HHS Public Access

Author manuscript

Nat Rev Neurol. Author manuscript; available in PMC 2022 January 10.

Published in final edited form as:

Nat Rev Neurol. 2015 July ; 11(7): 401–413. doi:10.1038/nrneurol.2015.99.

Interactions of the histamine and hypocretin systems in CNS disorders

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Abstract

Histamine and hypocretin neurons are localized to the hypothalamus, a brain area critical to autonomic function and sleep. Narcolepsy type 1, also known as narcolepsy with cataplexy, is a neurological disorder characterized by excessive daytime sleepiness, impaired night-time sleep, cataplexy, sleep paralysis and short latency to rapid eye movement (REM) sleep after sleep onset. In narcolepsy, 90% of hypocretin neurons are lost; in addition, two groups reported in 2014 that the number of histamine neurons is increased by 64% or more in human patients with narcolepsy, suggesting involvement of histamine in the aetiology of this disorder. Here, we review the role of the histamine and hypocretin systems in sleep–wake modulation. Furthermore, we summarize the neuropathological changes to these two systems in narcolepsy and discuss the possibility that narcolepsy-associated histamine abnormalities could mediate or result from the same processes that cause the hypocretin cell loss. We also review the changes in the hypocretin and histamine systems, and the associated sleep disruptions, in Parkinson disease, Alzheimer disease, Huntington disease and Tourette syndrome. Finally, we discuss novel therapeutic approaches for manipulation of the histamine system.

Introduction

The hypothalamus is a brain area with a critical role in the control of autonomic function and sleep. The involvement of the posterior hypothalamus in the maintenance of wakefulness was first recognized during an encephalitis lethargica epidemic (1918–1926) by the neurologist von Economo, who described extreme sleepiness associated with damage to this area.[1] The posterior hypothalamus is a heterogeneous structure that includes neurons containing histamine, glutamate, γ-aminobutyric acid (GABA), hypocretin (also known as orexin) and melanin-concentrating hormone (MCH).

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Author contributions

All authors participated in writing the article, and provided substantial contributions to the discussion of content and to the editing the manuscript before submission.

In normal individuals, hypocretin neurons are present throughout the hypothalamus. More than a decade ago, two groups[2,3] identified loss of hypocretin neurons as the cause of human narcolepsy with cataplexy. The discovery of this hypocretin deficiency led to a change in the International Classification of Sleep Disorders, with the 'narcolepsy' category being divided into 'narcolepsy type 1' and 'narcolepsy type 2'.

Narcolepsy is diagnosed in patients who have a daily irrepressible need for sleep. In narcolepsy type 1 (also called hypocretin deficiency syndrome or narcolepsy with cataplexy), patients demonstrate one or both of the following: cataplexy plus mean sleep latencies of ≤8 min and at least two sleep-onset rapid eye movement (REM) periods on a multiple sleep latency test, and/or low levels of hypocretin peptide 1 (≤110 pg/ml) in the cerebrospinal fluid (CSF). By contrast, patients with narcolepsy type 2 (initially called narcolepsy without cataplexy) also demonstrate mean sleep latencies of ≤8 min and at least two sleep-onset REM periods, but do not experience cataplexy, have normal CSF levels of hypocretin peptide 1 (if tested), and their hypersomnolence and/or sleep latency findings cannot be better described by another cause.[4] Recently, two groups reported a massive increase in the number of histamine neurons in narcolepsy type 1.[5,6]

Both histamine and hypocretin have been implicated in the modulation of brain functions, such as sleep–wake regulation, energy and endocrine homeostasis, reward-motivated behaviours and motor functions.[7–12] This Review focuses on the contribution of histamine and hypocretin to the control of the sleep–wake cycle. We review recent anatomical and physiological evidence for the role of histamine and hypocretin in normal sleep–wake behaviours, as well as recent findings concerning their involvement in a variety of pathologies, including narcolepsy, Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD) and Tourette syndrome (TS). Moreover, we pay special attention to recently published results on over-the-counter antihistamines, and histamine H_3 receptor (H_3R) antagonists and inverse agonists in treating sleep–wake abnormalities in these diseases.

Neurobiology

In the human brain, both histamine and hypocretin neurons are found in the medial, lateral and posterior hypothalamus, where they are intermixed with other types of neurons (Figure 1).[7,8]

Histamine neurons

Histamine metabolism and histamine receptors—Histamine neurons express L-histidine decarboxylase (HDC), which is the rate-limiting enzyme for neuronal histamine synthesis. In *ex vivo* studies, histamine neurons can be detected by immunological staining of HDC.[13,14]

Brain histamine is reduced to an inactivated form, tele-methylhistamine (t-MeHA), by histamine *N*-methyltransferase.[7,8] All four types of histamine receptors (H_1R–H_4R) in the brain belong to the G-protein-coupled receptor superfamily. H_1R has a primarily excitatory effect on neurons via G-protein-coupled depolarization.[7] H_3R can act as

either an autoreceptor or heteroreceptor, and suppresses the release of histamine and other neurotransmitters, including acetylcholine, dopamine, GABA and serotonin.[7,8] The functional similarities and differences, as well as the details of the localization of histamine receptors in the brain have been reviewed elsewhere.[7,8]

Co-transmitters and control of sleep–wake cycle—GABAergic signalling on histamine neurons alone does not seem to have a major role in controlling the sleep–wake cycle,[15] because genetic ablation of GABA receptors on histamine neurons in mice does not affect their sleep–wake cycle.[16] This result suggests that other transmitters, such as galanin or glutamate,[17] contribute to the control of the sleep–wake cycle via interactions with histamine. Relayed input from the suprachiasmatic or intracellular circadian regulation mechanisms could also be involved; indeed, a 2014 mouse study demonstrated that deletion of *Arntl* (also known as *Bmal1*) from histamine neurons resulted in prolonged wakefulness and fragmented sleep.[18]

Hypocretin neurons

A few hypocretin neurons are found in the anterior hypothalamus at the level where the fornix crosses the paraventricular nucleus (Figure 1).[19] At more caudal levels, the fornix projects to the mammillary bodies while passing through the perifornical nucleus, an area with a large number of hypocretin neurons.[19] There are also many hypocretin neurons at the junction of the fornix and the mammillary bodies.[20]

Hypocretin peptides are produced from the precursor molecule preprohypocretin. The longer hypocretin peptide, hypocretin-1, contains 33 amino acids, and the shorter, hypocretin-2, contains 28 amino acids.[21] Hypocretin receptors are 7-transmembrane G-protein coupled receptors. Hypocretin receptor type 1 (hypocretin 1R) is abundantly expressed in the locus coeruleus and dorsal raphe nucleus, and has a preferential affinity for hypocretin-1, whereas hypocretin receptor type 2 (hypocretin 2R) binds both forms of hypocretin with similar affinity, and is expressed in several brain areas.[21]

Co-transmitters—Hypocretin neurons also secrete dynorphin,[22,23] glutamate[24] and neuronal-activity-regulated pentraxin (NARP).[23,25,26] NARP secretion by hypocretin neurons is of particular interest, because it exhibits a circadian rhythm[27,28] and is a key regulator for diurnal plasticity of hypocretin neurons.[27,28]

Dynorphin has been reported to be packed in the same synaptic vesicles as hypocretin.[29] Interestingly, dynorphin can mediate depressive-like states in mice,[29] and has an opposite action to hypocretin on rewarding behaviours.[29] Individuals with narcolepsy have increased incidence of depression compared with individuals with comparably debilitating diseases,[30] and hypocretin release in humans is increased during pleasure and inhibited during pain.[9] The link between narcolepsy and depression might be explained by a disturbed dynorphin–hypocretin balance.[29]

Reciprocal connections

An *in situ* hybridization study has demonstrated that hypocretin and histamine neurons are often found adjacent to each other in the posterior part of the human hypothalamus (Figure 1).[19] Their projection areas also largely overlap, as extensively mapped by the Allen Brain Atlas Mouse Connectivity project (http://connectivity.brain-map.org/; Figure 2).[32] Moreover, immunohistochemistry and electron microscopy studies in the rodent brain have shown hypocretin fibres to be extensively distributed in the tuberomammillary nucleus (TMN) area,[33–36] and an immunochemical study found histamine fibres to project heavily to hypocretin neurons.[37] The axonal terminals of hypocretin neurons in the TMN contain both hypocretin and glutamate vesicles;[24] both of these transmitters excite histamine neurons.[37,38]

The histamine and hypocretin systems have been shown to regulate each other bidirectionally in zebrafish: translational inhibition of HDC reduced the level of hypocretin mRNA and the number of hypocretin neurons, and this reduction was rescued by overexpression of HDC mRNA[39] in an H_1R-dependent manner.[39] The comprehensive interactions between histamine and hypocretin during development and the functional roles of this interaction have been discussed in recent reviews.[40,41] It remains, however, unclear whether histamine neurons form synaptic connections with hypocretin neurons. In transgenic mice that retrogradely transfer green fluorescent protein (GFP) to terminals that project to hypocretin neurons, no evidence was found of synaptic connections from the TMN to hypocretin neurons.[42] A classical retrograde tracing study also did not find evidence for such connections.[43]

Regulation of the sleep–wake cycle

Histamine involvement

The histamine neurons of the TMN are active during wakefulness, have a very low level of neuronal activity during non-REM sleep, and reach their minimum activity level in REM sleep.[44,45] Knockout studies have implicated both histamine, H_1R, and H_3R in sleep–wake regulation. Specifically, *Hdc* knockout mice showed impaired wakefulness and increased REM sleep.[46] Mice lacking H_1R exhibited much fewer brief waking episodes than did wild-type mice.[47,48] Both *Hdc* and H_1R knockout mice demonstrate an increased ratio of delta–theta oscillations, an indicator of sleepiness, during the dark phase of the daily light–dark cycle (when they would normally be active), indicating that the H_1R could largely exert the function of histamine in the maintenance of wakefulness.[46,48] The H_3R knockout mice have been reported to show fragmented sleep and reduced wakefulness during the dark period.[49]

Hypocretin involvement

Hypocretin neurons can induce wakefulness via excitation of histamine neurons. Optogenetic studies in rodent brain slices have demonstrated fast glutamate transmission from hypocretin neurons to histamine neurons via the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.[38] Histamine neurons in the TMN can also be activated directly through hypocretin 2R.[34] In dog models of narcolepsy, a mutation

that inactivates the hypocretin 2R decreased histamine levels in the CSF[50] despite normal numbers of histamine neurons.

Co-regulation of sleep by hypocretin and histamine

The diurnal activity pattern of hypocretin neurons parallels that of the histamine neurons, with increased c-fos staining, a neuronal activity marker, as well as increased extracellular hypocretin-1 levels reported in rats during the night phase.[10,49,51] However, hypocretin and histamine have distinct roles in maintaining wakefulness. *Hcrt* knockout mice show increased REM sleep duration during the dark phase, whereas *Hdc* knockout mice show increases in REM sleep duration only during the light phase.[52] Most importantly, *Hcrt* knockout animals exhibit narcolepsy with cataplexy, which is absent in *Hdc* knockout mice.[52]

In line with the findings from mouse studies, human brain histamine and hypocretin-1 levels both show a diurnal pattern, being low at wake onset, upregulated in the late waking stage and downregulated during sleep. The expression of *HDC* mRNA in the human TMN, measured by radioactive quantitative *in situ* hybridization in the postmortem brain, reaches its highest level between 0800 h and 2000 h.[53] A similar profile is also seen in the CSF histamine level in squirrel monkeys[54] as well as in histamine metabolites (t-MeHA) in the human CSF.[55] A slightly increased hypocretin-1 level is also observed in the late afternoon (1100 h–1800 h) relative to that at night (1800 h–1100 h) in the CSF acquired via lumbar puncture from healthy humans participants.[56] It should be noted that there are several steps between brain histamine levels and the levels of metabolites in the CSF, including transcription, translation and degradation. Information from both transcript levels and CSF levels of histamine and histamine metabolites (t-MeHA) can provide additional information on the activity of the brain histamine system.

More evidence for the concerted action of the histamine and hypocretin systems in sleep regulation comes from the findings that intracerebroventricular infusion of pyrilamine, an H_1R antagonist, inhibits hypocretin-induced arousal in rats,[34] and that mice lacking the H_1R do not show hypocretin-induced wakefulness.[35] Moreover, H_1R knockout mice show reduced hypocretin levels, suggesting that H_1R activates hypocretin neurons *in situ*.[57]

Histamine and hypocretin in CNS disease

Narcolepsy

Narcolepsy was first described by Westphal (in 1877) and Gelineau (in 1880). Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone in response to certain strong emotions), REM sleep abnormalities (such as hypnagogic hallucinations at the transitions between wakefulness and sleep, sleep-onset REM periods during daytime naps) and sleep paralysis. Individuals with narcolepsy often have disturbed night-time sleep and tend to be obese.[58,59]

Loss of hypocretin neurons in narcolepsy—The number of hypocretin neurons in patients with type 1 narcolepsy is greatly reduced,[2,3] with an average depletion of 90% (Figure 3).[3] This specific and subtotal degeneration of hypocretin neurons has been

confirmed by quantitative analyses that have shown a similar loss of neurons containing the hypocretin co-transmitters dynorphin and NARP.[3,23,26] The loss of hypocretin neurons does not seem to be accompanied by a generalized degeneration of neurons in the hypothalamus, because the number of MCH neurons, which are intermixed with the hypocretin neurons, is unchanged in narcolepsy.[3]

Hypocretin-1 levels in the CSF of patients with narcolepsy type 1 are typically low or undetectable.[60–62] Although 10–30% of patients with narcolepsy without cataplexy also show undetectable levels of CSF hypocretin-1, most of them exhibit normal levels and thus have narcolepsy type 2.[61,62] A study of the brains of two patients with narcolepsy type 2 showed partial loss of hypocretin neurons,[63] suggesting that the extent of hypocretin loss determines the presence of cataplexy in narcolepsy.

Increased histamine neurons in narcolepsy type 1—In two dog strains with narcolepsy resulting from spontaneous loss-of-function mutations in the hypocretin 2R gene,[64] histamine content in the cortex and thalamus is decreased.[50] These dog strains were the first animal models of narcolepsy, and enabled investigation into the CNS mechanisms of cataplexy. In these dogs, cataplexy is linked to an abrupt cessation of action potentials in the locus coeruleus,[66] increased firing of a cluster of medial medullary inhibitory neurons,[67] and a maintained or increased firing of histamine cells.[68] These findings suggest that activity of histamine neurons is tightly coupled to the waking state that, by definition, persists in cataplexy, whereas locus coeruleus activity is linked to the maintenance of waking muscle tone, which is lost in cataplexy.[69]

A robust increase (64–94%) in the number of histamine neurons in the TMN has been reported by two independent groups (Figure 3).[5,6] However, we did not observe this increase of histamine neurons in a series of narcoleptic animal models we tested (hypocretin 2R mutant dogs, *Hcrt* knock-out mice, ataxin-3-hypocretin mice, and doxycycline-controlled diphtheria toxin A–hypocretin mice).[5] Of these animal models, the postnatal hypocretin cell loss and adult-onset symptoms seen in the doxycycline-controlled diphtheria toxin A–hypocretin mouse resembles the clinical characteristics human narcolepsy most closely.[70] Valko *et al.* reported only a small increase in the number of histamine cells in the *Hcrt* knockout mice, but not in the ataxin-3-hypocretin mouse.[6] These data lead us to conclude that the large increase in histamine neurons in human patients with narcolepsy is not a compensation for the loss of hypocretin neurons. Rather, it might result from or mediate the immune-based loss of hypocretin neurons in these patients (Box 1). As described below, the number of histamine neurons has not been reported to increase in other human neurodegenerative diseases in which hypocretin reduction occurs. In contrast with humans, the hypocretin abnormalities in animal models of narcolepsy are caused by genetic alterations, rather than the presumed immune-mediated neuronal loss in human narcolepsy (Box 1).[5]

Despite the greatly increased number of histamine neurons in human narcolepsy, decreased[65] or unchanged histamine levels[71] are seen in the CSF of these patients. Normal CSF levels of histamine and t-MeHA were seen in a large population of patients with narcolepsy type 1, as well as in patients with other non-hypocretin-1-deficient central

hypersomnias and in neurological controls, with no significant between-group differences and no associations with sleepiness or frequency of cataplexy.[71] CSF histamine and t-MeHA are, therefore, not useful biomarkers for assessing the aetiology or severity of centrally mediated hypersomnia.[71]

Autoimmunity, histamine and hypocretin neuron loss—The overwhelming majority of patients with narcolepsy type 1 express the human leukocyte antigen (HLA) subtype *DQB1*06:02*, which is present in only 20–30% of the general population.[31] Narcolepsy is also linked to T-cell receptor α polymorphisms,[72] adding to the evidence for an autoimmune-mediated mechanism of hypocretin cell destruction. As in other presumed autoimmune disorders, the development of narcolepsy sometimes seems to be triggered by environmental factors, such as upper airway infection, H1N1 influenza or H1N1 vaccination with squalene-based adjuvant (Figure 4a);[73–75] however, in most cases, such triggers cannot be identified. To date, there is no consistent evidence that specific autoantibodies cause hypocretin neuron degeneration.[76,77]

Histamine and histamine receptors have a crucial role in autoimmune diseases of the CNS.[78–80] For example, binding of histamine to histamine receptors expressed in endothelial cells along the ventricles increases blood–brain barrier permeability, and thereby facilitates T cell entry to the CNS (Figure 4b).[82–87] Histamine signalling also directly enhances the activity of type 1 T helper cells by binding to the H_1R expressed on these cells.[88] Histamine activation triggers T cells, B cells, macrophages, microglia and mast cells to secrete histamine and cytokines and chemokines, such as IFN-γ, tumour necrosis factor, quinolinic acid, glutamate and radical oxygen intermediates (Figure 4b),[78,89,90] initiating a local inflammatory response (Figure 4c).

In multiple sclerosis, aberrant local inflammation results in myelin sheath destruction[78]—a similar process might underlie hypocretin neuron degeneration in narcolepsy. Hypocretin neurons are particularly sensitive to autoinflammatory insult, which could explain why the damage is specific to hypocretin neurons (Figure 4c). For example, histamine induction can cause microglia to release nitric oxide,[91] which might mediate the selective degeneration via increased endoplasmic reticulum stress in hypocretin but not MCH neurons.[92] Similarly, histamine activation causes microglia and macrophages to secrete quinolinic acid,[93] which can lead to pathological activation of *N*-methyl-D-aspartate receptors and subsequent selective death of vulnerable hypocretin neurons, but not adjacent MCH neurons.[94]

Hypothetically, the above described processes might also affect TMN neurons: hitherto unknown factors (secreted by T cells, B cells, macrophages, microglia and mast cells) might increase the number of histamine neurons as a response to autoimmune insult.[5,6] Elevated extracellular histamine might accelerate the degeneration of adjacent hypocretin neurons and inhibit histamine production and release in TMN neurons via the H_3R autoreceptor (Figure 4).[5,6]

The role of increased histamine in narcolepsy pathogenesis might be similar to its role in PD, in which increased histamine levels in the substantia nigra contribute to an accelerated degeneration of dopaminergic neurons. Human postmortem studies have

reported an increased density of histaminergic fibres and augmented local histamine levels in the substantia nigra of patients with PD,[95–97] and in a classic rat model of PD (unilateral 6-hydroxydopamine lesions of the substantia nigra), an injection of HDC inhibitor α-fluoromethylhistidine at an early stage of degeneration greatly reduces the loss of dopaminergic neurons.[98,99] Whether inhibition of neuronal histamine could prevent hypocretin neuron loss in human narcolepsy is currently unknown.

Alzheimer disease

Sleep impairment and neuropathology—The signs of AD include impairment of episodic memory, and deficits in language, semantic memory, executive functioning and visuospatial abilities.[100] In addition, patients with AD have more-frequent and prolonged awakenings at night, a decreased amount of sleep, and REM sleep dysregulation.[101,102] In fact, the sleep disruption in AD is often the main reason for their institutionalization.[101,102] Progressive accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of tau protein are the two main neuropathological markers for AD.[103,104]

Hypocretin system involvement—A correlation between CSF hypocretin-1 and total tau protein levels has been demonstrated in patients with AD.[105] Hypocretin levels also seem to correlate with Aβ pathology in mice, and a hypocretin antagonist can reduce Aβ levels in the interstitial fluid.[106] Another 2014 study confirmed the correlation between hypocretin-1 and $A\beta_{42}$ levels in human patients with advanced AD.[81] The correlation between hypocretin and Aβ pathology is seen neither in other dementias (frontotemporal lobar degeneration, dementia with Lewy bodies) nor in narcolepsy type 1.[81]

The level of Aβ in the brain interstitial fluid is high during periods of wakefulness, indicating that increased wakefulness might promote the development of AD by increasing the accumulation of extracellular Aβ.[106] Because narcolepsy typically develops in the teens or twenties, one would expect it to protect from the subsequent development of AD; however, there is no evidence for a reduced prevalence of AD in patients with narcolepsy,[107] and coexistence of narcolepsy and AD has been observed. Moreover, in a postmortem study, the number of hypocretin neurons and levels of CSF hypocretin were reduced in patients with advanced AD.[108]

Histamine system involvement—Neurofibrillary tangles have been reported to accumulate in the TMN in the early stage of AD.[103] In the late stages of AD, the number of histamine neurons in the TMN is substantially decreased,[109,110] though the total HDC mRNA expression level is not significantly reduced,[110] which is in line with the finding that CSF t-MeHA is not significantly lowered in patients with AD.[111] These findings imply that the remaining TMN neurons are activated to maintain histamine levels. A similar apparent compensation effect has been observed in the locus coeruleus of patients with AD, where remaining noradrenergic neurons are capable of maintaining normal noradrenaline levels.[112,113] Both diminished and increased levels of histamine and t-MeHA levels have been reported in different brain regions associated with AD;[95] studies with larger sample sizes are necessary to resolve the discrepancy regarding histamine alterations in AD.

Challenges in translational studies—Antagonists and inverse agonists of the H_3R stimulate the release of various neurotransmitters, including acetylcholine, which might partly explain the beneficial effects of H_3R antagonists on cognition seen in animal studies, including animal models of AD.[114] However, H_3R antagonists have failed to improve cognition in patients with mild to moderate AD in several controlled trials.[115–117] Further trials using H_3R antagonists in AD are required to understand the effect of increasing brain histamine on noncognitive symptoms, such as excessive sleepiness during daytime.

Parkinson disease

PD is the second-most prevalent age-related neurodegenerative disorder, affecting approximately 1% of the population above the age of 65 years.[118] The main clinical features of PD are resting tremor, rigidity, slowness of voluntary movement and postural instability.[118] Most of these motor symptoms are linked to the extensive loss (about 80%) of dopaminergic neurons in substantia nigra, which results in reduced dopamine levels in the striatum.[118] Lewy neurites and Lewy bodies, the neuropathological hallmarks of PD, have been detected in various brain regions outside the substantia nigra—including the hypothalamus[119]—and could underlie the nonmotor symptoms in PD, such as autonomic dysfunction, and disorders of mood and sleep.[120]

Disturbed sleep patterns—About 15–50% of patients with PD show excessive daytime sleepiness with frequent napping and sleep attacks.[121] This symptom frequently precedes the motor symptoms of PD.[122] The combination of excessive daytime sleepiness, hypnagogic hallucinations, REM-sleep behaviour disorder and daytime sleep-onset REM periods are similar to symptoms seen in narcolepsy.[123] Excessive daytime sleepiness in PD is caused by several factors, some being disease-related, whereas others are driven by medication, reduced activity in daily living, pain, altered BMI, depression, and night-time sleep problems, such as apnoea.

It is noteworthy that daytime sleepiness in PD has rarely been objectively assessed using the multiple sleep latency test, which is the gold-standard neurophysiological evaluation of sleepiness.[124] In the largest study using this method, abnormally short sleep latencies were found in only 13% of 134 consecutive patients with PD, and none of the patients displayed two or more sleep-onset REM periods.[125]

Hypocretin system involvement—Hypocretin neurons are progressively lost over the course of PD; unlike in narcolepsy, MCH neurons are also lost in PD (Figure 5).[126,127] The higher number of spared hypocretin neurons (40–50%) in PD compared with narcolepsy with cataplexy (10%) might explain the lack of cataplexy in PD.[126,127] The levels of hypocretin-1 in the cortex and ventricular CSF of patients with PD are significantly reduced,[127,128] but levels are mostly normal in CSF drawn from lumber puncture, suggesting regional differences in hypocretin release in PD; it is also possible that hypocretin is released in spinal regions.[60,129,130]

Histamine as a potential modulator of PD pathology—In PD, Lewy bodies and Lewy neurites are found in the TMN (Figure 5),[131] but the number of histamine neurons

remains stable despite the reduced number of hypocretin neurons.[126,127] This finding is consistent with stable HDC mRNA expression in TMN neurons,[132] stable HDC enzymatic activity,[133] and stable CSF levels of t-MeHA isomer[134] in patients with PD.

Postmortem human and animal data collectively show that increased levels of histamine could accelerate degeneration of dopaminergic neurons in the substantia nigra of patients with PD. Inhibition of endogenous histamine production in a rat model of PD prevented the loss of dopamine neurons in the substantia nigra,[95] a finding supporting our hypothesis that the increased number of histamine neurons, which we reported in patients with narcolepsy,[5] could have caused the loss of hypocretin neurons in narcolepsy.

Trials assessing the benefits of H_3R antagonists, such as pitolisant, in PD are currently ongoing, with the primary objective of alleviation of excessive daytime sleepiness.[114] H_3R antagonists promote histamine release in the brain and might be of interest in treating overt sleepiness in PD because histamine neurons are spared in this disorder. However, the large variability in the phenotype, severity and pathogenesis of daytime sleepiness in PD could prevent the global effectiveness of any psychostimulant in this condition. Moreover, the possibility of degeneration caused by an increased local release of histamine in the substantia nigra of patients with PD[95] should remind us to administer these compounds with caution.

Huntington disease

HD is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion in the gene encoding huntingtin.[135] This CAG repeat in the *N*-terminal of the huntingtin gene (*HTT*) translates into an abnormally long polyglutamine tract. The disease occurs when the critical threshold of about 37 glutamine units is exceeded.[136] Patients develop characteristic motor, cognitive and behavioural deficits over the course of the disease,[135] with chorea as a core feature.[135]

Hypocretin system involvement—Among all the hypothalamic nuclei, the TMN and lateral hypothalamic area contain the highest frequency of the cytoplasmatic inclusions of mutant *HTT*.[137] The number of hypocretin neurons is reduced by about 30% in patients with HD,[137–139] and hypocretin neurons are also markedly reduced (by 70%) in an HD mouse model, R6/2,[139] which expresses exon 1 of the human mutant *HTT* with 150 CAG repeats, and displays several clinical symptoms of HD.[140]

The loss of hypocretin neurons in HD is relatively specific owing to their relative sensitivity: the number and size of MCH neurons adjacent to the hypocretin neurons in patients with HD did not differ from that in matched controls,[138] and several studies have shown that the level of hypocretin-1 peptide in the CSF of patients with HD is similar to that of healthy controls.[138,141] This result indicates that the levels of hypocretin-1 peptide in the CSF does not closely track the 30% loss of hypocretin cells seen in these patients.

Histamine system involvement—A postmortem assessment of brains of patients with HD has demonstrated a substantial increase in HDC mRNA expression without a change in the number of histamine neurons;[142] moreover, histamine *N*-methyltransferase mRNA was

upregulated in the inferior frontal gyrus of patients with HD, indicating increased histamine degradation.[142] Although this study did not evaluate protein and enzymatic activity of HDC, the reported augmentation of the histamine system in HD is consistent with a previous study that described increased levels of histamine metabolites in the CSF.[134]

An *in vitro* electrophysiological study showed that the response of histamine neurons to hypocretin is unchanged in HD model mice, suggesting that the histamine neurons remain functionally intact despite a markedly reduced input from hypocretin fibres;[143] however, neither the tuberomammillary complex nor the neuronal histamine system has been directly studied *in vivo*.

Alterations in both hypothalamic hypocretin and histamine levels in HD might explain, at least partly, the disintegration of circadian rhythm and sleep disorders in patients with HD.[144,145] However, despite the 30% loss of hypocretin neurons, these patients do not display REM sleep at sleep onset, cataplexy, hypnagogic hallucinations or sleep paralysis[146]—these symptoms probably occur only with more-extensive loss of hypocretin neurons, such as seen in narcolepsy type 1.

Tourette syndrome

TS is a childhood-onset neurological disorder that is characterized by motor and phonic tics. In a rare two-generation pedigree, an autosomal dominant mutation (Trp317X) of the *HDC* gene, which truncated full-length HDC protein from 662 amino acids to 316 amino acids, was reported to deplete the enzymatic activity of HDC.[147] This mutation occurred in one of the *HDC* alleles and caused haploinsufficiency in histamine production.[147] The association of TS with *HDC* was also supported by a larger sample of 520 European families.[148]

A 2014 study reported $Hdc^{+/-}$ knockout mice to have intermediate levels of brain histamine.[149] These mice exhibited tic-like behaviours and might serve as an animal model for TS. As we previously discussed, homozygous *Hdc* knockout mice show reduced wakefulness at lights-off, and signs of somnolence.[46] The sleep–wake pattern of the heterozygous *Hdc* knockout mice could mimic the sleep disorders described in TS.[150] One patient affected with TS plus hypersomnia had a dramatic decrease in daytime sleepiness after being treated with pitolisant, whereas tic scores remained constant.[151] A clinical investigation of H_3R antagonists in the treatment of TS symptoms is, therefore, warranted.

Therapeutic prospects

H_1R antagonists

H_1R antagonists are well known to cross the blood–brain barrier and cause drowsiness.[152] Several drugs with H_1R antagonist activity—such as diphenhydramine, chlorpheniramine, doxylamine and brompheniramine—have been prescribed to treat allergies, cold symptoms, itching, nausea, but also insomnia, and are available over-the-counter.[153] However, despite being widely used, very few data exist on the effectiveness of these drugs for the treatment of insomnia. Some antidepressants or antipsychotics reported to have beneficial effects on insomnia, such as doxepin, amitriptyline, olanzapine and risperidone, are also H_1R blockers.[153] However, most of the antidepressants and antipsychotics with H_1R antagonist

activity also substantially alter the sleep–wake cycle via mechanisms not related to histamine, with main actions on cholinergic, dopaminergic, serotonergic, and adrenergic receptors. These various actions could also explain the adverse events (constipation, nausea, urinary retention, fatigue and weight gain) that are commonly reported in association with these compounds.

Recently, a well designed placebo-controlled trial showed that a low dose (1–6 mg) of doxepin, a relatively selective H_1R antagonist, alleviated the symptoms of primary insomnia.[154] The improvement was observed mainly as prolonged sleep during the latter part of the night (that is, prevention of early morning awakening) rather than as decreased sleep-onset latency, as occurs with the use of most of the GABAergic sleep-promoting agents (such as the benzodiazepines).[154] Neither sedation nor impairment was found upon awakening in patients taking doxepin compared with those taking placebo.[154] Altogether, these results suggest a stronger efficacy of doxepin in the second part of the night, in accordance with the circadian histamine level being higher toward the end of the night.

H_3R agonists and antagonists

Drugs that inhibit histamine release through H_3R agonism could also promote sleep, as previous studies[114,155] have shown that increasing brain histamine levels promotes wakefulness. Thus, H_3R has been targeted for the treatment of daytime sleepiness in several neurological pathologies associated with hypersomnia.[114]

Pitolisant is one of the first H_3R antagonists found to have a good preclinical and clinical benefit–risk ratio; it has been reported to enhance the activity of histamine, acetylcholine, dopamine and noradrenaline neurons.[155] In *Hcrt* knockout mice (an animal model for narcolepsy) pitolisant significantly improved symptoms of narcolepsy, such as sleepiness, and decreased abnormally short REM sleep latency at sleep onset.[155] Two small pilot trials indicated that pitolisant decreased excessive daytime sleepiness in adults and children with narcolepsy.[155,156] In a double-blind randomized trial comparing pitolisant with placebo and modafinil, an approved pharmacological treatment for narcolepsy, pitolisant was found to ameliorate excessive daytime sleepiness in patients with narcolepsy at a level similar to that seen with modafinil (Figure 6), moreover, pitolisant use was linked to reduced number of cataplexy episodes.[157] Pitolisant at doses up to 40 mg was well tolerated in patients with narcolepsy, and no withdrawal symptoms, dependence or abuse were detected, which is in accordance with *in vitro* results that demonstrated no change in dopamine release in the striatal complex.[157]

The recent findings of a robust increase in the number of histamine neurons[5,6] and unchanged histamine levels[71] in patients with narcolepsy highlights the need for further study into the exact pharmacological effects of pitolisant. Taken together, the results suggest pitolisant as a promising treatment for narcolepsy. Other pitolisant trials—using lower doses, monitored on a long-term open basis, and assessing the anticataplectic activity in drug-free patients with narcolepsy—are currently ongoing. According to the NIH Clinical Trials Database (ClinicalTrials.gov), other H_3R antagonist are also being evaluated.

The studies discussed above will provide more insight into the role of central histamine levels in the regulation of daytime sleepiness associated with narcolepsy, with PD, AD and TS, and with residual excessive sleepiness associated with obstructive sleep apnoea syndrome despite continuous positive airway pressure therapy.

Conclusions

The neurodegenerative processes in AD, PD and HD can lead to a slow degeneration of hypocretin neurons over the course of the disease. By contrast, in narcolepsy type 1, loss of hypocretin neurons and peptide manifests close to the time of symptom onset.

Functionally, the substantial loss of hypocretin neurons in neurodegenerative diseases (40% in AD, 60% in PD, 30% in HD and 90% in narcolepsy) could contribute to the excessive daytime sleepiness and other sleep abnormalities seen in these disorders.

In addition, neuropathological findings by us[5] and others[6] demonstrate an increased number of histamine neurons in type 1 narcolepsy, in contrast with other neurological conditions involving loss of hypocretin neurons, namely AD, PD and HD. Recent results showed that increasing histamine release might alleviate narcolepsy, as indicated by positive results on a phase III clinical trial using an H_3R inverse agonist.[155,157] The increased number of histamine neurons in human narcolepsy deserves further investigation to determine the clinical effect of this increase, and to elucidate the possible link to hypocretin cell loss.

Acknowledgements

We thank the National Institutes of Health (NS14610, MH064109, DA034748) and the Medical Research Service of the US Department of Veterans Affairs for support. L.S. is supported by a 2014 NARSAD Young Investigator Grant from the Brain & Behaviour Research Foundation. The authors want to thank Dr Ronald McGregor for drawing Figure 4.

Competing interests

Y.D. has received funds for speaking and board engagements from Bioprojet, Jazz and UCB Pharma. L.S. and J.M.S. declare no competing interests.

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Key points

- Over-the-counter histamine H_1 receptor antagonists (antihistamines) block the effects of histamine, have sedating properties and are commonly used to treat insomnia
- A large increase in the number of histamine neurons is seen in type 1 narcolepsy (narcolepsy with cataplexy), but not in animal models of narcolepsy
- Low levels of cerebrospinal fluid (CSF) hypocretin are characteristic of type 1 narcolepsy; changes in CSF histamine levels are small and variable in this disorder
- In several neurological disorders including Parkinson and Alzheimer diseases, hypocretin-containing cells degenerate while the number of histamine cells and histamine levels are in the normal range
- Histamine H_3 receptor antagonists and inverse agonists promote histamine release and are a promising class of drugs for the promotion of wakefulness, as has been shown in patients with narcolepsy

Box 1 |

Hypotheses on increase in histamine neurons in narcolepsy

Adverse effect of narcolepsy medication

Virtually all patients with narcolepsy take medication to alleviate their symptoms. Pharmacotherapy has been proposed as the cause of the increased number of histamine neurons in human narcolepsy; consistent with this hypothesis, we have not detected an increased number of histamine neurons in any of the four (drug-free) animal models that we have examined.[5] The effect of antidepressants and antipsychotics on CSF levels of histamine remains controversial. In one study, a significant reduction in CSF histamine was demonstrated in unmedicated, but not medicated patients with hypocretin deficiency.[158] By contrast, another study found no association between treatment status and levels of CSF histamineor tele-methylhistamine,[71] and HDC mRNA levels have been reported to be stable in patients with depression who were being treated with antidepressants or antipsychotics.[159]

However, we are not aware of any drug that has been shown to alter the number of histamine neurons. The consistency and very large magnitude (64–94%[5,6]) of the increase in the number of histamine neurons in individuals with narcolepsy, independent of the category of the drug taken, makes the drug mediation hypothesis implausible.

‘Neurotransmitter respecification’

We have hypothesized[5] that increase in the number of histamine neurons could result from ‘neurotransmitter respecification’,[160] in which neurons that do not normally have detectable levels of a particular protein or the enzyme required for its synthesis—in this case the HDC enzyme necessary for histamine synthesis—develop this capacity.

Neurogenesis

We have also suggested[5] that postnatal neurogenesis[161,162] of histamine neurons is a potential mechanism explaining our observations.

Autoimmune response

Autoimmune insult might trigger T cells, B cells, macrophages, microglia and mast cells to secrete factors that increase the number of histamine neurons (Figure 4).

Abbreviations: CSF, cerebrospinal fluid; HDC, histidine decarboxylase.

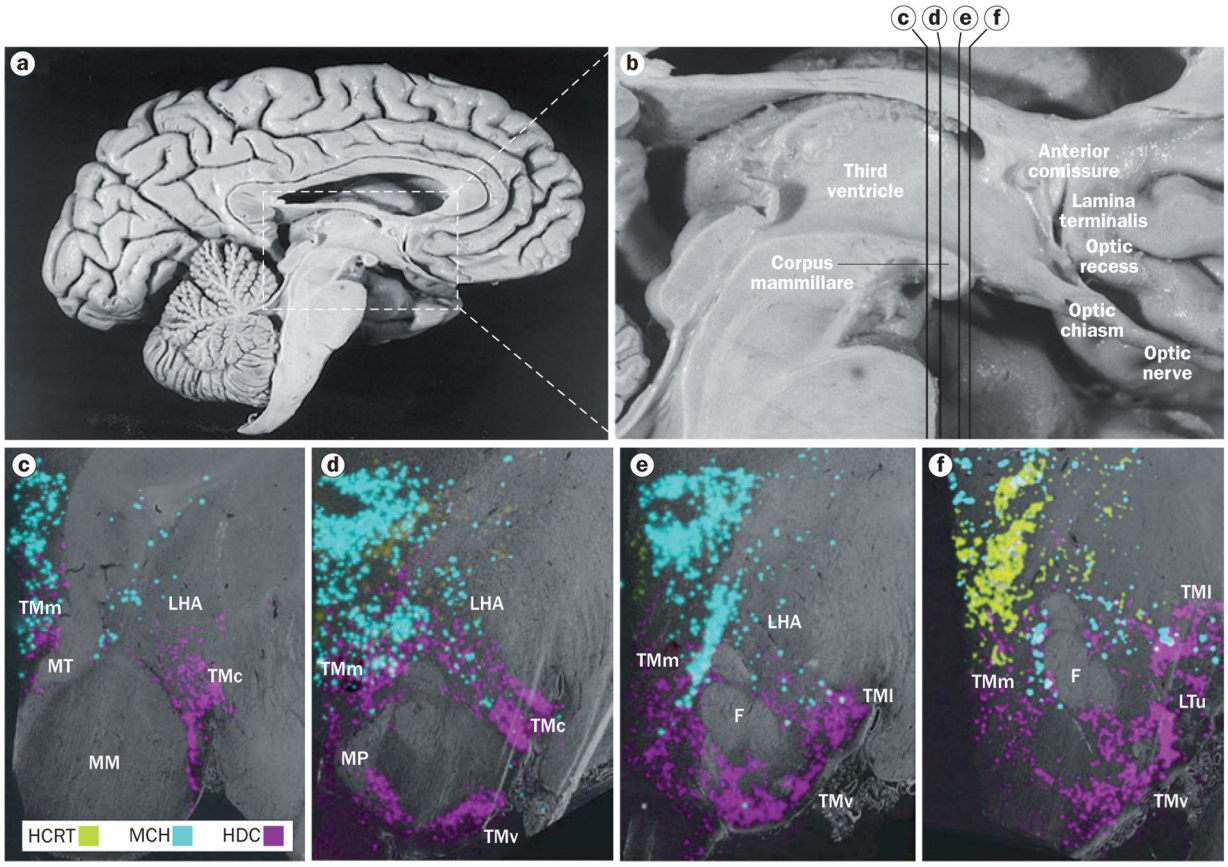

Figure 1 |.

Neurons containing histamine, hypocretin and melanin-concentrating hormone in the human hypothalamus. **a** | Overview of the medial surface of the human brain, and **b** | detail of the hypothalamus. The distribution of neurons containing histamine, hypocretin and melanin-concentrating hormone are shown with *in situ* hybridization in coronal sections of hypothalamus at the **c** | posterior level through the medial mammillary nucleus, **d** | rostromammillary level at the principal mammillary fasciculus, **e** | level of the caudal end of the fornix and **f** | premamillary level. In panels c–f, the third ventricle is on the left side. Abbreviations: F, fornix; HCRT, hypocretin neurons; HDC, histidine-decarboxylase-positive (histamine) neurons; LHA, lateral hypothalamic area; LTu, lateral segment of the lateral tuberal nucleus; MCH, melanin-concentrating hormone neurons; MM, medial mammillary nucleus; MP, mammillary peduncle; MT, mammillothalamic tract; TMc, caudal tuberomammillary nucleus; TMl; lateral tuberomammillary nucleus; TMm, medial tuberomammillary nucleus; TMv, ventral tuberomammillary nucleus. Panels a and b reprinted with permission from Elsevier © Handbook of Clinical Neurology Vol. 79. Swaab, D. F. *The human hypothalamus: basic and clinical aspects. Part 1: Nuclei of the human hypothalamus* 3–38 (2003). Parts c–f adapted with permission from John Wiley & Sons © Krolewski, D. M. *et al. J. Comp. Neurol.* 518, 4591–4611 (2010).

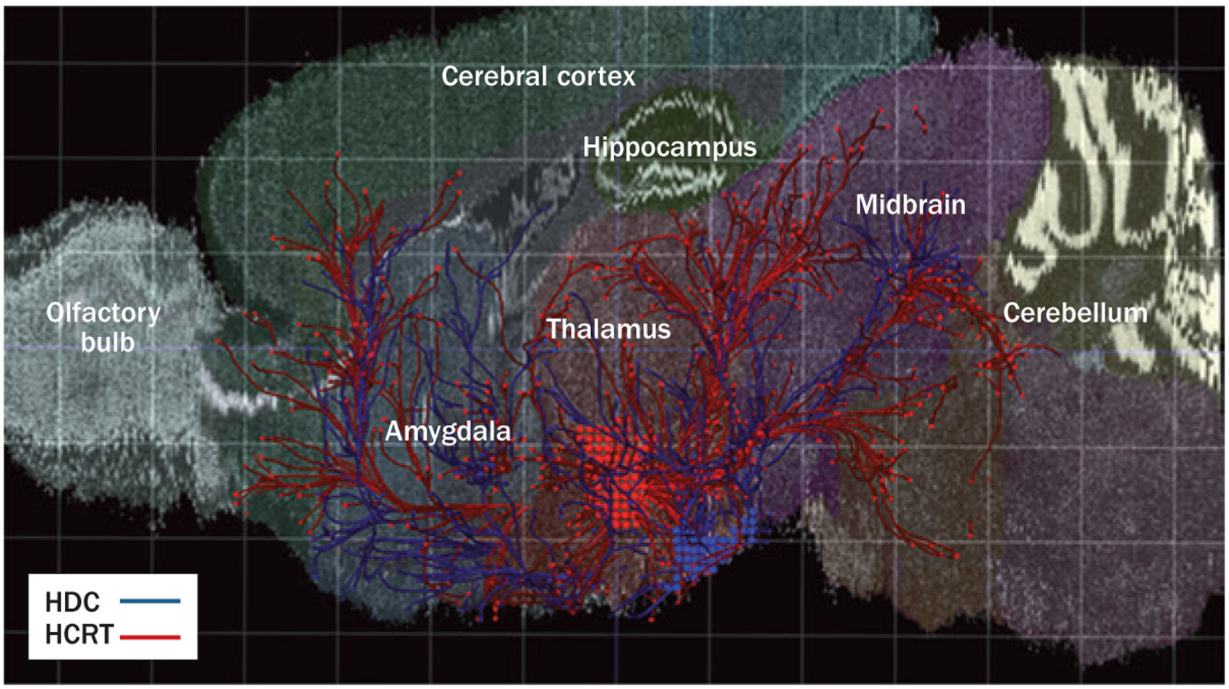

Figure 2 |.

The hypocretin and histamine systems in the mouse brain—origin and general projections. Red dots indicate the location and projections of hypocretin neurons. The blue dots and lines represent the location and innervations of histamine neurons. Mouse brain connectivity was mapped using hypocretin–Cre and histidine-decarboxylase–Cre mouse lines. Adeno-associated viral vectors expressing Cre-dependent enhanced green fluorescent protein was injected to trace axonal projections from both hypocretin (red) and histamine (blue) neurons. Abbreviations: HCRT, hypocretin neurons; HDC, histidine-decarboxylase-positive (histamine) neurons. Reprinted with permission. © 2014 Allen Institute for Brain Science. Allen Mouse Brain Connectivity Atlas [online]. Available from: http://connectivity.brain-map.org/.

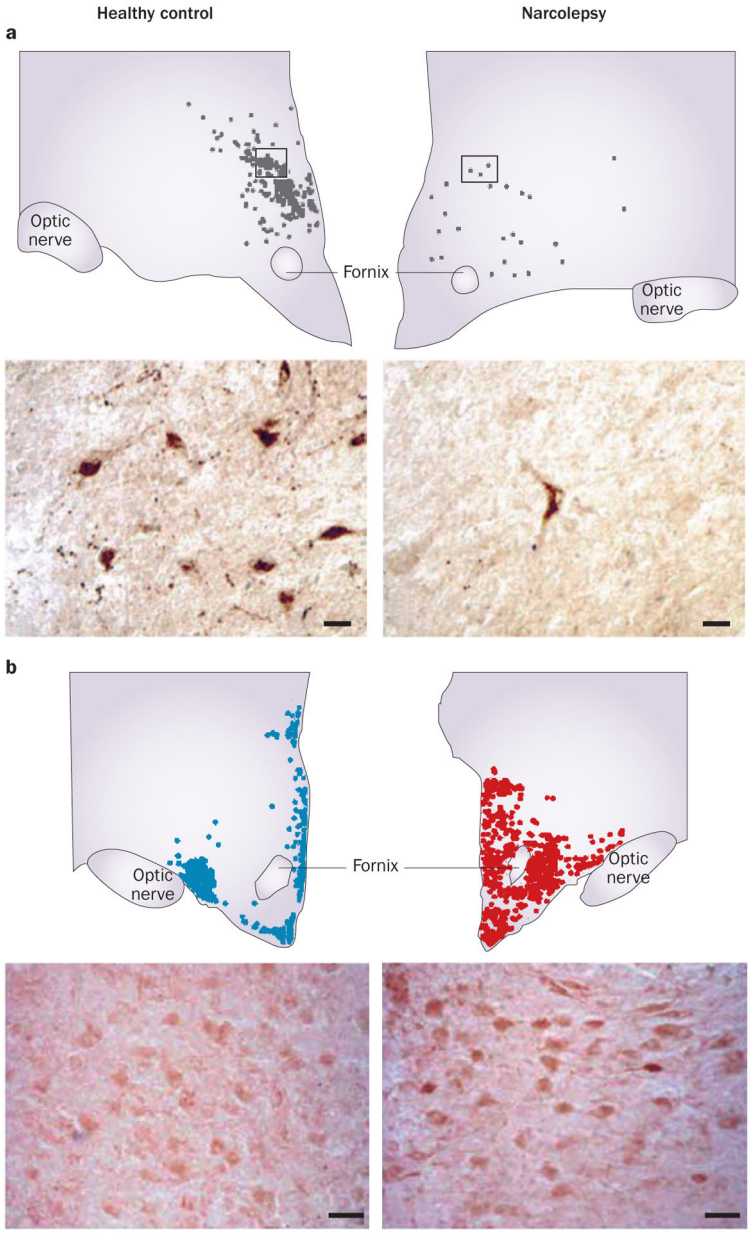

Figure 3 |.

Loss of hypocretin neurons and increase in histamine neurons in narcolepsy. **a** | Number and distribution of hypocretin neurons, and a representative cell staining of brain slices from a healthy control (left) and an individual with narcolepsy (right). Scale bars = 25 μm. **b** | Number and distribution of histamine neurons, and a representative cell staining from a healthy control (left) and an individual with narcolepsy (right). Scale bars = 50 μm. Part a reprinted with permission from Elsevier © Thannickal, T. C. *et al.* Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 27, 469–474 (2000). Part b adapted with permission from John Wiley & Sons © John, J. *et al. Ann. Neurol.* 74, 786–793 (2013).

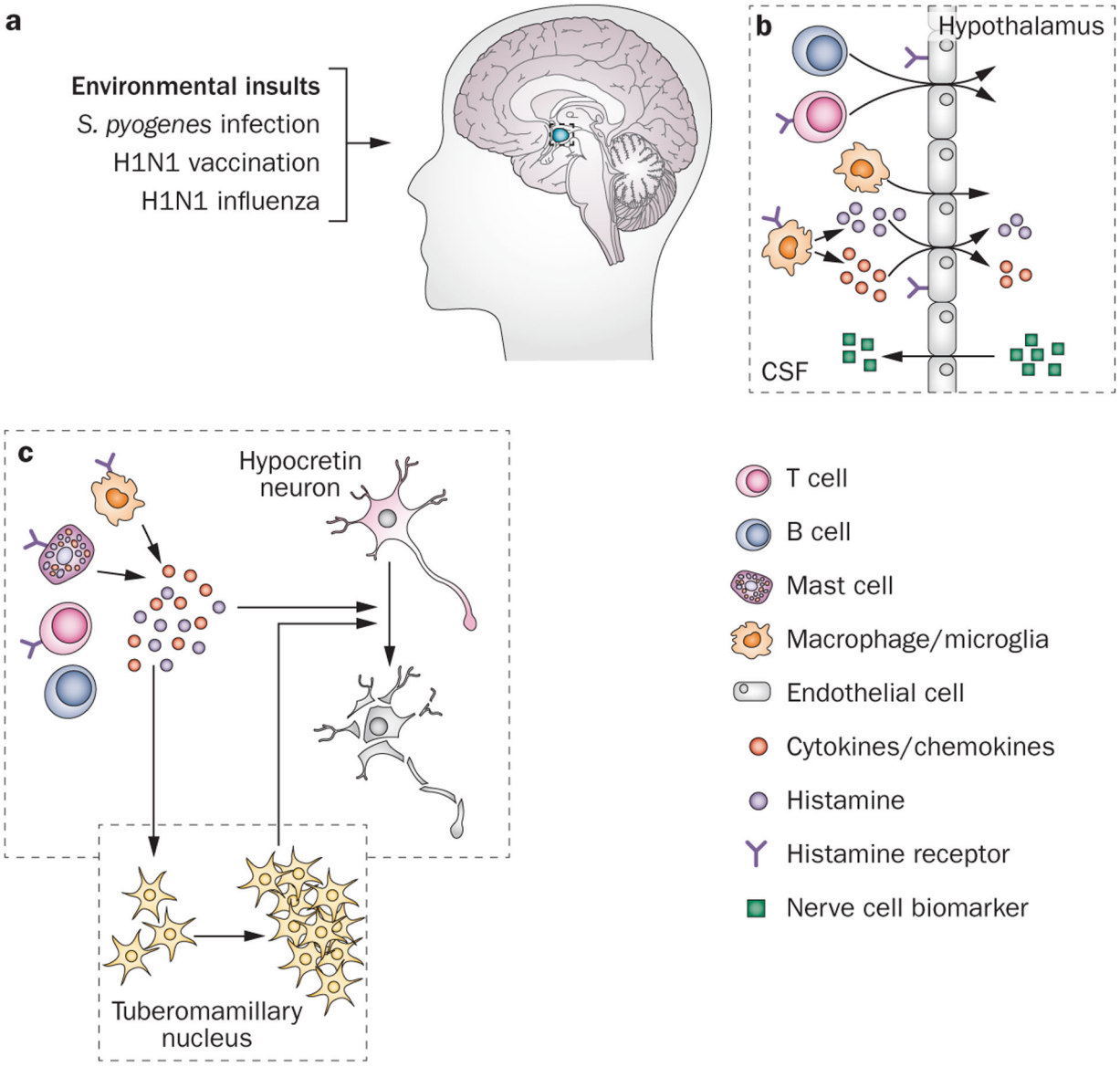

Figure 4 |.

A schematic model of autoimmune-triggered histaminergic involvement in hypocretin neuron degeneration. **a** | The development of narcolepsy can sometimes be triggered by environmental factors, such as *Streptococcus pyogenes* infection, upper airway infection, H1N1 influenza or H1N1 vaccination with squalene-based adjuvant. Histaminergic signalling has a crucial role in several autoimmune diseases of the CNS. **b** | For example, binding of histamine to endothelial cell histamine receptors increases the permeability of the blood–brain barrier, (as indicated by increased levels of neuron-specific markers Aβ, total tau protein, phosphorylated tau, and neuro-specific enolase in the CSF), thereby facilitating T cell entry to the CNS.[81–87] Moreover, histamine signalling enhances the activity of type 1 T helper cells through binding to histamine type 1 receptors located on these cells.[88] **c** | T cells, B cells, macrophages, microglia and mast cells secrete histamine and other cytokines

and chemokines,[78,89,90,163] triggering a local inflammatory response that can damage the sensitive hypocretin neurons. Abbreviations: Aβ, amyloid-β; CSF, cerebrospinal fluid.

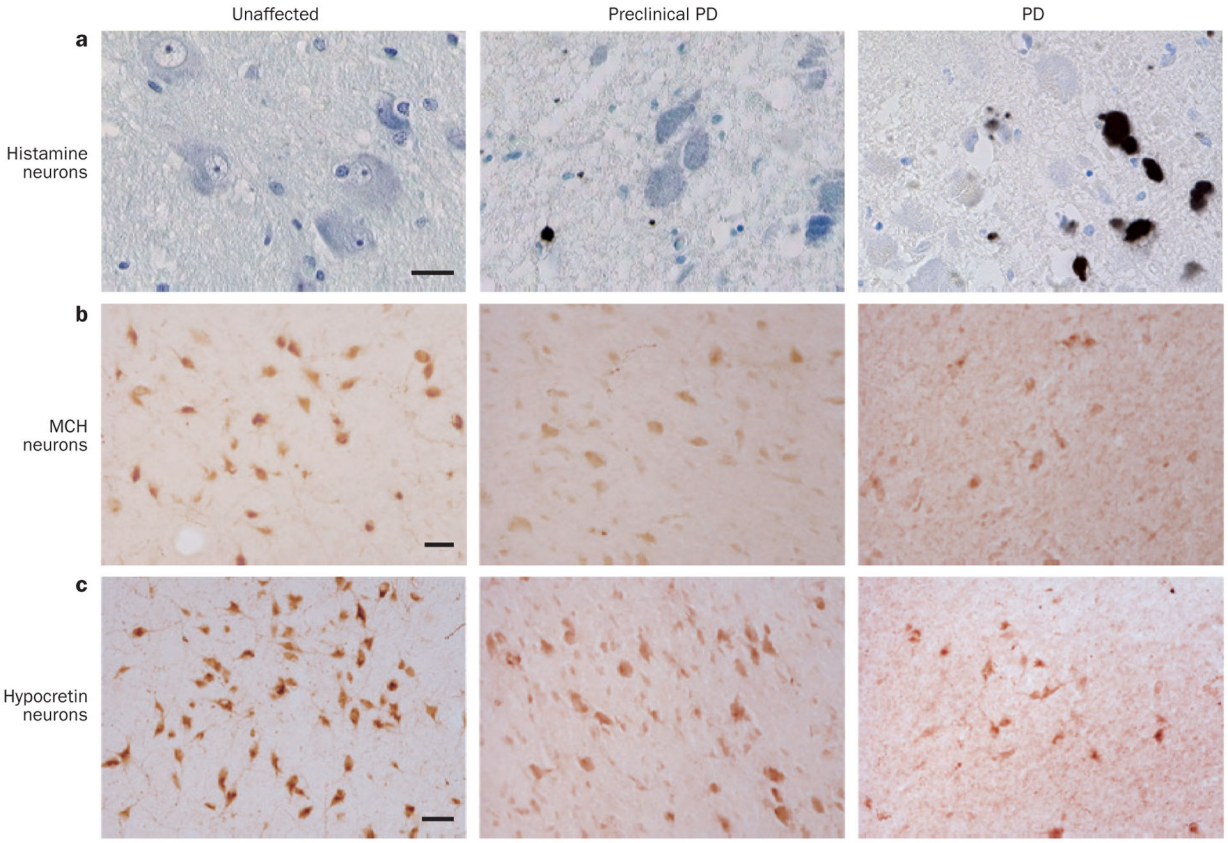

Figure 5 |.

Specific degeneration of histamine, MCH and hypocretin neurons in PD. The course of PD can be divided into several stages,[119] including unaffected, preclinical PD, and PD (from left to right). **a** | The number of histamine neurons in the TMN remains stable despite the accumulation of Lewy bodies and Lewy neurites. TMN neurons were stained for α-synuclein (brown) and counterstained by thionin (blue). Scale bar = 250 μm. The numbers of **b** | MCH neurons and **c** | hypocretin neurons decrease in line with increasing disease severity. MCH and hypocretin neurons were immunostained by their peptide-specific antibodies, followed by the diaminobenzidine colouring (reddish brown). Scale bars = 50 μm. Abbreviations: MCH, melanin-concentrating hormone; PD, Parkinson disease; TMN, tuberomamillary nucleus. Part a reprinted with permission from Elsevier Ltd © Shan, L. *et al.* Neuronal histamine production remains unaltered in Parkinson's disease despite the accumulation of Lewy bodies and Lewy neurites in the tuberomamillary nucleus. *Neurobiol. Aging* 33, 1343–1344 (2012). Parts b and c adapted with permission from Oxford University Press © Thannickal, T. C. *et al.* Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* 130, 1586–1595 (2007).

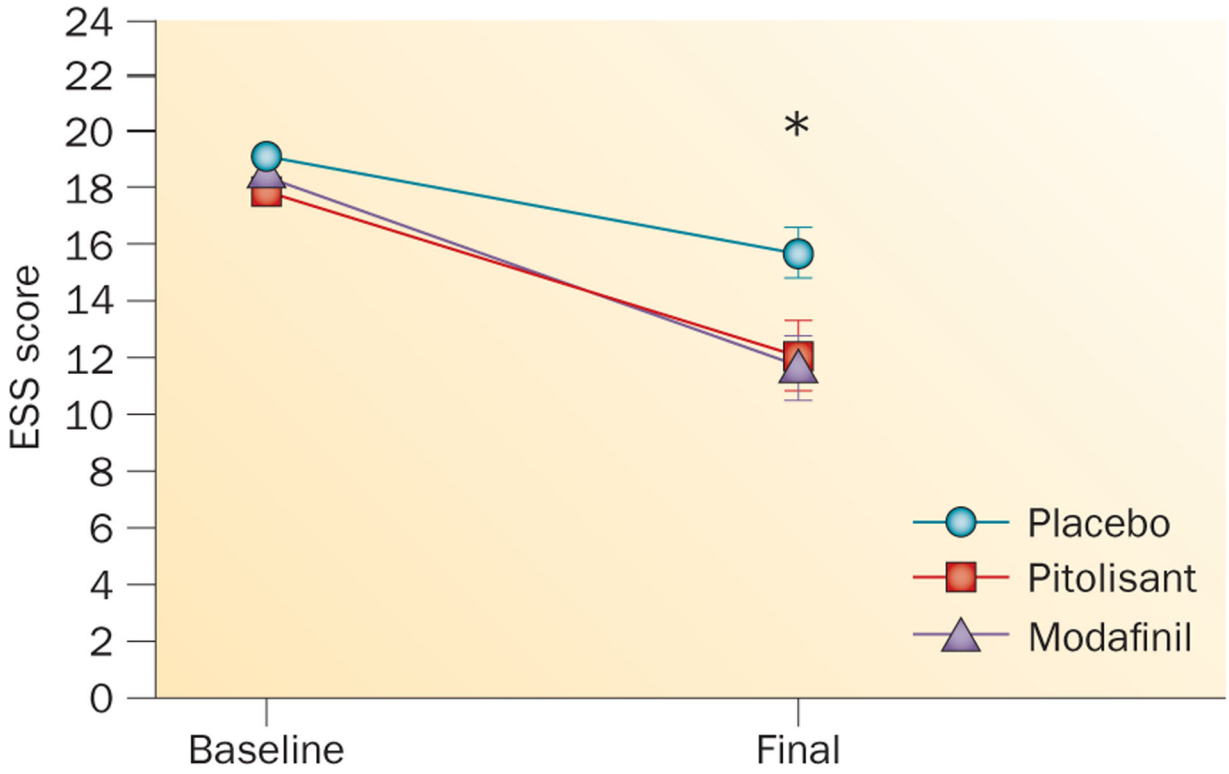

Figure 6 |.

Effects of pitolisant, modafinil and placebo on patients with narcolepsy. Changes in Epworth sleepiness scale (ESS) score from the beginning of a double-blind, randomized phase III study ('Baseline') to the end of the 9-week treatment period ('Final').[157] Data points indicate the mean ESS score; error bars indicate SEM. *A significant reduction in ESS was found for both modafinil and pitolisant versus placebo. No significant difference in ESS was found between pitolisant and modafinil.[157]