The human histaminergic system in health and neuropsychiatric disorders

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Ph.D. project Summary

The histaminergic system is involved in many brain functions, such as the sleep-wake cycle, energy and endocrine homeostasis, sensory and motor functions, cognition, attention, learning and memory.

My interest in the functions of the histaminergic system in the brain was awakened when I noticed that traditional antihistamines, such as the histamine receptor antagonists diphenhydramine, pyrilamine and doxepin, which increase sleepiness and decrease attention, came with a caution about strong side effects.

The posterior part of the hypothalamic tuberomammillary nucleus (TMN) is the exclusive source of neuronal histamine, produced by the key enzyme histidine decarboxylase (HDC). Four types of G-protein coupled HRs, i.e., H\textsubscript{1-4}R, have been found in the human brain. And histamine methyltransferase (HMT) is the inactivation enzyme for histamine in the brain.

In our first publication (see main publications 1.) we reviewed the data on the functions of the histaminergic system that are often gender and age-dependent and are disturbed in neuropsychiatric disorders such as Parkinson’s disease (PD), Huntington’s disease (HD), Alzheimer’s disease (AD). In addition, in this paper we tried to bridge the gap between the fundamental features of the histaminergic system in experimental animals and the recently observed alterations in postmortem tissue of patients with neuropsychiatric disorders. We consider this a matter of some urgency, because histamine-3-receptor antagonists/inverse agonists are making their way into the clinic as a potential treatment for AD, PD and schizophrenia, while the insights on alterations in histamine production, breakdown and receptors recently obtained from postmortem studies yield crucial information on the potential effects and side effects of these compounds.

Our second publication deals with an experiment in which a number of alterations were introduced into an otherwise routine protocol in order to create optimal in situ hybridization conditions for quantification of the messenger ribonucleic acid (mRNA) HDC in formalin-fixed, paraffin-embedded archival postmortem human brain tissue by radioactive probe.

One of the most pronounced effects of neuronal histamine is its crucial role in maintaining wakefulness, also in human. In various species a diurnal fluctuation of histamine has been described, with high levels during the waking stage and low levels during the sleeping period. However, such information is still lacking for humans, both in
physiology and in neurodegenerative disorders, where sleep-wake perturbations are a common feature.

In our third publication, we showed - for the first time - diurnal fluctuations in human histamine production, i.e. higher HDC-mRNA levels during the wake stage (08:00-20:00 hr) than during the sleep stage (20:00-08:00 hr) in control subjects. The estimation of the acrophase of HDC-mRNA expression in human healthy controls, i.e. at 18:09 hr, corresponded very well with the acrophase for the histamine rhythm at 17:49 hr in diurnal nonhuman squirrel monkeys. In addition, this day-night fluctuation was found to be strongly changed in patients with neurodegenerative diseases, i.e. in PD, AD and HD patients with an acrophase at 8:56 hr. Our observations thus add weight to the proposed ‘flip-flop’ hypothesis of the sleep switch, which says that TMN neurons may promote wakefulness in humans, too. Moreover, the inverted profile in neurodegenerative diseases may be involved in the restless nights and listless days that are so typical of these disorders.

Previous animal studies have shown that in the 6-hydroxydopamine (6-OHDA)-lesion rat, a classic PD model, inhibition of endogenous histamine production in an early stage of the disorder put a halt to dopaminergic neuron degeneration. In agreement with this possibility and on the basis of the abundant accumulation of the characteristic neuropathological PD lesions, i.e. Lewy bodies (LBs) and Lewy neurites (LNs), a severe destruction of the histaminergic system was presumed to occur in the TMN of PD patients. However, surprisingly, we did not observe any quantitative changes in TMN HDC-mRNA in PD, which tallied with the intact number of histaminergic neurons, as well as with the unchanged enzyme activity of HDC and with the unaltered tele-methylhistamine (t-MeHA) levels in the CSF in PD. Our observation showed an unchanged TMN HDC-mRNA, not only in late stage PD, but also in a preclinical stage of this disease (Paper No. 4). Furthermore, we observed that the expression of the histamine receptor-3 (H3R), which appeared to be localized immunocytochemically in the large pigmented neurons, was significantly decreased in the substantia nigra (SN) in PD (Paper No. 5). In that we also showed that there was an up-regulation of HMT-mRNA in the SN and putamen of PD patients, which may act as a protective mechanism as it metabolizes enhanced histamine levels in these areas. Because animal experiments have shown that increased histamine levels may cause degeneration of dopaminergic neurons in the SN, such a protective effect might be of importance. Moreover, an inverse correlation between HMT-mRNA expression and disease duration was observed in the SN of PD patients, suggesting that the more serious (and thus the shorter lasting) the disease, the more HMT-mRNA was expressed, which further supports the notion of such a compensatory mechanism.

Of all the nuclei in the hypothalamus, the TMN shows the highest presence of both nuclear and cytoplasmic inclusions of mutant huntingtin, the neuropathological hallmark of HD. Nevertheless, we found an increase in HMC-mRNA levels in the TMN and an increase in HMT-, H1R- and H3R-mRNA levels in the inferior frontal gyrus (IFG) of HD patients. In addition, we observed a significant negative correlation between age at onset of the disease and HMT-mRNA, which suggests that the more serious (and thus the shorter lasting) the disease, the more HMT-mRNA is expressed. Since the levels of histamine metabolites in CSF have also been shown to be increased in HD patients, all observations point to an enhanced activity of the neuronal histaminergic system in HD (Publication No. 6).
It is known that the accumulation of neurofibrillary tangles (NFT) in the TMN takes place in an early stage of the AD process, i.e., in Braak stage 3. Also, a loss of large histaminergic neurons has been reported in this nucleus in AD. Our study showed that the total HDC-mRNA expression level was only slightly (24%) and non-significantly decreased in the same patients, despite a significant (57%) overall loss of TMN neurons in AD (Publication No. 7). Our findings suggest that the remaining TMN neurons in AD compensate for the loss of histamine neurons. Interestingly, when the TMN was divided into 3 parts, a significant reduction in the number of neurons was found in all 3 TMN sub-regions in AD patients, while a significantly lower HDC-mRNA expression was only found in the middle part of the TMN, and not in the rostral or caudal part. In addition, only in females did we find a significantly increased H3R-, HMT-, mRNA expression in the prefrontal cortex, which is one of the major projection areas of histamine produced in the TMN, together with increased glial fibrillary acidic protein (GFAP)-, vimentin (VIM) and proteolipid protein (PLP)-mRNA levels. Moreover, and contrary to expectation, HMT-mRNA was exclusively located in neurons (Publication No.7), and not in astrocytes in the human PFC. However, we did observe a significant positive correlation between HMT, GFAP and VIM-mRNA levels in controls and AD patients.

Our study on postmortem human depression brain material (Publication No. 8) did not reveal any significant changes in the neuronal histaminergic system, either in the rate-limiting enzyme for histamine production, HDC, or in its receptors and breaking-down enzyme in the two main projection sites, the anterior cingulate cortex and the dorsolateral prefrontal cortex, despite the fact that animal experimental models for depression suggest the presence of changes in the histaminergic system.

In general, our post-mortem data supported that - as an adjunct form of medication - H3R antagonists might modulate the circadian rhythmicity of neuropsychiatric disorders (Publication No. 3). However, for improving cognitive impairment or locomotion, the effects of H3R antagonists were modest or indirect, and warrants careful future studies. Last but not least, for this complex medication to be used properly, the effects of H3R antagonists on the modulation of histamine and other neurotransmitters in the human brain must be studied with some urgency.

We performed our experiments on clinically and neuropathologically well characterized valuable postmortem human brain tissues from the Netherlands Brain Bank. A very warm thank you must go to the Netherlands Brain Bank, with its director Dr. Inge Huitinga. The Netherlands Brain Bank is a group of enthusiastic and experienced people, such as technical director Michiel Kooreman and management assistant Marleen Rademaker.

Main publications (* indicating authors contributed equally, IF = Impact factor (2012)):


