Abstract

Postmortem studies have shown that noradrenergic neurotransmission is impaired in Parkinson’s disease. This abnormality may have functional importance because α2-adrenoceptor antagonists, which increase central noradrenergic transmission, improve motor behaviour in various animal models of this disease.

Pilot clinical data suggest that α2-antagonists may indeed have several potential indications in the treatment of Parkinson’s disease: (i) 3 recent placebo-controlled studies reported an improvement in motor scores following short term intravenous or long term oral administration of two different α2-antagonists (idazoxan and efaroxan), suggesting that both drugs provide symptomatic benefit with regard to motor symptoms, especially rigidity and akinesia; (ii) an acute oral challenge with idazoxan reduced the severity of ‘peak-dose’ levodopa-induced...
dyskinesia, one of the most disabling complications of long term therapy with that drug, in a placebo-controlled study; (iii) biochemical and pharmacological experiments have suggested that levodopa-resistant parkinsonian symptoms, such as frozen gait, cognitive dysfunction, depressive state and dysautonomia, could be improved by enhancing central noradrenergic function; however, controlled clinical studies are necessary to evaluate the usefulness of \( \alpha_2 \)-adrenoceptor antagonists in these indications; and (iv) some preliminary experimental data support the hypothesis that noradrenergic mechanisms could be involved in the progression of Parkinson’s disease; thus, there is a rationale for testing the putative neuroprotective effects of \( \alpha_2 \)-adrenoceptor antagonists in this disorder.

It has yet to be determined whether the antiparkinsonian effects of \( \alpha_2 \)-antagonists are due to a direct effect of noradrenaline (norepinephrine) on motor systems or to an indirect effect, by means of noradrenergic interactions with dopamine or other neurotransmitters controlling motor behaviour or via other mechanisms.

A careful evaluation of \( \alpha_2 \)-antagonists in the treatment of Parkinson’s disease must also consider their potential adverse effects, because these drugs possess cardiovascular and psychiatric properties which might compromise their risk-benefit ratio.

The main hallmark of Parkinson’s disease is the loss of dopaminergic neuron cell bodies in the zona compacta of the substantia nigra, leading to a marked striatal dopamine denervation. In Parkinson’s disease, motor symptoms such as tremor, rigidity and hypokinesia result directly or indirectly from the degeneration of the nigrostriatal dopaminergic system. Levodopa ameliorates these motor symptoms but this drug is far from being an ideal treatment. Dopaminergically mediated psychiatric adverse events are not infrequent. Motor complications, including ‘wearing-off phenomena’ or ‘on-off fluctuations’, as well as abnormal involuntary movements such as ‘peak-dose’ dyskinesias, frequently occur after a few years of levodopa therapy, leading to severe disability. Moreover, several of the symptoms of Parkinson’s disease, mostly those which appear in the later stages, do not respond satisfactorily to levodopa treatment. Such symptoms (for example frozen gait, postural instability, dystarthria, cognitive disorders and autonomic dysfunction) are believed to be secondary to the involvement of nondopaminergic pathways. Finally, at least in theory, levodopa may display some toxicity towards dopamine neurons and this raises the question of its potential for accelerating the progression of Parkinson’s disease. Although levodopa remains the ‘gold standard’ in the treatment of Parkinson’s disease, the occurrence of such long term motor complications and the progression of the disease justify the search for new treatments. The main aims of such treatments are to demonstrate efficacy against the symptoms of parkinsonism, to reduce or avoid levodopa-type adverse effects, to alleviate symptoms which are unresponsive to levodopa and to delay disease progression.

New directions in the drug treatment of Parkinson’s disease have thus led to the development of agents which potentiate levodopa [such as monoamine oxidase (MAO)-B inhibitors and catechol-O-methyltransferase (COMT) inhibitors] and drugs which may replace levodopa (such as dopamine agonists). Drugs acting on other neurotransmitters putatively involved in the pathophysiology of Parkinson’s disease, such as glutamate, endorphins or noradrenaline (norepinephrine) have also been investigated. The involvement of central noradrenergic systems in the pathophysiology of Parkinson’s disease has been discussed on several occasions and it has been suggested that \( \alpha_2 \)-adrenoceptor antagonists could exert useful anti-