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Antagonists of glutamate in the treatment of Parkinson's disease: from laboratory to the clinic

Introduction

Nowadays it is practically impossible to talk about dopamine and the basal ganglia without mentioning glutamate. Studies carried out over the past ten years have clearly established that glutamate is an important neurotransmitter in afferent and efferent pathways of the striatum, where most of the brain's dopamine is found. As far as the control of movement is concerned, the two systems are inextricably entwined, with glutamate opposing the actions of dopamine on motor behaviour. In Parkinson's disease, loss of nigrostriatal dopamine cells results in overactivity of glutamate pathways within the basal ganglia, leading to early speculation that glutamate antagonists may prove to be useful antiparkinsonian agents. The purpose of this section, is to provide some insight into how such drugs might work, and in particular to consider how modifications to the glutamate system result in changes in activity in the neighbouring dopamine system.

Experience tells us that glutamate/dopamine interactions can take many forms, including effects of glutamate on dopamine cell firing, dopamine synthesis and release, and also on dopamine neurotoxicity. All of these topics will be visited in the papers that follow. Additionally, since the ultimate goal of this research is to improve our understanding and treatment of parkinsonism consideration is given to clinical studies, in which drugs with glutamate receptor antagonist activity have been administered to parkinsonian volunteers, since this places the experimental data in a meaningful context.

Up till now, most efforts aimed at unravelling the intricacies of glutamate/dopamine interactions have concentrated on the striatal complex. However, as the presentations in this section unfold, a different picture will gradually emerge, and I would draw the reader's attention to the fact that many glutamate/interactions now appear to have their site of origin in the midbrain. The first paper by Starr et al. provides new evidence for the behavioural observation that glutamate receptor blockade can potentiate the action of L-DOPA, by showing that the bioconversion of L-DOPA to dopamine in the substantia nigra, is greatly enhanced by NMDA receptor-channel blockers. Dopamine cell firing in the ventral tegmentum and dopamine release in the nucleus accumbens are likewise controlled by glutamate, and the next paper by Svennson et al. demonstrates that the motor stimulant effects of MK 801 and nicotine, are probably mediated indirectly by glutamate liberated in the ventral tegmentum. Local infusion of AMPA and NMDA receptor antagonists into the tegmentum are respectively found to attenuate both the behav-

ioural and dopamine-releasing actions of these two drugs. In a parallel study Zigmond et al. similarly conclude that glutamate release in the nigra is responsible for activating dopamine neurones in response to tail-shock stress because the ensuing release of dopamine in the striatum was attenuated by local intranigral infusion of APV.

The paper by Cheramy et al. draws attention to the role of arachidonic acid in the liberation of striatal dopamine by glutamatergic and cholinergic stimuli, since this is blocked by inhibitors of phospholipase. Next, Sonsalla et al. again brings the nigra into sharp focus as being the site at which glutamate-induced toxicity of dopamine cells can be effectively blocked with appropriate NMDA antagonists. This finding contrasts with the ambiguity concerning whether glutamate mediates methamphetamine-induced toxicity of the dopaminergic axon terminals in the striatum. The final paper by Verhagen et al. adds a clinical dimension to this section, by reporting the results of some clinical trials conducted with weak NMDA antagonists in groups of parkinsonian volunteers. On balance, the experimental data would lead us to believe that blocking glutamate receptors in the parkinsonian brain should have a beneficial effect on the patients' symptoms. The clinical work carried out with amantadine, dextromethorphan and dextrorphan, however, do not support this conclusion. If anything, the patients were made worse by these treatments, and no improvement in the overall effectiveness of L-DOPA was observed. By contrast, adjuvant treatment with all of these low affinity NMDA receptor-channel blockers did reduce the incidence of dyskinesias induced by L-DOPA, and reduced the motor fluctuations caused by the dopamine precursor. It is not clear how these clinical benefits are achieved, and it is left to the reader to make a connection between the experimental and the clinical findings.

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