



LJMU Research Online

Pomara, N and Bruno, D

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

<http://researchonline.ljmu.ac.uk/id/eprint/9177/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Pomara, N and Bruno, D (2018) Pathological increases in neuronal hyperactivity in selective cholinergic and noradrenergic pathways may limit the efficacy of A β -based interventions in MCI and Alzheimer's disease. *Journal of Alzheimer's Disease Reports*. 2 (1). pp. 165-167. ISSN 2542-4823

LJMU has developed [LJMU Research Online](#) for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

Commentary

Pathological Increases in Neuronal Hyperactivity in Selective Cholinergic and Noradrenergic Pathways May Limit the Efficacy of Amyloid- β -Based Interventions in Mild Cognitive Impairment and Alzheimer's Disease

Nunzio Pomara^{a,b,*} and Davide Bruno^c

^a*Division of Geriatric Psychiatry, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA*

^b*Department of Psychiatry, New York University School of Medicine, New York, NY, USA*

^c*School of Natural Sciences and Psychology, Liverpool John Moores University, Liverpool, UK*

Accepted 6 September 2018

Abstract. In spite of compelling evidence linking amyloid- β ($A\beta$) disturbances to the pathophysiology of Alzheimer's disease (AD), $A\beta$ -based treatments have consistently failed to produce any beneficial effects both in mild cognitive impairment (MCI) and AD, even with successful reductions of toxic aggregated and soluble $A\beta$ 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, amyloid- β -based treatments, cognitive dysfunction, mild cognitive impairment, neuronal hyperactivity

The repeated failure of amyloid- β ($A\beta$)-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 $A\beta$ /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 $A\beta$ plaques removal.

*Correspondence to: Dr. Nunzio Pomara, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, 10962, USA.
E-mail: Nunzio.Pomara@nki.rfmh.org.

This hypothesis was recently put forward by Busche and colleagues [4, 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 Ca^{2+} 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 $\text{A}\beta$ 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 $\text{A}\beta$ levels. They also showed that direct application of soluble $\text{A}\beta$ in wild type mice induced neuronal hyperactivity. These results are consistent with findings from a number of preclinical investigations [9, 10] linking soluble $\text{A}\beta$ 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 $\text{A}\beta$ 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 $\text{A}\beta$ 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 $\text{A}\beta$ plaques by targeting prefibrillary $\text{A}\beta$ 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 a 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 $\text{A}\beta$ 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 $\text{A}\beta$ 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 A β -based treatments for MCI and AD and a further assessment of A β /amyloid hypothesis.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

- [1] Hardy J, De Strooper B (2017) Alzheimer's disease: Where next for anti-amyloid therapies? *Brain* **140**, 853-855.
- [2] Mehta D, Jackson R, Paul G, Shi J, Sabbagh M (2017) Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. *Expert Opin Investig Drugs* **26**, 735-739.
- [3] Karran E, Mercken M, De Strooper B (2011) The amyloid cascade hypothesis for Alzheimer's disease: An appraisal for the development of therapeutics. *Nat Rev Drug Discov* **10**, 698.
- [4] Busche MA, Grienberger C, Keskin AD, Song B, Neumann U, Staufenbiel M, Förstl H, Konnerth A (2015) Decreased amyloid- β and increased neuronal hyperactivity by immunotherapy in Alzheimer's models. *Nat Neurosci* **18**, 1725.
- [5] Zott B, Busche MA, Sperling RA, Konnerth A (2018) What happens with the circuit in Alzheimer's disease in mice and humans? *Ann Rev Neurosci* **41**, 277-297.
- [6] Pomara N, Bagne CA, Stanley M, Yarbrough GG (1986) Prospective strategies for cholinergic interventions in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* **10**, 553-569.
- [7] Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Wiederhold KH, Haass C, Staufenbiel M, Konnerth A, Garaschuk O (2008) Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science* **321**, 1686-1689.
- [8] Busche MA, Chen X, Henning HA, Reichwald J, Staufenbiel M, Sakmann B, Konnerth A (2012) Critical role of soluble amyloid- β for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **109**, 8740-8745.
- [9] Palop JJ, Mucke L (2010) Synaptic depression and aberrant excitatory network activity in Alzheimer's disease: Two faces of the same coin? *Neuromolecular Med* **12**, 48-55.
- [10] Verret L, Mann EO, Hang GB, Barth AM, Cobos I, Ho K, Devidze N, Masliah E, Kreitzer AC, Mody I, Mucke L, Palop JJ (2012) Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. *Cell* **149**, 708-721.
- [11] Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR, Devidze N, Ho K, Yu GQ, Palop JJ, Mucke L (2012) Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *Proc Natl Acad Sci U S A* **109**, 2895-2903.
- [12] Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, Yassa MA, Bassett SS, Shelton AL, Gallagher M (2012) Reduction of hippocampal hyperactivity improves cognition in amnesic mild cognitive impairment. *Neuron* **74**, 467-474.
- [13] Bakker A, Albert MS, Krauss G, Specka CL, Gallagher M (2015) Response of the medial temporal lobe network in amnesic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. *Neuroimage Clin* **7**, 688-698.
- [14] Busche MA, Grienberger C, Keskin AD, Song B, Neumann U, Staufenbiel M, Förstl H, Konnerth A (2015) Decreased amyloid- β and increased neuronal hyperactivity by immunotherapy in Alzheimer's models. *Nat Neurosci* **18**, 1725-1727.
- [15] Meier SR, Syvänen S, Hultqvist G, Fang XT, Roshanbin S, Lannfelt L, Neumann U, Sehlin D (2018) Antibody-based in vivo PET imaging detects amyloid- β reduction in Alzheimer transgenic mice after BACE-1 inhibition. *J Nucl Med*, doi: 10.2967/jnumed.118.213140
- [16] Egan MF, Kost J, Tariot PN, Aisen PS, Cummings JL, Vellas B, Sur C, Mukai Y, Voss T, Furtek C, Mahoney E, Harper Mozley L, Vandenberghe R, Mo Y, Michelson D (2018) Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N Engl J Med* **378**, 1691-1703.
- [17] Keskin AD, Kekuš M, Adelsberger H, Neumann U, Shimshek DR, Song B, Zott B, Peng T, Förstl H, Staufenbiel M, Nelken I (2017) BACE inhibition-dependent repair of Alzheimer's pathophysiology. *Proc Natl Acad Sci U S A* **114**, 8631-8636.
- [18] Slotkin TA, Seidler FJ, Crain BJ, Bell JM, Bissette G, Nemeroff CB (1990) Regulatory changes in presynaptic cholinergic function assessed in rapid autopsy material from patients with Alzheimer disease: Implications for etiology and therapy. *Proc Natl Acad Sci U S A* **87**, 2452-2455.
- [19] Pomara N, Stanley M, LeWitt PA, Galloway M, Singh R, Deptula D (1992) Increased CSF HVA response to arecoline challenge in Alzheimer's disease. *J Neural Transm Gen Sect* **90**, 53-65.
- [20] DeKosky ST, Ikonomic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ (2002) Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. *Ann Neurol* **51**, 145-155.
- [21] Elrod R, Peskind ER, DiGiacomo L, Brodtkin KI, Veith RC, Raskind MA (1997) Effects of Alzheimer's disease severity on cerebrospinal fluid norepinephrine concentration. *Am J Psychiatry* **154**, 25-30.
- [22] Soncrant TT, Raffaele KC, Asthana S, Berardi A, Morris PP, Haxby JV (1993) Memory improvement without toxicity during chronic, low dose intravenous arecoline in Alzheimer's disease. *Psychopharmacology* **112**, 421-427.
- [23] Introini-Collison IB, Castellano C, McGaugh JL (1994) Interaction of GABAergic and beta-noradrenergic drugs in the regulation of memory storage. *Behav Neural Biol* **61**, 150-155.