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Anti-Dyskinetic activity in non-human Parkinsonian primates of AV 101 a prodrug acting as a NMDA receptor glycine antagonist

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The primary deficit in Parkinson's disease (PD) is the decrease of dopamine caused by the loss of brain dopamine neurons. The most common treatment for PD is L-Dopa, the precursor of dopamine but motor complications such as dyskinesias develop with time. Glutamate is the most abundant brain excitatory neurotransmitter. Glutamatergic neurotransmission is increased in the brain in PD and L-Dopa-induced dyskinesias (LID). Antagonists of ionotropic glutamate N-methyl-D-aspartate receptors (NMDA) reduce dyskinesias in PD patients but direct acting NMDA antagonists have side effects limiting their therapeutic utility. Blockade of NMDA receptors indirectly at the glycine (GlyB) co-agonist site affords a better safety profile. We showed that increasing kynurenic acid (KYNA) levels, an endogenous GlyB inhibitor, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys through blockade of kynurenine 3-hydroxylase, reduced LID. L-4 chlorokynurenine (4-Cl-KYN or AV-101) developed by VistaGen is a pro-drug of 7-chlorokynurenic acid (7 Cl KYNA), a potent and selective GlyB antagonist. 4-Cl-KYN, but not 7 Cl KYNA, crosses the blood-brain barrier. We hypothesize that AV-101 will decrease LID. The methodology used measures of motor behaviour in MPTP monkeys administered AV-101 with L-Dopa. Findings in a first pilot study using three MPTP monkeys showed that AV-101 reduced LID. Then a study using six other MPTP monkeys with already developed LID showed that AV-101 administration maintained their L-Dopa antiparkinsonian response measured with their locomotion (using the electronic monitoring system Vigie Primate, Viewpoint), and their antiparkinsonian score (using the Laval University Parkinson disability scale). AV-101 alone or with L-Dopa had no non-motor adverse effects in MPTP monkeys. AV-101 reduced LID in MPTP monkeys as measured with the Laval University dyskinesia scale. In conclusion, antidyskinetic activity of AV-101 comparable to amantadine was observed in nine MPTP monkeys. Better than amantadine, with its known side effects, we observed no adverse effects with AV-101. This excellent safety profile is consistent with multiple AV-101clinical studies.

Biography

Thérèse Di Paolo has research expertise in animal models of Parkinson's disease (PD) using behavioural, pharmacological and biochemical approaches. She has experience in post-mortem investigation of brains of PD patients with motor complications more specifically levodopa-induced dyskinesias (LID). She investigates LID in the MPTP monkey model the best model of this motor complication with excellent translational value for PD. She investigates the inhibition of LID in animals already displaying dyskinesias and tested numerous compounds some of which have later gone into clinical trials. She also investigates inhibition of the development of LID in de novo MPTP monkeys and the underlying biochemical correlates. She also studies the MPTP mouse model of PD to find neuroprotective compounds with a focus on repurposing drugs already in clinical use to treat endocrine conditions. Since 1986 she has published more than 122 articles with MPTP animals.

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