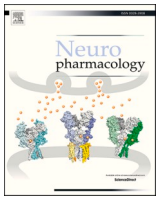
Neuropharmacology 284 (2026) 110786

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Inhibition of levodopa-induced abnormal involuntary movements (AIMs) using a selective α7 nicotinic positive allosteric modulator

Yasaman Malekizadeh [a], Kiana Hassankhani [a], Alice E. Kingslake [a], Lucy E. Annett [b], Mohammed Shoaib [a], Mahmoud M. Iravani [a,*]

[a] Department of Clinical, Biological and Pharmaceutical Sciences, School of Health, Medicine and Life Sciences, College Lane, University of Hertfordshire, Hatfield, AL10 9AB, UK

[b] Department of Psychology, Sport and Geography, School of Health, Medicine and Life Sciences, University of Hertfordshire, HatfieldCollege Lane, AL10 9AB, UK

ARTICLE INFO

Keywords:
α7 receptor antagonist
α7 receptor agonist
α7 positive allosteric modulator
AIMs
Dyskinesia
Levodopa
Methyllycaconitine
Nicotine
Parkinson's disease
PNU-120596
PHA-543613

ABSTRACT

Chronic administration of nicotine and nicotinic ligands have been shown to reduce levodopa-induced dyskinesia (LID) in rodents and primates. Due to its unique extra-striatal localisation and biochemical signalling properties, the α7 subtype of nicotinic acetylcholine receptors (nAChRs) may represent an important and unique target for drug development for the treatment of dyskinesia, particularly since positive allosteric modulator (PAM) at the α7 nAChRs subtype may provide an opportunity to reduce dyskinesia without side effects. In this study, we report on the anti-dyskinetic actions of a selective α7 PAM, PNU-120596 and compared its action to nicotine and other α7 nAChRs ligands. Unilaterally 6-OHDA lesioned female rats were primed with levodopa to display abnormal involuntary movements (AIMs) to model levodopa-induced dyskinesia. The effects of the α7 PAM, PNU-120596, an α7 agonist, PHA-543613 or the α7 antagonist, methyllycaconitine (MLA), as well as nicotine, a non-selective nAChR agonist were all examined on AIMs. Low doses of PNU-120596 and nicotine dose-dependently reduced AIMs, but combination of the PAM with nicotine produced only an additive effect which surprisingly, could not be demonstrated with the α7 agonist PHA-543613, while MLA dose-dependently reduced AIMS. The effects of PNU-120596 suggests that α7 PAMs may enhance the effect of basal acetylcholine on α7 receptors in the striatum and may provide a new avenue for the treatment of levodopa-induced dyskinesia. Reduction of AIMs by MLA suggests that the mechanism of AIMs reduction may involve the rapid desensitization of the α7 nAChRs subtype.

1. Introduction

Dyskinesia remains an intractable problem in the dopamine replacement treatment of Parkinson's disease (PD). At present, there is relatively little that can be done to control dyskinesia and there has been limited progress in developing drug treatments despite many attempts (Goetz et al., 2008; Vijayakumar and Jankovic, 2016). A variety of novel pharmacological targets have been examined for their effects to alleviate abnormal involuntary movements (AIMs) or dyskinesia in animal models. These range from NMDA receptor antagonists, GABAergic agonists and 5HT1A agonists (Iravani and Jenner, 2011). In a recent meta-analysis of randomised controlled trial amantadine was shown to be the most efficacious treatment (Yan et al., 2025). In a recent phase II clinical trial, NLX-112 (beferidol) targeting 5-HT1A receptors (Svenningsson et al., 2025) and in other on-going trials, targets such as NMDA, mGluR4, dopamine D3 receptors have also been investigated for the reduction of levodopa induced dyskinesia (Al-Kassmy et al., 2025).

Evidence from neurochemical and behavioural studies indicate that nicotine has not only a modulatory effect on dopaminergic neurotransmission in the basal ganglia, but also protects against nigrostriatal damage (Huang et al., 2009). Studies also show that nicotine reduces levodopa-induced dyskinesia in rodents and primates (Quik et al., 2013; Zhang et al., 2013). Given the multiple subtypes of nicotinic acetylcholine receptors (nAChRs) in the basal ganglia, distinguishing the roles of the nAChR subtypes in PD-related disorders is of great importance because selective engagement of nicotinic receptors might provide an

Abbreviations: 6-OHDA, 6-hydroxydopamine; AChRs, nicotinic acetylcholine receptors; AIMs, Abnormal involuntary movements; ALO, axial, limb and orofacial; LID, Levodopa-induced dyskinesia; MFB, Medial forebrain bundle; MLA, Methyllycaconitinen; PAM, Positive allosteric modulator; PD, Parkinson's Disease; PHA, PHA-543613; PNU, PNU-120596.

* Corresponding author.
E-mail address: m.iravani@herts.ac.uk (M.M. Iravani).

https://doi.org/10.1016/j.neuropharm.2025.110786
Received 26 August 2025; Received in revised form 9 November 2025; Accepted 25 November 2025
Available online 26 November 2025

opportunity to treat LID without the untoward side effects of nicotine.

Studies in transgenic mice deficient in α7 nAChRs showed that levodopa-priming resulted in a significantly greater level of AIMs compared to wild-type littermates suggesting that α7 nAChRs exert an inhibitory influence on expression of AIMs (Quik et al., 2013). Similarly, the selective α7 nAChRs agonist ABT-107 reduced AIMs (Zhang et al., 2014; Bordia et al., 2015). Neuronal α7-nAChRs are classic ligand-gated ion channels that upon acetylcholine (ACh) binding, open to allow rapid Ca^{2+} influx, which can influence downstream effects like activation of ERK1/2 and PKA, neurotransmitter modulation, and synaptic plasticity (Sinclaire and Kabbani, 2023). This suggests that the α7 nAChR subtype might play an important role in the expression of AIMs and levodopa-induced dyskinesia and modulation of α7 nAChRs may provide a novel and useful means of controlling levodopa-induced dyskinesia. In this regard, the discovery of positive allosteric modulators (PAMs) selective for α7 nAChRs has extended the repertoire of therapeutic strategies (Williams et al., 2011; Uteshev, 2014; Echeverria et al., 2016). The notion that α7 nAChR agonists can reduce LID in PD, is supported by several mechanisms and preclinical studies. While nAChRs are widely expressed in the striatum, predominantly located on the glutamatergic terminals, the α7 nAChR subtypes are largely absent from dopaminergic nerve terminals (Zhou et al., 2002). Activation of α7 receptors can modulate glutamate release and dopamine signalling, balancing excitatory and inhibitory inputs that are disrupted in Parkinson's and with chronic levodopa treatment. This normalization helps reduce the abnormal involuntary movements (dyskinesia). Also, α7 nAChRs are highly permeable to Ca^{2+} ions and can influence intracellular Ca^{2+} signalling (Perez et al., 2017). Proper calcium signalling modulates neuronal excitability and synaptic plasticity, which are dysregulated in LID (Perez et al., 2017). In accord with this a recent study in murine model of AIMs, PNU-120596, a PAM for α7 nAChRs, significantly reduced levodopa-induced dyskinesia modulating Ca^{2+} signalling (Gómez-Paz et al., 2025). Thus, targeting nAChRs using PAMs presents major advantages; as endogenous modulators they may exhibit less toxicity, better pharmacokinetic profile and greater selectivity for the receptor target than nicotine or other α7 agonists (McLean et al., 2012; Uteshev, 2014; Perez et al., 2017).

Alpha7 PAM, PNU-120596, is a classical PAM of α7 nAChR and is widely used to investigate the effect of α7 nAChR activation (Hurst et al., 2005; Uwada et al., 2020). PNU-120596 is a type-II PAM of α7. It dramatically reduces desensitization and prolongs channel open states when an orthosteric agonist (ACh or other agonists) is present. The net effect is amplified and prolongs receptor activity (King et al., 2018) which increases both agonist efficacy and open time of the α7 nAChR channel, resulting in extended nicotinic stimulation (Hurst et al., 2005). Moreover, PNU-120596 is a potent, selective type II PAM of α7 nAChRs which can cross the blood-brain barrier, being orally (p.o.), intraperitoneally (i.p.), subcutaneously (s.c.), and intravenously (i.v.) active in both rodents and humans (Hurst et al., 2005; Callahan et al., 2013).

Since there are few effective treatments of LID, the aim of this investigation was to evaluate and compare the effects of a selective α7 nAChRs PAM, PNU-120596 and the α7 nAChR agonist PHA-543613 and to compare this with nicotine in a unilaterally lesioned rat model of AIMs. A preliminary report of this study was presented at the British Neuroscience Association 2023 International Festival of Neuroscience (Malekizadeh et al., 2023).

2. Materials and methods

2.1. Animals

In this study we used female Sprague Dawley rats rather than using both sexes (Charles River UK, Harlow, Essex) weighing between 250 and 275g, housed 2 per cage under a 12 h–12 h light/dark cycle from 7:00AM to 7:00PM in a temperature-controlled room (20 ± 1 °C) with free access to food and water. The rationale for using female rats rather than animals of both sexes is that females gain less weight through the long length of the experiment and that during ageing the pharmacokinetic characteristic and behaviour of the male and female may not be comparable. All experiments complied with the ARRIVE guidelines and were carried out in accordance with the UK Animals (Scientific Procedures Act, 1986) and associated guidelines, EU Directive 2010/63/EU for animal experiments. All procedures and protocols were approved by the Animal Welfare and Ethical Review Board (AWERB) at the University of Hertfordshire, which were carried out under the UK Home Office approved Project Licence PD72555B4.

2.2. Unilateral 6-OHDA lesions

After seven days of acclimatisation, rats were unilaterally lesioned with 6-OHDA (Merck, UK) dissolved in 0.1 % L-ascorbic acid and 0.9 % saline (vehicle) as described previously (Cenci and Lundblad, 2007). To achieve the maximum level of dopaminergic lesions, two 2 μl injections of vehicle (0.1 % L-ascorbic acid in sterile saline) or two 8 μg of 6-OHDA were injected stereotaxically according to method of Cenci and Lundblad, 2007) but with small modification in the quantity of 6-OHDA administered at the following co-ordinates:

Injection 1: Tooth bar = −3.3 mm, AP = −4.4 mm, ML = +1.2 mm, DV = −7.8 mm

Injection 2: Tooth bar = +3.4 mm, AP = −4.0 mm, ML = −0.8 mm, DV = −8.0 mm

with reference to the atlas of Paxinos and Watson (1986). Administration of 6-OHDA was carried out using a 10 μl Hamilton syringe attached to an *Ultra Micro Pump* (IMP3T-1; World Precision Instruments) microinjector and a point style 3, 34-gauge needle (blunt-tip, Hamilton Sales & Services Ltd., Birmingham, UK) into the left medial forebrain bundle (MFB) under 2.5–3.0 % isoflurane anaesthesia. All injections were carried out at a rate of 1 μl/min and the syringe needle was left in place for 2 min after each injection before being slowly retracted. The following analgesics were administered during surgery: local anaesthetic bupivacaine (Marcaine; 2.0 mg/ml, Accord, UK) was applied topically to the scalp following incision, 0.03 mg/kg buprenorphine given subcutaneously peri-surgically and a bolus dose of warm saline containing 5 % glucose was also administered (10 ml/kg, s.c.) after suturing to aid rehydration and recovery. A further dose of 0.01 mg/kg buprenorphine was administered subcutaneously 6–8 h post-surgery. Twenty-four hours post-surgery, all animals received non-steroidal anti-inflammatory, oral liquid meloxicam (Metacam; 1.0 mg/kg, p.o. Boehringer Ingelheim, UK) once daily for up to 4 days. During the period of recovery, no adverse effects were seen in animals. Furthermore, drug treatment also caused no adverse events. The timeline for the preparation of animals is summarized in Fig. 1a.

2.3. Assessment of 6-OHDA-induced motor asymmetry

To assess lesion integrity, upon recovery from surgery, animals were tested for motor asymmetry using amphetamine and apomorphine to induce rotational behaviour (Ungerstedt and Arbuthnott, 1970) and by assessing forelimb akinesia, using the commonly known stepping test (Olsson et al., 1995). Briefly, the stepping tests were performed during daytime between 12:00–14:00 and repeated 3 times. The number of adjusted steps were counted for both paws in the backhand and forehand directions of movement. The rotational behaviour of unilateral 6-OHDA lesioned rats in response to amphetamine (5.0 mg/kg, i.p.) or apomorphine (0.5 mg/kg, s.c.) (Fig. 1b and c) was recorded in free moving animals using a video acquisition system in black Perspex open field (40 × 40 × 40 cm^3) boxes using infrared back-lighting and Noldus Ethovision XT (version15) software (Tracksys, Nottingham, UK). Rotation of each animal was defined by the angular relationship of three points (nose, centre, and tail) on animal's body by the infrared (Basler AG,

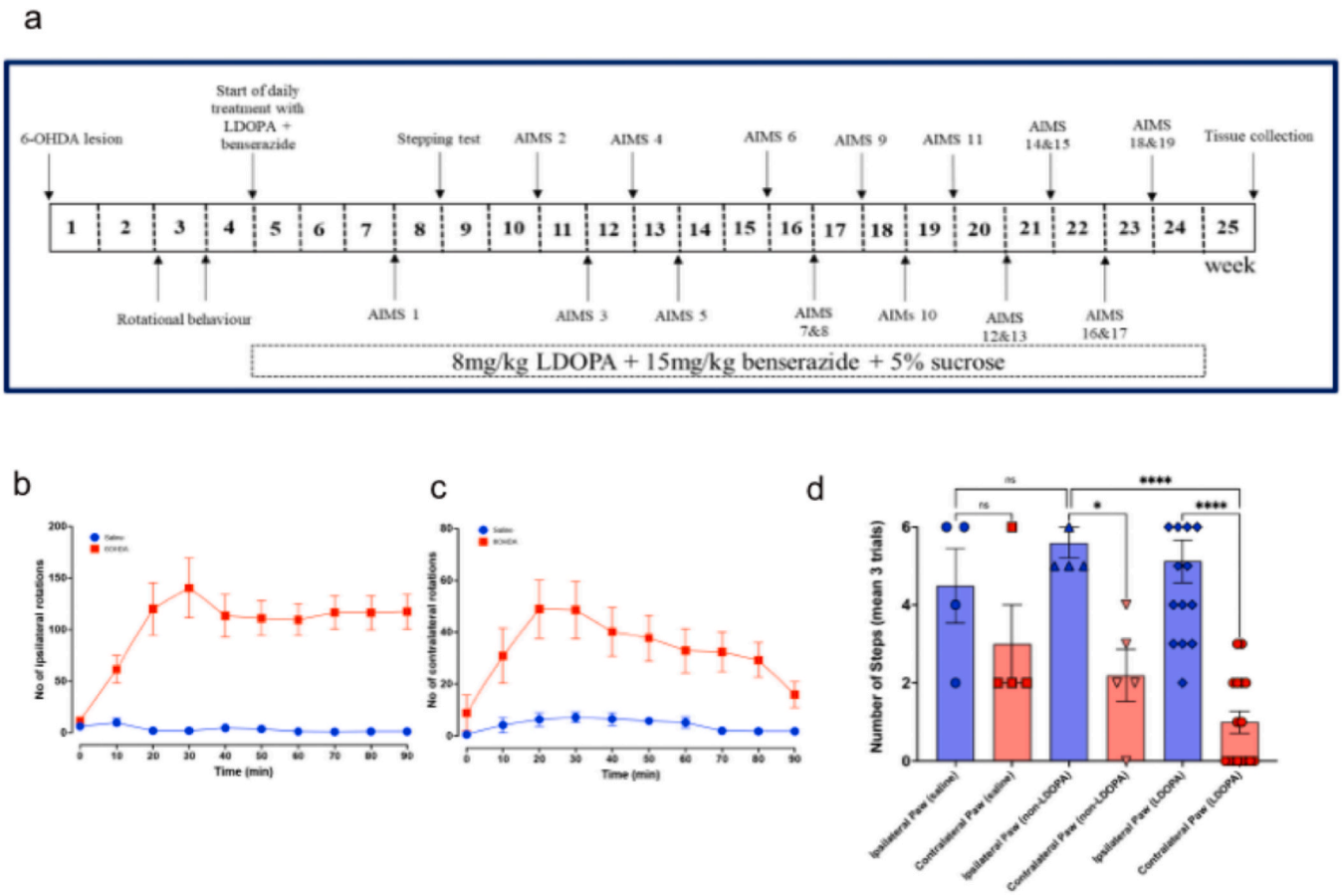


Fig. 1. Preparation of levodopa-primed rats for expression of AIMs. Unilaterally lesioned rats with 16 μg 6-OHDA underwent outlined series of procedures treated with daily doses 8 mg/kg levodopa and 15 mg/kg benserazide (a). Prior to levodopa priming lesion integrity was assessed by the mean ± SEM of the number of ipsiversive (b) and contraversive (c) rotations in response to 5 mg/kg (+)-amphetamine or 0.5 mg/kg apomorphine, respectively, in 6-OHDA (n = 24) compared against vehicle treated rats (n = 6; open symbols). All rats that performed ≥6 turns/min were included for priming. After 21 days of treatment with levodopa + benserazide rats were further tested using forelimb akinesia stepping test in absence of acute levodopa treatment. Vehicle (n = 6) or 6-OHDA treated groups, that were levodopa unprimed (non-levodopa; n = 6) and primed (levodopa; n = 12) rats produced greater level of limb asymmetry, "step adjustment test" respectively (d). Therefore, a group of n = 12 was used based on the expression of AIMs forelimb akinesia in the stepping test (d). In week 25, the direct effects 3 mg/kg nicotine, 3 mg/kg PNU-120596 and 10 mg/kg PHA-543613 on ipsiversive rotation (n = 12) were compared with 5 mg/kg (+)-amphetamine induced rotations (see Fig. 6). *P < 0.05, ***P < 0.001, mean ± SEM.
AIMS 1 = (8 mg/kg levodopa +15 mg/kg benserazide)
AIMS 2 = (PNU-120596 (vehicle))
AIMS 3 = (0.3 mg/kg PNU-120596)
AIMS 4 = (1 mg/kg PNU-120596)
AIMS 5 = (3 mg/kg PNU-120596)
AIMS 6–9 = (vehicle, 0.03, 0.1, 0.3 mg/kg Nicotine)
AIMS 10 = (1 mg/kg PNU-120596 + 0.03 mg/kg Nicotine)
AIMS 11 = (0.01 mg/kg Nicotine)
AIMS 12 = (1 mg/kg PNU-120596 + 0.01 mg/kg Nicotine)
AIMS 13 = (MLA (vehicle))
AIMS 14&15 = (2, 6 mg/kg MLA)
AIMS 16&17 = (vehicle, 3 mg/kg PHA-543613)
AIMS 18 = (10 mg/kg PHA-543613)
AIMS 19 = (1 mg/kg PNU-120596 + 3 mg/kg PHA-543613).

Ahrensburg, Germany) camera. Animals that displayed ≥6 ipsiversive turns/min at peak activity following amphetamine or ≥6 contraversive turns/min following apomorphine (n = 16), were deemed fully lesioned and underwent levodopa-priming. Those animals that failed these criteria were excluded from the study.

2.4. Levodopa-priming for abnormal involuntary movements (AIMs)

Fully lesioned animals (n = 16) received daily oral administration of 8.0 mg/kg levodopa methyl ester plus 15.0 mg/kg benserazide (Merck, UK) for a minimum of 21 days until deemed stably dyskinetic such that each subsequent dose of 8 mg/kg + 15 mg/kg levodopa and benserazide displayed the same level of motor abnormalities as assessed using a previously described AIMs rating scale (Cenci and Lundblad, 2007). Levodopa and benserazide were administered orally to minimize the stress associated with repeated parenteral injections to animals. Briefly, rats were placed in separate transparent boxes (40 × 40 × 40 cm^3) and scored individually for 5 min every 20 min, for a total of 140 min by an experienced observer. Each AIM component, axial (twisting and torsion the neck and upper body to the contralateral side), limb (involuntary,

tapping or other movements of the limbs and shoulder contralateral to the side of lesion) and orolingual (continuous repetitive movement of the jaw or tongue) (ALO) was scored on a scale ranging from 0 to 4 (0 = normal; 1 = mild <50 % of the observation time; 2 = moderate >50 % of the observation time; 3 = marked continuous but interrupted by external stimuli; 4 = severe, continuous AIMs, not interruptible by external stimuli) with a maximum possible score of 12 at any observation point. From the animals that were fully lesioned, only n = 12 displayed robust AIMs.

2.5. Experimental design

All experiments were performed between 10.00 h and 16.00 h. For the assessment of drug effects on AIMs, animals were randomised into blocks of four rats, with each rat receiving one of the following treatments: vehicle, low dose, medium dose, or high dose. The study employed a within-subject design, such that all rats received all four treatments across sessions in a counterbalanced order. The observations and data collection were conducted in a Latin-square, double-blind fashion, except for PNU-120596, which is highly lipid-soluble and likely to produce a carry-over effect; therefore, its administration was performed in escalating doses. A minimum washout period of 48 h was allowed between treatments to ensure complete drug clearance and to prevent carry-over effects. The observer was blinded to the treatment conditions in all instances. The scores for each AIMs subtype were combined and taken as an overall index of dyskinesia (Lundblad et al., 2002) or assessed individually to assess the effect of the drugs on each component differentially. When overall AIMs were compared over the experimental period of 120 min, area under the curve (AUC) was calculated to provide an overall measure to total AIMs in response to levodopa.

For all experiments, levodopa-primed animals were acclimatised to the AIMs observation boxes for 10 min and baseline AIMs measurements obtained prior to acute drug administration. A washout period of 48–72 h was considered between each dose within an experiment and between different drug treatments, except for PNU-120596, which had a washout period of 3 weeks due to its lipophilic nature and possible long-term interaction with α7 nicotinic receptors. No experiments were conducted during the washout period of PNU-120596.

At the end of the experimental period, rats were euthanised by exposure to carbon dioxide gas according to NIH guidelines (CO_2 flow rate: 5–6 L/min) in a Vet-Tech medium red Perspex chamber (Vet-Tech, UK).

2.6. Drugs

Levodopa (3,4-Dihydroxy-L-phenylalanine ethyl ester) and benserazide (DL-Serine 2-(2,3,4-trihydroxybenzyl) hydrazide hydrochloride) were obtained from Merck (UK) and dissolved in 5 % w/v sucrose in deionised water. They were administered orally, in combination (8.0 mg/kg levodopa +15.0 mg/kg benserazide), the time of which was considered 0 min. PNU-120596 (*N*-(5-Chloro-2,4-dimethoxyphenyl)-*N*'-(5-methyl-3-isoxazolyl)-ure) purchased from Stratech (UK) was dissolved in 1 % DMSO plus 30 % polyethylene glycol plus 1 % Tween 80 and administered subcutaneously at doses of 0.3, 1.0 and 3.0 mg/kg, 10 min prior to levodopa/benserazide administration. All other drugs were obtained from Biotechne (UK). PHA-543613 (*N*-(3*R*)-1-azabicyclo [2.2.2]oct-3-yl-furo[2,3-*c*]pyridine-5-carboxamide hydrochloride) was dissolved in deionised, sterile water and administered intraperitoneally at doses of 3.0 and 10.0 mg/kg, before levodopa/benserazide administration. Nicotine [(−)-nicotine bitatrate], was dissolved in vehicle (sterile saline) and the pH of the final concentration was adjusted to ~pH 7.0 by dropwise addition of NaOH. Because nicotine has a short half-life, (like that of levodopa), it was administered s.c. at doses of 0.01, 0.03, 0.1 and 0.3 mg/kg immediately after levodopa/benserazide administration. The α7 antagonist methyllycaconitine citrate (MLA) was dissolved in vehicle and administered intraperitoneally at doses of 2.0 and 6.0 mg/kg, 20 min prior to levodopa/benserazide administration. All dose calculations were based on free salt content of each compound used.

2.7. Statistical analysis

All data were assessed for normality of distribution using D'Agostino-Pearson test, and parametric statistical analysis was mandated on the results of this test being non-significant test. To measure the effect of each drug on rotation behaviour or AIMs subtype scores or AUCs, repeated measures one-way ANOVA followed by a Dunnett's or where multiple within treatment comparison were made using Tukey's *post-hoc* tests were used. In the data where the interactions of drug dose and time was compared, i.e. AIMs scores at the different doses at different time, a two-way ANOVA followed by a Dunnett's *post-hoc* test was used. Data from stepping test were analysed using two tailed, paired student t-test. Data were expressed as means ± standard error of the mean and a level of $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using the GraphPad Prism (version10) software.

3. Results

From the 30 animals, 24 received 6-OHDA, of which 19 fulfilled the rotation criteria and were deemed fully lesioned. Of the remaining animals, 5 did not meet the stated rotation criteria and the other 6 were sham lesioned. Rats lesioned with 6-OHDA and primed with levodopa/benserazide had a marked and significant ipsilateral or contralateral rotation to 5 mg/kg (+)-amphetamine [F(1,23) = 7.77; *P = 0.0105] and 0.5 mg/kg apomorphine [F(1,17) = 5.19; *P = 0.0359] respectively (Fig. 1b and c). All lesioned and primed animals were further assessed for lesion integrity using the stepping test (Olsson et al., 1995) but subsequently only 16 displayed a robust contralateral limb deficit (Fig. 1d). The rats with statistically significant limb bias were used to test the effects of various drugs. In those rats, acute p.o. administration of 8.0 mg/kg levodopa +15.0 mg/kg benserazide produced an almost immediate expression of both AIMs and contralateral rotational behaviour which lasted for more than 120 min with peak effect occurring between 40 and 80 min. Only 12 of the 16 rats with a robust lesion displayed robust AIMS and therefore 12 were used for the drug tests.

3.1. The effects of α7 PAM, PNU-120596

When the effects of the α7 PAM, PNU-120596 at 0.0 (vehicle), 0.3, 1.0 and 3.0 mg/kg were examined on ALO AIMs against time, there was a significant effect of time [F (3.517, 154.7) = 29.90, ****P < 0001] and dose [F (3, 44) = 5.195; *P = 0.0037] and dose × time interaction [F(35, 385) = 1.724, P = 0.0078] (Fig. 2a). The overall levodopa AIMs as assessed by AUC was reduced by approximately 40 and 50 % by 1.0 and 3.0 mg/kg PNU-120596, respectively (Fig. 2b), compared to the effects of levodopa and vehicle control. At the lowest dose of 0.3 mg/kg there was no statistically significant effect on levodopa-induced AIMs or any effect on any of the individual components of ALO AIMs. The most prominent effects of PNU-120596 were observed about 60 min after administration of levodopa. At the higher doses, 1.0 and 3.0 mg/kg of PNU-120596 caused significant reductions of peak AIMs at 100 (1.0 mg/kg: **P = 0.001; 3.0 mg/kg: P = 0.0047) and 120 min (1.0 mg/kg: **P = 0.0058; 3.0 mg/kg: *P = 0.0163). When the individual components of ALO AIMs were assessed using repeated measures one-way ANOVA, PNU-120596 at the doses 1.0 and 3.0 mg/kg significantly reduced total axial (*P = 0.0207; *P = 0.0175 respectively), limb (*P = 0.0381; *P = 0.0181 respectively) and orolingual (**P = 0.0027; ***P = 0.0004 respectively) scores over the period of 120 min by 40–50 % (Fig. 2c–d).

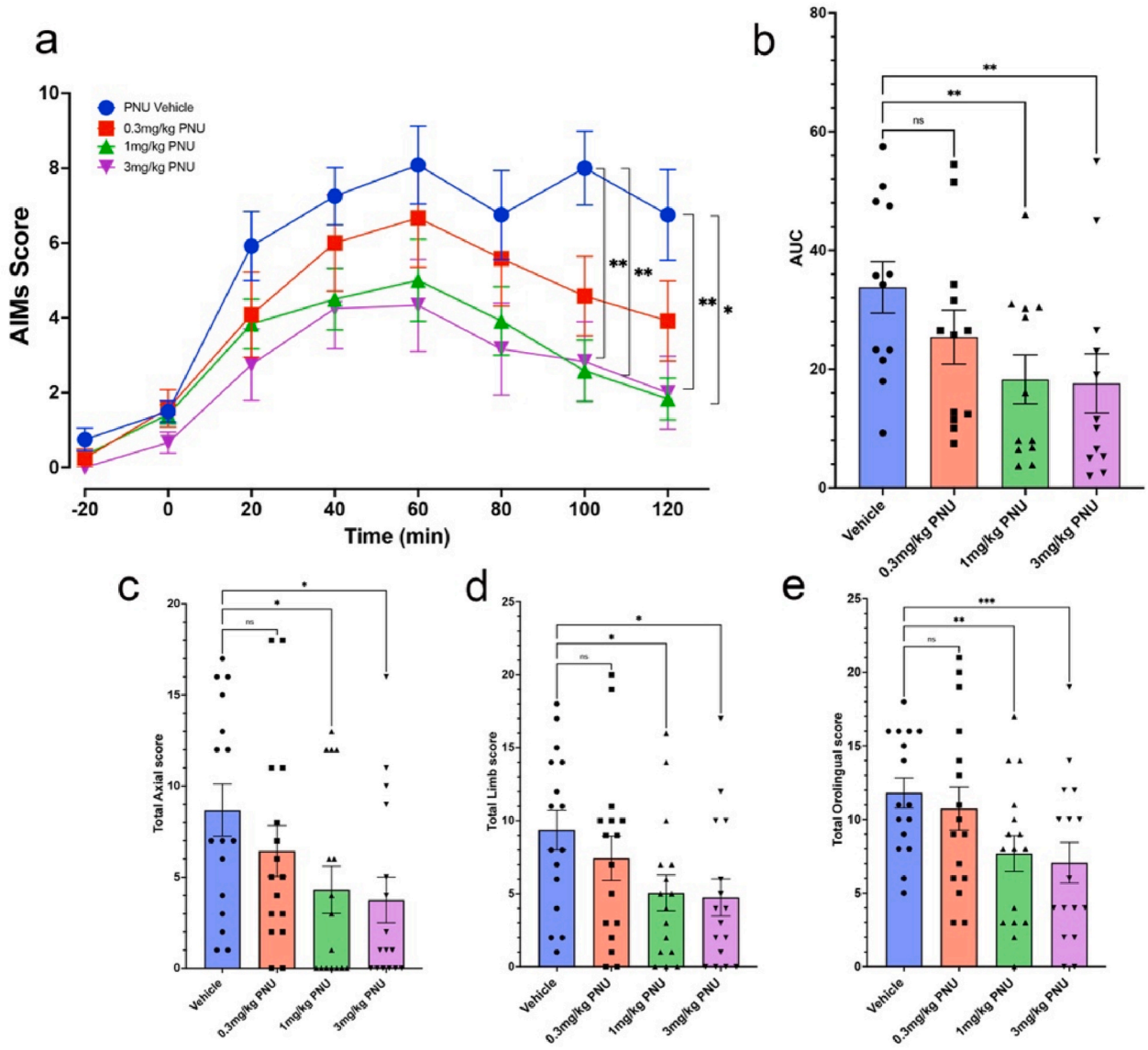


Fig. 2. The effects of de novo subcutaneous administration of an α7 positive allosteric modulator (PAM), PNU-120596, on unilaterally 6-OHDA lesioned AIMs in levodopa-primed rats (n = 12). After 100 min post-subcutaneous administration, PNU-120596 dose-dependently reduced peak total ALO AIMs (a). The grand total (AUC) of ALO AIMs over the course of 120 min was dose-dependently reduced (b). The effects of PNU-120596 on axial, limb and orolingual components of AIMs over 120 min are summarized in panels c, d and e. *P < 0.05, **P < 0.01, ***P < 0.001, mean ± SEM.

3.2. The effects of nicotine

Three weeks following the "wash-out" period after the last administration of PNU-120596, the effects of nicotine in doses ranging from 0.01 to 0.3 mg/kg were investigated on AIMs. The levodopa AIMs AUC was significantly reduced by all doses of nicotine treatment [F(2.975, 32.73) = 7.792; ***P = 0.0005] and time [F(11,44) = 2.622; *P = 0.0115]. Nicotine dose-dependently reduced levodopa-induced ALO AIMs [nicotine dose × time interaction, F(28, 497) = 1.512, *P = 0.0465] (Fig. 3a). The AUC for levodopa-induced AIMS over 120 min showed statistically significant AIMs (0.01 mg/kg, **P = 0.0074; 0.03 mg/kg, ***P = 0.0006; 1.0 mg/kg, **P = 0.0069; 3.0 mg/kg *P = 0.0120; one-way ANOVA Dunnett's *post hoc* test). However, these doses also significantly reduced axial, limb and orolingual components by a similar level (Fig. 3c–e). The lowest dose of nicotine (0.01 mg/kg) only reduced the orolingual component significantly (Fig. 3e).

3.3. The combined effects of nicotine and PNU-120596

To investigate whether α7 PAM, PNU-120596 enhances the anti-dyskinetic properties of nicotine, the medium dose of 1.0 mg/kg PNU-120596 was co-administered with low doses (0.01 and 0.03 mg/kg) of nicotine (Fig. 4a). In this set of experiments a combination of nicotine and PNU-120569 significantly affected the outcome of treatment [F (7,77) = 21.6; ****P < 00001] and time [F(5,55) = 5.25; ***P = 0.0005] and Time x drug treatment [F(35, 385) = 1.72; P = 0.0078] in levodopa-induced ALO AIMs (Fig. 4a). Application of 0.01 mg/kg nicotine reduced total AIMs by approximately 40 % (*P = 0.0187) whereas PNU-120596 (1.0 mg/kg) + nicotine (0.01 mg/kg) non-significantly reduced AIMs by 23 % in this set of experiments (P = 0.384). PNU-120596 (1.0 mg/kg) plus 0.03 mg/kg nicotine significantly reduced AIMs by 51 % (*P = 0.0018) compared to vehicle. When 0.01 mg/kg nicotine and 1.0 mg/kg PNU-120596 were co-administered, the overall levodopa AIMs score as assessed by AUC was significantly reduced by approximately 55 % (***P = 0.0008) whereas co-application of 0.03 mg/kg nicotine and 1.0 mg/kg PNU-120596 significantly

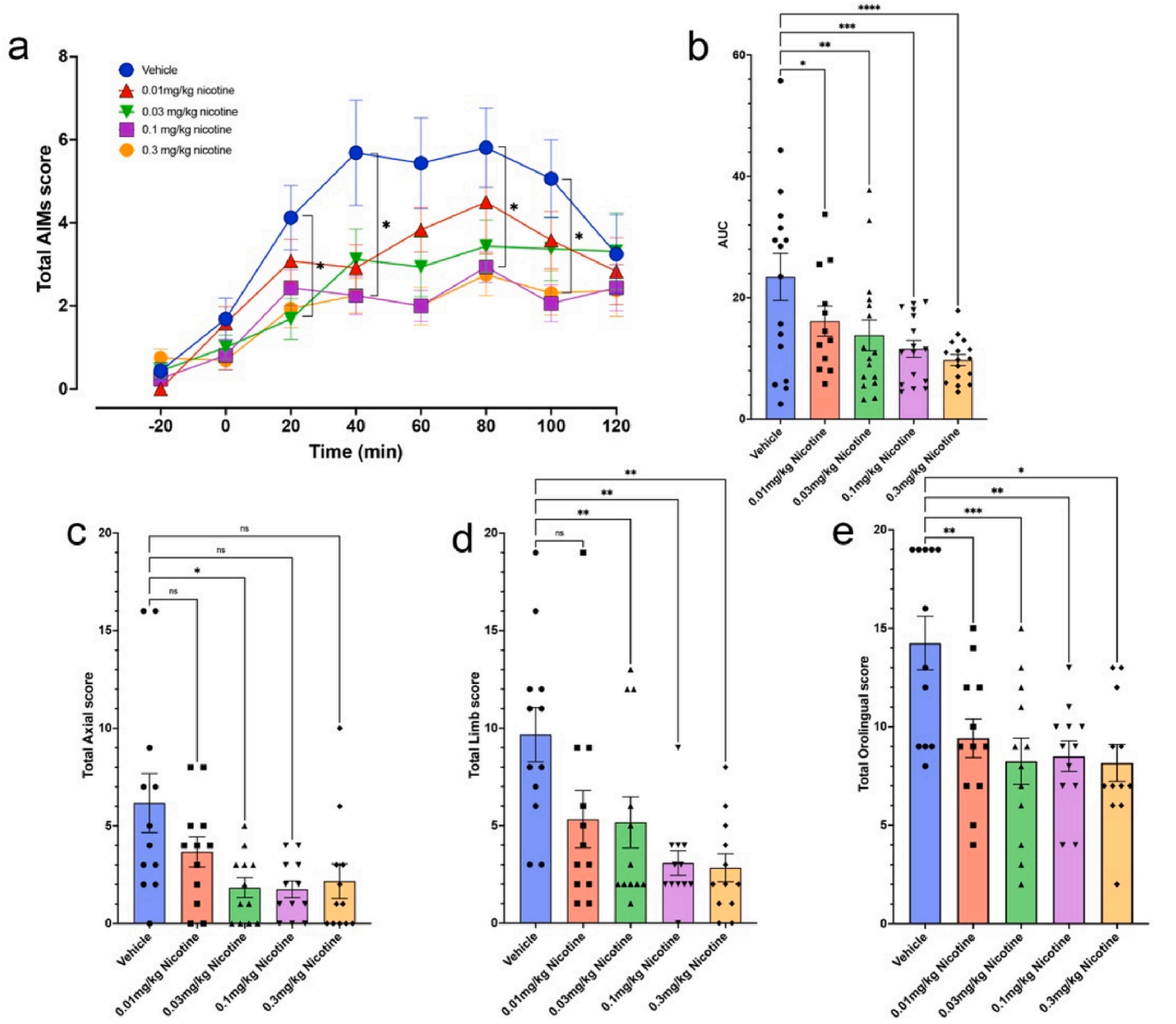


Fig. 3. The effects of subcutaneous administration of nicotine on unilaterally 6-OHDA lesioned AIMs in levodopa-primed rats (n = 12). Following 20 min post-subcutaneous administration, nicotine dose-dependently reduced peak total ALO AIMs between 20 and 80 min (a). The grand total of ALO AIMs over the course of 120 min was dose-dependently reduced by nicotine administration (b). The effects of nicotine on axial, limb and orolingual components of AIMs over 120 min are summarized in panels c, d and e. *P < 0.05, **P < 0.01, ***P < 0.001, mean ± SEM.

reduced total AIMs score by 60 % (P = 0.0002) (Fig. 4b). Combined administration of nicotine and PNU-120596 further decreased ALO AIMs components except axial (Fig. 4c–e). The limb component was not significantly reduced by either nicotine doses or the dose of PNU-120596 alone. However, the combination of nicotine and 1.0 mg/kg PNU-120596 significantly reduced the limb AIM scores (0.01 mg/kg: **P = 0.0047; 0.03 mg/kg: ***P = 0.0006) (Fig. 4d). Comparisons of the effects nicotine 0.01 and 0.03 mg/kg alone with 1.0 mg/kg PNU-120596 plus 0.01 mg/kg (P = 0.285) or 0.03 mg/kg (P = 0.356) nicotine combination using Tukey's *post hoc* test showed that the presence of PNU-120596 had no significant effect.

3.4. The effects of α7 agonist, PHA-543613 and its co-administration with PNU-120596

The effects of a selective α7 nicotinic agonist, PHA-543613 was also investigated on AIMs in the absence and in the presence of the PAM, PNU-120596. Only two doses of 3.0 and 10.0 mg/kg PHA-543613 were used which significantly reduced ALO AIMs dose [F(2.584, 28.43) = 3.484; *P = 0.0341 and time: F(1.988, 21.87) = 17.63; ****P < 0.0001]. Administration of 3.0 or 10.0 mg/kg PHA-543613 plus PNU-120569 vehicle dose-dependently reduced AIMs by 16 % at 3.0 mg/kg and 49 % at 10.0 mg/kg, respectively (Fig. 5a and b). Statistical significance was reached only at the highest dose (10.0 mg/kg) of PHA-543613, specifically at 20 (*P = 0.0409), 40 (*P = 0.0105) and 60 (**P = 0.0031) min post administration. The reduction of limb and axial, and orolingual scores were all statistically significant at 10.0 mg/kg PHA-543613 (Fig. 5c–e).

When the combined effects of 3.0 mg/kg PHA-543613 and 1.0 mg/kg PNU-120596 was investigated, unlike low dose nicotine plus PNU-120569 which resulted in a significant reduction in AIMs and ALO AIMs components, this had no effect on levodopa-induced AIMs or any of the ALO AIMs components (Fig. 5a–e).

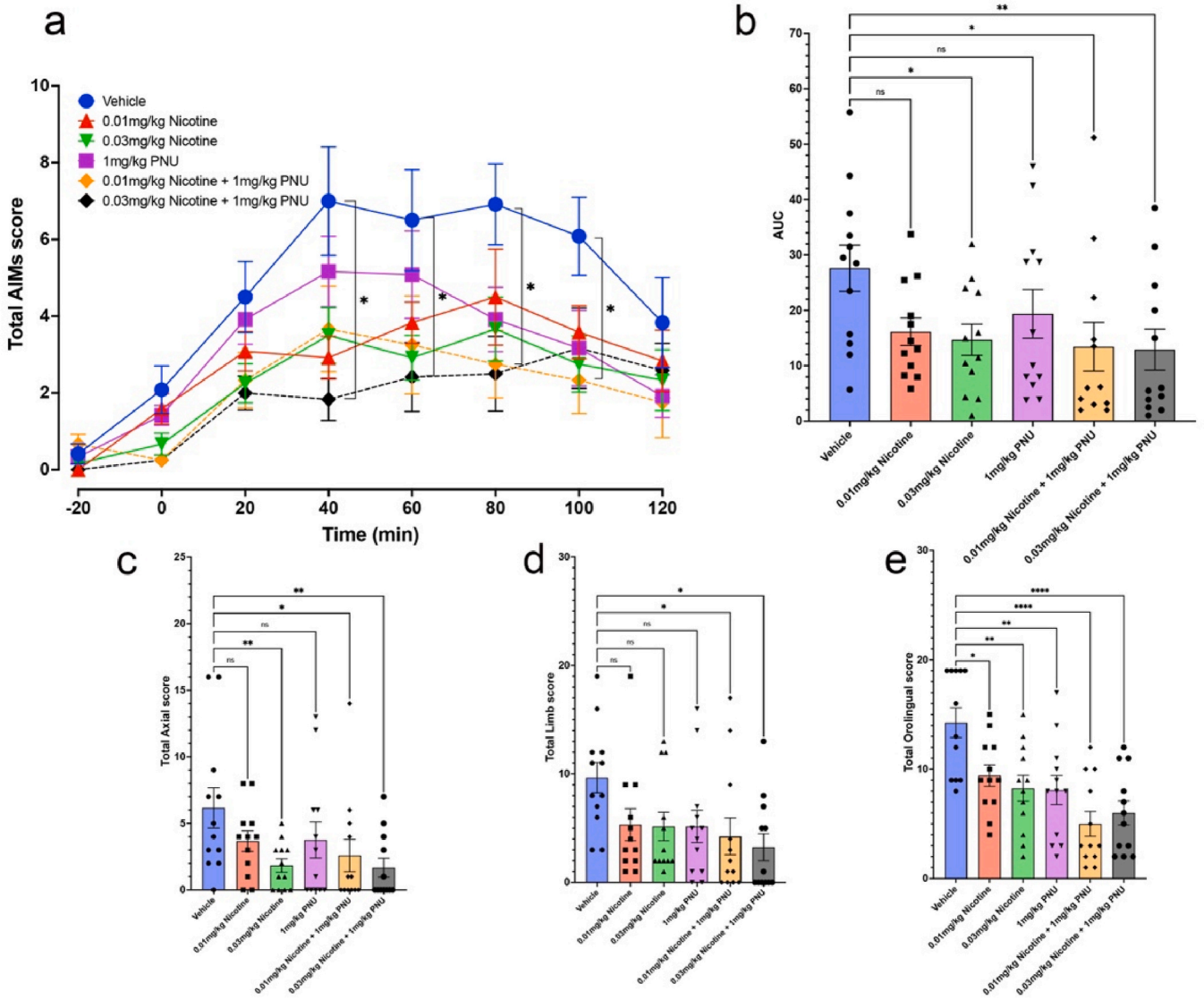


Fig. 4. The effects of combined administration of nicotine and α7 PAM, PNU-120596 on AIMs. Following 40 min post-subcutaneous administration, nicotine dose-dependently reduced peak total ALO AIMs between 40 and 100 min (a). While 1.0 mg/kg PNU-120596 on its own had no significant effects, it enhanced the anti-dyskinetic effects of 0.01 and 0.03 mg/kg nicotine. The grand total of ALO AIMs over the course of 120 min was dose-dependently reduced by nicotine administration (b). The effects of nicotine on axial, limb and orolingual components of AIMs over 120 min have been summarized in panels c, d and e. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, mean ± SEM.

3.5. The effects α7 antagonist, MLA on AIMs

To further emphasize the role of α7 nAChRs, the effect of the selective α7 nicotinic receptor antagonist methyllycaconitine citrate (MLA) on levodopa-induced AIMs was assessed (Fig. 6). MLA was examined at 2.0 and 6.0 mg/kg on ALO AIMs against time, there was a significant difference with time [F (4.480, 147.8) = 13.19, ***P < 0001)] and dose [(F (2, 33) = 4.204; *P = 0.0236] (Fig. 6a). Rather surprisingly, at time t = 20–40 min both doses of MLA at 2.0 and 6.0 mg/kg significantly reduced peak ALO AIMs but the dose of 2.0 mg/kg had shorter lasting effect, by 60 min the AIMs score was no different from control (Fig. 6a). However, 6.0 mg/kg MLA significantly suppressed AIMs up to 120 min. Overall when the AUC of AIMs scores were assessed, there was only a significant reduction of AIMs at 6.0 mg/kg MLA (Fig. 6b). Although each component of AIMs, namely axial, limb and orolingual were significantly by MLA, at 6.0 mg/kg, the orolingual component was the only component that was significantly reduced at 2.0 mg/kg (Fig. 6e).

3.6. The effects of nicotine and α7 agonists on ipsiversive rotation

To rule out any direct effects of α7 agonists on the ipsilateral intact dopaminergic systems, we compared the effects on rotation of maximum dose of nicotine, PNU-120596 and PHA-543613 used in this study against 5 mg/kg (+)-amphetamine. While (+)-amphetamine produced a robust ipsilateral rotation of 1278 ± 145, PNU-120596 and PHA-543613 produced 44 ± 7.8, 26 ± 11.5 and 22 ± 5.2 turns in 90 min of test period respectively (Fig. 7). There was a significant difference between the effects of nicotine and α7 agents [F (2, 36) = 2.521; *P = 0.045].

4. Discussion

A substantial body of preclinical literature demonstrates that pharmacological modulation of nicotinic acetylcholine receptors (nAChRs) can attenuate levodopa-induced dyskinesia (LID). Nicotine influences both nigrostriatal and corticostriatal neurotransmission by modulating dopamine and glutamate release (Meshul et al., 2002; Valjent et al.,

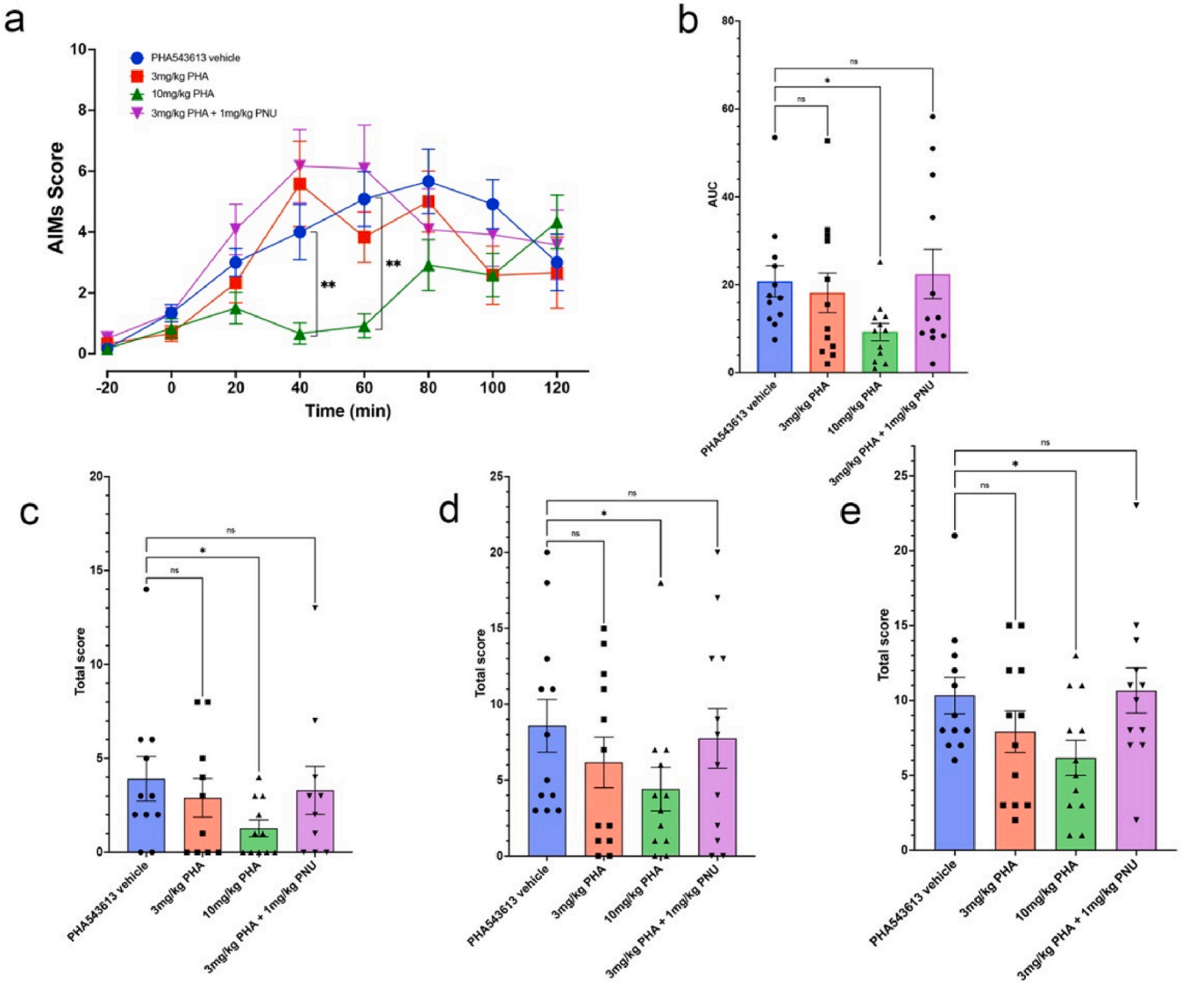


Fig. 5. The effects of subcutaneous administration of a selective α7 agonist, PHA-543613 (PHA), and PHA-543613 + PNU-120596 (PNU) on unilaterally 6-OHDA lesioned AIMs in levodopa-primed rats (n = 12). After 40 min post-subcutaneous administration, PNU-120596 dose-dependently reduced peak total ALO AIMs (a). The grand total of ALO AIMs over the course of 120 min was dose-dependently reduced (b). The effects PNU-120596 on axial, limb and orolingual components of AIMs over 120 min have been summarized in panels c, d and e. *P < 0.05, mean ± SEM.

2005; Quik et al., 2006; Xiao et al., 2009; Storey et al., 2016; Matityahu et al., 2022; Ye et al., 2024). Activation of nAChRs, or blockade of muscarinic receptors, similarly reduces LID expression (Bordia et al., 2010; Shen et al., 2015; Conti et al., 2018; Bordia and Perez, 2019; Chambers et al., 2019; Brugnoli et al., 2020). The therapeutic notion of nicotinic agents in Parkinson's disease (PD) was first inspired by epidemiological findings linking cigarette smoking to a lower PD incidence (Allam et al., 2004; Tanner, 2010). Subsequent animal experiments reinforced this hypothesis: chronic nicotine treatment in rodents and primates reduces LID in levodopa-primed models (Quik et al., 2007; Bordia et al., 2008).

It is suggested that the striatum is a principal locus for the pathological changes driving LID (Buck et al., 2010), however, α7 nAChRs are largely absent from dopaminergic nerve terminals (Zhou et al., 2002). Studies in lesioned rodents and primates show that α7 receptor levels remain stable despite the loss of dopaminergic innervation (Champtiaux et al., 2003; Grady et al., 2007; Zoli et al., 2002; Quik et al., 2006, 2011) implying that α7 nAChRs lie predominantly on corticostriatal glutamatergic afferents (Udakis et al., 2016; Stone, 2021), linking them to the modulation of excitatory drive to the striatum rather than direct modulation of dopamine release from dopaminergic terminals. Given that dyskinesia is often attributed to aberrant glutamatergic signalling (Herz et al., 2015), this anatomical arrangement is functionally meaningful. Notably, amantadine—currently the only clinically approved anti-dyskinetic agent—acts weakly as an NMDA antagonist, but recent evidence suggests that its primary effect at therapeutic levels is blockade of inwardly rectifying potassium (Kir2) channels (Shen et al., 2020). Because nicotine also suppresses Kir2 conductance (Wang et al., 2000), nAChR activation may act through converging ion channel pathways to stabilize network excitability. Modulation of Kir2 activity could thereby alter dopaminergic neuronal excitability and pacemaker firing dynamics, providing a mechanistic explanation for the anti-dyskinetic effects of nicotinic agonists in reducing AIMs. Recent data also implicate additional potassium channel mechanisms in dyskinesia regulation. Deletion of Kir6.2-containing K_{ATP} channels in dopaminergic neurons substantially reduced AIMs in levodopa-primed mice (Kuo et al., 2024). These findings suggest that modulation of K_{ATP} activity, possibly via GSK3β/AMPK-dependent signalling, might parallel Kir2-mediated effects in mitigating dyskinesia. Supporting this, α7 PAMs such as PNU-120596 have been shown to downregulate GSK3β and thereby

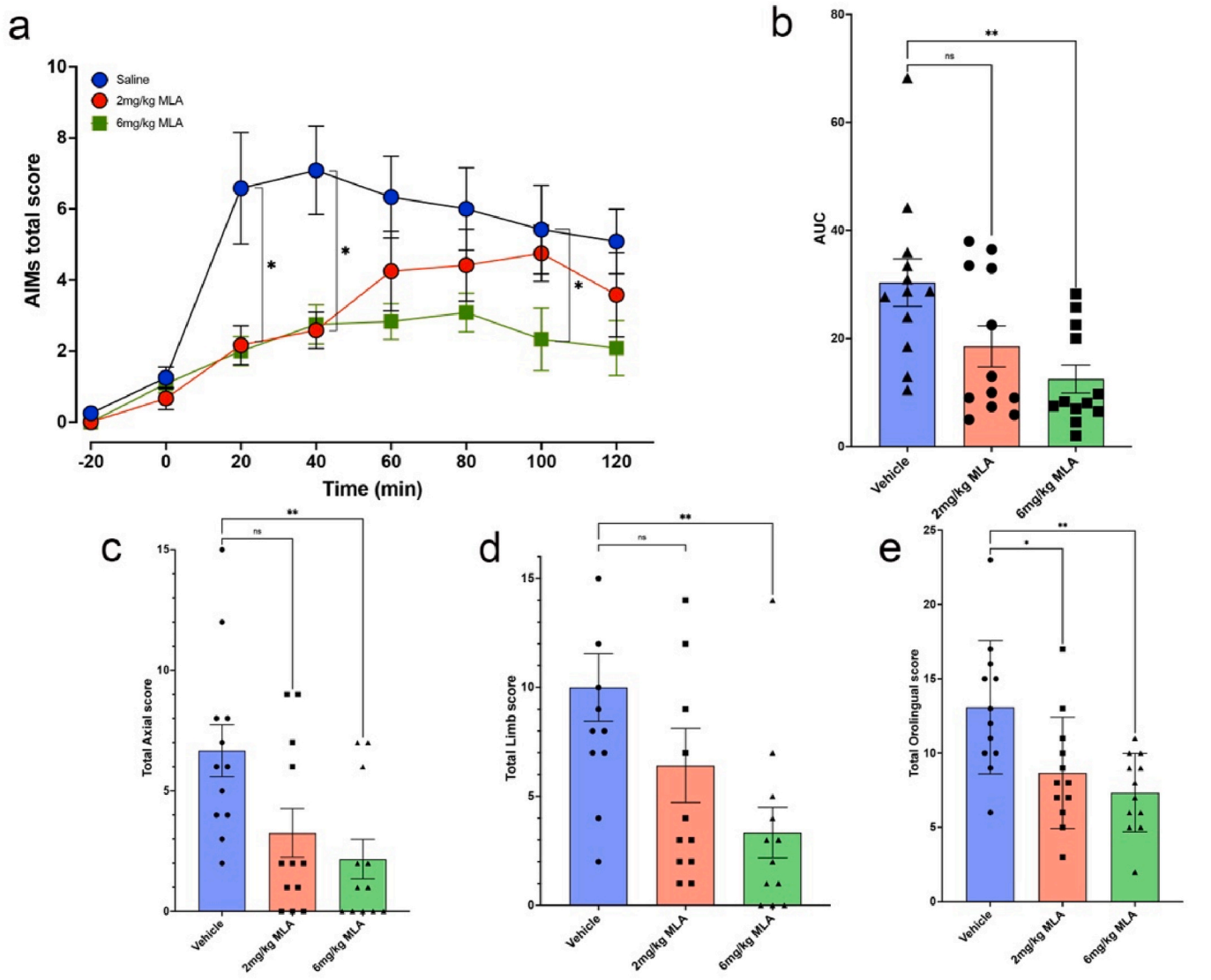


Fig. 6. The effects of subcutaneous administration of an α7 antagonist, methyllycaconitine (MLA), on unilaterally 6-OHDA lesioned AIMs in levodopa-primed rats (n = 12). After 20 min post-subcutaneous administration, MLA dose-dependently reduced peak total ALO AIMs (a). The grand total of ALO AIMs over the course of 120 min was dose-dependently reduced (b). The effects MLA is shown on axial (c), limb (d) and orolingual components (d) of AIMs over 120 min *P < 0.05, **P < 0.01, mean ± SEM.

suppress neuroinflammatory cascades (Gowayed et al., 2022). Altogether, these results point to a unifying framework in which nAChR activation regulates potassium channel conductance and intracellular energy-sensing pathways, thereby stabilizing dopaminergic neuron firing and synaptic homeostasis. By influencing GSK3β/AMPK signalling, nicotinic activation may normalize aberrant plasticity (LTP, LTD) in the striatum and restore balanced corticostriatal transmission.

α7 receptors are unique among nAChRs in their ability to operate through both classical ionotropic ($\alpha7^{i}$) and metabotropic ($\alpha7^{m}$) modes (Gaidhani et al., 2021; Papke and Horenstein, 2021; Sinclaire and Kabbani, 2023). In the ionotropic mode, ACh binding leads to calcium influx and activation of downstream kinases (e.g. ERK1/2, PKA), affecting neurotransmission and plasticity (Sinclaire and Kabbani, 2023). In the metabotropic configuration, $\alpha7^{m}$ receptors couple to G-proteins to mediate IP_3-driven release of intracellular Ca^{2+}, even under desensitized receptor states (Kabbani and Nichols, 2018). This dual signalling architecture offers flexible spatial and temporal control of neuronal Ca^{2+} dynamics, which may be critical in modulating dyskinesia-relevant circuits as evidenced by the work of Gómez-Paz et al. (2025).

In our experiments, the α7 PAM PNU-120596 alone (i.e. without nicotine or exogenous agonists) produced a dose-dependent reduction in ALO AIMs. α7 PAMs are thought to provide improved therapeutic windows by enhancing the effects of endogenous ACh (or choline) rather than directly activating receptors, thereby minimizing desensitization and off-target activation (Uteshev, 2014; Albin et al., 2022; Pifl et al., 2025; Ratna and Francis, 2025). We interpret these results as indicating that PNU-120596 amplifies basal cholinergic tone sufficiently to engage anti-dyskinetic signalling cascades.

In contrast, the selective α7 agonist PHA-543613 only reduced AIMs at a higher dose (10 mg/kg), while the lower dose (3 mg/kg) was ineffective - likely due to insufficient receptor engagement or rapid desensitization. Importantly, combining PNU-120596 with nicotine or PHA-543613 did not produce additive or synergistic effects, implying convergence on overlapping mechanisms or receptor states. This observation aligns with the notion that chronic exposure to nicotine, agonists, or PAM-induced receptor desensitization may be central to their therapeutic effects (Picciotto et al., 2008; Livingstone and Wonnacott, 2009). Indeed, non-selective antagonists such as mecamylamine suppress LID (Bordia et al., 2010), and Papke et al. (2018) demonstrated

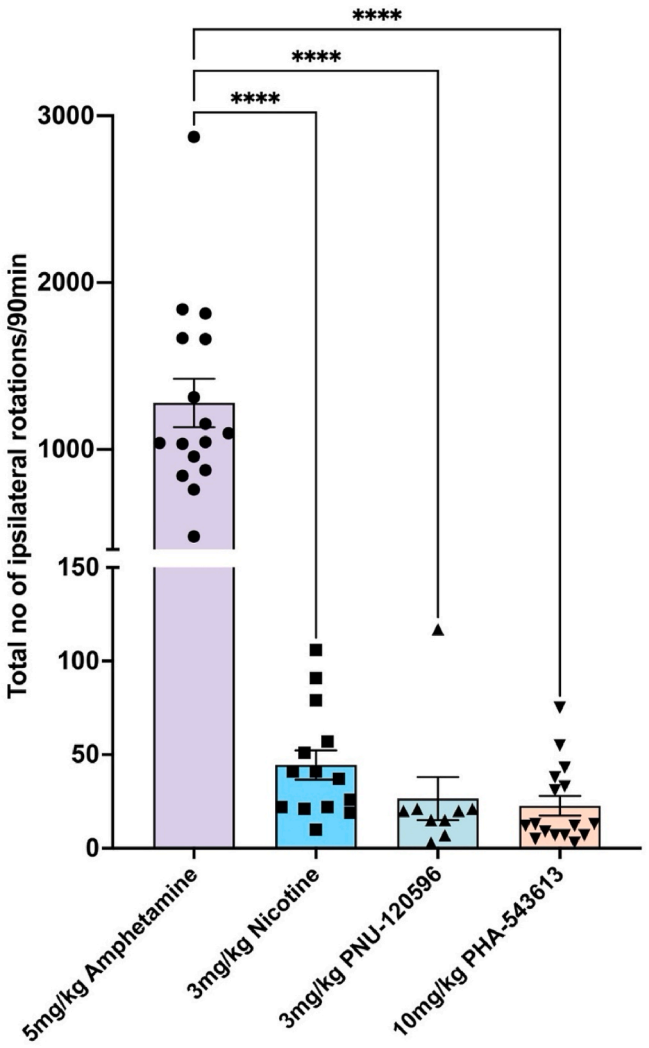


Fig. 7. The effects of nicotine, PNU-120596 and PHA-543613 compared to 5 mg/kg (+)-amphetamine on ipsiversive rotation of the 6-OHDA lesioned, levodopa primed rats (n = 12). ***P < 0.0001, mean ± SEM.

that both PAMs and silent desensitizers can stabilize α7 in non-conducting, desensitized conformations. As a type II PAM, PNU-120596 notably reduces desensitization and prolongs channel open states (Grønlien et al., 2007; King et al., 2018; Papke et al., 2023) and boosts dopamine release in prefrontal cortex (Livingstone et al., 2009) - a property that may extend to basal ganglia circuits relevant to dyskinesia.

Genetic evidence further supports the centrality of α7 in LID: α7 knockout mice fail to develop AIMs under repeated levodopa administration (Quik et al., 2013). Although α7 activation can promote glutamate release (Campos et al., 2010; Bortz et al., 2013; Ryu et al., 2017), the net physiological outcome may depend on receptor occupancy, desensitization dynamics, and the balance of direct and modulatory signalling. Moreover, α7 antagonists such as MLA may reduce glutamate release via presynaptic AMPA receptor interactions (Samengo et al., 2015), suggesting that distinct modes of α7 modulation - agonism, desensitization, or antagonism—may converge on common downstream pathways controlling corticostriatal balance.

Although these findings may hypothetically involve desensitization of nicotinic acetylcholine receptors, which has been proposed in previous studies to reduce aberrant cholinergic or dopaminergic signalling associated with dyskinesia. However, the present study does not provide direct evidence for such a mechanism, and this interpretation should therefore be regarded as speculative. Future studies employing receptor binding or electrophysiological assays will be required to determine whether nicotinic receptor desensitization contributes to the observed antidyskinetic effects.

5. Conclusions

This study offers two novel insights. First, even acute, low-dose nicotine and selective α7 agonist treatment can reduce AIMs, complementing prior findings from chronic administration paradigms. More importantly, we show that α7 PAMs such as PNU-120596, given de novo and without exogenous nicotinic stimulation, acutely suppress dyskinesia. These findings support the therapeutic potential of α7 PAMs as a more refined approach to modulating cholinergic signalling in PD. By targeting receptor conformations to harness endogenous cholinergic tone, α7 PAMs may stabilize corticostriatal networks, suppress neuroinflammation, and restore synaptic homeostasis - all with a favourable safety and specificity profile.

CRediT authorship contribution statement

Yasaman Malekizadeh: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Kiana Hassankhani:** Visualization, Validation, Investigation, Data curation. **Alice E. Kingslake:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Lucy E. Annett:** Writing – review & editing, Resources. **Mohammed Shoaib:** Writing – review & editing, Methodology, Funding acquisition. **Mahmoud M. Iravani:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Parkinson's UK for supporting this study through the project grant G-1805.

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