

The $\alpha 7$ Nicotinic Receptor Agonist ABT-107 Decreases L-Dopa-Induced Dyskinesias in Parkinsonian Monkeys

Danhui Zhang, Matthew McGregor, Michael W. Decker, and Maryka Quik

Center for Health Sciences, SRI International, Menlo Park, California (D.Z., M.M., M.Q.); and AbbVie, Inc., North Chicago, Illinois (M.W.D.)

Received May 7, 2014; accepted July 15, 2014

ABSTRACT

Previous studies in Parkinsonian rats and monkeys have shown that $\beta 2$ -selective nicotinic acetylcholine receptor (nAChR) agonists reduce L-Dopa-induced dyskinesias (LIDs), a serious complication of L-Dopa therapy for Parkinson's disease. Since rodent studies also suggested an involvement of $\alpha 7$ nAChRs in LIDs, we tested the effect of the potent, selective $\alpha 7$ agonist ABT-107 [5-(6-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy] pyridazin-3-yl)-1H-indole]. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-lesioned monkeys were gavaged with L-Dopa/carbidopa (10 and 2.5 mg/kg, respectively) twice daily, which resulted in stable LIDs. A dose-response study (0.03–1.0 mg/kg) showed that oral ABT-107 decreased LIDs by 40–60%. LIDs returned to control levels only after a 6-week ABT-107 washout, suggesting that long-term molecular changes were involved. Subsequent readministration of ABT-107 decreased LIDs by 50–60%, indicating that tolerance did

not develop. ABT-107 had no effect on Parkinsonism or cognitive performance. We next tested ABT-107 together with the $\beta 2$ agonist ABT-894 [(3-(5,6-dichloro-pyridin-3-yl)-1(S),5 (S)-3,6-diazabicyclo[3.2.0]heptane)], previously shown to reduce LIDs in Parkinsonian monkeys. In one study, the monkeys were first given oral ABT-894 (0.01 mg/kg), which maximally decreased LIDs by 50–60%; they were then also treated with 0.1 mg/kg ABT-107, a dose that maximally reduced LIDs. The effect of combined treatment on LIDs was similar to that with either drug alone. Comparable results were observed in a group of monkeys first treated with ABT-107 and then also given ABT-894. Thus, $\alpha 7$ and $\beta 2$ nAChR-selective drugs may function via a final common mechanism to reduce LIDs. The present results suggest that drugs targeting either $\alpha 7$ or $\beta 2$ nAChRs may be useful as anti-dyskinetic agents in Parkinson's disease.

Introduction

A critical unmet need for Parkinson's disease management is a strategy to reduce L-Dopa-induced dyskinesias (LIDs). These abnormal involuntary movements are a serious debilitating side effect of L-Dopa therapy, the gold standard of treatment of Parkinson's disease, and they develop in most patients with continued L-Dopa use (Obeso et al., 2010; Meissner et al., 2011; Schapira and Jenner, 2011; Wichmann et al., 2011; Irvani et al., 2012; Huot et al., 2013). Currently, the only drug approved for LIDs is amantadine, and it is of only limited effectiveness. There is, therefore, an ongoing search for new therapies. Drugs targeting numerous classes of neurotransmitter receptors, including glutamatergic, serotonergic, cholinergic, and others, reduce LIDs in animal models, suggesting that multiple mechanisms are involved (Fox et al., 2009; Brotchie and Jenner, 2011; Blandini and Armentero, 2012; Duty, 2012; Sgambato-Faure and Cenci, 2012; Huot et al., 2013).

More recent studies have also indicated that the nicotinic cholinergic system is involved in LIDs. Studies in mice, rats, and monkeys showed that the general nicotinic acetylcholine

receptor (nAChR) agonist nicotine consistently reduced LIDs in a dose-dependent manner (Quik et al., 2007, 2013d; Bordia et al., 2008; Huang et al., 2011b). Tolerance to the anti-dyskinetic effect of nicotine did not arise, even with months of treatment. Moreover, nicotine reduced LIDs, whether administered before L-Dopa treatment or once LIDs developed.

Nicotine generally exerts its effect by acting at nAChRs, of which there are multiple subtypes in both the peripheral and central nervous system. These subtypes include the $\alpha 1\beta 1^*$, $\alpha 3\beta 4^*$, and $\alpha 7$ nAChRs in the periphery, with the $\alpha 4\beta 2^*$, $\alpha 6\beta 2^*$ and $\alpha 7$ nAChRs being the primary ones in the brain (Millar and Gotti, 2009; Quik and Wonnacott, 2011). The asterisk denotes the possible presence of other nAChR subunits in the receptor. Studies with $\alpha 4$, $\alpha 6$, $\alpha 7$, and $\beta 2$ nAChR subunits null mutant mice suggest that $\alpha 4\beta 2^*$, $\alpha 6\beta 2^*$, and $\alpha 7$ nAChRs all influence the occurrence of LIDs (Quik et al., 2013b). These findings suggest that drugs targeting $\beta 2^*$ and/or $\alpha 7$ nAChRs may yield therapies to reduce LIDs. In fact, pharmacologic studies show that several $\beta 2^*$ nAChR agonists reduce LIDs in both rat and monkey models of LIDs (Huang et al., 2011a; Johnston et al., 2013; Quik et al., 2013a; Zhang et al., 2013a, 2014).

In the present study, we tested the effect of the $\alpha 7$ agonist ABT-107 [5-(6-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy] pyridazin-3-yl)-1H-indole] (from AbbVie, Inc., North Chicago, IL) since

This work was supported by the National Institutes of Health National Institute of Neurological Disorders and Stroke [Grants NS59910 and NS65851]. dx.doi.org/10.1124/jpet.114.216283.

ABBREVIATIONS: ABT-107, 5-(6-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy] pyridazin-3-yl)-1H-indole; ABT-894, (3-(5,6-dichloro-pyridin-3-yl)-1(S),5 (S)-3,6-diazabicyclo[3.2.0]heptane); DXMB, 3-(2,4-dimethoxybenzylidene)-anabaseine dihydrochloride; LIDs, L-Dopa, induced dyskinesias; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; nAChR, nicotinic acetylcholine receptor.

studies with $\alpha 7$ nAChR null mutant mice had indicated an involvement of $\alpha 7$ nAChRs in LIDs. We selected ABT-107 because of its potency and selectivity for $\alpha 7$ nAChRs over other available drugs (Briggs et al., 1997; Malysz et al., 2010) and because $\alpha 7$ nAChR drugs have excellent safety and tolerability profiles in clinical studies (Freedman et al., 2008; Othman et al., 2011). The results show that ABT-107 reduced LIDs ~50% with no worsening of Parkinsonism and no observable side effects. We also tested ABT-107 in combination with an $\beta 2^*$ nAChR agonist ABT-894 [(3-(5,6-dichloro-pyridin-3-yl)-1(S),5 (S)-3,6-diazabicyclo[3.2.0]heptane) (AbbVie, Inc.), and this drug combination yielded declines in LIDs similar to those after treatment with either drug along. These data suggest that drugs targeting either $\alpha 7$ or $\beta 2^*$ nAChRs have potential as antidyskinetic agents.

Materials and Methods

Animals. Squirrel monkeys ($n = 21$, *Saimiri sciureus*) ≥ 5 years of age of either sex were obtained from World Wide Primates (Miami, FL). As required by California state guidelines, they were quarantined for 30 days on arrival. Food consisted of monkey chow, fruits, and vegetables, with water freely provided. The monkeys were singly housed in a humidity- and temperature- controlled room on a 12-hour light/dark cycle. All studies were approved by the Institutional Animal Care and Use Committee and were done according to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

Induction of LIDs. The monkeys were injected subcutaneously with 2.0 mg/kg MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Sigma-Aldrich, St. Louis, MO) dissolved in saline to render them Parkinsonian (Quik et al., 2007). After 3 to 4 weeks of recovery from the systemic effects of the MPTP injection, the monkeys were rated for Parkinsonism, which was assessed by evaluating spatial hypokinesia, body bradykinesia, left and right manual dexterity, balance at rest and during movement, freezing during movement, and action tremor; each category was rated from 0 (normal) to 4 (severely Parkinsonian), as described by Quik et al. (2007, 2013d). The maximum Parkinsonian score is 28; however, individual scores are considerably lower because Parkinsonism is variably expressed in monkeys. Any single monkey may have deficits in manual dexterity but exhibit no freezing or tremor and move well, whereas another monkey may exhibit freezing and tremor but have no motor deficits. If the monkeys were not Parkinsonian, MPTP injection was repeated at 1.9 mg/kg. Parkinsonism was rated once weekly on Fridays throughout the study, before and 90 minutes after L-Dopa administration.

Monkeys then underwent gavage with L-Dopa (10 mg/kg) and carbidopa (2.5 mg/kg) twice a day at 8:30 AM and 12:30 PM from Monday to Friday inclusive (Quik et al., 2007, 2013d). Baseline LIDs were recorded from 8:00 to 8:30 AM. The monkeys then underwent gavage with L-Dopa, and recording was continued. The monkeys were given only fruits and vegetables in the morning to allow for optimal L-Dopa absorption, with more fruits and vegetables and monkey chow provided at ~3 PM. The LID scores provided in the figures represent the ratings averaged over the morning L-Dopa dosing period for Wednesday and Thursday of each week. LIDs were rated for a 1-minute period by a blinded rater from video recordings at the times depicted in the figures. Dyskinesias were assessed on a scale of 0 (no dyskinesias) to 4 (severe dyskinesias) using the following criteria: 1 = subtle dyskinesias that were not sustained (fewer than three trunk movements in a row); 2 = sustained dyskinesias (three or more trunk movements in a row); 3 = moderate dyskinesias that impaired the ability to remain stationary; and 4 = severe dyskinesias that were generalized and incapacitating (Tan et al., 2002; Quik et al., 2007, 2013d).

nAChR Drug Treatments. The monkeys had previously been treated with other nAChR agonists, followed by a 1-month washout period before initiating the current study. LID scores were at

vehicle-treated levels for all monkey groups at the start of the drug treatment regimens. The groups were as follows: a vehicle-treated group ($n = 6$), a nicotine-treated ($n = 5$) group, a group of monkeys first treated with ABT-107 and subsequently also given ABT-894 ($n = 5$), and a group first treated with ABT-894 and then also administered ABT-107 ($n = 5$). The number of males and females in each group was similar.

All monkeys received 50% diluted orange Gatorade (PepsiCo, Chicago, IL) in the drinking water as a vehicle control for nicotine

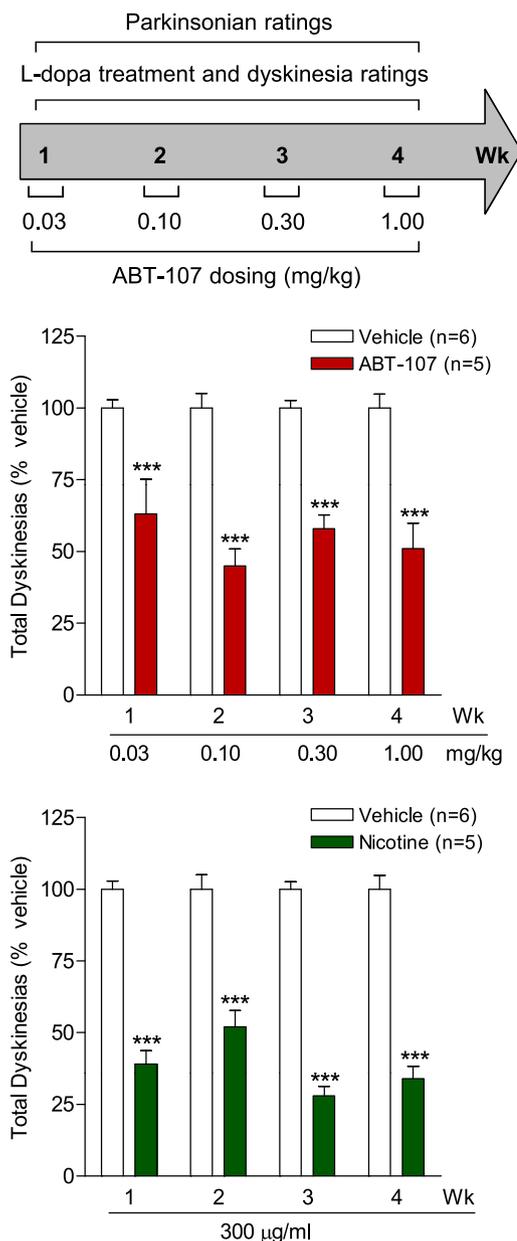


Fig. 1. The $\alpha 7$ agonist ABT-107 decreases LIDs in MPTP-lesioned monkeys. L-Dopa (10 mg/kg) plus carbidopa (2.5 mg/kg) was administered at 8:30 AM and 12:30 PM 5 days per week for 4 weeks, with ABT-107 given orally 30 minutes before each L-Dopa gavage. The overall treatment timeline is shown at top. The effect of increasing doses of ABT-107 (0.03–1.0 mg/kg) on total dyskinesia scores (expressed as % vehicle) is provided at middle. Any dose of ABT-107 was given for an entire week, with bars depicting the average score over 2 days. Bottom depicts the effect of nicotine (300 μ g/ml in the drinking water) on LIDs in a separate group of monkeys. Values represent the mean \pm S.E.M. of five or six monkeys. Significance of difference from vehicle treatment: *** $P < 0.001$ using two-way analysis of variance followed by a Bonferroni post hoc test.

treatment. The presence of the Gatorade was necessary to mask the bitter taste of nicotine [(-)-nicotine, free base; Sigma-Aldrich] in the nicotine-treated group. The dose of nicotine was started at 50 $\mu\text{g/ml}$ for 2 to 3 days, increased to 150 $\mu\text{g/ml}$ for a further 3 to 4 days and then to 300 $\mu\text{g/ml}$ nicotine, at which level it was maintained for the remainder of the study, as described (Quik et al., 2006, 2013d; Zhang et al., 2013a). Gatorade with and without nicotine was also added to the dry monkey chow. This nicotine dosing regimen yielded monkey plasma nicotine and cotinine levels similar to those in moderate smokers (Quik et al., 2006; Matta et al., 2007). ABT-107 or ABT-894 was administered orally 5 days per week via a small cracker 30 minutes before L-Dopa gavage. Each drug was applied to a small cracker in a 30- to 40- μl aliquot of water (depending on the monkey's weight) and immediately given to the monkeys. The drug had no effect on body weight; no adverse effects were noted on behavior.

Cognitive Testing. Since nAChR drugs are known to modulate cognitive abilities, we evaluated the effect of ABT-107 on cognition. We used an object retrieval task previously used for squirrel monkeys that measures a component of prefrontal cortex-dependent cognitive control involving inhibition of an initial learned response after subsequent spatial reversals (Lyons et al., 2000, 2004; Zhang et al., 2013a). The monkeys were scored for the average time and number of trials required to retrieve the marshmallow piece within a 30-second period (Lyons et al., 2000; Lyons and Schatzberg, 2003). Cognition was evaluated once weekly on Mondays.

Data Analyses. Statistical comparisons were done using GraphPad Prism (GraphPad Software, San Diego, CA). Total dyskinesias were determined by evaluating the area under the curve, with data analyzed by two-way analysis of variance followed by a Bonferroni post hoc test. The data are expressed as percentage of vehicle; that is, it was based on the mean of the vehicle-treated group for the specific day. Differences in Parkinsonian scores, which represent the total of

several behavioral parameters, were determined using a *t* test. The results are the mean \pm S.E.M. of the indicated number of monkeys. Differences in LID scores between groups of monkeys were determined using nonparametric tests (Mann-Whitney test) since the scores are integral values, with the median shown. $P \leq 0.05$ was considered significant.

Results

The $\alpha 7$ Agonist ABT-107 Reduces Established LIDs.

Monkeys were treated with varying doses of ABT-107 as depicted in the time line (Fig. 1, top panel). ABT-107 (0.03–1.0 mg/kg) was given orally in a cracker 30 minutes before L-Dopa. The results (Fig. 1, middle) show that ABT-107 significantly reduced LIDs by 40% at the 0.03 mg/kg dose and maximally by 50% at the 0.10 mg/dose. The effect of nicotine on LIDs is shown for comparison (Fig. 1, bottom). Nicotine significantly reduced LIDs by 50–70%. Both ABT-107 and nicotine treatment reduced LIDs throughout the 4-hour time course compared with vehicle; median scores are shown in Fig. 2. The dyskinesia scores in the vehicle-treated monkeys (Fig. 2) ranged from 1.0 to 2.0; thus, the monkeys were moderately dyskinetic. The dyskinesia scores decreased to 0–1.0 with drug treatment (Fig. 2). After the 4-week drug treatment regimen, ABT-107 and nicotine were discontinued. The results in Fig. 3 show that LIDs only returned to vehicle-treated levels by 6 weeks of either ABT-107 or nicotine washout.

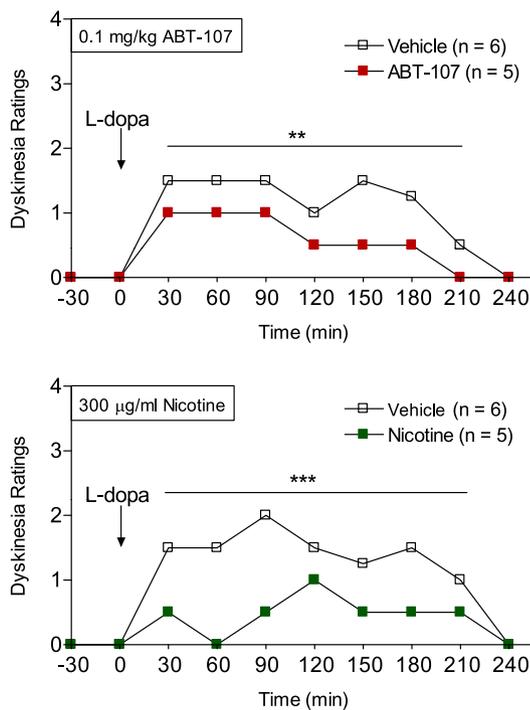


Fig. 2. ABT-107 administration reduces the hourly time course of LIDs. The monkeys were treated with ABT-107 as outlined in Fig. 1. The data shown at top were obtained using 0.1 mg/kg ABT-107, a dose that results in a maximal decline in LIDs. The effect of nicotine administration is shown at bottom. The symbols depict the median of five or six monkeys. Significance of difference from vehicle using a Mann-Whitney test: ** $P < 0.01$; *** $P < 0.001$.

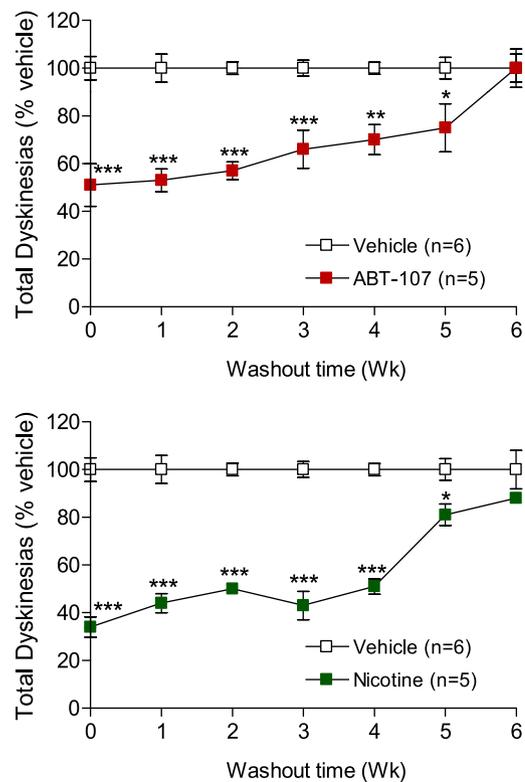


Fig. 3. ABT-107 discontinuation leads to a return of LIDs to vehicle-treated levels. ABT-107 treatment of L-Dopa-treated MPTP-lesioned monkeys (Fig. 1) was discontinued and the effects on LIDs determined. After 6 weeks of washout, LIDs were similar to those in vehicle-treated monkeys. The values depict the weekly average LID scores. Values are mean \pm S.E.M. of the number of monkeys indicated in parentheses. Significance of difference from vehicle: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ using two-way analysis of variance followed by a Bonferroni post hoc test.

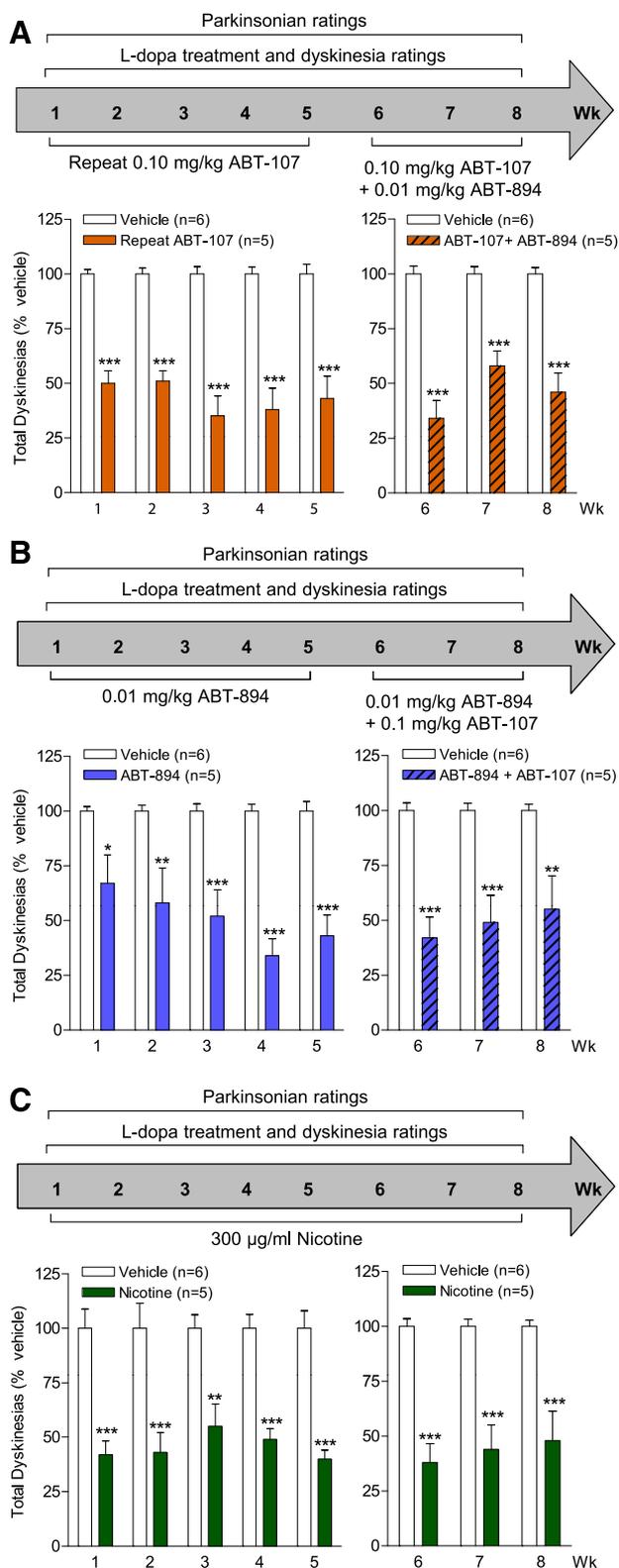


Fig. 4. Effect of ABT-107 in combination with ABT-894 on LIDs in MPTP-lesioned monkeys. After the nAChR drug washout shown in Fig. 3, the monkeys were readministered ABT-107 (0.10 mg/kg) orally 30 minutes before L-Dopa gavage (A). L-Dopa (10 mg/kg) plus carbidopa (2.5 mg/kg) was administered at 8:30 AM and 12:30 PM 5 days per week. After 5 weeks of ABT-107 administration, at which point its antidyskinetic effect was stable, the monkeys were also given the $\beta 2^*$ nAChR agonist ABT-894 (0.01 mg/kg). The decline in LIDs with combined ABT-107 and ABT-894 was similar to that observed with ABT-107 alone. In B, another set of L-Dopa-treated Parkinsonian monkeys was first administered ABT-894

Combined Effect of the $\alpha 7$ Agonist ABT-107 and the $\beta 2^*$ nAChR Agonist ABT-894 on LIDs. Our previous studies had shown that the $\beta 2$ nAChR agonist ABT-894 reduced LIDs by 60%, similar to the current results with $\alpha 7$ agonist ABT-107 (Zhang et al., 2014). This raised the question of whether combined treatment with the two different classes of nAChR agonists may yield a greater decline in LIDs than either drug alone. To evaluate this possibility, monkeys were treated with both drugs in combination as follows: one set of monkeys ($n = 5$) was first treated with 0.10 mg/kg ABT-107, a dose that maximally decreases LIDs (Fig. 4A). The monkeys were given ABT-107 orally for 5 weeks to ensure the drug effect had reached its plateau. A 50–60% decline in LIDs was obtained throughout the entire period. At week 6, the monkeys were also given ABT-894 orally at a dose that optimally reduced LIDs (0.01 mg/kg) (Zhang et al., 2014). The decline in LIDs with combined ABT-107 plus ABT-894 treatment was similar to that observed with ABT-107 alone (Fig. 4A).

Another set of monkeys (Fig. 4B) was first given ABT-894 orally at 0.01 mg/kg, a dose that optimally reduced LIDs (Zhang et al., 2014). The decline in LIDs reached its plateau by 5 weeks of ABT-894 treatment. At week 6, the monkeys were also administered ABT-107 at 0.10 mg/kg (Fig. 4B). No further decline in LIDs was observed with ABT-894 and ABT-107 in combination compared with single drug treatment. Thus, similar results were obtained regardless of the order of treatment of ABT-107 and ABT-894.

The effect of nicotine administration on LIDs in another set of monkeys, treated at the same time as in the studies already described, is shown in Fig. 4C for comparison. A 50–60% decline in LIDs was observed throughout.

The effect of ABT-107, ABT-894, the two drugs in combination, and nicotine on the hourly time course of LIDs is shown in Fig. 5. The average dyskinesia scores in the vehicle-treated monkeys ranged from 1.0 to 2.0 and in the drug-treated monkeys from 0 to 1.5, with the median score shown. The decline in LIDs was similar with all treatments (Fig. 5). The effect of drug washout is shown in Fig. 6. The time required for LIDs to return to vehicle-treated levels with the ABT-107 and ABT-894 drug combination was similar to that for the drugs alone (see Fig. 3).

Effect of the $\alpha 7$ Agonist ABT-107 and the $\beta 2^*$ nAChR Agonist ABT-894 on Parkinsonism. Vehicle-treated monkeys were moderately Parkinsonian. ABT-107 did not significantly affect Parkinsonism either on or off L-Dopa at any time point compared with vehicle (Table 1). The scores shown are for the last 4 weeks of treatment, with similar results throughout the study. In addition, ABT-107 had no effect on cognitive performance at any dose tested (Table 2).

(0.01 mg/kg) until its antidyskinetic effect had stabilized (5 weeks). They were subsequently also given ABT-107 (0.10 mg/kg). The decrease in LIDs resembled that seen in the monkeys treated with only ABT-894. Thus, combined drug treatment yielded a decline in LIDs similar to that with the use of either nAChR agonist alone. The effect of nicotine treatment in another set of monkeys is shown for comparison (C). Values are the mean \pm S.E.M. of five or six monkeys. Significance of the difference of drug treatment from vehicle: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ using two-way analysis of variance followed by a Bonferroni post hoc test.

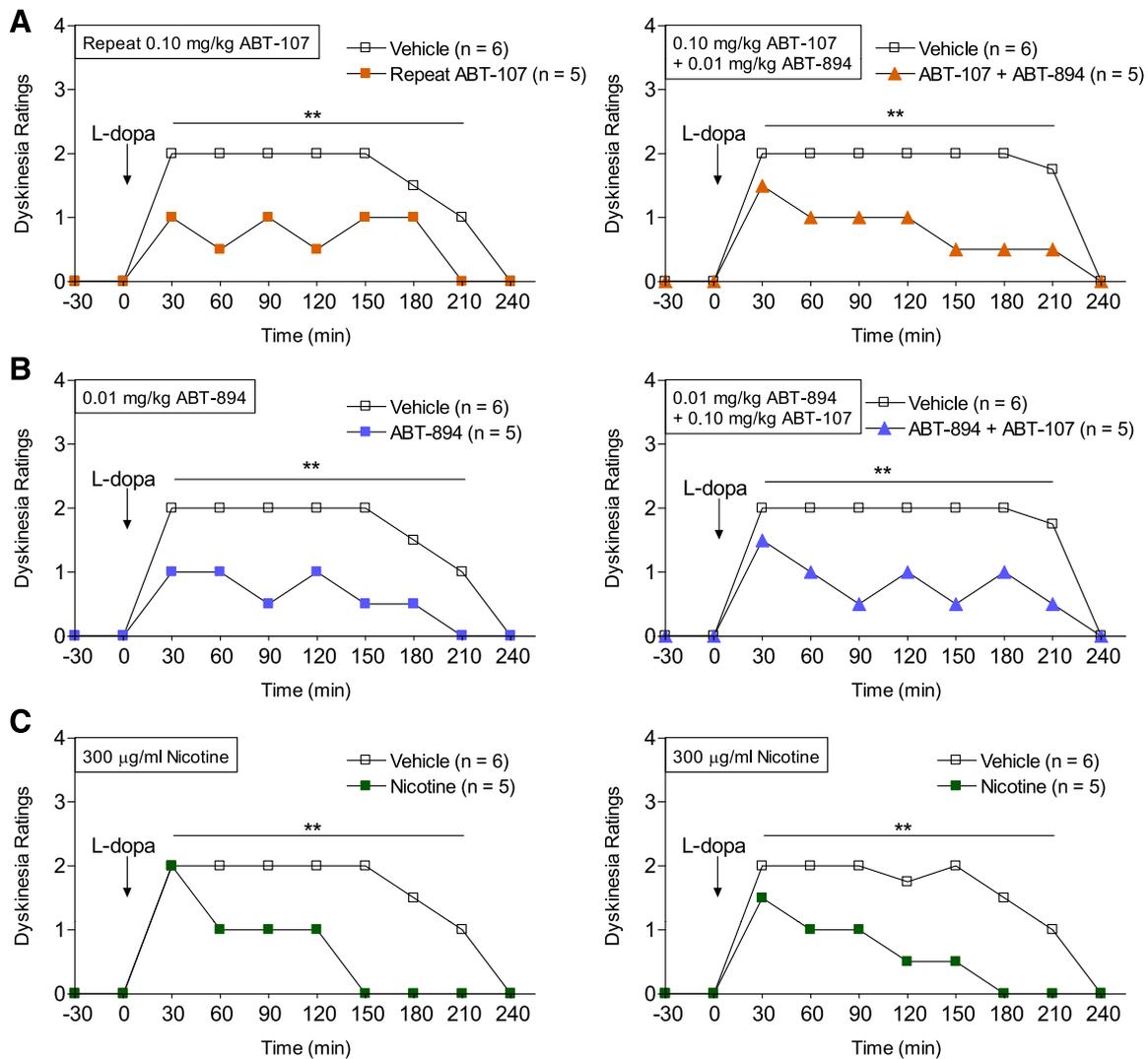


Fig. 5. Effect of ABT-107 in combination with ABT-894 on the hourly time course of LIDs. The monkeys were treated with ABT-107, ABT-894, or the drugs in combination as outlined in Fig. 4. The data shown for ABT-107 (A, left) are from week 4 and that for the combined ABT-107 plus ABT-894 data (A, right) from week 8, with similar results for the other weeks. The data shown for ABT-894 (B, left) is from week 4 and that for the combined ABT-894 plus ABT-107 data (B, right) from week 8, with similar results for the other weeks. The effect of nicotine on another set of monkeys during week 8 or 9 is shown in the lower panels (C). The symbols depict the median of five or six monkeys. Significance of difference from vehicle using a Mann-Whitney test: ** $P < 0.01$.

Discussion

The present results are the first to show that an $\alpha 7$ nAChR agonist reduces LIDs in Parkinsonian monkeys, a model that exhibits many features reminiscent of the dyskinesias that occur in L-Dopa-treated Parkinson's disease patients. Notably, the ABT-107-induced decrease in LIDs persisted over several months of treatment, indicating tolerance does not develop. The effect of the drug was fairly long-lasting, with 6 weeks of washout required before LIDs returned to values similar to those in vehicle-treated monkeys.

These observations suggest that $\alpha 7$ nAChR agonists may represent a promising class of drugs for the treatment of LIDs in Parkinson disease patients. ABT-107 offers the advantage over other $\alpha 7$ nAChR agonists, such as DMXB [3-(2,4-dimethoxybenzylidene)-anabaseine dihydrochloride], as the former drug is a potent and selective $\alpha 7$ nAChR agonist. Additionally, $\alpha 7$ nAChR drugs have been tested in healthy human volunteers and in schizophrenic patients and were

shown to be safe and well tolerated. Side effects were similar to those with placebo treatment (Freedman et al., 2008; Othman et al., 2011), despite the presence of $\alpha 7$ nAChRs in the peripheral nervous system. These characteristics suggest that $\alpha 7$ nAChR drugs may represent good candidates for further development for the treatment of LIDs in patients with Parkinson's disease.

Our previous data had shown that $\beta 2^*$ nAChR agonists reduced LIDs in Parkinsonian monkeys to a similar extent as the $\alpha 7$ agonist ABT-107 in the current study. Varenicline, which acts at $\beta 2^*$ and other nAChR subtypes, as well as $\beta 2^*$ -selective drugs, including A-85380, sazetidine, TC-2696, TI-10165, TC-8831, and TC-10600, all reduced LIDs to varying extents in rats with a unilateral 6-hydroxydopamine lesion (Huang et al., 2011a; Quik et al., 2013a). Additionally, varenicline and TC-8831 decreased LIDs ~50% in nonhuman primates with no tolerance, although a limitation of these drugs was the development of emesis (Johnston et al., 2013; Zhang et al., 2013a). We more recently tested two $\beta 2^*$ nAChR

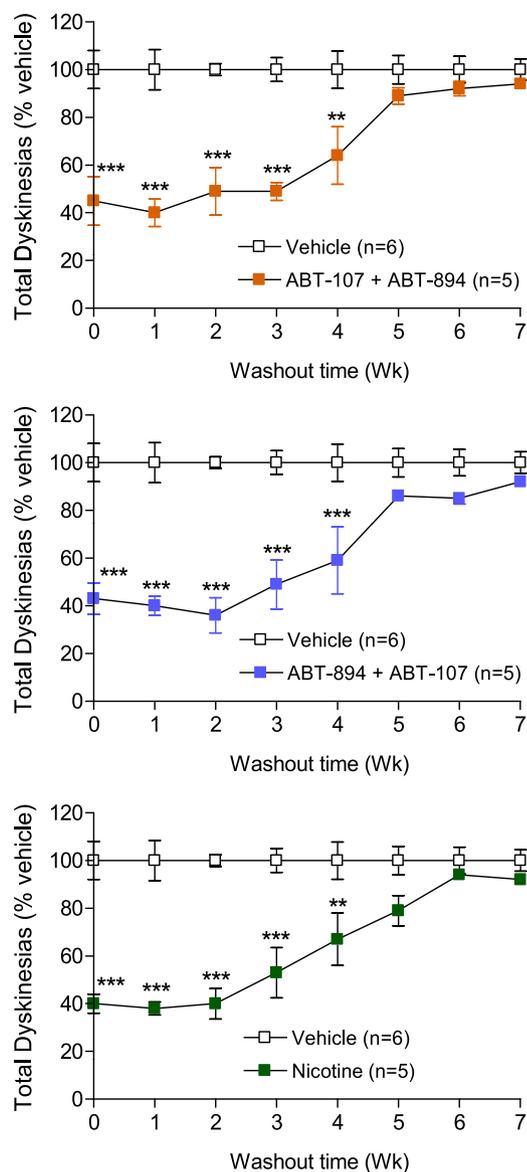


Fig. 6. Discontinuation of combined ABT-107 and ABT-894 treatments led to a return of LIDs to levels in vehicle-treated monkeys. The combination ABT-107 and ABT-894 drug treatment regimen is depicted in Fig. 4. After drug discontinuation, LIDs were similar to those in vehicle-treated monkeys by weeks 5 to 7. The values shown are the weekly average LID scores. Results are mean \pm S.E.M. of the number of monkeys indicated in parentheses. Significance of difference from vehicle: ** $P < 0.01$; *** $P < 0.001$ using two-way analysis of variance, followed by a Bonferroni post hoc test.

agonists that had previously been evaluated in phase 2 clinical trials for other indications (Zhang et al., 2014). These included ABT-089, a partial agonist (Decker et al., 1997; Sullivan et al., 1997; Anderson et al., 2009; Marks et al., 2009; Apostol et al., 2012), as well as a full agonist ABT-894 (Ji et al., 2007; Rowbotham et al., 2012; Bain et al., 2013). ABT-089 maximally decreased LIDs by 40% whereas ABT-894 reduced LIDs up to 60% in nonhuman primates (Zhang et al., 2014). None of the agonists worsened Parkinsonism, and there were no detectable side effects and no emesis (Zhang et al., 2014). Moreover, the effects of both the $\beta 2^*$ nAChR drug ABT-894, the $\alpha 7$ nAChR drug ABT-107, as well as nicotine, persisted for months with treatment and, in addition, remained for several weeks after drug continuation.

The $\alpha 7$ nAChRs are functionally and pharmacologically distinct from $\beta 2^*$ nAChRs. They exhibit a greater calcium conductance and faster desensitization and have a more direct impact on glutamatergic signaling (Albuquerque et al., 2009; Quik and Wonnacott, 2011). These differential characteristics raised the question of whether combination $\alpha 7$ and $\beta 2^*$ nAChR drug treatment may yield a greater decline in LIDs. However, when ABT-107 was tested together with the $\beta 2^*$ nAChR agonist ABT-894, the improvement in LIDs was comparable to that with either drug alone. In addition, it was similar to the effect of nicotine, a general agonist that acts at both $\alpha 7$ and $\beta 2^*$ nAChRs, although with lower affinity for the $\alpha 7$ subtype.

The finding that the $\beta 2^*$ and $\alpha 7$ nAChR agonists both reduce LIDs by $\sim 60\%$ but show no significant additive effect with combined treatments suggests that these classes of drugs either reduce LIDs by a common mechanism or decrease LIDs by affecting different mechanism(s), which ultimately converge to produce parallel downstream changes. A key brain region involved in the generation of LIDs is the striatum, which expresses both $\beta 2$ and $\alpha 7$ nAChRs. Although not at high density (Quik et al., 2000), $\alpha 7$ nAChRs are located on glutamatergic afferents from the cortex to the striatum to regulate dopamine release (Kaiser and Wonnacott, 2000). In addition, $\alpha 7$ nAChRs are present in the substantia nigra to control striatal dopaminergic function (Quik et al., 2000). $\beta 2^*$ nAChR receptors are also expressed in the striatum on striatal dopamine nerve terminals, as well as in other neuronal elements. Lesion studies suggest that the $\beta 2^*$ nAChRs on the dopamine nerve terminals are important for the nAChR-mediated reduction in LIDs because nicotine and nAChR drugs most effectively reduced LIDs in Parkinsonian animals with moderate nigrostriatal damage (Huang et al., 2011a,b; Quik et al., 2013c). Thus, a common mechanism by which $\alpha 7$ and $\beta 2^*$ nAChR drugs act to reduce LIDs may involve a reduction in striatal dopamine release. Further evidence for this suggestion stems from studies showing that long-term nicotine treatment reduces dopamine release from striatal synaptosomes (Bordia et al., 2013).

In addition to the nigrostriatal dopaminergic system, other neuronal pathways also appear to be involved in the nAChR-mediated decline in LIDs. Evidence for this idea stems from studies showing that nicotine and $\beta 2^*$ nAChR drugs still diminished LIDs up to 30% in rats with severe nigrostriatal damage. Possible candidates include nAChRs on nondopaminergic striatal neurons (GABAergic or cholinergic) or nAChRs in other brain regions (Huang et al., 2011a; Quik et al., 2013a). The effects of $\alpha 7$ nAChR drugs may also be mediated by $\alpha 7$ nAChRs in cortex, thalamus, cerebellum, and other brain regions linked to motor control as there is relatively high expression of $\alpha 7$ nAChRs in these regions (Quik et al., 2000).

With respect to the signaling pathways affected by nAChR drugs, activation of the nicotinic acetylcholine system has been linked to alterations in cAMP-linked intracellular signaling and in extracellular signal-regulated kinases (Ding et al., 2011; Feyder et al., 2011; Kawamata and Shimohama, 2011). Changes in the cAMP signaling cascade, including activation of cAMP, increased activity of the cAMP-dependent protein kinase, and of the dopamine- and cAMP-dependent phosphoprotein of 32 kDa have also been implicated in LIDs (Santini et al., 2007, 2010; Calabresi et al., 2008; Rangel-Barajas et al., 2010; Feyder et al., 2011). In addition, LIDs are associated with enhanced activity of extracellular signal-regulated kinase (Santini et al., 2010;

TABLE 1

No effect of single or multiple nAChR drug treatments on Parkinsonism assessed before or after L-Dopa treatment

nAChR drugs were administered orally in crackers 60 minutes before gavage with L-Dopa (10 mg/kg/carbidopa (2.5 mg/kg). Parkinsonism was measured 45 minutes before L-Dopa and again 90 minutes after L-Dopa administration once weekly. Drug doses were 300 μg/ml nicotine in the drinking water, 0.1 mg/kg ABT-107 orally, 0.01 mg/kg ABT-894 orally; the last two drugs were given on their own or in combination (see time lines in Fig. 4). For the nAChR drug combination studies, the drugs were administered in the order shown. Values represent the mean ± S.E.M. of the indicated number of monkeys.

Week	Group	No. of Monkeys	Parkinsonian Scores	
			Before L-Dopa	After L-Dopa
5	Vehicle	6	4.7 ± 0.9	2.5 ± 0.3*
	Nicotine	5	5.0 ± 0.3	3.2 ± 0.5*
	ABT-107	5	4.8 ± 0.4	2.8 ± 0.2**
	ABT-894	5	4.2 ± 0.4	2.2 ± 0.5*
6	Vehicle	6	4.3 ± 1.2	2.3 ± 0.5
	Nicotine	5	4.8 ± 0.6	3.0 ± 0.3*
	ABT-107 + ABT-894	5	4.8 ± 0.4	3.2 ± 0.4*
	ABT-894 + ABT-107	5	4.8 ± 0.8	2.6 ± 0.4*
7	Vehicle	6	4.0 ± 1.2	2.0 ± 0.4
	Nicotine	5	5.2 ± 0.4	2.8 ± 0.2***
	ABT-107 + ABT-894	5	3.8 ± 0.4	2.6 ± 0.2*
	ABT-894 + ABT-107	5	4.0 ± 0.5	2.4 ± 0.4*
8	Vehicle	6	3.7 ± 0.9	1.7 ± 0.2**
	Nicotine	5	4.0 ± 0.7	1.6 ± 0.2*
	ABT-107 + ABT-894	5	3.0 ± 0.5	0.8 ± 0.4**
	ABT-894 + ABT-107	5	4.0 ± 0.3	1.0 ± 0.3***

*P < 0.05; **P < 0.01; ***P < 0.001.

Feyder et al., 2011; Wang et al., 2012). These mechanisms and others may thus contribute to the nAChR-mediated reduction in LIDs.

The ability of ABT-894, ABT-107, and nicotine to reduce LIDs weeks after drug discontinuation suggests that they most likely induce their effect via long-lasting molecular adaptations. Indeed, long-term changes in gene expression, intracellular signaling pathways, neuronal plasticity, and morphology have all been linked to the expression of LIDs (Santini et al., 2009; Cenci and Konradi, 2010; Feyder et al., 2011; Huot et al., 2011; Rangel-Barajas et al., 2011; Zhang et al., 2013b). Moreover, these changes may occur via numerous neurotransmitter systems, such as the dopaminergic, glutamatergic, serotonergic, and others, which are all implicated in the development and maintenance of LIDs (Carta and Bezard, 2011; Huot et al., 2011; Blandini and Armentero, 2012; Duty, 2012; Rylander, 2012; Huot et al., 2013).

α7 nAChR agonists offer the advantage that they have also been linked to improvements in cognition in numerous animal

TABLE 2

No effect of single or multiple nAChR drug treatments on cognitive performance

Lesioned monkeys were gavaged with L-Dopa twice daily at 4-hour intervals and given nAChR drugs orally 30 min before L-Dopa. Cognitive performance was evaluated 90 min after the first L-Dopa gavage of the day once weekly. The drug doses were 300 μg/ml nicotine in the drinking water, 0.1 mg/kg ABT-107 orally, 0.01 mg/kg ABT-894 orally, with the latter two drugs given on their own or in combination (see time lines in Fig. 4). For the nAChR drug combination studies, the drugs were administered in the order shown. Values are the mean ± S.E.M. of the indicated number of monkeys.

Group	No. of Monkeys	Latency(s)	Attempts
Vehicle	6	18.1 ± 2.9	17.0 ± 2.4
Nicotine	5	18.8 ± 2.1	19.0 ± 2.3
ABT-107	5	15.7 ± 3.0	15.5 ± 3.1
ABT-894	5	14.3 ± 3.2	14.6 ± 2.0
ABT-107 + ABT-894	5	16.8 ± 3.4	14.4 ± 1.8
ABT-894 + ABT-107	5	16.1 ± 3.2	16.0 ± 1.7

models (Levin, 2012; Lendvai et al., 2013) and in various neurologic and psychiatric disorders (Geerts, 2012; Lieberman et al., 2013). These latter observations suggest that α7 nAChR drugs may also be helpful for the memory deficits with Parkinson's disease, in addition to improving LIDs.

In summary, the present data show that the α7 nAChR agonist ABT-107 reduces LIDs in Parkinsonian monkeys, without affecting Parkinsonism. Our previous work showed similar declines in LIDs with the β2* agonist ABT-894. These data suggest that development of subtype-selective nAChR drugs may offer not only greater specificity with reduced side-effect profiles but also may provide multiple therapeutic options.

Acknowledgments

The authors thank Tanuja Bordia and Xiomara Perez for helpful comments concerning the manuscript.

Authorship Contributions

Participated in research design: Quik, Zhang, Decker.
Conducted experiments: Zhang, McGregor.
Contributed new reagents or analytic tools: Decker.
Performed data analysis: Zhang, McGregor, Quik.
Wrote or contributed to the writing of the manuscript: Quik, Zhang, McGregor.

References

Albuquerque EX, Pereira EF, Alkondon M, and Rogers SW (2009) Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev* **89**:73–120.
 Anderson DJ, Malysz J, Grønlien JH, El Kouhen R, Håkerud M, Wetterstrand C, Briggs CA, and Gopalakrishnan M (2009) Stimulation of dopamine release by nicotinic acetylcholine receptor ligands in rat brain slices correlates with the profile of high, but not low, sensitivity alpha4beta2 subunit combination. *Biochem Pharmacol* **78**:844–851.
 Apostol G, Abi-Saab W, Kratochvil CJ, Adler LA, Robieson WZ, Gault LM, Pritchett YL, Feifel D, Collins MA, and Saltarelli MD (2012) Efficacy and safety of the novel α4β2 neuronal nicotinic receptor partial agonist ABT-089 in adults with attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled crossover study. *Psychopharmacology (Berl)* **219**:715–725.
 Bain EE, Robieson W, Pritchett Y, Garimella T, Abi-Saab W, Apostol G, McGough JJ, and Saltarelli MD (2013) A randomized, double-blind, placebo-controlled phase 2 study of α4β2 agonist ABT-894 in adults with ADHD. *Neuropsychopharmacology* **38**:405–413.
 Blandini F and Armentero MT (2012) New pharmacological avenues for the treatment of L-DOPA-induced dyskinesias in Parkinson's disease: targeting glutamate and adenosine receptors. *Expert Opin Investig Drugs* **21**:153–168.

- Bordia T, Campos C, Huang L, and Quik M (2008) Continuous and intermittent nicotine treatment reduces L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a rat model of Parkinson's disease. *J Pharmacol Exp Ther* **327**:239–247.
- Bordia T, McIntosh JM, and Quik M (2013) The nicotine-mediated decline in L-dopa-induced dyskinesias is associated with a decrease in striatal dopamine release. *J Neurochem* DOI: 10.1111/jnc.12179 [published ahead of print].
- Briggs CA, Anderson DJ, Brioni JD, Buccafusco JJ, Buckley MJ, Campbell JE, Decker MW, Donnelly-Roberts D, Elliott RL, and Gopalakrishnan M, et al. (1997) Functional characterization of the novel neuronal nicotinic acetylcholine receptor ligand GTS-21 in vitro and in vivo. *Pharmacol Biochem Behav* **57**:231–241.
- Brochie J and Jenner P (2011) New approaches to therapy. *Int Rev Neurobiol* **98**: 123–150.
- Calabresi P, Di Filippo M, Ghiglieri V, and Picconi B (2008) Molecular mechanisms underlying levodopa-induced dyskinesia. *Mov Disord* **23** (Suppl 3):S570–S579.
- Carta M and Bezdard E (2011) Contribution of pre-synaptic mechanisms to L-DOPA-induced dyskinesia. *Neuroscience* **198**:245–251.
- Cenci MA and Konradi C (2010) Maladaptive striatal plasticity in L-DOPA-induced dyskinesia. *Prog Brain Res* **183**:209–233.
- Decker MW, Bannon AW, Curzon P, Gunther KL, Brioni JD, Holladay MW, Lin NH, Li Y, Daanen JF, and Buccafusco JJ, et al. (1997) ABT-089 [2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride]: II. A novel cholinergic channel modulator with effects on cognitive performance in rats and monkeys. *J Pharmacol Exp Ther* **283**:247–258.
- Ding Y, Won L, Britt JP, Lim SA, McGehee DS, and Kang UJ (2011) Enhanced striatal cholinergic neuronal activity mediates L-DOPA-induced dyskinesia in parkinsonian mice. *Proc Natl Acad Sci USA* **108**:840–845.
- Duty S (2012) Targeting glutamate receptors to tackle the pathogenesis, clinical symptoms and levodopa-induced dyskinesia associated with Parkinson's disease. *CNS Drugs* **26**:1017–1032.
- Feyder M, Bonito-Oliva A, and Fisone G (2011) L-DOPA-induced dyskinesia and abnormal signaling in striatal medium spiny neurons: focus on dopamine D1 receptor-mediated transmission. *Front Behav Neurosci* **5**:71.
- Fox SH, Chuang R, and Brochie JM (2009) Serotonin and Parkinson's disease: on movement, mood, and madness. *Mov Disord* **24**:1255–1266.
- Freedman R, Olincy A, Buchanan RW, Harris JG, Gold JM, Johnson L, Allensworth D, Guzman-Bonilla A, Clement B, and Ball MP, et al. (2008) Initial phase 2 trial of a nicotinic agonist in schizophrenia. *Am J Psychiatry* **165**:1040–1047.
- Geerts H (2012) $\alpha 7$ Nicotinic receptor modulators for cognitive deficits in schizophrenia and Alzheimer's disease. *Expert Opin Investig Drugs* **21**:59–65.
- Huang LZ, Campos C, Ly J, Ivy Carroll F, and Quik M (2011a) Nicotinic receptor agonists decrease L-dopa-induced dyskinesias most effectively in partially lesioned parkinsonian rats. *Neuropharmacology* **60**:861–868.
- Huang LZ, Grady SR, and Quik M (2011b) Nicotine reduces L-DOPA-induced dyskinesias by acting at beta2* nicotinic receptors. *J Pharmacol Exp Ther* **338**:932–941.
- Huot P, Fox SH, Newman-Tancredi A, and Brochie JM (2011) Anatomically selective serotonergic type 1A and serotonergic type 2A therapies for Parkinson's disease: an approach to reducing dyskinesia without exacerbating parkinsonism? *J Pharmacol Exp Ther* **339**:2–8.
- Huot P, Johnston TH, Koprach JB, Fox SH, and Brochie JM (2013) The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. *Pharmacol Rev* **65**:171–222.
- Iravani MM, McCreary AC, and Jenner P (2012) Striatal plasticity in Parkinson's disease and L-dopa induced dyskinesia. *Parkinsonism Relat Disord* **18** (Suppl 1):S123–S125.
- Ji J, Schimpf MR, Sippy KB, Bunnelle WH, Li T, Anderson DJ, Faltynek C, Surowy CS, Dyhring T, and Ahning PK, et al. (2007) Synthesis and structure-activity relationship studies of 3,6-diazabicyclo[3.2.0]heptanes as novel alpha4beta2 nicotinic acetylcholine receptor selective agonists. *J Med Chem* **50**:5493–5508.
- Johnston TH, Huot P, Fox SH, Koprach JB, Szeliga KT, James JW, Graef JD, Letchworth SR, Jordan KG, Hill MP, and Brochie JM (2013) TC-8831, a nicotinic acetylcholine receptor agonist, reduces L-DOPA-induced dyskinesia in the MPTP macaque. *Neuropharmacology* **73**:337–347.
- Kaiser S and Wonnacott S (2000) Alpha-bungarotoxin-sensitive nicotinic receptors indirectly modulate [(3)H]dopamine release in rat striatal slices via glutamate release. *Mol Pharmacol* **58**:312–318.
- Kawamata J and Shimohama S (2011) Stimulating nicotinic receptors trigger multiple pathways attenuating cytotoxicity in models of Alzheimer's and Parkinson's diseases. *J Alzheimers Dis* **24** (Suppl 2):95–109.
- Lendvai B, Kassai F, Szájlí A, and Némethy Z (2013) $\alpha 7$ nicotinic acetylcholine receptors and their role in cognition. *Brain Res Bull* **93**:86–96.
- Levin ED (2012) $\alpha 7$ -Nicotinic receptors and cognition. *Curr Drug Targets* **13**:602–606.
- Lieberman JA, Dunbar G, Segreti AC, Girgis RR, Seoane F, Beaver JS, Duan N, and Hosford DA (2013) A randomized exploratory trial of an $\alpha 7$ nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. *Neuropsychopharmacology* **38**:968–975.
- Lyons DM, Lopez JM, Yang C, and Schatzberg AF (2000) Stress-level cortisol treatment impairs inhibitory control of behavior in monkeys. *J Neurosci* **20**:7816–7821.
- Lyons DM and Schatzberg AF (2003) Early maternal availability and prefrontal correlates of reward-related memory. *Neurobiol Learn Mem* **80**:97–104.
- Lyons DM, Yang C, Eliez S, Reiss AL, and Schatzberg AF (2004) Cognitive correlates of white matter growth and stress hormones in female squirrel monkey adults. *J Neurosci* **24**:3655–3662.
- Malysz J, Anderson DJ, Grönlien JH, Ji J, Bunnelle WH, Häkerud M, Thorin-Hagene K, Ween H, Helfrich R, and Hu M, et al. (2010) In vitro pharmacological characterization of a novel selective alpha7 neuronal nicotinic acetylcholine receptor agonist ABT-107. *J Pharmacol Exp Ther* **334**:863–874.
- Marks MJ, Wageman CR, Grady SR, Gopalakrishnan M, and Briggs CA (2009) Selectivity of ABT-089 for alpha4beta2* and alpha6beta2* nicotinic acetylcholine receptors in brain. *Biochem Pharmacol* **78**:795–802.
- Matta SG, Balfour DJ, Benowitz NL, Boyd RT, Buccafusco JJ, Caggiola AR, Craig CR, Collins AC, Damaj MI, and Donny EC, et al. (2007) Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology (Berl)* **190**:269–319.
- Meissner WG, Frasier M, Gasser T, Goetz CG, Lozano A, Piccini P, Obeso JA, Rascol O, Schapira A, and Voon V, et al. (2011) Priorities in Parkinson's disease research. *Nat Rev Drug Discov* **10**:377–393.
- Millar NS and Gotti C (2009) Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology* **56**:237–246.
- Obeso JA, Rodriguez-Oroz MC, Goetz CG, Marin C, Kordower JH, Rodriguez M, Hirsch EC, Farrer M, Schapira AH, and Halliday G (2010) Missing pieces in the Parkinson's disease puzzle. *Nat Med* **16**:653–661.
- Othman AA, Lenz RA, Zhang J, Li J, Awani WM, and Dutta S (2011) Single- and multiple-dose pharmacokinetics, safety, and tolerability of the selective alpha7 neuronal nicotinic receptor agonist, ABT-107, in healthy human volunteers. *J Clin Pharmacol* **51**:512–526.
- Quik M, Campos C, Bordia T, Strachan JP, Zhang J, McIntosh JM, Letchworth S, and Jordan K (2013a) $\alpha 4\beta 2$ Nicotinic receptors play a role in the nAChR-mediated decline in L-dopa-induced dyskinesias in parkinsonian rats. *Neuropharmacology* **71**:191–203.
- Quik M, Campos C, and Grady SR (2013b) Multiple CNS nicotinic receptors mediate L-dopa-induced dyskinesias: studies with parkinsonian nicotinic receptor knockout mice. *Biochem Pharmacol* **86**:1153–1162.
- Quik M, Cox H, Parameswaran N, O'Leary K, Langston JW, and Di Monte D (2007) Nicotine reduces levodopa-induced dyskinesias in lesioned monkeys. *Ann Neurol* **62**:588–596.
- Quik M, Mallela A, Chin M, McIntosh JM, Perez XA, and Bordia T (2013c) Nicotine-mediated improvement in L-dopa-induced dyskinesias in MPTP-lesioned monkeys is dependent on dopamine nerve terminal function. *Neurobiol Dis* **50**:30–41.
- Quik M, Mallela A, Ly J, and Zhang D (2013d) Nicotine reduces established levodopa-induced dyskinesias in a monkey model of Parkinson's disease. *Mov Disord* **28**: 1398–1406.
- Quik M, Parameswaran N, McCallum SE, Bordia T, Bao S, McCormack A, Kim A, Tyndale RF, Langston JW, and Di Monte DA (2006) Chronic oral nicotine treatment protects against striatal degeneration in MPTP-treated primates. *J Neurochem* **98**:1866–1875.
- Quik M, Polonskaya Y, Gillespie A, K Lloyd G, and Langston JW (2000) Differential alterations in nicotinic receptor alpha6 and beta3 subunit messenger RNAs in monkey substantia nigra after nigrostriatal degeneration. *Neuroscience* **100**:63–72.
- Quik M and Wonnacott S (2011) $\alpha 6\beta 2^*$ and $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors as drug targets for Parkinson's disease. *Pharmacol Rev* **63**:938–966.
- Rangel-Barajas C, Silva I, López-Santiago LM, Aceves J, Erlig D, and Florán B (2011) L-DOPA-induced dyskinesia in hemiparkinsonian rats is associated with up-regulation of adenylyl cyclase type V/V1 and increased GABA release in the substantia nigra reticulata. *Neurobiol Dis* **41**:51–61.
- Rowbotham MC, Arslanian A, Nothaft W, Duan WR, Best AE, Pritchett Y, Zhou Q, and Stacey BR (2012) Efficacy and safety of the $\alpha 4\beta 2$ neuronal nicotinic receptor agonist ABT-894 in patients with diabetic peripheral neuropathic pain. *Pain* **153**:862–868.
- Rylander D (2012) The serotonin system: a potential target for anti-dyskinetic treatments and biomarker discovery. *Parkinsonism Relat Disord* **18** (Suppl 1): S126–S128.
- Santini E, Alcaer C, Cacciatore S, Heiman M, Hervé D, Greengard P, Girault JA, Valjent E, and Fisone G (2009) L-DOPA activates ERK signaling and phosphorylates histone H3 in the striatonigral medium spiny neurons of hemiparkinsonian mice. *J Neurochem* **108**:621–633.
- Santini E, Sgambato-Faure V, Li Q, Savata M, Dovero S, Fisone G, and Bezdard E (2010) Distinct changes in cAMP and extracellular signal-regulated protein kinase signalling in L-DOPA-induced dyskinesia. *PLoS ONE* **5**:e12322.
- Santini E, Valjent E, Usiello A, Carta M, Borgkvist A, Girault JA, Hervé D, Greengard P, and Fisone G (2007) Critical involvement of cAMP/DARPP-32 and extracellular signal-regulated protein kinase signaling in L-DOPA-induced dyskinesia. *J Neurosci* **27**:6995–7005.
- Schapira AH and Jenner P (2011) Etiology and pathogenesis of Parkinson's disease. *Mov Disord* **26**:1049–1055.
- Sgambato-Faure V and Cenci MA (2012) Glutamatergic mechanisms in the dyskinesias induced by pharmacological dopamine replacement and deep brain stimulation for the treatment of Parkinson's disease. *Prog Neurobiol* **96**:69–86.
- Sullivan JP, Donnelly-Roberts D, Briggs CA, Anderson DJ, Gopalakrishnan M, Xue IC, Piattoni-Kaplan M, Molinari E, Campbell JE, and McKenna DG, et al. (1997) ABT-089 [2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine]: I. A potent and selective cholinergic channel modulator with neuroprotective properties. *J Pharmacol Exp Ther* **283**:235–246.
- Tan LC, Protell PH, Langston JW, and Terasaki DM (2002) The hyperkinetic abnormal movements scale: a tool for measuring levodopa-induced abnormal movements in squirrel monkeys. *Mov Disord* **17**:902–909.
- Wang F, Pan J, and Chen SD (2012) Kinases and kinase signaling pathways: potential therapeutic targets in Parkinson's disease. *Prog Neurobiol* **98**:207–221.
- Wichmann T, DeLong MR, Guridi J, and Obeso JA (2011) Milestones in research on the pathophysiology of Parkinson's disease. *Mov Disord* **26**:1032–1041.
- Zhang D, Bordia T, McGregor M, McIntosh JM, Decker MW, and Quik M (2014) ABT-089 and ABT-894 reduce levodopa-induced dyskinesias in a monkey model of Parkinson's disease. *Mov Disord* **29**:508–517.
- Zhang D, Mallela A, Sohn D, Carroll FI, Bencherif M, Letchworth S, and Quik M (2013a) Nicotinic receptor agonists reduce L-dopa-induced dyskinesias in a monkey model of Parkinson's disease. *J Pharmacol Exp Ther* **347**:225–234.
- Zhang Y, Meredith GE, Mendoza-Elias N, Rademacher DJ, Tseng KY, and Steece-Collier K (2013b) Aberrant restoration of spines and their synapses in L-DOPA-induced dyskinesia: involvement of corticostriatal but not thalamostriatal synapses. *J Neurosci* **33**:11655–11667.

Address correspondence to: Maryka Quik, Center for Health Sciences, SRI International, 333 Ravenswood Ave, Menlo Park, CA 94025. E-mail address: maryka.quik@sri.com