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Alzheimer's disease and acetylcholine receptors

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Review

Abstract. Cholinergic abnormalities, alongside senile plaques, neurofibrillary tangles, and extensive neuronal loss, are the major characteristics in Alzheimer's disease (AD). Both nicotinic and muscarinic acetylcholine receptors are decreased in AD, and it has been shown that the reduction in the number of acetylcholine receptors precedes other pathologic changes. Anti-cholinergic drugs induce amnesia, which can be reversed by withdrawal of the medication. Inhibition of the down-regulation of acetylcholine is, therefore, a strategy for the treatment of AD because it could augment acetylcholine levels within synaptic clefts. In this context, acetylcholinesterase inhibitors, which improve cognitive functions, are currently approved for the treatment of AD. Stimulation of acetylcholine receptors, nicotinic or muscarinic, is another strategy; some drugs are currently under investigation, and reported to be effective. In addition, nicotinic stimulation exerts a neuroprotective effect, and reduces the amyloid burden. Cholinergic therapy may counter the symptoms and progress of AD.

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INTRODUCTION

Alzheimer's disease (AD) is one of the neurodegenerative diseases presenting with dementia, and there are no definitive treatments or prophylactic agents. The presence of two types of abnormal deposits, senile plaques and neurofibrillary tangles, and extensive neuronal loss characterize the pathology of AD.

Cholinergic abnormalities have been observed in AD brains (Shimohama et al. 1986, Whitehouse et al. 1986). It has been reported that the protein level of acetylcholine receptors is reduced in AD (Nordberg 2001), and that dysfunction of cholinergic signal transmission could be responsible for the symptoms of AD. In addition, anti-cholinergic drugs, used for the treatment of Parkinson's disease, induce amnesia, which clinically resembles the symptoms of AD (Bymaster et al. 1993). The amnesia induced by anti-cholinergic drugs can be reversed by withdrawal of the drugs. This phenomenon implies that augmentation of the concentration of acetylcholine within the surviving synaptic clefts could counter the amnesic symptoms found in AD. Anti-cholinergic drug-induced amnesia is thought to be due to the blockade of muscarinic acetylcholine receptors since it has also been reported that muscarinic agonists improve memory (Terry Jr. et al. 2002).

Conversely, it has been shown that smoking improves arousal and attention, and memory. Nicotinic acetylcholine receptor stimulation might enhance the formation of memory (Potter et al. 1999) alongside its protective effect against the development of AD (Kihara et al. 1997, 1998, 2001, Shimohama et al. 1996). Subcutaneous administration of nicotine significantly improved attention performance as measured by Conners' continuous performance test (CPT) (White and Levin 1999). It has been reported that a significant reduction in errors of omission in the CPT occurred throughout the period of chronic nicotine administration. No improvement in motor or memory function was observed. Nicotine is known to act on presynaptic nicotinic acetylcholine receptors (nAChR) to enhance glutamatergic transmission. Nicotine from tobacco is thought to influence cognition by enhancing synaptic transmission. Conversely, decreased efficacy in transmission may account for the deficits associated with the loss of cholinergic innervation during AD. It is clear that smoking cannot be advocated for a variety of health reasons, but these data imply that nicotine could protect against the progression of AD.

Epidemiological studies have suggested that smoking is associated with a lower incidence of AD (Hillier and Salib 1997, Lee 1994, van Duijn and Hofman 1991), and an inverse association between smoking and Alzheimer's disease has been suggested by some studies. Nicotinic cholinergic stimulation might counter or delay the development of AD. However, these ideas are currently controversial.

In this review, the association of cholinergic abnormalities and AD, and implications for the treatment of AD will be discussed.

EPIDEMIOLOGICAL DATA OF AD

It is well known that aging is the most important risk factor for dementia including AD. The prevalence and incidence of dementia doubles every 5 years in persons over the age of 65.

A family history of dementia in first-degree relatives has been shown to increase the risk of developing dementia. Genetic abnormalities have been found in some families with autosomal dominant inheritance of AD. Amyloid-β protein precursor (AβPP), presenilin 1 and 2, have been associated with early onset of autosomal dominant inherited AD. It has been shown that these genetic abnormalities lead to the over-production of amyloid-β, which is the major protein component of senile plaques.

It is controversial whether smoking is associated with the incidence of AD. Some reports have indicated the negative relationship between smoking and AD (Hillier and Salib 1997, Lee 1994, van Duijn and Hofman 1991). Van Duijn and Hofman (1991) reported that the risk of Alzheimer's disease decreased with the increase in the daily number of cigarettes smoked before onset of disease (relative risk 0.3 in those smoking greater than 21/day vs. 1 in non-smokers). They concluded that there is an inverse association between smoking and AD, although smoking cannot be advocated for other health reasons. Hebert et al. (1992) suggested that smoking does not increase the risk of AD. Lee (1994) reviewed 19 case-control studies on the association between AD and smoking, and showed a highly significant ($P<0.001$) negative association (ever/never smokers, relative risk (RR) 0.64, 95% confidence interval (CI) 0.54-0.76). This negative or inverse association suggests that nicotine protects against AD.

Letenneur et al. (1994) showed, however, that although current smokers and past smokers had a lower

risk of cognitive deficit than non-smokers, this significant relationship disappeared after adjustment for potential confounding factors such as occupational category. They suggested that the apparent protective effect of smoking habits on cognitive abilities could be due to a confounding effect of occupational category. Launer et al. (1999) reported that smoking did not protect against AD, contrary to previous reports. Wang et al. (1999) also observed that smoking does not seem protective against AD or dementia. Other reports have suggested that smoking is one of the risk factors of AD (Doll et al. 2000, Meyer et al. 1999). Almeida et al. (2002) recently reviewed case-control and cohort studies, and concluded that the nature of the association between smoking and AD remains unclear. Overall, epidemiological data on the association between nicotinic acetylcholine dysfunction and AD is unclear, and much more information is required to establish the facts.

Muscarinic cholinergic abnormalities are also suspected in AD brains. The cholinergic antagonist, scopolamine, leads to memory impairment in humans (Drachman and Leavitt 1974, Ghoneim and Mewaldt 1977). It was reported that learning and acquisition of new information were impaired, and this phenomenon is similar to the early amnesic symptoms of AD. Another cholinergic antagonist, trihexyphenidyl, is prescribed for the treatment of Parkinson's disease, and this drug sometimes induces amnesia in these patients.

These findings suggest that both nicotinic and muscarinic acetylcholine receptors may be involved in AD pathogenesis, although the precise mechanism remains unclear.

PATHOLOGY ASSOCIATED WITH ACETYLCHOLINE RECEPTORS

The presence of two deposits, senile plaques (SPs) and neurofibrillary tangles (NFTs), and extensive neuronal death characterize the pathology of AD. Cholinergic abnormalities, such as the loss of presynaptic cholinergic markers in the cerebral cortex, are also found in AD brains.

SPs are extracellular structures composed of congophilic, fibrillar amyloid. There are two major plaque types: diffuse plaques and neuritic plaques. They are found in AD, and also in some non-demented elderly persons. Plaques with more amyloid and containing more abundant dystrophic neurites are called neuritic plaques. In these, the amyloid cores form fibrils staining with thioflavin-S. Neuritic plaques with neurites, both fusiform and bulbous, are surrounded by reactive glial cells.

A reduction in the number of nAChR in the cerebral cortex of AD patients has been detected using ligand binding techniques (Whitehouse et al. 1986). Shimohama et al. (1986) showed that, not only nicotinic receptors, but also muscarinic acetylcholine receptors are decreased in AD brains. The number of [^{3}H]nicotine binding sites in the AD brain was significantly reduced in the putamen and the nucleus basalis of Meynert. [^{3}H]QNB binding was significantly reduced in the hippocampus and nucleus basalis of Meynert. These findings suggest that there are significant changes in the level of both nicotinic and muscarinic cholinergic receptors in selected regions of AD brains. Perry et al. (1995) examined high-affinity nicotine binding, considered to primarily reflect the presence of CNS alpha4beta2 ($\alpha4\beta2$) nicotinic receptor subunits, autoradiographically in the brain regions most severely affected by AD pathology. Abnormalities in the nicotinic receptor were closely associated with primary histopathological changes: amyloid plaques and neurofibrillary tangles in subicular and entorhinal areas in AD brains. Therefore, it is notable that abnormalities in nicotinic receptors, especially alpha4beta2 ($\alpha4\beta2$) nAChR, occur in the early stages of the pathological process, not only in AD but also in other neurodegenerative diseases. It is possible that nicotinic receptor down-regulation precedes neurodegeneration and the difference between the diseases might depend upon the distribution of the abnormal nicotinic receptors.

Nordberg (2001) showed that the protein content of alpha4 ($\alpha4$), alpha3 ($\alpha3$), and alpha7 ($\alpha7$) nAChR is reduced in AD brains. The regional pattern of messenger RNA (mRNA) for nAChR does not strictly follow the regional distribution of nAChR ligand-binding sites in the human brain. Alpha4 and alpha3 mRNA levels were not changed in AD brains and the mRNA level of the alpha7 nAChR was increased in the hippocampus. These findings indicate that the subunit-specific changes in gene expression and the consequent loss of nicotinic-binding sites are not due to alterations at the transcription level. PET studies revealed deficits in nAChRs as early phenomena in AD, stressing the importance of nAChRs, which is consistent with the pathologically predicted data (Perry et al. 2000). Also, nAChRs are considered to be a potential target for drug intervention. The discrepancy between the protein level and mRNA level of nAChRs implies that translational

and/or posttranslational modification might be damaged in AD brains. One possibility is the posttranslational modification of nAChR by amyloid beta (Aβ).

AMYLOID HYPOTHESIS ON MEMORY DEFICIT AND nAChR

AD pathology is characterized by SPs which are composed of Aβ. In addition, several mutations found in familial AD are involved in amyloidogenesis. It has been shown that familial AD mutations in presenilin 1 (PS-1) enhance the generation of $A\beta_{1-42}$, indicating that PS-1 is involved in amyloidogenesis (Citron et al. 1992). Aβ must contribute to the pathogenesis, especially the neurodegeneration of AD.

Walsh et al. (2002) reported that Aβ oligomers inhibit hippocampal long-term potentiation (LTP). Aβ oligomers, in the absence of monomers and amyloid fibrils, disrupted synaptic plasticity at concentrations found in human brain and cerebrospinal fluid. This phenomenon might be one of the major mechanisms of memory disturbance found in the early stages of AD.

Itoh et al. (1999) showed that nicotinic signaling was impaired in Aβ-infused rats using an extracellular recording technique on hippocampal slices. LTP in CA1 pyramidal cells was also impaired in the Aβ-infused rats, and it was suggested that this dysfunction may be due to the blockade of nAChR by Aβ.

Recently it was reported that Aβ, especially fragment 1-42, binds to α7 nAChR. Binding of Aβ inhibits α7 nAChR-dependent calcium influx, which could explain the cognitive deficit of AD (Wang et al. 2000). Immunocytochemical studies on human sporadic Alzheimer's disease brains have demonstrated that $A\beta_{1-42}$ and α7 nAChR are both present in neuritic plaques and co-localize in individual cortical neurons. $A\beta_{1-42}$ and α7 nAChR can be co-immunoprecipitated, suggesting that they are tightly associated. Receptor binding experiments confirmed this association. Human neuroblastoma cells with α7 nAChR are killed by $A\beta_{1-42}$, and nicotine or epibatidine inhibited this death. In addition, $A\beta_{1-42}$ inhibits α7 nAChR-dependent calcium activation and acetylcholine release, which may be involved in memory and cognitive functions.

Dineley et al. (2001) indicated that Aβ activated the mitogen-activated protein kinase (MAPK) cascade *via* α7 nAChR. Aβ-induced activation through α7 nAChR might downregulate the MAPK-CREB phosphorylation system, which leads to the dysfunction of memory formation. CREB, cAMP-regulatory element binding protein, is thought to be one of the most important molecular components for hippocampus-dependent memory formation in mammals. From this point of view, blockade of the association between α7 nAChR and Aβ might be a strategy for the treatment of AD.

AMYLOID-INDUCED TOXICITY AND nAChR

There is still controversy over the role of Aβ in the neuronal loss found in AD brains. However, evidence is accumulating that Aβ causes neuronal death in many culture systems. Amyloid accumulation is one of the earliest changes in AD pathology, and this peptide may cause neuronal death in the CNS. The precise mechanism of Aβ -induced cytotoxicity remains unknown, although various hypotheses have been suggested. It has been reported that oxidative stress or free radical generation may mediate Aβ -induced cytotoxicity (Behl et al. 1994). Aβ stimulates nitric oxide (NO) production in astrocyte culture (Akama et al. 1998) and also calcium entry, triggered by activated N-methyl-D-aspartate (NMDA)-gated channels (Le et al. 1995). This might cause peroxynitrite generation and lead to cell death. Other reports suggested that Aβ inhibited glutamate uptake (Harris et al. 1996). These reports imply that Aβ -induced cytotoxicity might be mediated *via* glutamate toxicity. There are also some reports suggesting that Aβ enhances the toxicity induced by excitotoxin (Dornan et al. 1993, Morimoto et al. 1998). We also showed that $A\beta_{25-35}$ activity is mediated *via* NMDA receptors, and that $A\beta_{1-40}$ and $A\beta_{1-42}$ enhance glutamate neurotoxicity, which was mediated *via* NMDA receptors. An imbalance in glutamate signals leading to survival or death is the point of glutamate-induced neuronal death, and Aβ alters this balance to make neurons vulnerable to glutamate.

Nicotinic receptor stimulation inhibits Aβ toxicity (Kihara et al. 1997, 1998, 2001) and glutamate toxicity (Shimohama et al. 1996), and α7 receptors, in particular, contribute to PI3K-Akt phosphorylation, which is important for protection. In addition, the Bcl-2 family exists downstream of the PI3K-Akt cascade and works as an anti-neuronal death factor. Furthermore, nicotine modulates signal transduction to maintain the PI3K cascade which might be down-regulated by Aβ . Glutamate also activates the PI3K system, which might protect cells from radical formation-induced injury. We hy-

pothesized that Aβ-induced collapse of this system is the cause of vulnerability. The precise mechanism remains unknown, but nicotinic stimulation might up-regulate the PI3K cascade, which would contribute to maintain viability. Aβ binds to α7 nicotinic receptors (Wang et al. 2000), which might cause vulnerability because of the reduction in nicotinic signal transduction. Also, competitive stimulation of α7 nicotinic receptors might rescue cells from glutamate or NMDA receptor-induced toxicity.

Neuronal loss is one of the characteristics of AD pathology, and neuronal death may be induced by Aβ. Stimulation of nAChR could inhibit neuronal death, which would counter the progress of AD pathogenesis.

CLINICAL TRIAL

Cholinergic abnormalities are found in AD brains as described above. Bymaster et al. (1993) showed that the muscarinic antagonists scopolamine and trihexyphenidyl bind muscarinic acetylcholine receptors, and that these, but not a nicotinic antagonist, impaired memory performance in a spatial alternation task in rats. In particular, it has been reported that M1 receptors are associated with muscarinic antagonist-induced amnesia. In addition, it has been shown that M1 receptors are involved in memory processes using M1 receptor mutant mice (Anagnostaras et al. 2003). Conversely, muscarinic agonists could improve working memory. However, some reports showed little effect of muscarinic agonists on memory formation (Terry Jr. et al. 2002).

Alternatively, it has been reported that nicotinic receptor stimulation improves memory. The selective cholinergic channel activator (nicotinic agonist), ABT-418, significantly improved recall failure on a verbal learning task in AD patients (Potter et al. 1999). Qualitatively similar improvements were seen in non-verbal learning tasks such as spatial learning and memory, and repeated acquisition. Stimulation of central nicotinic receptors is shown to have an acute cognitive benefit in AD patients.

Both nicotinic and muscarinic receptors seem to be associated with memory disturbance, and stimulation of these receptors may be efficacious for the treatment of AD. However, there seems to be many problems to be resolved before an effective stimulant can be developed.

All of the prescription medications currently approved for the symptomatic treatment of AD are in a class of drugs called acetylcholinesterase inhibitors (AChEI) (Clark and Karlawish 2003, Kapaki et al. 2003). Four AChEI have been approved: tacrine (Cognex®), donepezil (Aricept®), galantamine (Reminyl®), and rivastigmine (Excelon®). These drugs produce the same degree of modest improvement in approximately 30-40% of patients with mild to moderate AD. The effect of AChEIs may depend on augmented acetylcholine levels. However, it has been reported that galantamine allosterically modulates nicotinic acetylcholine receptors in addition to the effect of AChEI (Maelicke and Albuquerque 2000). Direct stimulation of the nAChR might enhance the improvement of cognition. Recently, it has been shown that donepezil has a protective effect on glutamate-induced neuronal death through α7 nAChR (Takada et al. submitted). In our study, galantamine also exerted a neuroprotective effect on Aβ- and glutamate-induced neurotoxicity (Kihara et al. submitted). There may be many more possibilities for these drugs, and some clues might be found for the development of more effective drugs for the treatment of AD.

CONCLUSIONS

Cholinergic replacement therapy, using AChEIs, is currently available and effective for the treatment of AD. It is, however, controversial whether acetylcholine receptor agonists, nicotinic or muscarinic, would improve the symptoms of AD. Recent data has indicated that AChEIs possess a nicotinic receptor modulating effect, which might enhance the cognition improving effect. Abnormalities of the cholinergic system are prominent findings in AD, beside senile plaques, neurofibrillary tangles and neuronal loss. Appropriate and timely stimulation of acetylcholine receptors is necessary for the treatment of AD and it is important to develop such drugs as soon as possible.

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