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Genetic and Environmental Aspects of the Role of Nicotinic Receptors in Neurodegenerative Disorders: Emphasis on Alzheimer's Disease and Parkinson's Disease

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As neurodegenerative disorders are better characterized, the importance of genetic and environmental interactions is becoming more evident. Among the neurodegenerative disorders, Alzheimer's disease and Parkinson's disease are both characterized by large losses of nicotinic binding sites in brain. In addition, losses in nicotinic receptors occur during normal aging. Chronic administration of nicotine in man or experimental animals increases the number of nicotinic receptors in brain. Nicotine has been shown to possess some neuroprotective properties for both cholinergic and dopaminergic neurons. These neuroprotective properties, when better understood, may provide important information on normal aging and neurodegenerative disorder related neuronal cell death. Understanding the functional aspects of neuronal nicotinic receptor subtypes may lead to successful therapeutic treatments or disease preventative strategies for neurodegenerative disorders.

KEY WORDS: Nicotinic receptors; Alzheimer's disease; Parkinson's disease; genetics; environmental; neuroprotective.

INTRODUCTION

Genetic factors play an important role in the etiology of many neurological disorders. For Alzheimer's disease (AD), which is one of the most common forms of dementia, genetics are known to play an important role in conjunction with other risk factors. Recent studies in families with a positive history of AD have revealed a genetic linkage with chromosomes 14, 19, and 21 (Clark and Goate, 1993). Twins studies have shown an increased concordance in monozygotic pairs in comparison to dizygotic pairs (Nee *et al.*, 1987). Epidemiological studies have revealed the possibilities of several risk factors for AD which also covariate (Fratiglioni, 1993; Friedland, 1994). One of the risk factors often considered in epidemiological studies is cigarette smoking.

Several neurotransmitter systems are affected in AD. Studies in brain tissues obtained at autopsy from AD patients reveal losses in cholinergic, noradrenergic, serotonergic, and glutaminergic neurotransmitter systems, as well as the peptide somatostatin and corticotropin-releasing factor. (Hardy *et al.*, 1985; Nordberg, 1992). Parkinson's disease (PD) is also characterized by substantial loss of cholinergic as well as dopaminergic neurons (Aubert *et al.*, 1992). The significant loss of cholinergic innervation in AD has focused research on the basal forebrain a site of origin for one portion of the cholinergic system. Many excitotoxins (ibotenate, kainate, quisqualate, AMPA, quininolate, saporine) have been used to produce lesions in the nucleus basilis of Meynert in hope of producing an animal model of AD (Greenamyre and Young,

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1989; Lopez-Garcia *et al.*, 1993; Dunnett *et al.*, 1987; Page *et al.*, 1991; Bogdanovic *et al.*, 1993; Heckers *et al.*, 1994). An important step forward is anticipated with the development of a valid transgenic animal model.

The definite diagnosis of AD is based upon pathological confirmation from autopsy by the presence of neuritic plaques and neurofibrillary tangles. The major component of neuritic plaques is a β-amyloid peptide. The peptide has been purified from neuritic plaques and is derived from a larger amyloid precursor protein (APP). A single-point mutation in codon 717 of the APP precursor gene on chromosome 21 (Goate *et al.*, 1991) as well as a double mutation at codon 671/71 (Mullan *et al.*, 1992) has been found in families with the familiar form of AD; these observations strongly support the hypothesis that these mutations are pathogenic for AD. The β-amyloid protein production was markedly increased when the Swedish double mutation was expressed in kidney cells (Citron *et al.*, 1992).

The loss of nicotinic cholinergic receptors may play a role in attentional deficits (basal forebrain) and neurochemical imbalances leading to or accompanying AD (Sahakian *et al.*, 1994). Since pre- and/or postsynaptic nicotinic receptors have been suggested to play a role in signal transduction within the cholinergic and dopaminergic systems, it is not surprising to see similarities in epidemiological studies between AD and PD.

EPIDEMIOLOGY

Attempts have been made to correlate AD inversely with smoking, but in analyzing case and case-control studies no clear-cut risk factors have been delineated (Barclay and Kheyfets, 1988; Graves *et al.*, 1991). A negative relationship has been reported between smoking and familiar AD but not sporadic AD (van Duijn, 1991; van Duijn and Hofman, 1992). Brenner (1993), in a case-control study, reported a dose–response decrease in the likelihood of developing AD. In this study, smokers who consumed the lowest chronic quantity of cigarettes showed the lowest risk of developing AD. Interestingly, Brenner (1993) found a negative correlation between cigarette smoking and AD in higher-educated subjects with a history of hypertension, while Prince *et al.* (1994), in a case-control study, found a positive relationship with smoking.

Case studies have suggested that an inverse relationship exists between PD and smoking, though the mechanism of this protective effect is still unknown (Haack *et al.*, 1981; Baumann *et al.*, 1980; Calne *et al.*, 1986; Kessler and Diamond, 1971; Baron, 1986; Aquilonius, 1989; Mayeux *et al.*, 1994). PD patients have a severe degeneration of dopaminergic neurons in the substantia nigra and nicotinic receptors located on nigrostriatal and mesolimbic dopaminergic neurons. Nicotine evokes the release of dopamine (Giorguieff *et al.*, 1977) and inhibits the release of dopamine (Grady *et al.*, 1994) from these subcortical dopaminergic neurons. It is possible that the inhibition of dopamine release might protect these dopaminergic neurons. Fewer firings of these dopaminergic neurons might result in fewer endogenous or exogenous toxins from entering the neurons. A second possibility is that inhibition may reduce the energy expended by these dopaminergic neurons resulting in extended life. Not all studies have supported the protective effects of smoking and PD (Nefzger *et al.*, 1968, Marttila and Rinne, 1980; Rajput *et al.*, 1987; Golbe *et al.*, 1986). Riggs (1992) refuted the negative correlation between smoking and PD. Riggs reported using a Gompertzian analysis that PD deaths in the United States between 1955 and 1989 were due to earlier deaths of PD patients not a negative correlation to smoking. This is a plausible argument, but behavioral, receptor binding, and molecular biology studies oppose this conclusion.

The diversity of risk factors (positive and negative) points toward a complex interaction of environmental and genetic factors in developing AD or PD (Hofman *et al.*, 1989; Spencer *et al.*, 1987; Neary *et al.*, 1986; Newhouse and Hughes, 1991; Treves *et al.*, 1993a, b). Ward *et al.* (1983), in a twin study, suggested that there was no positive genetic relationship for PD. The appearance of negative correlations to smoking for PD and familiar AD suggests a genetic link between the two diseases. The protective effect of smoking (nicotine) in delaying the onset of these two diseases suggests that nicotine is providing protection for both cholinergic and dopaminergic neurons in the basal forebrain and the nigrostriatal and mesolimbic systems respectively. There are many possible mechanisms by which nicotine could be providing protection. Adding to puzzle is the inverse relationship of smoking and endometrial cancer, ulcerative colitis, and preclampsia (Hanauer, 1994; Jick

and Walker, 1983; Parazzini *et al.*, 1991; Jarvik, 1991).

One interesting possibility is that nicotine is inhibiting apoptosis (Carson and Ribeiro, 1993; Collins *et al.*, 1993; Vaux *et al.*, 1994). Apoptosis is the natural physiological means of cell death. β-Amyloid has been shown to induce apoptosis in central nervous system neurons (Loo *et al.*, 1993), while nicotine has been reported to inhibit apoptosis (Wright *et al.*, 1993). The inhibition of apoptosis by nicotine is not blocked by antagonists, suggesting that the inhibition is not receptor mediated. There is evidence in PD that the normal mechanisms of apoptosis may be flawed either due to a genetic mutation or from a previous endogenous or exogenous cell stressor (Calne *et al.*, 1986).

The epidemiological data suggest a link between smoking and both AD and PD. The etiological importance of this link is yet unknown, but the variability of the data clearly demonstrates the importance of individual differences. Individual differences may play a role in not only how humans are holistically effected by nicotine, but how they are affected on a molecular level.

GENDER AND INDIVIDUAL DIFFERENCES

It has been suggested that females (Grunberg, 1991) and males (Perkins, 1992) are more sensitive to the effects of nicotine. Whichever is the actual case it appears that gender differences do exist. However, Perkins (1994) reported no difference in the reinforcing value of smoking between men and women. Female Sprague–Dawley rats are behaviorally less sensitive to initial administration of nicotine (0.8 mg/kg, s.c., free base) than similar aged males (James, unpublished data).

Jones (1986) studied differences in heart rate, after smoking one cigarette containing 1.57 mg of nicotine, in 124 smokers male and female. Subjects were classified as either responsive, heart rate increase of more than 10 beats per min (bpm), or non-responsive, heart rate increases of less than 8 bpm. Twenty responsive and 20 nonresponsive subjects were tested over a 4-month period. No classification shifts were seen during this period for baseline heart rates or puff analysis. Jones (1986) suggested that the responsive smoker is not addicted to nicotine, while the nonresponsive smoker might be addicted. Another explanation is that the responsive smoker may not be capable of acute desensitization of nicotinic receptors, while the nonresponsive smoker may be acutely desensitizing nicotinic receptors and blocking the physiological effects of the nicotine. This premise is supported by the fact that not all subjects experience the same physiological effects of nicotine peripherally and or centrally (Ashton, 1979). The distinct individual differences seen in the Jones (1986) study are similar to those reported in Sprague–Dawley rats (James, 1994). The hypothesis that the nonresponsive human and acutely desensitizing rat are addicted to nicotine appears plausible. A nonresponsive human smoker as defined by Jones (1986), and an acutely desensitizing rat as defined by James (1994), might be experiencing a rapid desensitization of presynaptic nicotinic receptors which might mediate the aversive effects of nicotine. After desensitization a secondary effect mediated by presynaptic and/or postsynaptic nicotinic receptors located on dopaminergic neurons might activate the rewarding aspects of nicotine leading to an addictive state. The nonaddicted or responsive smoker and the nondesensitizing rat might experience a continual activation of nicotinic receptors which overrides the secondary rewarding effects activated by dopaminergic neurons. To understand the possible mechanisms of action that lead to specific individual differences, it is necessary to understand the complex signal transduction mechanism initiated by nicotine binding to neuronal nicotinic receptors.

NICOTINIC RECEPTORS IN THE CNS

The discoveries of the existence of nicotinic receptors in the brain and their involvement in higher functions including learning and memory are relatively new phenomena (Nordberg *et al.*, 1989a; Wonnacott *et al.*, 1990). Nicotine centrally activates reward mechanisms and is therefore presumed to be the reason why people smoke. To characterize nicotine's functions in the central nervous system, it is necessary to understand the interaction of the drug and neuronal nicotinic receptors.

Various nicotinic ligands have been used in *in vitro* studies to characterize nicotinic receptors in tissue obtained from rodent and human postmortem brains. Radioligands such as the agonists [^{3}H]acetylcholine, [^{3}H]cytisine, [^{3}H]methylcarbamylcholine, and [^{3}H]nicotine have primarily been used, as well

as the antagonists [^{125}I]α-bungarotoxin, [^{125}I]κ-bungarotoxin, [^{3}H]tubocurarine, and [^{3}H]dihydro-β-erythroidine, for characterizing various subtypes of nicotinic receptors in the brain (Nordberg, 1993). Autoradiography studies have shown that the regional distributions of receptors labeled by these ligands are not the same (Härfstrand *et al.*, 1988). At least three subtypes of nicotinic receptor binding sites (superhigh-, high-, and low-affinity sites) have been described in human brain (Nordberg *et al.*, 1988).

Molecular biology studies have revealed a whole family of genes coding for the nicotinic receptors (Deneris *et al.*, 1991; Changeux *et al.*, 1987). Presently seven distinct α subunits (α2–α8) and three β subunits (β2–β4) have been cloned and show regional distributions in rodent brain (Arneric *et al.*, 1995). The α4–β2 conformation has a high affinity for nicotinic agonists and, in rodent brain, has been shown to be the most abundant (Deneris *et al.*, 1991; Luetje *et al.*, 1990). The α7 subunit probably corresponds to the α-bungarotoxin binding site in brain (Bertrand *et al.*, 1992). The α4–β2 subtype has been suggested to correspond to nicotinic receptors presynaptically located and high-affinity binding sites (Goldman, 1987). The densities and distributions of the various subtypes of nicotinic receptor genes have not been fully characterized in the human brain, although some of the subunits have been cloned (Raimondi *et al.*, 1991). Wevers *et al.* (1994) studied the cellular distribution of the α3 and α4 subunits of the nicotinic receptor in human cortex. They found the α3 subunit being expressed mainly in layer 111–V1 of the cortex, while α4 was present in neurons throughout the cortical layers. *In situ* hybridization on metaphase chromosomes has localized human α3, β4, and α5 genes to the same locus on chromosome 15 (Chini *et al.*, 1991).

DEVELOPMENT OF NICOTINIC RECEPTORS

Nicotinic receptors are present early in the development of the brain. Different changes in number of nicotinic binding sites have been detected during development using various labeled nicotinic ligands (Falkeborn *et al.*, 1983; Larsson *et al.*, 1985; Slotkin *et al.*, 1987; Zhang *et al.*, 1990; Nordberg *et al.*, 1991). During the first postnatal days, only high-affinity nicotinic receptors can be measured in mouse brain, while both high- and low-affinity sites are present in adult brain (Nordberg *et al.*, 1991). Interestingly, neonatal exposure to low doses of nicotine (days 10–16) prevents the development of low-affinity nicotinic binding sites and can also change the behavior to nicotine in adult animals (Nordberg *et al.*, 1991). In a recent study the developmental changes in [^{3}H]nicotine binding were studied in human brain stem (Kinney *et al.*, 1993). The authors suggested that the nicotinic receptors may play a role in the development of the brain-stem tegmentum, since high numbers of nicotinic receptor binding sites were measured at midgestation.

AGING AND NICOTINIC RECEPTORS

Reductions in nicotinic receptors due to aging have been reported in animal and human studies. A significant reduction in number of nicotinic receptors has been measured using [^{3}H]nicotine in the cortex and midbrain with normal aging in rats (Zhang *et al.*, 1990). On the other hand, no differences were seen in *N*-[^{3}H]carbamylcholine binding comparing 3-month-old and 27-month-old rats in the cerebral cortex, striatum, hippocampus, and thalamus, respectively (Arajou *et al.*, 1989). A possible explanation for this discrepancy is that NMCC labels only high-affinity nicotinic binding sites. A similar difference in changes of nicotinic receptors with aging was obtained using [^{3}H]-nicotine and [^{3}H]acetylcholine in human brain (Nordberg *et al.*, 1992a). Wagster *et al.* (1990) reported in rhesus monkey 70% fewer cortical nicotinic receptors in 6 year olds compared to 2 year olds using [^{3}H]acetylcholine.

Human studies have shown rather large individual differences in the number of nicotinic receptors observed in normal brains with aging. These differences have been found for the various subtypes of nicotinic receptors (Nordberg, 1993). A significant decrease in [^{3}H]nicotine binding has been observed in the frontal cortex (Flynn and Mash, 1986; Nordberg *et al.*, 1992a), while an increase in binding with age has been observed in the thalamus (Nordberg *et al.*, 1992a). The number of [^{3}H]acetylcholine binding sites has been found to be unchanged with aging in cortex and the thalamus (Nordberg *et al.*, 1992a). The nicotinic antagonists [^{3}H]tubocurarine and [^{3}H]α-bungarotoxin have shown no change in number of nicotinic bind-

ing sites in the human hippocampus and cortex, while the total number of binding sites decreases in the thalamus with normal aging (Nordberg and Winblad, 1986a).

Aging has also been shown to produce alterations in nicotine-stimulated neurotransmitter release and losses of specific nicotinic receptor subtypes. Schulz *et al.* (1993) reported a 20% reduction in DA and DOPAC in striatal neurons between 25-month-old and 4-month-old rats. However, while no difference in the basal DA efflux was observed between the two ages, striatal slices exposed to 50 μM nicotine showed significantly less DA release in old rats compared to young rats. The reduction in DA release in the old rats appeared to have been compensated for by a longer period of DA release. Receptor binding (10 nM [^{3}H]nicotine) showed no differences among 4-, 10-, 16- and 25-month-old rats, while an age-related decline in binding sites was seen with [^{125}I]neuronal bungarotoxin (NBT) binding in the presence of nicotine and α-bungarotoxin. Similar results were observed in the presence of α-bungarotoxin alone (Schulz *et al.*, 1993). In other words, it appears that different subtypes of the nicotinic receptors decline with age in the rat, while other subtypes may remain stable. Nicotinic dopaminergic receptors on striatal slices appear to bind both nicotine and NBT. Further support is provided by the ability of NBT to block the nicotine evoked release of DA from striatal slices, while α-bungarotoxin fails to block nicotine-evoked DA release (Schulz, 1989). Luetje (1990) suggested that NBT was binding to the $\alpha 3$–$\beta 2$ receptor subtype. Recently, a loss of a subtype of striatal nicotinic receptors labeled by NBT has been reported to occur with aging in human brain (Schulz *et al.*, 1993).

CHANGES IN NICOTINIC RECEPTORS IN AD AND PD

Early studies indicated a preservation of nicotinic receptors in AD using [^{3}H]bungarotoxin and [^{3}H]tubocurarine (Nordberg and Winblad, 1986a). However, when [^{3}H]nicotine and [^{3}H]ACh were used as ligands for nicotinic receptors, a consistent loss of nicotinic receptors in cortical regions of AD brains was found (Nordberg and Winblad, 1986b; Whitehouse *et al.*, 1986), which has since been confirmed by several groups (Nordberg, 1992). Further analysis of changes in subtypes of nicotinic receptors has revealed a change in the proportion of high- and low-affinity nicotinic receptors (Nordberg *et al.*, 1988; Sugaya *et al.*, 1990). Since muscarinic receptors are preserved in AD, (Nordberg, 1992), nicotinic receptors seem to be the cholinergic receptors that are selectively impaired in AD (Schröder *et al.*, 1991). Positron emission tomography (PET) in human brain has shown lower uptake of [^{11}C]nicotine and binding to nicotinic receptors in AD patients (Nordberg *et al.*, 1990, 1995). A reduced number of nicotinic receptors have also been found in the postmortem cortex and hippocampus of PD patients (Perry *et al.*, 1987; Whitehouse *et al.*, 1988). Deficits have also been found in nicotinic receptors on peripheral lymphocytes of AD and PD patients (Adem *et al.*, 1986), and the decrease in number of receptors showed a positive correlation to severity of dementia (Nordberg, 1992).

As stated earlier, epidemiological studies suggest a genetic link between AD and PD. When comparing changes in brains of AD, PD, and AD/PD patients, the frontal cortex and temporal cortex showed a decrease in nicotinic receptors for all three diseases (Aubert *et al.*, 1992). However, in the striatum and thalamus no reduction was reported for AD, but 45% reductions were reported for both PD and AD/PD. Subcortical binding sites showed significant reductions only for PD and AD/PD. The significant reductions in nicotine binding sites for all three diseases suggest that AD, PD, and AD/PD patients should have equally severe dementia, which is not the case. PD patients showed even greater global cholinergic deficits than AD yet did not exhibit dementia as severe as AD patients. The nicotinic binding sites lost in the striatum and thalamus of PD patients may be postsynaptic and located on dopaminergic neurons, while the cortical losses seen for all three diseases may be presynaptic and concentrated on cholinergic neurons. It is possible that different types of memory and attention mechanisms and/or systems are being affected by specific cholinergic losses.

EFFECT OF NICOTINE EXPOSURE ON NICOTINIC RECEPTORS

Unlike most agonists, nicotine causes an unorthodox up-regulation nicotinic receptors. Up-regulation is hypothezied to be caused by rapid desensitization (antagonism) of the nicotinic recep-

tor by nicotine. *In vitro* studies support this rapid desensitize of the of the nicotinic receptor (Katz and Thesleff, 1957; Zaimis and Heads, 1976; Falkeborn *et al.,* 1983; Nordberg *et al.,* 1985, 1990; Larsson *et al.,* 1987; Romanelli *et al.,* 1988; Ochoa *et al.,* 1989; Sumikawa and Miledi, 1989; Bertrand *et al.,* 1990; Zhang *et al.,* 1994). James *et al.,* (1994) showed this acute nicotine desensitization process *in vivo* using an operant drug discrimination paradigm. In humans differences in nicotinic receptors have been reported between smokers and nonsmokers. Smokers have increased numbers of nicotinic receptors in brain as shown in receptor binding studies in postmortem tissue (Benwell *et al.,* 1988) and in PET studies (Nybäck *et al.,* 1989).

In the James *et al.,* (1994) study, rats were behaviorally and pharmacologically tolerant to nicotine, but still a subgroup of rats demonstrated acute tolerance to nicotine. It was suggested that desensitization and nondesensitization of nicotinic receptors explained the difference between rats demonstrating acute tolerance and rats not demonstrating acute tolerance. These results, taken with the nicotinic receptor increases reported by Benwell *et al.* (1988), suggest that the holistic consequences of nicotine administration (i.e., smoking, patch, smokeless, gum, nasal spray) are dependent on individual differences. Studies are now under way to determine if behavioral differences are explainable on a molecular level.

Desensitization of neuronal nitocinic receptors may play a role in actions of putative therapeutic agents designed to regulate acetylcholine release in neurological disorders. PET studies with AD patients treated with tacrine showed an increase in low-affinity nicotinic receptor sites as measured by uptake of $(+)^{-11}$ C-nicotine (Nordberg *et al.,* 1992b). This increase in $(+)^{-11}$C-nicotine uptake produces similar rates of uptake for $(-)^{11}$C-nicotine and $(+)^{-11}$C-nicotine that, prior to tacrine administration, showed a higher rate of uptake for $(-)^{-11}$C-nicotine (Nordberg *et al.,* 1990, 1992b). Further work is necessary to characterize differences in high- and low-affinity sites (Copeland *et al.,* 1991) that nicotine binds to with different affinities in both normal and AD brains. Genetic factors may influence the populations of high- and low-affinity nicotinic sites during development and/or aging. It is plausible that smokers with an increased number of high-affinity nicotinic receptor sites may show reduced losses of functional nicotinic sites with aging and, therefore, be less susceptible to the attentional deficits seen in AD.

GENETIC STUDIES: ANIMAL AND HUMAN

There are genetic differences in the behavioral and pharmacological effects of nicotine upon different mouse strains. Marks *et al.,* (1986a), using four mouse strains, reported variations in the development of tolerance and up-regulation of nicotinic receptors. Chronic nicotine treatment caused an up-regulation in the central binding sites receognized not only by [^{3}H]nicotine, but also by [^{125}I]α-bungarotoxin and [^{3}H]acetylcholine. These ligands appear to be binding to different subtypes of the nicotinic receptor in the brain. All four mouse strains showed an up-regulation of nicotinic receptors, but they did not develop tolerance equally. The least sensitive strain (C3H) to the initial injection of nicotine showed no tolerance to the acute effects of nicotine after chronic treatment.

Collins (1989) reported that mouse strains that are more sensitive to initial exposure to nicotine have higher numbers of nicotinic receptors in specific nuclei. The difference in total receptor numbers after chronic dosing was not significant, thus it appears that tolerance is regulated by some mechanism other than simply changes in total receptors numbers. Collins and Marks (1991) characterized 19 mouse strains in relation to neuronal nicotinic receptors and sensitivity and development of tolerance to nicotine. [^{125}I]α-Bungarotoxin binding correlated with seizure activity, and [^{3}H]nicotinic binding correlated with Y-maze activity and body temperature. The study also reported that C57BL/6 and A strains consumed different quantities of nicotine available in water and saccharine solutions. The work by Collins, Marks, and colleagues (Smolen and Marks, 1991; Marks *et al.,* 1986b; Miner *et al.,* 1984), showing differences in development of tolerance, behavioral measures, receptor binding, and self-administration, strongly suggests a genetic factor in the mechanism(s) of action of nicotine.

Several twin concordance studies have shown a probable genetic link between humans who smoke and those who do not smoke (Fisher, 1958; Raaschou-Nielsen, 1960; Dies and Reznikoff, 1969; Pedersen, 1981). Monozygotic twins are more likely either both to smoke or both not to

smoke than dizygotic twins. Smokers are also able to titrate their plasma level of nicotine differently, and these differences appear to be related to individual sensitivity to nicotine. Studies that have incorporated nonsmokers suggest that nicotine does not have the same physiological effects on smokers and nonsmokers. Nonsmokers respond differently to polacrilex than smokers (Heishman *et al.,* 1993), and no changes in cognitive functioning for nonsmokers have been reported, but reversal by nicotine of cognitive deficits produced by abstinence in smokers has been (Hindmarch *et al.,* 1990).

NEUROPROTECTIVE PROPERTIES

The differences seen in epidemiological, developmental, aging, genetic, and gender studies are an indication of the complexity of the mechanisms of action of nicotine and the importance of individual differences. Added to this complexity is the apparent protective properties nicotine possesses in some physiological systems. Several studies using a partial unilateral hemitransection of the ascending mesostriatal dopamine pathway have shown that nicotine has neuroprotective properties (Janson *et al.,* 1988; Owman *et al.,* 1989; Fuxe 1989). In this paradigm, (1) chronic infusion of nicotine blocks retrograde and anterograde degeneration of dopaminergic neurons (Janson *et al.*, (1989), (2) nicotine has a positive effect on glucose utilization (Owman *et al.*, 1989), and (3) desensitization of nicotinic receptors located on dopaminergic neurons may modulate dopamine utilization (Fuxe *et al.,* 1989). Decreased utilization of dopamine would require less energy to be expended by these neurons.

Nicotine also has been shown to possess neuroprotective properties against the cholinergic neurotoxin AF64A and the dopaminergic neurotoxin MPTP. Villaneuva *et al.* (1992), in an eight-arm radial maze working memory task (1-h delay), demonstrated the protective effect of nicotine against AF64A. Alzet minipumps (14 day) containing nicotine or saline were implanted prior to initiation of training. Testing after bilateral ventricular injections of AF64A (3 nmol/μl) produced significantly fewer errors for nicotine-treated rats compared to controls. Subcutaneous nicotine injections in conjunction with implantation of nicotine-containing alzet minipumps protected nigrostriatal dopaminergic neurons from the neurotoxin MPTP (Janson *et al.,* 1989).

Janson *et al.* (1993) reported an up-regulation of D2 receptors in saline-treated rats following partial mesodiencephalic hemitransection, but not in chronic nicotine-treated rats. In experiments with similar lesions, it has been reported that nicotine treatment decreases the firing of nigral DA neurons (Grenhoff, 1991) and reduces the utilization of DA (Fuxe, 1990). The ability of nicotine to modulate dopaminergic neurons with respect to firing rates and utilization of DA may be a primary factor in its neuroprotective properties.

In an aging study, chronic oral nicotine administration in male Fisher 344 rats reversed normal age-related losses of nigrostriatal D1 and D2 dopaminergic neurons. Age-related declines in behavioral measures were also attenuated in chronic nicotine-treated rats (Prasad *et al.,* 1994). The ability of nicotine to delay or attenuate the loss of dopaminergic neurons appears to be related to a reduction in activity of these neurons. If this effect is due to desensitization or some other mechanism as yet unknown, but taken with the protection against AF64A, a high-affinity choline uptake blocker, the answer probably is more complex than just the desensitization of nicotinic receptors.

CONCLUSION

Several subtypes of neuronal nicotinic receptors exist in brain which are coupled to various transmitter systems and hormones. Nicotinic receptors can be influenced directly and indirectly by genetic and environmental factors which might be of importance in the pathogenesis as well as for the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Studies indicate possible trophic and neuroprotective effects exerted by nicotine. Early exposure to nicotine might influence development of subtypes of nicotinic receptors and thus influence physiological and behavioral function. The negative correlation between nicotine and Parkinson's disease and possibly subtypes in brain might, in the future, represent novel therapeutic approaches in the treatment of neurodegenerative disorders.

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