Nevertheless, our data provide one piece of evidence indicating that the histaminergic system influences directly neurobiological processes underlying learning and memory. Infact, in our studies [26,27,30,35] histaminergic compounds were administered in restricted brain regions under deep anaethesia, and the mnemonic effects were tested several hours (days) afterwards, when the histaminergic ligands have, presumably, been completely metabolized.

3. Beyond learning and memory, histamine and cannabinoids are involved in feeding behavior

Endocannabinoids and histaminergic neurons exert complex actions on neurotransmitter networks involved in cognitive processes, locomotion, appetite and, interestingly, they command several, similar behavioural states. Until recently, though, no information was available on the possible interactions between these two systems. We recently studied the effect of systemic and intra-hypothalamic administration of selective CB1 receptor agonists on histamine release from several brain regions, with the double-probe microdialysis technique in freely-moving rats [44]. One microdialysis probe was inserted in the proximity of the histaminergic cell bodies of the TMN, the other one in the nucleus basalis magnocellularis (NBM) or the striatum, brain areas that receive histaminergic projections. CB1 receptor agonists were administered in the TMN and histamine release was measured from the TMN, as well as the NBM and striatum. Unexpectedly, CB1 receptor agonists increased histamine release all areas tested (Fig. 3A and B). Interestingly, when the endocannabinoid uptake and metabolism inhibitor AM404 was infused into the TMN, increased histamine release was observed only in the TMN, but not in the histaminergic projection areas [44]. Our current

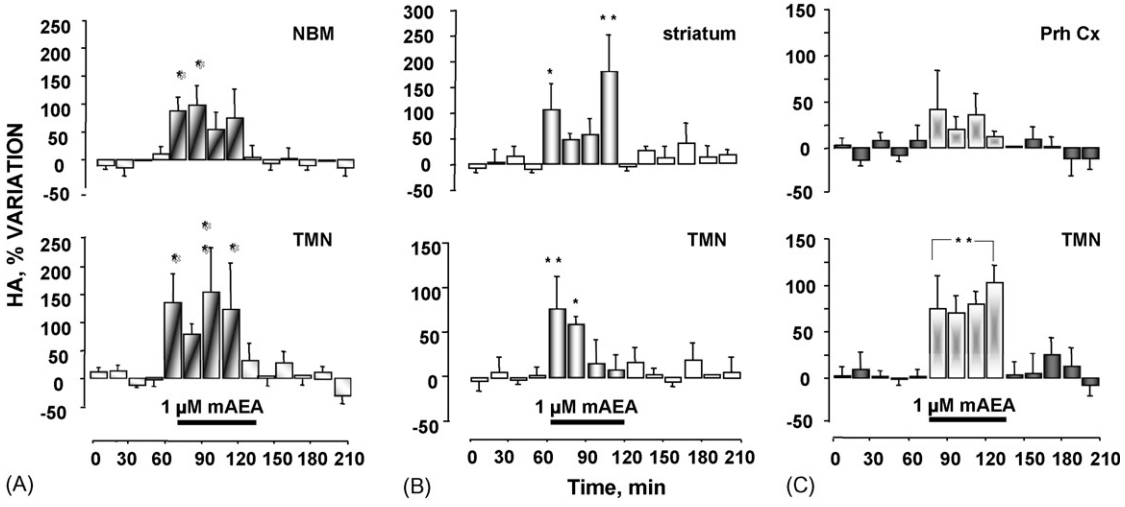

Fig. 3 – Influence of a CB1 receptor agonist administration into the TMN on histamine release from the TMN and histaminergic projection areas of freely moving rats. Each rat was implanted with two microdialysis probes. Methanandamide (mAEA, 1 μM) was infused into the TMN and histamine release was measured from the TMN (lower panels) and from several histaminergic projection areas: (A) nucleus basalis magnocellularis (NBM; upper panel); (B) striatum (upper panel) or (C) perirhinal cortex (Prh Cx; upper panel). Histamine was measured in 15 min fractions. Control values of spontaneous histamine release were calculated for each experiment by averaging the mean of four initially collected 15 min samples. Histamine release was expressed as a percentage of spontaneous release. Represented are means ± S.E.M. of four experiments per group. $^{*}P < 0.05$ vs. last $^{**}P < 0.01$; $^{*}P < 0.05$ vs. last sample before drug treatment (ANOVA and Fisher's test).

interpretation is that the increased endocannabinoid tone produced by AM404 augments histamine release only in the TMN, presumably by activating a more restricted, or different population of CB1 receptors than those activated by the administration of direct acting CB1 receptor agonists. Relevant to our study is that our results are in agreement with *in vivo* studies demonstrating that the administration of AM404 or URB597, an inhibitor of the metabolic pathway of the endocannabinoid anandamide, do not mimic the full spectrum of pharmacological responses produced by classical CB1 receptor agonists (see Refs. [45,46] for a review). Hence, understanding in what circumstances endocannabinoids are released and activate histaminergic cells warrants further investigations and may provide interesting hints to develop new therapeutic strategies in the treatment, for instance, of food intake disorders. In this regard, the role of brain histamine and endocannabinoids is gaining increasing attention, because of the prominent role that they play in regulating appetite.

4. Brain histamine and feeding behavior

The association of histamine with feeding behavior became clear when it was observed that antidepressants and antipsychotics stimulate appetite and induce weight gain and that these drugs are potent H_1 receptor blockers [47]. We now know that brain histamine is involved in feeding physiology by modulating the release of neurotransmitters and hormones that drive or inhibit feeding [48] (Fig. 1). A large body of literature links the histaminergic system with consumption of food, as a satiety signal: (a) intracerebroventricular injections of histamine suppress appetite, whereas depletion of histamine stimulates feeding [49]; (b) hypothalamic neuronal histamine has been implicated in the regulation of feeding behavior and body adiposity through activation of postsynaptic histamine H_1-receptor (H_1-R) in the ventromedial hypothalamic (VMH) and paraventricular (PVN) nucleus [50,51], two brain areas that secrete neuroactive peptides crucially involved in the regulation of feeding behavior [52]; (c) histaminergic neurons are the targets of leptin in the brain, and central administration of leptin increases histamine turnover in the hypothalamus [53,54]; (d) blockade of the histaminergic H_3 autoreceptor increases extracellular histamine levels in the hypothalamus and reduces food intake [55]. Indeed, antagonists of the H_3 receptors are being developed as anti obesity drugs [55,56]. However, a recent study suggested that in mice H_3 receptor agonists have an antiobesity effect with a mechanism apparently independent of histaminergic tone modulation [57]. Nowadays, though, it is generally accepted that histamine does more than only mediating satiety. Recently, it has become clear that food-anticipatory activity exhibits the characteristics of a circadian rhythm, although determining the anatomic location of the food-entrainable oscillator (FEO) has been very difficult. Histamine drives feeding anticipating arousal, an important actor in the FEO, and is probably involved in numerous other feeding related processes [58]. In fact, while the effects of the histaminergic system in the modulation of the consummatory phase of feeding have been shown to be robust, the role of histamine in the appetitive phase and underlying behavioral mechanisms remains unclear. The appetitive phase of motivated behaviors has distinctive preparatory physiological changes, such as increases in behavioral arousal [59] and core temperature [58]. Therefore, the histaminergic system is a good candidate to promote arousal during the appetitive state (Fig. 1). Indeed, histamine-containing neurons are the only aminergic neurons related to arousal that become active in anticipation of an upcoming meal, as rats rendered motivated for food by 24 h fasting and enticed with food that they cannot obtain, show a significant increase in c-Fos immunoreactivity in the TMN, much earlier than in other brain regions [60]. Recent reports demonstrated that the infralimbic cortex that receives visceral information [61] and coordinates motivated behavior [62], and the TMN are activated in a coordinated temporal way during the appetitive responses to food enticing [63].

Histamine neurons may participate in the appetitive aspects of feeding also modulating reward processes involved in the motivation to feed. The shell of the nucleus accumbens (NAcc, a reward related brain area) receives a dense histaminergic innervation [64] and local administration of histamine into the NAcc enhances dopamine release [65]. The role of histamine in reward-related processes, though, is controversial, as both inhibitory and facilitatory effects have been described [66,67], and nothing is known on the involvement of this pathway during feeding behavior.

5. Endocannabinoids and feeding behavior

There is convincing evidence that both exogenous cannabinoids and the endogenous cannabinoids anandamide and 2-arachidonoylglicerol (2-AG) stimulate feeding. Their action is mediated by activation of CB1 receptors distributed in all brain areas and peripheral tissues involved in the control of energy intake, including the hypothalamus and NAcc (reviewed in Ref. [68]). This effect is of therapeutic relevance, as cannabinoid agonists are currently used to alleviate anorexia and nausea in AIDS patients, whereas the CB1 antagonist rimonabant (SR141716A) is effective in the treatment of obesity [69].

It has been suggested that brain endocannabinoids control energy balance both in the appetitive phase, increasing the incentive to find food, and during the consummatory phase, increasing appetite, but the mechanisms involved remain to be elucidated. Recent evidence, though, indicates that both the mesolimbic reward mechanism and the homeostatic hypothalamic nuclei are involved in these two aspects of feeding behavior. Indeed, endocannabinoid levels vary in the hypothalamus and limbic forebrain with different nutritional manipulations, with levels being the highest with food deprivation and lowest during food consumption [70]. Furthermore, either 2-AG injections in the shell of the NAcc [70], or anandamide administration into the VMH induce hyperfagia [71]. In some aspect, the histaminergic and endocannabinoid systems seem to be regulated in an opposing fashion: for instance, systemic administration of leptin that signals to the hypothalamus the nutritional state and reduces food intake, facilitates histamine release from

the hypothalamus [72], whereas it downregulates endocannabinoids levels in the same region [73]. Furthermore, concentrations of hypothalamic histamine and tele-methylhistamine, a major histamine metabolite, are significantly lower in obese (*ob*/*ob*) and diabetic (*db*/*db*) mice, and fatty (*fa*/*fa*) rats, leptin-deficient and leptin-receptor defective animals, respectively, relative to lean littermates [54]. On the other hand, defective leptin signalling is associated with elevated hypothalamic levels of enocannabinoids in obese *db*/*db* and *ob*/*ob* mice and Zucker rats. These data made it clear that histamine controls heterogeneous aspects of feeding. Presumably, histamine drives food intake by increasing the arousal state of the animal [58]. Secondary to arousing the animal, brain histamine seems to coordinate satiety and the consolidation of temporal information associated with food consumption [74,75].

In conclusion, for both histamine and endocannabinoids the mechanisms involved in regulating food intake are not fully understood and nothing is known about the temporal and causal relationship between these two systems in controlling the appetitive behavior. The question arises then, if and where in the brain the endocannabinoids and the histaminergic system interact and whether these interactions are involved in the consummatory and/or appetitive behavior.

6. Histamine, cannabinoids and other functional implications

The deleterious effects that cannabinoids have on cognitive processes are well known [76]. Therefore it may seem counterintuitive that cannabinoids facilitate histamine release from the NBM, given that activation of histamine H_1 receptors in the NBM increases cortical ACh release [11] and improves rat performance in the object recognition test [77,78]. However, augmented histamine release is also an indicator of stress [79] and it is conceivable that protracted occupancy of CB1 receptors, as produced by administering cannabinoid agonists, disrupts the spatiotemporal specificity of histamine release in different brain regions, contributing to maladaptive behavioral responses.

Administration of CB1 receptor agonists in the TMN facilitates histamine release from the striatum as well (Fig. 3B), a brain region that provides the anatomical substrate for the integration of movements [80], and participates in learning and executing adequate behavioral responses to environmental stimuli [81]. Histamine induces hypokinetic effects that are accompanied by altered dopaminergic transmission in the striatum [82], whereas systemic administration of CB1 receptor agonists reduces locomotion [83]. It is conceivable that the augmented histamine release in the dorsal striatum following cannabinoid administration in the TMN may contribute to the direct actions of cannabinoids on striatal neurones [84–86], worsening locomotor activity.

Taken together, these results show that the administration of cannabinoids is associated with a hyperhistaminergic state. Whether this is important in controlling food related behavior, in contributing to the cannabinoid detrimental effects on cognitive and locomotor performance and to drug-motivated habits that are crucial for the establishment of addiction are all open questions. Answering these queries may provide hints for potential therapeutics targets to treat motivated behaviors such as obesity or drug addiction.

7. Are histaminergic neurons a heterogeneous cell population?

The major obstacle in identifying the histaminergic system as a target for specific therapeutic applications is the global nature of its function. Tracing studies failed to reveal any topographical organization of the histaminergic projections arising from the TMN, however, two recent studies suggest that histamine neurons are functionally heterogeneous, based on differential activation by acute stress [87], and on the expression of different γ-subunits that confer different sensitivity to exogenous GABA [88]. As reported previously [44], infusions of the CB1 receptor agonist methanandamide (mAEA) in the posterior hypothalamus in the proximity of the histaminergic cell bodies, increase histamine release from histaminergic projection areas such as the NBM and striatum (Fig. 3A and B). However, during perfusion of the posterior hypothalamus with mAEA, histamine release from the perirhinal cortex (Prh Cx) does not change significantly (Fig. 3C), despite the profuse histaminergic innervation of the perhinal cortex [64] and the presence of histaminergic receptors [89]. Therefore, mAEA-induced excitation of histaminergic neurons might not necessarily produce a broad activation of all histaminergic projections, as subpopulations of histaminergic cells projecting to different brain regions respond differently to the same pharmacological manipulation. In addition, preliminary results from our laboratory using the double-probe microdialysis technique in freely moving rats suggest that subpopulations of histaminergic cells projecting to different brain regions respond differently to bicuculline or thioperamide [90].

The observation that histaminergic neurons are not a homogenous neuronal population may have relevant consequences in the development of target specific drugs that affect only subset of histaminergic cells, and in reducing the occurrence of collateral or undesired effects.

8. Concluding remarks

Our knowledge of the functional roles of brain histamine is far from complete. For as much as it may seem that the role of the histaminergic system is redundant in modulating the sleep–wake cycle, it is becoming clear that histamine in the brain finely orchestrates diverse aspects of behavioral responses that require an aroused state. For example, histamine supposedly drives food intake by increasing the arousal state of the animal [58], and secondary to arousing the animal, histamine coordinates satiety and the consolidation of temporal information associated with food consumption [74,75]. Augmented histamine release is also an indicator of stress and disrupting the spatiotemporal specificity of histamine release may contribute to maladaptive behavioral responses.

The many actions of the histaminergic system are achieved through interactions with other neurotransmitter systems,

and some of the interplay between histaminergic neurons and other neurotransmitter system has been described (Fig. 1). For instance, the sleep–wake cycle and learning are presumably influenced by the control that histamine exerts on the forebrain cholinergic neurons. On the other hand, the unexpected excitatory effect that cannabinoids exert on histaminergic cells is still orphan of a functional explanation. Obviously, new discoveries create great expectations and great effort is being channeled into developing ever more selective histaminergic compounds for the treatment of neuropsychiatric disorders and metabolic dysfunctions. This will be a great challenge in the years to come.

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