Chapter 10
Heterogeneity of Histaminergic Neurons

Patrizia Giannoni

Abstract The central histaminergic system has a complex neuroanatomical and functional organisation. It originates in a small area of the posterior hypothalamus, the tuberomammillary nucleus (TMN). Despite the restricted location of cell bodies, anatomical studies showed that histamine neurons project to almost the entire brain. Indeed, neuronal histamine (HA) has been proven to modulate a plethora of body functions. The TMN was initially considered a single functional entity with neurons working in a coordinated and synchronous way. Recently though, several works are indicating that histaminergic neurons are organised in heterogeneous populations with distinct roles. Accumulating evidence based on multiple techniques suggests different properties among histamine TMN neurons. Although further studies are needed to fully characterise the organisation of the central histaminergic system and its activation following specific stimuli, interesting observations are emerging on the selective activity of clusters of histaminergic neurons according to the homeostatic or behavioural status. The heterogeneity of histamine neurons might represent the key for a fine-tuned modulation of specific functions regulated by neuronal HA. With the present chapter, we analyse the main findings and discuss future directions.

Keywords Neuronal histamine • Tuberomammillary nucleus (TMN) • Heterogeneity • Projection areas • Stressors • Stoichiometry

10.1 Introduction

In the brain, histamine (HA) is produced from neurons and mast cells. Yamatodani and colleagues in the early 1980s estimated that approximately 50 % of HA content in the brain derives from brain mast cells [1]. Although a recent study performed in mast cell-deficient mice (W/Wv) demonstrated that mast cell-derived HA is involved in sleep regulation, feeding behaviour, anxiety and depression [2], most studies conducted on histaminergic functions in the CNS focused on HA released from neurons. The source of central neuronal HA has been established simultaneously by

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two different laboratories more than 30 years ago. Thanks to the development of selective antibodies, the origin of the central histaminergic system was located in the tuberomammillary nucleus (TMN), a region of the posterior hypothalamus. In 1983, Watanabe and colleagues showed histamine-containing cells in the rat brain by indirect immunofluorescent histochemistry [3] with an antibody against histidine decarboxylase (HDC), the enzyme converting L-histidine to HA [4]. Numerous HDC immunoreactive neurons were shown in the posterior hypothalamic area; furthermore, HDC-immunopositive nerve fibres with a varicose appearance were found widely distributed in the brain. With a similar approach, using an antibody against HA, Panula and collaborators described in 1984 a comparable distribution of histaminergic neurons [5]. Histamine-immunoreactive neuronal cell bodies were found only in the hypothalamic and premamillary areas. The largest group of cells was seen in the caudal magnocellular nucleus and medially on the dorsal and ventral aspects of the ventral premamillary nucleus. Immunoreactive nerve fibres, but not cell bodies, were detected in other parts of the brain. Histamine-containing neurons appeared organised in clusters. In the rat brain, neuronal populations named E1, E2 and E3 have been described in the posterior hypothalamus, E4 in the ventromedial area and E5 in the more dorsal part [3, 5–9]. Recently, a similar organisation has been described in the mouse brain [10]. Slight differences between species, Wistar rats and C57/Bl6 mice, were mostly attributed to a different body mass. It is well documented that histaminergic neurons send projections to almost the entire brain. Several studies [6–8, 11] showed that retrograde tracers injected into different brain regions labelled histaminergic cell bodies scattered through the TMN. Thus, although divided in clusters, projection neurons do not seem to be organised in a highly topographic way, and individual TMN neurons give rise to both ascending and descending projections. Interestingly, histaminergic neurons originate from the TMN in all vertebrates studied so far [6, 12, 13]. In the rat brain a total of about 4600 histaminergic neurons is estimated [7], while an approximately 64,000 were estimated in the human brain [14]. The arborisation of histaminergic neurons present diffuse varicosities containing synaptic vesicles, and rarely form classical synapses, like other neurotransmitter systems [15]. Given these neuroanatomical features, HA can exert specific and selective actions through direct contacts, but it also can diffuse from the site of release and act as a local hormone [16]. The activation of histaminergic neurons was initially associated to the wake state and arousal [17, 18]. Recent elegant works from the groups of Wisden [19] and Arrigoni [20] have shown the complex action of HA in concert with co-released GABA in the control of the wake/sleep cycle and alertness.

Considering its widespread distribution in the central nervous system, it is not surprising that neuronal histamine is involved in the regulation of several brain functions ranging from homeostatic to cognitive ones (Fig. 10.1). Histamine controls thermoregulation [21] and vestibular function [22]; it controls appetite and satiety in concert with other neurohormones [23–25]; it affects learning and memory associated to adverse events [26, 27]. It is becoming clear that the diverse effects that follow the activation of the histaminergic system impose a selective recruitment of specific histaminergic pathways in a coordinated manner according to the

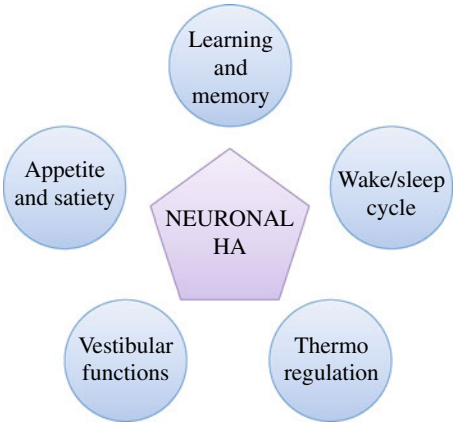

Fig. 10.1 Body functions modulated by neuronal histamine. Research evidence has proven the implication of neuronal histamine in the modulation of numerous body functions. To note, histamine often works in concert with other neurotransmitters and/or neurohormones to exert this modulatory activity (see text for details)

environmental challenges. Indeed, despite the retrograde studies indicating the unitary nature of the TMN, there is now convincing evidence that histaminergic neurons are functionally and neuroanatomically heterogeneous. Here we review our current knowledge on the complexity of histaminergic neuron organisation.

10.2 Evidences of Histamine Neuron Heterogeneity

10.2.1 Histaminergic Neurons Differ in Sensitivities to Activity-Modulating Neurotransmitters

The activity of histaminergic neurons is strictly dependent on behavioural state. They fire tonically during waking, little during slow-wave sleep and not at all during rapid eye movement (REM) sleep [28]. Inhibition of the histaminergic system is fundamental for sleep induction. Investigating the contribution of different systems to histaminergic inhibition, Sergeeva and colleagues found evidence of heterogeneity in histaminergic neurons [29]. Enzymatically isolated neurons were used to verify the contribution of glycine to histaminergic inhibition. In a whole-cell patch-clamp configuration, the majority of TMN cells (64 %) had pronounced glycine responses, whereas in 28 % of cells, the response to glycine was negligible. The remaining 8 % did not respond at all. Therefore, a different sensitivity to glycine stimulation suggested for the first time the presence of heterogeneous subpopulations of TMN neurons. Furthermore, glycine sensitivity correlated with soma size. Indeed, pronounced responses to glycine were associated with large cell bodies (25 μm), while smaller ones (19.5 μm) gave very small or no response at all. Two different subpopulations of TMN neurons were described as a function of glycine sensitivity and soma size. The physiological heterogeneity of TMN neurons was confirmed investigating GABAA receptor expression on TMN neurons [30]. It was known that GABAergic innervation from the ventrolateral preoptic area (VLPO)

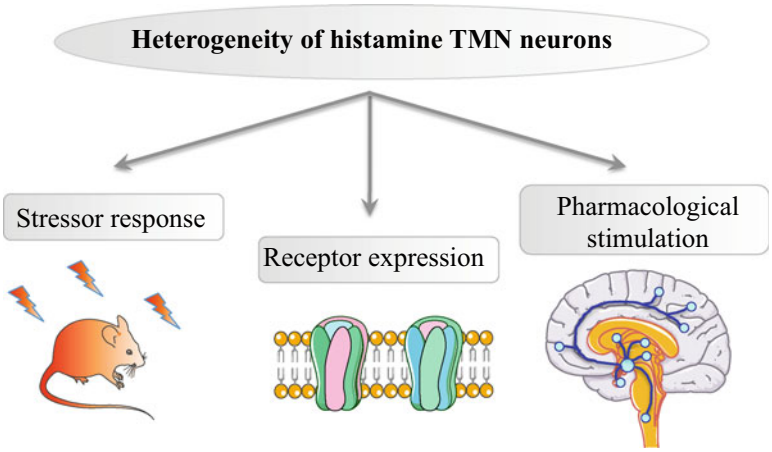

Fig. 10.2 Evidence of histamine TMN neuron heterogeneity. The presence of distinct subpopulations among histamine TMN neurons is strongly suggested by recent findings. Main approaches applied to experimental investigations are schematically represented in the figure

regulates the firing of histaminergic neurons in the TMN [31]. Electrophysiology experiments coupled to biochemical studies investigated GABAA receptor subunit composition and stoichiometry in individual neurons in relation to GABA-evoked responses [28]. All 14 subunits previously identified were screened by PCR. Among the α subunits, α1, α2 and α5 were detected, while β1, β2 and β3 and γ1 and γ2 were described for the β and γ subunits. In some cases, a ε subunit was found.

Patch-clamp experiments revealed differences in sensitivity to GABA in the modulation of IPSC-decay times by zolpidem in those histaminergic neurons that express the γ subunits at different levels.

Summarising, different stoichiometries were found in the population of TMN neurons analysed, as they presented one or two γ subunits. It is suggested that, most likely, the majority of functional GABAA receptors in the TMN are assemblies either constituted by α2, β3 and γ2 or α2, β3 and γ1 subunits. The presence of one or two γ subunits is correlated with GABA sensitivity. Therefore, different sensitivity to GABA appears to be associated with receptor subunit stoichiometry and to correlate with receptor function (Fig. 10.2). These seminal observations hint to the possibility of heterogeneous assembly of other types of receptors in different populations of TMN neurons.

10.2.2 Subpopulations of Histaminergic Neurons Are Selectively Activated by Different Stressors

The implication of histamine in stress-related responses is well documented. Several observations indicate a crosstalk between HA, adrenocorticotropin (ACTH) and corticosterone secretion [32, 33]. Experiments following central administration of

HA or interference with histaminergic transmission with H3 receptor agonists and H1 or H2 receptor antagonists confirmed that HA is involved in responses to specific stressors that increase ACTH, β-endorphin and prolactin. In 2001, Haxhiu and colleagues demonstrated that, together with noradrenergic, dopaminergic and serotonergic neurons, histaminergic neurons were activated in response to hypercapnic stress [34] as assessed evaluating c-fos expression, a marker of neuronal activity. The authors suggested that the role of histaminergic neurons in response to hypercapnia might be related in part to the control of behavioural state. While in fact breathing is impaired by loss of wakefulness during sleep, histamine neuron stimulation might determine a respiratory response also regulated by the increased state of alertness. Interestingly, Miklós and Kovács in 2003 [35] demonstrated the presence of heterogeneous subpopulations of TMN neurons that specifically respond to different stressors (Fig. 10.2). Rats were exposed to a number of different stress stimuli (restraint, footshock, immobilisation, dehydration, hypoglycaemia, hypertonic salt, ether or LPS). Histaminergic neurons were identified by IHC and in situ hybridisation for HDC. Activation of specific subsets of histaminergic neurons was demonstrated by using c-fos immunostaining. The impact of the circadian rhythm was taken into account. No differences in neuronal activation were found between light and dark cycle. In control animals no c-fos staining was found in the E5, E2 and E1 subdivisions, while 0.2 % and 0.4 % histaminergic neurons were activated, respectively, in E3 and E4 subgroups. Noticeable differences in stress-induced c-fos activation emerged between subgroups, as restraint was the only stressor impacting on all histaminergic subdivisions (E1–E5). Footshock and insulin-induced hypoglycaemia preferentially activated the rostral subgroups (E3–E5), while immobilisation and dehydration acted mostly on E5 and E4. Hyperosmotic stimulation, ether stress and LPS treatment did not result in significant c-fos activation in any subgroup of histaminergic cells. Thus, histaminergic neurons do not respond generically to all stressors. The highest percentage of histaminergic neurons activated was determined by restraint, while intermediate responses were obtained with footshock, dehydration and immobilisation. The lack of significant activation following LPS stress was further confirmed by a recent study [36] demonstrating that LPS treatment reduced behavioural activity, in particular motivated behaviour such as exploration, play behaviour, social interaction and sweetened milk consumption. The behavioural responses were associated with reduction of c-fos expression in TMN neurons, an effect suggested to be mediated by the activation of the dorsal vagal complex (DVC). Hence, the histaminergic system represents an important component in the neuronal circuitry relevant for sickness behaviour. No clear anatomical segregation of histaminergic neurons according to the type of stressor was ever observed as histaminergic neurons activated by emotional stressors (e.g. restraint and footshock) intermingled with others activated by stressors classified as systemic challenge (e.g. hypoglycaemia). Nonetheless, these findings demonstrate the existence of functional subpopulations of histaminergic neurons.

Recently, Umehara and colleagues [37–39] identified a specific subpopulation of histaminergic neurons that are activated during food restriction by assessing suppression of c-fos expression with antihistamine pretreatment. The target region of

these histaminergic neurons is the caudal part of the arcuate nucleus of the hypothalamus (cARC).

It is well known that histaminergic neurons convey satiety signalling by activating H1 receptors in the hypothalamic paraventricular (PVH) and the ventromedial (VMH) nuclei [40, 41]. Food deprivation under scheduled feeding induced c-fos expression in the cARC, while no differences were seen in the PVH and VMH [38]. Double immunofluorescent staining in the cARC showed that c-fos-positive cells also expressed H1 receptors. Thus, cARC neurons receive projections from the TMN and are activated by food deprivation through H1 receptors. Furthermore, while in normally fed rats c-fos expression in TMN was observed in the E1, E2 and E3 subdivisions of the TMN, food deprivation under scheduled feeding strongly and selectively activated the E3 group of TMN neurons, whereas the E1 and E2 subregions showed little or no activation [38]. These results suggested that the E3 subpopulation makes direct connection with the H1R-expressing cARC neurons, and the TMN-cARC circuit is selectively activated by food deprivation under restricted feeding [38]. Clearly, the activation of this histaminergic circuit is not related to the anorectic function of histaminergic neurons, but it may be related to a stress response induced by withdrawal of anticipated food under restricted feeding schedule [38].

10.2.3 Pharmacological Stimulation Demonstrates the Existence of Histamine Neuron Subpopulations that Project to Specific Brain Areas

Investigations on the function of histaminergic cells in response to drug treatments can be performed by microdialysis experiments. This technique enables continuous collection of interstitial fluid samples and monitoring of neurotransmitter levels. The effect of pharmacological stimulation can be verified in specific brain areas after systemic or local administration of a compound, and dual-probe experiments allow investigations in projection areas (Fig. 10.3). Studies performed with this technique suggested a possible selective pharmacological manipulation of specific subsets of histaminergic neurons. Among the first reports, investigations of the interaction between the endocannabinoid system and histaminergic neurons are found [42, 43]. Several functions such as cognition, locomotion, appetite and processing of emotional information are controlled by both systems [44–46], although evidence of a real interaction has been missing. CB1 receptor ligands were administered systemically as well as locally in the TMN. Histamine release was monitored directly in the TMN but also in the nucleus basalis magnocellularis (NBM) in the striatum and perirhinal cortex, all brain structures that receive histaminergic projections. The NBM is known to modulate the cortical activity [47, 48], and the stimulation of H1 receptors in the NBM increases acetylcholine release in the cortex [49]. The striatum presents a high concentration of H2 and H3 receptors and principally controls motor functions and stimulus–response habit formation [50],

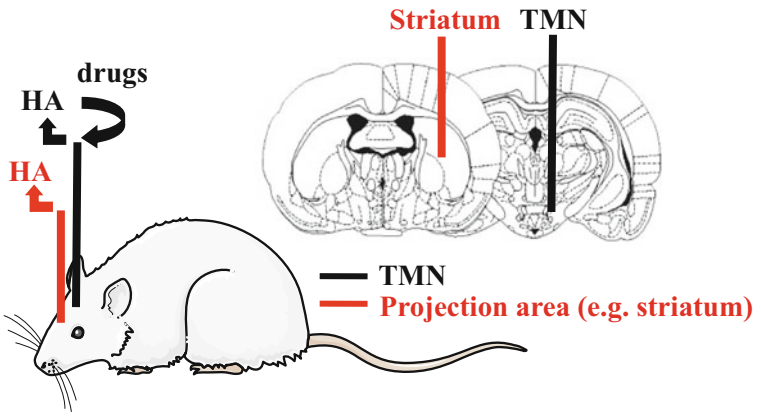

Fig. 10.3 Schematic representation of a dual-probe microdialysis experiment. Rats were implanted two guide cannulae, one in the TMN and the second one in a histaminergic projection area (e.g. the striatum). Dialysates from both structures were analysed through HPLC to measure histamine content

whereas the perirhinal cortex is part of a neural circuit involved in recognition memory [51]. These studies demonstrated that systemic administration (i.p.) or intra-TMN perfusion of arachidonyl-2′ chloroethylamide/N-(2chloroethyl)-5Z, 8Z,11Z,14Z-eicosatetraenamide (ACEA) or R(+)-methanandamide (mAEA), two selective CB1 receptor agonists, significantly increased histamine release in the TMN, NBM and dorsal striatum, but not from the perirhinal cortex. Interestingly, the administration of an endocannabinoid membrane uptake blocker (AM404) determined an increase of HA release in the TMN, but not in the NBM nor in the striatum. Thus, exogenous and endogenous cannabinoids are suggested to exert different effects. When administered in the TMN, both ACEA and bicuculline significantly increased HA release from the TMN, whereas only the CB1 receptor agonist augmented HA release also from the NBM. Therefore, these observations indicate that excitation of histaminergic neurons might not necessarily produce a broad activation of all histaminergic projections and suggest the existence of subpopulations of histaminergic cells that respond differently to pharmacological manipulations and/or project to different brain regions.

Immunohistochemical analysis showed an overall low expression of CB1 receptors in the hypothalamus. To note, CB1 receptor immunostaining surrounded clusters of HDC-immunonegative cells. No colocalisation of CB1 receptor and HDC-positive cells was found [43].

Following these outcomes, other investigations were directly aimed at verifying whether histaminergic neurons are organised into functionally distinct circuits impinging on different brain regions [52, 53]. These studies used the double probe microdialysis technique with one probe in the proximity of the TMN, the other in one of the histaminergic projection areas, and HA release was measured in all these regions upon TMN perfusion with different compounds acting on different

receptors known to be present on TMN neurons (H3 and GABAA receptors) (Fig. 10.2). The studies [52, 53] showed consistent effects on HA release of H3 receptor antagonists such as GSK189254 thioperamide, or ABT-239 administered into the TMN, where blockade of somatic and presynaptic H3 autoreceptors converge in augmenting HA levels in the synaptic cleft and increase histaminergic cell firing [54]. Acting as auto- and hetero-receptors, H3 receptors modulate also the release of numerous neurotransmitters, including acetylcholine (ACh), glutamate, noradrenaline and serotonin [55–58]. The results were compared to those obtained with intra-TMN infusion of the GABAA receptor antagonist bicuculline, that by blocking GABAA receptors on TMN neurons, local HA release and cell firing increase [52]. H3 antagonists were chosen as they have been proposed as drugs for the treatment of highly debilitating and socially devastating pathologies like obesity, sleep disorders, Alzheimer's and Parkinson's disease [59], although only one of them, pitolisant [60], was recently approved for the treatment of narcolepsy (http://www.ema.europa.eu)[61]. It was demonstrated that histaminergic neurons respond differently to the administered drugs despite the fact that both classes of ligands increase HA output within the posterior hypothalamus. While both bicuculline and H3 receptor antagonists always determined an increase of histamine release in the TMN, the effects in projection areas were strikingly different. Both classes of drugs increased HA release in the prefrontal cortex, whereas only H3 receptor antagonists increased HA output in the NBM; conversely, only bicuculline increased HA release in the nucleus accumbens (NAcc). None of the drugs augmented HA in the dorsal striatum. Single-probe experiments showed also that thioperamide infusion directly in the NBM or the prefrontal cortex increased HA release, but not from the dorsal striatum nor the NAcc [52].

To gather further insight into the mechanism of action of H3 receptor antagonists, the pattern of c-fos activation was examined in rat brain regions after perfusion of the TMN with ABT-239 [55]. In keeping with the microdialysis results, increased expression of c-fos with ABT-239 occurred in the prefrontal cortex and in the NBM, but neither in the NAcc nor in the striatum. Hence, despite neuroanatomical studies had shown that TMN histaminergic neurons are a rather homogeneous cell group with diffuse, overlapping projections throughout the neuraxis [8], the microdialysis studies support the hypothesis that subsets of histaminergic neurons form independent functional units modulated by selective mechanisms according to their respective origin and terminal projections.

Immunostaining performed with antibodies directed against HDC and H3 receptors revealed in the E2–E3 subdivision of TMN two histaminergic neuronal populations that differed significantly for H3R expression levels [62]. In fact, as confirmed by other authors, H3 receptor expression is a reliable marker for histaminergic neurons. The group of Sergeeva [63] recently verified the expression of H3 receptors in histaminergic neurons by single-cell RT-PCR and further characterised their response. Notably, even neurons projecting to the striatum, as shown by retrograde tracing, expressed H3 receptors. Thus, the lack of increase in HA release in this area after systemic or intra-TMN administration with an H3 antagonist [47, 48] cannot be explained on the basis of lack

of expression of H3 receptors on striatum-projecting neurons. Sergeeva and co-authors [53] rightly speculate that GABA co-released with HA in the striatum may generate a tonic inhibitory effect counteracting histamine action [19]. Also, response to H3 receptors antagonists may be dampened within the striatum by activation of the TRPV1 channel [64], which is highly expressed in the dorsal striatum. Indeed, the striatum produces high levels of a "capsaicin-like" substance, N-arachidonoyl dopamine (NADA) that may decrease H3 receptor-mediated autoinhibition. Nonetheless, it is conceivable that the magnitude of neuronal responses to extracellular signals may depend on membrane receptor density with histaminergic neurons displaying low levels of the H3R, which are presumably those that innervate the NAcc or striatum.

Despite these seemingly unresolved questions, it is now clear that histaminergic neurons are not a homogenous neuronal population, and presumably functional differences of response relate to their heterogeneity with respect to projection fields, local environment (e.g. striatum) and co-release of other neurotransmitters.

As already mentioned, TMN neurons synthesise GABA [65] that is released from histaminergic neurons presumably in a paracrine manner similar to histamine in the cortex and striatum, as demonstrated by optogenetic studies [19]. The authors suggest that these TMN "GABA-histamine" neurons contribute to tonic inhibition of many neural circuits simultaneously. A different scenario was described in the posterior hypothalamus where the wake-active TMN and sleep-active ventrolateral preoptic nucleus (VLPO) are reciprocally connected [20], suggesting that each region can inhibit its counterpart when activated. Arrigoni and coworkers found that photostimulation evoked histamine release in the ventrolateral TMN (vlTMN) and the VLPO but found no evidence of GABA release. These results suggest that GABA is not released from histaminergic collaterals in the vlTMN.

Taken together, these observations clearly demonstrate the functional heterogeneity of histaminergic neurons impinging on different neuronal circuits to enhance wakefulness and alertness to shape motivation, cognition, locomotion and feeding.

10.3 Conclusions

The histaminergic nervous system has been the focus of extensive studies in the last three decades. Numerous advances have been done in order to clarify its complex structure and physiological organisation. Notably, central histamine regulates a plethora of body functions [62, 66]. If in the beginning TMN histamine neurons were suggested to act as a single functional entity, several findings based on functional and biochemical studies are now proving their organisation in heterogeneous subpopulations. Such heterogeneity is not based on topographical organisation, as evidenced by retrograde tracer investigations, but other characteristics as receptor expression or subunit stoichiometry have been proven. In some cases, experimental observations

were not followed by univocal interpretations, and further studies are required to fully elucidate the underlying mechanisms. Experimental conditions and methodology limitations, as well as species differences, revealed to be key factors. As it emerges from this concise overview, additional investigations are needed, but recent findings open fascinating possibilities of a fine-tuned modulation of the histaminergic system. Results might help in the development of selective and safe drugs for the treatment of pathologies with a high social impact, ranging from obesity to cognitive disorders.

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