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