The MAO-B inhibitor Rasagiline induced Neuroprotection in PC12 Dopaminergic Neuronal model by regulation of the Akt/Nrf2 redox signaling pathway

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Parkinson's disease (PD) is a progressive, neurodegenerative disorder. One strategy for PD treatment relies on inhibition of dopamine metabolism by inhibiting the monoamine oxidase B (MAO- B). Selegiline (L-Deprenyl) and Rasagiline (Azilect) are selective MAO-B inhibitors which provide symptomatic benefit in PD treatment and found to exert neuroprotective effects. However, slowing or halting the neurodegenerative process has not yet been accomplished in PD patients using these drugs and therefore, neuroprotection is still considered an unmet clinical need. We investigated in the PC12 dopaminergic neuronal model, exposed to oxygen-glucose deprivation (OGD), the neuroprotective signalling pathways of these MAO-B inhibitors (1-3). Exposure of neurons to OGD for 3 hr followed by 18 hr of reoxygenation caused about 30-40% cell death. Rasagiline induced dose-dependent 50% neuroprotection when added either before or after the OGD insult. Clorgyline, a monoamine oxidase-A inhibitor, did not protected the neurons towards OGD-induced cell death suggesting that the neuroprotective effect of Rasagiline is independent of MAO A inhibition (4,5). Selegiline reduced OGD-induced apo-necrotic cell death by 30%. L-methamphetamine, a major Selegiline metabolite, but not 1-R-aminoindan, the major Rasagiline metabolite, enhanced OGD-induced cell death by 70%. Concomitant exposure of the cultures under OGD, to a combination of either Selegiline and L-methamphetamine or Rasagiline and 1-R-Aminoindan, indicated that L-methamphetamine, but not 1-R-Aminoindan, blocked the neuroprotective effect of the parental drug. These results suggest a neuroprotective advantage of Rasagiline over Selegiline (6). Both survival kinases phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK) were activated by Rasagiline in relation to the neuroprotective effect. Rasagiline-induced nuclear shuttling of transcription factor Nrf2 and increased the expression of antioxidant heme oxygenase-1 (HO-1). Rasagiline decreased production of neurotoxic reactive oxygen species and preserved mitochondrial membrane integrity. These results indicate that Rasagiline provides neuroprotection via improving mitochondrial integrity, as well as increasing mitochondria-specific antioxidant enzymes by a mechanism involving the Akt/Nrf2 redox signaling pathway. These findings may be exploited to develop third generation of MAO-B inhibitors with improved neuroprotection in PD therapy.

Biography

Philip Lazarovici graduated in pharmacology and toxicology at the Hebrew University, post graduated on neurobiology at the Weizmann Institute of Science and conducted neurochemical and molecular research at the National Institutes of Child Health and Human Development, NIH, Bethesda, USA. He was a visiting professor in the School of Biomedical Engineering, Science and Health Systems, Drexel University and Faculty of Engineering, Temple University, Philadelphia, USA. He is a member of 15 international and national academic societies, published about 250 scientific articles and reviews and edited six books.

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