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REGULAR ARTICLE

Beta-amyloid exhibits antagonistic effects on alpha 7 nicotinic acetylcholine receptors in orchestrated manner

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Abstract Although beta-amyloid (Aβ) has been regarded as the principal toxic factor in the pathogenesis of Alzheimer's disease (AD), it plays important physiological roles in phenomena such as neuron survival, synaptic plasticity, and memory formation. There are numerous plausible reasons to assume that all of the mentioned pathological and physiological functions of Aβ may be partially mediated via alpha 7 nicotinic acetylcholine receptor (nAChR). Agonistic and antagonistic aspects of Aβ on nAChRs may explain this paradox in peptide–receptor function. It seems that Aβ shows antagonistic effects on α7 nAChR in a dose-dependent manner, and its pathologic function may partially correlate with antagonization of the receptor.

If this hypothesis is supported, the related mechanisms of neurotoxicity, neuroprotection, memory formation, and AD pathogenesis might be identified. In addition, such knowledge helps make a more valid interpretation of neuron signaling and a better design of AD animal models. In addition, it may provide new insights into AD therapy development via reducing the amount of Aβ and inhibiting peptide aggregation.

Introduction

Alzheimer's disease (AD) is the most common type of dementia and affects the quality of life in the elderly accounting for 50–60% of all senile dementia cases [1]. Numerous factors have been introduced to contribute to the emergence and deterioration of AD. Beta-amyloids (Aβ) are fundamental constituents of senile plaques and considered as major pathological

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entities in AD [2]. β and γ secretases are responsible for the sequential cleavage of the amyloid precursor protein (APP) and the production of Aβ protein [3].

In young brain and normal conditions, there is an equilibrium between production and elimination of Aβ which maintains Aβ in steady-state levels [4] and this equilibrium is regulated through a cascade of degradative enzymes [5] In aging, pathologic conditions, and excitotoxicity, Aβ formation and clearance [6] are impaired which eventually leads to Aβ accumulation [4]. Accumulation phase starts with low molecular weight fractions of Aβ (monomer, dimers, or trimers) and continues with larger oligomers or insoluble amyloid fibrils. Various factors such as biochemical structure, chaperoning intermediations, and generalized enzymatic dysfunction are partially involved [3].

Being permeable to Ca^{2+} and Na^{+}, nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels [7]. α7 subtype of nAChRs is highly permeable to Ca^{2+} ions and has been known to be of great importance because of their functions [8,9]. They have also been suggested to accelerate the progression of AD and are highly expressed in sections involved in cognitive processes [10,11]. α7 subtype can be found in presynaptic, postsynaptic, and non-synaptic sites [12].

As AD progresses, both accumulation of Aβ and expression of α7 nAChR can be observed in the basal forebrain cholinergic system. Interestingly, the alteration of α7 nAChR expression has been held responsible for the impairment of cholinergic neurotransmission [13]. In addition, recent studies have demonstrated that Aβ has a high affinity to nAChRs [14,15] and α7 nAChR which contribute to the initiation and development of amyloid pathology in the AD brain [16].

Furthermore, Aβ could also be found in the brain of healthy people and is suggested to play vital physiological roles [17]; impairment in Aβ production would lead to neuronal death [18]. Moreover, Aβ plays a regulatory role in ion channel expression, neuronal excitability [19], synaptic plasticity [20], and memory formation [17,21]. Interestingly, synthetic Aβ monomers not only protect already-developed neurons against excitotoxic death but also guarantee the endurance of developing neurons [22]. Majority of these actions are mediated via α7 nAChRs, while most experimental evaluations show that both partial and full α7 nAChR agonists have positive effects on human cognitive functioning [23].

Furthermore, both agonistic and antagonistic effects of Aβ on the α7 nAChR have frequently been mentioned in different researches [24–27]. Surprisingly, these contradictory functions may lead to either toxicity or neuroprotective effects through different cellular signaling pathways [28,29] Such complicated interactions of Aβ–nAChR and related mechanisms need to be clarified and discovered.

The hypothesis

Aβ concentrations in the brain of healthy people have been reported to amount to picomole values, whereas in AD patients, these concentrations increase to nanomole quantities [30] which may trigger the formation of insoluble plaques. However, prior to insoluble plaque formation, numerous varied conformations occur converting Aβ peptides into monomers, oligomers, globulomers, protofibrils, and aggregated forms [31]. In addition, the molecular weight of oligomer peptides is distributed over a wide range (from <10 to >100 kDa), with structural polymorphism seen in oligomers of similar sizes [3].

In physiologic conditions and at low concentrations, this peptide can be found in monomer and soluble forms and it not only has no neurotoxicity [22] but also exhibits neuroprotective properties. Neuroprotection might be mediated through agonistic effects of Aβ monomers on α7 nAChRs, which in turn could prompt internal protective signaling pathways such as extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK) [29], and phosphatidyl inositol-3-kinase (PI-3-K) pathways [22].

Moreover, it seems that increase in Aβ levels and oligomerization and accumulation of Aβ during AD might hinder the neuroprotective properties of α7 nAChR through its antagonistic effects that might be related to three-dimensional, physical, and morphological characteristics of oligomers [30] (Fig. 1).

Considering their high Ca^{2+} permeability, important roles of α7 nAChRs have been suggested in modulation of neurotransmitter release, neuroprotection, neurotoxicity, and gene expression [8]. In addition, nanomole concentrations of Aβ might inhibit Ca^{2+} responses, while, picomole concentrations directly evoke constant surges in presynaptic Ca^{2+} through nAChRs leading to either physiologic neuroprotection or pathologic signaling of AD [17].

Evaluation of the hypothesis

To evaluate the interaction of Aβ and α7 nAChR, a combination of some molecular and electrophysiological tests is necessary. For this purpose, the α7 nAChR sequence should be

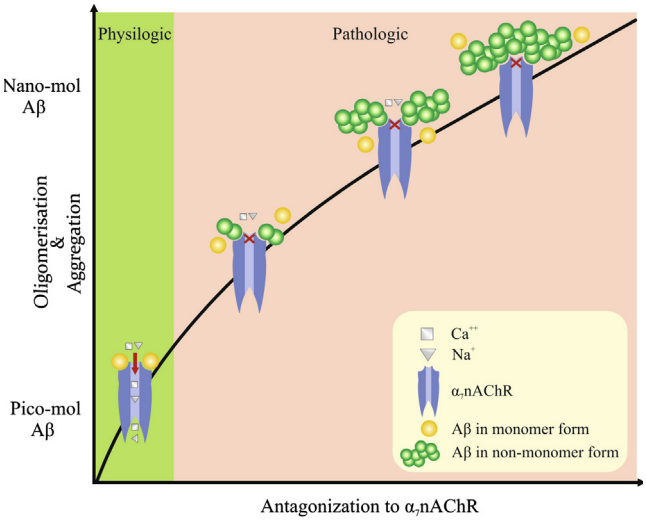

Fig. 1 Schema of Aβ–α7 nAChR interaction at various concentrations of Aβ.

transfected into the appropriate neural cells such as NG108-15. Next, engineered neurons should be cultured in fortified media. In order to investigate receptor–peptide interaction, diluted concentrations of Aβ (physiologic and pathologic concentrations) should be added to the culture. Later, cell viability can be determined by 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay, while α7 nAChR-related internal signaling pathways such as those involving ERK, MAPK, and PI-3-K can be assessed using western blot technique.

Furthermore, electrophysiological methods such as the patch-clamp method are attractive choices for ion channel evaluations. Moreover, the number of ion channel-targeted agents would necessitate monitoring of compound activity using electrophysiological techniques [32].

Discussion and conclusion

As a probable functional target for picomolar Aβ, homomeric α7 nAChRs potentially interact with Aβ to adjust their presynaptic function and possibly activate α7 nAChRs via extracellular domain of the receptor [33].

Functional activity and upregulation of α7 nAChRs are responsible for Aβ-induced neuronal hyperexcitation and probably pathogenesis of AD [34], indicating the direct correlation between α7 nAChRs and Aβ. Furthermore, the activation of α7 nAChRs by Aβ regulates some of the unanticipated pharmacologic pathways. Wu et al. argued that the transient surge in dopamine discharge induced by Aβ is facilitated by activation of α7 nAChRs which in turn would lead to the disruption of synaptic signaling; this may have an effect on AD [35].

The above-mentioned interactions suggest that α7 nAChR stimulatory medications might control Aβ–α7 nAChR pathogenic signaling mechanisms in patients with AD [36]. According to Kroker et al., Aβ oligomers decrease long-term potentiation (LTP) in a concentration-dependent manner with a maximum effect at 100–1000 nM concentration and α7 nAChR partial agonist (SSR180711) increases the Aβ-induced LTP reduction [37].

Therefore, it seems that AD pathogenesis at primary stages may be partially mediated through antagonization of α7 nAChR by Aβ. Although some studies have shown that Aβ increases neuroprotection via agonistic effect on α7 nAChR, this only occurs under physiological conditions and picomolar concentrations. Hence, we hypothesized that Aβ may show antagonistic effects on α7 nAChR in a dose-dependent manner. If this hypothesis pans out, more accurate judgments can be made on the physiologic and pathologic interactions of Aβ–α7 nAChR. Consequently, the identification of the mechanisms of neurotoxicity, neuroprotection, memory formation, and AD pathogenesis might be facilitated. In addition, knowledge of agonistic and antagonistic effects of Aβ at different concentrations could promote better perception of neuron signaling and lead to the development of more accurate designs of AD models in animals. These ongoing discussions provide new insights into working out strategies for the development of AD therapy via reducing the amount of Aβ and inhibiting peptide aggregation.

Overview box

First Question: What do we already know about the subject?

Many theories have been developed on the role of Aβ in the development of cognition dysfunction. It is believed that high concentrations of Aβ lead to the formation of senile plaques disrupting neuronal function. Although its complicated molecular function is poorly understood, the possible interaction between α7 nAChR and Aβ is one of the major controversies in the field of neuroscience.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

This hypothesis introduces a novel possible molecular mechanism in the AD pathogenesis based on varied concentrations of Aβ and α7 nAChR. In addition, knowledge of agonistic and antagonistic properties of Aβ at different concentrations could promote better perception of neuronal signaling and lead to the development of new strategies for approaching towards an appropriate AD therapy via the reduction of Aβ amount and inhibition of peptide aggregation.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

For this purpose, the α7 nAChR sequence should be transfected into the appropriate neural cells. In order to investigate receptor–peptide interaction, diluted concentrations of Aβ should be added to the culture. Later, cell viability can be determined by the MTT assay, while, α7 nAChR-related internal signaling pathways such as those involving ERK, MAPK, and PI-3-K can be assessed using western blot technique. Additionally, electrophysiological methods like patch-clamp method are considered attractive choices for ion channel evaluations.

Conflict of interest

We declare that there is no conflict of interest with regard to the content of this article.

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