

ORAL PRESENTATION

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Upregulation of astrocytic $\alpha 7$ nicotinic receptors in Alzheimer's disease brain- possible relevant to amyloid pathology

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Background

Alzheimer's disease (AD) is characterized by extracellular deposits of β -amyloid ($A\beta$), intracellular neurofibrillary tangles and inflammation response. The $\alpha 7$ nicotinic receptors (nAChRs) were proposed to be directly relevant to the pathogenesis of AD by interacting with $A\beta$. The $\alpha 7$ nAChRs and $A\beta 1-42$ are co-localized in neuritic plaques and neurons and can form a high affinity stable complex. The up-regulation of $\alpha 7$ nAChRs on activated astrocytes has been reported in the AD brain. However, because of the poor specificity of currently available $\alpha 7$ nAChR antibodies, it is important to develop new ways to investigate the discrete distribution of $\alpha 7$ nAChRs in nervous tissue.

Material and methods

$\alpha 7$ nAChR single immunocytochemistry, double and triple-labeling immunocytochemistry were performed on formalin-fixed paraffin-embedded sections from 8 brain samples of neuropathologically confirmed sporadic AD and age-matched controls. Tissues were obtained from the Quebec Brain Bank (QBB; Douglas Institute, Montréal, QC, Canada). Immunohistochemical staining was performed as described previously (Yu et al., 2005). Primary cortical and hippocampal astrocytic cultures were prepared from the brains of newborn mouse (129S6 strain) according to the procedure of McCarthy and de Vellis (1980). The purified astrocytes were exposed to 100 nM $A\beta 1-42$ oligomers for 24h at 37 C with or without co-treatment with a series of concentration of PNU282987 and S24795 for 12 h. To inhibit $\alpha 7$ nAChR activities, cells were pretreated with methyllycaconitine (MLA) for 45 min before $A\beta 1-42$ oligomers/PNU282987/S24795. After

$A\beta 1-42$ treatments for 24 hours, the culture media were collected and was concentrated using Centricon YM-3 (Millipore, Temecula, CA). To prepare cell lysates, the treated cells were rinsed with 1x PBS, quick frozen then lysed on ice for 30 min in a lysis buffer. The lysates were then centrifuged at $10,000 \times g$ for 15 min, and the supernatant was collected. Protein concentrations were determined and equalized before samples were applied to western blotting for measuring $A\beta$ oligomers.

Results

We successfully characterized the distribution of $\alpha 7$ nAChRs in AD brains using biotin conjugated α -bungarotoxin. Our morphological data show the upregulation of $\alpha 7$ nAChRs in activated astrocytes in the AD brain. A certain proportion of $\alpha 7$ nAChRs positive astrocytes were morphologically associated with amyloid plaques. In mouse primary cultured astrocytes, treatments with different $\alpha 7$ nAChR agonists (PNU282987, S24795) significantly enhanced astrocytic $A\beta$ phagocytosis and inhibited $A\beta 1-42$ aggregation.

Conclusion

Take together, our study suggest that astrocytic $\alpha 7$ nAChRs possibly contribute to the initiation and development of amyloid pathology in the AD brain and thus should be considered as a potential therapeutic target, in addition to the better characterized neuronal nicotinic receptors.

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