Neuropharmacology xxx (2015) 1–11

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

Neuronal histamine and cognitive symptoms in Alzheimer's disease

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Histamine receptors
Dementia
Histamine receptor knockout mice
Episodic-like memory

ABSTRACT

Alzheimer's disease is a neurodegenerative disorder characterized by extracellular amyloid plaque deposits, mainly composed of amyloid-beta peptide and intracellular neurofibrillary tangles consisting of aggregated hyperphosphorylated tau protein. Amyloid-beta represents a neurotoxic proteolytic cleavage product of amyloid precursor protein. The progressive cognitive decline that is associated with Alzheimer's disease has been mainly attributed to a deficit in cholinergic neurotransmission due to the continuous degeneration of cholinergic neurons e.g. in the basal forebrain. There is evidence suggesting that other neurotransmitter systems including neuronal histamine also contribute to the development and maintenance of Alzheimer's disease-related cognitive deficits. Pathological changes in the neuronal histaminergic system of such patients are highly predictive of ensuing cognitive deficits. Furthermore, histamine-related drugs, including histamine 3 receptor antagonists, have been demonstrated to alleviate cognitive symptoms in Alzheimer's disease. This review summarizes findings from animal and clinical research on the relationship between the neuronal histaminergic system and cognitive deterioration in Alzheimer's disease. The significance of the neuronal histaminergic system as a promising target for the development of more effective drugs for the treatment of cognitive symptoms is discussed. Furthermore, the option to use histamine-related agents as neurogenesis-stimulating therapy that counteracts progressive brain atrophy in Alzheimer's disease is considered.

This article is part of a Special Issue entitled 'Histamine Receptors'.

1. Alzheimer's disease

Alzheimer's disease is a progressive disabling and lethal disorder with no permanent cure. A central hallmark of this disease is a deterioration of learning and memory as well as other cognitive symptoms leading to a profound negative impact on the patient's daily life (Babic, 1999; Bianchetti et al., 2006; Brodaty et al., 2001). Alzheimer's disease accounts for at least 50–75% of dementia cases and represents the most common cause of dementia among the elderly (Aguero-Torres et al., 1998; Povova et al., 2012; Ropacki and Jeste, 2005; Suh et al., 2001). Both sporadic and genetic-familial forms of Alzheimer's disease have been identified. However the exact causes of Alzheimer's disease are still not completely understood at this time (Takizawa et al., 2014). Major histopathological hallmarks of Alzheimer's disease include neurodegeneration, the loss of synapses as well as an increase in extracellular Aβ plaque deposits and intracellular neurofibrillary tangles in the brain (McGhee et al., 2014; Yankner, 2000).

In the past two decades a vast research effort has been devoted to the investigation of etiological mechanisms underlying monogenetic forms of Alzheimer's disease. However, monogenetic forms of Alzheimer's disease, such as mutations in the presenilin 1 gene or APOE4 carrier status, represent only 5% of Alzheimer's disease cases. Presenilin 1 participates in γ-secretase activity and plays a central role in the process of amyloidogenesis (Carrera et al., 2013; Cheng et al., 2013). Treatment and rescue attempts aimed to reduce

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http://dx.doi.org/10.1016/j.neuropharm.2015.05.007
0028-3908/

amyloid load and/or to immunize against Aβ accumulation so far yielded mixed results (Bennett et al., 2005; Dickstein et al., 2006; Fox et al., 2005; Moretto et al., 2007; Nicoll et al., 2003). In fact, the role of insoluble amyloid depositions, initially considered as principal trigger of neuronal dysfunction and neurodegeneration, has been questioned for a long time (Yankner, 1989; Yankner et al., 1989).

Alzheimer's disease is associated with changes in a number of neurotransmitter systems. The most prominent changes pertain to the glutamatergic system, mostly concerning the activation and expression of NMDA receptors (Bleich et al., 2003; Reisberg et al., 2003) and the acetylcholinergic system (Villarroya et al., 2004; Wilkinson et al., 2004), which is especially affected by neurodegeneration. There are also reports of changes in other central neurotransmitter systems in Alzheimer's disease, including the serotoninergic (Cross et al., 1988; Newhouse et al., 2002), dopaminergic (Cortes et al., 1988; Sweet et al., 2001) and noradrenalinergic systems (Yates et al., 1981), which are, however, most probably the result of global brain atrophy when the diseases progresses.

Regarding the NMDA receptor, it has been proposed that extracellular beta-amyloid deposits can induce an internalization of synaptic NMDA receptors, leading to a reduction of the cell-surface expression of NMDA receptors, as well as an over-activation of extra-synaptic NMDA receptors via the blockade of neuronal glutamate reuptake from the extracellular space (Robinson et al., 2006; Wang et al., 2013).

Changes in the acetylcholinergic system include a loss of acetylcholine-synthetizing neurons in the basal forebrain, a reduction in brain acetylcholine levels, and a decrease in both muscarinergic and nicotinergic acetylcholine receptors in the brain. These changes are associated with a loss of the cholinergic tone in the brain that has been proposed to be responsible for the cognitive symptoms of Alzheimer's disease (Anand et al., 2013; Bianchetti et al., 2006).

Current treatment options for Alzheimer's disease are highly limited. There is no cure for Alzheimer's disease, nor can one stop or even only slow down its progression. Moreover, the anti-Alzheimer drugs that are currently prescribed (including acetylcholine esterase inhibitors and NMDA-receptor antagonists) have several side-effects and/or are only partly effective in ameliorating the cognitive symptoms. In addition, they are seemingly only effective during early stages of the disease. More recent therapeutic approaches, based on the amyloid-beta toxicity hypothesis, including immunization strategies, have been essentially ineffective, so that Alzheimer researchers still attempt to refine the existing medications (Allgaier and Allgaier, 2014).

Therefore, it is worth exploring novel pharmacological treatments and anatomical targets in order to develop better and alternative medications. In this regard, brain histamine, as a potential target to combat the cognitive symptoms of Alzheimer's disease, has been largely neglected, despite the evidence that it had been implicated in Alzheimer's disease for some time (Airaksinen et al., 1991a, 1991b). It is also important to note that a possible beneficial effect of histamine-related drugs on Alzheimer's disease might not be solely due to a simple symptomatic relief of cognitive symptoms, but could be also the consequence of disease modifying actions, e.g. through the facilitation of hippocampal neural cell adhesion molecule mediated neuroplasticity (Foley et al., 2009). Furthermore, histamine-related drugs might also have a direct effect on neuropathological hallmarks of the disease. Such drugs might enhance the degradation of extracellular plaque deposits (Maneiro et al., 1997; Medhurst et al., 2009) and intracellular tau-aggregation via increasing brain autophagy (Nixon, 2007; Yan et al., 2014) or they could counteract the cell loss in memory-related brain structures via the stimulation of adult neurogenesis (Ambree et al., 2014).

2. The neuronal histaminergic system in the brain

Neuronal histamine in the brain is derived from neurons located in the tuberomamillary nucleus in the posterior part of the hypothalamus. Histamine-synthetizing neurons project to wide parts of the brain including to regions especially important for cognitive functions such as the frontal cortex, basal forebrain, hippocampus and amygdala (Fig. 1).

Histamine synthesis is catalyzed by the enzyme L-histidine-decarboxylase (HDC) which converts histidine to histamine. Four histamine receptors, numbered 1 (H1R), 2 (H2R), 3 (H3R) and 4 (H4R) have been so far identified in the mammalian brain (Haas et al., 2003, 2008; Panula et al., 2013). Among these, the H3R is especially interesting, since it seems to modulate transmitter release and synthesis in the brain. While the H1R and H2R are post- and extra-synaptic receptors (Mizuguchi et al., 1991), the H3R can act also as an autoreceptor on histaminergic axon terminals, where it modulates histamine release and turnover via feedback inhibition of histamine synthesis. It can also function as a heteroreceptor, when it is located at non-histaminergic fibers (Arrang et al., 1985; Gbahou et al., 2012). Here, the stimulation of the H3R can inhibit the synthesis and release of various other neurotransmitters including GABA, dopamine, serotonin and acetylcholine. Finally, the H3R is also present at the post-synapse, for example, on inhibitory medium spiny neurons in the striatum. The H4R, that was initially thought to be only present in peripheral tissues, has been implicated in inflammatory and immune processes (Chazot et al., 2008; Connelly et al., 2009; Correa et al., 2015).

The central histamine receptors differ in terms of their cellular transduction processes and intracellular second messenger coupling (Brown et al., 2001; Haas et al., 2008; Hill et al., 1997; Panula et al., 2013). The H1R has an excitatory effect on neurons and is G-protein coupled. H1R activation stimulates phospholipase C, which, in turn, gives rise to IP3 and Ca2+ release from intracellular Ca2+-stores as well as diacylglycerol formation. The latter, in turn, activates the proteinkinase G that can phosphorylate intracellular proteins. H1R activation also stimulates forskolin-induced cAMP synthesis as well as phospholipase A, which induces arachidonic acid formation. Arachidonic acid was proposed to be a post-

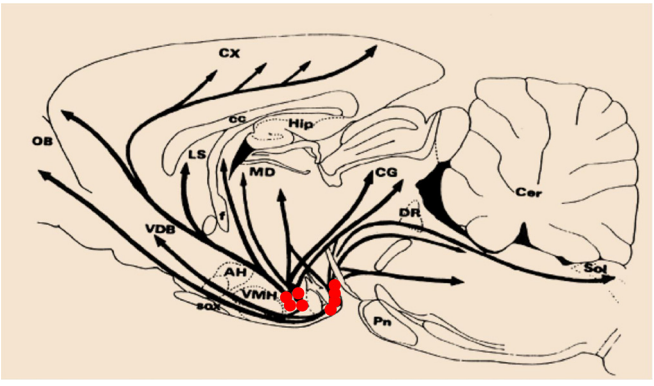

Fig. 1. Neuronal histaminergic system in the rodent brain: location of histamine synthesizing neurons (red circles) and their projections to memory-relevant structures. AH: anterior hypothalamic area, Arc: arcuate nucleus, Cc: corpus callosum, Cer: cerebellum, CG: central gray, CX: cerebral cortex, DR: dorsal raphe nucleus, F: fornix, Hip: hippocampus, LS: lateral septum, MD: mediodorsal thalamus, MMn: medial mammillary nucleus OB: olfactory bulb, Pn: pontine nuclei, Sol: nucleus of solitary tract, Sox: supraoptic decussation, VDB: Vertical limb of the diagonal band, VMH: ventromedial hypothalamus.

Please cite this article in press as: Zlomuzica, A., et al., Neuronal histamine and cognitive symptoms in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.05.007