The effects of L-threo-3,4-dihydroxyphenylserine on the total norepinephrine and dopamine concentrations in the cerebrospinal fluid and freezing gait in parkinsonian patients

H. Tohgi, T. Abe, and S. Takahashi

Department of Neurology, Iwate Medical University, Morioka, Japan

Accepted April 8, 1992

Summary. We studied the effects of L-threo-DOPS (L-DOPS) on the concentrations of total (conjugated and unconjugated) dopamine (DA) and norepinephrine (NE) in the cerebrospinal fluid (CSF) of parkinsonian patients with freezing phenomenon. The NE concentration increased remarkably and dose-dependently after administration of L-DOPS in both L-dopa/carbidopa-pretreated and untreated patients. The DA concentration also increased mildly but significantly in L-dopa/carbidopa-untreated patients. Freezing phenomenon improved in 6 out of 8 patients at Hoehn and Yahr’s stage III, and 1 out of 5 patients at stage IV. These results indicate that L-DOPS administration increases the NE concentration dose-dependently, and is effective for freezing of gait of moderate severity.

Keywords: L-threo-DOPS, freezing of gait, norepinephrine, dopamine, cerebrospinal fluid.

Introduction

In the early stage of Parkinson’s disease (PD), the gait disturbance may be alleviated by augmenting the deficient DA. However, PD patients at advanced stages or with a history of long-term L-dopa treatment gradually develop a difficulty in stepping forward and turning (freezing phenomenon) which does not satisfactorily respond to L-dopa. Since rigidity and akinesia in such patients still respond sufficiently to L-dopa, it is possible that freezing phenomenon may be related to neurotransmitter defects other than the dopaminergic nigrostriatal system.

Several lines of evidence suggest that norepinephrine (NE) deficiency is related to the freezing of gait. It has been reported that the levels of dopamine-β-hydroxylase were significantly decreased in the brain tissue (Nagatsu et al., 1977, 1979) and in the cerebrospinal fluid (Nagatsu et al., 1982; Narabayashi et al., 1981) of patients with a long-term history of Parkinson’s disease. The reduction in the NE concentration in the CSF correlated significantly with the severity of freezing of gait (Tohgi
et al., 1990). Clinical trials have shown the effectiveness of L-threo-3,4-dihydroxyphenylserine (L-DOPS), a synthetic norepinephrine precursor, on the freezing phenomenon (Narabayashi et al., 1981, 1987). However, it has been reported that free NE (Suzuki et al., 1984) and 3-methoxy-4-hydroxyphenylglycol (MHPG) (Yamamoto et al., 1986) concentrations in the CSF did not change after administration of L-threo-DOPS.

In a previous study, we demonstrated that administration of L-DOPS remarkably increased the total (conjugated and unconjugated) NE concentration in the CSF and alleviated the freezing phenomenon in some parkinsonian patients (Tohgi et al., 1990). In this paper, we have extended our study to include a larger number of patients and to investigate the effects of doses of L-DOPS on the concentrations of NE as well as DA in the CSF and on the freezing phenomenon.

**Patients and methods**

**Patients**

We studied 13 patients with Parkinson’s disease at Hoehn and Yahr’s stages 3 or 4. Nine patients (mean age 58.9 ± 6.3 years) had received L-dopa/carbidopa (200/21.6–600/64.8 mg/day) and then additionally received L-DOPS. For these patients, CSF samples had been collected before the L-dopa/carbidopa medication, and their CSF was obtained before and after additional L-DOPS medication (Table 1). Four patients (mean age 67.8 ± 6.2 years) had not received L-dopa/carbidopa, and received only L-DOPS (Table 2). Their CSF was obtained before and after L-DOPS medication. The patients received L-DOPS starting at 100 mg/day with a weekly increase of 100 mgs up to the usual maintenance dose of 600 mg/day (Narabayashi et al., 1987) or more (maximum dose of 900 mg/day). Since the dosage at which the freezing gait symptoms ameliorated was different for the 13 patients, we were able to study the dose-dependency of the effects of L-DOPS. In three patients (Cases 2 and 4 in Table 1, and case 10 in Table 2), we were only able to evaluate the NE concentration at moderate doses (300 mg/day or less) which were still ineffective for freezing gait symptoms.

**Diagnostic criteria**

The diagnosis of Parkinson’s disease was made based upon characteristic clinical symptoms. We excluded patients with parkinsonian syndrome associated with cerebrovascular disease, striatonigral degeneration, progressive supranuclear palsy, and other degenerative diseases based upon the clinical symptoms, CT, and MRI.

**Clinical evaluation**

The severity of Parkinson’s disease was graded according to Hoehn and Yahr’s (1967) stages. The severity of gait disturbance was assessed based upon the criteria of Lieberman (1980) by asking the patients to walk 10 meters and return: grade 0 for no gait disturbance, grade 1 for decreased arm swing only (no freezing), grade 2 for hesitation on turning only (no freezing), grade 3 for occasional freezing, and grade 4 for frequent freezing. Improvement of gait disturbance by more than one grade after L-DOPS medication was considered significant.