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The nicotinic acetylcholine receptor: smoking and alzheimer's disease revisited

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1. ABSTRACT

Epidemiological studies regarding Alzheimer's disease (AD) in smokers currently suggest inconsistent results. The clinicopathological findings also vary as to how AD pathology is affected by smoking behavior. Even though clinicopathological, functional, and epidemiological studies in humans do not present a consistent picture, much of the *in vitro* data implies that nicotine has neuroprotective effects when used in neurodegenerative disorder models. Current studies of the effects of nicotine and nicotinic agonists on cognitive function in both the non-demented and those with AD are not convincing. More data is needed to determine whether repetitive activation of nAChR with intermittent or acute exposure to nicotine, acute activation of nAChR, or long-lasting inactivation of nAChR secondary to chronic nicotine exposure will have a therapeutic effect and/or explain the beneficial effects of those types of drugs. Other studies show multifaceted connections between nicotine, nicotinic agonists, smoking, and nAChRs implicated in AD etiology. Although many controversies still exist, ongoing studies are revealing how nicotinic receptor changes and functions may be significant to the neurochemical, pathological, and clinical changes that appear in AD.

2. INTRODUCTION

Cholinergic dysfunction is one of the key features in Alzheimer's disease (AD). AD is exemplified by loss of acetylcholine production, decreased enzymatic activities of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), cholinergic receptor loss, and degeneration of cholinergic neurons. Initially, many believed that only the muscarinic type cholinergic receptor was primarily lost in AD. Further studies have shown that muscarinic receptors are relatively preserved, especially for the high-affinity M1 subtype. In contrast, although additional research is necessary to address the lingering questions regarding these measures and how they might be changed by long-term nicotine exposure (90), numerous studies have demonstrated the loss of radioligand binding sites and nAChR proteins (141).

It is likely that the changes, loss, and/or dysfunction of the nAChRs are involved in the etiology and/or symptomatology of AD. As such, it is crucial to find ascertain whether and how drugs and/or agents that act at the nAChR alter the symptoms and/or progression of AD. Smoking is currently the most common method for exogenous nicotine delivery, so there is a great deal of

interest in understanding the relationship between smoking and AD. Contrary to the conflicting epidemiological indications, much of the *in vitro* data suggests nicotine has neuroprotective properties when used in models of neurodegenerative disorders despite studies on smoking revealing mixed signals. This review discusses some of these controversies and attempts to reveal how nicotinic receptor changes may be important to the neurochemical, pathological, and clinical changes that appear in AD.

3. THE NICOTINIC ACETYLCHOLINE RECEPTOR, NICOTINE, AND ITS *IN VIVO* AND *IN VITRO* EFFECTS

3.1. The nicotinic receptor in the CNS

Nicotinic receptors are expressed throughout the CNS and affect neurotransmitter release, synaptic plasticity, and circuit excitability (23). There are multiple subtypes of nAChRs, and each subtype consists of subunits. The specific types and numbers of subunits per nAChR subtype vary for each subtype. There are nine nicotinic receptor alpha subunits (alpha2-alpha10) and three beta subunits (beta2-beta4). Each is encoded by a different gene, and they are the primary components of nAChR in the brain (141). Heterologous expression studies indicate that beta2 and beta4 subunits can combine with alpha2, alpha3, alpha4, and alpha6 subunits in order to create "binary" nAChR complexes in an $(alpha)_2$ $(beta)_3$ stoichiometry. "Ternary" complexes can be formed when a binary complex is incorporated with an alpha5 or beta3 subunit which would change the ligand recognition properties and receptor function. There are some heterologously expressed nAChRs that are able to have more than one of the alpha2, alpha3, alpha4 or alpha6 kind of subunit and/or both beta2 and beta4 subunits too. In heterologous expression systems, there can be alpha9 and alpha10 subunit-containing and alpha7 and alpha8 subunit-containing heteromeric receptors. Additionally, homomeric receptors can be formed from alpha7, alpha8 (identified so far only in chick), alpha9, and alpha10 subunits. The stoichiometries and subunit combinations of naturally formed nAChR are less understood in comparison.

The most commonly seen subtype in the human brain is an alpha4beta2-nAChR subtype. It has a high affinity for nicotine, the $(alpha4)_2$ $(beta2)_3$ stoichiometry, and both pre- and post-synaptic dispositions (83), (71). In comparison, the alpha7-nAChR has a lower affinity for nicotine and is naturally expressed as a homomer, but it too is commonly expressed in the human brain pre- and post-synaptically (3), (4), (71). NAChR containing other subunits have been shown to exist, localized in important brain regions, but they are less abundant and less well studied and understood.

A study by Counts *et al.* showed that up-regulation of alpha7-nAChR expression contributes to cellular degeneration. The up-regulation may signal a compensatory response to preserve basocortical cholinergic activity as AD progresses. Although the increase in alpha7-nAChR may be a compensatory neuroprotective action, when alpha7-nAChRs interact with beta-amyloid precursor protein and beta-amyloid peptides, it causes the formation of senile plaques in AD. This may provide a pathogenic mechanism for cholinergic dysfunction. The increase of alpha7-nAChR expression may also serve as an indicator for the worsening of AD (18). The loss of nAChRs during AD upsets the normal mechanism that contributes to proper neurotransmitter release, synaptic plasticity, and circuit activity (23).

3.2. Chronic nicotine exposure induces changes in nAChR

Many studies have shown that up-regulation of CNS nAChR can be induced through chronic nicotine exposure in human smokers and animals *in vivo*, but there may be some strain-specific and regional exceptions (9), (145), (17), (69), (70). Chronic nicotine exposure *in vitro* also causes up-regulation of naturally or heterologously expressed alpha4beta2-nAChR sites (92), (8). Long-term nicotine exposure can also cause the native muscle-type alphal-nAChR, autonomic alpha3beta4-nAChR, or naturally or heterologously expressed alpha7-nAChR to increase (122), (69), (50), (91). It is believed that these changes post-transcriptional since the up-regulation happens in spite of the subunit genes being under artificial (heterlogous expression vector) or natural promoter control and because the differences in amounts of messenger RNA coding for nAChR subunits are absent or very miniscule (141). It is reasonable to hypothesize that there may be a decreased occurrence of neurodegenerative disorders in smokers since the up-regulatory effects of nicotine exposure on nAChRs are the opposite of the effects on nAChR seen in AD. To examine this query, mice aged from 24-28 months, were given nicotine orally for six weeks. This exposure to nicotine did not prevent or reverse age-related nAChR declines. However, the nAChR levels were maintained at a higher level in mice exposed to nicotine for a longer time period (11 months) and at a younger age (aged 14 months) when compared to the control mice (107).

In regards to functional effects, both acetylcholine (Ach) and acute nicotine exposure activates the nAChR function. There are quite a few fail-safe mechanisms to make certain that nAChRs are not continuously exposed to ACh and to ensure that nAChRs are periodically rather than consistently activated by pulses of ACh release. Nevertheless, regular use of tobacco products creates chronic exposure to nicotine. Research from several laboratories demonstrates that chronic nicotine exposure creates a loss of nicotine-sensitive nAChR functional activity in the brain that can last for days *in vivo* (117), (118), (59), (60), (44), (42), (75), (76), (38). Through a process call "persistent inactivation," the functions of nAChRs are lost due to chronic nicotine exposure in a time- and dose-dependent manner that is specific for each subtype. This process is different from nAChR "desensitization" which is more readily reversible (17), (50), (103).

3.3. Nicotine is neuroprotective *in vitro*

The neuroprotective effects of nicotine have been established *in vitro*. Nicotine can prevent the switch from

an alpha-helix to beta-sheet conformation which can inhibit beta-amyloid aggregation (113), (53). Although nicotine and nicotinic agonists are not protective against AMPA-induced excitotoxicity, they have demonstrated protective effects against NMDA-induced excitotoxicity (93), (74), (29). In cultured hippocampal neurons, nicotine is neuroprotective against the dexamethasone potentiation of kainic acid-induced neurotoxicity (116). However, nicotine does not appear to have a protective effect against the toxicity from nitric oxide (NO) formation in cell culture (121), (120), (52). Ca^{2+} entry into the neuron caused by NMDA-receptor activation stimulates NO synthase (NOS), which then exerts free-radical damage. Nicotine can inhibit the NMDA-induced cytotoxicity mediated through NOS activation by working at either the NMDA receptors or the effectors leading to NOS stimulation. Thus, the nicotine would cause a protective effect. Nicotine also enhances alpha-secretase activity, resulting in increased soluble APP release *in vitro (*57), (33).

Nicotine may be neuroprotective against beta-amyloid toxicity as well (55). Neuronal loss induced by beta-amyloid can be blocked by nicotine (146). The reduction of neurotoxicity from nicotine blocking beta-amyloid is receptor specific. It is suggested that the alpha7 and the alpha4beta2 nicotinic receptors are responsible for this attenuation (57), (56), (139). The phospholipase A2 activation induced by beta-amyloid is also inhibited by nicotine (123). Moreover, Linert *et al.* show that nicotine seems to have antioxidant effects *in vitro* (64). Nicotine also inhibits cell cycle progression and apoptosis in such a way that favors it neuroprotective effects. Chronic nicotine treatment activates the alpha7-nAChRs through the MAPK, NF-kappaB, and c-myc pathways and also prevents buildup and deposition of beta-amyloid in the hippocampus (67). Shimohama showed that nAChR stimulation protects neurons from glutamate-induced cytotoxicity. The stimulation activates PI3K, which in turn phosphorylates Akt and that causes an up-regulation of Bcl-2 and Bcl-x. This helps increase cell survival (120), (13). Multiple studies have shown that nAChR stimulation protected neurons from beta-amyloid-induced, rotenone-induced and 6-OHDA-induced toxicity (120), (13), (20), (2), (41). Thus, nicotine appears to have potent neuroprotective effects *in vitro (*60).

4. NICOTINIC RECEPTOR CHANGES AND INTERACTIONS BETWEEN NICOTINIC RECEPTORS AND SUSPECTED ETIOLOGICAL FACTORS IN AD

Structurally, the losses of synapses seen in many regions are related to the severity of dementia (26), (128). Neurochemically, the considerable loss of ChAT is widely known (22). Many losses are seen in the glutaminergic, cholinergic, serotonergic, and noradrenergic systems too (47).

Changes in the cholinergic systems have been studied extensively. At first, it was believed that high affinity M1 muscarinic receptors were lost in AD (22), (82), (87), but subsequent studies do not confirm this. It has been shown that the M2 receptor is changed and we have shown that the M4 is changed in AD (51), (96), (86), (84), (6).

AD causes a considerable loss of high affinity nAChRs, likely to be of the alpha4beta2 subtype (36), (125), (96), (106), (114), (115), (86), (6), (37), (95), (140), (109). This loss likely happens in the early phases of AD (85). Furthermore, loss also appears to be regionally specific (court), and the alpha4 subunit appears to be specifically lost in AD (19), (93). There are a number of causes that may cause receptor loss, which range from the death of neurons with receptors to the loss of synapses bearing receptors, or it may simply be down-regulation of receptors from surviving neurons. It may likely be a combination of these effects. The subunit mRNAs show no differences at the transcription level. The alpha4 subunit also suggests a decreased amount of protein (141). On the contrary, the alpha7-nAChR seems to be safe (21), (125), (77), (102), but some studies have described a loss of alpha7-nAChRs in AD (7).

The relationship between nAChR and AD has other features that have been investigated as well (85). Having the apolipoprotein E genotype does not affect the loss of nAChR (126), (101). The tangle and plaque counts in the subicular and entorhinal areas match the NAChR loss seen in AD (95), but such is not the case in the frontal cortex (110). It has been shown that nAChR loss tends to correlate less with senile plaques and more with the amount of beta-amyloid42 (93). NAChR loss may be linked with dementia severity (93), but it is not linked with cognitive decline in AD or Dementia with Lewy Bodies (DLB) (110). We have also found that the decrease of nAChR binding does correlate with the decrease of synapses. However, the loss of ChAT activity does not correlate with the loss of synapses in AD (109). On the other hand, the loss of ChAT activity does correlate significantly with loss of nAChR in DLB patients (102). Perry *et al.* demonstrated that hippocampal ChAT and nAChR losses are worse in smokers with AD versus non-smokers with AD (94).

In experimental models by Itoh *et al.*, a loss of nAChR was created when rats were infused with amyloid (46). There are many studies that have shown the interactions between the different nAChR subtypes and beta-amyloid, and a few of these interactions had effects on the function of nAChR (138), (27), (66), (98). Sparks *et al.* performed an immunohistochemical study that helped to localize a nAChR subunit-like immunoreactive material which has been seen in fibers and neurons in control groups and in tangles and plaques in AD groups (124). A direct correlation was not found between nAChR loss and tangles and plaques in the amyloid precursor protein (APP) 670/671 double Swedish mutation (85).

Recent studies have shown that soluble beta-amyloid oligomers are probably the most important neurotoxic species in AD. Reversing the synaptic failure created by beta-amyloid is crucial to stopping the progress of AD as beta-amyloid itself alters the nAChR function. Nicotinic agonists rapidly induce receptor desensitization

(which decreases efficacy), but compounds that block beta-amyloid binding would not be hindered by this limitation (49). The selective, high-affinity effects of oligomeric beta-amyloid $_{1-42}$ on alpha7beta2-nAChRs may contribute to the interference of cholinergic signaling and decreased memory and learning capabilities. As such, drugs targeting alpha7beta2-nAChRs to restore functionality or protect them against beta-amyloid effects may be an avenue for future treatment (65).

In animal studies, it was demonstrated that disrupting the alpha7-nAChR function could be useful in the treatment of AD. A transgenic mouse model of AD overexpressing a mutated form of APP and a model lacking the alpha7-nAChR gene (APPalpha7KO) were used. It was shown that despite the high levels of APP and amyloid deposits, the deletion of that subunit in a transgenic mouse with AD created a protection from the dysfunction in synapses and memory and learning performance. The mice that overexpress the APP had similar levels of beta-amyloid and APP compared to the APPalpha7KO mice, but they were unable to solve cognitive challenges like the Morris water maze (31). Another animal study showed that the absence of alpha7-nAChR during the early stages of cognitive impairment induced by increased beta-amyloid and APP metabolites increases the susceptibility of the hippocampus to neuronal loss and volume (41).

Ikonomovic *et al.* demonstrated that there are no detectable changes in the cortical alpha7-nAChR binding levels that could be associated with the cognitive decline in mild-moderate AD. On the contrary, beta-amyloid concentration was increased in AD and correlated with increasing cognitive impairment (45). These studies suggest possible links between beta-amyloid and nAChR in AD.

A PET study quantified the nAChR distribution *in vivo* with 2- (18F)fluoro-A-85380 (2-FA) in 15 incipient AD patients compared to 14 age-matched, healthy controls in order to determine if nAChR is lost in those with significant cognitive deficit. This study found no evidence of *in vivo* loss of nAChR in early AD; however; it was noted that the 2-FA may not be sensitive enough to pick up such a change (34). Another PET study using ^{123}I-5IA-85380 SPECT showed the *in vivo* loss of alpha4beta2 (88). A different study using ^{123}I-5IA-85380 SPECT is consistent with the result that the decrease in nAChR and other cholinergic activities in AD are late-stage occurrences, and that nAChR is preserved in the earlier stages (79).

5. SMOKING, AD, AND COGNITION

5.1. Epidemiological studies of cigarette smoking effects on AD are mixed

There are some epidemiological studies that have found that smokers have a lower risk for AD after controlling for coronary artery disease, emphysema, and cancer. Brenner *et al.* (12) demonstrated an odds-ratio (OR) of 0.61 for developing AD in smokers vs. nonsmokers. A relative risk (RR) of 0.64 was derived from a meta-analysis in smokers vs. nonsmokers (32). In another study, smoking was found to possible delay age of onset by 4.2 years on average in familial AD (135). There were concerns of a possible sample bias due to higher mortality in smokers that have the apolipoprotein epsilon4 (Apo E4) allele, which is a marker for increased AD susceptibility, but follow-up studies have shown that this in not the case (134). A Canadian study reported that smoking did not affect the RR getting (132). Tyas *et al.* also looked at three other Canadian data sets and saw that smoking is protective when alcohol is introduced as a variable (131). Aggarwal *et al.* reported that former smokers had a reduced risk of developing AD. The odds of getting AD increased by half for every 10 years of smoking cessation (OR = 1.3, CI = 0.9-1.7). Current smoking, however, was associated with an increased risk of AD (OR = 3.4 95% CI 0.5-1.7) when compared to those who had never smoked. Additionally, former smokers who carried the Apo E4 allele were less likely to develop AD than nonsmokers (1). Another study demonstrated that the speculation that smoking-related deaths create a bias was not justified due to the fact that smokers had a reduced risk of AD in all scenarios which include no relation between smoking and AD, decreased risk in smokers, and increased risk in smokers. For each scenario, two incidence density ratios were calculated: one included phantoms that developed AD (ignoring the smoking-related deaths), and the other did not (mimicking real life), and all of these demonstrated a reduced risk in smokers (24).

Many other studies do not show a lower incidence of AD in smokers. The Canadian Health Study of Aging demonstrated that smokers did not have a reduced incidence of AD (25) and that smokers actually had a higher risk in heavy smokers (> 37 pack-years, OR = 2.8). The United Kingdom Medical Research Council (MRC) performed a survey which concluded that the OR for developing AD in mild smokers (<10 cigarettes/day) was 1.4, and in moderate to heavy smokers (>10 cigarettes/day) was 2.6 (100). A study by Doll *et al* found that smoking had no protective effects (28). Another study found that the risk of dementia is doubled in smokers when compared to nonsmokers. More specifically, the risk of developing AD was even higher (89). This occurrence may be affected by Apo E4 status such that smokers lacking the Apo E4 allele had RR of 4.6 and those with the allele had a RR of 0.6 for developing AD (89). A study by Merchant *et al.* also demonstrated that smoking increases the risk of developing AD (78). This may occur because of the nonsmokers outliving the smokers which could lead to higher rates of those who are Apo E4 negative compared to those who have the allele (105). A meta-analysis performed by Launer *et al.* reported that "current smoking" status increased the incidence of AD (RR= 1.74) (61). Thus, many studies find that smoking is not protective against developing AD in the elderly. Several of the earlier studies that suggested smoking had a protective effect may have been driven by sample bias (58) since more current studies demonstrate either no or even an increased risk of AD development. Wang and colleagues support this view with a study that showed a lower prevalence but not a lower incidence of AD in smokers. Further, AD smokers had an increased 5-year mortality rate. They found that

smoking does not protect against AD (136). Cataldo *et al.* found a significant increase in AD risk (RR 1.72) associated with tobacco smoking when controlling for tobacco industry affiliation (16). Luchsinger and colleagues found that current smoking, diabetes, hypertension, and heart disease are all associated with an increased risk of AD ($p<0.1$) when analyzed separately. Smoking and diabetes were the strongest risk factors when isolated (68). Cataldo and Glantz reported that smoking cessation should become a crucial part in the prevention and treatment of AD given that it is such a significant risk factor for AD. That the risk of cardiovascular disease (CVD) would also significantly decrease is also beneficial given that CVD itself is a risk factor for AD (15). Another review had a meta-analysis of 50 studies that concluded that current smoking has an increased risk of developing AD (SR 1.79 95% CI 1.43-2.23). However, the risk in ex-smokers is nearly identical to those who had never smoked (SR 0.99 95% CI 0.81-1.23) (97). A population-based prospective cohort study 6,868 individuals over 7.1 years demonstrated that current smoking increased the risk of AD (HR 1.56 95% CI 1.21-2.02). This effect is more dramatic in individuals without the Apo E4 allele than those who carry the allele (104). A cross-sectional study in which 685 AD patients were assessed for the Apo E4 genotype, smoking, and drinking demonstrated that Apo E4, heavy drinking, and heavy smoking (> or = 1 pack per day) lower the age of onset for AD in additive manner (39).

The effects of smoking in other neurodegenerative diseases are far clearer and show a reduced risk. For example, Morens *et al* (80), (81) concluded that cigarette smokers have 50% reduced risk of develop Parkinson's disease (PD) compared to a nonsmoker. This may be because nicotine exposure upregulates dopaminergic neurotransmission or because tobacco smoke may inhibit monoamine oxidase activity. A prospective community-based study by Tsuang *et al.* suggested that there is a significantly decreased risk of Lewy-related pathology in multiple brain areas but not in AD-type pathologic changes in heavy (>50 pack years) smokers (130). However, more work is needed to evaluate reasons why data on smoking behavior and AD risk does not corroborate the protection that smoking appears to have against PD.

5.2. Clinical-pathological studies of cigarette smoking effects on AD are mixed

Some of the neuropathological changes seen in AD may be caused by nicotine exposure according to some clinical-pathological studies. For instance, Ulrich *et al* (133) showed that smoking has varied effects on the phenotypic expression of AD. This can be seen with lower senile plaques (SPs) in only female smokers with AD, but on the whole a rise is seen in the amount of neurofibrillary tangles (NFTs) and a higher Braak stage in all smokers with AD. However, this study did not distinguish between former and current smokers, and it did not quantify the amount of tobacco consumed.

We performed a clinical-pathological analysis to compare the phenotype of AD in current, former, and nonsmokers who were matched for age and education at death. There were no differences seen between current, former, and nonsmokers concerning the ChAT activity, disease duration, severity of dementia at death, or counts of synapses, neuritic plaques or total plaques when not stratifying by Apo E4. The data suggests that the clinical course of AD is not affected by tobacco use. Nonsmokers were phenotypically indistinguishable from current smokers. The exogenous exposure of nicotine from smoking may influence the degree of neurofibrillary change in AD, but only in the presence of apo-E4 (111).

A study by Almeida *et al.* measures the gray matter density through voxel-based morphometry using statistical parametric mapping of T1-weighted magnetic resonance images (MRI). It shows that smokers have decreased gray matter density in the precuneus and posterior cingulate bilaterally, right thalamus and frontal cortex bilaterally when compared to people who have never smoked. They concluded that smoking is associated with decreased gray matter density in areas of the brain that are associated with early AD (5).

Thus, newer clinicopathological studies demonstrate some effects of smoking on hallmarks of AD pathology. There are no published data on tobacco products like snuff and/or chewing tobacco and AD.

5.3. Effects of smoking or nicotine administration reveal modest clinical benefit in cognition

Although cigarette smoking has not proven to protect against developing AD, it has been associated with a lower risk of attention and visuospatial decline in those without AD (62). In contrast, smoking has been shown decrease cognitive function in elderly men without dementia; however, this risk is lowered in those who have the Apo E4 allele (14). An increase in nAChR activity on hippocampus, thalamus, and cortex has been seen in smokers (11), (90), (9). These studies imply that smoking has a biological and clinical effect.

Prospective studies on nicotine and nicotine agonists as therapy for AD support the potential cognitive benefits that nicotine possesses. Many small trials have been conducted which demonstrate that subcutaneous and intravenous administration of nicotine has mild benefits in cognition in AD subjects, especially in areas of short-term memory, attention, and information processing (82), (90), (112), (48). Nicotine patches have also been found to have positive effects on attention in AD (107), (42), (105) (47). Large trials of ABT-418, a nicotinic agonist have been undertaken (143). A trial of ABT-418 demonstrated improvement on memory, recall, and spatial learning, (Potter) although it has now been discontinued. Another nAChR agonist (ABT 089) has been investigated. Several full and partial nicotinic receptor agonists are in development for treatment of AD. These include S24795, JN403, SEN12333/WAY-317538, ABT-107, TC-1734, A-867744, EVP-6124, and SEN34625/WYE-103914 (137), (35), (40), (108), (72), (10), (30), (73), (43).

A review by Swan and Lessov-Schlaggar suggested that smoking is clearly associated with

accelerated cognitive decline such as in the areas of executive functions, verbal memory, and speed of processing and an increased risk for dementia (both AD and vascular dementia). Work at the cellular level suggests that tobacco smoke induces an inflammatory response, which may directly or indirectly promote neuropathology associated with AD. Administration of nicotine is, however, shown to improve vigilance, working memory, selective attention, and verbal memory (127).

The administration of chronic and acute nicotine only affects certain kinds of memory. One such example in animal studies is that nicotine improved working memory, but it did not help with reference or response latency. Behavioral studies have shown that the best responses are seen in subjects with cognitive impair or performing difficult tasks (23). Thus, studies of brain function are varied concerning the effects of nicotine and smoking.

6. CONCLUSION

This review attempts to clarify the relationships between nicotine, nicotinic receptors, AD, and smoking. Some general notions and crucial questions come forth that might direct ongoing research to elicit these relationships. An important notion is that cigarette smoking is in now way equivalent to directly administering nicotine. Tobacco contains a myriad of toxic compounds, all of which would counteract any of the acute beneficial cognitive effects or neuroprotective properties of nicotine. As such, it is unlikely that smoking would have the same effects as nicotine alone or nicotinic drugs on the incidence or progression of AD symptoms. All the same, there would be a significant advance if smoking truly does lower the incidence of AD. Another notion the nicotinic drugs and smoking may only have therapeutic effects on a specific subset of the population. Smoking, in and of itself, is seen only a subset of the population. Additional data is necessary to ascertain more accurately the therapeutic goals of possible nicotinic drug treatment of AD. More data is also needed to determine the mechanism (s) involved in the potential cognitive benefits seen in both smoking behavior and or nicotinic drugs.

One crucial question is to determine if cognitive benefits or neuroprotection occur through immediate activation, constant activation, or long-term inactivation of nAChR function or some combination thereof. We do know that nicotine administration can help to preserve nAChR when given over a longer range (107). It is also necessary to determine if and how such interactions are interweaved across the numerous nAChR subtypes responsible for brain function, and if the changes in the number of receptors has any significance of such effects. Nicotine has been shown to be neuroprotective against NMDA-induced excitotoxicity and that nAChR stimulation protected neurons from rotenone-induced, 6-OHDA-induced and beta-amyloid-induced toxicity (57), (33), (120), (13), (20), (2), (41). Now, there is a question of whether or not these neuroprotective properties that are shown *in vitro* are also present *in vivo*. Also crucial is whether the neuroprotective or therapeutic effects of nicotine can change any of the pathophysiological hallmarks of AD. This is line of questioning may provide a renewing vigor to further explore whether or not nicotinic receptors are promising therapeutic drugs. This is perhaps the most promising line of inquiry that would provide renewed impetus to explore further whether nicotinic receptors are desirable therapeutic targets.

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8. REFERENCES

1. N.T. Aggarwal, J.L. Bienias, D.A. Bennett, R.S. Wilson, M.C. Morris, J.A. Schneider, R.C. Shah, D.A. Evans: The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology* 26, 140-6 (2006)

2. Akaike, Y. Takada-Takatori, T. Kume, Y. Izumi: Mechanisms of neuroprotective effects of nicotine and acetylcholinesterase inhibitors: role of alpha4 and alpha7 receptors in neuroprotection. *J Mol Neurosci* 40, 211-6 (2010)

3. E. Albuquerque, M. Alkondon, E. Pereira, N. Castro, A. Schrattenholz, C. Barbosa, R. Bonfante-Cabarcas, Y. Aracava, H.M. Eisenberg, A. Maelicke: Properties of neuronal nicotinic acetylcholine receptors, pharmacological characterization and modulation of synaptic function. *J Pharmacol Exp Ther* 280, 1117-1136 (1996)

4. E. Albuquerque, E. Pereira, M. Alkondon, H. Eisenberg, A. Maelicke: Neuronal nicotinic receptors and synaptic transmission in the mammalian central nervous system. Berlin Springer, 337-358 (2000)

5. O.P. Almeida, G.J. Garrido, N. Lautenschlager, G.K. Hulse, K. Jamrozik, L. Flicker: Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. *American Journal of Geriatric Psychiatry* 16, 92-8 (2008)

6. Aubert, D.M. Araujo, D. Cecyre, Y. Robitaille, S. Gauthier, R. Quirion: Comparative alterations of nicotinic and muscarinic binding sites in Alzheimer's and Parkinson's diseases. *J Neurochem* 58, 529-41 (1997)

7. C. Banerjee, J.R. Nyengaard, A. Wevers, R.A. de Vos, E.N. Jansen Steur, J. Lindstrom, K. Pilz, S. Nowacki, W. Bloch, H. Schröder: Cellular expression of alpha7 nicotinic acetylcholine receptor protein in the temporal cortex in Alzheimer's and Parkinson's disease--a stereological approach. *Neurobiol Dis* 7, 666-72 (2000)

8. M. Bencherif, K. Fowler, R.J. Lukas, P.M. Lippiello: Mechanisms of up-regulation of neuronal nicotinic acetylcholine receptors in clonal cell lines and primary

cultures of fetal rat brain. *J Pharmacol Exp Ther* 275, 987-94 (1995)

9. M. Benwell, D. Balfour, J. Anderson: Evidence that tobacco smoking increases the density of nicotine binding sites in human brain. *J Neurochem* 50, 1243-1247 (1988)

10. R.S. Bitner, W.H. Bunnelle, M.W. Decker, K.U. Drescher, K.L. Kohlhaas, S. Markosyan, K.C. Marsh, A.L. Nikkel, K.E. Browman, R. Radek, D. Anderson, J. Buccafusco, M. Gopalkrishnan: *In vivo* pharmacological characterization of a novel selective alpha7 neuronal nicotinic acetylcholine receptor agonist ABT-107: preclinical considerations in Alzheimer's disease. *J Pharmacol Exp Ther*, (2010)

11. C.R. Breese, C. Adams, J. Logel, C. Drebing, Y. Rollins, M. Barnhart, B. Sullivan, B.K. Demasters, R. Freedman, S. Leonard: Comparison of the regional expression of nicotinic acetylcholine receptor alpha7 mRNA and (125I)-alpha-bungarotoxin binding in human postmortem brain. *J Comp Neurol* 387, 385-98 (1997)

12. D.E. Brenner, W.A. Kukull, G. van Belle, J.D. Bowen, W.C. McCormick, L. Teri, E.B. Larson: Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study, *Neurology* 43, 293-300 (1993)

13. S.D. Buckingham, A.K. Jones, L.A. Brown, D.B. Sattelle: Nicotinic acetylcholine receptor signaling: roles in Alzheimer's disease and amyloid neuroprotection. *Pharmacol Rev* 61, 39-61 (2009)

14. D. Carmelli, G.E. Swan, T. Reed, G.D. Schellenberg, J.C. Christian: The effect of apolipoprotein E epsilon4 in the relationships of smoking and drinking to cognitive function. *Neuroepidemiology* 18, 125-33 (2009)

15. J.K. Cataldo, S.A. Glantz: Smoking cessation and Alzheimer's disease: facts, fallacies, and promise. *Expert Rev Neurother* 10, 629-31 (2009)

16. J.K. Cataldo, J.J. Prochaska, S.A. Glantz: Cigarette smoking is a risk factor for Alzheimer's disease: an analysis controlling for tobacco industry affiliation. *J Alzheimers Dis* 19, 465-80 (2009)

17. A.C. Collins, M. Marks: Are nicotinic acetylcholine receptors activated or inhibited following chronic nicotine treatment?. *Drug Dev Res* 38, 231-242 (1996)

18. S.E. Counts, B. He, S. Che, M.D. Ikonomovic, S.T. DeKosky, S.D. Ginsberg, E.J. Mufson: alpha7 nicotinic receptor up-regulation in cholinergic basal forebrain neurons in Alzheimer disease. *Arch Neurol* 64, 1771-6 (2007)

19. J. Court, C. Martin-Ruiz, M. Piggott, D. Spurden, M. Griffiths, E. Perry: Nicotinic receptor abnormalities in Alzheimer's disease. *Biol Psychiatry* 49, 175-84 (2001)

20. W.Y. Cui, M.D. Li: Nicotinic modulation of innate immune pathways via alpha7 nicotinic acetylcholine receptor. *J Neuroimmune Pharmacol*, (2010).

21. P. Davies, S. Feisullin: Postmortem stability of alpha-bungarotoxin binding sites in mouse and human brain. *Brain Res* 216, 449-54 (1981)

22. K.L. Davis, H.I. Yamamura: Cholinergic under-activity in human memory disorders. *Life Sci* 23, 1729-33 (1978)

23. J.A. Dani, D. Bertrand: Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annu Rev Pharmacol Toxicol* 47, 699-729 (2007)

24. S.M. Debanne, R.A. Bielefeld, V.K. Cheruvu, T. Fritsch, D.Y. Rowland: Alzheimer's disease and smoking: bias in cohort studies. *J Alzheimers Dis* 11, 313-21 (2007)

25. M. Defever: Long term care: the case of the elderly. *Health Policy* 19, 1-18 (1991)

26. S.T. DeKosky, S.W. Scheff: Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann Neurol* 27, 457-64 (1990)

27. K.T. Dineley, M. Westerman, D. Bui, K. Bell, K.H. Ashe, J.D. Sweatt: Beta-amyloid activates the mitogen-activated protein kinase cascade via hippocampal alpha7 nicotinic acetylcholine receptors: *In vitro* and *in vivo* mechanisms related to Alzheimer's disease. *J Neurosci* 21, 4125-33 (2001)

28. R. Doll, R. Peto, J. Boreham, I. Sutherland: Smoking and dementia in male British doctors: prospective study. *BMJ* 320, 1097-102 (2000)

29. D.L. Donnelly-Roberts, I.C. Xue, S.P. Arneric, J.P. Sullivan: *In vitro* neuroprotective properties of the novel cholinergic channel activator (ChCA), ABT-418. *Brain Res* 719, 36-44 (1996)

30. G.C. Dunbar, P.H. Boeijinga, A. Demazières, C. Cisterni, R. Kuchibhatla, K. Wesnes, R. Luthringer: Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. *Pyschopharmacology (Berl)* 191, 919-29 (2007)

31. G. Dziewczapolski, C.M. Glogowski, E. Masliah, S.F. Heinemann: Deletion of the alpha7 nicotinic acetylcholine receptor gene improves cognitive deficits and synaptic pathology in a mouse model of Alzheimer's disease. *J Neurosci* 29, 8805-15 (2009)

32. D. Edwards, R. Deuel, C. Baum, J. Morris: A quantitative analysis of apraxia in senile dementia of the Alzheimer type: Stage-related differences in prevalence and type. *Dementia* 2, 142-149.

33. S. Efthimiopoulos, D. Vassilacopoulou, J.A. Ripellino, N. Tezapsidis, N.K. Robakis: Cholinergic agonists stimulate secretion of soluble full-length amyloid precursor protein in neuroendocrine cells. *Proc Natl Acad Sci U S A* 93 , 8046-50 (1996)

34. J.R. Ellis, V.L. Villemagne, P.J. Nathan, R.S. Mulligan, S.J. Gong, J.G. Chan, J. Sachinidis, G.J. O'Keefe, K.A. Wesnes, G. Savage, C.C. Rowe: Relationship between nicotinic receptors and cognitive function in early Alzheimer's disease: a 2- (18F)fluoro-A-85380 PET study. *Neurobiol Learn Mem* 90, 404-12 (2008)

35. D. Feuerbach, K. Lingenhoehl, H.R. Olpe, A. Vassout, C. Gentsch, F. Chaperon, J. Nozulak, A. Enz, G. Bilbe, K. McAllister, D. Hoyer: The selective nicotinic acetylcholine receptor alpha7 agonist JN403 is active in animal models of cognition, sensory gating, epilepsy, and pain. *Neuropharmacology* 56, 254-63 (2009)

36. D.D. Flynn, D.C. Mash: Characterization of L- (3H) nicotine binding in human cerebral cortex: comparison between Alzheimer's disease and the normal. *J Neurochem* 47, 1948-54 (1986)

37. E. Giacobini: Nicotine acetylcholine receptors in human cortex: aging and Alzheimer's disease. In: Lippiello PNM, Raven Press, New York, 183-194 (1992)

38. S.R. Grady, M.J. Marks, A.C. Collins: Desensitization of nicotine-stimulated. *J Neurochem* 62, 1390-8 (1994)

39. D.G. Harwood, A. Kalechstein, W.W. Barker, S. Strauman, P. St George-Hyslop, C. Iglesias, D. Loewenstein, R. Duara: The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. *Int J Geriatr Psychiatry* 25, 511-8 (2010)

40. S.N. Haydar, C. Ghiron, L. Bettinetti, H. Bothmann, T.A. Comery, J. Dunlop, S. La Rosa, I. Micco, M. Pollastrini, J. Quinn, R. Roncarati, C. Scali, M. Valacchi, M. Varrone, R. Zanaletti: SAR and biological evalution of SEN12333/WAY-317538: novel alpha 7 nicotinic acetylcholine receptor agonist. *Bioorg Med Chem* 17, 5247-58 (2009)

41. C.M. Hernandez, R. Kayed, H. Zheng, J.D. Sweatt, K.T. Dineley: Loss of α7 nicotinic receptors enhances β-amyloid oligomer accumulation, exacerbating early-stage cognitive decline and septohippocampal pathology in a mouse model of Alzheimer's disease. *J Neurosc,* 30, 2442-53 *(*2010)

42. C.J. Hillard, J.J. Pounds: Effects of chronic nicotine treatment on the accumulation of (3H)tetraphenylphosphonium by cerebral cortical synaptosomes. *J Neurochem* 60, 687-95 (1993)

43. D. Hilt, B. Safirstein, D. Hassman, J. Apter, S. Thein, P. Maruff, J. Harrison, M. Gawryl, G. Koenig: EVP-6124 – Safety, tolerability, and cognitive effects of a novel α7 nicotinic receptor agonist in Alzheimer's disease patients on stable donepezil or rivastigmine therapy. (2009)

44. B.A. Hulihan-Giblin, M.D. Lumpkin, K.J. Kellar: Effects of chronic administration of nicotine on prolactin release in the rat: inactivation of prolactin response by repeated injections of nicotine. *J Pharmacol Exp Ther* 252, 21-5 (1990)

45. M.D. Ikonomovic, L. Wecker, E.E. Abrahamson, J. Wuu, S.E. Counts, S.D. Ginsberg, E.J. Mufson, S.T. Dekosky: Cortical alpha7 nicotinic acetylcholine receptor and beta-amyloid levels in early Alzheimer's disease. *Arch Neurol* 66, 646-51 (2009)

46. Itoh, A. Nitta, M. Nadai, K. Nishimura, M. Hirose, T. Hasegawa, T. Nabeshima: Dysfunction of cholinergic and dopaminergic neuronal systems in beta- amyloid protein--infused rats. *J Neurochem* 66, 1113-7 (1996)

47. J.R. James, A. Nordberg: Genetic and environmental aspects of the role of nicotinic receptors in neurodegenerative disorders: emphasis on Alzheimer's disease and Parkinson's disease. *Behav Genet* 25, 149-59 (1995)

48. G.M. Jones, B.J. Sahakian, R. Levy, D.M. Warburton, J.A. Gray: Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology (Berl)* 108, 485-94 (1992)

49. S. Jürgensen, S.T. Ferreira: Nicotinic receptors, amyloid-beta, and synaptic failure in Alzheimer's disease. *J Mol Neurosci* 40, 221-9 (2010)

50. L. Ke, C.M. Eisenhour, M. Bencherif, R.J. Lukas: Effects of chronic nicotine treatment on expression of diverse nicotinic acetylcholine receptor subtypes. I. Dose- and time-dependent effects of nicotine treatment. *J Pharmacol Exp Ther* 286, 825-40 (1998)

51. K.J. Kellar, P.J. Whitehouse, A.M. Martino-Barrows, K. Marcus, D.L. Price: Muscarinic and nicotinic cholinergic binding sites in Alzheimer's disease cerebral cortex. *Brain Res* 436, 62-8 (1987)

52. T. Kihara, S. Shimohama, Nicotinic agonists protect neurons from glutamate and □-amyloid neurotoxicity. Springer Publishing, New York, 217-222 (2000)

53. T. Kihara, S. Shimohama, A. Akaike: Effects of nicotinic receptor agonists on beta-amyloid beta-sheet formation. *Jpn J Pharmacol* 79, 393-6 (1999)

54. T. Kihara, S. Shimohama, H. Sawada, J. Kimura, T. Kume, H. Kochiyama, T. Maeda, A. Akaike: Nicotinic receptor stimulation protects neurons against beta-amyloid toxicity. *Ann Neurol* 42, 159-63 (1997)

55. T. Kihara, S. Shimohama, S. Sawada, *et al*: Neuroprotective effect of nicotine against beta amyloid

cytotoxicity. *Neurobiology of Aging* 17, S429 (1996)

56. T. Kihara, S. Shimohama, M. Urushitani, H. Sawada, J. Kimura, T. Kume, T. Maeda, A. Akaike: Stimulation of alpha4beta2 nicotinic acetylcholine receptors inhibits beta-amyloid toxicity, *Brain Res* 792, 331-4 (1998)

57. S.H. Kim, Y.K. Kim, S.J. Jeong, C. Haass, Y.H. Kim, Y.H. Suh: Enhanced release of secreted form of Alzheimer's amyloid precursor protein from PC12 cells by nicotine. *Mol Pharmacol* 52, 430-6 (1997)

58. W.A. Kukull: The association between smoking and Alzheimer's disease: effects of study design and bias. *Biol Psychiatry* 49, 194-9 (2001)

59. P.A. Lapchak, D.M. Araujo, R. Quirion, B. Collier: Effect of chronic nicotine treatment on nicotinic autoreceptor function and N- (3H)methylcarbamylcholine binding sites in the rat brain. *J Neurochem* 52, 483-91 (1989)

60. E.P. Lapin, H.S. Maker, H. Sershen, A. Lajtha: Action of nicotine on accumbens dopamine and attenuation with repeated administration. *Eur J Pharmacol* 160, 53-9 (1989)

61. L.J. Launer, Andersen K., M.E. Dewey, L. Letenneur, A. Ott, L.A. Amaducci, C. Brayne, J.R. Copeland, J.F. Dartigues, P. Kragh-Sorensen, A. Lobo, J.M. Martinez-Lage, T. Stijnen, A. Hofman: Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. *Neurology* 52, 78-84 (1999)

62. D. Leibovici, K. Ritchie, B. Ledesert, J. Touchon: The effects of wine and tobacco consumption on cognitive performance in the elderly: a longitudinal study of relative risk. *Int J Epidemiol* 28, 77-81 (1999)

63. E. Levin, C. Conners, D. Silva, S.C. Hinton, W.H. Meck, J. March, J.E. Rose: Transdermal nicotine effects on attention. *Psychopharmacology* 140, 135-141 (1998)

64. W. Linert, M.H. Bridge, M. Huber, K.B. Bjugstad, S. Grossman, G.W. Arendash: *In vitro* and *in vivo* studies investigating possible antioxidant actions of nicotine: relevance to Parkinson's and Alzheimer's diseases. *Biochim Biophys Acta* 1454, 143-52 (1999)

65. Q. Liu, Y. Huang, F. Xue, A. Simard, J. DeChon, G. Li, J. Zhang, L. Lucero, M. Wang, M. Sierks, G. Hu, Y. Chang, R.J. Lukas, J. Wu: A novel nicotinic acetylcholine receptor subtype in basal forebrain cholinergic neurons with high sensitivity to amyloid peptides. *J Neurosci* 29, 918-29 (2009)

66. Q. Liu, H. Kawai, D.K. Berg: beta -Amyloid peptide blocks the response of alpha 7-containing nicotinic receptors on hippocampal neurons. *Proc Natl Acad Sci U S A* 98, 4734-9 (2001)

67. Q. Liu, J. Zhang, H. Zhu, C. Qin,, Q. Chen, B. Zhao: Dissecting the signaling pathway of nicotine-mediated neuroprotection in a mouse Alzheimer disease model. *FASEB*, 21, 61-73 (2007)

68. J.A. Luchsinger, C. Reitz, L.S. Honig, M.X. Tang, S. Shea, R. Mayeux: Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 65, 545-51 (2005)

69. R. Lukas, L. Ke, M. Bencheirf, C. Eisenhoukr: Regulation by nicotine by its own receptors. *Drug Dev Res* 38, 136-148 (1996)

70. R. Lukas: Neuronal nicotinic acetylcholine receptors. Springer-Verlag, Berlin, and R.G. Landes Company, Georgetown, TX, 145-173 (1998)

71. A. Maelicke, M. Samochocki, R. Jostock, A. Fehrenbacher, J. Ludwig, E.X. Albuquerque, M. Zerlin: Allosteric sensitization of nicotinic receptors by galantamine, a new treatment strategy for Alzheimer's disease. *Biol Psychiatry* 49, 279-88 (2001)

72. J. Malysz, D.J. Anderson, J. Ji, W.H. Bunnelle, M. Haakerud, K. Thorin-Hagene, H. Ween, R. Helfrich, M. Hu, E. Gubbins, S. Gopalkrishnan, P.S. Puttfarcken, C. Briggs, J. Li, M.D. Meyer, T. Dyhring, P.K. Ahring, E.O. Nielsen, D. Peters, D.B. Timmermann, M. Gopalkrishnan: *In vitro* pharmacological characterization of a novel selective {alpha}7 neuronal nicotinic acetylcholine receptor agonist ABT-107. *J Pharmacol Exp Ther*, (2010)

73. J. Malysz, J.H. Grønlien, D.J. Anderson, M. Håkerud, K. Thorin-Hagene, H. Ween, C. Wetterstrand, C.A. Briggs, R. Faghih, W.H. Bunnelle, M. Gopalkrishnan: *In vitro* pharmacological characterization of a novel allosteric modulator of alpha 7 neuronal acetylcholine receptor, 4- (5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide (A-867744), exhibiting unique pharmacological profile. *J Pharmacol Exp Ther* 330, 257-67 (2009)

74. P. Marin, M. Maus, S. Desagher, J. Glowinski, J. Premont: Nicotine protects cultured striatal neurones against N-methyl-D- aspartate receptor-mediated neurotoxicity. *Neuroreport* 5, 1977-80 (1994)

75. M.J. Marks, S.R. Grady, A.C. Collins: Down-regulation of nicotinic receptor function after chronic nicotine infusion. *J Pharmacol Exp Ther* 266, 1268-76 (1993)

76. M.J. Marks, S.R. Grady, J.M. Yang, P.M. Lippiello, A.C. Collins: Desensitization of nicotine-stimulated 86Rb+ efflux from mouse brain synaptosomes. *J Neurochem* 63, 2125-35 (1994)

77. C.M. Martin-Ruiz, J.A. Court, E. Molnar, M. Lee, C. Gotti, A. Mamalaki, T. Tsouloufis, S. Tzartos, C. Ballard, R.H. Perry, E.K. Perry: Alpha4 but not alpha3 and alpha7 nicotinic acetylcholine receptor subunits are lost from the temporal cortex in Alzheimer's disease. *J Neurochem* 73, 1635-40 (1999)

78. C. Merchant, M.X. Tang, S. Albert, J. Manly, Y. Stern, R. Mayeux: The influence of smoking on the risk of Alzheimer's disease. *Neurology* 52, 1408-12 (1999)

79. E.M. Mitsis, K.M. Reech, F. Bois, G.D. Tamagnan, M.G. MacAvoy, J.P. Seibyl, J.K. Staley, C.H. van Dyck: ^{123}I-5IA-85380 SPECT imaging of nicotinic receptors in Alzheimer's disease and mild cognitive impairment. *Journal of Nuclear Medicine* 50, 1455-63 (2009)

80. D.M. Morens, A. Grandinetti, D. Reed, L.R. White: Smoking-associated protection from Alzheimer's and Parkinson's disease. *Lancet* 343, 356-7 (1994)

81. D.M. Morens, A. Grandinetti, D. Reed, L.R. White, G.W: Ross, Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue?. *Neurology* 45, 1041-51 (1995)

82. P.A. Newhouse, J.R. Hughes: The role of nicotine and nicotinic mechanisms in neuropsychiatric disease. *Br J Addict* 86, 521-526 (1991)

83. A. Nordberg: Human nicotinic receptors--their role in aging and dementia. *Neurochem Int* 25, 93-7 (1994)

84. A. Nordberg: Neuroreceptor changes in Alzheimer disease. *Cerebrovasc Brain Metab Rev* 4, 303-28 (1992)

85. A. Nordberg: Nicotinic receptor abnormalities of Alzheimer's disease: therapeutic implications. *Biol Psychiatry* 49, 200-10 (2001)

86. A. Nordberg, I. Alafuzoff, B. Winblad: Nicotinic and muscarinic subtypes in the human brain: changes with aging and dementia. *J Neurosci Res* 31, 103-11 (1986)

87. A. Nordberg, B. Winblad: Reduced number of (3H)nicotoine and (3H)acetylcholine binding sites in the frontal cortex of Alzheimer brains. *Neurosci Lett 2* 1, 115-119 (1986)

88. J.T. O'Brien, S.J. Colloboy, S. Pakrasi, E.K. Perry, S.L. Pimiott, D.J. Wyper, I.G. McKeith, E.D. Williams: Alpha4beta2 nicotinic receptor status in Alzheimer's disease using ^{123}I-5IA-85380 single-photon-emission computed tomography. *J Neurol Neurosurg Psychiatry* 78, 356-62 (2007)

89. A. Ott, A.J. Slooter, A. Hofman, F. van Harskamp, J.C. Witteman, C. Van Broeckhoven, C.M. van Duijn, M.M. Breteler: Smoking and risk of dementia and Alzheimer's disease in a population- based cohort study: the Rotterdam Study. *Lancet* 351, 1840-3 (1998)

90. J.R. Pauly: Nicotinic Cholinergic Receptor Deficits in Alzheimer's Disease: Where's the smoke?. *J Alz Dis* 1, 221-230 (1999)

91. J.H. Peng, L. Lucero, J. Fryer, J. Herl, S.S. Leonard, R.J. Lukas: Inducible, heterologous expression of human alpha7-nicotinic acetylcholine receptors in a native nicotinic receptor-null human clonal line. *Brain Res* 825, 172-9 (1999)

92. X. Peng, V. Gerzanich, R. Anand, P.J. Whiting, J. Lindstrom: Nicotine-induced increase in neuronal nicotinic receptors results from a decrease in the rate of receptor turnover. *Mol Pharmacol* 46, 523-30 (1994)

93. E. Perry, C. Martin-Ruiz, M. Lee, M. Griffiths, M. Johnson, M. Piggott, V. Haroutunian, J.D. Buxbaum, J. Nasland, K. Davis, C Gotti, F. Clementi, S, Tzartos, O. Cohen, H. Soreq, E. Jaros, R. Perry, C. Ballard, I. McKeith, J. Court: Nicotinic receptor subtypes in human brain aging, Alzheimer and Lewy body diseases. *Eur J Pharmacol* 393, 215-22 (2000)

94. E.K. Perry, J.A. Court, S. Lloyd, M. Johnson, M.H. Griffiths, D. Spurden, M.A. Piggott, J. Turner, R.H. Perry: Beta-amyloidosis in normal aging and transmitter signaling in human temporal lobe. *Ann N Y Acad Sci* 777, 388-92 (1996)

95. E.K. Perry, C.M. Morris, J.A. Court, A. Cheng, A.F. Fairbairn, I.G. McKeith, D. Irving, A. Brown, R.H. Perry: Alteration in nicotine binding sites in Parkinson's disease, Lewy body dementia and Alzheimer's disease: possible index of early neuropathology. *Neuroscience* 64, 385-95 (1995)

96. E.K. Perry, C.J. Smith, J.A. Court, R.H. Perry: Cholinergic nicotinic and muscarinic receptors in dementia of Alzheimer, Parkinson and Lewy body types. *J Neural Transm Park Dis Dement Sect* 2, 149-58 (1990)

97. R. Peters, R. Poulter, J. Warner, N. Beckett, L. Burch, C. Bulpitt: Smoking, dementia, and cognitive decline in the elderly, a systematic review. *BMC Geriatr* 8, (2008).

98. D.L. Pettit, Z. Shao, J.L. Yakel: Beta-Amyloid (1-42) peptide directly modulates nicotinic receptors in the rat hippocampal slice. *J Neurosci* 21, RC120 (2001)

99. Potter, J. Corwin, J. Lang, M. Piasecki, R. Lenox, P.A. Newhouse: Acute effects of the selective cholinergic channel activator (nicotinic agonist) ABT-418 in Alzheimer's disease. *Psychopharmacology (Berl)* 142, 334-42 (1999)

100. M. Prince, M. Cullen, A. Mann: Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. *Neurology* 44, 97-104 (1994)

101. R.T. Reid, M.N. Sabbagh, L.J. Thal: Does apolipoprotein E (Apo-E) genotype influence nicotinic receptor binding in Alzheimer's disease. *J Neural Transm* 108, 1043-50 (2001)

102. R. Reid, M. Sabbagh, J. Corey-Bloom, P. Tiraboschi, L. Thal: Nicotinic receptor in dementia with Lewy Bodies: comparisons with Alzheimer's disease. 741-446 (2000)

103. R. Reitstetter, R.J. Lukas, R. Gruener: Dependence of nicotinic acetylcholine receptor recovery from desensitization on the duration of agonist exposure. *J Pharmacol Exp Ther* 289, 656-60 (1999)

104. Reitz, T. den Heijer, C. van Dujin, A. Hofman, M.M. Breteler: Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. *Neurology* 69, 998-1005 (2007)

105. J.E. Riggs: The influence of smoking on the risk of Alzheimer's disease. *Neurology* 54, 777-8 (2000)

106. J.O. Rinne, T. Myllykyla, P. Lonnberg, P. Marjamaki: A postmortem study of brain nicotinic receptors in Parkinson's and Alzheimer's disease. *Brain Res* 547, 167-70 (1991)

107. S.W. Rogers, L.C. Gahring, A.C. Collins, M. Marks: Age-related changes in neuronal nicotinic acetylcholine receptor subunit alpha4 expression are modified by long-term nicotine administration. *J Neurosci* 18, 4825-32 (1998)

108. R. Roncarati, C. Scali, T.A. Comery, S.M. Grauer, S. Aschmi, H. Bothmann, B. Jow, D. Kowal, M. Gianfriddo, C. Kelley, U. Zanelli, C. Ghiron, S. Haydar, J. Dunlop, G.C. Terstappen: Procognitive and neuroprotective activity of novel alpha7 nicotinic acetylcholine receptor agonist for treatment of neurodegenerative and cognitive disorder. *J Pharmacol Exp Ther*, 329¸ 459-68 (2009)

109. M.N. Sabbagh, R.T. Reid, J. Corey-Bloom, T.S. Rao, L.A. Hansen, M. Alford, E. Masliah, A. Adem, G.K. Lloyd, L.J. Thal: Correlation of nicotinic binding with neurochemical markers in Alzheimer's disease. *J Neural Transm* 105, 709-17 (1998)

110. M.N. Sabbagh, R.T. Reid, L.A. Hansen, M. Alford, L.J. Thal: Correlation of nicotinic receptor binding with clinical and neuropathological changes in Alzheimer's disease and dementia with Lewy bodies. *J Neural Transm* 108, 1149-57 (2001)

111. M.N. Sabbagh, S.L. Tyas, S.C. Emery, L.A. Hansen, M.F. Alford, R.T. Reid, P. Tiraboschi, L.J. Thal: Smoking affects the phenotype of Alzheimer's disease. *Neurology* 64, 1301-3 (2005)

112. B. Sahakian, G. Jones, R. Levy, J. Gray, D. Warburton: The effects of nicotine on attention, information processing, and short- term memory in patients with dementia of the Alzheimer type. *Br J Psychiatry* 154, 797-800 (1989)

113. A.R. Salomon, K.J. Marcinowski, R.P. Friedland, M.G. Zagorski: Nicotine inhibits amyloid formation by the beta-peptide. *Biochemistry* 35, 13568-78 (1996)

114. H. Schroder, E. Giacobini, R.G. Struble, K. Zilles, A. Maelicke: Nicotinic cholinoceptive neurons of the frontal cortex are reduced in Alzheimer's disease. *Neurobiol Aging* 12, 259-62 (1991)

115. H. Schroder, E. Giacobini, R.G. Struble, K. Zilles, A. Maelicke, P.G. Luiten, A.D. Strosberg: Cellular distribution and expression of cortical acetylcholine receptors in aging and Alzheimer's disease. *Ann N Y Acad Sci* 640, 189-92 (1991)

116. J. Semba, R. Miyoshi, S. Kito: Nicotine protects against the dexamethasone potentiation of kainic acid-induced neurotoxicity in cultured hippocampal neurons. *Brain Res* 735, 335-8 (1996)

117. B.M. Sharp, H.S. Beyer: Rapid desensitization of the acute stimulatory effects of nicotine on rat plasma adrenocorticotropin and prolactin. *J Pharmacol Exp Ther* 238, 486-91 (1986)

118. B.M. Sharp, H.S. Beyer, A.S. Levine, J.E. Morley, K.M. McAllen: Attenuation of the plasma prolactin response to restraint stress after acute and chronic administration of nicotine to rats. *J Pharmacol Exp Ther* 241, 438-42 (1987)

119. S. Shimohama: Nicotine agonists prevent neuronal cell death by glutamate and amyloid beta protein: *Neurobiology of aging* 17, S40 (1996)

120. S. Shimohama: Nicotinic receptor-mediated neuroprotection in neurodegenerative disease models. *Biol Pharm Bull*, 32, 332-6 (2009)

121. S. Shimohama, A. Akaike, J. Kimura: Nicotine-induced protection against glutamate cytotoxicity. Nicotinic cholinergic receptor-mediated inhibition of nitric oxide formation. *Ann N Y Acad Sci* 777, 356-61 (1996)

122. H.N. Siegel, R.J. Lukas: Nicotinic agonists regulate alpha-bungarotoxin binding sites of TE671 human medulloblastoma cells. *J Neurochem* 50, 1272-8 (1988)

123. I.N. Singh, G. Sorrentino, D.S. Sitar, J.N. Kanfer: (-)Nicotine inhibits the activation of phospholipases A2 and D by amyloid beta peptide. *Brain Res* 800, 275-81 (1998)

124. D.L. Sparks, T.G. Beach, R.J. Lukas: Immunohistochemical localization of nicotinic beta2 and alpha4 receptor subunits in normal human brain and individuals with Lewy body and Alzheimer's disease: preliminary observations. *Neurosci Lett* 256, 151-4 (1998)

125. K. Sugaya, E. Giacobini, V.A. Chiappinelli: Nicotinic acetylcholine receptor subtypes in human frontal cortex: changes in Alzheimer's disease. *J Neurosci Res* 27, 349-59 (1990)

126. Svensson, U. Warpmen, E. Hellstrom-Lindahl, N. Bogdanovic, L. Lannfelt, A. Nordberg: Nicotinic

receptors, muscarinic receptors and choline acetyltransferase activity in the temporal cortex of Alzheimer patient with differing apoliproprotein genotypes. *Neurosci Lett* 232, 37-40 (1997)

127. G.E. Swan, C.N. Lessov-Schlaggar: The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol Rev* 17, 259-73 (2007)

128. R.D. Terry, E. Masliah, D.P. Salmon, N. Butters, R. DeTeresa, R. Hill, L.A. Hansen, R. Katzman: Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann.Neurol* 30, 572-580 (1991)

129. J. Toyohara, K. Ishiwata, M. Sakata, J. Wu, S. Nishiyama, H. Tsukada, K. Hashimoto: *In vivo* evaluation of alpha7 nicotinic acetylcholine receptor agonists (11C)A-582941 and (11C)A-844606 in mice and conscious monkeys. *PLoS One* 5, e8961 (2010)

130. Tsuang, E.B. Larson, G. Li, J.B. Shofer, K.S. Montine, M.L. Thompson, J.A. Sonnen, P.K Crane, J.B. Leverenz, T.J. Montine: Association between lifetime cigarette smoking and lewy body accumulation. *Brain Pathol* 20, 412-8 (2010)

131. S.L. Tyas, J.J. Koval, L.L. Pederson: Does an interaction between smoking and drinking influence the risk of Alzheimer's disease? Results from three Canadian data sets. *Stat Med* 19, 1685-96 (2000)

132. S.L. Tyas, J. Manfreda, L.A. Strain, P.R. Montgomery: Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. *International Journal of Epidemiology* 30, 590-597 (2001)

133. J. Ulrich, G. Johannson-Locher, W.O. Seiler, H.B. Stahelin: Does smoking protect from Alzheimer's disease? Alzheimer-type changes in 301 unselected brains from patients with known smoking history. *Acta Neuropathol (Berl)* 94, 450-4 (1997)

134. C.M. van Duijn, L.M. Havekes, C. Van Broeckhoven, P. de Knijff, A. Hofman: Apolipoprotein E genotype and association between smoking and early ons*et al*zheimer's disease. *BMJ* 310, 627-31 (1995)

135. C.M. van Duijn, A. Hofman: Relation between nicotine intake and Alzheimer's disease. *BMJ* 302, 1491-4 (1991)

136. H.X. Wang, L. Fratiglioni, G.B. Frisoni, M. Viitanen, B. Winblad: Smoking and the occurrence of Alzheimer's disease: cross-sectional and longitudinal data in a population-based study. *Am J Epidemiol* 149, 640-4 (1999)

137. H.Y. Wang, K. Bakshi, C. Shen, M. Frankfurt, C. Trocmé-Thibierge, P. Morain: S 24795 limits beta-amyloid-alpha7 nicotinic receptor interaction and reduces Alzheimer's disease-like pathologies. *Biol Psychiatry* 67, 522-30 (2010)

138. H.Y. Wang, D.H. Lee, M.R. D'Andrea, P.A. Peterson, R.P. Shank, A.B. Reitz: Beta-Amyloid (1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. *J Biol Chem* 275, 5626-32 (2000)

139. H.Y. Wang, A. Stucky, J. Liu, C. Shen, C. Trocme-Thibierge, P. Morain: Dissociating beta-amyloid from alpha 7 nicotinic acetylcholine receptor by a novel therapeutic agent, S 24795, normalizes alpha 7 nicotinic acetylcholine and NMDA receptor function in Alzheimer's disease brain. *J Neurosci* 29, 10961-73 (2009)

140. U. Warpman, A. Nordberg: Epibatidine and ABT 418 reveal selective losses of alpha 4 beta 2 nicotinic receptors in Alzheimer brains. *Neuroreport* 6, 2419-23 (1995)

141. A. Wevers, H. Schroder: Nicotinic Acetylcholine Receptors in Alzheimer's Disease. *J Alz Dis* 1, 207-219 (1999)

142. H.K. White, E.D. Levin: Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology (Berl)* 143, 158-65 (1999)

143. P.J. Whitehouse, R.N. Kalaria: Nicotinic receptors and neurodegenerative dementing diseases: basic research and clinical implications. *Alzheimer Dis Assoc Disord* 9 Suppl 2, 3-5 (1995)

144. A.L. Wilson, L.K. Langley, J. Monley, T. Bauer, S. Rottunda, E. McFalls, C. Kovera, J.R. McCarten: Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 51, 509-14 (1995)

145. S. Wonnacott: The paradox of nicotine acetylcholine recetpor upregulation by nicotine. *Trends Phar Sci* 11, 216-219 (1990)

146. M.R. Zamani, Y.S. Allen, G.P. Owen, J.A. Gray: Nicotine modulates the neurotoxic effect of beta-amyloid protein (25- 35)) in hippocampal cultures. *Neuroreport* 8, 513-7 (1997)

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