SIR:

Girault et al.\(^1\) draw similar conclusions from their studies of the regulation of protein phosphorylation by dopamine and glutamate in striatonigral neurones as we did on the basis of behavioural findings, i.e. that dopamine and glutamate may exert opposite effects within the neostriatum\(^2\). Admittedly, this view is over-simplified, but this transmitter balance does seem to be relevant to the parkinsonian symptoms akinnesia and rigidity. Several effects noted by Girault et al.\(^3\) are paralleled by behavioural findings. From the model of DARPP-32 phosphorylation one may conclude that a certain degree of D\(_1\) stimulation is a prerequisite for facilitated DARPP-32 phosphorylation by NMDA antagonists. When we compared reserpine-induced catalepsy with haloperidol-induced catalepsy the results bore out this prediction: while the NMDA antagonist, MK-801 failed to restore complete mobility in monoamine-depleted rats (5 mg/kg reserpine i.p.), it did restore mobility in haloperidol-pretreated rats\(^4\). Haloperidol blocks mainly D\(_2\) receptors, leaving D\(_1\) sites active. Thus, some remaining monoamines, or D\(_1\) activity, appear to be necessary for NMDA antagonists to exert full anticataleptic effects.

We agree with Girault et al.\(^5\) that the use of NMDA antagonists like phencyclidine or MK-801 in the treatment of Parkinson's disease is limited because of the psychotomimetic actions of these drugs (as predicted by the glutamate hypothesis of schizophrenia\(^6\)) and because of amnesic effects. In rats, MK-801 produced short-term memory deficits in the eight-arm radial maze\(^7\) as well as attentional deficits\(^8\). MK-801 in doses above 0.1 mg/kg i.p. induced strong stereotyped sniffing that may be considered to represent an animal model for schizophrenia. Several antipsychotics, including haloperidol and clozapine, potently antagonized this form of stereotypy\(^9\).

Although, at present, the side-effects of NMDA antagonists limit their use in the therapy of Parkinson's disease, the NMDA receptor complex offers several possibilities for specific pharmacological intervention. (1) NMDA antagonists may be useful in low doses, when given in combination with other monoamine or D\(_1\) agonists. (2) Regional subtypes of NMDA receptors have been postulated, and the NMDA receptor may exist in multiple affinity states\(^10\). (3) Besides the competitive and the non-competitive binding site the NMDA receptor has other modulatory sites, i.e. the glycine and the polyamine binding site. Also, the sigma site is reported to interact with NMDA receptors\(^11\).

These multiple sites for pharmacological intervention may provide the basis for the development of drugs with the specificity required to act against parkinsonian symptoms.

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