Review Article

Brain Imaging of Nicotinic Receptors in Alzheimer's Disease

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Neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels which are widely distributed in the human brain. Several lines of evidence suggest that two major subtypes ($\alpha4\beta2$ and $\alpha7$) of nAChRs play an important role in the pathophysiology of Alzheimer's disease (AD). Postmortem studies demonstrated alterations in the density of these subtypes of nAChRs in the brain of patients with AD. Currently, nAChRs are one of the most attractive therapeutic targets for AD. Therefore, several researchers have made an effort to develop novel radioligands that can be used to study quantitatively the distribution of these two subtypes in the human brain with positron emission tomography (PET) and single-photon emission computed tomography (SPECT). In this paper, we discuss the current topics on *in vivo* imaging of two subtypes of nAChRs in the brain of patients with AD.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the elderly and has become a major worldwide health problem. Several reports indicated that it is affecting almost 1 in 10 individuals over the age of 65 [1], and as life expectancy increases, over 37 million people suffer with AD, and it is projected to quadruple by 2050 [2]. AD accounts for over 50% of senile dementia and the majority of presenile dementia cases and is characterized by progressive deterioration of higher cognitive functions including the loss of memory [3, 4].

van Duijn and Hofman [5] reported the inverse relationship between smoking history and early onset AD, suggesting that smoking may protect against AD [6]. Furthermore, Rusted and Trawley [7] reported acute improvements in prospective memory following nicotine administration. Although Swan and Lessov-Schlaggar [8] discuss the effects of tobacco smoke and nicotine on cognition in their review, smoking is associated with increased risk for negative preclinical and cognitive outcomes in younger people as well as in older adults. More recently, a meta-analysis including longitudinal studies published between 1995 and 2007 reported that current smokers relative to never-smokers were at increased risk of AD, vascular dementia, any dementia, and cognitive decline, in over the age of 65 [9]. Several lines of evidence demonstrated that smoking almost doubled the risk of AD and that smoking cessation might contribute to a reduction of risk factors for AD and cardiovascular disease [10, 11]. Noteworthy, the later is also known as a risk factor for AD. These results suggest that smoking cessation may play an important role in not only primary but also secondary prevention of AD. In contrast, although the discussion about neuroprotection by smoking has been continued, it is possible that nicotinic acetylcholine receptors (nAChRs) in the brain might play a role in the pathophysiology of AD.

The nAChRs are one of the main classes of AChRs, which have a pentameric structure composed of five membrane spanning subunits, of which nine different types have thus far been identified and cloned. To date, twelve neuronal nAChR subunits have been described [12]; nine ($\alpha2$–$\alpha10$) code for subunits [12] based on the presence of adjacent cysteine residues in the predicted protein sequences, in a region homologous to the putative agonist-binding site of the muscle, a subunit ($\alpha1$) and three referred to as non-α or β-subunits ($\beta2$–$\beta4$). Among the several nAChR subtypes in the human central nervous system (CNS), the heteromeric $\alpha4\beta2$ and homomeric $\alpha7$ subtypes (Figure 1) are predominant in the brain [13, 14]. It has been reported that other subtypes (e.g., $\alpha3$, $\alpha6$) exist in the brain [15, 16] and that $\alpha6$ subtype
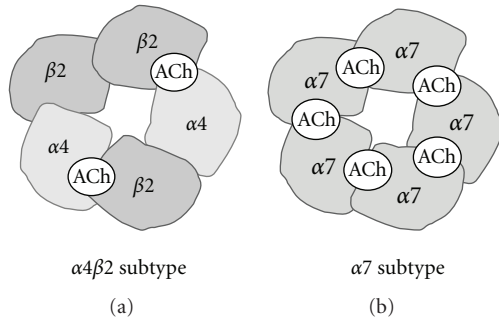
FIGURE 1: Structures of $\alpha 4\beta 2$ nAChR (a) and $\alpha 7$ nAChR (b).

might be mainly involved in the pathophysiology of Parkinson's disease [16]. Furthermore, studies using postmortem human brain samples have demonstrated alterations in the levels of $\alpha 4$ and $\alpha 7$ nAChR in the brains of patients with AD [15, 17–19]. Despite its lower number, loss of $\alpha 3$ subtype consistent with $\alpha 4$ and $\alpha 7$ nAChR subtypes was also observed in the brains of patients with AD [15]. Taken together, it is likely that these two subtypes ($\alpha 4\beta 2$ and $\alpha 7$) of nAChR might play a role in the pathogenesis of AD. Therefore, it is of great interest to examine whether these two subtypes of nAChR are altered in the living brain of patients with AD using brain imaging techniques.

In this paper, we discuss the recent findings on imaging of these two nAChRs ($\alpha 4\beta 2$ and $\alpha 7$) in the brain with AD using positron emission tomography (PET) and single-photon emission computed tomography (SPECT).

2. $\alpha 4\beta 2$ nAChRs Subtype

2.1. Relationship between Amyloid-β and $\alpha 4\beta 2$ nAChR. Amyloid β protein (Aβ) is a major constituent of senile plaques and one of the candidates for the cause of the neurodegeneration found in AD. It has been shown that the accumulation of Aβ precedes other pathological changes and causes neurodegeneration or neuronal death *in vitro and in vivo* [20, 21]. The loss of memory seen in AD is thought to be associated with Aβ-induced impairment of synaptic plasticity such as long-term potentiation (LTP) in the hippocampus. There are lines of evidence suggesting that nAChR activation provides protection against Aβ-induced neurotoxicity in cultured cortical neurons [22, 23]. These results indicated that nicotine protects against Aβ-induced neuronal death, and similar effect has been also observed in those selective $\alpha 4\beta 2$ nAChR agonists such as cytosine and epibatidine, but this neuroprotection is blocked by the selective $\alpha 4\beta 2$ nAChR antagonist dihydro-β-erythroidine (DHβE). Moreover, recently, Wu et al. [24] investigated a possible role of $\alpha 4\beta 2$ nAChR in mediating the impairment of long-term potentiation (LTP) by various forms of Aβ in *in vivo*. They reported that intracerebroventricular injection of Aβ_{40}, Aβ_{25--35}, or Aβ_{31--35} significantly suppressed high-frequency stimulation-induced LTP. Similarly, epibatidine dose dependently suppressed the induction of LTP. Whereas DHβE showed no effect on the induction of LTP, it significantly reversed Aβ_{31--35}-induced LTP impairment.

These findings suggest that $\alpha 4\beta 2$ nAChR, which can be directly activated by Aβ, is required for Aβ suppression of LTP *in vivo*. The mechanisms by which nicotine enhanced the inhibition of LTP by Aβ were not clear. A possible explanation is that nicotine could activate nAChRs present in inhibitory interneurons, thereby potentiating inhibitory inputs to hippocampal neurons.

2.2. Cognition and $\alpha 4\beta 2$ nAChR Agonists. It is likely that reduced density of nAChR is related to dementia severity, assessed using a global rating. Nicotine has been postulated to be a possible treatment for AD, improving cognition in humans [25]. Recently, Loughead et al. [26] reported novel evidence that the $\alpha 4\beta 2$ partial agonist varenicline increased working memory-related brain activity after 3 days of nicotine abstinence, particularly at high levels of task difficulty, with associated improvements in cognitive performance among highly dependent smokers.

2.3. Postmortem Studies of $\alpha 4\beta 2$ nAChR in the Brain of Patients with AD. Not only transmitter release but also receptor-binding sites may be altered in the brain of AD patients [27–29]. Postmortem studies showed the reduction (up to 50%) of $\alpha 4\beta 2$ subtype of nAChRs in brain of patients with AD [30], and it may occur very early in the course of AD [31]. Both $\alpha 4$ and $\alpha 7$ subunits are known to be important constituents in $\alpha 4\beta 2$ and $\alpha 7$ receptor subtypes, respectively. Investigation using the autopsy samples of human cerebral cortex has clearly shown that these two subtypes ($\alpha 4$ and $\alpha 7$ isoforms) are significantly decreased in their protein amount in the cortices of AD patients [15, 19, 32].

2.4. Imaging of $\alpha 4\beta 2$ nAChR Subtype. Considering the role of $\alpha 4\beta 2$ nAChR in the pathophysiology of AD, it is of great interest to study $\alpha 4\beta 2$ nAChR in the living human brain using PET/SPECT. Much effort has been devoted to visualize $\alpha 4\beta 2$ nAChR in the brain by PET/SPECT. Currently, two PET ligands, including [^{11}C]nicotine and 2-[^{18}F]fluoro-3-(2 (*S*)azetidinylmethoxy)pyridine (2-[^{18}F]F-A-85380), and a SPECT ligand, 5-[^{123}I]iodo-3-(2 (*S*)-2-azetidinylmethoxy)pyridine (5-[^{123}I]I-A-85380), (Figure 2) for *in vivo* imaging of $\alpha 4\beta 2$ nAChR in the human brain have been used in clinical studies [33–35].

2.5. [^{11}C]Nicotine. The development of radiolabelled nicotine [36, 37] has allowed for evaluating the uptake and distribution of nAChR in the living human brain [38–40]. The data obtained by [^{11}C]nicotine is generally consistent with the known pattern of nAChR measured by *in vitro* binding in autopsy brain tissue [39]. [^{11}C]nicotine-PET has been used to study $\alpha 4\beta 2$ nAChR in human brain, and a severe loss of the nAChR has been detected in the brain of patients with AD [13]. Cortical nAChRs in mild AD patients are robustly associated with the cognitive function of attention [35] and have revealed a significant negative correlation between severity of cognitive impairment and density of brain nAChR [40]. It will be, therefore, of interest to study an alteration in $\alpha 4\beta 2$ nAChR at a presymptomatic stage of AD. Furthermore, the *in vivo* cortical AChE inhibition and
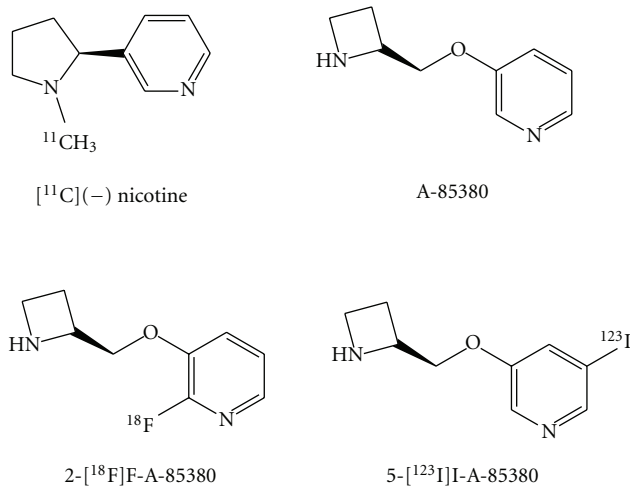
FIGURE 2: Chemical structures of radioligands for nAChRs.

[^{11}C]($-$) nicotine

A-85380

2-[^{18}F]F-A-85380

5-[^{123}I]I-A-85380
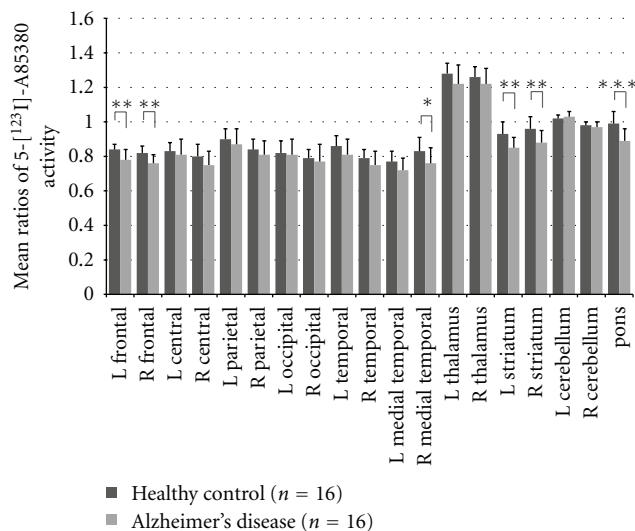

■ Healthy control ($n = 16$)
■ Alzheimer's disease ($n = 16$)

FIGURE 3: Comparison with regional uptake values of 5-[^{123}I]I-A85380 in age-matched healthy control and patients with Alzheimer's disease. Significant bilateral reductions in nicotinic receptor binding were identified in frontal, striatal, right medial temporal, and pons in patients with AD compared to controls. (Data is from the paper of O'Brien et al. [59].) *$P < .05$, **$P < .005$, ***$P < .001$.

[^{11}C]nicotine binding were associated with changes in the attention domain of cognition rather than episodic memory when administering galantamine [41]. Thus, [^{11}C]nicotine-PET may be also used for monitoring treatment efficacy in AD patients [41, 42].

Unfortunately, [^{11}C]nicotine displays high levels of non-specific binding, rapid metabolism, and rapid washout of the brain [43]. The heterogeneity of [^{11}C]nicotine binding in the brain also precludes the identification of a reference region which may be used to accurately determine nonspecific binding. Taken together, it is unlikely that [^{11}C]nicotine might be a suitable PET ligand for *in vivo* imaging of $\alpha 4\beta 2$ nAChR in human brain.

2.6. 2-[^{18}F]F-A-85380 and 5-[^{123}I]I-A-85380. A-85380 [3-(2(S)-azetidinylmethoxy) pyridine] is a potent and selective agonist with high affinity for $\alpha 4\beta 2$ nAChR subtype and low affinity for other nAChR subtypes [44]. A-85380 is effective in a wide range of preclinical models of CNS disorders [45, 46]. Recently, A-85380 was successfully labeled using ^{18}F or $^{125/123}$I with a high affinity ($K_i = 50$ pM for F and $K_i = 15$ pM for I) for $\alpha 4\beta 2$ nAChR [44, 47, 48]. These radioligands have been evaluated *in vitro* and *in vivo* as PET/SPECT radioligands to visualize $\alpha 4\beta 2$ nAChR subtype in the brain [49, 50]. In healthy nonsmoking human brain, both 2-[^{18}F]F-A85380 and 5-[^{123}I]I-A-85380 have revealed a pattern of highest uptake in the thalamus, intermediate in the midbrain, pons, cerebellum, and cortex, and lowest in white matter [50–52], which is consistent with the regional distribution of $\alpha 4\beta 2$ nAChR.

Furthermore, a study of age-related decline in nicotinic receptor availability showed that regional $\beta 2$ nAChR availability were inversely correlated with decline ranging from 32% (thalamus) to 18% (occipital cortex) over the adult lifespan, or up to 5% per decade [53]. These results may corroborate postmortem reports of decline in high-affinity nicotine binding with age and may aid in elucidating the role of $\beta 2$-nAChR in cognitive aging. In addition, 2-[^{18}F]F-A-85380 or 5-[^{123}I]I-A-85380 have been used to evaluate the effect of smoking on occupancy of $\alpha 4\beta 2$ nAChR [54,

55]. Smoking 0.13 (1 to 2 puffs) of a cigarette resulted in 50% occupancy of $\alpha 4\beta 2$ nAChR for 3.1 hours after smoking. Smoking a full cigarette (or more) resulted in more than 88% receptor occupancy and was accompanied by a reduction in cigarette craving. The extent of receptor occupancy found herein suggests that smoking may lead to withdrawal alleviation by maintaining nAChR in the desensitized state.

Both 2-[^{18}F]F-A-85380 and 5-[^{123}I]I-A-85380 have been used in AD patients [51, 56–60]. In 17 patients with moderate to severe AD and 6 subjects with amnestic mild cognitive impairment (MCI) compared with 10 healthy control subjects, Sabri et al. [56] found significant reductions of $\alpha 4\beta 2$ nAChR in brain regions (hippocampus, caudate, frontal cortex, temporal cortex, posterior cingulate, anterior cingulate, and parietal cortex) in the brain of AD by using 2-[^{18}F]F-A-85380. Most recently, Kendziorra et al. [57] reported that both patients with AD and those with MCI showed a significant reduction in 2-[^{18}F]F-A-85380 binding potential in typical AD-affected brain regions and that the 2-[^{18}F]F-A-85380 binding potential correlated with the severity of cognitive impairment. In addition, only MCI patients who converted to AD in the later course ($n = 5$) had a reduction in 2-[^{18}F]F-A-85380 binding potential. Thus, it is likely that 2-[^{18}F]F-A-85380 PET might give prognostic information about a conversion from MCI to AD. Similar findings were also reported by 5-[^{123}I]I-A-85380, showing significant reductions in the activity ratios of the region of interest to cerebellum in the frontal, striatal, right medial temporal, and pontine regions in 16 patients with AD compared with 16 healthy control subjects [59] (Figure 3). These findings suggest that a reduction in $\alpha 4\beta 2$ nAChR

occurs during symptomatic stages of AD and that the $\alpha4\beta2$ nAChR availability in these regions correlated with the severity of cognitive impairment. In contrast, there were no differences in distribution volume (DV) of nAChR between the healthy controls and early AD patients (Figure 4) [51, 58].

2-[^{18}F]F-A-85380 PET has been used to observe outcome of drug treatment for the improvements of cognition in patients with mild AD [61]. However, no significant correlations were found between cognitive measures and nAChR simplified DV (Figure 5). These results are similar to the results reported by Kadir et al. [41] in their studies using [^{11}C]nicotine. The relationship between cognition in AD and cholinergic dysfunction may be related to a number of factors, including the degree of cholinergic system (or receptor) loss, the other nAChR subtypes, or other neurochemical systems.

3. $\alpha7$ nAChR Subtype

3.1. Relationship between Aβ and $\alpha7$ nAChR.

Of the two major subtypes of nAChRs in the CNS, $\alpha7$ subtype has lower affinity for ACh compared to $\alpha4\beta2$ subtype [62]. Accumulating evidence suggests that $\alpha7$ nAChR plays a role in the pathophysiology of AD. Aβ has picomolar affinity for $\alpha7$ nAChR [63, 64], which results in the formation of Aβ-$\alpha7$ nAChR complex. This complex is known to move intracellularly and cause neurotoxicity [63–65]. Interestingly, this neurotoxicity is not present in transgenic mouse model of AD overexpressing a mutated form of the human amyloid precursor protein (APP) and lacking the $\alpha7$ nAChR [66]. Recently, Bencherif and Lippiello [67] pointed out that the $\alpha7$-JAK2-(NF-κB; STAT3)-Bcl2 prosurvival pathway is important for the neuroprotective role of $\alpha7$ nAChR (Figure 6). By blocking cytosolic cytochrome C, which is released from the mitochondria via Aβ_{1--42}, Bcl2 fully counteracts the Aβ_{1--42}-induced apoptosis of cells [68]. The fact that this antiapoptotic pathway is further related with ApoE4 [69], GSK-3β-activated tau phosphorylation [70], and Wnt signaling pathways [71] denotes the critical role of $\alpha7$ nAChR in pathophysiology of AD.

The 3xTg-AD mice [72], which are triple transgenic mice expressing APP, presinilin-1, and Tau, were shown to have an age-dependent reduction of $\alpha7$ nAChR. This reduction was limited to brain regions where intraneuronal Aβ_{42} accumulation occurred [73]. The early cognitive deficits of 3xTG-AD mice also correlate with intracellular Aβ accumulation, and the clearing of this Aβ accumulation by immunotherapy reverses the early cognitive impairment [74].

Tg2576 transgenic mice (APPswe) dramatically reduced Aβ plaque expression with chronic administration of nicotine for 5.5 months [75]. It is further reported that a 10-day administration of nicotine reduced the guanidinium-soluble Aβ levels by 46 to 66%, whereas the intracellular Aβ levels remained unchanged [76]. This treatment with nicotine also resulted in less glial fibrillary acidic protein- (GFAP-) immunoreactive astrocytes around the amyloid plaques and increased numbers of $\alpha7$ nAChR in the cortex of APPswe mice [76]. Bencherif [68] points out the importance of these
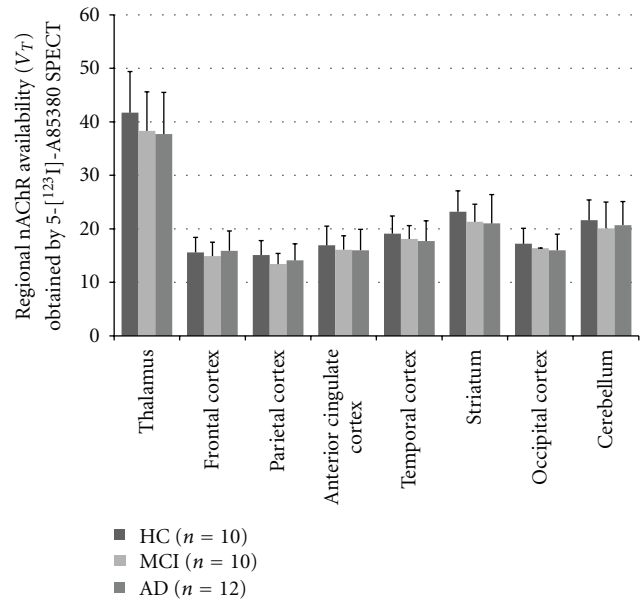

FIGURE 4: Regional $\alpha4\beta2$-nAChR availability (V_T) of 5-[^{123}I]I-A85380 in age-matched healthy control (HC), mild cognitive impairment (MCI), and Alzheimer's disease (AD) groups. No significant regional differences among the subject groups for any of the 8 regions, including the 4 neocortical regions, were identified. (Data is from the paper of Mitsis et al. [58].)

data, as reduction of Aβ with anti-Aβ antibody treatment is reported to rapidly recover the associated neuritic dystrophy in living animals [77].

Orr-Urtreger et al. [78] generated $\alpha7$ nAChR gene knockout (KO) mice, and the resulting $\alpha7$ nAChR KO mice did not show any morphological central nervous system abnormalities [78, 79], but behavioral tests point out some cognitive deficits in KO mice, such as impaired sustained attention [80, 81], impairment in working memory [82], and impairment in performance under high attentional demand [83]. The cognitive deficits seen in APP transgenic mice worsen when $\alpha7$ nAChR is absent at the same time [84]. These $\alpha7$ nAChR KO APP mice showed significant reduction in hippocampal and basal forebrain choline acetyltransferase activity and loss of hippocampal neurons and markers; stereological analyses indicated more pronounced loss of hippocampal pyramidal neurons and volume loss compared with APP mice [84]. Taken all together, it is likely that $\alpha7$ nAChR might play an important role in the process of Aβ disposition which was detected in the brain of patients with AD.

3.2. Cognition and $\alpha7$ nAChR Agonists.

A number of $\alpha7$ nAChR agonists are reported to improve recognition memory in rodents. These agonists include tropisetron [85], ABBF [86], AR-R 17779 [87], SSR180711 [88, 89], A-582941 [90], and SEN123333 [91]. In nonhuman primates, improvements in long-delay performance of delayed matching tasks are reported by $\alpha7$ nAChR agonists GTS-21 [92] and A-582941 [93].

It is reported that nicotine inhibits Aβ deposition and aggregation in the cortex and hippocampus of APP transgenic mice [94]. RNA interference experiments indicated
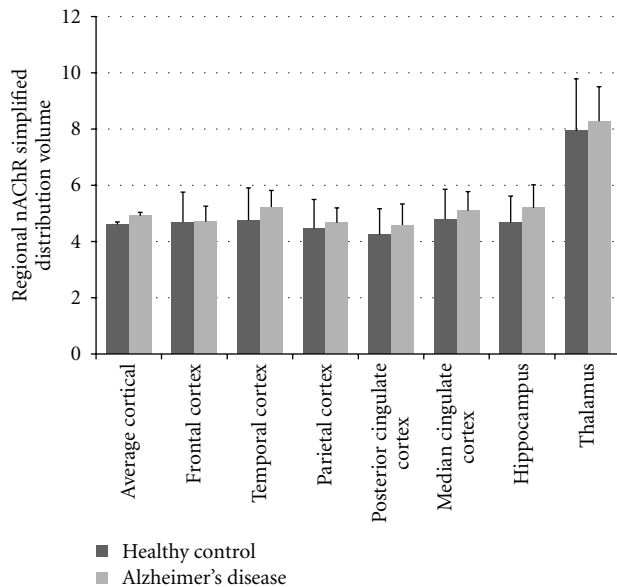
FIGURE 5: Regional nAChR simplified distribution volume (DV(s)) of 2-[^{18}F]F-A85380 in healthy control (HC) and Alzheimer's disease (AD) groups. No significant difference in nAChR DV(s) was found between both groups. (Data is from the paper of Ellis et al. [51].)

that these nicotine-mediated effects require $\alpha 7$ nAChR. In another study [70], the selective $\alpha 7$ nAChR agonist A-582941 led to increased phosphorylation of the inhibitory regulating amino acid residue Ser-9 on glycogen synthase kinase 3β (GSK3β), a major kinase responsible for tau hyperphosphorylation in AD neuropathology. This was observed in mouse cingulate cortex and hippocampus and was not observed in $\alpha 7$ nAChR KO mice. S9-GSK3β phosphorylation was also seen in the hippocampus of Tg2576 (APP), as well as wild-type mice by steady-state exposure of A-582941. Moreover, continuous infusions of A-582941 decreased phosphorylation of tau in hippocampal CA3 Mossy fibers in a hypothermia-induced tau hyperphosphorylation mouse model and also decreased spinal motoneurons in AD double transgenic APP/tau mouse line. This group points out that $\alpha 7$ nAChR agonists may have therapeutic potential through GSK3β inhibition followed by reduction of tau hyperphosphorylation and further suggest that this pharmacology may have the potential to provide disease modifying benefit in the treatment of AD.

It is reported that the $\alpha 7$ nAChR agonist GTS-21 prevented Aβ_{25--35}-induced impairment of acquisition performance and probe trail test in Morris water maze [95]. Their study showed first *in vivo* evidence that treatment with GTS-21 ameliorates the Aβ-induced deficit in spatial cognition through not only activating $\alpha 7$ nAChR but also preventing the Aβ-impaired $\alpha 7$ nAChR.

Using a novel selective $\alpha 7$ nAChR partial agonist S 24795, Wang et al. [96] showed that, in contrast to anti-AD drugs, galantamine (a cholinesterase inhibitor) and memantine (an *N*-methyl-D-aspartate (NMDA) receptor antagonist), S 24795 reduced or limited Aβ_{42}-$\alpha 7$ nAChR association,

Aβ_{42}-induced tau phosphorylation, Aβ_{42} accumulations, and Aβ_{42}-mediated inhibition of $\alpha 7$ nAChR Ca^{2+} influx in rodent brain [96]. S 24795 more importantly restored $\alpha 7$ nAChR functional deficits which had resulted from continued exposure to exogenous Aβ_{42}.

Taken all together, $\alpha 7$ nAChR is one of the therapeutic targets for AD [97, 98].

3.3. Postmortem Studies of $\alpha 7$ nAChR in the Brain of Patients with AD.

In the postmortem brain of patients with AD, decline of $\alpha 7$ nAChR appears early in the disease and was associated with the progression of cognitive deficits [99–101]. Although the protein levels are reduced in the cortex and hippocampus of AD patients [15, 19, 32, 100, 102], contradictions arise at the level of gene transcription. For example, levels of $\alpha 7$ nAChR protein were reduced by 36% in the hippocampus of AD patients [15], but $\alpha 7$ nAChR mRNA expression is increased by 65% [18]. Furthermore, no differences in [^{125}I]α-bungarotoxin binding were found in the frontal cortex of AD patients [103] and negative reduction of the $\alpha 7$ nAChR protein levels [104].

3.4. Imaging of $\alpha 7$ nAChR in the Brain.

Given the role of $\alpha 7$ nAChR in the pathogenesis of AD, it is of great interest to study $\alpha 7$ nAChR in the living human brain using PET/SPECT. Much effort has been devoted to visualize $\alpha 7$ nAChR in the brain by PET/SPECT, but the development of a radioligand that depicts $\alpha 7$ nAChR specifically has been problematic due to its relatively low amount in the brain [105–108]. Generally, α-bungarotoxin and MLA are well known as specific $\alpha 7$ nAChR antagonists. However, due to their large molecular weights, they have difficulty passing through the blood-brain barrier which makes them unfavorable for radioligands [109–111]. Consequently, a number of radioligands for $\alpha 7$ nAChR are being developed and evaluated as PET/SPECT radioligand. However, all radioligands except [^{11}C]CHIBA-1001 were unsuccessful [112].

3.5. [^{11}C]CHIBA-1001 as a Novel PET Ligand for $\alpha 7$ nAChR.

We developed a novel PET ligand, 4-[^{11}C]methylphenyl 1,4-diazabicyclo[3.2.2.]nonane-4-carboxylate ([^{11}C]CHIBA-1001) (Figure 7). A PET study using conscious monkeys demonstrated that the distribution of radioactivity in the brain regions after intravenous administration of [^{11}C]CHIBA-1001 was blocked by pretreatment with the selective $\alpha 7$ nAChR agonist SSR180711 (5.0 mg/kg), but not the selective $\alpha 4\beta 2$ nAChR agonist A85380 (1.0 mg/kg) [89]. In addition, we reported that the order of drugs for the inhibition of [^{3}H]CHIBA-1001 binding to rat brain membranes was similar to $\alpha 7$ nAChR pharmacological profiles [113]. We also reported a preliminary PET study of [^{11}C]CHIBA-1001 in a healthy human [114, 115]. Very recently, we reported that [^{125}I]CHIBA-1006, an iodine derivative of SSR180711, has a high affinity for $\alpha 7$ nAChR as compared with CHIBA-1001 [116]. Considering the good brain permeability of derivatives (e.g., SSR180711 and CHIBA-1001) of CHIBA-1006, it would be of great interest
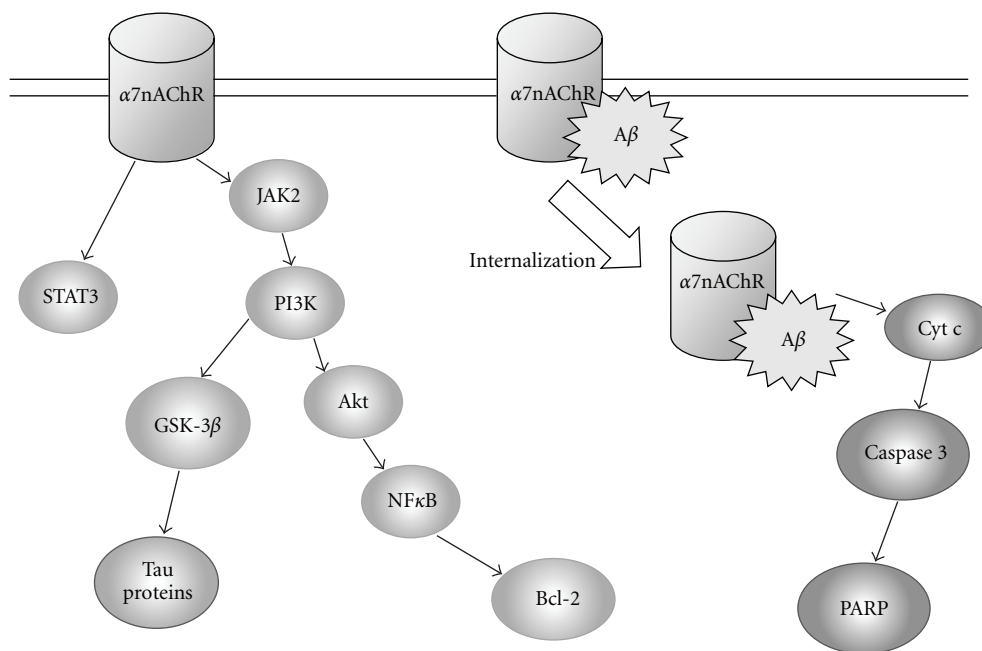
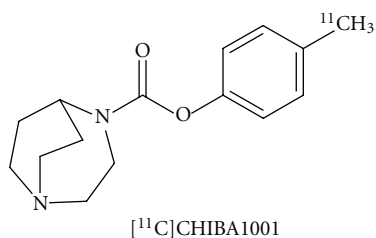Figure 6: Schematic representation of neuroprotective role of α7 nAChR.

Figure 7: Chemical structure of [^{11}C]CHIBA-1001.

to examine whether [^{123}I]CHIBA-1006 and [^{124}I]CHIBA-1006 are suitable radioligands for *in vivo* labeling of α7 nAChRs in the brain using SPECT and PET, respectively [116].

At present, [^{11}C]CHIBA-1001 is the only PET ligand which can be available for *in vivo* study of α7 nAChRs in intact human brain [114]. PET studies of [^{11}C]CHIBA-1001 in patients with AD are currently underway with [^{11}C]Pittsburgh compound D ([^{11}C]PiB)-PET and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET. This study aims to evaluate the relationship between the distribution of α7 nAChR (assessed by [^{11}C]CHIBA-1001) and Aβ disposition (assessed by [^{11}C]PiB), while estimating the stage and cognitive levels (assessed by [^{18}F]FDG-PET and neuropsychological examinations) for each AD patient.

4. Conclusions

Considering the importance of early prevention of onset of AD, it is very important to detect alternations in nAChRs at the presymptomatic stage of AD. In patients with MCI, the early detection and early therapeutic intervention would

be beneficial. Therefore, brain imaging of nAChRs using PET and SPECT will be a powerful tool to study the mechanisms underlying pathological brain processes of cognitive disturbances in these patients. Currently, some PET and SPECT ligands for both subtypes (α4β2 nAChR and α7 nAChR) have been used to investigate the changes in receptor densities and functions of patients with AD. Gaining a better understanding of the role of nAChRs in the pathophysiology of AD is expected to provide new perspectives for treating this disorder.

Conflict of Interests

The authors have no conflict of interests.

Abbreviations

AD: Alzheimer's disease
DV: Distribution volume
GFAP: Glial fibrillary acidic protein
LTP: Long-term potentiation
nAChR: Nicotinic acetylcholine receptor
PET: Positron emission tomography
SPECT: Single-photon emission tomography.

Acknowledgments

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