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Focus on α4β2* and α6β2* nAChRs for Parkinson's Disease Therapeutics

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Abstract

L-dopa is one of the best treatments for the motor symptoms of Parkinson's disease. However, its use is limited by the fact that it provides only symptomatic relief and chronic therapy leads to dyskinesias. There is therefore a continual search for novel therapeutic approaches. Nicotine, a drug that acts at nicotinic acetylcholine receptors (nAChRs), has been shown to protect against nigrostriatal damage and reduce L-dopa-induced dyskinesias. NAChRs may therefore represent novel targets for Parkinson's disease management. Since there are multiple nAChRs throughout the body, it is important to understand the subtypes involved in striatal function to allow for the development of drugs with optimal beneficial effects. Here we discuss recent work from our laboratory which indicates that α6β2* and α4β2* nAChRs are key in regulating striatal dopaminergic function. Experiments in parkinsonian rats using cyclic voltammetry showed that both α6β2* and α4β2* nAChR-mediated evoked-dopamine release in striatal slices is affected by nigrostriatal damage. These subtypes also appear to be important for neuroprotection against nigrostriatal damage and the nicotine-mediated reduction in L-dopa-induced dyskinesias in parkinsonian animal models. Our combined findings indicate that α4β2* and α6β2* nAChRs may represent useful therapeutic targets for Parkinson's disease.

Keywords

Dopamine; Dyskinesias; Neuroprotection; Nicotinic receptors; Parkinson's; disease nigrostriatal damage

Overview

Parkinson's disease is a progressive neurodegenerative disorder characterized by rigidity, tremor, bradykinesia and postural instability. To date, L-dopa remains the most successful therapy to manage disease symptoms (1–6). However, its use is limited by the appearance of side effects including abnormal involuntary movements or dyskinesias, which can become as debilitating and hard to manage as Parkinson's disease itself (7, 8). There is thus a great need to develop alternative therapeutic strategies, particularly since L-dopa only yields symptomatic relief with a continual disease progression.

A better knowledge of the molecular and cellular deficits that arise during the neurodegenerative process is important as it may help identify more effective drugs for Parkinson's disease. A primary focus has been the nigrostriatal dopaminergic system because of the marked degeneration that occurs in Parkinson's disease. However, numerous

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other neuronal pathways known to influence dopaminergic function are also affected in this disorder. The nicotinic cholinergic system is one that is receiving increasing attention because of its extensive crosstalk with the striatal dopaminergic system. This appears to involve an action of acetylcholine at nicotinic acetylcholine receptors (nAChRs) on nigrostriatal dopaminergic terminals (9–11).

In fact, accumulating studies suggest that nAChR modulation of dopaminergic function may be of benefit in neurological disorders such as Parkinson's disease. Extensive epidemiological work has shown that there is a decreased incidence of Parkinson's disease with smoking (12–18). Further experiments in parkinsonian animal models suggest that the nicotine in smoke may contribute, at least in part, to this neuroprotective effect (19–23). In addition, studies indicate that nicotine may be useful for reducing the abnormal involuntary movements or dyskinesias that arise with L-dopa treatment for Parkinson's disease (24–26). However, there are multiple nAChRs that are differentially affected with nigrostriatal damage (27–30). It is therefore important to elucidate how expression and function of these different nAChR subtypes is altered during the neurodegenerative process.

Here, we discuss our recent findings which show that both α4β2* and α6β2* nAChR-mediated function is altered with nigrostriatal damage, but in a differential manner. We also show that drugs that interact at both nAChR subtypes may have a therapeutic role in the treatment of L-dopa-induced dyskinesias.

Cyclic Voltammetric Studies Delineate the nAChR Subtypes That Regulate Striatal Dopamine Release

One approach that we are currently using to understand the role of the nicotinic cholinergic system in modulating dopaminergic activity involves measurement of dopamine release from striatal slices using cyclic voltammetry. This technique offers the advantage that it allows for real-time measurement of neuronal function under varying stimulus conditions. Dopamine neurotransmission in the striatum is highly regulated by tonically active cholinergic interneurons. These neurons provide a pulsed source of acetylcholine that acts at nAChRs to modulate dopamine release (10, 11). Current work suggests that several nAChR subtypes influence striatal dopamine function, including the α4β2* and α6β2* receptor populations (31–33).

Voltammetry studies have shown that acetylcholine acting at these nAChRs modulates dopaminergic function by suppressing dopamine release at low stimulation frequencies and facilitating release under phasic firing conditions (10, 34–39). The specific role of α4β2* and α6β2* nAChRs was evaluated through the use of α4 and β2 knockout mice, as well as nAChR subtype antagonists (10, 34–40). Under control conditions, α6β2* receptors regulate ~75% of tonic nAChR-mediated release in striatum, while α4β2* nAChRs control only ~25% of release. These data suggest that both α4β2* and α6β2* nAChR populations play a role in regulating striatal dopamine release but the α6β2* subtype predominates.

Changes in nAChR-mediated Dopamine Function with Nigrostriatal Damage

To understand whether drugs that target the α4β2* and α6β2* nAChRs may be beneficial in Parkinson's disease, it is important to know how nAChR expression and function is altered with nigrostriatal damage. To evaluate this, we used 6-hydroxydopamine (6-OHDA) lesioned rats with varying degrees of dopamine transporter loss (40). The nAChR antagonists α-conotoxinMII, which interacts specifically with α6β2* nAChRs, and mecamylamine, which acts at both α4β2* and α6β2* nAChRs, were used to differentiate

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α6β2* and α4β2* nAChR-mediated function. Dopamine neurons normally fire at low frequencies of 5-10Hz to maintain dopaminergic tone. However, their firing rate increases with initiation or execution of movement to result in an enhanced dopamine release (41, 42). Our results and those of others using cyclic voltammetry showed that striatal dopaminergic denervation affects both low frequency (tonic) and high frequency (burst) dopamine release (40, 43). More recent studies showed that both the α4β2* and α6β2* nAChR subtypes are important in maintaining striatal dopaminergic tone, since declines in tonic release mediated by both subtypes paralleled the loss in the dopamine transporter (Figure 1) (40).

In addition, both α6β2* and α4β2* nAChRs modulate phasic or burst-induced dopamine release, although the two subtypes influenced function in a differential fashion with increasing nigrostriatal damage (40). As stated earlier, blockade of nAChRs leads to enhanced phasic dopamine release in control striatum. A significant reduction in this nAChR-mediated facilitation of burst-induced dopamine release was observed with increasing nigrostriatal damage (40). This phenomenon appeared mainly due to a progressive decline in α4β2* nAChR responsiveness, which was abolished with only a 75% loss in the dopamine transporter. In contrast, α6β2* nAChR-mediated facilitation remained constant up to at least a 75% loss in the dopamine transporter (40). Interestingly, motor deficits do not become evident in parkinsonian animal models or in Parkinson's disease until there is ~75% dopaminergic loss in the striatum. These findings suggest that a loss of α4β2* function and/or a disruption in the balance between α4β2* and α6β2* nAChR-mediated phasic dopaminergic function contributes to the appearance of Parkinson’s disease symptoms. They also indicate that α6β2* nAChRs primarily regulate dopaminergic activity with more severe nigrostriatal damage.

Overall, the above work supports the idea that both α4β2* and α6β2* nAChRs modulate striatal dopamine function but that they may have somewhat differing roles throughout the course of degeneration (Figure 2).

L-dopa-induced Dyskinesias; a Role for α4β2* and α6β2* nAChRs

As mentioned earlier, the dopamine precursor L-dopa greatly improves Parkinson's disease motor symptoms particularly in the early stages of the disease. However, chronic use results in the development of side effects such as dyskinesias (2, 4, 44–46). These abnormal involuntary movements of the head, trunk and/or extremities may become very severe and arise in the majority of patients with long term L-dopa treatment (47). Current therapeutic options to reduce dyskinesias are very limited and consist primarily of amantadine, a drug with only limited efficacy (2, 4, 44–46). Novel agents would thus be of great value for the management of L-dopa-induced dyskinesias in Parkinson's disease patients.

In fact, extensive work is currently being done to investigate the antidyskinetic potential of drugs targeting multiple CNS neurotransmitter systems (48–54). This includes studies in our laboratory to evaluate the involvement of the nicotinic cholinergic system (24, 55–57). Our research has shown that chronic administration of nicotine via multiple routes of administration attenuated L-dopa-induced dyskinetic movements in parkinsonian mice, rats and monkeys by interacting at nAChRs (24, 55–57). This data suggests that nicotine may be of therapeutic use in the treatment of L-dopa-induced dyskinesias.

A drawback of nicotine for the treatment of L-dopa induced dyskinesias is that it interacts with multiple nAChRs in both the peripheral and central nervous system. Thus, a better therapeutic approach would be to develop selective nAChR agonist to minimize the likelihood of side effects. Since the studies described in the preceding section showed that α4β2* and α6β2* nAChRs were the receptor subtypes of relevance to nigrostriatal dopaminergic function (see Figure 2), we tested the effect of agonists directed to these

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subtypes for their antidyskinetic potential in unilateral 6-hydroxydopamine-lesioned rats (58). Varenicline, an agonist that interacts with multiple nAChR including the α4β2* and α6β2* subtypes (59, 60), reduced L-dopa-induced dyskinetic-like movements by 50% in parkinsonian rats (Figure 3). A similar decline was obtained with iodo-A-85380, a nAChR agonist that interacts preferentially with α4β2* and α6β2* nAChRs (Figure. 3). The data with iodo-A-85380 suggest that these latter two nAChR populations are key in reducing L-dopa-induced abnormal involuntary movements. The nAChR-mediated declines in dyskinesias were more pronounced in rats with partial (~70%) as compared to near-complete (~99%) nigrostriatal lesions (58). These data suggest that α4β2* and α6β2* nAChRs present on dopaminergic and non-dopaminergic neurons throughout the brain represent key targets.

Summary

Current evidence suggests that drugs directed to nAChRs may be of therapeutic value in Parkinson's disease to attenuate L-dopa-induced dyskinesias and for long-term neuroprotection against nigrostriatal damage. A role for the nicotinic cholinergic systems may stem from its close interrelationship with the dopaminergic system, particularly in the striatum a region dramatically affected in Parkinson's disease. Of the multiple nAChRs present throughout the peripheral and central nervous system, the α4β2* and α6β2* subtypes may be of particular relevance as CNS drug targets.

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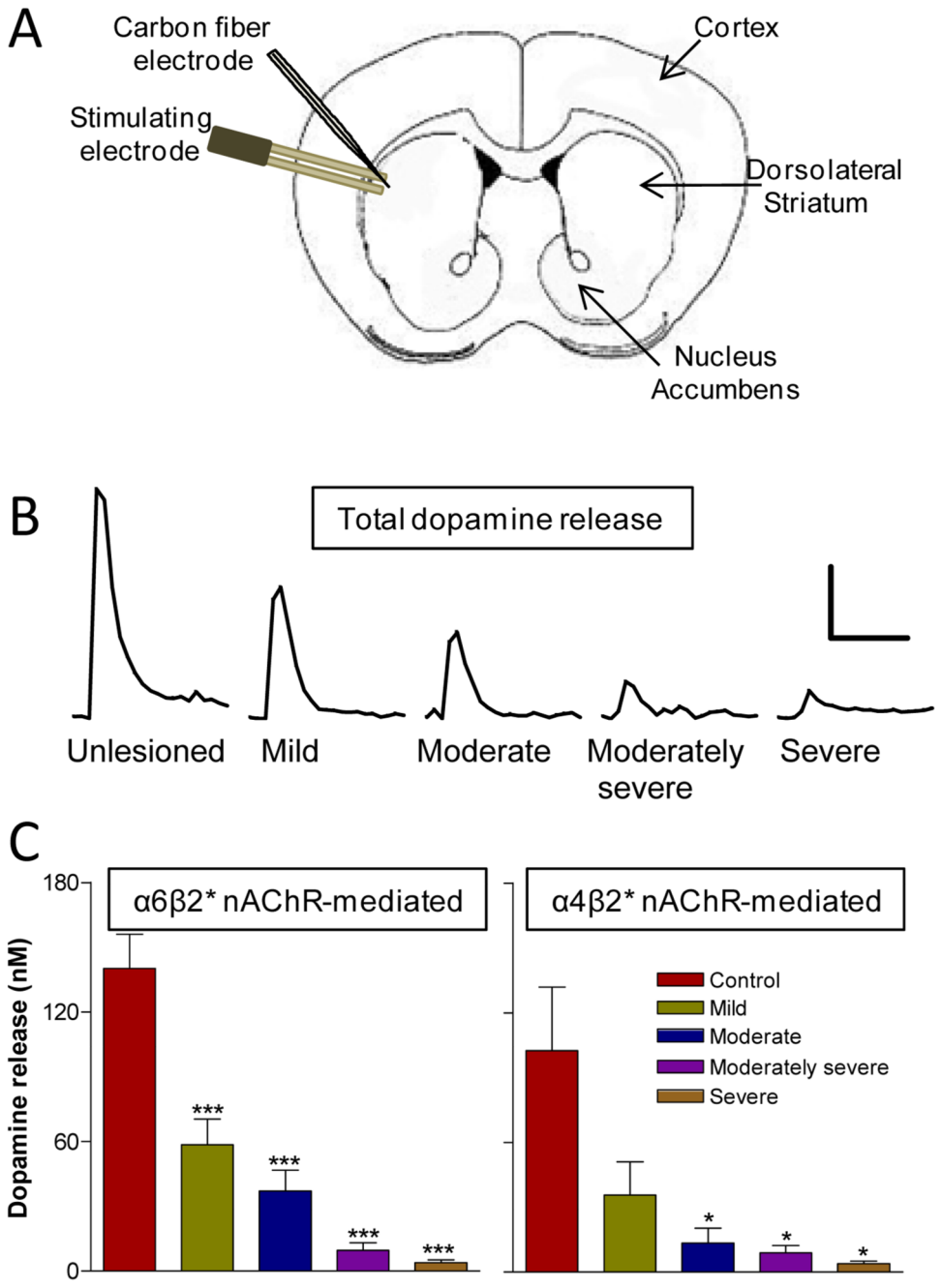


Figure 1. Progressive decrease in nAChR-mediated dopamine release with increasing nigrostriatal damage

A. Electrically stimulated dopamine release was determined using cyclic voltammetry in coronal rat brain slices containing the striatum. Release was measured in the dorsolateral striatum as this area is most affected with Parkinson's disease. Release was elicited through a bipolar stimulating electrode and detected by a carbon fiber recording microelectrode manufactured in house as previously described (Perez et al., 2008). **B.** Sprague Dawley rats were lesioned with varying doses of 6-OHDA to achieve different degrees of striatal dopamine denervation. Representative traces of single-pulse stimulated total dopamine release show that release decreased proportionately with increasing nigrostriatal damage. **C.**

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Dopamine release was measured in the absence and presence of the α6β2* nAChR antagonist α-CtxMII (100nM) or the general nAChR blocker mecamylamine (100μM). α6β2* nAChR-mediated release was determined by subtracting release in the presence of α-CtxMII from total release. α4β2* mediated release was determined by subtracting release in the presence of mecamylamine from that in the presence of α-CtxMII. There were significant decreases in α6β2* and α4β2* nAChR-mediated release with nigrostriatal damage. Values represent the mean ± SEM of 4–9 rats. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ indicate significance of difference from control using a Newman-Keuls multiple comparisons *post hoc* test. Taken in modified form with permission from Perez et al., 2010.

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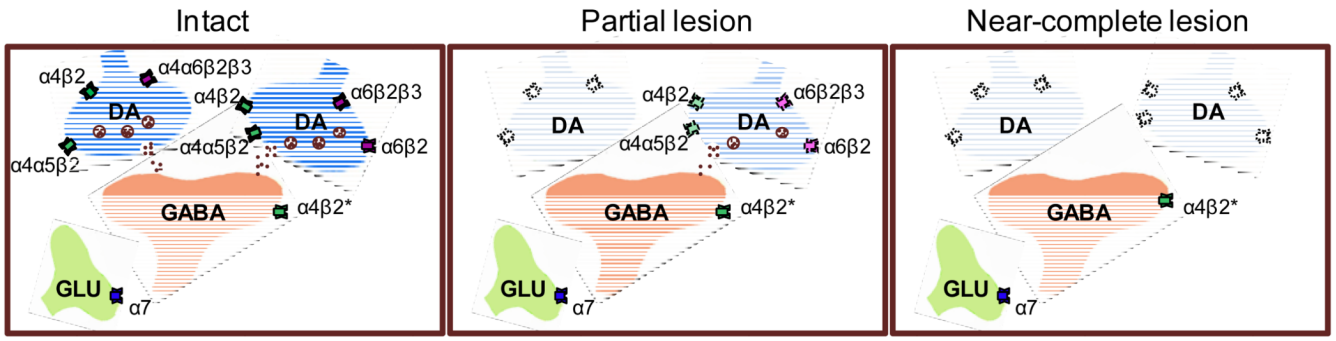


Figure 2. Schematic of the putative changes in neuronal nAChR expression occurring with moderate and near-complete nigrostriatal damage

Representative striatal dopaminergic (DA), GABAergic (GABA) and glutamatergic (GLU) neuronal populations are depicted. In the intact striatum (left panel), five different nAChR subtypes are expressed presynaptically on dopaminergic terminals: α6 α4β2β3, α6β2β3, α6β2, α4 α5β2 and α4β2 nAChRs. α4β2* and α7 nAChRs are also expressed in post-synaptic GABAergic and glutamatergic neurons, respectively. Declines in DA terminal density are illustrated with a decrease in the color intensity. Partial lesions (middle panel) associated with 60–80% decreases in dopamine transporter result in a complete loss of dopamine terminals expressing α6α4β2β3 nAChRs (shown in gray). This receptor subtype is preferentially decreased with nigrostriatal damage and thus is hypothesized to be localized to a selectively vulnerable population of dopamine terminals (61). In addition, smaller declines in dopamine terminals expressing other nAChRs are also observed (shown in lighter blue). This terminal loss is associated with a partial decrease in α6β2β3, α6β2, α4 α5β2 and α4β2 nAChR expression (as depicted by their lighter color and dashed outlines). It is currently unknown whether α6β2* and α4β2* nAChRs are co-expressed in the same dopamine terminals thus α4 α5β2 and α4β2 nAChRs have been placed in all dopamine neuron populations. All presynaptic α6β2* and α4β2* nAChRs are essentially lost with a near-complete loss of dopamine terminals (right panel) as illustrated by their white color and dashed outlines. By contrast, postsynaptic α4β2* nAChR are unaffected by nigrostriatal damage, as are α7 receptors.

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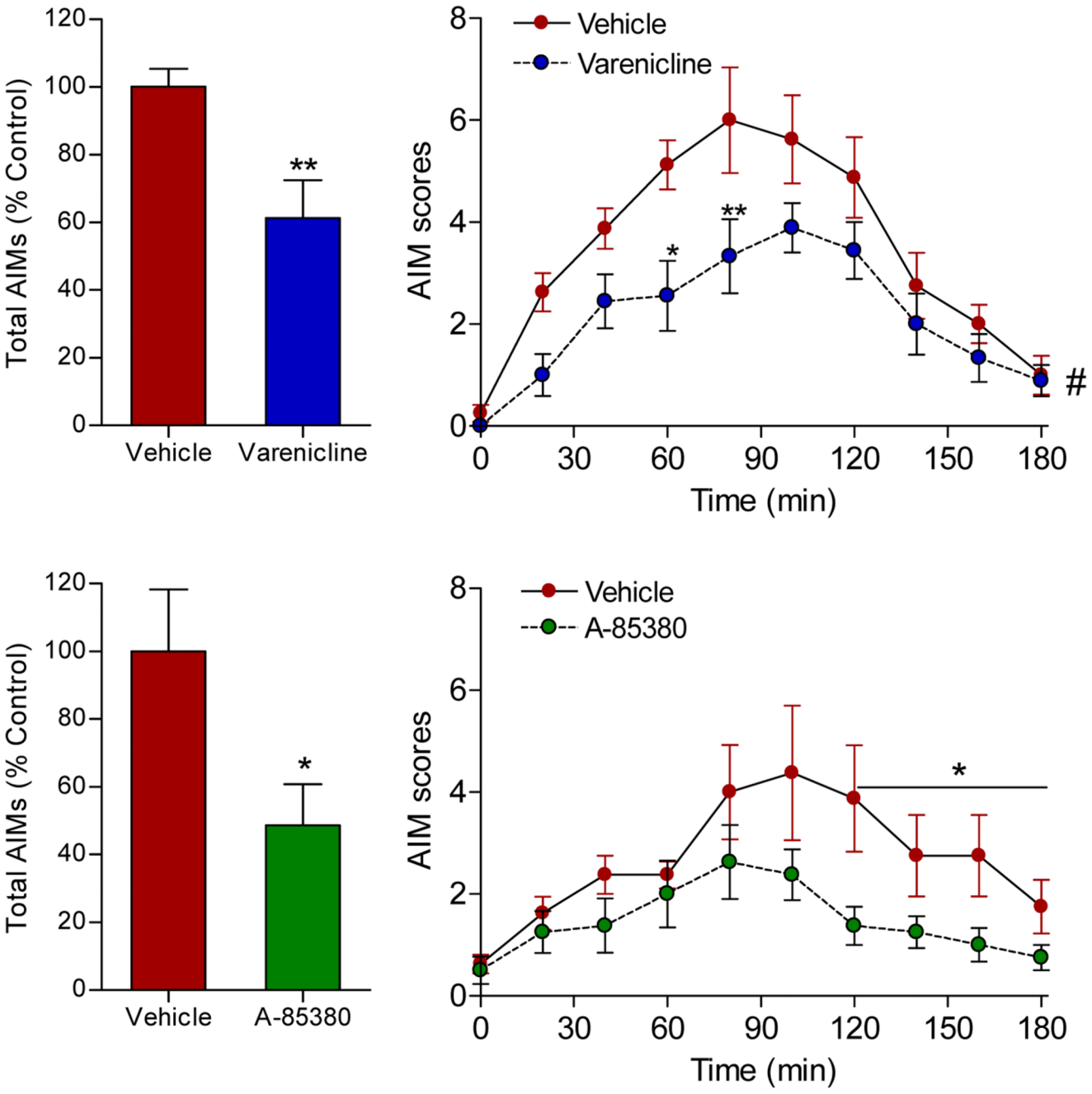


Figure 3. NAChR agonists decrease L-dopa induced dyskinesias

Lesioned rats were administered varenicline (0.5 mg/kg/d) or A-85380 (0.37 umol/kg/d) twice daily at 8-h intervals for 4 consecutive days. L-dopa methyl ester (8 mg/kg s.c.) plus benserazide (15 mg/kg s.c.) was administered 10 min after the first dose of either agonist. After 4 days of treatment, total AIMS were evaluated as a sum of oral, forelimb and axial AIMS. Values represent the mean ± SEM of 8 animals per treatment group. Significance of difference from vehicle using a Mann-Whitney test or one-way repeated ANOVA followed by a Bonferroni post hoc test (for time course), *$p < 0.05$; **$p < 0.01$. Significant main effect of nicotine with time; $^{\#}p < 0.05$. Taken in modified form with permission from Huang et al., 2010.