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Nicotine as a potential neuroprotective agent for Parkinson's disease

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Abstract

Converging research efforts suggest that nicotine and other drugs that act at nicotinic acetylcholine receptors (nAChRs) may be beneficial in the management of Parkinson's disease. This idea initially stemmed from the results of epidemiological studies which demonstrate that smoking is associated with a decreased incidence of Parkinson's disease. The subsequent finding that nicotine administration protected against nigrostriatal damage in parkinsonian animal models led to the idea that nicotine in tobacco products may contribute to this apparent protective action. Nicotine most likely exerts its effects by interacting at nAChRs. Accumulating research indicates that multiple subtypes, including α4β2, α6β2 and/or α7 containing nAChRs, may be involved. Stimulation of nAChRs initially activates various intracellular transduction pathways primarily via alterations in calcium signaling. Consequent adaptations in immune responsiveness and trophic factors may ultimately mediate nicotine's ability to reduce/halt the neuronal damage that arises in Parkinson's disease. In addition to a potential neuroprotective action, nicotine also has anti-depressant properties and improves attention/cognition. Altogether, these findings suggest that nicotine and nAChR drugs represent promising therapeutic agents for the management of Parkinson's disease.

Keywords

Neuroprotection; Nicotine; Nicotinic; Nigrostriatal damage; Parkinson's disease

Introduction

A critical unmet need in the management of Parkinson's disease is the development of strategies to slow, stop, or preferably reverse the neurodegenerative process. Parkinson's disease is a neurological disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta that results in tremor, rigidity and bradykinesia [1–7]. Although the nigrostriatal dopaminergic deficits are the most severe, there are also declines in numerous other CNS neurotransmitter systems. These most likely underlie the non-motor problems associated with Parkinson's disease, including autonomic deficits, psychiatric symptoms, behavioral changes, dementia, sleep disorders and others [1–7].

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Dopamine replacement therapies provide effective control of the motor symptoms, particularly in the early stages of the disease. However, they do not adequately manage the non-motor deficits and, in addition, induce a variety of motor and psychiatric side effects. Moreover, they provide only symptomatic relief while the underlying disease continues to worsen. These shortcomings highlight the importance of identifying novel treatment strategies that delay or halt disease progression, or ideally restore function in Parkinson's disease.

Development of neuroprotective agents for Parkinson's disease

Although drug development has yielded numerous agents for the symptomatic control of motor impairments in Parkinson's disease, there are as yet no approved drugs capable of reducing disease progression. One reason for this relates to uncertainty as to the cause of Parkinson's disease (Table 1). Accumulating evidence indicates that exposure to environmental agents, such as fungicides, herbicides, pesticides and metals, is associated with an increased risk of Parkinson's disease [8–12]. In addition, specific gene defects have been linked to familial and sporadic forms of Parkinson's disease including mutations in LRRK2, alpha-synuclein, parkin, DJ-1, PINK1 and others [13–15]. However, it is unclear how these environmental insults and/or gene mutations contribute to the degenerative changes observed in Parkinson's disease brain, for instance, mitochondrial dysfunction, oxidative stress, modifications in protein handling, adaptations in immune-modulators, as well as alterations in other molecular and cellular functions [1, 15]. An understanding of the factors involved in the etiology of Parkinson's disease and how they mediate subsequent pathological changes is essential for the development of rational neuroprotective strategies. Moreover, this knowledge may lead to the identification of an early biomarker for Parkinson's disease. Symptoms only arise when there is already considerable neuronal degeneration; early detection would allow for the administration of protective treatments before the onset of disease symptoms.

Other factors (Table 1) that have hampered the identification of clinically effective neuroprotective agents for Parkinson's disease include the lack of parkinsonian animal models that precisely mimic the pathogenesis of the disease with respect to its etiology, slow progressive nature and pattern of cell loss [16–20]. Most of the neurotoxin-induced or genetic animal models lack one or more of these key features, although a more recent rotenone model may represent a better alternative [16–21]. This shortcoming is exacerbated by difficulties in translating the animal data to the design of an effective clinical trial with respect to optimal drug dosage and timing. A drug treatment regimen in an animal model may not be suitable in Parkinson's disease patients because of differences in drug metabolism, pharmacokinetics and pharmacodynamics. Another obstacle in the development of effective neuroprotective strategies is an inability to discriminate between the acute and long term effects of a drug. For instance, the drug of interest may acutely improve the same clinical symptoms that are also the endpoint of the neuroprotective trial, thus complicating data interpretation. Continued pre-clinical and clinical research is necessary to resolve these issues and identify targeted neuroprotective drugs.

Putative neuroprotective strategies for Parkinson's disease

Despite the above limitations, there is optimism in the development of disease modifying strategies for Parkinson's disease. An expanding pre-clinical effort provides support for a growing number of agents that may be useful for neuroprotection against nigrostriatal damage. Results from *in vitro* and *in vivo* work have led to the design of a number of trials investigating neuroprotection in Parkinson's disease patients (Table 2). Drugs under study include compounds that modulate mitochondrial function like creatine and coenzyme

Q [22–24] and the antioxidant glutathione [25]. Trophic factors [26, 27], immune-modulators [28–31], and the calcium channel blocker isradipine [32] have or are being tested for their ability to delay disease progression. The diversity of agents initially appears somewhat daunting but may simply reflect the numerous interactive mechanisms that play a role in neurodegeneration under different conditions.

Epidemiological work has also been instrumental in identifying agents that may protect against Parkinson's disease [10, 11, 33, 34]. The most consistent and notable of these findings are the inverse associations between Parkinson's disease and elevated uric acid levels, coffee drinking and smoking. Uric acid, an antioxidant found in high concentrations in serum and brain, had been hypothesized to protect against oxidative damage and cell death as occurs in Parkinson's disease. Indeed, subsequent studies showed an inverse correlation between elevated uric acid and Parkinson's disease [35–38]. These combined findings formed the basis for a clinical trial to test inosine, which elevates urate levels, for its potential to modify Parkinson's disease progression (Table 2). An environmental factor that has been associated with a decreased incidence of Parkinson's disease is coffee drinking. Coffee may be beneficial via an antagonistic action of caffeine at adenosine A2a receptors [34, 39, 40]. A clinical trial to test the adenosine A2a antagonist preladenant is currently in progress (Table 2). Another lifestyle factor inversely correlated to the development of Parkinson's disease is smoking. The epidemiological evidence for this association and the components in tobacco smoke that may be responsible for smoking's apparent protective effect is the focus of the remainder of this review.

Smoking is linked to a reduced incidence of Parkinson's disease

An extensive epidemiological literature quite unexpectedly showed that tobacco use is associated with a lower incidence of Parkinson's disease [10, 11, 33]. Over 50 studies done over the last half century consistently demonstrate a reduced prevalence of Parkinson's disease among smokers compared to never-smokers [12, 41–43]. This inverse association between Parkinson's disease and smoking is correlated with increased intensity and duration of smoking, is more pronounced in current compared with former smokers, decreases with years after quitting smoking and was observed with different types of tobacco products. Importantly, it did not appear to be due to selective survival of Parkinson's disease cases or reporting bias [42–51]. These combined findings provide strong evidence for a negative association between smoking and Parkinson's disease.

Nicotine protects against nigrostriatal damage in parkinsonian animal models

Such compelling evidence for a decreased incidence of Parkinson's disease with smoking prompted studies to identify the active component(s) as such work may yield insight about potential neuroprotective strategies. A drawback is that tobacco and its combustion products contain thousands of chemicals any of which may improve neuronal integrity. However, despite the extensive number of reagents, tobacco constituents have been identified that protect against nigrostriatal damage in animals models.

One of these is 2,3,6-trimethyl-1,4-naphthoquinone (TMN) an inhibitor of monoamine oxidase (MAO) A and B activity [52–54]. TMN partially protects against MPTP-induced neurodegeneration in mice by reducing endogenous dopamine metabolism and consequently decreasing oxidative stress. It may also protect by blocking MAO-mediated activation of exogenous neurotoxins [55, 56]. An example of a synthetic MAO B inhibitor currently used in the treatment of Parkinson's disease is rasagiline. This drug appears to provide symptomatic relief and may also protect against nigrostriatal damage because of its ability to decrease

dopamine metabolism and prolong the action of dopamine [56]. In fact, rasagiline delayed the need for antiparkinsonian drugs in a recent clinical trial [57] (Table 2).

In addition to MAO inhibitors, another chemical in tobacco that has been the focus of intense research is nicotine. The rationale for investigating a role for nicotine is based on results demonstrating a close anatomical relationship between the nicotinic cholinergic and dopaminergic neurotransmitter systems in the striatum [58]. Moreover, nicotine influences dopaminergic activity by acting at nicotinic receptors (nAChRs) on dopaminergic terminals and modulating dopamine release [59, 60]. Such actions of nicotine may ultimately result in its overall functional effects including protection against nigrostriatal damage [61–63].

Numerous experimental studies have shown that nicotine administration enhances dopaminergic integrity in the striatum of parkinsonian rodents and monkeys [60–62]. This includes protection against MPTP-, 6-hydroxydopamine- or paraquat-induced toxicity in rats and mice [64–70]. Chronic nicotine administration also reduced MPTP-induced striatal damage in nonhuman primates, a model that shares many resemblances with the human disease [71, 72]. Several months of nicotine exposure improved striatal tyrosine hydroxylase, the dopamine and vesicular monoamine transporters, dopamine levels, nAChR expression and normalized lesion-induced over activity of the nigrostriatal pathway. This effect of nicotine appears to be due to protection against ongoing degeneration, as nicotine treatment did not enhance dopaminergic measures when administered to animals with pre-existing nigrostriatal damage (Fig. 1) [66]. These latter observations suggest that early treatment would yield optimal therapeutic benefit in Parkinson's disease patients.

Altogether, these data form the basis for the idea that nicotine may contribute, at least in part, to the apparent neuroprotective effect of tobacco use in Parkinson's disease.

Nicotine acts at nicotinic receptors

An important question is by what mechanisms nicotine protects against neuronal damage as such knowledge may allow for the development of drugs that selectively target the relevant molecular deficits. Considerable evidence suggests that nicotine primarily exerts its effects by acting at nAChRs. These are pentameric ligand-gated cation channels composed of varying combinations of different α and β subunits. The naturally occurring neurotransmitter for this receptor is acetylcholine which binds to the α or ligand binding subunit, of which there are 5 types in mammalian brain (α2, α3, α4, α6 and α7). In addition, the receptor may contain subunits which do not bind acetylcholine including the β2, β3, β4 and also the α5 subunit [73, 74].

These receptor subunits co-assemble to form a diverse family of nAChRs, the most abundant of which are homomeric α7 nAChRs and heteromeric β2 containing nAChRs (Fig. 2). These latter subtypes generally also contain α4 or α6 subunits to form two primary subpopulations, the α4β2* and α6β2* nAChRs (the asterisk denoting the possible presence of other subunits in the receptor complex). The α4β2* nAChRs are widely distributed throughout the brain, including the nigrostriatal pathway, while α6β2* nAChRs exhibit a more restricted CNS distribution that includes the nigrostriatal system [59, 74, 75]. Homomeric α7 nAChRs, like the α4β2* nAChRs, are also extensively localized throughout the brain although α7 receptors are expressed at a very low density in the nigrostriatal system of rats and monkeys. These findings suggest that, if α7 receptors influence nigrostriatal function, it would be through secondary effects on other brain regions.

Evidence derived from studies using multiple experimental strategies have further helped define the composition of the α4β2* and α6β2* nAChR populations (Fig. 2). This includes immunoprecipitation experiments with nAChR subtype selective antibodies, lesions of

specific neuronal pathways and the use of genetically modified nAChR mice. These combined approaches indicate that the primary populations in the nigrostriatal system are composed of α4β2, α4α5β2, α6α4β2β3 and α6β2β3 subunits [60, 76]

Nicotinic receptor subtypes that mediate neuroprotection

Our understanding of the specific nAChR subtypes involved in nicotine-mediated protection against neurotoxic insults is primarily derived from studies with cells in culture [61, 62, 77–79]. Experiments using neuronal cell lines or primary cultures from striatal, nigral, cortical, cerebellar and other brain regions show that nicotine pre-treatment can reduce damage from toxic insults by acting at α4β2* or α7 nAChRs [61, 62, 77–79]. This includes nicotine-mediated protection against glutamate-, β-amyloid- and ethanol-induced toxicity, as well as against nerve growth factor deprivation. The diversity of nicotine's action against varying toxic insults in cultures from different brain regions suggests that nicotine has the capacity to exert a widespread protective action. This could be important for Parkinson's disease since the neuronal deficits in this disorder are known to extend throughout the peripheral and central nervous system [80–82].

Knowledge concerning the specific nAChR subtypes through which nicotine protects nigrostriatal damage in parkinsonian animal models is much more limited because of the scarcity of subtype selective nAChR drugs currently available. However, the use of nonselective nAChR antagonists demonstrates that the effect of nicotine is mediated through nAChR [65]. Furthermore, work with α4 nAChR null mutant mice indicate that protection is reduced in striatum of such animals suggesting that the α4β2* nAChR subtype is important [68]. Other studies using rats with nigrostriatal lesions show that nicotine-mediated protection is not observed when the α6α4β2β3 nAChR subtype is lost, providing indirect evidence for an involvement of this receptor subtype[66].

The combined results of the *in vitro* and *in vivo* studies suggest that both β2* and α7 nAChR drugs may be useful for protection against the motor and non-motor deficits associated with Parkinson's disease pathology.

Molecular signaling mechanisms that mediate effects of nicotine

The next question is how an interaction at nAChRs leads to overall functional effects such as protection against neuronal damage. Although the intracellular mechanisms whereby nicotine mediates neuroprotection are only beginning to be understood, an important first step most likely involves alterations in calcium signaling, although calcium independent nAChR-mediated mechanisms have also been reported (Fig. 3) [62, 77, 79, 83–87]. Increased intracellular calcium may occur via an influx of calcium through nAChRs, secondarily via other membrane channels and/or through local increases in cellular calcium.

nAChR-mediated increases in calcium then trigger diverse downstream signaling molecules to ultimately modify neuronal function (Fig. 3) [62, 77, 79, 83–87]. Cellular molecules activated in response to nAChR-mediated changes in calcium include kinases such as protein kinase A (PKA) and extracellular signal-regulated mitogen-activated protein kinase (ERK/MAPK). Another signal transduction pathway activated by nicotine is one involving the calcium effector protein calmodulin (CaM) and phosphatidylinositol 3-kinase (PI3K)/Akt-or protein kinase B-dependent signaling [69]. There may also be modifications in the JAK2 (Janus kinase 2)/PI3K and/or JAK2/STAT3 (signal transducer and activator of transcription 3) pathways, with the latter possibly being calcium independent [83]. Activation of these diverse signalling cascades has been reported to modulate caspase activity (3, 8 and 9), cell survival proteins such as Bcl-2 (B-cell lymphoma 2) and Bcl-x, NFκB (nuclear factor-kappaB), CREB (cAMP response element-binding), tyrosine hydroxylase and other molecular

components [62, 77, 79, 83–87]. These in turn may lead to decreased apoptosis, enhanced neuronal survival, modified immune responsiveness and alterations in synaptic plasticity. Of specific relevance to neuroprotection are nicotine-induced changes in basic fibroblast growth factor-2 (FGF-2), brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in brain dopaminergic and other regions, which could attenuate neuronal damage [88–91]. Nicotine may also act by modulating immune function, as cytokine production has been shown to protect against toxic insults and promote neuronal repair [83, 92–94].

Although nicotine mediates its effects primarily by interacting at nAChRs, receptor-independent mechanisms may also contribute to nicotine's neuroprotective potential. These include a reduction in mitochondrial complex 1 activity, inhibition of reactive oxygen species generation, oxidative or anti-oxidative potential and radical scavenging properties [95–99].

Overall, current evidence suggests that multiple molecular transduction mechanisms may be involved in nicotine-mediated adaptive changes, such as neuroprotection against neuronal injury. This finding may reflect the interactive nature of these processes or suggest that distinct signaling events are involved under various pathological conditions.

Usefulness of nicotine for Parkinson's disease therapeutics

In addition to a role for nicotine as a protectant against nigrostriatal damage, it may also be useful in reducing the dyskinesias that arise with long term L-dopa use in Parkinson's disease. Evidence for this idea stems from data from parkinsonian animal models which show that nicotine decreases L-dopa-induced dyskinesias in MPTP-lesioned monkeys, when administered before the onset of dyskinesias or once they are established [63]. There was also an improvement in L-dopa-induced abnormal involuntary movements in parkinsonian rodents treated with nicotine via several routes including drinking water, minipump or injection [100–102]. The mechanism whereby nicotine reduces L-dopa-induced dyskinesias is currently uncertain, but may involve an interaction at nAChRs, specifically β2* subtypes [102]. This basic work in parkinsonian animal models has led to a clinical trial to test nicotine against L-dopa-induced dyskinesias in Parkinson's disease patients; the results suggest that nicotine (designated NP002) may be beneficial (http://www.neuraltus.com).

An important question is whether nicotine directly affects Parkinson's disease motor symptoms. Our research studies indicate that acute nicotine administration did not modify parkinsonism in monkeys, rats or mice either ON or OFF L-dopa [63, 100, 102]. On the other hand, it did enhance the effects of L-dopa in other reports [103, 104], leaving its effects on parkinsonism in experimental animal models unclear. The role of nicotine for motor symptoms in Parkinson's disease patients are also uncertain. The results of clinical trials and case studies showed that nicotine treatment improved symptoms in five of ten published studies, with no effect in four and a worsening in one [105–113]. The reason for these differential outcomes may relate to variations in the mode of administration of nicotine (patch, gum, intravenous), inadequate dosing, timing or duration (days to weeks) of treatment, as well as differences in the degree of parkinsonism and type of trial (open-label versus double-blinded). In summary, results from both animal and clinical studies shed doubt on a direct beneficial effect of nicotine on motor symptoms [114, 115]. By contrast, current findings do yield compelling evidence that nicotine may be useful for the treatment of L-dopa-induced dyskinesias and for neuroprotection against ongoing disease progression.

An important issue with respect to therapeutic management is what would be the most effective nicotine delivery system for Parkinson's disease patients. Tobacco use is not an option since it leads to major health problems worldwide and decreases life expectancy due

to tobacco-related cancers, cardiovascular disease, pulmonary disease and other adverse health conditions [116–120]. However, nicotine itself exhibits a favorable safety profile and is widely available over-the-counter as a smoking cessation aid, with several nicotine formulations readily accessible at relatively low cost, including the transdermal nicotine patch, gum, lozenge, inhaler and spray [116–120]. With respect to optimal protective potential, it should be noted that nicotine appears to reduce ongoing neuronal damage in parkinsonian animal models but is not neurorestorative. These findings suggest that therapeutic intervention would be most effective in early stage Parkinson's disease. A double-blinded, placebo-controlled clinical trial currently in progress to test the transdermal nicotine patch in newly diagnosed patients (Table 2) should help evaluate nicotine's neuroprotective potential for Parkinson's disease.

Concluding Remarks

Extensive evidence from epidemiological and basic research studies indicates that nicotine may represent a drug with potential for protection against Parkinson's disease. Since nicotine acts at nAChRs, these data suggest that administration of nicotine and/or nAChR agonists in early Parkinson's disease may slow down and/or halt disease progression. This would help retard declines in motor function and also in non-motor deficits, including olfactory and autonomic problems, sleep disorders, cognitive declines, depression and pain [4, 7, 121, 122]. In addition to a neuroprotective role, nicotine treatment may directly improve some of these non-motor complications as an extensive literature shows that acute nicotine and/or nAChR drugs facilitate cognitive performance, reduce pain and alleviate depression in experimental animal models [123–130].

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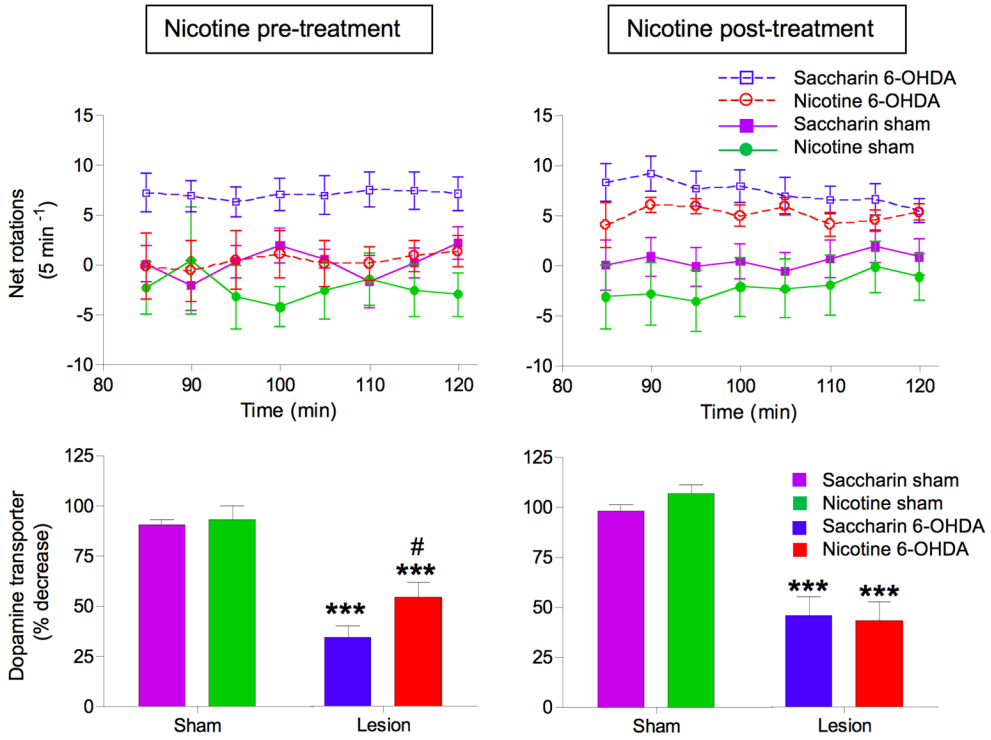

FIG. 1.

Nicotine is neuroprotective when administered before/during but not after nigrostriatal damage. For the pre-treatment studies, rats were first given nicotine in drinking water (50 μg/ml) for 2 wk after which they were lesioned with 6-hydroxydopamine, with nicotine maintained. Amphetamine-induced rotations were determined 2–3 wk later as an index of motor disability. The rats were then killed 2–3 wk later and the dopamine transporter measured. In the nicotine post-treatment study, rats were first lesioned and amphetamine-induced rotation measured 2 wk later. Immediately after behavioral assessment, nicotine treatment was initiated and maintained throughout. Rotational behavior was re-evaluated 3–4 wk after the start of nicotine dosing and the rats killed 3–4 wk later, such that the total number of wk on nicotine treatment was similar in the two paradigms. Top panels: Parkinsonism assessed by amphetamine-induced ipsilateral turning. Three-way ANOVA analyses showed a significant ($p < 0.001$) main effect of 6-OHDA lesioning and a significant ($p < 0.05$) interaction between nicotine treatment and 6-OHDA lesioning in rats treated with nicotine prior to the onset of nigrostriatal lesion. By contrast, nicotine treatment after completion of nigrostriatal damage yielded a significant main effect of 6-OHDA lesioning ($p < 0.001$) but no interaction. Bottom panels: Effects of nicotine pre- and post-treatment on neuronal damage. Dopamine transporter expression was significantly elevated in lesioned rats with nicotine pre- but not post-treatment. Significance of difference by two-way ANOVA followed by a Bonferroni *post hoc* test from the saccharin-sham group, $***p < 0.001$; from the saccharin-lesioned group, $^{\#}p < 0.05$. Values represent the mean ± SEM of 6–9 rats per group. Taken with permission [66].

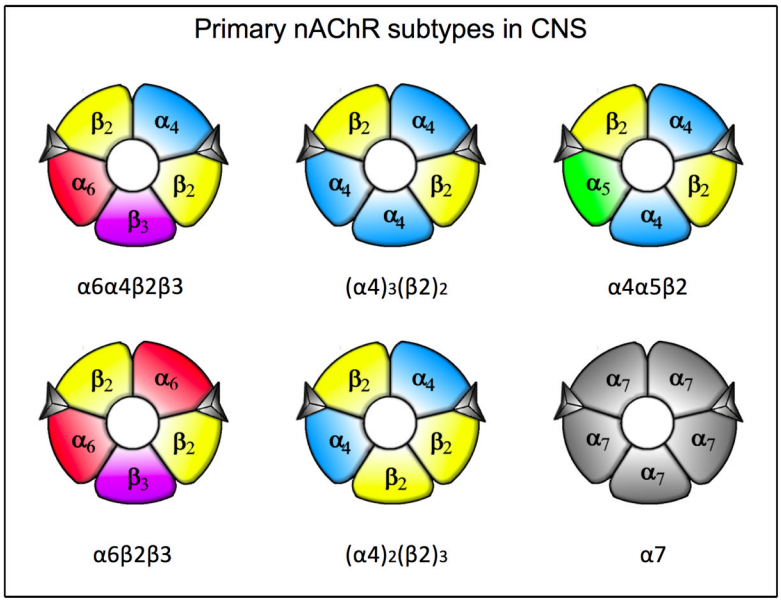

FIG. 2.

Primary nAChR subtypes in the mammalian CNS. The α6α4β2β3 and α6β2β3 nAChRs have a relatively restricted distribution in the CNS, including the nigrostriatal system. By contrast the α4β2 nAChRs, which exists in two unique conformations, and the α4α5β2 nAChR are widely present throughout the brain, including the nigrostriatal pathway. The homomeric α7 nAChR also exhibits an extensive distribution in the mammalian CNS, although this subtype is not densely expressed in the rat and monkey nigrostriatal system.

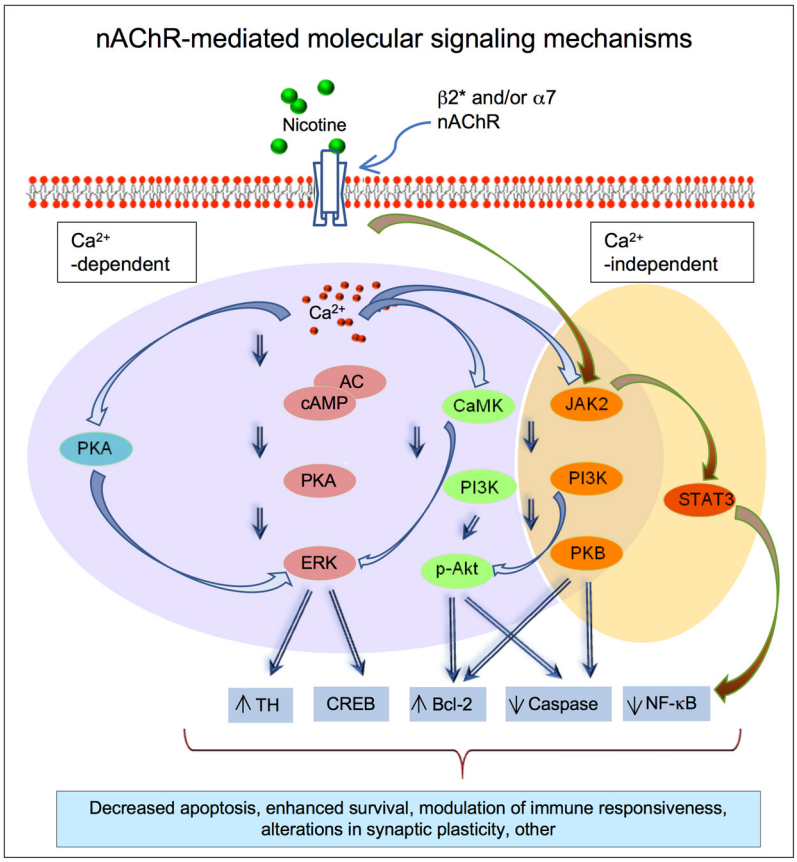

FIG. 3.
Molecular mechanisms through which nicotine mediates its effects in the nervous system.

TABLE 1

Difficulties in developing neuroprotective strategies against Parkinson's disease

1	Multifactorial etiology, including genetic and environmental factors
2	Variability in the pathogenesis of Parkinson's disease
3	Lack of an early biomarker
4	Animal models only partially mimic Parkinson's disease with respect to etiology, pathology and behavioral measures
5	Discrepancies in drug pharmacokinetics and pharmacodynamics between the animal models and Parkinson's disease

TABLE 2

Neuroprotection trials for Parkinson's disease

Drug/compound	ClinicalTrials. gov #	Purpose	Mechanisms of action	Status	Outcome
Green Tea Polyphenol	NCT00461942	Delay disease progression	Antioxidant	Completed March 2009	No Results Posted on ClinicalTrials.gov
Minocycline	NCT00063193	Delay disease progression	Anti-inflammatory	Completed July 2005	No Results Posted on ClinicalTrials.gov
Coenzyme Q10	NCT00740714	Neuroprotection	Modulates mitochondrial function	Completed Aug 2011	No efficacy over placebo
Isradipine	NCT00753636	Delay disease progression	Calcium channel blocker	Completed Feb 2010	No significant change in UPDRS
GPI 1485	NCT00076492	Neuroprotection	Immunophilin compound	Completed	No Results Posted on ClinicalTrials.gov
Erythropoietin	NCT01010802	Safety and tolerability for neuroprotection	Trophic factor	Completed May 2009	No Results Posted on ClinicalTrials.gov
Rasagiline	NCT00256204	Delay disease progression	Monoamine oxidase inhibitor	Completed June 2009	Delayed need for symptomatic antiparkinsonian drugs [57]
MitoQ	NCT00329056	Delay disease progression	Antioxidant	Completed Nov 2007	No Results Posted on ClinicalTrials.gov
Folic acid and L-methylfolate	NCT00853879	Delay disease progression	Decrease homocysteine levels	Completed	No Results Posted on ClinicalTrials.gov
GM1 Ganglioside	NCT00037830	Neuroprotection	Improves lipid function	Ongoing	
Creatine	NCT00449865	Neuroprotection	Modulates mitochondrial function	Ongoing	
Inosine	NCT00833690	Safety and tolerability for neuroprotection	Urate elevation	Ongoing/recruiting	
Bee venom	NCT01341431	Symptomatic & neuroprotective	Not known	Ongoing	
Deep brain stimulation	NCT00282152	Safety and tolerability	Not known	Ongoing	
VIUSID/ALZER	NCT01016470	Delay disease progression	Antiviral/anti-oxidant	Ongoing	
Nicotine	NCT00873392	Neuroprotection	Acts at nicotinic receptors	Recruiting	
Nicotine	MJFF clinical trial	Neuroprotection	Acts at nicotinic receptors	Recruiting	
Deferiprone	NCT00943748	Neuroprotection	Iron chelator	Recruiting	
Exendin-4	NCT01174810	Disease-modifying	Antidiabetic	Recruiting	
Granulocyte-colony Stimulating Factor	NCT01227681	Neuroprotection	Trophic factor	Recruiting	

Drug/compound	ClinicalTrials. gov #	Purpose	Mechanisms of action	Status	Outcome
Pioglitazone	NCT01280123	Neuroprotection	Antidiabetic	Recruiting	
Glutathione	NCT01398748	Safety and tolerability for subsequent neuroprotection	Modulates mitochondrial function	Recruiting	
Preladenant	NCT01155479	Safety and efficacy	Adenosine A2a antagonist	Recruiting	
Autologous Adipose-derived stromal cells	NCT01453803	Improve disease pathology	Cell protection, repair and restoration	Recruiting	
Safinamide	NCT01028586	Delay disease progression	MAO-B and glutamate release inhibitor	Recruiting	
N-Acetylcysteine	NCT01470027	Neuroprotection	Antioxidant	Not yet recruiting	