Short report

Biopterin in Parkinson’s disease

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SUMMARY Tetrahydrobiopterin is an essential co-factor in the natural synthesis of dopamine. Oral tetrahydrobiopterin was given in small doses to four patients with early Parkinson’s disease but had no discernible effect.

The major pathology identified in Parkinson’s disease is a loss of nigrostriatal dopamine cells and a decrease in striatal dopamine.1 The low dopamine levels can be corrected by giving levodopa, which is converted to dopamine in the brain, and its administration reverses many of the clinical features of Parkinsonism. Unfortunately, although this replacement therapy is now conventional, there are many problems associated with its use so that it is important to consider alternative approaches.

Tetrahydrobiopterin is an essential co-factor of tyrosine hydroxylase, the rate-limiting enzyme in the natural synthesis of dopamine. Levodopa therapy by-passes this step. In Parkinsonian subjects, the bipterin content of cerebrospinal fluid is reduced to 50% of that in control subjects,2 while in post mortem striatal samples it is reduced by 80%.3 It has been postulated that tetrahydrobipterin supplements might increase tyrosine hydroxylase activity in Parkinsonian patients and boost endogenous dopamine production.

Some preliminary findings using this approach have been published. However, the results are conflicting and in each report the number of subjects is small. Although 10 mg/kg intravenous tetrahydrobipterin appeared to have no benefit when given for three consecutive days,4 single oral doses of 1 g of tetrahydrobipterin temporarily abolished hypokinesia and rigidity and reduced tremor5 when given in an open trial to two subjects previously treated with dopamine. Other workers have also documented a similar mild and short-lived effect of tetrahydrobiopterin.6 The therapeutic trials producing benefit used a single-shot oral regime in patients who had already been treated with conventional dopaminergic preparations.

In a randomised double-blind placebo controlled crossover trial, we investigated the effects of repeated small doses of tetrahydrobiopterin in Parkinsonian patients who had received no previous dopaminergic therapy.

Patients and methods

Permission was obtained from the hospital ethical committee to carry out the study, and informed consent was obtained from patients. Four subjects, two men and two women, were selected whose Parkinson’s disease had been diagnosed by a consultant neurologist but who had not yet received treatment. Their characteristics are outlined in the table. They each had clear-cut bradykinesia and rigidity but only two were tremulous.

All examinations were performed in hospital at approximately the same time of day, which was about two hours after the morning dose of the trial drug. Patients were assessed twice in the week before commencing treatment to establish a baseline and minimise any learning effect and then on each day of treatment and one week later. They were assessed again after levodopa plus benserazide therapy was established.

In each assessment patients were rated using

1) The Hoehn and Yahr scale, which allocates patients roughly into one of five grades of Parkinsonism.
2) The Webster scale, which grades the severity of certain individual symptoms and signs to give an aggregate score.
3) A rated neurological examination, which is similar to the Webster scale but scores different body parts indi-
The role of tetrahydrobiopterin in dopamine synthesis is similar to its place in the biosynthesis of catecholamines and serotonin. In hyperphenylalaninaemia, the ability to synthesise tetrahydrobiopterin is deficient, and treatment with tetrahydrobiopterin supplements alone has been successful. Although the drug does not cross the blood-brain barrier easily, it can do so when given in high dosage (1 g). Endogenous tetrahydrobiopterin is present in striatal dopaminergic terminals, and it has been suggested that more lipophilic analogues of tetrahydrobiopterin would reach this site more easily. In rats a two to threefold increase of catecholamine synthesis in the striatum was found by one group of investigators following injection of tetrahydrobiopterin into the cerebral ventricles, but others could not confirm this although high tissue levels of tetrahydrobiopterin were achieved.

Tetrahydrobiopterin is effective in hyperphenylalaninaemia because there is a severe reduction in endogenous levels of tetrahydrobiopterin, without reduction of hydroxylase enzyme levels. The lesser diminution of tetrahydrobiopterin levels in Parkinson's disease may merely reflect loss of dopaminergic neurons, so that the ratio of co-factor to tyrosine hydroxylase in surviving neurons is normal. Thus tetrahydrobiopterin administration in Parkinson's disease would be aimed at increasing the activity of existing tyrosine hydroxylase above the level induced by endogenous tetrahydrobiopterin. That this may be possible is suggested by the existence of multiple forms of tyrosine hydroxylase, with some forms being in a less active state and subsaturated with endogenous tetrahydrobiopterin.

In Parkinson's disease, 70–80% of striatal dopamine cells may be lost before clinical features are apparent, and up to this point there are several compensatory mechanisms for the surviving dopaminergic cells. Treatment aimed at restoring or boosting natural metabolic function is more likely to be effective in patients with relatively early disease. It is possible that treatment with exogenous dopamine...
Biopterin in Parkinson's disease

reduces striatal capacity to produce endogenous dopamine, so that patients not treated with levodopa may be more likely to respond to tetrahydrobiopterin. Biopterin is expensive and scarce, and so has been tested in only small numbers of patients. Sometimes Parkinson's disease is difficult to distinguish from other causes of Parkinsonism not responsive to levodopa until quite late in the course of the illness. For this reason, it is worth ensuring that patients in small clinical trials who do not respond to tetrahydrobiopterin do actually have levodopa-sensitive Parkinsonism.

References