Preservation of cortical histamine H3 receptors in ischemic vascular and mixed dementias

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A B S T R A C T

Aim: Histamine H3 receptor antagonists have been proposed as a novel therapeutic approach for the symptomatic treatment of Alzheimer’s disease (AD). However, it is unclear whether there is a neurochemical basis for extending their potential use in vascular and mixed dementias. In this study, we measured cortical H3 receptors in patients with subcortical ischemic vascular dementia (SIVD) and mixed SIVD/AD (MIX).

Materials and methods: Radioligand binding assays using [3H]GSK189254 were used to measure H3 receptors in the postmortem frontal cortex, anterior cingulate gyrus and hippocampus of a cohort of longitudinally assessed SIVD, MIX and age-matched controls.

Results: H3 receptor levels were unchanged in SIVD and MIX in all areas studied. Furthermore, frontal H3 receptor densities negatively correlated with predeath assessment of cognition using Mini-Mental State Examination (MMSE) scores.

Conclusion: Our data suggest that H3 receptors are preserved in SIVD and MIX, thus supporting further assessments of H3 antagonists as potential therapeutics in these dementias.

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1. Introduction

Vascular dementia (VAD) is the second most common cause of dementia after Alzheimer’s disease (AD) in both developed and developing countries [1,2]. VAD is closely linked to cerebrovascular disease, and is a direct consequence of cerebral hemorrhages, infarcts and white-matter lesions [3]. Several subtypes of VAD have been described based on the size, number and location of infarcts as well as the presence of white matter or other vascular lesions [4]. Of these, subcortical ischemic vascular dementia (SIVD) has a relatively homogenous clinical presentation characterized by frontal deficits (e.g., executive dysfunction) and relatively mild dementia [5], both of which are thought to arise from the disruption of frontal-subcortical loops or long association fibers by lacunar infarcts or deep white matter disease [6]. Furthermore, concomitant VAD and AD (mixed dementia) is now considered to be more prevalent than previously recognized, and will become increasingly common in elderly patients [6,7]. However, unlike AD, where findings of cortical cholinergic deficits and glutamatergic dysfunction have led to development of cholinesterase inhibitors (ChEIs) and memantine as the mainstay of pharmacologic treatment at different stages of disease [8], there is at present no widely approved pharmacotherapy for VAD. Indeed, the healthcare focus has been on primary prevention by identifying and treating risk factors such as hypertension [9]. There is some evidence that cholinergic deficits occur in hereditary forms of subcortical VAD in the absence of AD [10], and clinical trials using ChEIs on VAD have reported modest improvements in cognitive assessment scores with unclear clinical significance [11]. Similarly, studies on the glutamatergic system in vascular and mixed dementias have only just begun [12,13], and the limited efficacy of memantine indicates that further investigations are needed before its widespread use in VAD can be supported [11,14].

Therefore, there is a clear need for the identification of novel targets for rational therapeutic strategies based on a good understanding of the neurochemical status of VAD. For example, there is increasing evidence of critical roles in learning and cognition for neuromodulator systems utilizing histamine [15]. Histaminergic neurons are localized to the tuberomamillary nucleus and project throughout the cortex, where their diverse functions are mediated by four currently known receptor subtypes (H1–H4, see [16]). Of these, the H3 receptors have important regulatory roles in the brain, both as inhibitory autoreceptors [17] and

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