

Comparison of neuroprotective and neurorescue capabilities of rasagiline and selegiline, against lactacystin induced nigrostriatal degeneration

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INTRODUCTION

Nigrostriatal neurodegeneration in Parkinson's disease (PD) has been postulated to be caused by a combination of damaging processes, including mishandling of cellular proteins, mitochondrial defects, and oxidative stress. Pharmacological strategies designed to interfere with these pathological pathways may effectively counteract the degeneration. Monoamine oxidase type B (MAO-B) inhibitors of propargylamine family have been extensively investigated for their potential neuroprotective properties. Selegiline (N-propargyl-methamphetamine), the prototype of this class of compounds, has shown antioxidant and neuroprotective effects in experimental studies, although the neuroprotective activity in PD patients has remained controversial. Comparatively, rasagiline [N-propargyl-(1R)-aminindan], the most potent propargylamine, which is different from selegiline in that it is not metabolized to amphetamine and/or methamphetamine, has shown to exert neuroprotective effects against a variety of insults in both in vitro and in vivo models. Recently rasagiline has been indicated to possess neurorescue effects in MPTP mice. Since inhibition of proteasomal function contributes to the neurodegeneration in PD, in present study, we explored and compared the neuroprotective and neurorescue potentials of rasagiline and selegiline in mice against nigrostriatal dopamine (DA) neurons degeneration induced by the proteasome inhibitor, lactacystin.

METHODS

60 C57BL/6 mice were bilateral injected with lactacystin (1.25ug in 2ul NS v.s. vehicle control at equal volume) into medial forebrain bundle (MFB). Continuous intraperitoneal administration of rasagiline (0.2mg/kg) or selegiline (1mg/kg/day) was introduced 7 days before or after the microinjection. The animals were sacrificed 28 days after the microinjection with lactacystin. Rotarod and locomotive activity tests were performed weekly to evaluate the behavioral changes. Proteasome activity assay were applied to determine the proteasomal dysfunction produced by lactacystin. Neurodegeneration and nigrostriatal deficiency induced by lactacystin were indicated by immunostaining of TH-positive cells and HPLC assay of DA and its metabolites. Immunostaining of CD11b-positive cells were introduced to indicate the microglial activation after microinjection of lactacystin.

Fig.1 Neuroprotective and neurorescue capabilities of rasagiline or selegiline against lactacystin-induced neurodegeneration in SN

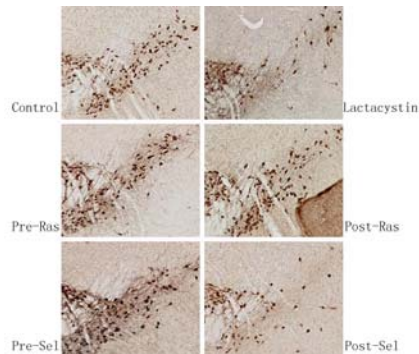


Fig.2 Capabilities of rasagiline and selegiline against nigrostriatal deficiency

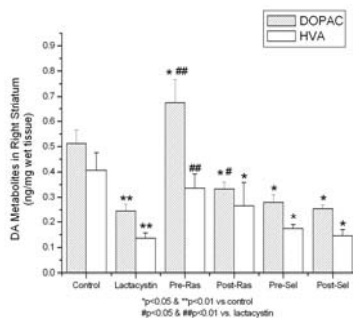
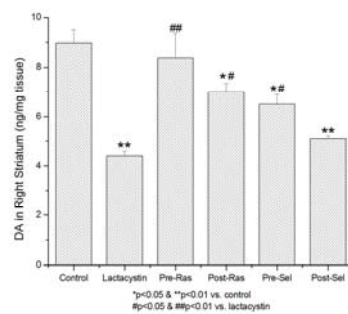


Fig.3 Proteasome activity in ventral midbrain

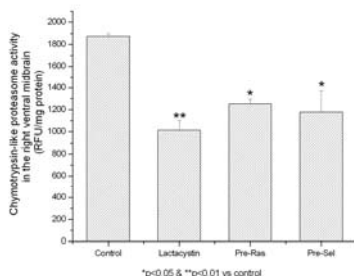


Fig.4 Rasagiline and selegiline against microglial activation

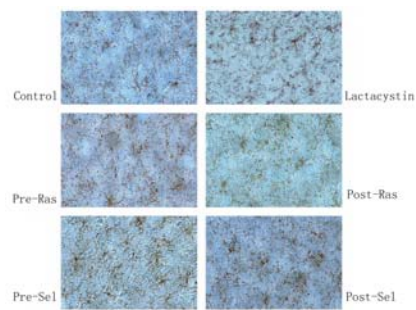


Fig.5 Time-dependent locomotive changes

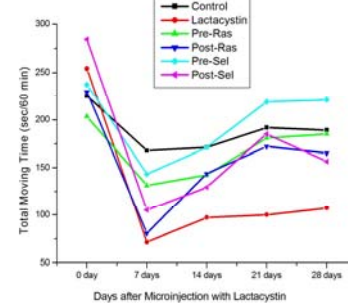
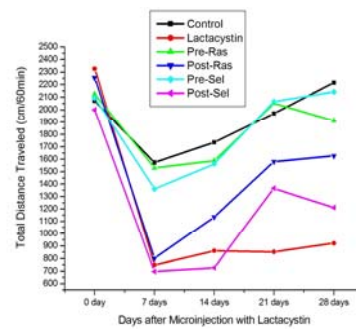
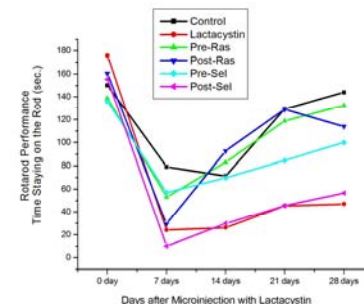


Fig.6 Time-dependent Rotarod Performance



RESULTS

One month after microinjection with lactacystin (1.25ug/side) into MFB, around 60% loss of nigral DA neurons ($p < 0.01$) and about 30% inhibition of proteasomal activity ($p < 0.05$) were evident in ipsilateral SN (Fig.1, 2, 3). A moderate activation of microglia still could be seen 28 days after the microinjection (Fig. 4). Severe movement dysfunctions had been indicated by both rotarod and locomotor tests since the 7th day after lactacystin was injected, and there were no significant improvements until the animals were sacrificed (Fig. 5, 6). Pretreatment with rasagiline or selegiline could effectively alleviate the movement decline. While post-treatment with rasagiline but not selegiline could improve the movement dysfunctions (Fig. 5). Both rasagiline and selegiline exerted a significant neuroprotective effect against lactacystin-induced DAergic neurodegeneration. The drugs attenuated DA neurons loss by 55.0% and 34.3%, respectively ($p < 0.01$). Comparatively, only rasagiline but not selegiline had shown a neurorescue potential by attenuating DA neurons loss by 31.2% ($p < 0.01$) (Fig. 2). However, both drugs alleviated microglial activation with equal potency (Fig. 4). Furthermore, both rasagiline and selegiline showed a moderate, but statistically not significant, protection against lactacystin-induced inhibition of proteasomal activity (Fig. 3).

CONCLUSIONS

- Both rasagiline and selegiline exert neuroprotective effects against neurodegeneration induced by UPS failure, while rasagiline is more potent.
- Only rasagiline but not selegiline possesses neurorescue potential against neurodegeneration induced by UPS failure.
- The mechanisms of these neuroprotective and neurorescue properties require further investigation.

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