Dose- and time-dependent therapeutic and adverse effects of Mucuna pruriens extract in the 6-OHDA rat model of Parkinson’s disease

Gramsbergen, Jan Bert; Jørgensen, Monica; Christensen, Lars Porskjær

Published in:
Journal of Neurochemistry

Publication date:
2011

Document version
Publisher's PDF, also known as Version of record

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal?

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Dose- and time-dependent therapeutic and adverse effects of *Mucuna pruriens* extract in the 6-OHDA rat model of Parkinson’s disease

Jan Bert Gramsbergen1, Monica Jørgensen2 and Lars Parajal Christensen2

1Institute of Molecular Medicine, 2Department of Biotechnology and Environmental Technology, University of Southern Denmark, Odense, Denmark

Introduction

In traditional Ayurvedic Indian medicine, preparations of *Mucuna pruriens* seeds (fig. 1) are used in the treatment of Parkinson’s disease (PD). It has been suggested that *Mucuna* preparations may possess some clinical advantages over conventional, synthetic L-DOPA/carbaltropine preparations, including a rapid onset of action and longer on time with consequent increases in akinesias (Katzenschlager et al. 2004, Kasture et al. 1999, Liu et al. 2010). Alkaloidic extracts of *M. pruriens* are rich in L-DOPA, but other, as yet unknown compounds may contribute to its therapeutic effects.

Objectives

1. Therapeutically effective doses of a methanol extract of *M. pruriens* seeds and of (synthetic) L-DOPA without additional levodopa.
2. Abnormal involuntary movements (AIMs) during chronic treatment at therapeutically effective doses.
3. Dose-dependent effects of *Mucuna* extract and L-DOPA in the presence of benzerazide (peripheral decarboxylase inhibitor).
4. Effects of a *Mucuna* preparation lacking L-DOPA.

Materials and Methods

Twenty-four *M. pruriens* (6-OHDA) lesioned rats were used (Sprague Dawley, males, 6 µg 6-OHDA free base in 2 µl saline, 0.1% ascorbic acid stereotaxically injected into left medial forebrain bundle), all displaying significant contralateral forelimb akinesia and amphetamine-induced rotations 2-3 weeks postlesion. Ten rats were assigned to a chronic “dose-finding” study (series M1, two periods of 4 weeks treatment) and 14 rats assigned to a comparative study of therapeutic and adverse effects of chronic *Mucuna* versus L-DOPA treatments without additives (series M2-D2, 4 daily injections in week 1, 5 injections in week 2 and 7 injections in week 3). After a wash-out period of 4 weeks the latter group of 14 rats was used to study effects of *Mucuna* and L-DOPA in the presence of benzerazide and of *Mucuna* extract lacking L-DOPA.

Forelimb akinesia, therapeutic and adverse effects (i.e. abnormal involuntary movements, AIMs) of *Mucuna* or L-DOPA treatments were assessed using the cylinder test, recorded on video and rated on a scale from 0-6 (Lundblad et al. 2002).

*Mucuna* extract containing ca. 20% L-DOPA (dry weight extract) was prepared and the chemical profiles of different batches were determined by HPLC with electrochemical detection (Gramsbergen et al. 2002).

Results

**Figure 1.** Therapeutic dose-finding: *Mucuna* without benzerazide.

**Figure 2.** Therapeutic effect chronic treatment.

**Figure 3.** Effects of benzerazide on therapeutic and adverse effects.

**Figure 4.** Long Duration Response days after treatment.

**Figure 5.** Time (min) procy. ~45 µg benzerazide.

**Figure 6.** Specific dopamine receptor occupancy.

**Figure 7.** Cumulative drug responses following chronic *Mucuna* or L-DOPA treatments. *Mucuna* extract (hatched bars) vs. L-DOPA (solid bars) treatments. 20 mg/kg i.p. (week 2-3) and 25 mg/kg (day 19-21). Two-way ANOVA: p<0.05 effect of treatment, N=7 vs N=7.

**Figure 8.** Rotational behavior following combined *Mucuna*+benserazide or L-DOPA+benserazide treatments. Equivalent DOPA doses of 12.5, 25 and 50 mg/kg i.p., all treatments were given in addition to 45 µg benzerazide and compared with L-DOPA + benserazide. Two-way ANOVA: no significant difference between treatment groups, N=7 vs N=7.

**Figure 9.** Cumulative drug responses following chronic *Mucuna* or L-DOPA treatments. *Mucuna* extract (hatched bars) vs. L-DOPA (solid bars) treatments. 20 mg/kg i.p. (week 2-3) and 25 mg/kg (day 19-21). Two-way ANOVA: p<0.05 effect of treatment, N=7 vs N=7.

**Figure 10.** Cumulative drug responses following chronic *Mucuna* or L-DOPA treatments. *Mucuna* extract (hatched bars) vs. L-DOPA (solid bars) treatments. 20 mg/kg i.p. (week 2-3) and 25 mg/kg (day 19-21). Two-way ANOVA: p<0.05 effect of treatment, N=7 vs N=7.

**Figure 11.** Cumulative drug responses following chronic *Mucuna* or L-DOPA treatments. *Mucuna* extract (hatched bars) vs. L-DOPA (solid bars) treatments. 20 mg/kg i.p. (week 2-3) and 25 mg/kg (day 19-21). Two-way ANOVA: p<0.05 effect of treatment, N=7 vs N=7.

Conclusions

- Chronic *Mucuna* treatments induced a sustained motor improvement that took days to build up and lasted for 3-4 days after cessation of treatment, i.e., similar to the long duration response of L-DOPA treatment. Determination of the lowest, therapeutically effective doses required therefore repeated dosing.
- *Mucuna* extract was more effective than (synthetic) L-DOPA at equivalent L-DOPA doses of 12.5-25 mg/kg (i.p.). However, chronic treatment with these doses of *Mucuna* extract caused also more severe AIMs (predominantly limbic, but also axial and orofacial dyskinesias) than L-DOPA alone.
- Co-treatments with benzerazide in *Mucuna* or L-DOPA-sensitized rats, did not reveal differences in therapeutic or adverse effects of *Mucuna* or L-DOPA.
- *Mucuna* extract lacking L-DOPA did not show any therapeutic effect.

This study in 6-OHDA lesioned rats did not reveal clinical benefits of *Mucuna* treatment over conventional L-DOPA therapy.

Acknowledgements

This work is supported by Veluxfonden and Dansk Parkinsonforening.

References