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Brief Review

Central histaminergic modulation of vestibular function — a review

F. Bergquist, M.B. Dutia*

Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, Edinburgh EH8 9XD, UK

Abstract: Histaminergic drugs have long been used to treat balance disorders in man, but their mechanisms of action in the vestibular system are poorly understood. In this article we review the current literature on histaminergic neurotransmission in the brain focussing particularly in the brainstem vestibular nuclei, and the role of histamine in brain plasticity during "vestibular compensation", the behavioural recovery that takes place after unilateral peripheral vestibular damage. Evidence that histaminergic compounds may facilitate vestibular compensation is reviewed, and we discuss the potential of histaminergic drugs for clinical use.

Key words: histamine; vestibular system; plasticity; vestibular compensation

前庭功能的中枢组胺能神经调制

F. Bergquist, M.B. Dutia*

英国爱丁堡大学生物医学科学学院整合生理学中心，爱丁堡 EH8 9XD，英国

摘　要：组胺能药物已经长期用于治疗人类的平衡紊乱，但对于它们在前庭系统中作用的机制还缺乏了解。在本文中，我们综述了关于脑内(特别是脑干前庭核中)的组胺能神经传递，以及组胺在脑可塑性—— "前庭代偿"(一种单侧外周前庭损伤之后发生的行为学恢复)中作用的新近文献。我们在综述组胺能类药物促进前庭代偿证据的同时，也讨论了这类药物临床应用的可能性。

关键词：组胺；前庭系统；可塑性；前庭代偿
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The discovery that histamine affects physiological processes dates back to 1910 and Dale and co-authors' findings that histamine induces uterine contraction[1,2]. However, it was only in 1927 that evidence for an endogenous source of histamine emerged[3], and the neuronal histaminergic pathways in the central nervous system (CNS) were not clearly identified until recently[4-6]. In the 1960s, when histamine and the histamine analogue betahistine were first introduced in the treatment of motion sickness and balance disorders, histamine was therefore not looked upon as the CNS transmitter and neuromodulator it is known to be today. Consequently it is not surprising that from early on, research on histaminergic regulation of vestibular function focussed on peripheral mechanisms like regulation of blood flow in the inner ear[7,8], and more recently the histaminergic control of the afferent end organ of the labyrinth[9-11]. With increasing understanding of central histaminergic neurotransmission the focus has gradually changed to include histaminergic modulation of neurotransmission in the vestibular nuclei in the brain stem[12-14, reviewed in Ref.15], and should include the role of histamine for central synaptic plasticity and cognitive functions[16,17] and perhaps also its involvement in stress responses[18-20].

This review aims at summarizing recent research on central histaminergic neurotransmission which may have bearings on vestibular function as well as "vestibular compensation", the behavioural recovery which occurs after unilateral vestibular de-afferentation and which is a long standing model for neural and synaptic plasticity in the adult brain.

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*Corresponding author. Tel: +44-131-6503252; Fax: +44-131-6506527; E-mail: m.b.dutia@ed.ac.uk

Physiology and pathophysiology of vestibular nuclei

Several comprehensive reviews on the physiology and pathophysiology of the central vestibular system have been published over the last ten years[21-24], and only a brief overview will be given here.

The vestibular system continuously monitors the orientation of the head with respect to gravity and the acceleration of the head in space. This information, together with other sensory inputs, is fundamentally important for spatial orientation, navigation, motor control and all tasks which in one way or another depend on knowing the orientation of the body in space. Although the vestibular system integrates information from a number of sensory sources, including proprioceptive information from muscle spindle afferents and vision, its major afferent input comes from the hair cells in the semicircular canal and otolith receptors in the inner ears of the two sides. The otolith (macular) receptors are sensitive to linear acceleration and signal information about the orientation of the head in the field of gravity. Angular head accelerations (rotations of the head) stimulate hair cells in the semicircular canals. The velocity and direction of head rotation are signalled by a differential response from the pair of canals in the appropriate plane, so that for example a horizontal turn to the right will stimulate the discharge of afferent neurons in the right horizontal canal, but inhibit the discharge rate of neurons in the left horizontal canal. This differential signal from the two ears converges on the vestibular nuclei in the brainstem, where it is amplified and optimised by a reciprocal, commissural inhibitory system which connects the vestibular nuclei of the two sides. The commissural reciprocal inhibitory system is most prominent in the medial and superior vestibular nuclei, which are concerned with eye movements in the horizontal and vertical planes respectively. Commissural inhibition also operates in an analogous manner to optimise response sensitivity in the otolith system, which is concerned largely with vestibulo-spinal reflexes and postural control[25-27].

Neurons in the vestibular nuclei project to eye motor nuclei and spinal motor neurones. The vestibular influence on eye motor nuclei serves to stabilize gaze by keeping the gaze-direction stationary in space as the head moves. This control system is expressed as the vestibulo-ocular reflex (VOR), and is mediated by neurons in the medial and superior vestibular nuclei. Their influence on spinal motor centres serves to adjust muscle tone in the neck, trunk and limb muscles in order to preserve postural stability through vestibulo-collic and vestibulo-spinal reflexes. Vestibular information also projects to autonomic nuclei, where information about changes in body posture allows adjustment of the cardiovascular system to prevent inappropriate falls in blood pressure, for example when the body changes position from supine to upright[28].

Damage to the vestibular receptors of the inner ear or to the vestibular nerve has long been known to cause a characteristic, debilitating syndrome which evolves over time. The initial syndrome after unilateral vestibular damage is dominated by "static symptoms" (symptoms that are apparent even when the head is stationary), including ocular nystagmus, postural imbalance and in the case of humans, the reported feeling of rotational vertigo, as well as vegetative autonomic symptoms. Over a relatively short time however these static symptoms subside and largely disappear, through a process of neural and synaptic plasticity known as vestibular compensation. By contrast "dynamic symptoms" and signs, which are observed in response to vestibular stimulation and include a defective VOR, improve at a much slower rate and may persist indefinitely. Considerable efforts have been made in recent years to elucidate the cellular mechanisms which bring about the rapid recovery of the initial static symptoms. We will later discuss the influence of histaminergic neuromodulation in vestibular system plasticity, but for a fuller account of putative mechanisms of vestibular compensation the reader is referred to recent comprehensive reviews[21,22,29].

Histaminergic neurotransmission in the CNS

Anatomy of histaminergic projections

It would be beyond the scope of this review to try to fully account for the anatomy and function of the brain histaminergic system, but we will give an overview with emphasis on anatomical and physiological characteristics of importance for the vestibular system. We refer to recent comprehensive reviews for more details[2,16,20].

There are two sources of histamine in the brain: histamine containing mast cells and histaminergic neurons of the tuberomamillary nuclei in the posterior hypothalamus. Histamine in mast cells are generally thought to belong to a pool with slow turnover, and it is unclear if mast cell histamine contributes to the neuronal effects of histamine in the CNS. However, mast cells account for some 20% of the total brain histamine content[2].

The neuronal source of brain histamine is the histaminergic cell group of the tuberomammillary nucleus, which projects widely over the brain but most intensely to thala-

mus and to cortical domains. The vestibular nuclei have, like other brain stem structures, a moderately dense histamine innervation[30, 31].

Brain histamine receptors

There are four characterised histamine receptors, H1~4, of which H1~3 are expressed in neurons of the CNS. The H1~H3 receptors were initially characterised pharmacologically[2,32,33], but have later been cloned[34-36].

The H1 receptor is, like the H2 receptor, encoded by an intronless gene, and similar to the H2 and H3 receptors it is a G-protein coupled receptor. H1 receptor actions are mediated through G-protein G_{q11}, and activation of the receptor leads to increases in intracellular calcium via the inositol-1,4,5-triphosphate pathway. The rise in intracellular calcium will in turn activate several calcium-dependent processes, including opening of cation channels that leads to depolarisation, NO synthesis, as well as opening of K^+-channels promoting hyperpolarisation[16,20]. In the brain the H1 receptor stimulates wakefulness and alertness, as illustrated by the sedative effects of H1 antagonists that pass the blood-brain barrier.

The H2 receptor was discovered in the exploration of histaminergic regulation of gastric secretion[37,38]. The receptor is coupled to the G_s protein and its stimulation promotes accumulation of cAMP via activation of adenylyl cyclase. H2 receptor activation also leads to phosphokinase A activation and subsequent inhibition of the small conductance calcium-dependent potassium current, via phosphorylation. In neurons that display afterhyperpolarisation mediated by this current, H2 receptor activation lends them more excitable, and they will respond more easily to a given stimulus[16].

The existence of a histamine autoreceptor was demonstrated pharmacologically in 1983[39], and it is known as the H3 receptor. The molecular characterisation of this receptor turned out to be more elusive than what was the case with H1 and H2 receptors, and it was not cloned until 1999[36]. Since then the understanding of this receptor system has increased immensely, and some extensive reviews on this topic have recently been published[17,40,41]. As was initially demonstrated by Arrang and co-workers, the H3 receptor acts as an autoreceptor and downregulates histamine release and synthesis in histaminergic terminals[39]. H3 receptors are also located on histaminergic dendrites and cellbodies where they inhibit the firing of histamine neurones[42,43]. H3 receptor signalling is mediated via another G-protein pathway; the $G_{i/o}$-mediated downregulation of cAMP production by adenylyl cyclase, and via inhibition of high threshold voltage sensitive calcium channels[40]. The H3 receptor is however not exclusively expressed on histaminergic neurones as an autoreceptor; it is also found on the terminals of other neurones, where it acts as an inhibitory heteroreceptor, regulating the release of other neurotransmitters. The H3 receptor is considered an attractive target for the treatment of a number of conditions both because of its regulatory effect on brain histaminergic transmission and its potential for the regulation of the release of many other neurotransmitters. H3 receptor ligands are currently being developed with the intention to treat obesity, sleep disorders, cognitive disorders and disorders of attention[17,44,45]. The pharmacological characterisation of H3 receptors has turned out to be surprisingly complicated. One reason for this is that the H3 receptor has a considerable constitutive activity[41]. As a result of that, the classical simple agonist-antagonist classification is insufficient to describe the action of H3 ligands. When this was discovered, several drugs which were originally considered to be antagonists, had to be reclassified as reverse agonists. Interestingly some ligands that were initially classified as H3 receptor antagonists have turned out to be ligands with protean properties, meaning that their action can range from agonism to reverse agonism depending on the activity of the receptor, and which assay is used[46,47]. It is also clear that the potency of H3 agonists can vary between different tissues. Such a heterogeneity is also present within the brain, where H3 agonists show potencies varying by approximately one order of magnitude depending on which area of the brain is investigated[2,48-50]. To some extent this can be explained by the H3 receptor being subject to alternative splicing, rendering a number of different variants of the receptor with different sensitivity to H3 receptor ligands[40], but differences in constitutive receptor activity could also account for some of these variations.

Physiological functions of brain histamine

Histaminergic influences on different systems in the CNS have been extensively reviewed elsewhere[2,16,20,51], and we will here only briefly mention some features that may be of indirect importance for the vestibular system. The direct histaminergic effects on the vestibular nuclei will be dealt with further on.

As in the case of other brain amines, like dopamine, serotonin and noradrenaline, histaminergic neurotransmission appears to take place mostly outside synaptic specialisations

by release and diffusion from axonal swellings or varicosities that make few contacts with the recipient cells[52]. It is therefore not surprising that brain histamine acts mainly as a neuromodulator, which changes strength and responsiveness of fast neurotransmission. Modulation of neuronal activity can occur in response to postsynaptic H1 or H2 receptor activation, as has been demonstrated for example in hippocampal[53], and hypothalamic neurones[54-56].

As mentioned, histamine also modulates neurotransmission via the presynaptic H3 receptor. H3 receptor-mediated presynaptic inhibition of neurotransmitter release is known to occur with many neurotransmitters of the CNS, notably, GABA[49,50] glutamate[53], noradrenaline and serotonin[48,57,58], all transmitters that are implicated in central vestibular neurotransmission[59].

The earliest discovered histaminergic influence on the CNS was its promotion of wakefulness and alertness. This effect has been attributed to histaminergic stimulation of a number of brain structures including cholinergic projections to the cortex[60,61], cortex itself[62, see however Ref. 63], thalamus and hypothalamus as well as the reticular formation[64 for review]. Cortical arousal is of importance for vestibular compensation, since sedative drugs slow the recovery process after peripheral de-afferentation, whereas stimulants appear to improve it[65].

The vestibular system provides a relatively simple model of neuronal plasticity in the adult brain. The VOR is in this respect particularly attractive, because it provides a sensitive, accurate and easily accessible measure of plastic changes. Histaminergic modulation of synaptic plasticity has however been more extensively investigated in the hippocampus, and in terms of memory functions. Such models can be of relevance for vestibular plasticity provided that the mechanisms can be extrapolated. There is however also evidence for interactions between cognitive and vestibular functions[66-68].

The hippocampus is not densely innervated by histaminergic neurons, but histamine has been shown to promote long term potentiation in hippocampal neurons via two distinct mechanisms, one which is H2 receptor-mediated, and one which is mediated by a direct effect of the polyamine histamine at the spermidine binding site of the NMDA-receptor[16]. The histaminergic influence on memory processes is however complex, because although intracerebroventricular injection of histamine appears to enhance some memory functions[51], depletion of histamine can both improve and inhibit spatial memory[69,70], and both improvement of water maze performance and impaired object recognition was recently described in histidine decarboxylase deficient mice, which do not produce histamine[71].

Activation of the stress axis has a somewhat contentious role for vestibular compensation. Glucocorticoid receptor antagonists prevent cellular plastic changes associated with vestibular compensation, but excessive stress has been shown to impair vestibular compensation[72,73, reviewed in Ref.74]. Brain histamine stimulates the secretion of stress related messengers like ACTH, prolactin, and vasopressin[75-78]. There is therefore a possible connection between brain histamine and glucocorticoidal regulation of vestibular functions, but probably also between brain histamine and peripheral regulation of vestibular organs, since vasopressin influences the production of endolymph, and has been suggested to be involved in the pathophysiology of Meniere's disease[74].

Histamine and the central vestibular system

Electrophysiological effects of histaminergic drugs in vivo and in vitro

Early studies of iontophoretically applied histamine onto vestibular neurones *in vivo* indicated mixed, but largely inhibitory effects that could be blocked by the H2 receptor antagonist metiamide, but not by the H2 blocker cimetidine[79,80].

In vitro, histamine depolarises the majority of neurones tested in slice preparations of medial vestibular nuclei[12,14,81,82]. A number of technical explanations have been put forward to explain this discrepancy compared to *in vivo* findings, including methods of anaesthesia, uncertainty of neuronal identity, and small number of investigated neurons[83]. One may add to this that some of the antagonists used in the early studies have later been found less selective than initially believed[32].

Behavioural effects

There is only one study *in vivo*, that directly explores the behavioral influence of histaminergic neurotransmission in the vestibular nuclei[81] (data also in[13]), and it supports the findings from *in vitro* slice studies that histamine has an overall stimulating influence on vestibular nuclei *in vivo*. Unilateral disruption of histaminergic neurotransmission in the vestibular nuclei, either with the H2 receptor antagonist cimetidine or the H3 receptor agonist alphamethylhistamine, leads to a syndrome similar to that seen after ipsilateral peripheral de-afferentation, only less pronounced. The authors also reported decreased gain of the horizontal

VOR after systemic treatment with the H3 reverse agonist thioperamide, a phenomenon that was previously also found with betahistine[84,85], another H3 receptor antagonist. This may appear somewhat contradictory, considering that histamine stimulates vestibular neurones and that H3 antagonists increase the activity of histaminergic neurones, but as de Waele *et al.* point out[81], the systemic effects of H3 inhibition may include action in several parts of the nervous system. In the face of more recent insights on the physiology of H3 receptors, the possible role of histaminergic presynaptic inhibition of the release of other neurotransmitters in the vestibular nuclei should also be considered. We have recently discovered that histamine can inhibit GABA-release from slices containing the medial vestibular nucleus (Bergquist *et al.*, unpublished findings), and if that reflects a histaminergic control of the commissural inhibitory pathways, a decreased gain in the horizontal VOR would be a consequence of increased histamine release in the medial vestibular nuclei.

Histaminergic responses to vestibular stimulation and over-stimulation

As can be expected from a neuromodulator which responds to stress, sustained or unbalanced activity of the vestibular system leads to activation of the histaminergic system. Histamine release in the anterior hypothalamus of rats increases in response to unilateral vestibular stimulation, but not to an unspecific cold stressor[86]. It was shown that the histamine content of the medullary pontine part of the brain increases in normal rats in response to rotation around two separate axes — a conflicting vestibular stimulus that can be used to evoke motion sickness, but no increase was observed when bilaterally labyrinthectomised rats were stimulated in this way[87]. Indirect evidence for increased histaminergic activity and histamine release in vestibular nuclei has also been reported after unilateral labyrinthectomy in cats[88,89]. Although these investigations indicate that conflicting vestibular input activates the histaminergic system, it is not quite clear whether this is a specific vestibular response or if it is a more general stress response (see previous section), since the only study where the effects of another stressor was reported, used a very mild stressor and anaesthetised animals[86]. An interesting observation made in unilaterally stimulated animals is that unbalanced or conflicting vestibular inputs lead to a pronounced increase in plasma vasopressin[90]. This could also be related to increased histamine signalling, since vasopressinergic neurons are under histaminergic control[56].

Histamine and vestibular compensation

Vestibular compensation in animals is a long standing model for neuronal plasticity in adult brain, and histamine is of particular interest in this context given its role for plasticity in other parts of the brain, for learning and for wakefulness.

Brain histamine can influence vestibular compensation at several levels, as outlined above. Some of these influences will be specific to the vestibular system; examples of this are the stimulatory effects of histamine on vestibular neurons in brain slices, and its role as a presynaptic modulator of neurotransmitter release. Other effects are unspecific and can be exemplified by histaminergic promotion of alertness, which is a pre-requisite for effective learning, as well as by histamine's role in the general stress response, which is linked with the course of vestibular compensation. In the following section we will list the different mechanisms by which histamine could modulate vestibular compensation, and we will then summarize the evidence for central histaminergic modulation of vestibular compensation derived from clinical studies and from behavioural animal studies.

Local histaminergic modulation of synaptic input?

Direct histaminergic modulation of synaptic input to the vestibular nuclei is most likely mediated by H3 receptor mediated presynaptic inhibition of neurotransmitter release. The expression of H3 receptor mRNA changes during the course of vestibular compensation in rats[91]. A decrease in H3 receptor binding was also found in cats treated with betahistine, which itself has a histamine depleting effect on vestibular nuclei that is similar to the effect of vestibular de-afferentation[88].

Vestibular second order neurons are stimulated mainly by the afferent input from the VIIIth nerve, and are inhibited by commissural neurons and Purkinje cells. Vestibular de-afferentation removes the excitatory influence from the VIIIth nerve, and neurons of the ipsilesional vestibular nucleus fall silent short after. This early silencing of ipsilesional vestibular neurons is not the result of the lost input from the eighth nerve only, but depends on the commissural inhibitory connections between the two nuclei[92]. This reciprocal inhibitory system is therefore believed to play an important role both in the development and the recovery of static symptoms after the loss of input from one labyrinth. There is some evidence that the efficacy of the

commissural inhibitory pathway may change in response to histaminergic drugs as indicated by a decreased gain of the VOR[13,85]. Barresi and co-workers[93] recently evaluated the effect of intraperitoneal administration of the H1/H3 ligand betahistine on the responsiveness of vestibular neurones to labyrinthine stimulation in rat. It was found that betahistine could either increase or decrease the gain of responding neurones, and although the location of drug action is not known, presynaptic regulation of neurotransmitter release was suggested to play a role[93]. A possible explanation of the histaminergic inhibition of vestibular gain may be H3 receptor-mediated inhibition of GABA release in the medial vestibular nucleus (Bergquist *et al.*, unpublished). This histaminergic inhibition of GABA release is in agreement with a histaminergic down modulation of the commissural pathways which normally amplifies vestibular gain.

Local inhibition of release could also influence the GABAergic cerebellar input to vestibular neurones. This input increases on the contralesional side after unilateral de-afferentation and probably contributes in some extent to the rebalancing of vestibular activity[94]. Inhibition of contralesional cerebellar projections would not improve compensation, but on the ipsilesional side, such a mechanism could tentatively aid the recovery of firing rates.

Local histaminergic modulation of vestibular neurones?
The recovery of spontaneous firing of ipsilesional vestibular neurones has been shown to be, at least partly, explained by an increase in intrinsic excitability[29,95-97]. Histamine increases the sensitivity of neurones in the hippocampus via H2 receptor activation and this effect persists for at least 45 min after a short application[98]. The mechanism of this phenomenon involves decreased after hyperpolarisation via inhibition of calcium-dependent potassium channels[16,20]. As previously mentioned histamine has H2 recepeor-mediated excitatory effects also on vestibular neurons, leading to increases in firing rates[12,19], but not necessarily via calcium-dependent potassium channels[14] and the effects are only transient[12]. So, although histamine has been shown to induce prolonged changes in excitability in other neurons, this does not seem to be the case in vestibular neurones. *In vivo*, a sustained increase in histamine release in vestibular nuclei could still be important for restoration of the resting activity of ipsilesional vestibular neurones. It was recently demonstrated that after unilateral vestibular de-afferentation in cats, histidine decarboxylase mRNA, encoding the enzyme needed for histamine production, is strongly up-regulated in the ipsilesional tuberomamillary body[89]. This up-regulation persists for at least three weeks, indicating that histamine release is increased in ipsilesional vestibular nuclei during the early phases of vestibular compensation. Postlesional increases in ipsilesional vestibular histamine release are probably also enhanced by the down-regulation of H3 receptors that occurs in ipsilesional vestibular nuclei after unilateral vestibular de-afferentation[89].

Histaminergic modulation of vestibular stress responses
The interplay between stress responses and vestibular compensation has received particular attention. It is often claimed that stress is a triggering factor for episodes of vertigo in Meniere's disease, and although this has been difficult to confirm[99]. Recent investigations indicate that patients with Menieres disease display changes in the expression of stress related genes that are not evoked by simply experiencing the stress of vestibular symptoms[100]. Furthermore patients with Meniere's disease have been shown to have higher levels of the stress markers prolactin and vasopressin than what is seen in control patients, even between episodes of vertigo[101,102]. However, the exact role of stress hormones in this context still needs to be determined. A certain amount of glucocorticoid activation appears to be necessary for the appearance of compensatory increases in intrinsic excitability of vestibular neurones after labyrinthectomy[72], but additional immobilisation stress impairs vestibular compensation[73]. It was suggested by Cameron and Dutia[72] that the slower vestibular compensation which is observed after long-acting anaesthetics could be related to a delayed stress response. However, a study addressing this possibility found no difference in time to behavioural recovery between animals that were awakened directly after labyrinthectomy, and others that were kept anaesthetised with halothane for four hours[103]. The delayed compensation in animals that have received long-acting anaesthetics is therefore more probably related to the characteristics of the anaesthetic drugs used.

The mechanisms by which stress affects vestibular compensation are still unclear, but regardless of whether stress improves or impairs vestibular compensation, it provides another possible mechanism by which histamine may modulate vestibular function. This may occur as result of central histaminergic regulation of stress hormones acting at the level of the cerebellum or brainstem, but also by a peripheral vasopressin mediated regulation of vestibular endorgans (see Section "Histamine as a part of stress response").

Histaminergic regulation of the cerebellum?

The cerebellum has received a lot of attention for its possible role in vestibular compensation, but the evidence is not unequivocal. On one hand, removing the cerebellar flocculus prevents the early increases in excitability in ipsilesional vestibular neurones[104], and many studies have demonstrated biochemical changes in the cerebellum after labyrinthectomy[22,105]. On the other hand, available behavioural data do not provide unanimous support for a causal role for the cerebellum in vestibular compensation[22]. A conservative interpretation of the studies performed this far is that the cerebellum is influential, but not crucial for vestibular compensation. There is evidence for a neuromodulatory effect of histamine in the cerebellum too[106-109]. Functional consequences of the relatively sparse histaminergic innervation were until recently not known, but a recent report indicates that histaminergic neurotransmission in the cerebellum facilitates motor functions in balance and endurance tests[110]. It is not known whether this also involves a histaminergic influences on cerebellar inputs to the vestibular systems.

Histamine and behavioural animal models of vestibular compensation

Relatively few studies have evaluated the role of histamine for vestibular compensation in animals. Histamine analogues with primarily H3 receptor affinity (betahistine and thioperamide) have been shown to improve the recovery after vestibular de-afferentation in cats[89,111] and to reduce acute symptoms in rats[112]. In contrast, the H1 antagonist dimenhydrinate slowed down recovery after unilateral de-afferentation[83], and similar effects have been seen with other sedative compounds[65]. More recently an H1-antagonist, chlorpheniramine, was reported to accelerate compensation in hemilabyrinthectomised goldfish[113]. The chlorpheniramine induced improvement in body tilt did however only occur after one week, when the symptomatology had stabilized and could possibly be explained by symptomatic relief rather improved compensation.

Clinical evidence for histaminergic modulation of vestibular compensation

H1 receptor antagonists that pass the blood brain barrier (typical compounds are diphenhydramine, promethazine, dimenhydrinate) have sedative as well as vestibulo-depressant effects. Their use for motion sickness is well established, and the mechanism of action is believed to include anti-emesis via histaminergic effects on emetic centres in the brain[114,115], as well as unspecific sedative effects of the drugs. H1 antagonists may also have some direct vestibulostatic effects as indicated by the H1/H2 receptor-mediated excitation of vestibular neurones[12]. It is likely that the overall sedative effect of H1 antagonists postpones compensation (see previous section), but this issue has not been investigated clinically. It is also worth noting that several clinically used H1 antagonists are not selective for histamine H1 receptors, but also have antimuscarinergic effects[116], which may contribute to the amelioration of autonomic symptoms of motion sickness.

The anti-vertigo effects of two calcium channel antagonists, flunarizine and cinnarizine has also been attributed to H1 receptor antagonism[83], but these drugs have a particularly promiscuous pharmacology, as is exemplified by the high risk of drug-induced parkinsonism which is associated with their use[117].

Betahistine was introduced in the treatment of vestibular symptoms some 30 years ago. The drug is a histamine analogue displaying partial H1 agonism and H3 antagonism[118], and has been evaluated in a number of small clinical studies, but due to doubts regarding the efficacy of the drug it is no longer registered in the United States of America and several other countries. The clinical evidence for its use in Meniere's disease was recently reviewed by James and Burton[119], and they concluded that larger randomised double blinded studies were needed to determine if betahistine was superior to placebo treatment. Since then, an Italian multi-centre study, sponsored by the pharmaceutical research company Grünenthal-Formenti has been published[120]. This study is the largest single study of betahistine *vs*. placebo for peripheral vertigo, including 81 patients with Meniere's disease and 63 with benign positional vertigo, as defined by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria. Significant improvements of frequency, duration and intensity of vertigo attacks compared to placebo, were reported in both patient groups taking betahistine, with improvements in most measures approaching twice those seen in the placebo group.

Summary

Histamine is a neuromodulator with widespread distribution in the brain. It promotes neuronal plasticity at several levels of the nervous system. Both clinical and experimental evidence indicate that the vestibular system is directly and indirectly under histaminergic control, but even though histaminergic drugs have been a mainstay in the treatment

of vestibular disorders for many decades, our knowledge of action mechanisms remains insufficient. Over the last ten years, genetic and pharmacological advances have fundamentally changed the understanding of central histaminergic neurotransmission, and the pharmaceutical industry is currently exploring the potential of novel histaminergic drugs for treatment of neurological, behavioural and psychiatric disorders. The introduction of novel histaminergic compounds may shed further light on the action mechanisms by which histamine regulates vestibular functions and may also provide new therapeutic alternatives for treatment of vestibular dysfunction.

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