

LY503430: Pharmacology, Pharmacokinetics, and Effects in Rodent Models of Parkinson's Disease

¹Michael J. O'Neill, ¹Tracey K. Murray, ²Michael P. Clay,
²Terry Lindstrom, ²Charles R. Yang, ²Eric S. Nisenbaum

¹Eli Lilly & Co. Ltd., Lilly Research Centre, Windlesham, Surrey, UK;
²Eli Lilly & Co., Lilly Corporate Center, Indianapolis, USA

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ABSTRACT

Glutamate is the major excitatory transmitter in the brain. Recent developments in the molecular biology and pharmacology of the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-subtype of glutamate receptors have led to the discovery of selective, potent and systemically active AMPA receptor potentiators. These molecules enhance synaptic transmission and play important roles in plasticity and cognitive processes. In the present studies we characterized a novel AMPA receptor potentiator, LY503430, on recombinant human GLU_{A1-4} and native preparations *in vitro*, and then evaluated the potential neuroprotective effects of the molecule in rodent models of Parkinson's disease. Results indicated that at submicromolar concentrations LY503430 selectively enhanced glutamate-induced calcium influx into HEK293 cells transfected with human GLU_{A1} , GLU_{A2} , GLU_{A3} , or GLU_{A4} AMPA receptors. The molecule also potentiated AMPA-mediated responses in native cortical, hippocampal and substantia nigra neurones. LY503430 had good oral bioavailability in both rats and dogs. We also report here that LY503430 provided dose-dependent functional and histological protection in animal models of Parkinson's disease. The neurotoxicity following unilateral infusion of 6-hydroxydopamine (6-OHDA) into either the substantia nigra or the striatum of rats and that following systemic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice were reduced. Interestingly, LY503430 also had neurotrophic actions on functional and histological outcomes when treatment was delayed until well after (6 or 14 days) the lesion was established. LY503430 also produced some increase in brain derived neurotrophic factor (BDNF) in the substantia nigra and a dose-dependent increase in growth asso-

Address correspondence and reprint requests to: Dr. Michael J. O'Neill, Eli Lilly & Co., Ltd., Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK.
Tel.: +44 (1276) 483547; Fax: +44 (1276) 483525. E-mail: Oneill_Michael_J@Lilly.com

ciated protein-43 (GAP-43) expression in the striatum. Therefore, we propose that AMPA receptor potentiators such as LY503430 offer the potential of a new disease modifying therapy for Parkinson's disease.