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The selective 5-HT$_{1A}$ receptor agonist, NLX-112, exerts anti-dyskinetic effects in MPTP-treated macaques

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ABSTRACT

Background: Long-term treatment of Parkinson's disease (PD) with L-DOPA typically leads to development of L-DOPA induced dyskinesia (LID). Amantadine, an NMDA antagonist, attenuates LID, but with limited efficacy and considerable side-effects. NLX-112 (also known as befiradol or F13640), a highly selective and efficacious 5-HT$_{1A}$ receptor agonist, reduced LID when tested in rodent and marmoset models of PD.

Methods: The effects of NLX-112 (0.03, 0.1 and 0.3 mg/kg PO) on established LID evoked by acute challenge with L-DOPA (27.5 ± 3.8 mg/kg PO) were assessed in MPTP-treated cynomolgus macaques. Amantadine (10 mg/kg PO) was tested as a positive control. Plasma exposure of NLX-112 (0.1 mg/kg PO) was determined.

Results: NLX-112 significantly and dose-dependently reduced median LID levels by up to 96% during the first hour post-administration (0.3 mg/kg). Moreover, NLX-112 reduced the duration of 'bad on-time' associated with disabling LID by up to 48% (0.3 mg/kg). In contrast, NLX-112 had negligible impact on the anti-parkinsonian benefit of L-DOPA. NLX-112 exposure peaked at ~50 ng/ml at 30 min post-administration but decreased to ~15 ng/ml at 2h. Amantadine reduced by 42% 'bad on-time' associated with L-DOPA, thereby validating the model.

Conclusion: These data show that, in MPTP-lesioned cynomolgus macaques, NLX-112 exerts robust anti-dyskinetic effects, without reducing the anti-parkinsonian benefit of L-DOPA. These observations complement previous findings and suggest that selective and high efficacy activation of 5-HT$_{1A}$ receptors by NLX-112 may constitute a promising approach to combat LID in PD, providing an alternative for patients in whom amantadine is poorly tolerated or without useful effect.

1. Introduction

Parkinson's disease (PD) causes long term suffering for patients and a considerable economic burden to society. Pharmacological treatment of PD relies primarily on L-3,4-dihydroxyphenylalanine (L-DOPA) which ameliorates most motor abnormalities. Unfortunately, many patients progressively develop dose-limiting dyskinesia, characterized by hyperkinetic movements, including chorea and dystonia [1–3]. Such L-DOPA-induced dyskinesia (LID) can become troublesome, and there is a lack of highly efficacious and well-tolerated pharmacological treatments, although useful amelioration can be achieved with the glutamate receptor antagonist, amantadine, in some patients [4].

Recently, the serotonin (5-hydroxytryptamine, 5-HT) system has attracted attention as a key element in the etiology of LID and its treatment by 5-HT$_{1A/1B}$ receptor agonists. Different mechanisms have been proposed that may underlie their activity, including inhibition of descending cortico-striatal glutamatergic projections and direct activation of striatal 5-HT$_{1A}$ receptors [5,6]. One of the best-characterized mechanisms is based on the observation that 5-HT neurons possess the enzymes necessary to convert exogenous L-DOPA to dopamine (DA), which can then be stored in vesicles and released as a 'false neurotransmitter' [7,8]. However, 5-HT neurons lack appropriate control mechanisms to regulate synaptic DA levels (such as inhibitory D2 auto-receptors), resulting in excessive and physiologically inappropriate

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DA release and a pulsatile stimulation of post-synaptic DA receptors that generates dyskinesia [9]. The false neurotransmitter release of DA from 5-HT neurons can be reduced by targeting inhibitory pre-synaptic receptors such as 5-HT_{1B} on neuronal terminals or 5-HT_{1A} receptors on cell bodies [10]. Accordingly, several 5-HT_{1A} receptor agonists, such as buspirone, sarizotan or eltoprazine, have been clinically tested to alleviate LID, albeit with limited efficacy. Moreover, some of these also reduce the beneficial anti-parkinsonian effects of L-DOPA, probably because of their lack of receptor specificity and modest agonist efficacy and/or because of their differential targeting of pre- versus post-synaptic 5-HT_{1A} receptors in different brain regions, as discussed previously [11,12].

In contrast, the novel 5-HT_{1A} receptor agonist, NLX-112, (also known as befiradol or F13640) is a potent (nanomolar affinity) and highly selective (>1000-fold over a wide palette of off-target sites) 'full' agonist at 5-HT_{1A} receptors [13], features that distinguish it from previous serotonergic compounds [14]. Moreover, unlike other 5-HT_{1A} receptor agonists, NLX-112 exhibits distinctive biased agonist properties in vitro, preferentially activating Gαo proteins rather than other G-protein subtypes [15]. In vivo, NLX-112 rapidly penetrates the brain following systemic dosing. Imaging studies in rat, cat, non-human primate (NHP; macaque) and human show that NLX-112 binds specifically to brain 5-HT_{1A} receptors [16,17].

In a rodent model of LID (6-OHDA-lesioned hemi-parkinsonian rats chronically treated with L-DOPA), NLX-112 elicited a robust reduction of the L-DOPA-induced surge in striatal DA release. Accordingly, L-DOPA-induced Abnormal Involuntary Movements (AIMs), a rodent homologue of LID, were dose-dependently eliminated by NLX-112, an effect entirely reversed by a selective 5-HT_{1A} receptor antagonist [18]. In addition, the anti-AIMs activity of NLX-112 was maintained upon repeated treatment (14 days) [19]. Moreover, NLX-112 elicited marked ipsilateral rotations in hemi-parkinsonian rats, suggestive of motor facilitation effects [18].

These positive data in rodents were recently confirmed in a first NHP model of LID: MPTP-lesioned marmosets chronically treated with L-DOPA. In this model, NLX-112 (0.025, 0.1 and 0.4 mg/kg PO) reduced LID scores at early time-points after administration, whilst only minimally affecting L-DOPA-induced reversal of motor disability [11]. In contrast, the prototypical 5-HT_{1A} receptor agonist, (+)8-OH-DPAT (0.6 and 2 mg/kg PO), reduced LID but also abolished the anti-parkinsonian activity of L-DOPA. Taken together, these studies show that NLX-112 has strong anti-LID activity in rats and in marmoset. However, no information is yet available regarding the effects of NLX-112 in a higher NHP model of LID. Specifically, the purpose of the present study was to test NLX-112 in MPTP-lesioned macaques (*Macaca fascicularis*) chronically treated with L-DOPA, a model which has shown high translational predictivity to human [20] and may be more representative than marmosets (or rats) of potential unwanted motor interference by 5-HT_{1A} receptor agonists seen in these two lower species [11]. Additionally, the present study included the clinically-employed reference compound, amantadine, whose extended release formulation (Gocovri®) gained FDA approval for treating LID in PD patients in mid-2017. Prior to assessing behavioral effects, the pharmacokinetics of NLX-112 were characterized to effectively bridge from lower species and provide information on plasma exposure.

2. Methods

2.1. Animals, husbandry and welfare

Eleven female cynomolgus macaques (*Macaca fascicularis*; 3.8–5.4 kg, 10.3–16.0 years, Suzhou-Xishan-Zhongke Company, PRC) were used in this study (N = 3 for plasma exposure determination, N = 8 for behavioural assessment). Fresh-fruit, primate pellets and water were available ad libitum other than at times of overnight-fasting (from 5 p.m.) prior to days of pharmacokinetic or behavioural assessment. Animals were group-housed with cage sizes exceeding Council of Europe, UK, EU, NIH and CCAC minimum recommendations. Cages were enriched with environmental stimuli including perch, foraging boards and toys. Housing rooms were subjected to a 12-h light-dark cycle at 20–25 °C. All efforts were made to reduce to a minimum the number of animals necessary for statistically valid analyses and to minimise animal suffering. All studies were performed with local IACUC approval and in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the NIH (Institute of Laboratory Animal Resources (U.S.) Committee on Care and Use of Laboratory Animals, 1996).

2.2. Plasma pharmacokinetics of NLX-112

Blood samples were taken from the saphenous veins immediately prior to dosing (0.1 mg/kg, PO) then at 15, 30 min, 1, 2, 3, and 8 h post-drug administration. Plasma samples were prepared and then analysed for levels of NLX-112 via LC-MS/MS. The quantification was carried out by 3D BioOptima Co. Ltd. (Suzhou, PRC)

2.3. Behavioral effects of NLX-112

Methods are adapted from [21]. Briefly, animals were rendered parkinsonian with MPTP (0.2 mg/kg SC) and a parkinsonian syndrome allowed to develop over 90-days. LID were then evoked via once-daily oral L-DOPA (25 mg/kg, Madopar™, Roche) for at least 4-months. For each animal, an oral dose of L-DOPA was defined that produced optimal anti-parkinsonian benefit accompanied by disabling dyskinesia (range 25–35 mg/kg, mean 27.5 ± 3.8 mg/kg). Acute effects of five treatment combinations were assessed according to a partial Latin-square design. L-DOPA was co-administered with either NLX-112 (0.03, 0.1 or 0.3 mg/kg PO), amantadine (10 mg/kg PO) or vehicle. Animals were then transferred to individual observation cages and the effects of treatments on dyskinesia, parkinsonian disability and duration and quality of anti-parkinsonian benefit (on-time) assessed for 5 min in every 10 min epoch across the whole 6 h observation period. HD-video footage of the animals was analysed by a movement disorders neurologist blinded to treatment. Duration of anti-parkinsonian action ('on-time') was defined as the number of minutes for which the bradykinesia score was zero. In addition, on-time with disabling dyskinesia ('bad on-time') was calculated as the number of minutes for which bradykinesia was absent while the dyskinesia score was greater than 2. On-time without disabling dyskinesia ('good on-time') was determined as the number of minutes for which bradykinesia was absent while the dyskinesia score was 2 or less.

2.4. Statistical analyses

Data derived from assessment of plasma NLX-112 levels, duration and quality (i.e. 'good' or 'bad') of on-time were expressed as mean ± SD (plasma exposure determination) or SEM (behavioural assessment). Statistical analyses for these data were performed using parametric repeated measures two-way ANOVA, followed by Fisher's Least Squares Difference tests. Data for measures of parkinsonian disability and dyskinesia were graphed as median scores per 10 min epoch (time course) or with individual values (cumulated 0–2 h totals). Time course data for parkinsonian disability and dyskinesia were first ranked within each animal across all treatments using Excel's RANKAVG function. These transformed data were then analysed in GraphPad Prism (v 7.03) and subjected to non-repeated measures 2-way ANOVA followed by Holm-Sidak multiple comparison tests. Cumulated disability and dyskinesia data were analysed using a Friedman test followed by a Dunn's Multiple Comparisons test. For amantadine, analysis of 'bad on-time' was carried out by a Student t-test. For cumulated data (0–2 h), total dyskinesia score and parkinsonian disability were analysed with Wilcoxon tests.

2.5. Drugs

NLX-112 (3-Chloro-4-fluorophenyl-[4-fluoro-4-([(5-methylpyridin-2-yl)methylamino] methyl)piperidin-1-yl]methanone, fumarate) was provided by Neurolixis and dissolved in distilled water to prepare a stock solution and then diluted in a 10% w/v sucrose solution to provide the required dose and administered orally at a volume of 2 ml/kg. Amantadine (UHN Shanghai, Shanghai, PRC) was administered orally at a volume of 1 ml/kg. In all cases, drug doses are expressed as the weight of the free base.

3. Results

3.1. Plasma levels of NLX-112

Peak plasma exposure of NLX-112 occurred at 15–30 min post-dosing with levels of ~50 ng/ml (Fig. 1). Plasma concentration followed similar kinetics in the 3 macaques and NLX-112 was eliminated such that levels decreased to around 10–20 ng/ml within 2 h.

3.2. Effects of NLX-112 and amantadine on duration and quality of on-time

NLX-112 produced no change in the total duration of on-time but improved the quality of on-time associated with L-DOPA (Fig. 2A). Assessed over the 6-h period of observation there was a significant effect of treatment on duration of bad-quality on-time ($F(1.837,12.86) = 5.908$, $P = 0.0167$). NLX-112 (0.3 mg/kg) produced a significant reduction in 'bad on-time' of 48% compared to vehicle treatment (81 min vs. 156 min respectively, $P < 0.05$).

Amantadine (10 mg/kg) also produced no change in the total duration of on-time but improved its quality, such that bad-quality on-time was significantly reduced by 42% vs. vehicle ($P < 0.05$, *t*-test, Fig. 2B).

3.3. Effects of NLX-112 and amantadine on L-DOPA-induced dyskinesia

L-DOPA elicited 'severe' dyskinesia in the macaques, with maximal scores of 4 at about 2 h post-treatment. NLX-112 produced a significant and dose-dependent reduction in dyskinesia evoked by L-DOPA. Examining the whole 6 h time-course, there was a significant effect of treatment on dyskinesia ($F(3,28) = 4.629$, $P = 0.0094$), an interaction between treatment and time ($F(105,980) = 2.153$, $P < 0.0001$) but no effect of time alone ($F(35,980) = 0.000$, $P > 0.9999$) (Fig. 3A). Compared to L-DOPA/vehicle treatment, L-DOPA in combination with higher doses of NLX-112 (0.1 and 0.3 mg/kg) reduced dyskinesia across multiple individual 10-min epochs within the first 3 h (all $P < 0.05$). Indeed, LID was reduced by as much as 96% (i.e. down to 'mild' or 'absent') during the first hour post-administration. Data cumulated over the 2-h period of peak effect (0–2 h) revealed a significant effect of L-DOPA/NLX-112 combination treatment (0–2 h; Friedman Statistic (FS) = 17.49, $P = 0.0006$, Fig. 3B) on dyskinesia evoked by L-DOPA with median dyskinesia levels in animals that received high-dose NLX-112 (0.3 mg/kg) reduced by 39% compared to L-DOPA/vehicle such that median levels were reduced to below moderate (i.e. non-disabling, $P < 0.01$).

Across the 6 h observation period there were also significant effects of amantadine on dyskinesia ($F(1,14) = 17.02$, $P = 0.001$), an

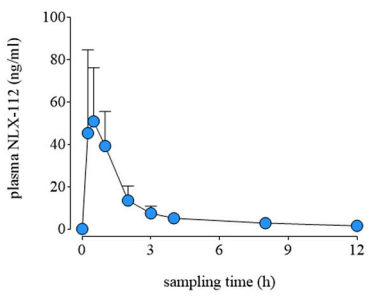

Fig. 1. Plasma profile following oral administration of NLX-112 (0.1 mg/kg) in the MPTP-lesioned macaque. Plasma samples were prepared at times up to 12 h following administration. Data are N = 3, mean ± SD.

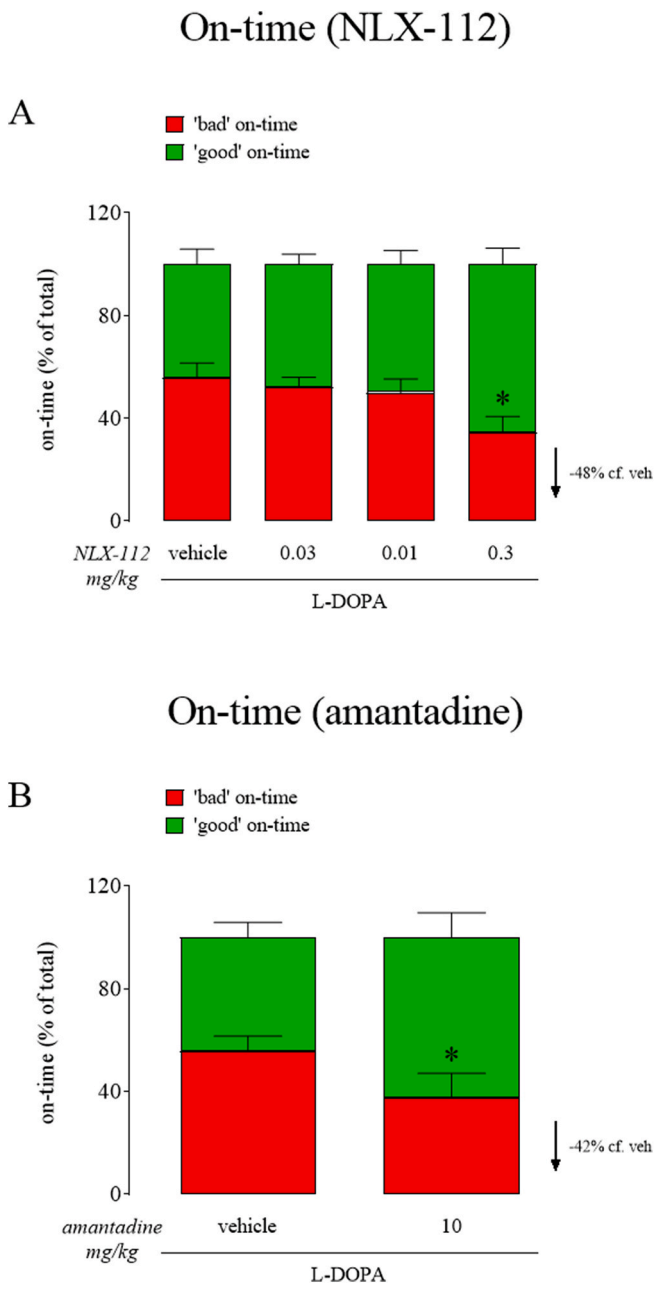

Fig. 2. Effect of acute administration of NLX-112 and amantadine on duration of quality of on-time associated with L-DOPA in the MPTP-lesioned macaque. Total on-time was calculated as that time for which bradykinesia was absent while quality of on-time was assessed as the duration for which bradykinesia was absent but accompanied by either no or mild/moderate dyskinesia (non-disabling) or marked/severe dyskinesia (disabling). Data, as a percentage of total on-time, are expressed as mean ± SEM. N = 8 for all treatment groups. *represents $P < 0.05$ vs. vehicle-treatment.

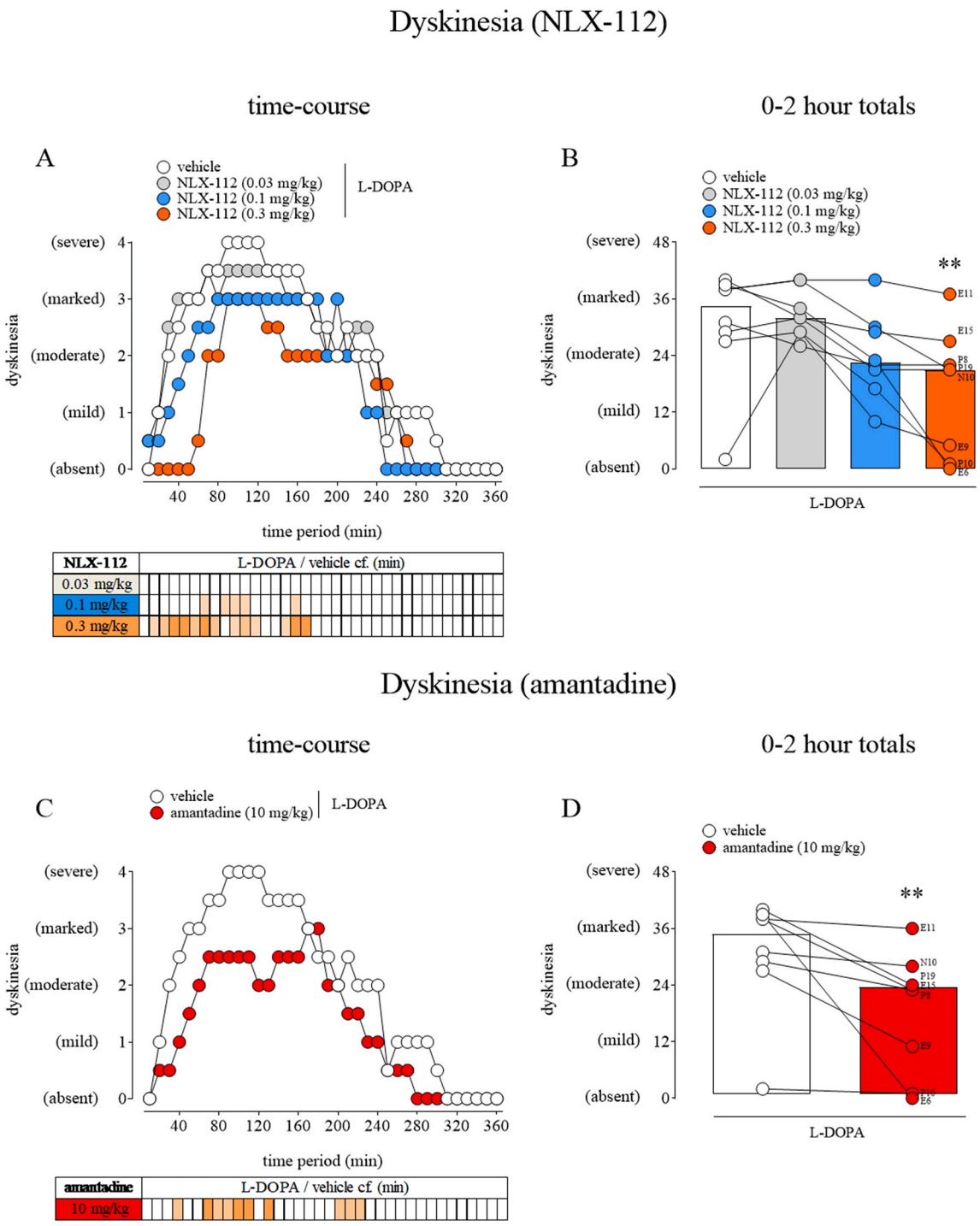

Fig. 3. Effect of acute administration of NLX-112 and amantadine on L-DOPA-induced dyskinesia in the MPTP-lesioned macaque. Levels of dyskinesia were assessed over a 6 h period every 10 min (A and C) or cumulated across the 0–2 h period of peak-effect (B and D). Data are median (A and C) with individual values (B and D). N = 8 for all treatment groups. (*/**/*** respectively) represents $P < 0.05$, $P < 0.01$ or $P < 0.001$ vs. vehicle-treatment.

interaction of treatment and time ($F(35,490) = 3.884$, $P < 0.0001$) but no effect of time alone ($F(35,490) = 0.000$, $P > 0.9999$) (2-way RM-ANOVA, Fig. 3C). Comparing to L-DOPA/vehicle treatment, *post hoc* analysis revealed significant decreases in dyskinesia evident across individual 10-min epochs within the first 3 h in response to combination amantadine (10 mg/kg, all $P < 0.05$). Over the 0–2 h peak effect period amantadine was associated with a significant reduction in dyskinesia evoked by L-DOPA ($P < 0.01$, Wilcoxon test, Fig. 3D) with median dyskinesia levels reduced by 33% compared to L-DOPA-vehicle such that median levels were reduced to below moderate (non-disabling).

3.4. Effects of NLX-112 and amantadine on parkinsonian disability

NLX-112 produced negligible change in the anti-parkinsonian benefit associated with L-DOPA at any point across the 6-h observation, compared to vehicle treatment. Thus, across the whole 6 h time-course period of observation there was no effect of NLX-112 treatment on parkinsonian disability scores ($F(3,28) = 0.1995$, $P = 0.8958$) (Fig. 4A). Levels of parkinsonism cumulated over the 2-h period of peak effect (0–2 h) also revealed no effect of combination NLX-112 treatment (Friedman Statistic (FS) = 7.481, $P = 0.058$, Fig. 4B) with no significant

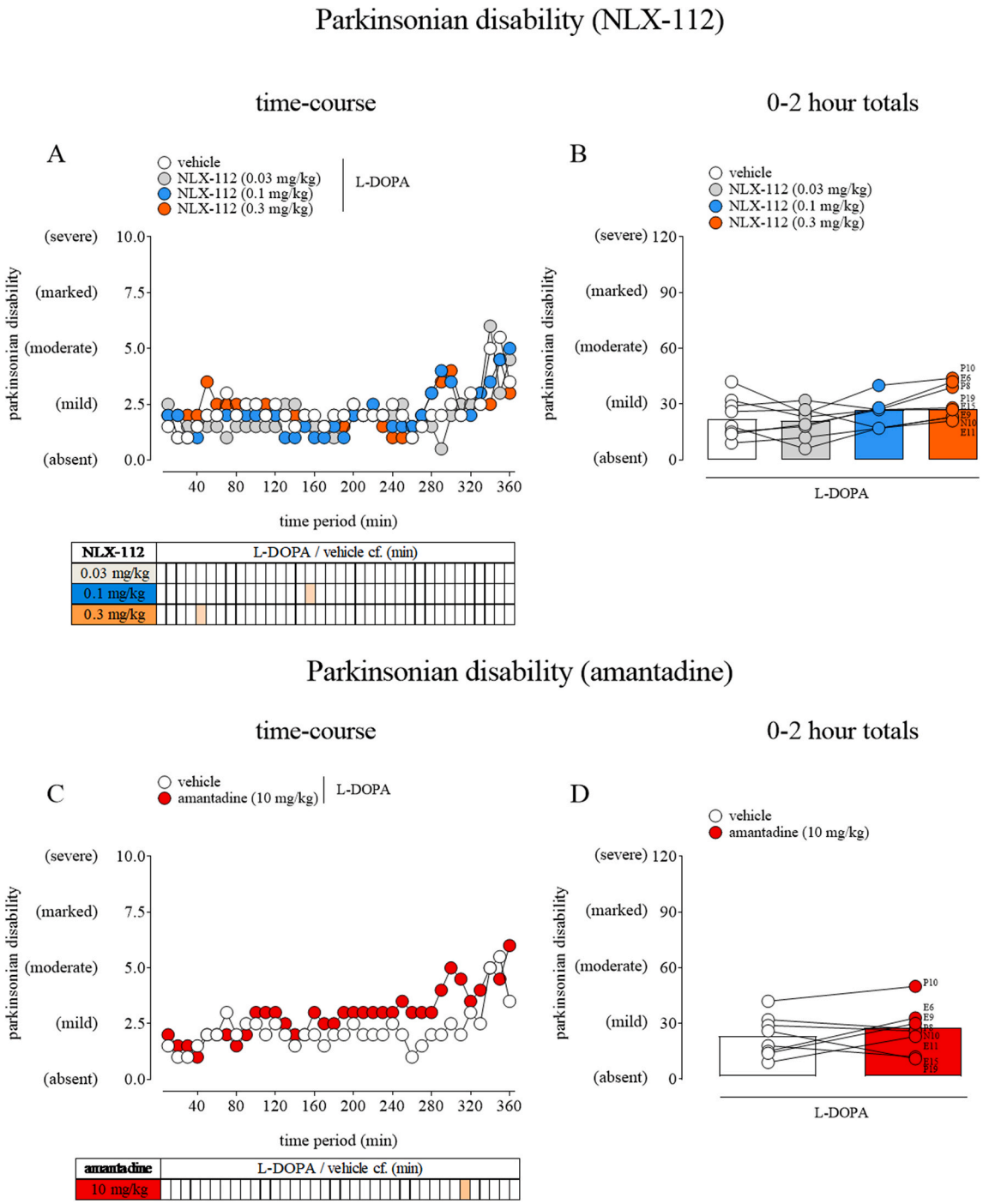

Fig. 4. Effect of acute administration of NLX-112 and amantadine on parkinsonian disability in the MPTP-lesioned macaque. Levels of parkinsonian disability were assessed over a 6 h period every 10 min (A and C) or cumulated across the 0–2 h period of peak-effect (B and D). Data are median (A and C) with individual values (B and D). N = 8 for all treatment groups. (*/**/*** respectively) represents $P < 0.05$, $P < 0.01$ or $P < 0.001$ vs. vehicle-treatment.

difference in levels of disability following NLX-112 treatment with combined L-DOPA compared to those seen following L-DOPA alone (all $P > 0.05$).

Over the 6 h observation period, amantadine did show a significant effect of treatment on parkinsonian disability ($F(1,14) = 4.691$, $P = 0.0481$) (Fig. 4C). However, at no time following L-DOPA administration were levels of disability following L-DOPA/amantadine treatment meaningfully different to those observed following L-DOPA/vehicle-treatment. Similarly, when cumulated over the 0–2 h period, there was no significant difference between disability levels in animals that received amantadine combination treatment to those that received L-DOPA alone ($P > 0.05$, Wilcoxon test, Fig. 4D).

4. Discussion

NLX-112 is a high affinity, high efficacy and high selectivity 5-HT_{1A} receptor agonist, being developed for the treatment of LID [15]. It has been shown to exert anti-LID activity in rodent (6-OHDA lesioned hemi-parkinsonian rats) and NHP (MPTP-lesioned parkinsonian marmosets) models of PD [11,16,18,19,22]. This is the first report of its effects in a higher NHP model, the MPTP-lesioned cynomolgus macaque. The main findings are as follows: (i) NLX-112 displayed clear and

dose-dependent anti-LID activity which was particularly robust during the first and second hours of observation; (ii) NLX-112 produced a significant improvement in the quality of L-DOPA benefit such that the proportion of 'bad-quality' on-time was reduced; (iii) Time to peak plasma level following oral administration of NLX-112 was approximately 30 min, consistent with the pronounced anti-LID effects at early time-points; (iv) The anti-LID activity of NLX-112 was observed in the absence of any meaningful impact on the anti-parkinsonian benefit of L-DOPA; and (v) the reference compound, amantadine, tested as a positive control, exhibited the expected anti-LID activity, validating the present study.

4.1. NLX-112 displays anti-LID activity without interfering with the anti-parkinsonian activity of L-DOPA

NLX-112 reduced LID scores in parkinsonian macaques at several time-points following drug administration. Most notably, the 0.1 mg/kg dose reduced LID score by about half (i.e. from "moderate" to "mild"), while the higher dose (0.3 mg/kg) almost totally abolished LID over the first hour post-dosing. Interestingly, NLX-112, at all doses tested and over the 6 h recording period, did not interfere with the beneficial activity of L-DOPA against parkinsonian disability. A finer analysis revealed that the amount of 'good quality on-time' elicited by L-DOPA was not modified, whilst NLX-112 reduced 'bad quality on-time'. These data extend to macaques the observations previously reported in MPTP-treated marmosets, where NLX-112 potently and efficiently reduced dyskinesia scores over a similar dose-range, and particularly at early time-points following administration. In fact, the present data show that NLX-112 attains peak plasma exposure at about 30 min, consistent with a maximal anti-dyskinetic effect in the first couple of hours following administration. Beyond this period, the duration of anti-LID activity of NLX-112 in MPTP-lesioned macaques was likely limited by the marked reduction in plasma levels seen within 2 h post-dosing, a pharmacokinetic profile which more closely resembles that of rats [23] and marmosets [11] than that of human subjects, where NLX-112 exhibits prolonged exposure ($t_{½}$ >20 h [24]).

It should be noted that, in addition to its anti-LID activity, NLX-112 may have additional beneficial properties in treatment of PD. In 6-OHDA-lesioned hemi-parkinsonian rats, NLX-112 stimulated rotation behavior when administered by itself, suggesting that it has a pro-motor effect [18]. This agrees with observations in MPTP-lesioned marmosets, where NLX-112 (0.1, 0.2 mg/kg PO), reduced motor disability scores by about half of the extent elicited by L-DOPA [11], suggesting that it may have motor facilitation effects of its own. Such activity of NLX-112 may be important in preserving the beneficial therapeutic-like effects of L-DOPA in this model.

In other studies, NLX-112 exhibits potent antidepressant-like activity in rodent behavioral tests [18] and elicits increases in extracellular DA concentrations in the medial prefrontal cortex of rats [25], consistent with potential activity against mood deficits. NLX-112 is also potently active in a range of rat pain models [26]. These pharmacological activities suggest that, as well as reducing dyskinesia, NLX-112 might alleviate non-motor symptoms such as depressive states, cognitive dysfunction and chronic pain experienced by many PD patients [27,28]. Such a broad profile of activity has not been previously reported for other serotonergic agonists and may reflect NLX-112's strikingly selective 'full agonist' effects at 5-HT_{1A} receptors coupled with its preferential activation of particular signaling pathways in vitro and in vivo [15,29]. Notably, the distinctive 5-HT_{1A} receptor binding profile of NLX-112 in brains of rat, cat and macaque [16] appears to translate well to human, as indicated by initial PET studies in healthy volunteers using [^{18}F]NLX-112 as a radiotracer [17]. This suggests that the promising profile of activity seen for NLX-112 in preclinical studies may be similarly seen in a clinical setting.

Amantadine, 10 mg/kg PO, reduced dyskinesia scores by about 30–50% over 4 h post-administration, in accordance with a previous study in cynomolgus macaques using a methodology similar to the one used here [30]. This result therefore facilitates comparisons between the present study and those carried out previously. In addition, because amantadine is clinically approved for use as an anti-dyskinetic drug, these observations suggest that selective and high-efficacy agonist targeting of 5-HT_{1A} receptors by NLX-112 may also have clinical utility for treatment of LID.

4.2. Absence of motor effects produced by NLX-112

An interesting point noted in the present study concerns the absence of unusual motor behaviors associated with 5-HT_{1A} receptor activation. In the present study, NLX-112 did not elicit any unusual motor effects in the macaques, whereas previous observations in MPTP-lesioned parkinsonian marmosets treated with NLX-112 or the reference 5-HT_{1A} receptor agonist, (+)8-OH-DPAT, found that they produced dose-dependent unusual behaviors, including sedation, scratching, wet dog shakes and dystonia in the tail. These motor signs are reminiscent of the 'serotonergic behavioral syndrome' observed upon acute (but not chronic) administration in rat, that include forepaw treading, flat body posture, Straub tail and slowed behavior [18,31,32].

However, NLX-112 has previously undergone regulatory 3-month toxicology studies in cynomolgus macaques and did not induce such behaviors. Moreover, no overt motor signs are observed when NLX-112 is administered to humans, the side-effects consisting principally of nausea and dizziness (unpublished observations and [24]). Taken together, these observations underline the necessity for caution when attempting to extrapolate side-effects profiles from one species to another. In addition, they suggest that macaques might be a more predictive species than marmosets (and rats) for side-effects of 5-HT_{1A} receptor agonists in humans.

The benign side-effects profile of NLX-112 observed in cynomolgus macaques and humans is in contrast to that described for amantadine. In macaques, amantadine at doses higher than 10 mg/kg interferes with the anti-parkinsonian action of L-DOPA [33,34] and, in PD patients treated for LID, amantadine causes a substantial incidence of neuropsychiatric symptoms such as hallucinations, confusion and delirium as well as peripheral side-effects including constipation, cardiovascular dysfunction including QT prolongation, orthostatic hypotension, nausea and oedema [35].

5. Conclusions

The present observations in MPTP-lesioned macaques chronically dosed with L-DOPA indicate that NLX-112 can exert robust anti-dyskinetic effects, critically, without liability to reduce the anti-parkinsonian benefit of L-DOPA. These data complement and extend previous findings observed in 6-OHDA-lesioned rats and MPTP-lesioned marmosets. NLX-112 could constitute a novel and innovative approach to combat LID in PD patients and provide an alternative or superior pharmacotherapy option for the patients in whom amantadine is poorly tolerated or without useful effect. Of note, the benign side-effect profile of NLX-112 in macaque and in human further positions the compound as a promising candidate for clinical trials in patients suffering from PD-LID or, potentially, from other movement disorders.

Declaration of competing interest

AN-T and RD are employees and stockholders of Neurolixis SAS. TJ and JB are consultants to, and stockholders of Atuka Inc.

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