Experimental Gerontology 48 (2013) 603–607

Contents lists available at SciVerse ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Neuronal histaminergic system in aging and age-related neurodegenerative disorders

Ling Shan [a,b], Dick F. Swaab [b], Ai-Min Bao [a,*]

[a] Department of Neurobiology, Key Laboratory of Medical Neurobiology of Ministry of Health of China, Zhejiang Province Key Laboratory of Neurobiology, Zhejiang University School of Medicine, Hangzhou, China

[b] Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 31 May 2012
Received in revised form 26 July 2012
Accepted 2 August 2012
Available online 11 August 2012

Section Editor: Kurt Borg

Keywords:
Histamine
Histidine decarboxylase
Histamine-methyltransferase
Histamine receptor
Parkinson's disease
Alzheimer's disease

ABSTRACT

The neuronal histaminergic system is involved in many physiological functions and is severely affected in age-related neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). The properties of the neuronal histaminergic system in experimental animals and the alterations observed in postmortem brain material of PD or AD patients are reviewed. The production of neuronal histamine shows diurnal fluctuations in control subjects who had no neuropsychiatric disorders, while this fluctuation was strongly altered in patients with neurodegenerative diseases, including PD and AD. In addition, different alterations shown as expression levels of histidine decarboxylase (the key enzyme for histamine production), histamine-methyltransferase (the histamine deactivating enzyme), and histamine receptors ($H_{1-4}R$) were found in various neurodegenerative disorders. Discrepancies between results from animal models and postmortem human brain material studies have made clear that the validation of animal models is absolutely necessary and that studies on patients and human postmortem material are essential to understand the changes of neuronal histaminergic system occurring in neuropsychiatric disorders.

1. Introduction

The neuronal histaminergic system is involved in a number of basic physiological functions, such as the sleep–wake cycle, energy and endocrine homeostasis, sensory and motor functions, cognition, attention, learning and memory, which has been the subject of a number of animal experimental reviews (Haas et al., 2008). These functions are often gender-, age- and time of the day-dependent and are severely affected in certain human brain disorders, including in age-related neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) (Haas et al., 2008). The present review aims to bridge the gap between the fundamental properties of the histaminergic system in experimental animals and the alterations recently observed in postmortem tissue of patients with PD or AD. This topic seems to be timely since histamine-receptor-3 (H_3R) antagonists/inverse agonists are advancing into the clinics as a potential treatment of AD and PD (Brioni et al., 2011; Passani and Blandina, 2011) while the recently obtained insights from postmortem studies on the alterations in histamine receptors (HRs) seem to reveal crucial information on the potentials of these compounds. Our observations illustrate that animal models may differ from the human observations and that studies on human brain are thus critical for understanding the neuronal histaminergic system in our species.

2. Neuronal histaminergic system in the brain

2.1. Tuberomamillary nucleus

The tuberomamillary nucleus (TMN) that is localized in the posterior hypothalamus consists of large, irregularly bordered lipofuscin-laden neurons that have intensely stained endoplasmic reticulum. They surround the lateral tuberal nucleus, the final descending course of the fornix, and the mamillary body. The TMN can already be distinguished at 34 weeks of gestation. An earlier study in 3 subjects, who had no clear neurological disease, reported that each side of human hypothalamus there were about 32,000 large and multipolar histaminergic neurons. We have found a comparable number of TMN neurons (37,052 ± 5181) based upon 9 control subjects (patients without neurological or psychiatric disease) (Shan et al., in press).

Recent tracing and pharmacological studies in rodents have shown that histaminergic neurons are organized in functionally distinct circuits that influence different brain areas. Although histaminergic fibers have been reported in the prefrontal cortex (PFC), thalamus and substantial nigra (SN) of the human brain, information of the regional origin in the TMN of the different histaminergic innervations is, however, lacking in our species for obvious reasons.

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; HDC, histidine decarboxylase; HRs, histamine receptors; HMT, histamine-methyltransferase; 6-OHDA, 6-hydroxydopamine; LBs, Lewy bodies; LNs, Lewy neuritis; MT, melatonin receptor; PD, Parkinson's disease; PFC, prefrontal cortex; SCN, suprachiasmatic nucleus; SN, substantial nigra; t-MeHA, tele-melthylhistamine; TMN, tuberomamillary nucleus; TH, tyrosine hydroxylase.

* Corresponding author. Tel.: +86 571 88208789.
E-mail address: baoaimin@zju.edu.cn (A.-M. Bao).

0531-5565/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.exger.2012.08.002

Neuronal histamine is exclusively synthesized in the TMN from the amino acid histidine by histidine decarboxylase (HDC) which is the key enzyme for histamine production. Knock-out or pharmacological manipulation of HDC significantly decreases histamine production in rodents. In the human TMN, the histaminergic neurons are characterized by HDC expression, while most of HDC-positive neurons co-localize gamma-aminobutyric acid, characterized by its synthesizing enzyme glutamic acid decarboxylase (Trottier et al., 2002). In addition, acetylcholinesterase-, monoamine oxidase-, and the food-regulating neuropeptide cocaine- and amphetamine-regulated transcript-positive neurons have been described in the human TMN. It should be noted that, although in a previous study TMN was negative to galanin staining (Trottier et al., 2002), our recent study with a novel galanin antibody showed galanin-positive neurons in the TMN (Garcia-Falgueras et al., 2011).

In order to study neuronal histamine production in formalin-fixed, paraffin-embedded archival postmortem human brain tissue, we have optimized a radioactive *in situ* hybridization protocol to quantify HDC-mRNA expression (Liu et al., 2010). In our subsequent studies we observed that HDC-mRNA expression levels in the postmortem human TMN showed the same direction of changes in levels of histamine or the histamine metabolite, tele-melthylhistamine (t-MeHA) reported in cerebrospinal fluid (CSF) in PD or AD (see below).

TMN neurons are sensitive to sex hormones and may show related sexual differentiation. Both estrogen receptor (ER)-α and -β are expressed in TMN neurons (Kruijver et al., 2003). In addition, a stronger cytoplasmic ER-β staining was observed in women than in men, which may be targeted by the fluctuating estrogen levels in females (Kruijver et al., 2003). In a small sample size, we observed that the total number of TMN neurons was slightly, but not significantly, higher (32%) in 4 female than in 5 male control subjects, which is in line with the HDC-mRNA expression showing significantly higher (46%) levels in females than in males, and is also in line with the slightly but not significantly higher histaminergic system activity that was reported in the higher levels of CSF-t-MeHA levels in healthy females (Shan et al., in press). Moreover, a positron emission tomography (PET) study demonstrated a higher H_1R binding potential in females compared to age matched males (Yoshizawa et al., 2009).

In many species, neuronal histamine displays a diurnal rhythm with higher levels during the waking period and lower levels during sleep. An increase in histamine release, higher c-fos expression in the TMN and increased neuronal activity in the TMN are shown during the dark period in nocturnal animals, e.g. in rodents. In addition, microdialysis and quantitative radioenzymatic assays revealed a considerably higher histamine concentration in the cat preoptic/anterior hypothalamic area during the waking stage, as compared to the sleep stage. We have demonstrated for the first time that the total expression of HDC-mRNA in the human TMN exhibits higher levels between 8:01–20:00 and lower levels in 20:01–8:00, which supports a role for neuronal histamine in regulating day-night patterns (Shan et al., 2012). Interestingly, some recent systematic observations revealed that the circadian rhythm of histamine in the CSF of a diurnal mammal, i.e. squirrel monkey, reached acrophase values at 17:49 (Zeitzer et al., 2011), which fits very well with the maximum values of HDC-mRNA we observed in the human TMN around 18:09. Our results that indicate more HDC-mRNA expression in the TMN during daytime are also in agreement with previous findings of a diurnal variation of t-MeHA in the CSF of rhesus monkeys and human beings (Shan et al., 2012). These observations support the proposed "flip-flop" hypothesis of the sleep switch with evidence that TMN neurons may promote wakefulness (Saper et al., 2001). Diurnal histamine fluctuations are crucial for the modulation of the circadian rhythmicity of the sleep–wake cycle (Saper et al., 2001). The central circadian pacemaker is the hypothalamic suprachiasmatic nucleus (SCN). In rodents, chronic depletion of histamine results in an abolishment of the circadian rhythmicity of cortisol (Itowi et al., 1989). The influence of histamine on circadian rhythms is further illustrated by the observation that the TMN and SCN are reciprocally connected. Moreover, histamine containing fibers were found in the pineal gland where melatonin, the circadian hormonal messenger, is produced. The observations that the human TMN expresses melatonin receptor (MT)-1 (Wu et al., 2006), while MT-2 is absent in this nucleus (Shan et al., unpublished data) indicated that melatonin provides an alternative mechanism for the interaction between the SCN and TMN. Furthermore, the SCN provides long lasting inhibition of the sleep-promoting center in the rat ventrolateral preoptic nucleus, which closely interacts with the TMN. Interestingly, recent evidence shows that HDC- or H_1R-knockout mice have a disturbance of clock gene expression in many brain areas, such as cortex and striatum, but not in the SCN. All these observations imply that the diurnal fluctuations in the histaminergic system may play a crucial role in the modulation of circadian functions in the SCN and other brain areas.

2.2. $H_{1-4}R$ and histamine-methyltransferase

Classic antihistamines have strong sedative properties - they induce sleepiness and cognitive deficits via H_1R. The severity of these side effects is correlated with the amount of antihistamine that penetrates the human cerebral cortex. In the postmortem human brain material, the highest binding density of H_1R is observed in the internal layers (lamina V and VI) of the neocortex. In addition, the claustrum, hippocampal formation and thalamus and the two segments of the globus pallidus also show high levels of H_1R-binding. This distribution is consistent with mapping by PET (Yanai et al., 1992b).

Details on the functions of H_1Rs come from the phenotypes of H_1R deficient mice. H_1R knockout mice show late-onset obesity, associated with a disturbance of the circadian rhythm of food intake and of locomotor activity. The H_1R knockout mice also show lower hyprocretin/orexin levels (Lin et al., 2002), which is synergistically functioning with histamine in sleep–wake cycle modulation (Saper et al., 2001). Combined H_1R and H_2R deficient mice exhibit impaired cognition, which is in line with decreased long-term potentiation in the hippocampal cornu ammonis-1 area (Dai et al., 2007). H_1R knockout mice were also found to have a lower pain sensitivity (Haas et al., 2008). In addition, women showed higher H_1R-binding potential compared with age-matched men (Yoshizawa et al., 2009).

H_2R-binding shows a high density in the basal ganglia, amygdala, hippocampus and cerebral cortex in both primates and rodents. The distribution of H_2R in human cerebral cortex is, in contrast to H_1R, denser in the superficial layers (I and II), where there was also a denser histaminergic innervation. The H_2R distribution is thus consistent with the histamine projection in the cortex in both human and rodents. A close functional relationship between the histamine production and projection system is also supported by the observation that the H_2R expression is significantly lower in HDC-knockout mice brain.

Interestingly, neither the H_1R knockout nor H_2R knockout mice, but only the combined H_1R and H_2R knockout mice show suppressive roles of histamine on methamphetamine-induced behavioral sensitization (Ogawa et al., 2009). In addition, histamine increases excitability of rat spinal motoneurons via either H_1R or H_2R (Wu et al., 2012). Both observations imply that H_1R and H_2R are synergistically functioning in locomotion.

H_3R was firstly discovered in 1983, by the group of J.C. Schwarts as a presynaptic autoreceptor, regulating the synthesis and release of histamine. Following the cloning of this receptor 15 years later, H_3R was found to consist of a large number of receptor isoforms with different distribution and pharmacological profiles. High H_3R expression levels were observed in the deep layers of the cerebral cortex, dentate gyrus and subiculum of hippocampal formation. H_3R radioligand binding sites were observed in the middle layers (III, IV) of the cerebral cortex and in the thalamus in human postmortem tissue (Jin and Panula, 2005; Jin et al., 2002). Our qPCR and immunohistochemistry studies showed that both H_3R-mRNA and H_3R protein expression levels are higher in putamen than in SN or caudate, which is in

agreement with previous reports showing that both H_3R-mRNA and protein levels are higher in the striatum than in the SN in both rodents and human (Shan et al., 2011a). The H_3R knockout mouse shows decreased spontaneous locomotor activity, decreased wheel running ability and decreased body temperature. In addition, histamine is modulating the core body temperature of mice by acting at anterior hypothalamic neurons that express H_1R and H_3R. The H_3R knockout mouse also shows as a metabolic syndrome with hyperphagia, late-onset obesity associated with hyperinsulinemia and leptinemia and increased severity for neuro-inflammatory diseases. These data indicate the involvement of H_3R in a variety of brain functions including arousal, locomotor activity, thermoregulation and food intake.

H_3R is not only localized on the somata, dendrites and axons of the TMN, as an autoreceptor. Activation of H_3R as a heteroreceptor localized in different brain areas inhibits the release of various neurotransmitters (see review in Sander et al., 2008). In animal models, inverse agonist/antagonists of H_3R increase the release of neuronal histamine, acetylcholine, norepinephrine and dopamine in different brain areas by not well understood synaptic signals. Therefore, several H_3R antagonists/inverse agonists are advanced into preclinical trials to treat different symptoms of neurological diseases such as sleep–wake disorders in PD and narcolepsy, and cognitive disorders in AD and attention deficit hyperactivity disorder (Brioni et al., 2011; Lin et al., 2011). According to our postmortem brain material findings, so far, however, the application of H_3R antagonist/inverse agonist in PD and AD deserves careful consideration (see below). It should also be noted that in a recent clinical pilot study one H_3R-antagonists/inverse agonist did not show a positive effect in AD treatment (Egan et al., 2012).

The novel receptor H_4R has been reported to be functionally expressed in the human brain, e.g. in the deep layers of human cortex (lamina VI and V, Connelly et al., 2009). Since H_4R shares a high sequence similarity with H_3R, it is not surprising that H_4R is targeted by various imidazole containing H_3R ligands. Therefore, some of the previous H_3R pharmacology and binding studies urgently require revaluation by more specific ligands. In addition, we have reported for the first time an increase in H_4R-mRNA expression in the striatum in PD (Shan et al., 2011a), which deserves further studies to uncover its functional relevance and clinical implications.

Histamine in the brain is inactivated by histamine-methyltransferase (HMT), which transfers a methyl group from S-adenosyl-L-methionine to the nitrogen atom of the imidazole ring, yielding t-MeHA and S-adenosyl-L-homocysteine. Although the glia compartment was proposed to play a major role in histamine inactivation, we did not observe co-localization of HMT-mRNA in astrocytes in the human PFC (Shan et al., in press).

2.3. Neuronal histaminergic system in development and aging

The function of the neuronal histaminergic system has been reported to be age dependent. The CSF-t-MeHA level shows a developmental pattern with a peak level in infants that decreased to near-adult values in adolescent subjects, according to a study done in 81 children with ages ranging from 3 months to 14.6 years (Kiviranta et al., 1994). Age-related decline in H_1R-binding in the normal human brain was reported by PET studies, especially in the prefrontal, temporal, cingulate and parahippocampal regions (Higuchi et al., 2000; Yanai et al., 1992a). In elderly subjects (97 non-demented controls, age range 34–101 years), the CSF-t-MeHA levels were found to be positively correlated with age (Motawaj et al., 2011). In spite of these alterations in metabolites, we did not observe any age-related changes in the level of HDC-mRNA expression in the TMN in the pool of control subjects of our studies ($n = 35$, age range 44–93). Therefore it deserves investigation whether the age-dependent changes of the neuronal histaminergic system are exhibited exclusively in the event of inactivating histamine in the brain. The neuronal histaminergic system does, however, show clear alterations in all components in age-related neurodegenerative disorders as discussed below.

3. Neuronal histaminergic system in age-related neurodegenerative disorders

3.1. PD

There were conflicting opinions about the nature of alterations of the neuronal histaminergic system in PD. On the basis of the abundant accumulation of the characteristic neuropathological PD lesions, i.e. Lewy bodies (LBs) and Lewy neurites (LNs) in the TMN of PD patients, a severe destruction of this nucleus was presumed to occur in the course of this disorder (Braak et al., 2003). In contrast, in the 6-hydroxydopamine (6-OHDA)-lesioned rat, a classic PD model, an increase of endogenous histamine appeared to enhance the apomorphine-induced turning behavior and to increase the loss of tyrosine hydroxylase (TH) in the SN (Liu et al., 2008). In addition, a decrease of endogenous histamine by injection of α-fluoromethylhistidine, an irreversible inhibitor of HDC, strongly reduced rotation behavior and prevented the loss of TH-expressing cells in an early stage of the 6-OHDA lesion in the rat (Liu et al., 2007). Consequently an increased histamine activity was presumed to occur in PD (Anichtchik et al., 2000, 2001).

In contrast to the presumed degeneration of the TMN in PD, we observed no clear quantitative changes in TMN HDC-mRNA in PD (Shan et al., 2011b). This is in line with the intact number of histaminergic neurons, as well as unchanged enzyme activity of HDC and with the unaltered t-MeHA levels in the CSF in PD. The unchanged TMN HDC-mRNA in PD showed for the first time that the accumulation of LBs and LNs in the TMN was not influencing HDC-mRNA expression. Moreover, not only in clinical PD, but also in preclinical PD we found an unchanged HDC-mRNA expression, while there was no or little accumulation of LBs and LNs in the TMN (Shan et al., 2011b). Furthermore, we found a significant decrease of H_3R-mRNA in the SN in PD (Shan et al., 2011a). A nearly exclusive localization of H_3R-ir in the large neuromelanin-containing neurons in the SN was found by immunocytochemistry in the same subjects. The lower density of these neurons in PD thus offers an explanation for the decreased H_3R expression levels in the SN in PD.

An increase in the density of histaminergic fibers in the SN of PD patients has been reported (Anichtchik et al., 2000, 2001). This observation supported the possibility that in PD the histamine levels may be increased in selective brain areas, such as the putamen and SN (Rinne et al., 2002). Our recent study observed that in the same brain areas of PD patients there was an up-regulation of HMT-mRNA (Shan et al., 2011a), which may act as a protective mechanism by metabolizing enhanced histamine levels in these areas. Such a protective effect might be of importance, since animal experiments have shown that increased histamine levels in the SN may cause degeneration of dopaminergic neurons (Liu et al., 2007). In addition, we observed an inverse correlation between HMT-mRNA expression in the SN and disease duration of PD, suggesting that the more serious (thus the shorter lasting) the disease is, the more HMT-mRNA is expressed, which further supports such a compensatory mechanism. This also implies that special attention should be paid to the ongoing Phase III clinical trials of H_3R-antagonist/inverse agonists for PD (Benarroch, 2011; Passani and Blandina, 2011), which may potentailly increase the histamine release even more and thus accelerate degeneration of neurons e.g. in the Putamen or SN in PD.

3.2. AD

It is known that accumulation of neurofibrillary tangles takes place in the TMN in early stages of the AD process, i.e. in Braak stage 3 (Braak et al., 1993). In addition a loss of large histaminergic neurons has been described in the rostral TMN in AD (Nakamura et

al., 1993). These observations are in accordance with high performance liquid chromatography results which showed diminished histamine levels in different brain areas in AD, including the hippocampus, frontal and temporal cortex (Panula et al., 1998) and with the decreased neuronal metabolic activity of the TMN in AD (Salehi et al., 1995). Several other reports claimed, however, that the histaminergic system may be hyperactive both in aging (Prell et al., 1988) and in the course of AD (Fernandez-Novoa and Cacabelos, 2001). Increased histamine levels have been reported not only in the frontal cortex, basal ganglia and hippocampus, but also, together with its metabolites, in the CSF of AD patients (Fernandez-Novoa and Cacabelos, 2001). It should be noted that the differences in putative confounding factors, such as postmortem delay, gender and age, may have contributed to the varying results (Panula et al., 1998).

Our recent studies confirmed that the TMN neurons were significantly (57%) lost in AD. It is of interest to notice, however, that the total HDC-mRNA expression level was not significantly decreased (24%) in these patients. The recently found slightly but not significantly lower level of t-MeHA (22%) in the CSF of AD patients fully supports our finding (Shan et al., in press). This implies that the significant (57%, as we observed) loss of large TMN neurons in AD patients is largely compensated. The mechanism underlying such a functional compensation of the TMN in AD certainly deserves further study. In addition, we observed increased H_3R- and HMT-mRNA expression in the PFC of AD patients, but only in females. Moreover, in females there was a significant positive correlation between the H_3R-mRNA and HMT-mRNA levels on the one hand and between H_3R-mRNA levels and AD Braak-stages on the other. Furthermore, although there was a positive correlation between HMT-mRNA and the astrocyte marker GFAP-mRNA in both, controls and AD patients, HMT-mRNA was found to only present in neurons in the PFC.

It is noted that our data may provide a rationale for the use of H_3R-antagonists in particular in female AD patients, since these compounds increase the release of histamine, acetylcholine, noradrenalin and dopamine, and may in this way modulate cognitive processes in PFC. However, regarding the small H_3R-mRNA increase we observed, together with insignificantly changes of binding density in this area (Medhurst et al., 2009), the positive effect of H_3R-antagonists would be expected to be modest. In fact a recent clinical pilot study on one of H_3R-antagonists/inverse agonists appeared to be non-effective in improving cognitive function in mild to moderate AD patients who were on concomitant symptomatic AD treatment (Egan et al., 2012). In addition it should be noted that, because the activity of the remaining TMN neurons is already higher, H_3R-antagonist application should be conservative in order to prevent degeneration of these neurons.

4. Conclusions

The production of neuronal histamine shows diurnal fluctuations in control subjects who had no neuropsychiatric disorders, with the highest levels around 18:09. This fluctuation was strongly altered in a group of patients with neurodegenerative diseases, including PD and AD. In addition, although more clinical and/or postmortem data are needed to elucidate whether/how the function of the neuronal histaminergic system changes with aging, clear histaminergic system alterations have been observed in expression levels of HDC, HMT, and $H_{1-4}R$ in various age-related neurodegenerative disorders. Moreover, discrepancies between results from animal models and postmortem human brain material studies have made clear that the validation of animal models is very necessary and that studies on patients and human postmortem material are essential to understand the changes of neuronal histaminergic system occurring in neuropsychiatric disorders.

One may hypothesize, on basis of available data, that the neuronal histaminergic system be a potential target for the treatment of the circadian rhythm disorders in PD and AD. H_3R-antagonists could thus be a valuable adjunct treatment for these diseases. The administration of H_3R-antagonist in PD and AD should be under strict control, because of their potential side effects, such as the induction of degeneration of dopaminergic neurons in the SN in PD or the over-activation of the remaining TMN neurons in AD.

Acknowledgments

The authors are grateful to the Netherlands Brain Bank for providing human brain material and clinical details. This work was supported by the China Scholarship Council for State Scholarship Fund [grant number (2007) 3020] to Mr. L Shan. Drs. A-M. Bao and D.F. Swaab were supported by the China Exchange Program of the Royal Netherlands Academy of Arts and Sciences (KNAW) (project 10CDP037).

References

Anichtchik, O.V., Rinne, J.O., Kalimo, H., Panula, P., 2000. An altered histaminergic innervation of the substantia nigra in Parkinson's disease. Exp. Neurol. 163, 20–30.
Anichtchik, O.V., Peitsaro, N., Rinne, J.O., Kalimo, H., Panula, P., 2001. Distribution and modulation of histamine H(3) receptors in basal ganglia and frontal cortex of healthy controls and patients with Parkinson's disease. Neurobiol. Dis. 8, 707–716.
Benarroch, E.E., 2011. Histamine in the CNS: multiple functions and potential neurologic implications. Neurology 75, 1472–1479.
Braak, H., Braak, E., Bohl, J., 1993. Staging of Alzheimer-related cortical destruction. Eur. Neurol. 33, 403–408.
Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211.
Brioni, J.D., Esbenshade, T.A., Garrison, T.R., Bitner, S.R., Cowart, M.D., 2011. Discovery of histamine H3 antagonists for the treatment of cognitive disorders and Alzheimer's disease. J. Pharmacol. Exp. Ther. 336, 38–46.
Connelly, W.M., Shenton, F.C., Lethbridge, N., Leurs, R., Waldvogel, H.J., Faull, R.L., Lees, G., Chazot, P.L., 2009. The histamine H4 receptor is functionally expressed on neurons in the mammalian CNS. Br. J. Pharmacol. 157, 55–63.
Dai, H., Kaneko, K., Kato, H., Fujii, S., Jing, Y., Xu, A., Sakurai, E., Kato, M., Okamura, N., Kuramasu, A., Yanai, K., 2007. Selective cognitive dysfunction in mice lacking histamine H1 and H2 receptors. Neurosci. Res. 57, 306–313.
Egan, M., Yaari, R., Liu, L., Ryan, M., Peng, Y., Lines, C., Michelson, D., 2012. Pilot randomized controlled study of a histamine receptor inverse agonist in the symptomatic treatment of AD. Curr. Alzheim. Res. 9, 481–490.
Fernandez-Novoa, L., Cacabelos, R., 2001. Histamine function in brain disorders. Behav. Brain Res. 124, 213–233.
Garcia-Falgueras, A., Ligtenberg, L., Kruijver, F.P., Swaab, D.F., 2011. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. J. Comp. Neurol. 519, 3061–3084.
Haas, H.L., Sergeeva, O.A., Selbach, O., 2008. Histamine in the nervous system. Physiol. Rev. 88, 1183–1241.
Higuchi, M., Yanai, K., Okamura, N., Meguro, K., Arai, H., Itoh, M., Iwata, R., Ido, T., Watanabe, T., Sasaki, H., 2000. Histamine H(1) receptors in patients with Alzheimer's disease assessed by positron emission tomography. Neuroscience 99, 721–729.
Itowi, N., Yamatodani, A., Cacabelos, R., Goto, M., Wada, H., 1989. Effect of histamine depletion on circadian variations of corticotropin and corticosterone in rats. Neuroendocrinology 50, 187–192.
Jin, C.Y., Panula, P., 2005. The laminar histamine receptor system in human prefrontal cortex suggests multiple levels of histaminergic regulation. Neuroscience 132, 137–149.
Jin, C.Y., Kalimo, H., Panula, P., 2002. The histaminergic system in human thalamus: correlation of innervation to receptor expression. Eur. J. Neurosci. 15, 1125–1138.
Kiviranta, T., Tuomisto, L., Airaksinen, E.M., 1994. Diurnal and age-related changes in cerebrospinal fluid tele-methylhistamine levels during infancy and childhood. Pharmacol. Biochem. Behav. 49, 997–1000.
Kruijver, F.P., Balesar, R., Espila, A.M., Unmehopa, U.A., Swaab, D.F., 2003. Estrogen-receptor-beta distribution in the human hypothalamus: similarities and differences with ER alpha distribution. J. Comp. Neurol. 466, 251–277.
Lin, L., Wisor, J., Shiba, T., Taheri, S., Yanai, K., Wurts, S., Lin, X., Vitaterna, M., Takahashi, J., Lovenberg, T.W., Koehl, M., Uhl, G., Nishino, S., Mignot, E., 2002. Measurement of hypocretin/orexin content in the mouse brain using an enzyme immunoassay: the effect of circadian time, age and genetic background. Peptides 23, 2203–2211.
Lin, J.S., Sergeeva, O.A., Haas, H.L., 2011. Histamine H3 receptors and sleep–wake regulation. J. Pharmacol. Exp. Ther. 336, 17–23.
Liu, C.Q., Chen, Z., Liu, F.X., Hu, D.N., Luo, J.H., 2007. Involvement of brain endogenous histamine in the degeneration of dopaminergic neurons in 6-hydroxydopamine-lesioned rats. Neuropharmacology 53, 832–841.
Liu, C.Q., Hu, D.N., Liu, F.X., Chen, Z., Luo, J.H., 2008. Apomorphine-induced turning behavior in 6-hydroxydopamine lesioned rats is increased by histidine and decreased by histidine decarboxylase, histamine H1 and H2 receptor antagonists, and an H3 receptor agonist. Pharmacol. Biochem. Behav. 90, 325–330.

Liu, C.Q., Shan, L., Balesar, R., Luchetti, S., Van Heerikhuize, J.J., Luo, J.H., Swaab, D.F., Bao, A.M., 2010. A quantitative in situ hybridization protocol for formalin-fixed paraffin-embedded archival post-mortem human brain tissue. Methods 52, 359–366.

Medhurst, A.D., Roberts, J.C., Lee, J., Chen, C.P., Brown, S.H., Roman, S., Lai, M.K., 2009. Characterization of histamine H3 receptors in Alzheimer's Disease brain and amyloid over-expressing TASTPM mice. Br. J. Pharmacol. 157, 130–138.

Motawaj, M., Peoc'h, K., Callebert, J., Arrang, J.M., 2011. CSF levels of the histamine metabolite tele-methylhistamine are only slightly decreased in Alzheimer's disease. J. Alzheimers Dis. 22, 861–871.

Nakamura, S., Takemura, M., Ohnishi, K., Suenaga, T., Nishimura, M., Akiguchi, I., Kimura, J., Kimura, T., 1993. Loss of large neurons and occurrence of neurofibrillary tangles in the tuberomammillary nucleus of patients with Alzheimer's disease. Neurosci. Lett. 151, 196–199.

Ogawa, S., Yanai, K., Watanabe, T., Wang, Z.M., Akaike, H., Ito, Y., Akaike, N., 2009. Histamine responses of large neostriatal interneurons in histamine H1 and H2 receptor knock-out mice. Brain Res. Bull. 78, 189–194.

Panula, P., Rinne, J., Kuokkanen, K., Eriksson, K.S., Sallmen, T., Kalimo, H., Relja, M., 1998. Neuronal histamine deficit in Alzheimer's disease. Neuroscience 82, 993–997.

Passani, M.B., Blandina, P., 2011. Histamine receptors in the CNS as targets for therapeutic intervention. Trends Pharmacol. Sci. 32, 242–249.

Prell, G.D., Khandelwal, J.K., Burns, R.S., LeWitt, P.A., Green, J.P., 1988. Elevated levels of histamine metabolites in cerebrospinal fluid of aging, healthy humans. Compr. Gerontol. A 2, 114–119.

Rinne, J.O., Anichtchik, O.V., Eriksson, K.S., Kaslin, J., Tuomisto, L., Kalimo, H., Roytta, M., Panula, P., 2002. Increased brain histamine levels in Parkinson's disease but not in multiple system atrophy. J. Neurochem. 81, 954–960.

Salehi, A., Heyn, S., Gonatas, N.K., Swaab, D.F., 1995. Decreased protein synthetic activity of the hypothalamic tuberomamillary nucleus in Alzheimer's disease as suggested by smaller Golgi apparatus. Neurosci. Lett. 193, 29–32.

Sander, K., Kottke, T., Stark, H., 2008. Histamine H3 receptor antagonists go to clinics. Biol. Pharm. Bull. 31, 2163–2181.

Saper, C.B., Chou, T.C., Scammell, T.E., 2001. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 24, 726–731.

Shan, L., Bossers, K., Luchetti, S., Balesar, R., Lethbridge, N., Chazot, P.L., Bao, A.M., Swaab, D.F., 2011a. Alterations in the histaminergic system in the substantia nigra and striatum of Parkinson's patients: a postmortem study. Neurobiol. Aging 33 (7), 1488.e1–1488.e13.

Shan, L., Liu, C.Q., Balesar, R., Hofman, M.A., Bao, A.M., Swaab, D.F., 2011b. 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.

Shan, L., Hofman, M.A., van Wamelen, D.J., Van Someren, E.J., Bao, A.M., Swaab Dick, F., 2012. Diurnal fluctuation in histidine decarboxylase expression, the rate limiting enzyme for histamine production, and its disorder in neurodegenerative diseases. Sleep 35, 713–715.

Shan, L., Bossers, K., Unmehopa, U., Bao, A.M., Swaab, D.F., in press. Alterations in the histaminergic system in Alzheimer's disease: a postmortem study. Neurobiol. Aging. http://dx.doi.org/10.1016/j.neurobiolaging.2011.1012.1026.

Trottier, S., Chotard, C., Traiffort, E., Unmehopa, U., Fisser, B., Swaab, D.F., Schwartz, J.C., 2002. Co-localization of histamine with GABA but not with galanin in the human tuberomamillary nucleus. Brain Res. 939, 52–64.

Wu, Y.H., Zhou, J.N., Balesar, R., Unmehopa, U., Bao, A., Jockers, R., Van Heerikhuize, J., Swaab, D.F., 2006. Distribution of MT1 melatonin receptor immunoreactivity in the human hypothalamus and pituitary gland: colocalization of MT1 with vasopressin, oxytocin, and corticotropin-releasing hormone. J. Comp. Neurol. 499, 897–910.

Wu, G.Y., Han, X.H., Zhuang, Q.X., Zhang, J., Yung, W.H., Chan, Y.S., Zhu, J.N., Wang, J.J., 2012. Excitatory effect of histamine on rat spinal motoneurons by activation of both H and H receptors in vitro. J. Neurosci. Res. 90, 132–142.

Yanai, K., Watanabe, T., Meguro, K., Yokoyama, H., Sato, I., Sasano, H., Itoh, M., Iwata, R., Takahashi, T., Ido, T., 1992a. Age-dependent decrease in histamine H1 receptor in human brains revealed by PET. Neuroreport 3, 433–436.

Yanai, K., Watanabe, T., Yokoyama, H., Hatazawa, J., Iwata, R., Ishiwata, K., Meguro, K., Itoh, M., Takahashi, T., Ido, T., et al., 1992b. Mapping of histamine H1 receptors in the human brain using [11C]pyrilamine and positron emission tomography. J. Neurochem. 59, 128–136.

Yoshizawa, M., Tashiro, M., Fukudo, S., Yanai, K., Utsumi, A., Kano, M., Karahasi, M., Endo, Y., Morisita, J., Sato, Y., Adachi, M., Itoh, M., Hongo, M., 2009. Increased brain histamine H1 receptor binding in patients with anorexia nervosa. Biol. Psychiatry 65, 329–335.

Zeitzer, J.M., Kodama, T., Buckmaster, C.L., Honda, Y., Lyons, D.M., Nishino, S., Mignot, E., 2011. Time-course of cerebrospinal fluid histamine in the wake-consolidated squirrel monkey. J. Sleep Res. 21, 189–194.