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Invited review

Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment

Sylvia Lombardo [a, b, *], Uwe Maskos [a, b]

[a] Département de Neuroscience, Institut Pasteur, Unité Neurobiologie Intégrative des Systèmes Cholinergiques, Paris Cedex 15, France
[b] CNRS, UMR 3571, Paris, France

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ABSTRACT

Alzheimer's Disease (AD) is the major form of senile dementia, characterized by neuronal loss, extracellular deposits, and neurofibrillary tangles. It is accompanied by a loss of cholinergic tone, and acetylcholine (ACh) levels in the brain, which were hypothesized to be responsible for the cognitive decline observed in AD. Current medication is restricted to enhancing cholinergic signalling for symptomatic treatment of AD patients. The nicotinic acetylcholine receptor family (nAChR) and the muscarinic acetylcholine receptor family (mAChR) are the target of ACh in the brain. Both families of receptors are affected in AD. It was demonstrated that amyloid beta (Aβ) interacts with nAChRs. Here we discuss how Aβ activates or inhibits nAChRs, and how this interaction contributes to AD pathology. We will discuss the potential role of nAChRs as therapeutic targets.

This article is part of the Special Issue entitled 'The Nicotinic Acetylcholine Receptor: From Molecular Biology to Cognition'.

1. Introduction

Dementia is a debilitating condition frequent in ageing populations, and Alzheimer's Disease (AD) accounts for 70% of all dementia cases. AD is characterized by neuropathological hallmarks consisting of an accumulation of Amyloid β peptide (Aβ) in extracellular plaques, intracellular deposits of tau protein, neuronal loss and, more recently, a prominent synaptic loss was identified (Braak and Braak, 1991; Masliah et al., 2001; Selkoe, 1991; Spires-Jones and Hyman, 2014). In addition, anatomical studies in AD patients showed a massive loss of brain white matter and a specific reduction of cholinergic neurons of the basal forebrain (Auld et al., 2002; Bowen et al., 1976; Coyle et al., 1983; Kim et al., 2013; Whitehouse et al., 1981, 1982). Cholinergic neurons are organized in dense nuclei with widespread projections that entirely cover the central nervous system. In particular, the cholinergic neurons, whose cell bodies are in the basal forebrain, send their long projections to the neocortex and hippocampus (Bigl et al., 1982; Mesulam et al., 1983). Several studies demonstrated the pivotal role of these cholinergic nuclei in cognitive functions. Woolf (1998) proposed a model in which acetylcholine (ACh) release leads to the modulation of cortical circuitry that finally encodes for storage of long-term memory. The cholinergic system is also involved in attention processes (Muir et al., 1993; Sarter and Bruno, 1997; Wenk, 1997). In a mouse model, the lack of ACh receptors in the prefrontal cortex (PFC) was demonstrated to be responsible for attention deficit, restored by the expression of the receptor in this area (Guillem et al., 2011).

The neurotransmitter ACh binds to two families of receptors, nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). Both families of receptors regulate the cognitive processes mentioned above (Ghoneim and Mewaldt, 1977; Petersen, 1977; Sarter and Paolone, 2011), and are both affected in AD.

Binding studies performed with the use of [3H]-nicotine and [3H]-ACh showed a significant reduction in nicotine and ACh binding sites in cerebral cortex of patients suffering from AD, demonstrating a decrease of both nAChR and mAChR populations (Gotti et al., 2006a; Paterson and Nordberg, 2000; Perry et al., 1981, 1985, 1987, 1988; Shimohama et al., 1986; Whitehouse et al., 1981, 1982, 1986). In addition to nAChRs and mAChRs, the enzyme

Abbreviations: ACh, Acetylcholine; AChE, Acetylcholinesterase; AD, Alzheimer's Disease; Aβ, Amyloid β peptide; APP, Amyloid precursor protein; ChAT, Choline Acetyltransferase; dFBr, desformylflustrabromine; fAD, familial AD; FLNA, Filamin A; KO, Knock-out; MLA, Methyllycaconitine; mAChRs, muscarinic acetylcholine receptors; nAChRs, nicotinic acetylcholine receptors; PREGS, Pregnenolone sulfate; PAM, positive allosteric modulator; PFC, prefrontal cortex; SV, Simvastatin.

* Corresponding author. Département de Neuroscience, Institut Pasteur, Unité Neurobiologie Intégrative des Systèmes Cholinergiques, Paris Cedex 15, France.
E-mail address: sylvia.lombardo@pasteur.fr (S. Lombardo).

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choline acetyltransferase (ChAT), involved in ACh production, is also affected in AD. The activity of this ChAT enzyme, and consequently the synthesis of ACh, is decreased in AD brains. In addition, several authors observed a reduction in the activity of acetylcholinesterase (AChE), the enzyme that metabolises ACh after its release in the synaptic cleft (Auld et al., 2002; Bowen et al., 1976; Coyle et al., 1983; Davies and Maloney, 1976; Perry et al., 1978). The role of the cholinergic system in cognition and the modification observed in neurodegenerative diseases, and in particular in the case of AD, led to the formulation of the "cholinergic hypothesis" of geriatric disorders (Bartus et al., 1982; Contestabile, 2011), according to which the reduction in cholinergic innervation is responsible for the cognitive decline observed in AD patients.

In this context, we will focus on nAChRs, since their involvement in AD has been largely demonstrated, while the contribution of mAChRs has been under-explored. The purpose of this review is to present evidence implicating the role of nAChRs in AD, discuss the data supporting their interaction with Aβ, and the consequences of the perturbation of this interaction in murine models.

2. Brief overview of nAChR subtypes involved in AD

Nicotinic receptors are transmembrane pentameric proteins that belong to the "cys-loop" superfamily of ligand-gated ion channels together with GABAA, GABAC, glycine and 5-hydroxytryptamine (5-HT3) ionotropic receptors (Changeux and Edelstein, 1998; Le Novère and Changeux, 1995). They are composed of a variety of α and β subunits, which determine the pharmacological and kinetic properties of the receptor (Albuquerque et al., 2009; Giniatullin et al., 2005). The five subunits that compose the receptor are assembled around a central hydrophilic pore that mediates the flow of the cations K^+, Na^+ and Ca^{++}. In the human nervous system, there are eight α subunits (α2-α7, α9, α10) and three β subunits (β2-β4) that assemble in different combinations to generate a variety of nAChR subtypes with distinct electrophysiological properties and brain localization (Albuquerque et al., 2009; Gotti et al., 2006b, 2007, 2009).

The use of radioactive ligands allowed nAChR classification into two distinct groups, αBungarotoxin sensitive and αBungarotoxin insensitive receptors (Gotti and Clementi, 2004). Homopentameric α7 nAChRs belong to the first class, while heteropentameric nAChRs containing the β2 subunit belong to the second class. In this context we will focus on these α7 and β2 subunits, that were shown to interact with Aβ (Liu et al., 2009, 2012; Søderman et al., 2008; Sudweeks and Yakel, 2000; Wang et al., 2000a, 2000b).

The α7 homomeric receptor demonstrates a wide-spread localization in the brain and is characterized by a high calcium ion permeability and a fast desensitization rate (Dani and Bertrand, 2007; Quick and Lester, 2002). α7 nAChR on presynaptic terminals mediate release of others neurotransmitters (Wonnacott et al., 2006), while a postsynaptic or somatic localization elicits important changes in intracellular Ca^{++} concentration, that can activate second messenger pathways mediating cellular processes such as neuronal survival and gene expression (Berg and Conroy, 2002; Messi et al., 1997; Morley and Happe, 2000). Moreover, it was demonstrated that the activation of α7 nAChRs is important during development for the maturation of glutamatergic synapses (Lozada et al., 2012).

The role of α7 in memory and attention has been investigated for a long time. Knock-out (KO) mice for this subunit did not show a clear cognitive or attention deficit, except when the behavioural paradigm used implied prolonged sessions (Young et al., 2004, 2007). Historically, the first nAChR subunit identified to interact with Aβ was α7 (Wang et al., 2000a, 2000b). Later it was shown that Aβ is able to activate also β2*-nAChRs (β2 subunit-containing nAChRs). This subunit commonly forms heteropentameric receptors in combination with the α4 subunit. The pharmacological and functional characteristics of these heteromeric receptors are determined by both the contributing α and β subunits. The subtype α4β2 is characterized by lower calcium ion permeability and a slow desensitization rate compared to the homopentameric α7 nAChR (Quick and Lester, 2002). The "classic" high-affinity nAChR is composed of α4 and β2 subunits (Zoli et al., 1998). In addition to the α4β2 subtype, it was demonstrated that the α7 subunit is able to co-assemble with the β2 subunit to form a heteropentameric receptor. This novel α7β2 subtype was first investigated by expressing the heteromer in *Xenopus* oocytes. Recently, the α7β2* nAChR subtype was found in basal forebrain cholinergic neurons and hippocampal interneurons of mouse brain, and in the human basal forebrain (Moretti et al., 2014). This class of receptors seems to be particularly sensitive to Aβ-induced toxicity (Khiroug et al., 2002; Liu et al., 2009, 2012). The existence of this novel subtype was further confirmed in a human cell line (SHEP-1) transfected with the cDNA for α7 and β2 subunits. Under these experimental conditions, α7 and β2 are able to co-assemble into a functional receptor that localizes at the cell surface. The ability of α7 and β2 subunits to form a functional receptor was confirmed in *Xenopus laevis* oocytes. This heteromer displayed only a modest difference in the electrophysiological response to pharmacological agents compared to the homomeric α7 nAChR (Murray et al., 2012). The exact stoichiometry of this recently discovered subtype was not defined. It is clear that functional ligand binding domains could only be formed at the α7-α7 interface. Murray et al. (2012) proposed a schematic model of all the possible stoichiometries for the α7β2 subtype.

The importance of β2 in maintaining brain homeostasis during normal ageing was highlighted in the KO mouse for this subunit. Aged β2 null mutant mice have a thinner cortex compared to age-matched wild-type controls (Zoli et al., 1999). This work should be pursued further as it indicates a "neurotrophic" action of β2 receptor activation by endogenous ACh (Zanardi et al., 2007). Null mutant β2 mice were also tested to determine the role of this subunit in cognition. Guillem et al. (2011) showed that these mice exhibit an attention deficit which was restored by re-expression of this subunit with a lentiviral vector in the PFC.

We will now present and discuss the data demonstrating the existence of a physical interaction between nAChR and Aβ, the functional consequences of this interaction and the intracellular pathways activated.

3. Interaction between nAChRs and Aβ

The interaction between the α7 nAChR and Aβ is widely demonstrated. The first indication of this interaction came from the experiments of Wang et al. (2000a, 2000b). They showed that α7 subunits co-localize with $Aβ_{1–42}$ in senile plaques of brain slices obtained from patients that suffered from sporadic AD. In this context, no co-localization was found between Aβ and the α4 subunit. The strong and specific association between Aβ and α7, and no other subunits of the nAChRs, was further demonstrated with immunoprecipitation and Western Blot analysis. This set of experiments showed that $Aβ_{1–42}$ is able to immunoprecipitate α7, which was not the case for other nAChR subunits such as α1, α3, α4, α8 or β2. The same result was obtained with the reciprocal experiment, α7 immunoprecipitation and $Aβ_{1–42}$ detection, meaning that the two proteins strongly interact. Experiments performed with fragments of Aβ helped identify the sequence responsible for the interaction with α7, which corresponds to the amino acid residues 12–28 of the Aβ sequence (Wang et al., 2000b). Subsequently, competition studies performed by incubating α7 nAChRs with Aβ and αBungarotoxin showed that the application of αBungarotoxin is