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Role for the nicotinic cholinergic system in movement disorders; therapeutic implications

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Abstract

A large body of evidence using experimental animal models shows that the nicotinic cholinergic system is involved in the control of movement under physiological conditions. This work raised the question whether dysregulation of this system may contribute to motor dysfunction and whether drugs targeting nicotinic acetylcholine receptors (nAChRs) may be of therapeutic benefit in movement disorders. Accumulating preclinical studies now show that drugs acting at nAChRs improve drug-induced dyskinesias. The general nAChR agonist nicotine, as well as several nAChR agonists (varenicline, ABT-089 and ABT-894) reduce L-dopa-induced abnormal involuntary movements or dyskinesias up to 60% in parkinsonian nonhuman primates and rodents. These dyskinesias are potentially debilitating abnormal involuntary movements that arise as a complication of L-dopa therapy for Parkinson's disease. In addition, nicotine and varenicline decrease antipsychotic-induced abnormal involuntary movements in rodent models of tardive dyskinesia. Antipsychotic-induced dyskinesias frequently arise as a side effect of chronic drug treatment for schizophrenia, psychosis and other psychiatric disorders. Preclinical and clinical studies also show that the nAChR agonist varenicline improves balance and coordination in various ataxias. Lastly, nicotine has been reported to attenuate the dyskinetic symptoms of Tourette's disorder. Several nAChR subtypes appear to be involved in these beneficial effects of nicotine and nAChR drugs including α4β2*, α6β2* and α7 nAChRs (the asterisk indicates the possible presence of other subunits in the receptor). Overall, the above findings, coupled with nicotine's neuroprotective effects, suggest that nAChR drugs have potential for future drug development for movement disorders.

Keywords

Ataxia; L-Dopa-induced dyskinesias; Nicotine; Nicotinic acetylcholine receptors; Tardive dyskinesia; Tourette's syndrome

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The authors declare that there are no conflicts of interest.

1. Introduction

The control of movement under physiological conditions is extremely complex and involves the integrated input from numerous central and peripheral nervous system circuits. Multiple neurotransmitter systems have been implicated in locomotion including the glutamatergic, dopaminergic, serotonergic, GABAergic, histaminergic, adrenergic, noradrenergic and peptidergic systems. Extensive preclinical studies also demonstrate a prominent role for the nicotinic cholinergic system in the regulation of motor activity. Systemic administration of nicotine to rodents induces complex changes in locomotor activity, with an acute transient depression followed by a persistent stimulation (Balfour, Benwell, Birrell, Kelly, & Al-Aloul, 1998; Benwell & Balfour, 1992; Clarke, 1990; Stolerman, 1990). These findings raised the idea that aberrant nicotinic cholinergic function may contribute to movement disorders and that treatment with drugs targeting nAChRs may be beneficial.

nAChRs are ligand-gated ion channels composed of five membrane-spanning subunits of which there are multiple subtypes in both the peripheral and central mammalian nervous system (Albuquerque, Pereira, Alkondon, & Rogers, 2009; Millar & Gotti, 2009). These channels are composed of combinations of α (α1–α7), β (β1–β4) and other subunits (δ, γ), but may also consist of only α subunits that express the acetylcholine or agonist binding site (Albuquerque, et al., 2009; Millar & Gotti, 2009). The nAChRs in the CNS vary somewhat from those in the rest of the body, with the receptors in the periphery primarily composed of α1β1γδ, α3β4* and α7 subunits while the principle ones in the brain are the α4β2*, α6β2* and α7 receptors (the asterisk indicates the presence of other possible subunits in the receptor complex) (Quik & Wonnacott, 2011). Although α7 receptors are present both in the central and peripheral nervous system, drugs targeting these receptors do not appear to have appreciable effects in the periphery. CNS nAChRs may also contain the α2, α3, and/or α5 subunits; however, these are present to a much lesser degree (Quik & Wonnacott, 2011).

Here, we review some of the more recent developments supporting a role for the nicotinic cholinergic system and the use of α4β2*, α6β2* and α7 nAChR drugs in several movement disorders including drug-induced dyskinesias, ataxia and Tourette's syndrome.

2. Role for nicotine and nAChR agonists in reducing L-dopa-induced dyskinesias

An accumulating literature indicates that nicotine and nAChR drugs may be beneficial in reducing the abnormal involuntary movements or dyskinesias that arise with L-dopa treatment for Parkinson's disease. Although L-dopa is the gold standard treatment for Parkinson's disease motor symptoms, its use leads to the development of side effects, including dyskinesias (Huot, Johnston, Koprich, Fox, & Brotchie, 2013; Iravani, McCreary, & Jenner, 2012). L-dopa-induced dyskinesias (LIDs) may occur after only a few months of therapy and arise in the majority of patients with extended treatment (Ahlskog & Muenter, 2001). They can be quite incapacitating and are a major drawback in Parkinson's disease management. Currently there are only limited therapeutic options for LIDs (Meissner, et al., 2011; Obeso, et al., 2010; Schapira, 2009; Schapira & Jenner, 2011; Wichmann, DeLong,

Guridi, & Obeso, 2011). New treatment strategies to reduce LIDs are therefore a key research focus.

Drugs targeting numerous neurotransmitter systems have been shown to attenuate LIDs in animal models of Parkinson's disease including those interacting at the dopaminergic, serotonergic, glutamatergic, opioid, GABAergic and other systems (Blandini & Armentero, 2012; Brotchie & Jenner, 2011; Cenci, 2007; Duty, 2012; Fox, Chuang, & Brotchie, 2009; Gasparini, Di Paolo, & Gomez-Mancilla, 2013; Huot, et al., 2013; Iravani, et al., 2012; Quik, Mallela, Ly, & Zhang, 2013; Rylander, 2012; Sgambato-Faure & Cenci, 2012). In addition, more recent studies indicate that alterations in nicotinic cholinergic mechanisms modulate LIDs.

Initial work investigating a role for the nicotinic cholinergic system on LIDs was done in MPTP-lesioned nonhuman primates. Lesioned monkeys exhibit parkinsonian motor symptoms very similar to those in Parkinson's disease and develop abnormal involuntary movements with L-dopa treatment analogous to those in L-dopa-treated Parkinson's disease patients (Duty & Jenner, 2011; Iderberg, Francardo, & Pioli, 2012; Jenner, 2009). Nicotine administration to L-dopa-treated monkeys led to ~60% decrease in LIDs (Fig. 1). This nicotine-mediated attenuation in LIDs endures across time (months), suggesting that nicotine would effectively reduce LIDs in patients with prolonged treatment (Quik, et al., 2007; Quik, Mallela, Chin, et al., 2013; Quik, Mallela, Ly, et al., 2013). The antidyskinetic effect of nicotine required several weeks to develop but also remained for weeks after its removal (Fig. 1) (Quik, et al., 2007; Quik, Mallela, Ly, et al., 2013), indicating that long term molecular and cellular changes underlie the nicotine-mediated decline in LIDs. Nicotine administration reduced LIDs equally well in L-dopa-naïve or L-dopa-primed monkeys, that is, animals with established LIDs (Quik, Mallela, Ly, et al., 2013). This is an important observation for Parkinson's disease therapy, as it suggests that nicotine treatment may be initiated in patients after LIDs develop with no loss of efficacy.

The antidyskinetic effect of nicotine was also investigated in rodent models because their use offers the advantage that they allow for studies to investigate varying treatment paradigms and molecular mechanisms. Nicotine reduced LIDs when administered by any one of several methods, including oral application, injection and slow-release minipump, with no decline in its effectiveness with time. Moreover, nicotine treatment attenuated LIDs to a similar extent in L-dopa-treated parkinsonian rats and mice, indicating the effect occurred across species (Bordia, Campos, McIntosh, & Quik, 2010; L. Huang, Grady, & Quik, 2011; M. Quik, C. Campos, & S. R. Grady, 2013b; Quik, et al., 2007; Quik, Mallela, Ly, et al., 2013).

In addition to these preclinical studies, a small clinical trial has been conducted to evaluate the antidyskinetic potential of nicotine in Parkinson's disease patients. Oral nicotine (designated NP002) administration to 50 patients for several months significantly reduced a variety of outcome measures related to LIDs (http://www.neuraltus.com/pages/news.html).

2.1. Nicotine exerts its anti-dyskinetic effect by acting at nAChRs

Nicotine's mechanism of action to reduce LIDs is an important question because such knowledge may yield more selective therapies. Two approaches have been used to evaluate the nAChRs through which nicotine exerts its effects. One of these involves the use of nAChR null mutant mice. Since β2 containing nAChRs (α4β2* and α6β2* subtypes) are widespread throughout the brain and highly expressed in the nigrostriatal pathway, initial studies were done with mice lacking the β2 subunit. Baseline LID levels were reduced in such mice while nicotine did not decrease LIDs, indicating that β2* nAChRs are necessary for both the occurrence of LIDs and the antidyskinetic effect of nicotine (L. Huang, et al., 2011). Follow up studies with mice lacking the α6 nAChR subunit yielded very similar results suggesting a key involvement of α6β2* nAChRs (Quik, Park, et al., 2012). Nicotine had no antidyskinetic effect in mice lacking α4β2* nAChRs, although there was no change in baseline LIDs in such null mutant mice. These combined data suggest that both α6β2* and α4β2* nAChRs populations play a major role in LIDs but in somewhat distinct manners. Similar studies showed that baseline LIDs were actually increased in α7 nAChR null mutant mice, while nicotine treatment still reduced LIDs (M. Quik, C. Campos, & S. Grady, 2013a). Thus, in contrast to the β2* nAChRs, α7 nAChRs appear to exert an inhibitory control on the occurrence of LIDs. The distinct regulation of LIDs by β2* as compared to α7 nAChRs may not be that unexpected as α7 and β2* nAChRs exhibit very different pharmacological and functional characteristics (Changeux, 2010; Giniatullin, Nistri, & Yakel, 2005; Picciotto, Addy, Mineur, & Brunzell, 2008; Quik, Perez, & Bordia, 2012; Wonnacott, Sidhpura, & Balfour, 2005). Since multiple nAChR subtypes differentially regulate LIDs, diverse nAChR subtype drugs may be effective in reducing LIDs. This idea is further suggested from the results of studies which show that the status of nAChR receptors depends on the extent of nigrostriatal damage and/or L-dopa treatment regimen (Quik, Polonskaya, Kulak, & McIntosh, 2001; Quik, Sum, et al., 2003)(Quik, Bordia, et al., 2003).

A second approach to discern the nAChRs implicated in nicotine's therapeutic effect involves pharmacological studies in parkinsonian animal models. These data support the results with null mutant mice and show that compounds acting at α4β2*/α6β2* nAChRs reduce LIDs. Varenicline, A-85380, sazetidine, TC-2696, TI-10165, TC-8831 and TC-10600 all attenuated LIDs to varying extents in parkinsonian rats (Fig. 1) (L. Z. Huang, Campos, Ly, Carroll, & Quik, 2011; Quik, Campos, Bordia, et al., 2013). Additionally, varenicline and TC-8831 decreased LIDs ~50% in nonhuman primates, although a limitation with these drugs was the development of emesis (Johnston, et al., 2013; D. Zhang, et al., 2013). ABT-089, a partial α4β2*/α6β2* nAChR agonist, and ABT-894, a full α4β2* and α6β2* agonist, two drugs that have both been approved for use in clinical trials and show little emesis, have also been tested for their ability to reduce LIDs in parkinsonian monkeys (Anderson, et al., 2009; Apostol, et al., 2012; Bain, et al., 2013; Decker, et al., 1997; Ji, et al., 2007; Marks, Wageman, Grady, Gopalakrishnan, & Briggs, 2009; Rowbotham, et al., 2012; Sullivan, et al., 1997). ABT-089 and ABT-894, decreased LIDs 40% and 60%, respectively, without worsening parkinsonism, causing emesis or inducing other side effects (D. Zhang, et al., 2014). Currently available nAChR drugs all act at both α4β2* and α6β2*

receptors, and thus it has not been possible to evaluate a role for the individual subtypes in LIDs using a pharmacological approach. α7 nAChR drugs remain to be tested.

In summary, drugs targeting α4β2*/α6β2* nAChRs reduced LIDs up to 60% in parkinsonian monkeys for extended periods of time. Since ABT-089 and ABT-894 have previously been evaluated in phase 2 clinical trials for other indications, these drugs could readily be transitioned to the clinic to evaluate their ability to reduce LIDs.

2.2. Mechanism of action of nicotine to decrease LIDs

A mechanism whereby agonists that act at β2* nAChRs improve L-dopa-induced AIMs may involve nAChR desensitization. It is well known that acetylcholine and nAChR agonists lead to an initial receptor activation that is rapidly followed by molecular alterations that result in channel closing and an effective block of receptor function or desensitization (Buccafusco, Beach, & Terry, 2009; McCarthy, Zhang, Neff, & Hadjiconstantinou, 2011; Picciotto, et al., 2008). The idea that such a molecular mechanism may underlie LIDs is supported by several findings. First, the nAChR antagonist mecamylamine reduces LIDs in parkinsonian rats to a similar extent as the desensitizing agonist nicotine (Bordia, et al., 2010). Second, treatment of nicotine via injection, which involves transient pulsatile administration, or via minipump that involves chronic slow nicotine exposure and desensitization, both result in similar declines in LIDs (Bordia, et al., 2010). Lastly, sazetidine and varenicline, two agonists that reduce LIDs in rats (L. Z. Huang, et al., 2011), are postulated to exert their effects via nAChR desensitization or inactivation (Hussmann, et al., 2012; Rezvani, et al., 2012; Rollema, et al., 2010; Zwart, et al., 2008).

2.3. Localization of CNS nAChRs that mediate antidyskinetic effects of nAChR drugs

The cellular localization and brain regions expressing the nAChRs involved in the nicotine-mediated antidyskinetic effect is an important question. Lesion studies indicate that the striatum makes a major contribution to the nAChR-mediated decline in LIDs. Both nicotine and nAChR drugs most effectively reduce LIDs in mice, rats or monkeys with moderate nigrostriatal damage, that is, when the dopaminergic system is still partially intact (L. Huang, et al., 2011; L. Z. Huang, et al., 2011; Quik, Mallela, Chin, et al., 2013). These results suggest that α6β2* and/or α4β2* nAChRs on nigrostriatal dopamine terminals play an important role in the nAChR-mediated decline in LIDs (Fig 2). However, since nicotine does reduce LIDs to some extent even with severe nigrostriatal damage, nAChRs on non-dopaminergic neurons may also contribute. Alternatively, α4β2* nAChRs in the thalamus, cortex and cerebellum, regions linked to motor control and coordination, may be important. Additionally, α7 nAChRs on cortical afferents to the striatum and/or α7 receptors in other CNS regions may contribute to the antidyskinetic effect of nicotine (Fig. 2). The observation that nicotine most effectively reduces LIDs with moderate nigrostriatal damage, suggests that nAChR drugs may be most effective in reducing LIDs in early stage Parkinson's disease. However, since multiple compensatory mechanisms may arise with slow progressive nigrostriatal damage and long term L-dopa treatment in Parkinson's disease, it may be difficult to predict efficacy. This is especially true since the association between the severity of dyskinesia, extent of nigrostriatal damage and length of L-dopa treatment is variable in animal models. For instance, LIDs do not necessarily develop in L-dopa-treated

lesioned animals and the level of LIDs is not always dependent on the extent of nigrostriatal damage (Cenci, Lee, & Bjorklund, 1998; Guigoni, et al., 2005; Pearce, Heikkila, Linden, & Jenner, 2001; Togasaki, et al., 2001; Y. Zhang, et al., 2013).

In summary, α4β2* and α6β2* nAChRs on dopamine terminals in the nigrostriatal pathway contribute to the expression of LIDs. Other striatal α4β2* and α7 nAChRs may also be involved, as well as nAChRs in other brain regions. The idea that multiple nAChRs in various brain regions are important is consistent with studies showing that the striatal dopaminergic system is tightly interconnected with numerous neurotransmitter systems involved in movement.

2.4. Anti-dyskinetic effect of non-nAChR drugs

As mentioned earlier, changes in numerous neurotransmitter systems contribute to the etiology of LIDs. These most likely modulate LIDs via multiple molecular mechanisms including alterations in presynaptic dopaminergic function, enhanced activation of the direct dopaminergic pathway, aberrant release of L-dopa via serotonergic neurons, excessive glutamatergic signaling, modulation of opioid activity and others (Blandini & Armentero, 2012; Cenci, 2007; Gasparini, et al., 2013; Huot, et al., 2013; Iravani, et al., 2012; Rylander, 2012). Consistent with this multifactorial origin of LIDs, drugs targeting the glutamatergic, serotonergic, opioid, adenosine and other systems have all been reported to attenuate LIDs to varying extents in parkinsonian animal models (Blandini & Armentero, 2012; Brotchie & Jenner, 2011; Duty, 2012; Fox, 2013; Fox, et al., 2009; Huot, et al., 2013; Samadi, Bedard, & Rouillard, 2006; Sgambato-Faure & Cenci, 2012). Since multiple mechanisms underlie LIDs, it is not unexpected that the reduction in LIDs produced by a drug targeting any one neurotransmitter system is generally not complete (Huot, et al., 2013). Interestingly, recent studies in parkinsonian animal models show that combined treatment with drugs known to partially reduce LIDs yields additive or synergistic declines (Bezard, et al., 2013; Dupre, et al., 2008; Hill, et al., 2004; Iderberg, Rylander, Bimpisidis, & Cenci, 2013; Kobylecki, Hill, Crossman, & Ravenscroft, 2011). These observations imply that the optimal therapy to alleviate LIDs may involve drug combinations or the use of drugs that target several neurotransmitter systems.

3. Nicotine and the nAChR agonist varenicline decrease antipsychotic-induced tardive dyskinesias in animal models

Recent preclinical studies also suggest that nicotine and nAChR agonists improve another class of drug-induced abnormal involuntary movements, the tardive or late dyskinesias that arise with chronic antipsychotic use. Antipsychotics are a very important class of drugs approved for the management of schizophrenia and bipolar disorder, and are also used off-label for depression, autism, attention deficit hyperactivity disorder, obsessive compulsive disorder and post-traumatic stress disorder (Gershanik & Gomez-Arevalo, 2011; Maher & Theodore, 2012; Tarsy, Lungu, & Baldessarini, 2011; Zupancic, 2011). These drugs are dopamine receptor antagonists, and are thought to induce their therapeutic effect by dampening excess dopaminergic activity (Seeman, 2010; Tarsy, et al., 2011; Turrone, Remington, Kapur, & Nobrega, 2003). However, antipsychotics not only modulate aberrant

dopaminergic activity linked to psychiatric disorders, but also affect motor function. Thus, although antipsychotics are very valuable clinically, their continued use results in side effects including tardive dyskinesia, which afflicts ~25% of treated patients (Saha, Chant, Welham, & McGrath, 2005). These dyskinesias consist of repetitive abnormal involuntary movements primarily of the face and limbs that may become severe and eventually debilitating (Correll, Leucht, & Kane, 2004; Tarsy, et al., 2011). There is currently little treatment other than antipsychotic dose modification. The use of second-generation antipsychotics has been reported to cause less tardive dyskinesia (Peluso et al., 2012). However, randomized clinical trials show that the decrease is less than anticipated (Correll & Schenk, 2008; Peluso, Lewis, Barnes, & Jones, 2012; Tarsy, et al., 2011; Woods, et al., 2010).

Because of the success of nicotine and nAChR drugs in reducing LIDs, studies were conducted to investigate their potential to reduce tardive dyskinesia in rodents. Nicotine treatment attenuated haloperidol-induced abnormal movements or vacuous chewing movements (VCMs) in both a rat and mouse model of tardive dyskinesia, with a maximal reduction in VCMs of 50% (Fig. 3) (Bordia, Carroll, & Quik, 2013; Bordia, McIntosh, & Quik, 2012). The nicotine-mediated decline in haloperidol-induced VCMs was independent of the mode of administration of haloperidol, that is, injection or a subdermal-slow release pellet. It was also independent of the nicotine treatment regimen with similar declines in VCMs whether nicotine was given orally or via subcutaneous minipump (Fig. 3A, B, C). These data suggest that either oral nicotine administration or the nicotine patch may be useful clinically. Nicotine reduced haloperidol-induced VCMs when given before VCMs had developed and was also effective against established VCMs, with no tolerance following continued use. The general nicotinic agonist varenicline, which interacts with high affinity at $\alpha4\beta2^*$ and $\alpha6\beta2^*$ nAChRs, as well as $\alpha3\beta4^*$ and $\alpha7$ nAChRs (Bordia, Hrachova, Chin, McIntosh, & Quik, 2012; Coe, et al., 2005; Mihalak, Carroll, & Luetje, 2006; Rollema, et al., 2007), also reduced haloperidol-induced VCMs (Fig. 3D) (Bordia, et al., 2013; Bordia, McIntosh, et al., 2012). These data provide proof-of-principle that nicotine exerts its effect via an interaction at nAChRs. Varenicline reduced VCMs to a greater extent than nicotine, a finding that may relate to varenicline's ability to interact with 5-HT receptors (Creed-Carson, Oraha, & Nobrega, 2011; Creed, Hamani, Bridgman, Fletcher, & Nobrega, 2012; Lummis, Thompson, Bencherif, & Lester, 2011; Naidu & Kulkarni, 2001).

As mentioned above, antipsychotics are one of the principle therapies for the treatment of schizophrenia. It is well documented that schizophrenic patients are very heavy smokers and may consume several packs of cigarettes per day, that is, be exposed to relatively large quantities of nicotine. This raises the question whether schizophrenics who are heavy smokers exhibit less tardive dyskinesia since animal studies show that nicotine reduces dyskinesias. However, a search of the literature yielded conflicting results on the link between smoking and tardive dyskinesia in humans. An early study indicated that the prevalence of tardive dyskinesia in chronic psychiatric outpatients was significantly higher in smokers than in nonsmokers (Yassa, Lal, Korpassy, & Ally, 1987). In another study, patients who smoked received significantly higher doses of neuroleptics but did not have more frequent or more severe tardive dyskinesia, suggesting that smoking may suppress the occurrence of neuroleptic-induced tardive dyskinesia (Menza, Grossman, Van Horn, Cody,

& Forman, 1991). By contrast, Nilsson and coworkers found that dyskinetic men had higher daily cigarette consumption than men without dyskinesia, but the former group also had greater exposure to neuroleptics, higher frequencies of psychiatric morbidity and alcohol dependence, thus confounding results (Nilsson, Waller, Rosengren, Adlerberth, & Wilhelmsen, 1997). A more recent report showed that the prevalence of tardive dyskinesia did not significantly differ between smokers and non-smokers (X. Y. Zhang, et al., 2011). A carefully controlled, double-blind clinical trial appears necessary to understand the relationship between smoking (nicotine intake) and tardive dyskinesia in the clinic.

In summary, studies using rodent models of tardive dyskinesia clearly demonstrate a decline in antipsychotic-induced abnormal movements with nicotine use. Well-controlled clinical trials are the next step to determine the effectiveness of nicotine and/or nAChR drugs to ameliorate anti-psychotic-induced tardive dyskinesia in patients.

4. Nicotine and varenicline treatment attenuate ataxia

The idea that enhanced nicotinic cholinergic stimulation may reduce ataxia stems from both preclinical and clinical studies. Ataxia is characterized by a lack of coordination of voluntary muscle movements involving the cerebellum as well as other CNS regions (van de Warrenburg, et al., 2014). Multiple types of ataxia have been identified including spinocerebellar ataxia, Friedreich's ataxia and Fragile X associated ataxia. A variety of genetic factors, including missense, inframe deletions, and frameshift insertions/deletions or trinucleotide repeat expansions underlie their pathophysiology, which may involve mitochondrial and other cellular deficits (Gonzalez-Cabo & Palau, 2013; Koeppen & Mazurkiewicz, 2013; Rub, et al., 2013). Treatment has proved challenging and is generally symptomatic only.

Preclinical studies investigating the effect of nicotine and nAChR drugs in animal models of ataxia show that acute intracerebellar nicotine or the α4β2* nAChR agonist RJR-2403 dose dependently attenuated ethanol-induced ataxia (Al-Rejaie & Dar, 2006). Intracerebellar administration of the α4β2* nAChR antagonist dihydro-β-erythroidine attenuated this effect, indicating that cerebellar α4β2* nAChRs play a role (Taslim, Al-Rejaie, & Saeed Dar, 2008). In addition, nicotine and the nAChR agonist varenicline reduced ataxia in rats with a lesion of the olivocerebellar pathway via a nAChR-mediated mechanism (Wecker, et al., 2013). α7 nAChR drugs also decreased the occurrence of ethanol-induced ataxia, indicating that multiple nAChR populations modulate ataxia (Taslim & Saeed Dar, 2011).

The suggestion that nAChR drugs may be useful for the treatment of ataxia in patients initially stemmed from studies using drugs that enhance CNS cholinergic activity. This includes work with physostigmine, a centrally acting acetylcholinesterase inhibitor, which is well known to increase brain acetylcholine levels. Physostigmine treatment improved the symptoms of spinocerebellar degenerations and various inherited ataxias in open label and double-blind randomized trials, possibly via an interaction with the nicotinic cholinergic system (Kark, Blass, & Spence, 1977; Kark, Budelli, & Wachsner, 1981; Rodriguez-Budelli, Kark, Blass, & Spence, 1978). This effect appears to be selective for specific ataxias as physostigmine did not improve symptoms in patients with autosomal dominant cerebellar

ataxia and idiopathic cerebellar ataxia (Wessel, Langenberger, Nitschke, & Kompf, 1997). Other studies with the acetylcholine precursor choline also showed improvements in patients with Friedreich's ataxia, idiopathic cerebellar degeneration, multiple sclerosis-linked ataxia, and ataxias associated with sporadic cerebellar degeneration and atypical spinocerebellar degeneration, although no improvements were observed in other ataxias (Livingstone, Mastaglia, Pennington, & Skilbeck, 1981) (Blattel, 1979; Legg, 1978; Philcox & Kies, 1979). Since choline may represent an endogenous ligand for α7 nAChRs, these reports may suggest that α7 nAChRs play a role (Alkondon, Pereira, Cortes, Maelicke, & Albuquerque, 1997).

More recent studies with the general nAChR agonist varenicline further supported a role for the nicotinic cholinergic system in patients with various types of ataxic neurodegenerative disorders. Case reports initially showed that varenicline, which was being used for smoking cessation, improved ataxia and imbalance in a man with Fragile X tremor/ataxia syndrome (Zesiewicz, Sullivan, Freeman, & Juncos, 2009). It also improved proprioception in the extremities in two patients with Friedreich's ataxia (Zesiewicz, Sullivan, Gooch, & Lynch, 2009) and gait, balance and depth perception in a patient with spinocerebellar ataxia (Zesiewicz & Sullivan, 2008). A subsequent double-blind, placebo-controlled, randomized trial with 20 patients with spinocerebellar ataxia showed that 2 months of varenicline ameliorated axial symptoms and rapid alternating movements (Zesiewicz, et al., 2012), although poor tolerability and little therapeutic benefit was also reported in a mixed ataxia population (Connolly, Prashanth, Shah, Marras, & Lang, 2012).

In summary, both preclinical and clinical studies support the idea that drugs targeting nAChRs may improve components of ataxia.

5. Nicotine administration improves motor symptoms associated with Tourette's syndrome

Over the last two decades, reports have indicated that the use of nicotine gum and the transdermal nicotine patch potentiated the therapeutic effects of neuroleptics in reducing the frequency and severity of tics in Tourette's (Sanberg, et al., 1997). Tourette's syndrome is a neurodevelopmental disorder characterized by sudden, rapid and brief motor and vocal tics, as well as a wide spectrum of other behavioral problems including obsessions, compulsions, impulsivity, distractibility, and hyperactivity (Roessner, et al., 2013; Termine, Selvini, Rossi, & Balottin, 2013; Thomas & Cavanna, 2013). Although the etiology of Tourette's is currently unclear, hyperactivity of the brain dopaminergic system appears to be involved as dopamine blockers symptomatically improve the motor and vocal tics (Roessner, et al., 2013; Termine, et al., 2013; Thomas & Cavanna, 2013). However, currently available drugs are only partially effective and associated with side effects and thus new therapies are constantly being sought.

Initial open label studies with the nicotine gum showed a substantial decrease in tics and improvement of concentration/attention span in Tourette's syndrome patients treated with haloperidol, although nicotine alone appeared to have little effect (McConville, et al., 1991; Sanberg, et al., 1989). However, side effects, such as nausea and bitter taste limited the

usefulness of the nicotine gum. Subsequent open-label studies showed that the low dose transdermal nicotine patch led to varying reductions in tic severity with an average duration of effect lasting up to 4 weeks (Dursun & Kutcher, 1999; Dursun, Reveley, Bird, & Stirton, 1994; Silver, Shytle, Philipp, & Sanberg, 1996). Importantly, positive results were also observed in a subsequent double-blind placebo-controlled trial in which seventy Tourette's patients on haloperidol were randomly assigned to either low transdermal nicotine or placebo patches for several weeks (Silver, Shytle, Philipp, et al., 2001). Transdermal nicotine was superior to placebo in reducing the symptoms of Tourette's disorder for several weeks after nicotine discontinuation. Nicotine may thus have potential as an adjunct to neuroleptic therapy for Tourette's syndrome, although side effects may limit its chronic use.

It had been noted that the benefits of the nicotine patch in Tourette's outweighed those of the nicotine gum in terms of duration of the response, with the effects of the patch lasting much longer than those of the gum (Sanberg, Vindrola-Padros, & Shytle, 2012). These observations led to the hypothesis that desensitization of nAChRs may represent a mechanism underlying the beneficial effect of nicotine in Tourette's. Desensitization of nAChRs on striatal dopamine terminals would subsequently result in a functional nAChR blockade with a consequent decrease in dopamine release and a dampening of striatal dopaminergic activity (Sanberg, et al., 2012; Shytle, Silver, & Sanberg, 2000). This possibility is supported by results suggesting that nicotine exerts its beneficial effects on other behaviors, such as dyskinesias via receptor desensitization (Bordia, et al., 2010).

This idea that nicotine may exert its effects via a functional blockade led to the hypothesis that a nAChR antagonist, such as mecamylamine, may prove useful in Tourette's but be associated with fewer side effects that arise with nicotine treatment. Mecamylamine, which had originally been used for the treatment of hypertension, was subsequently tested in a retrospective, open-label study. A significant improvement was observed in motor and vocal tics, and also in mood and behavior disturbances of children, adolescents, and adults with Tourette's with no significant peripheral parasympathetic effects (Silver, Shytle, & Sanberg, 2000). A subsequent double-blind placebo-controlled study to examine the efficacy of mecamylamine as a monotherapy was subsequently carried out; however, the results suggested it was not effective although it was tolerated (Silver, Shytle, Sheehan, et al., 2001).

In summary, clinical trial data indicate that nAChR drugs have potential to attenuate the occurrence of tics in Tourette's syndrome, although no further studies appear to have been conducted since the work reported above.

6. Concluding remarks

Mounting evidence in experimental animal models indicate that nicotine and nAChR drugs improve motor deficits (summarized in Table 1) and may be useful for attenuating movement disorders in the clinic (summarized in Table 2). As well, nAChR drugs hold promise as neuroprotectants against neuronal degeneration as occurs in Parkinson's disease (Picciotto & Zoli, 2008; Quik, Perez, et al., 2012). In fact, the Michael J Fox Foundation is currently funding a clinical trial to investigate the neuroprotective ability of transdermal

nicotine in early Parkinson's disease (ClinicalTrials.gov Identifier NCT01560754). Overall, these observations suggest that drugs interacting with nAChRs may be of therapeutic benefit in the management of neurodegenerative disorders.

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Abbreviations

LIDs	L-dopa-induced dyskinesias
nAChRs	nicotinic acetylcholine receptors
VCMs	vacuous chewing movements

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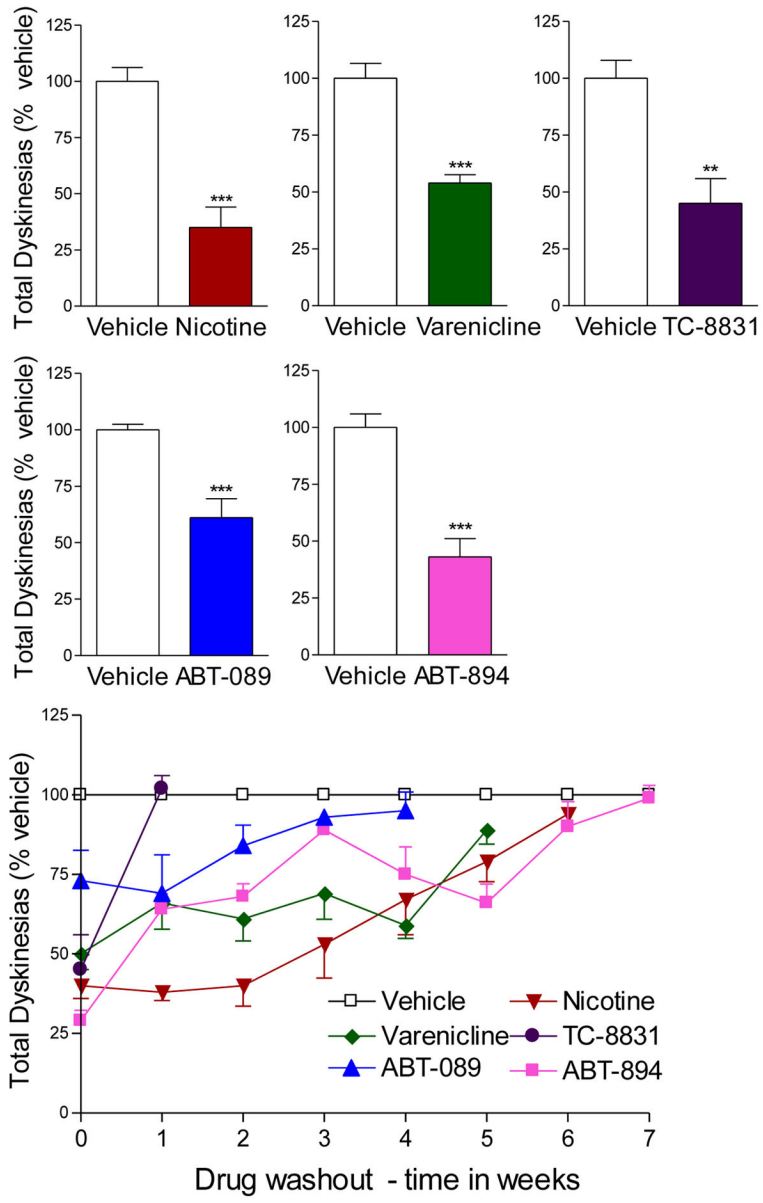

Fig. 1.

Nicotine and nAChR drugs reduce L-dopa-induced dyskinesias in parkinsonian monkeys. MPTP-lesioned monkeys were treated with L-dopa (10 mg/kg) and carbidopa (2.5 mg/kg) twice daily until stably dyskinetic. They were then given the indicated drugs immediately prior to L-dopa gavage. The bars are representative of the maximal decline in LIDs with the optimal drug dose as follows: nicotine, 300 μg/ml in the drinking water; varenicline, 0.03 mg/kg orally; TC-8831, 0.05 mg/kg orally; ABT-089, 0.1 mg/kg orally; and ABT-894, 0.01 mg/kg orally. The drug doses of nicotine, varenicline, ABT-089 and ABT-894 were within the range of those used in clinical trials. Several weeks of treatment were required for a maximal antidyskinetic effect. Tolerance did not develop to any of the nAChR drugs with months of treatment. Drug washout (lower panel) led to a return of LIDs to values similar to those in vehicle-treated monkeys. Values are the mean ± SEM of 5–12 animals per group.

Significance of difference from vehicle-treated, **p < 0.01, ***p < 0.001 using Student's t-test. Data taken in modified form from (D. Zhang, et al., 2014; D. Zhang, et al., 2013).

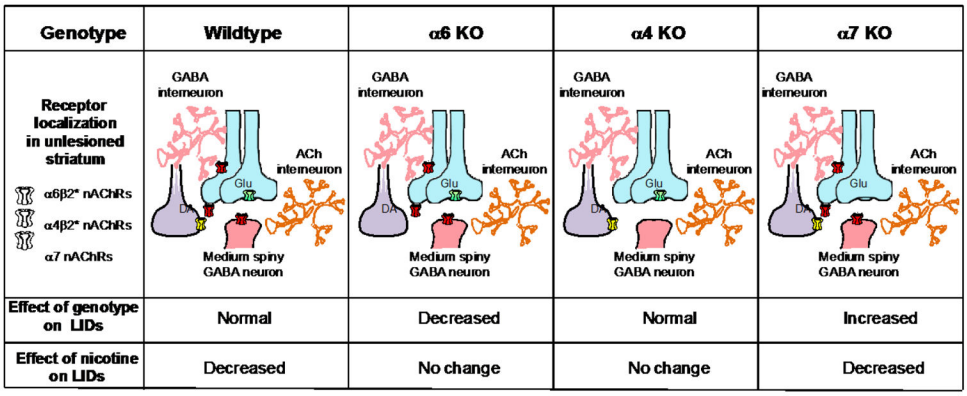

Fig. 2.

Studies with nAChR null mutant mice indicate that receptors containing α4, α6 or α7 nAChR subunits all play a role in the occurrence of LIDs. Studies with genetically modified mice, nAChR subtype-specific antibodies and drugs, as well as nAChR subunit chimeras and concatamers show that the principle receptors in striatum are the α6β2*, α4β2* and α7 subtypes (Millar & Gotti, 2009; Quik & Wonnacott, 2011). The α6β2* nAChRs are present primarily on dopaminergic terminals originating in the substantia nigra. The α4β2* nAChRs are expressed on dopaminergic terminals and also on GABA interneurons and medium spiny neurons in striatum. By contrast, striatal α7 nAChRs are primarily localized to glutamatergic afferents from the cortex. Experiments with α4, α6 and α7 nAChR subunit knockout mice show that α6β2* and α7 nAChRs are involved in the development of LIDs, as the absence of these receptors decreases and increases baseline LID expression, respectively. In addition, the α6β2* and α4β2* nAChR subtypes are involved in the antidyskinetic effect of nicotine since deletion of the α6 and α4 nAChR subunit prevents nicotine from decreasing LIDs. Data taken in modified form from (L. Huang, et al., 2011; Quik, Campos, & Grady, 2013b; Quik, Park, et al., 2012).

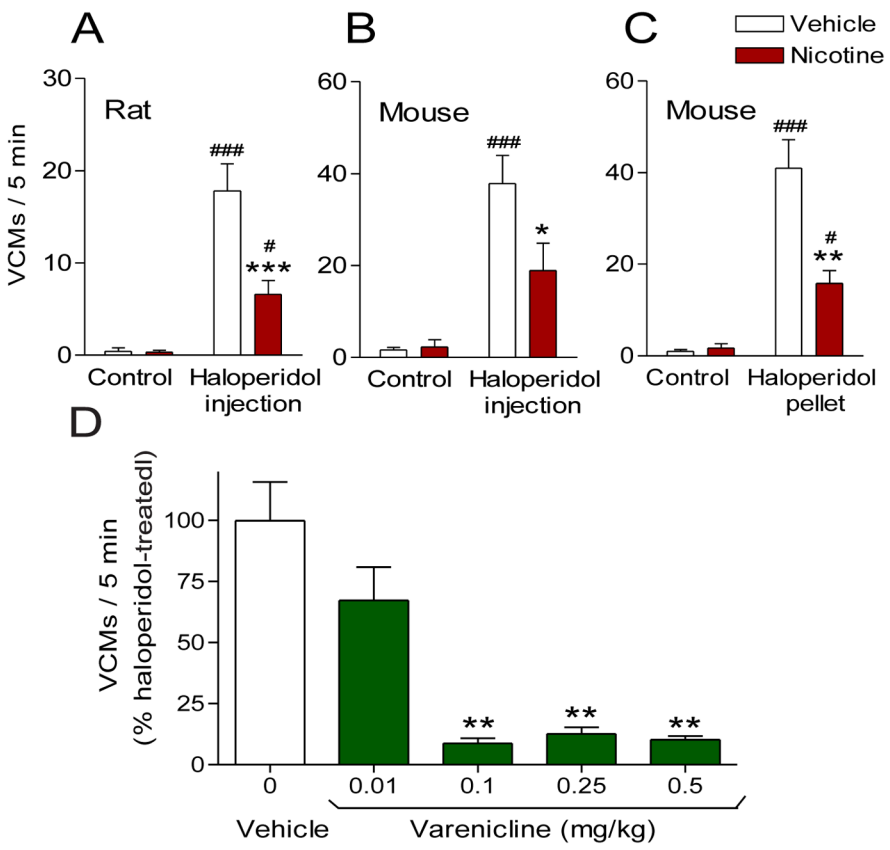

Fig. 3.

Nicotine treatment reduces vacuous chewing movements (VCMs) in a well-established rodent model of tardive dyskinesia. Rats or mice were pretreated with vehicle or nicotine given via minipump (A) or the drinking water (B and C). Two weeks later, they were treated with haloperidol via injection or surgically implanted with sub-dermal pellets that may mimic depot delivery of haloperidol in humans. Both forms of haloperidol treatment led to the development of VCMs, a motor side effect of antipsychotic therapy. (A–C) Chronic nicotine treatment reduced VCMs compared to vehicle-treated animals in rats and mice with either mode of haloperidol administration (injection or pellet), demonstrating the robustness of this effect. (B) The general nAChR agonist varenicline also reduced haloperidol-induced VCMs, indicating the reduction in VCMs is nAChR-mediated. Values are the mean ± SEM of 6–12 animals per group. Significance of difference from the vehicle-treated control, #$p < 0.05$, ###$p < 0.001$: from the vehicle-haloperidol-treated group, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ using two-way ANOVA followed by a Bonferroni post hoc test or using one-way ANOVA followed by a Dunnett's *post hoc* test. Data taken in modified form from (Bordia, et al., 2013; Bordia, McIntosh, et al., 2012).

Table 1

nAChR drugs improve motor abnormalities in animal models of movement disorders

Animal model	nAChR drug	Species used	Effect of nAChR drug	References
L-dopa-induced dyskinesias	Nicotine, varenicline, ABT-089, ABT-894,	NHPs	Up to 60% decline in L-dopa-induced dyskinesias	(Quik, Campos, Bordia, et al., 2013; Quik, et al., 2007; Quik, Mallela, Chin, et al., 2013; Zhang, et al., 2014; D. Zhang, et al., 2013)
L-dopa-induced dyskinesias	Nicotine, varenicline, A85380, sazetidine, TC-2696, TC-8831, TC10600, TI-10165	Rodents	Up to 60% decline in L-dopa-induced dyskinesias	(Bordia, Campos, Huang, & Quik, 2008; L. Z. Huang, et al., 2011)
Tardive dyskinesia	Nicotine, varenicline	Rodents	Up to 90% decline in tardive dyskinesias	(Bordia, et al., 2013; Bordia, McIntosh, et al., 2012)
Ataxia	Nicotine, varenicline, PNU-282987	Rodents	Up to a near complete reduction in ataxia	(Al-Rejaie & Dar, 2006; Taslim, et al., 2008; Taslim & Saeed Dar, 2011; Wecker, et al., 2013)
Tourette's syndrome	Nicotine	Rodents	Reduced haloperidol- induced hypokinesia	(Elazar & Paz, 1999; Emerich, Zanol, Norman, McConville, & Sanberg, 1991; Sanberg, et al., 1989)

Table 2

Nicotine and varenicline improve motor abnormalities in clinical studies

Disorder	nAChR drug	Study	Effect of nAChR drug	References
L-dopa-induced dyskinesias	Oral nicotine	Double-blind, placebo-controlled	Reduced some components of dyskinesias	http://www.neuraltus.com/pages/news_rel12_03_10.html
Ataxia	Oral varenicline	Case reports	Improve ataxia in Fragile X, Friedreich's ataxia and spinocerebellar ataxia	(Zesiewicz & Sullivan, 2008; Zesiewicz, Sullivan, Freeman, et al., 2009; Zesiewicz, Sullivan, Gooch, et al., 2009)
		Double-blind, placebo-controlled	Improved ataxia in spinocerebellar ataxia	(Zesiewicz, et al., 2012) but see (Connolly, et al., 2012)
Tourette's syndrome	Nicotine gum or patch	Open-label	Decreased tics or tic severity	(Dursun & Kutcher, 1999; Dursun, et al., 1994; McConville, et al., 1991; Sanberg, et al., 1989; Silver, et al., 1996)
	Nicotine patch	Double-blind, placebo-controlled	Decreased tic severity	(Silver, Shytle, Philipp, et al., 2001)