NICOTINE, MEMORY AND OXIDATIVE STRESS

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INTRODUCTION

Tobacco smoke consists of thousands of compounds including nicotine. Although tobacco smoking is a widespread and historic addiction of long standing, interest in brain nicotinic acetylcholine receptors (nAChRs) began to grow only some 15 years ago, when genetic studies revealed the amazing possible diversity of this type of receptor.

Combined electrophysiologic, pharmacologic and genetic studies allowed characterizing the structure and properties of various brain nAChRs, but despite a vast amount of work invested in the area, the roles of these receptors in various brain functions remain largely unknown.

Many constituents of tobacco smoke have known toxicity to the brain, cardiovascular, and pulmonary systems. Nicotine, on the other hand, by virtue of its short-term actions on the cholinergic system, has positive effects on certain cognitive domains including working memory and executive function and maybe, under certain conditions, neuroprotective (Swan and Lessov-Schlaggar, 2007). .

Clinical and laboratory studies indicated the involvement of nAChRs in complex brain functions such as memory, attention and cognition but also in the pathogenesis of several neuropsychiatric afflictions such as Alzheimer’s and Parkinson’s diseases, which are characterized by decreased nAChRs density, or autosomal dominant nocturnal frontal lobe epilepsy and possibly schizophrenia, which are likely produced by genetic alterations that affect nAChRs functions (Mihailescu and Drucker-Colin, 2000). Clinical studies indicated that tobacco smoking may represent a form of self-medication in psychiatric diseases such as schizophrenia, attention deficit/hyperactivity disorder, and depression. Nicotine has been used successfully, either as a unique or a complementary drug for the treatment of Parkinson’s disease, Alzheimer’s disease, attention deficit/ hyperactivity disorder, Gilles de la Tourette’s syndrome and depression. The use of nicotine in therapy is severely limited by its carcinogenic and cardiovascular side effects. This inconvenience is nearly overcome due to synthesis of selective nAChR agonists (Mihailescu and Drucker-Colin, 2000).

Experimental studies on animals and human showed contradictory results concerning the influence of nicotine on learning and memory. While some researchers (Decker et al., 1995; Hefco et al., 2003) reported an improving effect of nicotine on memory, others (Dunnet and Martel, 1990; Heisham et al., 1994) did not observe any effect or, on the contrary reported negative effects. Also, recent evidence implicated medicinal nicotine as potentially harmful to both neurodevelopment in children and to catalyzing processes underlying neuropathology in Alzheimer’s disease (Swan and Lessov-Schlaggar, 2007).

Several plausible theories have arisen to explain nicotine's beneficial effects on oxidative stress. One popular theory suggested that nicotine serves as a potent antioxidant scavenging the free radicals produced by monoamine oxidase-B (MAO-B). Produced by the body to metabolize monoamines such as dopamine, MAO-B generates hydrogen peroxide by-products, which react with iron to form free radicals. Parkinson's disease (PD) patients typically have an elevated level of iron in the striatum, increasing oxidative stress, neurotoxicity, lipid peroxidation, and DNA injury (Iida et al., 1999). On the other hand, nicotine might in fact act directly to decrease MAO-B levels, which would lower free radical production. Another possible mechanism involved growth factors such as fibroblast growth factor-2 (FGF-2) and brain-derived neurotrophic factor, both of which purportedly increase dopaminergic neuron survival in vivo and rescue dopaminergic function (Ho, 2002). The mechanism behind the role of growth factors in PD is still being investigated. Nonetheless, the elevated growth factor levels were muted by nicotinic receptor antagonists, confirming that nicotine is indeed the responsible substance.

Finally, nicotine's neuroprotective properties might arise from its ability to restore cerebral blood flow, which is substantially diminished in the forebrain regions of PD patients. In ultrasonic Doppler studies done on humans, a dose response effect was found, with increased nicotine resulting in increased flow (Boyajian and Otis, 2000). Cholinergic neurons are generally believed to regulate blood flow in the brain, and so destruction of these neurons likely result in the cognitive deficits seen in PD patients. Restoration could have important preventive effects that are still under study. The possible roles of nicotine acetylcholine receptors (nAchRs) could lead to novel therapeutic treatments for PD, and already have provided dramatic insight on the inception of PD. It is important to note that a small number of studies paradoxically show no change to worsening of PD symptoms upon administration of nicotine, casting doubt on its true effect (Quik and Jeyarasasingam, 2000). However, these studies might be faulted for differing dose amounts or means of injection. Activation above or below a certain level might produce the contradictory effects observed in these studies (McGehee D et al., 1995).

NICOTINE AND ALZHEIMER'S DISEASE

Alzheimer-type senile dementia is associated with degeneration of basal forebrain cholinergic neurons innervating the cortex, amygdala, and hippocampus, which results in a decreased capacity of maintaining sustained attention and in profound cognitive impairments (Coyle et al., 1983).

Drugs that block acetylcholine muscarinic receptors (e.g. scopolamine) produce selective deficits in recent memory but do not impair long-term memory when administered in young volunteers (Drachman and Leavitt, 1976). Therefore, scopolamine-induced dysfunction in cognition was proposed as a model of AD (Sunderland et al., 1986; Hefco et al., 2003).

The involvement of nAChRS in the pathogenesis of AD represents a relatively recent development. Sugaya et al. (1990) and Perry et al. (1995) proved that AD is associated with a loss of high-affinity [^{3}H]-nicotine receptors (especially in the subicular complex, parahippocampal gyrus, entorhinal cortex, and temporal neocortex), but not with a loss of α-bungarotoxin receptors. Spontaneously hypertensive rats, known to have a reduced number of both high-affinity [^{3}H]-cystine binding sites and low-affinity ^{125}I α-Bgtx binding sites, have impaired abilities for learning and memory-related tasks (Gattu et al., 1998). In mutant mice with homozygous deficiency in β2 subunits, there is a loss of high-affinity ^{3}H-nicotine binding nAChRs that is accompanied by a significant impairment of spatial learning tasks (Zoli et al., 1997) and improvement in passive-avoidance tasks (Picciotto et al., 1998).

Nicotine enhances cognitive performance in normal animals (Levin, 1992; Hefco et al., 2003) and animals with lesions of forebrain cholinergic nuclei (Decker et al., 1992) or with age-induced memory deficits (Buccafusco et al., 1991). Nicotine's effects on cognition seem to be dependent on dopamine release, because they are not shared by lobeline-which, in contrast to nicotine, does not induce dopamine release-and are prevented by D1/D2 dopamine receptor blockers (Brioni et al., 1993; Hefco et al., 2003).

Several recent clinical studies revealed that nicotine improves cognitive function in AD patients. Thus, nicotine, administered subcutaneously or intravenously to patients with AD improves sustained visual attention, reaction time, and perception, but does not improve auditory and visual short-term memory (Jones et al., 1992). Nicotine also improves attention in normal persons, but this action is significantly stronger in aged persons than in young ones (Jones et al., 1992). Long-term memory enhancement induced by nicotine seems to be due to improvement of acquisition and/or encoding, and not to improvement of consolidation (Newhause et al., 1988). Nicotine has also been shown to antagonize the deleterious effects of anticholinergic drugs such as scopolamine on rapid information-processing tasks in humans (Wesnes et al., 1984) and to exert neuroprotective effects in experimental models of AD (Kihara et al., 1997).

The mechanisms through which nicotine improves memory and attention in Alzheimer's disease are yet unknown but may be related to nicotinic stimulation of the remaining population of cholinergic receptors and/or modulation of the ascending catecholaminergic systems' activity, such as coerulocortical, noradrenergic and mesolimbic dopaminergic projections (Brazell et al., 1991).

Several recently synthesized nAChR agonists show potential therapeutic use in AD. One of these compounds is SIB-1533A which exhibits selective affinity for α2β4 nAChRs and is very efficacious in releasing acetylcholine and dopamine from rat hippocampal and striatal slices (Lloyd et al., 1998). SIB-I533A improves cognition (spatial and nonspatial working memory) in various experimental models of AD (aged rats and monkeys, rats with lesions of the cholinergic neurons).

GTS-21 [(3-(2,4-dimethoxybenzylidene)-anabaseine, or DMXBA] is a selective but weak agonist of a subunit-containing nAChRs. In rats, it does not increase locomotor activity or dopamine turnover in striatum (Nanri et al., 1998), and it does not stimulate cortical acetylcholine release (Tani et al., 1998).

ABT-418 [(S)(-3-methyl-2-pyrrolidinyl)-isoxazole], an isoxasole analog of (-) - nicotine, is a potent ligand of α4β2 sub-unit-containing nAChRs but has low activity at α7 subunit-containing nAchRs. Similar to nicotine, ABT-418 enhances memory and cognition in aged nonhuman primates (Prendergast et al., 1997) and has neuroprotective actions (Donnelly-Roberts et al., 1996), which make it potentiallv useful for AD treatment.

NICOTINE AND PARKINSON'S DISEASE

Muscular rigidity, tremor, and bradykinesia characterize Parkinson's disease (PD). PD may be primary (idiopathic) or secondary to viral infections of the brain, exposure to manganese, carbon monoxide, organophosphates and pethidine analog MTTP (l-methyl-4-phenyl-1,2,3,6-tetrahydropy-ridine) (Calne and Langston, 1983). Several uncommon disorders, such as Wilson's disease, Huntington's chorea, and progressive supranuclear palsy, may have parkinsonian manifestations.

Perry et al. (1995) found a decrease in high-affinity nACh.Rs density in humans with PD by 70% in *the pars compacta of substantia nigra* and by 40 to 50% in the laterodorsal tegmental nucleus.

The first report concerning the use of nicotine in the treatment of PD came from Moll (1926). He showed that patients with post-encephalitic PD manifested a marked improvement of their symptomatology when treated with

progressively increasing doses of subcutaneous nicotine. Fagerstrom et al. (1994) showed that nicotine administered as a combination of patch and gum significantly reduced rigidity, tremor, disorganized thinking, and depression in nonsmoking patients with PD. The mechanisms of the beneficial actions of nicotine in PD appear to depend on increased dopamine release in *the substantia nigra* on inhibition of monoamine oxidase B, the enzyme involved in the breakdown of dopamine (Mihailescu et al., 1998), and on potentiation of dopamine mesolimbic secretion (Kita et al., 1992).

Nicotine also has protective effects against PD. Follow-up studies showed that the risk of parkinsonism is 20 to 70% more reduced in smokers than in nonsmokers, whereas case-control studies indicated that smoking subjects have one-half the risk of nonsmoking patients in developing PD (Baron, 1986). These epidemiological findings closely match the experimental findings of Janson et al. (1989) and Fuxe et al. (1990), who found that chronic nicotine administration protects against degeneration of central dopamine neurons induced by mechanical or chemical lesions.

A new nAChR agonist, SIB-1508Y, has proven active in experimental models of PD. SIB-1508Y has a high selectivity for α4β2 subunit-containing nAChRs and is a powerful stimulator of striatal dopamine and hippocampal norepinephrine release from rat slices (Saccan et al., 1997). SIB-1508Y has a low activity at α3β4 subunit-containing nAChR, which indicates the potential low cardiovascular effects of the drug (Lloyd et al., 1998). In monkeys with MTTP-induced PD, monotherapy with SIB-1765F (racemate of SIB-1508Y) only slightly improved the motor and cognitive manifestation of PD. SIB-1765F, in combination with L-dopa, reversed reserpine-induced hypolocomotion in rats by increasing dopamine release from reserpine-sensitive and -insensitive pools (Menzaghi et al., 1997).

NICOTINE AND OXIDATIVE STRESS

Understanding the complex nature of AD has evolved with an increased appreciation for pathways that involve the generation of reactive oxygen species (ROS) and oxidative stress, apoptotic injury that leads to nuclear degradation in both neuronal and vascular cell populations, and the early loss of cellular membrane asymmetry that mitigates inflammation and vascular occlusion. Oxidative stress is considered to play a significant role in the onset and progression of AD. Transient hypoxia in sporadic AD can lead to mitochondrial dysfunction, impaired membrane integrity, and amyloid precursor protein cleavage. During the progression of AD, lipid peroxidation, protein oxidation, and DNA oxidation occur. There exists a close correlation between oxidative stress and amyloid β deposition. Amyloid β has been found to result in the generation of ROS, such as hydrogen peroxide, through metal ion reduction and, subsequently, to oxidative toxicity in neurons. Application of the free radical antioxidant vitamin E has been demonstrated to prevent neurotoxicity from amyloid β. Cellular oxidative pathways that proceed through apoptosis appear to be a predominant factor in the cell loss observed during AD (Butterfield et al. 2006; Mazza et al., 2007).

Compared with non-smokers, on average, active smokers have more than 25% lower circulating concentrations of antioxidants such as ascorbic acid, α carotene, β carotene, and cryptoxanthin. The associations observed with active smoking also appear to hold for passive smoking. Cigarette smoke is a significant source of oxidative stress. This direct exposure from cigarette smoke represents only a portion of the total oxidative stress eventually experienced by the smoker. Cigarette smoke also contributes to additional endogenous oxidant formation through effects on the inflammatory immune response pathway. Cigarette smoke could also result in increased metabolic turnover with antioxidant micronutrients expended in response to the increased oxidative stress caused by cigarette smoking or, alternatively, smoking could decrease micronutrient absorption (Alberg, 2002).

Oxidative stress damage is also intimately linked to glutamate neurotoxicity. An excessive concentration of extracellular glutamate overactivates ionotropic glutamate receptors, resulting in intracellular calcium overload and a cascade of events leading to neuronal cell death (Butterfield et al., 2006). Exposure of rat brain to cigarette smoke, results in an increase of ROS and nitric oxide synthase (NOS) leading to lipid peroxidation, protein oxidation, and DNA damage. In this model, cigarette smoke also induces heat shock proteins and apoptosis, a conserved response to various conditions including oxidative stress (Anbarasi et al., 2006). Long-term exposure to sidestream smoke has also been shown to result in the activation of markers indicative of oxidative stress in mouse brain. Following 6 months of exposure, an increase of ROS was noted in the cerebellum, frontal cortex, hippocampus, and striatum along with an increase in lipid peroxidation. An increase in pro-inflammatory markers in all areas of the brain was also observed (Manna et al., 2006).

Cadmium, a component of tobacco smoke, induces cellular death in cortical neurons in culture, possibly through apoptotic or necrotic mechanisms as a secondary effect of oxidative stress (Lopez et al., 2006). Nicotine, on the other hand, in low, acute doses could act as an antioxidant (Zhang et al., 2007).

CONCLUSIONS

Despite general progress in knowledge of the structure and functions of brain nAChRs, the mechanisms of their involvement in the pathogenesis of neuropsychiatric disorders remain unclear. A promising trend for therapy is the synthesis of new agonists with high nAChR subtype selectivity, which do not exhibit nicotine’s side effects and do show clear neuroprotective effects and beneficial actions in experimental models of Parkinson’s and Alzheimer’s diseases.

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