

## Excitatory amino acids and Parkinson's disease

SIR:

Recently, Klockgether and Turski proposed that antagonists of excitatory amino acids may be beneficial in the treatment of Parkinson's disease<sup>1</sup>. This suggestion, previously put forward by others<sup>2-4</sup>, is supported by recent findings of animal experiments as well as by clinical data. On the basis of these findings, a somewhat different conclusion can be drawn about the role of glutamate in the basal ganglia nuclei.

When either kynurenic acid, a broad-spectrum antagonist of glutamatergic transmission<sup>5</sup>, or 2-amino-5-phosphonopentanoic acid (AP-5), a selective antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, is injected locally into the striatum of rats, they exert stimulatory effects on behaviour, for example, continuous forward locomotion and stereotyped sniffing<sup>6</sup>. Striatal output neurons bearing NMDA receptors may be considered to mediate these responses since striatal lesions with quinolinic acid produce similar effects. Quinolinic acid acts preferentially via NMDA receptors and destroys spiny projecting neurons that use GABA or substance P as their transmitter<sup>7</sup> (striatal interneurons and striatal afferent fibres are spared). Further, neuroleptic-induced catalepsy, an animal model of Parkinson's disease is antagonized by AP-5 (Geltz, U. and Schmidt, W. J., unpublished observations) or prevented by striatal kainate<sup>8</sup> or quinolinic acid lesions<sup>9,10</sup>. Furthermore, when NMDA itself is injected into the striatum, it exerts just the opposite behavioural effects: it reduces locomotion, sniffing, rearing and feeding<sup>11</sup>.

Systemic administration of the NMDA antagonist MK-801 is in line with the idea outlined above: MK-801 stimulates locomotion in monoamine-depleted mice<sup>3</sup> and reverses neuroleptic-induced catalepsy<sup>4</sup>. As is known from local injections of dopamine antagonists or agonists, the effects of intrastriatal injections are not as pronounced as systemic injections with regard to their cataleptogenic or anti-cataleptic effects, respectively. Extrastriatal mechanisms may therefore contribute to the pronounced anticataleptic effects of MK-801. Thus, in animal experiments at least, NMDA antagonists act to some extent like dopamine agonists. This suggests that this class of drugs may have anti-parkinsonian potential.

Klockgether and Turski<sup>1</sup> account for parkinsonian symptoms by suggesting an imbalance between the glutamatergic system projecting from the cortex via the subthalamic nucleus to the basal ganglia output nuclei on the one hand and the GABAergic striatopallidal and striatonigral projection to these nuclei on the other. However, the obvious evidence of an involvement of the dopamine/glutamate balance in the caudate-putamen (striatum) provides a more parsimonious interpretation and may also explain the imbalance in the striatal output systems.

Further evidence supporting the view of NMDA antagonists as putative anti-parkinsonian drugs derives from recent findings concerning the mechanism of action of memantine (1-amino-3,5-dimethyl adamantane). This substance reverses neuroleptic-induced catalepsy in rats, and is used clinically in the treatment of spasticity and Parkinson's disease. Recently Bormann<sup>12</sup> reported, on the basis of patch-clamp record-

ings of NMDA-activated membrane currents, that memantine, like MK-801, blocks NMDA receptor channels in cultured neurons. At the same time, Kornhuber *et al.*<sup>13</sup> showed that memantine displaces [<sup>3</sup>H]MK-801 at therapeutic concentrations in postmortem human frontal cortex.

Since the dopamine mimetic effects of memantine are not pronounced enough to account for its therapeutic potency, these new results showing that memantine is an NMDA receptor antagonist provide an exciting alternative explanation of the anti-parkinsonian effects of this drug.

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