Accepted Manuscript

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PII: S0304-3940(13)00260-7
DOI: <http://dx.doi.org/doi:10.1016/j.neulet.2013.02.066>
Reference: NSL 29651

To appear in: *Neuroscience Letters*

Received date: 24-12-2012
Revised date: 6-2-2013
Accepted date: 24-2-2013

Please cite this article as: S. Ayton, J.L. George, P.A. Adlard, A.I. Bush, R.A. Chernya, D.I. Finkelstein, The effect of dopamine on MPTP-induced rotarod disability, *Neuroscience Letters* (2013), <http://dx.doi.org/10.1016/j.neulet.2013.02.066>

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The effect of dopamine on MPTP-induced rotarod disability

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17 pages, 2 figures

Abstract

Dopamine depletion in Parkinson's disease (PD) results in bradykinesia and tremor. Therapeutic administration of the dopamine precursor, L-Dopa, alleviates these symptoms but dyskinesia's can manifest with chronic treatment. In the MPTP toxin mouse model of PD, lesion severity is often assessed by the rotarod behavioral assay. Dopamine depletion by MPTP is thought to induce rotarod behavioral decline. Here we surveyed rotarod behavior and striatal dopamine at timed intervals post MPTP. Paradoxically, rotarod disability coincided with gradual striatal dopamine restoration. L-Dopa supplementation exacerbated rotarod disability, whereas dopamine antagonism restored performance. Conclusion: dopamine restoration, not depletion, precipitates rotarod disability after MPTP intoxication, and caution should be applied when using this assay for MPTP.

Highlights

- MPTP-induced rotarod disability corresponds with time-dependent dopamine recovery in mice
- L-Dopa therapy worsens rotarod performance
- Dopamine antagonist, SCH23390 improves rotarod performance

Keywords

Parkinson's disease, MPTP, dopamine, rotarod

Abbreviations

SN: Substantia nigra pars compacta. PD: Parkinson's disease. L-Dopa: L-3,4-dihydroxyphenylalanine. MPTP: *1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine*. LIDS: L-Dopa induced dyskinesias

Introduction

The substantia nigra pars compacta (SN) is a mid-brain nucleus that supplies dopamine to the striatum. This nucleus degenerates in Parkinson's disease (PD) resulting in motor symptoms of the disease such as tremor and bradykinesia. These symptoms are alleviated by treatment with the dopamine precursor, L-Dopa (L-3,4-dihydroxyphenylalanine). L-Dopa utility is complicated by side effects including L-Dopa induced dyskinesias (LIDS) which become more frequent and have greater intensity as the disease progresses [7], highlighting that both dopamine depletion and excess can precipitate motor disability in PD.

PD has been extensively modeled with selective SN toxin, *1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine* (MPTP) [6], which is used as a platform for drug screening and to interrogate disease mechanism. MPTP lesions are typically assayed histologically (by stereological estimation of nigral neurons), biochemically (by quantifying striatal dopamine) and/or by a number of behavioral tests. A commonly applied motor behavior test is the rotarod. This instrument employs a bar that rotates at a fixed or variable rate, upon which mice are placed and required to walk until they fall off [21]. The time and/or the speed at which the mouse falls off is thought to reflect motor ability; however this technique has been applied in different ways with conflicting results [17,20,23,25].

The time of testing post MPTP intoxication has not been specifically investigated, and could influence rotarod performance. Deficits in rotarod behavior have been observed 1 day post intoxication [9,14,23]. Some reports have shown rotarod disability three days after MPTP administration [25], while others show no difference [23]. Similarly, conflicting reports are observed at 7 days post lesion [1,17,20]. Impairment is consistently observed 40 days or more post lesion [11,21]. In pursuit of clarity and a robust drug screening platform, we aimed to characterize rotarod behavior in mice after MPTP administration and investigate determinants influencing rotarod performance.

Methods

Mice

All mice were housed according to standard animal care protocols and fed standard laboratory chow and tap water *ad libitum*. C57/Bl6 male mice were obtained from Monash animal services (Monash University, Australia).

MPTP Time course: Mice were injected with four doses of 10mg/kg MPTP (intraperitoneal; Sigma) at 2 hour intervals. Mice were killed on day 3, 7, 10, 21 and 45 after intoxication and untreated littermate controls were used for comparison (n=10 per group). Treated and control mice were killed with sodium pentobarbitone (Lethabarb, Virbac Australia) and perfused with PBS via the aorta. The left SN and striatum were microdissected for dopamine measurement by HPLC-ECD [13]. The right SN was removed for stereological estimation of neurons as we previously described [15].

MPTP, L-Dopa, SCH23390 study: Mice were separated into control and experimental groups (n=10 per group). Experimental mice were administered MPTP (Sigma; 4x12.5mg/kg; I.P.).

Mice were housed for 21 days before rotarod challenge was performed on both control and experimental mice. Mice were then administered L-Dopa (Madopar, Roche; 100mg/kg levodopa, 25 mg/kg benserazide) by gavage and rotarod challenge was performed after 3 hours [16]. Mice were housed for a total of 55 days post MPTP injection after which rotarod challenge was again performed. All mice were then administered 0.1mg/kg SCH23390 (intraperitoneal, Sigma Aldrich), 1 hour before rotarod studies were conducted [18].

Rotarod

Mice were placed on a rotating rod (Panlab, Barcelona, Spain), spinning at 4 RPM. Lane width, 50mm, rod diameter 30mm. Once stabilized, mice were subjected to an incrementally increasing speed of 1 RPM per 8 seconds. Each animal underwent 3 trials. The length of time that the mice managed to remain on the rod, and the speed at which they fell off the apparatus, were recorded. The average of the three trials was used for further analysis.

Statistics

Before t-tests or ANOVA, a Leven's test for homogeneity of error variance was performed; all data sets compared in this study had homogeneous variance. Kaplan-Meier survival curves used the Mantel-Cox test of equality of survival distributions for the different levels of treatment. All statistical procedures were performed with SPSS version 14.0 software (Lead Technologies).

Results

1. Analysis of rotarod performance and dopamine physiology at timed intervals post MPTP intoxication.

Fifty mice administered MPTP at the same time were randomly assigned into 5 groups of 10, sequentially tested on the rotarod and euthanized at intervals of 3, 7, 10, 21 and 45 days post MPTP intoxication. These were compared to 10 non-lesioned controls. Rotarod performance was only significantly diminished 45 days post MPTP lesion, as measured by time spent on rotarod ($t(19)=2.52$, $P=0.021$; Fig 1A) and by speed survival ([Kaplan-Meier] $\chi^2(1,N=20)=6.6$, $P=0.01$; Fig 1B).

We surveyed perturbations of the nigral/striatal dopaminergic system that could influence altered rotarod performance at the different time points. The number of SN neurons showed initial rapid decline up to day 3 post MPTP, with a gradual decline thereafter (Fig 1C). Interestingly, the SN neuron number at day 21 was comparable to day 45 post lesion, despite rotarod disability emerging during this time. The occurrence of rotarod disability, despite no change in neuron number, may be resultant from changes in dopamine at the striatum. In contrast to the number of SN neurons, the striatal dopamine supplied by these neurons was most severely diminished 3 days post lesion and recovered gradually over the subsequent days (Fig 1D).

The recovery of dopamine at the striatum is thought to be influenced by two mechanisms of restoration. Firstly, early after the MPTP lesion the dopamine rate-limiting enzyme, tyrosine hydroxylase (TH), is nitrated and inhibited [2]. *de novo* TH expression could account for recovery of dopamine at the striatum. Second, although SN neurons deteriorate over the experimental period, remaining neurons undergo re-sprouting and dopaminergic terminals

increase at the striatum over time [4,24] with recovered TH protein levels [19] and dopamine [12]. These processes are best illustrated when the ratio of striatal dopamine per SN neuron is graphed (Fig 1E). The ratio declines immediately after injury, but recovers to be comparable to pre-lesion levels by 45 days.

2. L-Dopa administration impairs rotarod performance after MPTP

Since the restoration of dopamine at the striatum was associated with rotarod behavioral decline, we hypothesized that synaptic dysregulation of dopamine after neuron loss precipitated the disability. L-Dopa is the dopamine precursor used as pharmacotherapy in PD, however chronic L-Dopa therapy in PD patients can induce dyskinesia movement abnormalities [5]. Since poor rotarod performance post-MPTP was associated with elevated striatal dopamine, we investigated the effect of supplemented dopamine on rotarod performance post MPTP. Mice were assayed by rotarod 21 days after MPTP administration and compared with untreated controls. We choose a moderately high dose of L-Dopa (100mg/kg) in order to uncover a response, but not so high as to precipitate disability in health mice. We hypothesized that differences in dopamine handling between control and lesioned mice when the system is stressed by L-Dopa might account for differential performance on the rotarod. MPTP and untreated control mice were administered L-Dopa 3 hours before undergoing the rotarod challenge. The treatments resulted in significant differences (Two-factor ANOVA: $F(3,39)=8.1, P=0.007$; Fig 2A). Simple main effects analysis revealed that MPTP alone did not cause a rotarod deficit, nor did L-Dopa supplementation to normal mice ($P>0.05$), however MPTP-lesioned mice remained on rotarod for less time after they received L-Dopa when compared to non-lesioned/L-Dopa supplemented ($P=0.013$) and lesioned/non-supplemented mice ($P=0.001$).

Mice treated with L-Dopa 21 days after MPTP intoxication showed reduced speed survival on the accelerating rotarod ([Kaplan-Meier] $\chi^2(1,n=20)=9.5$, $P=0.002$; Fig 2B). No difference in rotarod speed survival was observed between control mice +/- L-Dopa, and mice intoxicated with MPTP without L-Dopa ($P>0.05$).

3. D₁ antagonist SCH23390 rescues MPTP rotarod deficit

To determine if physiological dopamine restoration was the cause of MPTP induced rotarod disability observed at later time points, we administered SCH23390, a D₁ receptor antagonist, to MPTP-treated mice. The striatum is rich in D₁ receptors that stimulate the post synaptic cells in response to dopamine; over-stimulation can cause movement disorders and possibly dyskinesia [3]. Mice were housed for a total of 55 days post MPTP injection after which rotarod challenge was again performed. All mice were then administered 0.1mg/kg, one hour before rotarod studies were conducted [18]. There was a significant toxin/treatment effect on rotarod performance (Two-factor ANOVA: $F(3,39)=3.1$, $P=0.04$; Fig. 2C). Simple main effects analysis revealed that after 55 days, MPTP administered mice fell before controls ($P=0.009$) and this disability was rescued by SCH23390 treatment ($P=0.018$). SCH23390 had no effect on non-lesioned mice ($P>0.05$). 55 days post MPTP lesion, mice showed reduced speed survival compared to control ([Kaplan-Meier] $\chi^2(1,n=20)=6.7$, $P=0.01$) which was recoverable with D₁ receptor antagonist SCH23390 ([Kaplan-Meier] $\chi^2(1,n=20)=4.5$, $P=0.034$; Fig. 2D). Non-lesioned mice treated with SCH23390 had comparable speed survival on the rotarod ($P>0.05$).

Discussion

The prevailing hypothesis is that depletion of dopamine at the striatum causes rotarod disability, indeed this is the very reason why it is employed in the MPTP paradigm. The present study however, argues that dopamine depletion has little to no effect on rotarod performance. Three days post MPTP administration, striatal dopamine levels were the lowest recorded in this study (Fig. 1D), probably owing to TH inactivation [2], yet rotarod performance was preserved (Fig 1A,B). Similarly, administration to control mice of the D₁ antagonist, SCH23390, did not decrease latency to fall or speed survival in normal mice (Fig. 2C,D). Dopamine reduction therefore is not consistent with rotarod disability. The experiments suggest that raising dopamine levels with L-dopa (Fig 2A,B) or allowing dopamine levels to approach pre-MPTP levels (Fig 1D), gives rise to impaired rotarod performance. However, there is no indication that the dopamine levels are excessive in either model. Together these data have implications for the use and interpretation of the rotarod assay.

Our observations of dopamine-mediated behavioral disability in mice may be analogous to dopamine therapy in PD, where chronic L-Dopa treatment often precipitates dyskinesia [7]. Therefore, either decreased striatal dopamine (e.g. PD bradykinesia) or excess striatal dopamine (e.g. L-Dopa associated dyskinesia) can perturb motor function and there is a need to consider both types of disability when interpreting motor behavior assays. L-dopa therapy can also cause noradrenalin levels to rise in the brain, which potentially could have influenced the mouse performance in the assay, however prior research has shown that noradrenalin was not altered in the brain at the dose of L-dopa used and time at which the mice were tested [8].

The rotarod behavioral task has been employed to assay PD motor related physiology [11], pharmacology [10] and genetics [20], yet interpretation of the data is complicated by conflicting reports. This study provides insight into incongruent results previously presented. The timing of assay post MPTP is of particular importance, as the assay is sensitive to dopamine fluctuations that are observed after intoxication. Rotarod disability is most consistently reported very early (Day 1)[9,14,23] or late (>40days) [11,21] post MPTP, while intermediate timeframes yield inconsistent results [17,20,22,23,25].

Given the cumulative evidence, the rotarod task is unlikely to assay the state of SN degeneration accurately. However, given that methodological approaches to the rotarod (e.g. stable speed/increasing speed, maximum speed, rotarod diameter, training) are variably employed across research groups, and different mouse strains are differentially affected by MPTP [23], it is conceivable that other approaches may be more sensitive to the size of the lesion. Researchers using this behavioral assay are encouraged to interpret their own results and methodology in light of the current findings. Importantly, rotarod is frequently employed to screen compounds for efficacy in protection against MPTP degeneration. If, as shown here however, rotarod performance reflects the combination of both dopamine perturbation and nigral degeneration, the researcher must question if the compound has any effect on dopamine levels, or cellular release of dopamine, that might account for rotarod 'rescue'. For example, post synaptic D1 dopamine antagonism was shown to improve rotarod performance (Figure 2C,D), yet this approach would be a poor choice for PD pharmacotherapy, even though agents that antagonize dopamine would screen positive in the assay.

Previously it was thought MPTP-induced rotarod disability was caused by dopamine depletion resulting in bradykinesia. This work shows that rotarod disability more accurately reflects

dopamine excess and dopamine dysregulation. Caution should be applied for interpretation of this assay, and the time of behavioral assessment post MPTP should be chosen with care.

Acknowledgements

Supported by funds from the Australian Research Council, the Australian National Health & Medical Research Council, the CRC for mental health, and Operational Infrastructure Support Victorian State Government.

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Figure legends

Figure 1. Rotarod performance and nigrostriatal parameters at 3, 7, 10, 21 and 45 days after MPTP intoxication. Five groups of MPTP-treated mice (n=10 each) underwent the rotarod on the post-MPTP treatment day indicated. Ten control mice that did not receive MPTP were used as comparison (designated T=0). **A.** The latency to fall off the rotarod was recorded. **B.** Mice were subjected to increasing rotarod RPM, the speed at which mice fell was recorded. **C.** The mice were then euthanized on the days indicated. The left brain hemisphere was removed and SN sectioned. Nigral neurons were counted by unbiased stereology. **D.** The right striatum was microdissected and dopamine levels were measured. **E.** The ratio for the amount of striatal dopamine per SN neuron was graphed. Error bars represent standard error. * $P < 0.05$

Figure 2. The effect pharmacological manipulation of dopamine on rotarod performance after MPTP. **A.** Mice were administered MPTP and housed for 21 days then assayed on the

rotarod apparatus. Mice were next administered L-Dopa and subsequently assessed by rotarod.

B. Mice were subjected to increasing rotarod RPM; the speed at which mice fell was recorded before and after L-Dopa administration. **C.** 55 days post MPTP lesion, mice were assayed by the rotarod. Mice were then administered D1 selective antagonist, SCH23390 before further rotarod analysis **D.** 55 day post MPTP lesion mice were subjected to increasing RPM on the rotarod before and after SCH23390 treatment and the speed at which mice fell was recorded. Error bars represent standard error. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

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Date:

2013-05-24

Citation:

Ayton, S., George, J. L., Adlard, P. A., Bush, A. I., Cherny, R. A. & Finkelstein, D. I. (2013). The effect of dopamine on MPTP-induced rotarod disability. NEUROSCIENCE LETTERS, 543, pp.105-109. <https://doi.org/10.1016/j.neulet.2013.02.066>.

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