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Targeting nicotinic receptors for Parkinson's disease therapy

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Abstract

A promising target for improved therapeutics in Parkinson's disease is the nicotinic acetylcholine receptor (nAChR). nAChRs are widely distributed throughout the brain, including the nigrostriatal system, and exert important modulatory effects on numerous behaviors. Accumulating evidence suggests that drugs such as nicotine that act at these sites may be of benefit for Parkinson's disease treatment. Recent work indicates that a potential novel therapeutic application is the use of nicotine to reduce levodopa-induced dyskinesias, a side effect of dopamine replacement therapy for Parkinson's disease. Several clinical trials also report that nicotine may diminish disease symptoms. Not only may nAChR drugs provide symptomatic improvement, but they may also attenuate the neurodegenerative process itself. This latter idea is supported by epidemiological studies which consistently demonstrate a ~50% reduced incidence of Parkinson's disease in smokers. Experimental work in parkinsonian animal models suggests that nicotine in tobacco may contribute to this protection. These combined findings suggest that nicotine and nAChR drugs offer the possibility of improved therapeutics for Parkinson's disease.

Keywords

Nicotine; nicotinic receptors; levodopa; dyskinesias; neuroprotection; parkinsonian; Parkinson's disease

INTRODUCTION

Parkinson's disease is a neurodegenerative movement disorder characterized by a generalized neuronal decline in the CNS, with a particularly prominent loss of nigrostriatal dopaminergic neurons [1]. Dopamine replacement provides excellent therapeutic relief in the early stages of the disease. However, there is a constant search for new pharmacotherapies for Parkinson's disease management because of limitations associated with current treatment [1-2]. Effectiveness in reducing Parkinson's disease symptoms diminishes with continued use and side effects develop, including on-off phenomena and dyskinesias. Another drawback with current treatment is that it primarily provides symptomatic relief, with an inevitable disease progression.

Emerging studies suggest that nicotine treatment might be a useful adjunct therapy for Parkinson's disease. Recent work in monkey, mouse and rat parkinsonian animal models show that nicotine reduces levodopa-induced dyskinesias, a side effect of dopamine replacement therapy that may be as debilitating as the disease itself [3]. Clinical studies also suggest that nicotine has antiparkinsonian effects [4]. Lastly, nicotine protects against nigrostriatal damage in different experimental models [3a, 5]. These latter findings form the

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basis for the suggestion that nicotine in tobacco products may be associated with the decreased incidence of Parkinson's disease observed with smoking [4, 6].

The goal of this paper is to discuss the interaction between the dopaminergic and nicotinic cholinergic systems to provide a framework for understanding a role for nicotine in Parkinson's disease. We also review some promising pre-clinical work which indicates that nicotine and/or nAChR drugs may be useful for improving levodopa-induced dyskinesias in Parkinson's disease and for protection against long-term nigrostriatal damage.

RELATIONSHIP BETWEEN THE NICOTINIC CHOLINERGIC AND DOPAMINERIGIC SYSTEM

Knowledge of the anatomical interrelationship between the striatal cholinergic and dopaminergic systems has contributed significantly to our understanding of the role of nicotine in Parkinson's disease therapy. Numerous studies have shown that the terminals from the ascending nigrostriatal dopaminergic projections from the substantia nigra extensively overlap with acetylcholine interneurons present in the striatum [7]. These cholinergic neurons represent a small percentage (~2-3%) of the neuronal cell bodies in the striatum, the greater majority (~95%) of which are GABAergic. However, despite their limited number, the cholinergic neurons are quite large. Importantly, their dendritic arborization forms a dense network in striatum whose distribution closely matches that of the dopaminergic terminals, with a very similar expression pattern of dopaminergic (dopamine, tyrosine hydroxylase, dopamine transporter) and cholinergic (acetylcholine, choline acetyltransferase and acetylcholinesterase) markers [8]. Cholinergic interneurons tonically secrete acetylcholine, which modulates neurotransmitter release from striatal dopaminergic neurons, and also to a lesser extent from cortical glutamatergic terminals. Acetylcholine exerts these effects on dopamine release via an interaction at nAChRs, of which there are multiple subtypes [9].

NICOTINIC RECEPTOR SUBTYPES

Structurally the CNS nAChR has as its basic motif, a pentamer of five subunits around a central pore that lies within the membrane bilayer. Molecular cloning has identified nine α (α2-α10) and three β (β2-β4) subunits. Select α (α2-α6) and β (β2-β4) subunits assemble into heteropentamers. Homopentamers composed only of α subunits also exist and may contain only α7, α8 and α9 subunits or combinations of α7α8 and α9α10 subunits [9]. The binding of acetylcholine to the receptor complex occurs at the recognition site present on the α subunit. However, the β subunit also contributes towards the pharmacological properties of the receptor binding site by modulating the interaction of the ligand with the α subunit at the binding interface that lies between the α (α2, α3, α4, α6) and β (β2 or β4) subunits in heteromeric receptors. The α5 and β3 subunits do not participate in the acetylcholine binding site and are termed accessory subunits. The binding interface in the pentameric complexes composed of only α (α7-α10) nAChR subunits occurs between two α subunits to result in five identical acetylcholine binding sites [9a, 9c].

Extensive studies using a wide variety of approaches now show that multiple receptor subtypes are generated by the association of different α and β subunits, with the primary ones in the CNS being the α4β2* (the asterisk denotes the possible presence of other nAChR subunits in the receptor complex) and α7 subtypes [9c, 10]. These nAChRs are widely distributed throughout the brain, and are localized presynaptically and also somato-dendritically on postsynaptic neurons [9]. One of their primary functions is to modulate synaptic transmission and plasticity mediated via other neurotransmitter systems with resultant changes in attention, cognition, depression and affect [9, 11].

The α4β2* and α7 nAChRs are also involved in controlling striatal dopamine function [12] with consequent effects on motor and reward-related responses [11, 12b, 13]. Receptors containing solely α4β2 subunits are present on both striatal dopaminergic and glutamatergic terminals, with a subpopulation of α4α5β2 nAChRs expressed only on dopaminergic terminals in rats [10a, 10c, 12a]. Receptors containing the α4β2 subunits can exist in two different forms, a high sensitivity subtype with a stoichiometry of $(\alpha4)_2(\beta2)_3$ and a low sensitivity receptor with a stoichiometry of $(\alpha4)_3(\beta2)_2$.[14] Thus, both varying α4β2* subunit composition and stoichiometry can generate subtypes with a distinct pharmacological and functional characteristics under different treatment conditions [15]. Although the role of striatal postsynaptic α7 nAChRs is still unclear, those localized presynaptically on cortical glutamatergic afferents influence striatal dopamine release.

Pentameric complexes of α6β2* nAChR subtypes are uniquely restricted to CNS catecholaminergic neurons including those in the dopaminergic mesolimbic and nigrostriatal pathway. They are present on dopaminergic terminals and thought to be involved in reward, addiction and motor activity [16]. The use of various experimental strategies has identified the presence of two major α6β2* nAChRs, the α6β2β3 and α6α4β2β3 subtypes, as well possibly as a small population expressing only α6β2 subunits [9a, 10a, b, 12a, 17].

In summary, the primary nAChR populations in the striatum includ the α4β2, α4α5β2, α6β2β3, α6α4β2β3 and α7 subtypes. These may be expressed pre- and/or post-synaptically on dopaminergic, glutamatergic, GABAergic and/or other neurons, with a primary role of the presynaptic receptors to modulate dopamine release. The observed heterogeneity in subtypes may be important for fine-tuning of striatal dopaminergic function under varying physiological and pathological conditions.

NACHR MODULATION OF NIGROSTRIATAL DOPAMINE FUNCTION

As mentioned earlier, dopamine neurotransmission is regulated by tonically active cholinergic interneurons that act as a pulsed source of acetylcholine to modulate dopamine release via pre- and postsynaptic nAChRs. NAChR activation subsequently changes membrane excitability and initiates a calcium signaling cascade that ultimately results in neurotransmitter release [7a, 12b, 18]. This can occur via direct stimulation of nAChRs on striatal dopaminergic terminals or through the stimulation of nAChRs on striatal glutamatergic terminals [10b, 19].

One approach to measure presynaptic nAChR-mediated dopamine release involves the use of striatal synaptosomes and slices preloaded with ^{3}H-dopamine [12a]. This technique, coupled with the use of genetically modified mouse models and the α6 selective neurotoxin α-conotoxinMII, has greatly expanded our understanding of the functional role of nAChR subtypes on the dopamine system [20]. Several nAChR subtypes modulate striatal dopamine function, including the α4β2, α4α5β2, α4α6β2β3 and α6β2β3 subtypes, with the α4β2* nAChRs responsible for 50-70% of nAChR-mediated dopamine release and the α6β2* nAChRs the remainder [10c, 12a, 16a].

Another advance that has provided invaluable information about the role of nAChRs in regulating dopamine release is fast scan cyclic voltammetry using striatal slices [12b, 21]. This technique allows for the real-time assessment of endogenous dopamine release stimulated electrically at biologically relevant frequencies that mimic typical neuronal firing rates. Experimental studies indicate that nicotine has differential effects on dopamine release depending on the neuronal firing rate with a suppression of release at low stimulation frequencies but not under phasic firing conditions [12b, 21]. Studies with slices from knockout mice suggest that β2* nAChR primarily modulate striatal dopamine release [21g]. The α6β2*

subtype mediates ~80% of nAChR-regulated dopamine release at low firing rates, with the α4β2* receptor population regulating the remainder [21a-c, 22].

In vivo studies have also been done to study the role of nAChRs in the control of striatal dopamine levels. These generally involve microdialysis followed by high pressure liquid chromatography to measure dopamine levels. Acute systemic nicotine or local perfusion of nicotine through the microdialysis probe both increase dopamine levels in striatum [23]. Studies with α4, α6 and β2 nAChR knockout mice suggest that the α4β2 nAChR plays a major role in regulating striatal dopamine release *in vivo* [10b, 24].

These combined results indicate that α6β2* and α4β2* nAChRs play a pivotal role in the control of striatal dopaminergic signaling. This knowledge is fundamental for understanding the nature of the dysfunction in neurological disorders such a Parkinson's disease and developing optimal treatment regimens.

Nigrostriatal damage reduces nAChR-mediated dopamine release

Studies in parkinsonian mice, rats and monkeys show that striatal nAChR subtypes are decreased with striatal dopaminergic denervation [9a, 25]. Nigrostriatal degeneration results in differential receptor subtype loss depending on the extent of damage, with a predominant loss of the α6α4β2β3 nAChR with moderate lesioning, a decrease in the α6β2β3 subtype with greater nigrostriatal damage, and a decrease in the α4β2 subtype only with very severe degeneration [17b, 25]. Similar results were obtained in brains from Parkinson's disease cases, with 30 to 75% declines in nAChRs in the caudate, putamen and substantia nigra that appear to correlate with the extent of nigrostriatal damage [26]. A comparison of changes in α4β2* versus α6β2* nAChRs, showed that greater declines were observed in α6β2* receptors, with the most prominent loss in the α6α4β2β3 as compared to the α6β2β3 nAChR subtype. The α4β2* nAChRs were decreased only with severe degeneration [17b, 17d, 27]. Consistent with the animal studies, α7 nAChRs were not changed with nigrostriatal damage. This disparate receptor subtype loss raises the intriguing possibility that the different nAChR subtypes are present on different neuronal populations some of which are more susceptible to neurodegenerative processes than others.

The finding that striatal nAChR subtypes and their function are differentially vulnerable to nigrostriatal damage supports the notion that the different nAChR subtypes are present on different neuronal populations some of which are more susceptible to neurodegenerative processes than others. Such an idea is also supported by the results of cyclic voltammetric studies, which show that there is a different distribution of nAChRs on dopaminergic fibers with various electrophysiological characteristics [21b]. For instance, evoked dopamine release from fibers with a low action potential threshold is modulated primarily by α6β2* nAChRs. By contrast, evoked released is influenced predominantly by α4β2* nAChRs for fibers exhibiting higher action potential thresholds. The presence of varying nAChR subtypes on these different classes of striatal fibers may make them differentially vulnerable to neurotoxic agents. Continued studies are in progress to investigate this hypothesis.

The question now arises whether there might be a differential regulation of striatal dopamine release with the preferential loss of one or other nAChR subtype. In rodent striatum, nAChR stimulated dopamine release is decreased with dopaminergic degeneration, as expected. In this species, there was a very close correspondence between the decline in dopamine release and the loss of nAChR receptors [28]. Results also suggested that dopamine release mediated by the α4β2* and α6β2* nAChR subpopulations are altered in a corresponding fashion by nigrostriatal damage [28]. These data contrast with those obtained in a similar series of experiments in nonhuman primates. Although MPTP-treatment induces similar decreases in nAChRs in monkey and rodent striatum, this decline in receptor density was not associated

with a concomitant decrease in either α4β2* or α6β2* mediated dopamine release with moderate nigrostriatal damage [29]. These data suggest that there is presynaptic compensation in the release process of monkeys with nigrostriatal damage that involves both the α4β2* and α6β2* nAChR population. These findings are also supported by voltammetry studies that show increased dopamine release in primates after moderate nigrostriatal damage [21d].

Overall, these data show that nAChRs influence dopamine release under control conditions and in the presence of nigrostriatal damage. The primary subtypes involved are the α4β2* and α6β2* nAChR which may be present on different populations of dopaminergic neurons. Their presence on select neuronal populations may play a part in the differential sensitivity of various dopaminergic neurons to nigrostriatal damage. Notably, there appear to be differences in the nAChR mediated regulation of dopamine release in rodents and primates with compensation after moderate damage in nonhuman primates but not rodents. Continued studies in different parkinsonian animal models are essential for a clear understanding of the role of nAChRs in controlling dopamine function in Parkinson's disease.

Chronic nicotine treatment alters nAChR-mediated release

As mentioned, accumulating work suggests that nicotine treatment may be of benefit in Parkinson's disease since it reduces levodopa-induced dyskinesias in parkinsonian animal models and may also play a neuroprotective role against nigrostriatal damage. An important question is thus how chronic nicotine treatment may affect striatal dopamine function. Numerous studies have shown that long term nicotine administration upregulates α4β2* nAChR expression in rodents, non-human primates and human brain [29a, 30]. This receptor increase is linked to a concomitant increase in nAChR-mediated dopamine release as measured in brain slices or by microdialysis [31], although a decrease or no change was observed when measured in striatal synaptosomes [30a, 32]. This apparent discrepancy now appears to be due to the fact that the enhanced α4β2* receptor expression is accompanied by a downregulation of α6β2* nAChRs such that there is no net change in nAChR mediated dopamine release [30a, 32a, 32d, e].

Some of these results in striatal synaptosomes are supported by our recent cyclic voltammetry studies in striatal slices from rats and primates. In rats, chronic nicotine treatment enhanced nonburst and burst stimulated endogenous dopamine release similar to the overall increase in nAChR-mediated dopamine release in synaptosomes [22]. Interestingly, long term nicotine treatment also attenuated the α6β2* nAChR-mediated regulation of striatal dopaminergic function with burst firing, an observation consistent with the nicotine-induced decline in α6β2* nAChR expression and function [22]. In contrast, in monkeys, chronic nicotine administration did not enhance either nonburst or burst release and attenuated both α4β2* and α6β2* nAChR-mediated responsiveness in some although not all striatal regions [21c].

These voltammetric data demonstrate that chronic nicotine exposure modulates nAChR-mediated dopamine release in striatum, although the precise functional implications of these cellular changes remain to be elucidated. Greater knowledge of the alterations in nAChR expression and function is important for a clear understanding of the effect of drug treatment under varying pathological conditions such as Parkinson's disease [25].

POTENTIAL ROLE OF NICOTINIC RECEPTOR ACTIVATION IN NIGROSTRIATAL FUNCTION

The morphological overlap coupled with the functional interaction between the dopaminergic and nicotinic cholinergic system provides the biological basis for nicotine's potential to influence behaviors linked to Parkinson's disease. These include the ability of

nicotine (1) to reduce levodopa-induced dyskinesias, a debilitating side effect of levodopa therapy, (2) to improve motor symptoms in Parkinson's disease and (3) to protect against nigrostriatal damage. Evidence for such roles for nicotine and the potential importance to Parkinson's disease therapeutics is discussed below.

Nicotine treatment reduces levodopa-induced dyskinesias

Experimental evidence from several animal models now suggests that nicotine may be useful for improving levodopa-induced dyskinesias in Parkinson's disease. These are abnormal involuntary movements that arise with levodopa treatment, the gold-standard for Parkinson's disease therapy. They may be quite mild or so problematic that they compromise the antiparkinsonian effectiveness of levodopa [1, 33]. They may develop very rapidly (months) and or more slowly such that the majority of patients develop dyskinesias within 5-10 years [34]. Dyskinesias are extremely difficult to prevent. One strategy to postpone their onset involves the initial use of low dose levodopa, but since Parkinson's disease generally progresses with time, increasing doses of levodopa are inevitably required to manage symptoms [1, 33]. Dopamine agonists are also less prone to inducing dyskinesias; however they are also less effective at controlling motor symptoms, less well-tolerated overall, and associated with psychiatric and other adverse effects. Drug treatments for reducing levodopa-induced dyskinesias are very limited, with amantadine currently the only accepted pharmacologic approach for reducing their occurrence, although its effects are modest [35]. A host of drugs influencing the dopaminergic, serotonergic, glutamatergic, adrenergic, cholinergic, opioid, adenosine and various peptidergic systems are being/have also been tested but in general the drugs tested appear to have limited efficacy [2b, 4, 35b, 36]. Additional therapies to reduce levodopa-induced dyskinesias are therefore critical.

Our recent studies show that drugs interacting with the nicotinic cholinergic system are effective in attenuating levodopa-induced dyskinesias. Nicotine, a drug that interacts with multiple nAChR subtypes, reduces levodopa-induced abnormal involuntary movements (AIMs) in three different parkinsonian animal models. Nicotine significantly attenuated dyskinesias in levodopa-treated MPTP-lesioned monkeys, when given either before the onset of dyskinesias or when they were established [3a]. We obtained similar results in parkinsonian rodent models of levodopa-induced dyskinesias, attesting to the robustness of the effect of nicotine across species. Nicotine given via several modes of administration (drinking water, minipump or injection) significantly improved levodopa-induced AIMs in rat and mouse parkinsonian models (Bordia et al., 2008). These modes of administration readily lend themselves to use in Parkinson's disease patients, for instance, as an oral formulation or a slow release mode (nicotine patch). Notably, nicotine did not modify the anti-parkinsonian effect of levodopa in any species. This basic work has led to the initiation of a clinical trial to test nicotine against levodopa-induced dyskinesias in Parkinson's disease patients.

The mechanisms whereby nicotine reduces levodopa-induced dyskinetic-like movements are not yet know. However, studies with the nAChR blocker mecamylamine show it involves an interaction at nAChRs [37]. The select nAChR populations remain to be elucidated, although the α4β2* and α6β2* subtypes are probably important since these are the primary ones involved in striatal function [9c, 12, 38]. Studies with agonists that interact with both α4β2* and α6β2* nAChRs show that such drugs reduce levodopa-induced AIMs almost as effectively as the nonselective nAChR agonist nicotine [39]. Studies are currently in progress to identify the role of the α4β2* versus α6β2* nAChR subtypes and the mechanisms whereby an interaction at nAChRs reduces levodopa-induced dyskinesias.

Nicotine and Parkinson's disease motor symptoms

Another question that arises is whether nicotine may improve motor symptoms in Parkinson's disease patients since it is well known to stimulate striatal dopamine release [7a, 12b, 18]. Work to address this issue shows that nicotine improves parkinsonian symptoms in ~50% of reports/trials, with improvement in five, no effect in four and a worsening in one [4]. The reason for these differences among studies may relate to variations in the mode of administration of nicotine (patch, gum, intravenous), inadequate dosing, timing or duration (days to weeks) of treatment, differences in the degree of parkinsonism and type of trial (open-label versus double-blinded) [40]. Work in parkinsonian rats and monkeys show that chronic nicotine treatment in the drinking water or via minipump did not lead to a reduction in parkinsonism either on or off Levodopa [3a, b]. These findings in animal models support the results of the trials demonstrating no beneficial effect of nicotine on Parkinson's disease symptoms.

Continued work is necessary to ascertain whether or not nicotine improves Parkinson's disease motor symptoms. Overall, however, these data indicate that nicotine and nicotinic agonists do not worsen, and possibly improve, motor symptoms if such drugs were used for the treatment of levodopa-induced dyskinesias in Parkinson's disease.

Nicotine and neuroprotection

In addition to its effects on Parkinson's disease motor symptoms and dyskinesias, nicotine may also have a long term beneficial action by protecting against nigrostriatal damage. Evidence for such a possibility initially stemmed from the results of epidemiological studies. These showed that a reduced incidence of Parkinson's disease is associated with smoking, in contrast to the enhanced risk associated with other factors such as age, gender, and pesticide exposure [4, 6, 41]. An average 50% lower incidence of Parkinson's disease was observed for those who smoked ~20 years prior to disease diagnosis. Moreover, there appeared to be a dose-response relationship, with decreasing Parkinson's disease risk correlated with increasing pack-years smoked.

The putative neuroprotective effect of smoking has been attributed to the ability of nicotine in tobacco to attenuate nigrostriatal data. This possibility is based on results of both *in vitro* and *in vivo* experimental studies [5b, 31b, 42]. For instance, nicotine protects primary cultured neurons against MPTP or LPS-induced toxicity [42c, d]. Moreover, chronic nicotine pretreatment improves neurotoxin-induced nigrostriatal damage in rodents and nonhuman primates, with protection dependent on the extent of neuronal damage and nicotine dosing regimen [31b, 42a, b, 42e, f]. As mentioned earlier, the etiology of Parkinson's disease is currently uncertain, with a potential role for both genetic and environmental factors. Experiments done to date investigating nicotine-mediated protection have all involved neurotoxic-induced animal models of nigrostriatal damage that may represent an environmental model of Parkinson's disease. A question that arises is whether nicotine also protects against slowly progressive genetic animal models of Parkinson's disease, such as those involving α-synuclein or other mutations [43]. This is an important issue that awaits further study.

In the above *in vivo* studies nicotine was given prior to and during the development of nigrostriatal damage, a protocol which provides for an assessment of the neuroprotective potential of nicotine. However, epidemiological studies show that once the disease is diagnosed, smoking does not appear to improve Parkinson's disease [44]. These latter findings raise the question whether nicotine is only neuroprotective or whether it can also restore function of damaged neurons. Our recent experimental studies in parkinsonian rats and monkeys show that nicotine had no beneficial effect when administrated after nigrostriatal

damage is complete. Thus, nicotine's primary role appears to be neuroprotective and not neurorestorative [42b].

The mechanisms underlying nAChR-mediated neuroprotection are currently being investigated. Accumulating evidence suggests that nicotine acts via β2* and α7 nAChRs. The β2* nAChRs, which include the α4β2* and α6β2* subtypes, are expressed on striatal dopamine terminals and appear to be the primary populations involved in protection [42a, b, 45]. Further work has identified two α6β2* receptor subpopulations, the α6β2β3 and α6α4β2β3 subtypes, with the latter the most susceptible to neurodegeneration [17b, 42b]. Interestingly, the α6α4β2β3 subtype is not decreased in parkinsonian compared to sham-lesioned rats with nicotine treatment. This finding suggests that the presence of the α6α4β2β3 subtype may confer a protective action against nigrostriatal damage [42b]. Studies using cultured nigral dopaminergic neurons also suggest that α7 nAChRs present may be important in neuroprotection by modifying immune responsiveness [42d, 46]. Taking together, the heteromeric α4β2* nAChR and/or homomeric α7 nAChR appear to contribute to nAChR-mediated neuroprotective effects against nigrostriatal damage.

NAChR activation may mediate neuroprotection by triggering diverse signaling pathways, with the first step most likely involving alterations in cytoplasmic calcium dynamics [47]. Elevated intracellular calcium may subsequently activate kinases involved in modulating apoptosis, immune modulator and neurotrophic factor expression [42g, 48]. Nicotine decreases the level or activity of pro-apoptotic factors such as caspases and JNK kinases and increase the activity of anti-apoptotic factors [46a, 49]. In addition, nicotine treatment enhances FGF-2 and NGF in cell culture, as well as in various brain regions in rats. Altered apoptotic mechanisms coupled with enhanced neurotrophic factor expression may promote survival and protect damaged dopaminergic neurons [21g, 50]. Accumulating evidence suggests that inflammatory processes participate in the cascades leading to neuronal degeneration in Parkinson's disease [51]. Nicotine has been shown to attenuate immune responses within various brain regions via receptors expressed on microglia and astrocytes [52]. Lastly, dopamine released in response to nAChR activation may compete with endogenous or exogenous toxic agents for entry into the dopamine terminal, and thus attenuate neurodegenerative effects.

A point of note is that this reduced disease incidence with smoking appears specific for Parkinson's disease. Similar epidemiological approaches find inconsistent declines in Alzheimer's disease with smoking [53]. These discrepancies may be related to the minimum age at study entry with a relative rate for smokers versus nonsmokers ranged from 0.27 to 2.72 for Alzheimer's disease with age (55 to 75 years) [53a]. The cellular/molecular basis for protection against nigrostriatal damage as occurs in Parkinson's disease is not known; however, the selective protection against Parkinson's disease may suggest that it involves an interaction between the nicotinic and dopaminergic systems as discussed above.

To conclude, nicotine is neuroprotective although not neurorestorative against nigrostriatal damage, most likely via an interaction at nAChRs. The receptors implicated in this neuroprotection appear to involve the α6β2* and α4β2* subtypes, as well as the α7 receptors. Stimulation of these different subtypes by nicotine may then result in neuroprotection by modulating a host of downstream signaling pathways.

CONCLUSION

Converging evidence suggests that nicotine and/or nicotinic agonists may prove beneficial in the management of Parkinson's disease. This includes their use in the treatment of levodopa-

induced dyskinesias, a debilitating side effect that arises in the majority of treated patients. Nicotine may also reduce Parkinson's disease symptoms, although definitive proof awaits further study. Lastly, nicotine treatment may slow down Parkinson's disease progression. This neuroprotection is of particular importance as this implies that nicotine administration may reduce the need for symptomatic treatments.

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ABBREVIATIONS

AIMs	abnormal involuntary movements
nAChR	nicotinic acetylcholine receptor
*****	indicates the possible presence of other subunits in the receptor complex

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