Drug interaction between fibrillar amyloid β and α7 nicotinic receptor in Alzheimer brain

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease. The accumulation of amyloid β (Aβ) in the brain is one of the hallmarks of AD. Emerging evidence suggested a link between amyloid pathology and nicotinic acetylcholine receptors (nAChRs), which plays an important role in mediating cognitive and neuroprotective function. The neurotoxicity of Aβ has been suggested mediated in part through an interaction between Aβ and α7 nAChRs. The amyloid positron emission tomography tracer PIB that binds selectively to fibrillar Aβ provides opportunity for visualizing amyloid deposition in living patients and for understanding the pathological mechanism in autopsy brain.

Aims

To examine how different cholinergic and anti-amyloid drugs influence ^{3}H-PIB binding to fibrillar Aβ in autopsy AD and control brains.

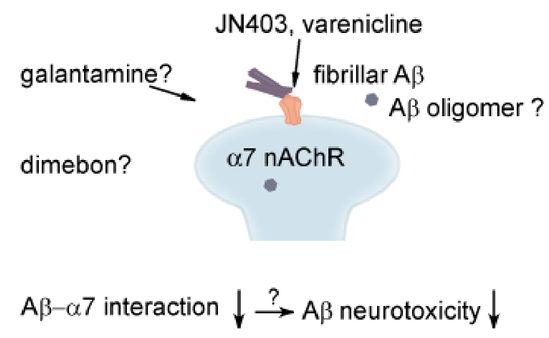

Fig. 1. Illustration of proposed interactions between different forms of Aβ and α7 nAChR, as well as the effect of α7 nAChR agonists on this interaction.

Methods:

In vitro saturation and competition assays with amyloid tracer ^{3}H-PIB (0.5 - 200nM) on AD autopsy brain. ^{3}H-PIB binding assays in the presence of investigating drugs in frontal cortical AD (n=5, age 69.6 ± 4.2 years) and control brain (n=5, age 67.4 ± 3.9 years).

Results:

• *In vitro* saturation assays revealed that amyloid tracer ^{3}H-PIB binds to fibrillar Aβ in the AD brain with high affinity (Fig.2A).

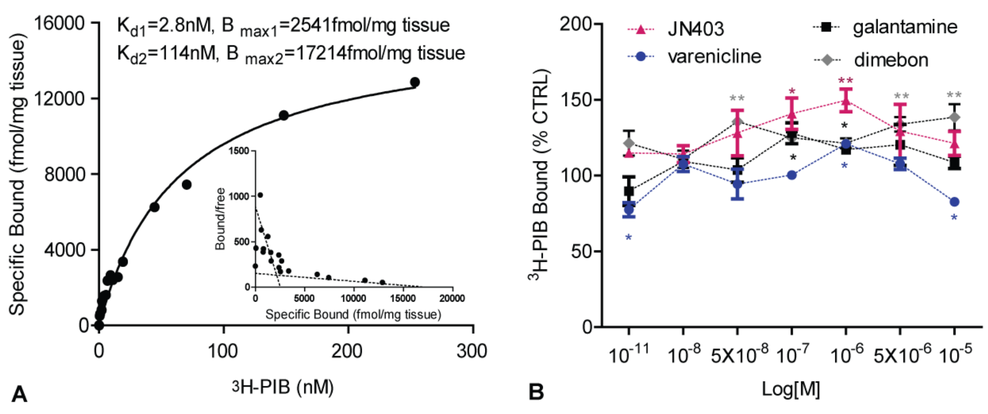

Fig. 2. A) *In vitro* ^{3}H-PIB saturation assay; B) ^{3}H-PIB Bound (% CTRL) in the presence of 10^{-11}-10^{-5} M JN403, varenicline, dimebon and galantamine on two frontal cortical AD autopsy brain. Results are Mean ±S.E.M; *p<0.05, **p<0.01 compared with control.

Effects of JN403, varenicline, galantamine and dimebon, nicotinic antagonists on ^{3}H-PIB binding in autopsy brain

• α7 nAChR agonists JN403 and varenicline (also α4β2 agonist) elicited significant increases in ^{3}H-PIB binding in AD and control brain.

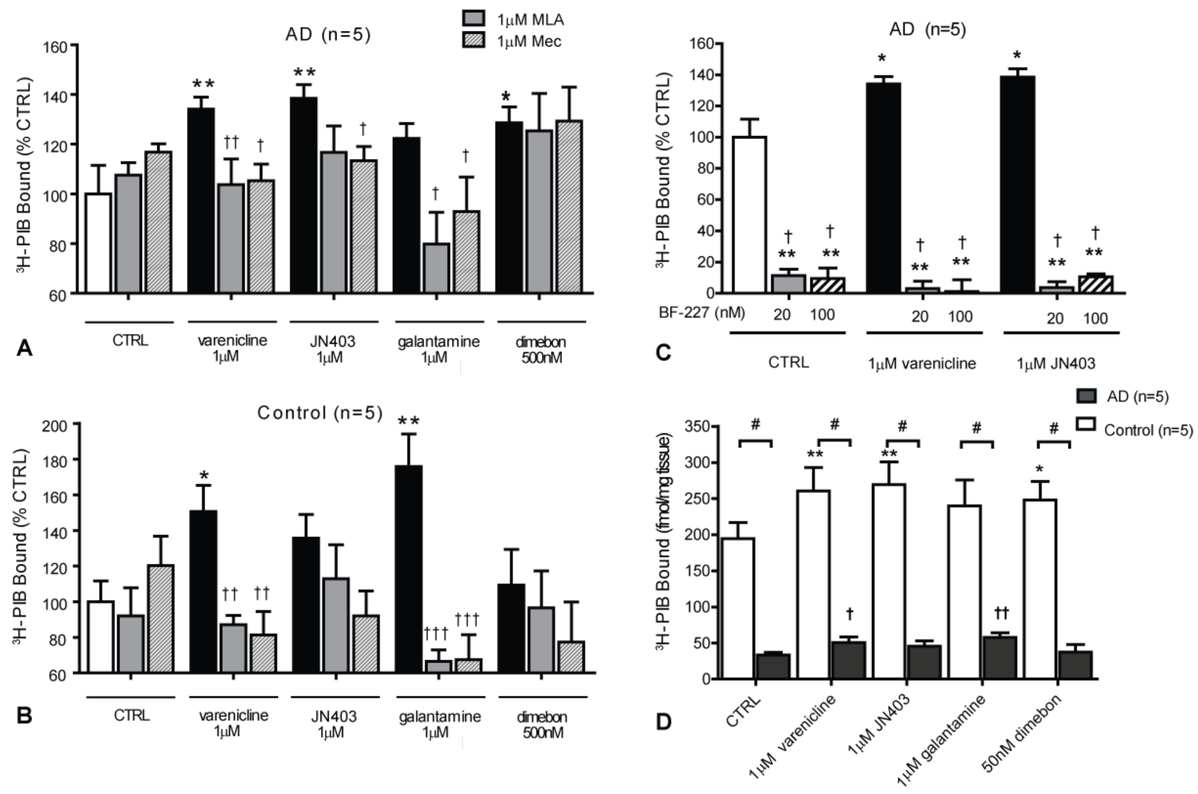

Fig. 3. A-D) Effects of JN403, varenicline, galantamine, dimebon, in combination of MLA or Mec and BF227 on ^{3}H-PIB binding on frontal cortical tissue from AD (n=5) and control (n=5). Results are Mean ±S.E.M; *p<0.05, **p<0.01 AD compared with control group; †p<0.05, ††p<0.01 compared with untreated; MLA: Methyllycaconitine; Mec: Mecamylamine.

• Galantamine, the clinically used acetylcholinesterase inhibitor with a dual action of nAChR allosteric potentiating dual drug, only markedly increased ^{3}H-PIB binding in control but not in AD brain (Fig. 3A,B). Dimebon, increased the ^{3}H-PIB binding in AD brain, however, in an α7 nAChR-independent mechanism (Fig.3A).

• The ^{3}H-PIB binding increase led by JN403 and varenicline is sensitive to the blockade of nAChR antagonists mecamylamine (Mec) and α7 nAChR specific antagonist methyllycaconitine (MLA), and fully displaceable by amyloid tracer BF-227,suggesting that fibrillar Aβ may exert an antagonist effect on α7 nAChRs (Fig. 3).

Conclusion:

Our observation suggests that fibrillar Aβ may exert an antagonist effect on α7 nAChR. Thus α7 nAChR agonists that interrupting the interaction between Aβ and α7 nAChRs may mediate neuroprotection against Aβ induced toxicity and pathology.

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No potential conflict of interest.