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Pathological increases in neuronal hyperactivity in selective cholinergic and noradrenergic pathways may limit the efficacy of Aβ-based interventions in MCI and Alzheimer's disease

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ABSTRACT

In spite of compelling evidence linking Aβ disturbances to the pathophysiology of Alzheimer's disease, Aβ based treatments have consistently failed to produce any beneficial effects both in mild cognitive impairment (MCI) and Alzheimer's disease (AD) even with successful reductions of toxic aggregated and soluble Aβ species. Before abandoning both the hypothesis and approach, there is a need to examine some overlooked factors that may have contributed to the lack of efficacy, such as the potential drug-induced increases in neuronal hyperactivity leading to adverse cognitive effects. In particular, we posit that selective cholinergic and noradrenergic pathways will be especially vulnerable to this adverse effect. If confirmed, this idea could help identify a potentially preventable and treatable obstacle for enhancing the efficacy of therapeutic agents in MCI and AD.

KEYWORDS

Alzheimer's disease, Mild Cognitive Impairment, Amyloid beta-based Treatments, Neuronal Hyperactivity, Cognitive Dysfunction

The repeated failure of Aβ-lowering drugs to demonstrate efficacy in the treatment of mild cognitive impairment (MCI) and Alzheimer's disease (AD) have led many pharmaceutical sponsors to abandon these approaches, and are posing a serious challenge to the Aβ/amyloid hypothesis of AD pathophysiology. However, although several attempts have been made to explain these failures from within the amyloid framework [e.g., 1-3], a further explanation has been largely neglected. Namely, that this therapeutic failure might have been caused by a potentially treatable complication of these treatments: an accentuation of neuronal hyperactivity from successful brain Aβ plaques removal. This hypothesis was recently put forward by Busche and colleagues [4, see also 5], but the notion that hyperactivity of certain neuronal systems could contribute to the pathophysiology of cognitive dysfunction in AD has an even longer publication history [6].

In a series of experiments conducted by Busche and colleagues [7] using two-photon Ca2+ imaging mouse model of AD, 29% of layer 2/3 cortical neurons showed a reduction in neuronal activity, whereas 21% showed hyperactivation. They also showed that the appearance of hyperactive neurons correlated with the density of plaques and impairments in the animals' learning ability. Furthermore, they also demonstrated that neuronal hyperactivity was decreased by diazepam, an agonist of the GABA-A receptor, resulting in enhanced GABAergic tone, and increased by a GABA-A receptor antagonist. Thus, these findings suggest that a greater sensitivity of inhibitory GABAergic neurons to the neurotoxic effects of soluble factors in the vicinity of plaques mediated the increased hyperactivity of excitatory neurons.

In a subsequent investigation, the same group [8] provided evidence that increased soluble Aβ species, rather than plaques, resulted in neuronal hyperactivation. They demonstrated that hyperactivation of hippocampal neurons was present in a young mouse model of AD prior to the development of plaques, and that it could be prevented by the administration of the gamma secretase inhibitor LY-411575, which decreased soluble Aβ levels. They also showed that direct application of soluble Aβ in wild type mice induced neuronal hyperactivity. These results are consistent with findings from a number of preclinical

investigations [9, 10] linking soluble Aβ species to a dysfunction of inhibitory cortical interneurons, aberrant increases in excitatory activity, and cognitive deficits

Consistent with preclinical findings [11], Bakker and colleagues [12, 13] reported that in individuals with MCI, who showed increased high-resolution fMRI BOLD activation in the left hippocampal dentate gyrus/CA3 (DG\CA3) sub-regions and entorhinal cortex following a memory task, chronic treatment with a low dose of the marketed anti-epileptic drug levetiracetam resulted in a normalization of fMRI BOLD response and improved cognition.

In a more recent investigation [14], it was reported that administration of monoclonal antibodies against Aβ and successful removal of brain amyloid plaques in transgenic AD models, rather than producing a reduction in cortical neuronal hyperactivity, as had been previously observed with a reduction in soluble Aβ species after gamma secretase inhibition, actually resulted in a pathological increase. Additionally, other studies have shown that treatment with BACE1 inhibitors, which may also reduce Aβ plaques by targeting prefibrillary Aβ surrounding the plaques [15, 16], may actually correct the brain circuit abnormality, neuronal hyperactivity and associated cognitive deficit in a mouse AD model [17]. However, as pointed out by these authors, the relevance of these results based on an mouse model of AD to humans remains to be established especially since clinical trials with BACE 1 inhibitors (e.g., verubecestat, lanabecestat) in MCI and AD have also failed to demonstrate any efficacy.

In AD, the presence of amyloid plaques is not limited to the neocortex, but also extends to other brain areas, including sub-cortical cholinergic and adrenergic nuclei, which suffer extensive degeneration. However, studies have demonstrated that concomitant upregulation of selective cholinergic [6, 18-20] and adrenergic [21] pathways also may emerge in both MCI and AD. Thus, any drug-induced removal of Aβ plaques from these regions may potentially yield even further increases in the activity of selective pathways, eventually reaching a tipping point beyond which more activity would exacerbate negative outcomes, following an inverse U relationship between activity and performance [22, 23]. However, as no direct evidence has been provided so far, in animal models, to test this conjecture, future studies using

high field fMRI and other emerging techniques should determine if treatment with BACE1 inhibitors, and other amyloid-based treatments, normalize or accentuate neuronal hyperactivity in selective cholinergic and noradrenergic pathways implicated in cognition and memory.

All in all, the observations from the preclinical literature that some amyloid-based treatments can induce neuronal hyperactivity and impair cognition, whereas others such as BACE1 inhibitors can actually correct these abnormalities, highlight the need to study the effect of these classes of drugs on neuronal hyperactivity in AD and MCI – and especially on specific cholinergic and adrenergic pathways providing input to the hippocampus, and other brain regions implicated in cognition including attention and memory. This endeavor will allow us to determine if neuronal hyperactivity is accentuated in conjunction with successful drug-induced reductions in existing or newly formed brain Aβ plaques, and if these changes are associated with a worsening or a lack of significant improvement in cognition. Abnormal neuronal activity is potentially preventable and treatable. Therefore, if the hypothesized association is confirmed, it could provide an approach for overcoming the current limitations of potentially disease modifying Aβ-based treatments for MCI and AD and a further assessment of Aβ/amyloid hypothesis.

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