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Treatment of Alzheimer's Disease-Nicotinic Receptors as a New Target

Agneta Nordberg, M.D.

Karolinska Institute, Department of Clinical Neuroscience, Occupational Therpy and Elderly Care Research (NEUROTEC), Division of Molecular Neuropharmacology, Huddinge University Hospital, Stockholm, Sweden

Address for correspondence

Agneta Nordberg, M.D.
KI, Department of NEUROTEC Division of Molecular Neuropharmacology Huddinge University Hospital B84 S-141 86 Stockholm Sweden
Tel: 46-8-58585467
Fax: 46-8-6899210
E-mail : Agneta.Nordberg@neurotec.ki.se

Alzheimer's disease is the most common form of dementia. The disease is accompanied by several distinct molecular events including formation and accumulation of beta amyloid (Aβ), hyperphosphorylation of tau proteins and neurochemical changes including neurotransmitter function.The neuronal nicotinic acetylcholine receptors (nAChRs) in the brain are important for functional processes, including cognitive and memory functions. The nAChRs acting as neuromodulators in communicative processes regulated by different neurotransmitters and show a relatively high abundance in human cortex, with a laminar distribution of the nAChRs of super-high to high, and low affinity in human cortex. Consistent losses of nAChRs have been measured in vitro in autopsy brain tissue of Alzheimer patients (AD), as well as in vivo by positron emission tomography (PET). Measurement of the protein content of nAChRs showed reduced levels of the α4, α3, α7_nAChR subtypes. The α4 and α3 mRNA levels are not changed in AD brains suggesting that the losses in high affinity nicotinic binding sites have to be searched for at the translational and/or posttranslational level. The increased mRNA level of the α7 nAChR subtype in the hippocampus indicates that subunit specific changes in gene expression of the α7 nAChR might be associated with AD. PET studies have revealed deficits in nAChRs early in the course of AD disease, stressing the importance of nAChRs as a potential target for drug intervention. Different cholinesterase inhibitors are presently clinical used. The effect is mainly considered to be symptomatic although influcence on the disease progression cannot be excluded . Except for a direct inhibition of acetylcholinesterase and buturylcholinesterase a indirect effect via an allosteric site on the nicotinic receptor may improve the clinical outcome.The nAChR appears to mediate neuroprotective effects. We have recently found that longterm treatment with nicotine to APPsw trangenic mice significantly reduce the Aβ amyloides in the brain. Further studies on neuroprotective mechanisms mediated via nAChR subtypes are exciting new avenues.

Key Words: *AD, human brain, Alzheimer's disease, Treatment strategies, Neuronal nicotinic receptor subtypes, PET ligands, Nicotinic agonists, Cholinesterase inhibitors*

INTRODUCTION

Alzheimer's disease (AD) is one of the most devastating diseases of the middle-aged and elderly. Although the last decade has witnessed a steadily increasing effort directed at discovery of the aetiology [3, 9] the genetics [2, 13, 60] and neurochemical mechanisms involved in the disease there is still no cure. However, extensive research activities have stimulated the development of new treatment strategies in AD, and several drugs that improve cholinergic transmitter activity have reached clinical use [59]. Presently, there is a great interest to understand the role of beta amyloid (Aβ) in the pathology and the amyloid precursor protein (APP). β-amyloid (Aβ) is also an important factor, which may initiate and promote AD [54]. Recently, the possible role of Aβ as a neuromodulator in the brain has stressed the possible regulatory mechanisms between Aβ and cholinergic neurotransmission, and nAChRs in the brain [1, 16]. The nicotinic receptors (nAChR) has been suggested to be coupled to the Aβ mechanisms. The role of nAChRs in AD will be discussed below, focusing mainly on new therapeutic implications.

The neuronal nicotinic acetylcholine receptors (nAChRs) are transmitter-gated ion channels that belong to a super family of ion channels of homologous receptors including gamma aminobutyric acid (GABA), glycine, $5HT_3$ [51]. The nAChRs are obvious candidates for transducing cell surface interactions. The naChRs are receptors for ACh in the cholinergic nerv terminal (Fig. 1) , but also for other neurotransmitters

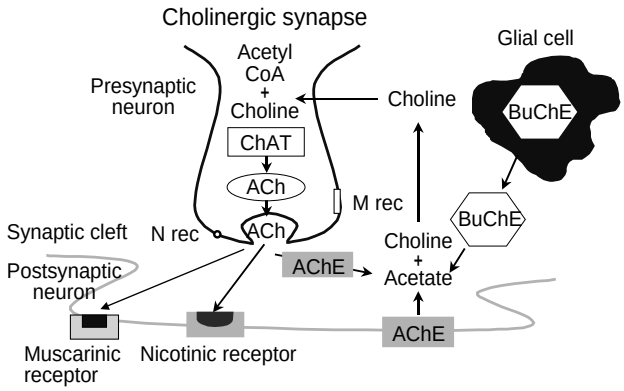

Fig. 1. Cholinergic nerve terminal with nicotinic and muscarinic receptors.

[19, 67]. Experimental data suggest that the nAChRs might act as neuromodulators in communicative processes in the brain [19, 67]. It is therefore of great importance to define by which mechanisms the nAChRs exert their action in the brain. The nAChRs is probably involved in the the pathophysiology of several CNS disorders including AD, Parkinson's disease, schizophrenia, Tourette's syndrome, anxiety, depression, and epilepsy [32, 33, 47]. The exact role of nAChRs and their full potential as a therapeutic target in these diseases have yet to be clarified. Interestingly enough, a considerable body of evidence exists to suggest that the nAChRs are involved in cognitive and memory functions [25, 32, 50].

The nAChR are distributed in many regions of the human brain. So far the nAChRs subunits α3, α4, α5, α7, and β2, β3, β4 have been cloned (29). The distribution of the nAChRs and their transcripts have been mapped in human autopsy brain [4, 55]. Receptor binding studies with available radioligand suggest that nAChRs are heterogeneous and can be rationalized to three different nAChR sites (super-high, high, low affinity) [Nordberg et al. 1988; 28, 65]. The nAChR show a laminar distribution in the human cortex with a general number of nAChRs in layer 1, 11, and V, with particularly high levels in the layer of primary sensory motor cortex and the inferior frontal sulcus [55]. The distribution of mRNA for different nAChR subunits has been examined in different cortical layers [52]. The α4 mRNA seems to be abundant in all layers except 1 and IV of the frontal cortex [52]. The α3 mRNA has been found to be most prominently expressed in the pyramidal neuron layers 111-V1, moderately expressed in layer 11 and minimally expressed in layer IV of the human cortex [52, 66]. A high expression of α7 mRNA was observed in layer 11 and 111, moderate in layer V and V1, and low in layer I and IV of human cortex [52].

Changes of nicotinic receptors in Alzheimer's disease

Autopsy studies show a consistent, significant loss of nAChRs in the cerebral cortex from AD patients compared to age-matched healthy subjects [46, 47]. A decrease in the protein levels of the α3, α4 nAChR subunits have been observed in the temporal cortex and the _α3, α4, α7 nAChR subtypes in the hippocampus of AD brains as compared with age-matched controls [11, Martin-Ruiz et al. 1999, 24]. These changes suggest that in nAChR losses seen in AD brains may be related to alterations of the nAChR synthesis on different levels such as transcription, translation and postranslation modifications, and receptor turnover. Examination of the regional expression of mRNA of the nAChR _4 and _3 subunits has shown no difference in autopsy AD brain tissue in any region analyzed [14, 61], whereas the level of the α7 mRNA was significantly higher in the hippocampus [14]. The studies suggest that the nAChRs deficits in AD brains mainly reflect posttranscriptional events [14, 53].

A significant reductions in the number of nAChRs has been found in the cortical regions of AD patients carrying the Swedish APP 670/671 mutation [28, 30]. The reduction in nAChRs was more pronounced in the mutation carrying subjects than in the sporadic AD cases when compared with age-matched controls [28]. No strict correlation was observed between losses of nAChR and the amount of neuronal plaques or neurofibrillary tangles.This finding suggests that these processes may be closely related but not directly dependent on each other.

PET studies of nicotinic receptors in AD patients

Significant progress has been made during recent years to develop and apply functional brain imaging techniques to allow for early diagnosis of AD and evaluation of drug treatment efficacy. PET might be a suitable method for functional studies of pathological changes in the brain, not only revealing dysfunctional changes early in the course of the disease, but also providing a deep insight into the functional mechanisms of new potential drug treatment strategies. A limited number of PET ligands are so far available for mapping the cholinergic system in the human brain (Table 1). PET ligands are available to measure acetylcholinesterase activity, cholinergic terminals, nicotinic and muscarinic recptors (Table 1). PET studies have revealed a reduced cortical acetylcholinesteserase activity in AD patients [17, 22]. A progressive

loss of cortical acetylcholinesterase activity has been observed in AD patients with cognitive decline [58]. The presynaptic vesicular ACh transporter vesamicol ([^{123}I] IBVMhas been used in vivo as a marker of presynaptic cholinergic activity in SPECT studies [23]. Greater reduction in [^{123}I] IBVM binding was observed throughout the cerebral cortex in AD patients with early-onset compared to late-onset of the disease [23]. The nAChR deficits in AD brains probably represents early phenomenon in the course of the disease since they can be detected in vivo by positron emission tomography (PET) in patients with mild AD [Nordberg et al. 1990; Nordberg et al. 1995, 1997]. The cortical nAChR deficits significantly correlate with cognitive impairment in AD patients [34, Nordberg et al. 1997, 44] and deifficts in ^{11}C-nicototine binding can be observed even in patients with mild cognitive impairment (MCI) (Fig. 2). The past several years have seen an expanded effort to develop PET probes for non-invasive study of nAChRs. This has also led to the search for new nAChR PET ligands. A ligand with selectivity for the $\alpha 4\beta 2$ nAChRs would be particularly preferable since the $\alpha 4\beta 2$ has been recognized as the predominant subtype that is deficient in AD [57].

PET studies do not only allow measurement of nAChRs in steady state situation in AD, but also measurement of nAChRs during functional activation studies. By measuring changes in nAChRs in different brain regions prior and during task performances eg attentional tests it is possible to obtain further insights into the regional network in the brain where nAChRs play an important role and also to understand how certain drug treatment can improve brain function (Nordberg et al submitted).

Table 1. PET and SPECT ligands for visualization of cholinergic activity in human brain

Parmameter	Radioligand	Imaging	References
Acetylcholinesterase	[^{11}C]MP4A	PET	Iyo et al. 1997
	[^{11}C]PMP	PET	Kuhl et al. 1999
Cholinergic terminals	[^{123}I]IBVM	SPECT	Kuhl et al. 1996
Nicotinic receptors	[^{11}C]nicotine	PET	Nordberg et al. 1990; 1995
			Muzic et al. 1998
Muscarinic receptors	[^{11}C]benztropine	PET	Dewey et al. 1990
	[^{11}C]NMPB	PET	Zubieta et al. 1998

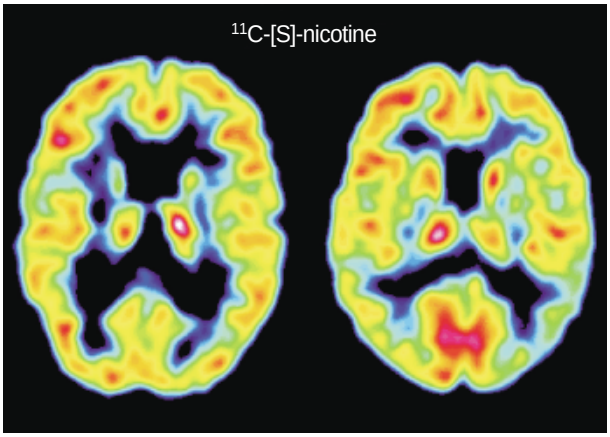

Fig. 2. Horizontal PET image of the uptake and distribution of [^{11}C] nicotine at the level of the basal ganglia of a patients with mild cognitive impairment (MCI) (left) and mild Alzheimer's disease (right). The figure represents a summation picture of the brain uptake of [^{11}C]-radioactivity following an intravenous tracer dose of [^{11}C] nicotine. The colour scale indicates radioactivity expressed in nCi/cm3/body weight; red=high; yellow=medium; green=low uptake.

Nicotinic receptors as a target for AD treatment

Transmitter replacement therapy forms the mainstay treatment for AD. Cholinergic therapy is based on the assumption that low levels of ACh are responsible for the cognitive decline associated with AD. Cholinesterase inhibitors including tacrine, donepezil, rivastigmine, and galantamine have in clinical studies shown palliative effects on symptoms and some trend to slow down disease progression [10, 45, 62]. It is likely that the therapeutic benefit of cholinesterase inhibitors occur at least in part, through activation of the nAChRs, by the direct action of increased levels and/or through a direct activation of the allosteric site on the nAChR [26, 27]. Fig. 3 illustrate the nAChR with its ACh binding sites and allo-

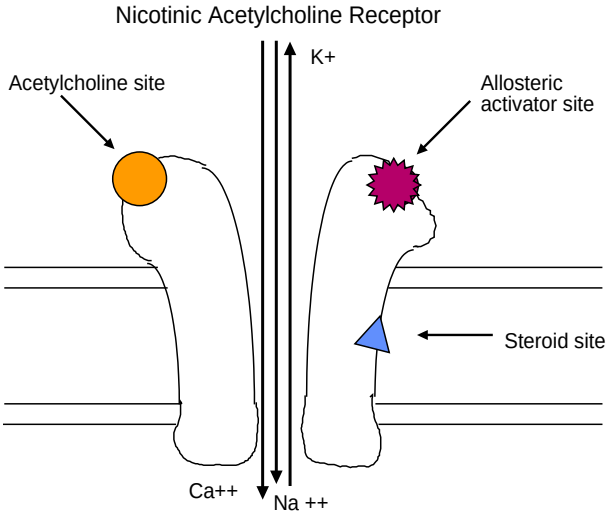

Fig. 3. Illustrative figure of the nAChR with ACh binding sites and allosteric binding sites.

steric sites.

PET and SPECT studies performed in Alzheimer patients under treatment with cholinergic drug therapy have shown an improvement in the cerebral blood flow and glucose metabolism [35, 36]. PET studies also have revealed an improvement in nAChRs in AD patients during long-term treatment with cholinesterase inhibitors such as tacrine, NXX-066 [36, 39, 42]. While the cholinesterase inhibitor rivastigmine causes a persistent inhibition of acetylcholinesterase activity in CSF after longterm treatment in AD patients [5], an enhanced activity of acetylcholinestease has been measured in CSF following long-term treatment with tacrine [Nordberg et al. 1999], galantamine, donepezil [6]. The latter effect might be a consequence of an increased acetylcholinesterase gene expression through a putative feedback mechanism possibly via muscarinic or nicotinic receptors or both [20]. Nerve growth factor intraventricularly administered to AD patients for three months resulted in an increased [^{11}C]nicotine binding [8], while treatment with the $5HT_3$ blocker ondansetron showed a decreased number of cortical nAChRs [Nordberg et al. 1997]. The few PET studies performed so far in AD patients illustrate that the nAChRs might be sensitive markers for modulatory processes induced by AD drug.

The potential therapeutic benefit in AD of nAChR stimulation is based upon the fact that nicotine improves memory in animals, healthy subjects and AD patients [25, 32, 33, 49]. Administration of the nicotinic antagonist mecamylamine to elderly subjects and AD patients produced cognitive impairment [32] while acute administration of nicotine to AD patients has resulted in a measurable short-termed improvement in learning, memory and attentional performance [18]. The nicotinic agonist ABT-418 has been shown to improve verbal learning and memory on selective reminding task in AD patients [48]. The cholinesterase inhibitors produce similar improvement in cognitive function in AD patients (Nordberg et al. 1998). Although epidemiological data are somewhat conflicting about the possibility that smoking could protect against AD [63, Doll et al. 2000] experimental data suggest that a neuroprotective effects against Aβ toxicity might be obtained via the nAChR (eg. the α7 subtype) [21, 59, 68]. Aβ has been suggested to bind the α7 nAChR with high affinity [64] however other investigators have not been able to confirm the results [Guan et al. 2002]. Cholinesterase inhibitors have also in in vitr studies shown neuroprotective effects against Aβ toxicity [59]. Estrogen, which in epidemiological studies have shown to reduce the risk of AD [15] has in experimental studies in PC 12 cells, shown neuroprotective effects against Aβ toxicity which at least to some part are mediated part via the the α7 subtype nAChR [59]. In a recent study we administered nicotine in the drinking fluid for 5 months in 9 months old mice carrying the APPsw mutation [41]. A marked reduction in the cortical amount of Aβ especially the unsoluble form was observed compared to saline treated mice [41]. It is reasonable to assume in order to obtain significant neuroprotective effects the drug in AD patients has to be given at very early stage of AD probably already at a presymptomatic level. There is a tremendous scope for the development of nAChR agonists as potential therapeutic agents in AD.

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