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Norio Ogawa* Hiroo Kuroda† Mitsutoshi Yamamoto‡

Itaru Nukina** Zensuke Ota††

*Okayama University,
†Okayama University,
‡Okayama University,
**Okayama University,
††Okayama University,

Improvement in freezing phenomenon of Parkinson's disease after DL-threo-3, 4-dihydroxyphenylserine.*

Norio Ogawa, Hiroo Kuroda, Mitsutoshi Yamamoto, Itaru Nukina, and Zensuke Ota

Abstract

A 77-year-old man with Parkinson's disease of long standing, under treatment with L-DOPA and benserazide, was administered DL-threo-3, 4-dihydroxyphenylserine (DL-threo-DOPS), a precursor of norepinephrine, for 10 days. With this administration the patient's freezing phenomenon was remarkably improved, and his dysarthria also showed improvement. When DL-threo-DOPS was suspended, the frozen gait returned on the third day to almost the former level, even though he continued to receive L-DOPA and benserazide. After administration of DL-threo-DOPS, the CSF level of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine, was 127.5% of the pretreatment level. These observations suggest that DL-threo-DOPS can pass through the blood-brain barrier and change to norepinephrine, and that DL-threo-DOPS may be beneficial in the treatment of the freezing phenomenon of Parkinson's disease.

KEYWORDS: DL-threo-DOPS, MHPG, freezing phenomenon, Parkinson's disease

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IMPROVEMENT IN FREEZING PHENOMENON OF PARKINSON'S DISEASE AFTER DL-THREO-3, 4-DIHYDROXYPHENYLSERINE

Norio OGAWA, Hiroo KURODA,* Mitsutoshi YAMAMOTO,** Itaru NUKINA* and Zensuke OTA*

*Institute for Neurobiology, * Third Department of Internal Medicine and ** Department of Neuropsychiatry, Okayama University Medical School, Okayama 700, Japan*

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Abstract. A 77-year-old man with Parkinson's disease of long standing, under treatment with L-DOPA and benserazide, was administered DL-threo-3, 4-dihydroxyphenylserine (DL-threo-DOPS), a precursor of norepinephrine, for 10 days. With this administration the patient's freezing phenomenon was remarkably improved, and his dysarthria also showed improvement. When DL-threo-DOPS was suspended, the frozen gait returned on the third day to almost the former level, even though he continued to receive L-DOPA and benserazide. After administration of DL-threo-DOPS, the CSF level of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine, was 127.5 % of the pretreatment level. These observations suggest that DL-threo-DOPS can pass through the blood-brain barrier and change to norepinephrine, and that DL-threo-DOPS may be beneficial in the treatment of the freezing phenomenon of Parkinson's disease.

Key words : DL-threo-DOPS, MHPG, freezing phenomenon, Parkinson's disease.

The treatment of Parkinson's disease has recently focussed on the administration of L-DOPA to compensate for the dopamine deficiency in the striatum. In Parkinson's disease cases having a course of several or more years, L-DOPA appears to produce adequate therapeutic effects on rigidity and tremor, but the freezing phenomenon remains in the foreground. The freezing phenomenon is paradoxically aggravated by an increased dosage of L-DOPA, and it seems that other drugs and operative treatments have little effect.

It is known that Parkinson's cases of long standing show a deficiency of not only dopamine but also norepinephrine. Recently Nagatsu *et al.* reported that dopamine-β-hydroxylase (DβH), a synthetic enzyme of norepinephrine, is decreased in brain tissue and cerebrospinal fluid (1-3), suggesting the possibility that the freezing phenomenon is related to a norepinephrine deficiency. Narabayashi *et al.* (3) administered DL-threo-3, 4-dihydroxyphenylserine (DL-threo-DOPS), a precursor of norepinephrine, to nine patients with Parkinson's disease of long duration, and the freezing phenomenon was improved. In the study reported here the authors administered DL-threo-DOPS to a patient who had Parkinson's disease for

a long time with the freezing phenomenon as the major symptom. The clinical course and the CSF levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) are presented.

CASE REPORT

The patient was a 77-year-old male dentist with a 4-year history of Parkinson's disease. Four years ago a tremor developed in both upper extremities, followed by tremors in both lower extremities, and gradually aggravated gait disturbances. Three years ago dysarthria developed, and a diagnosis of Parkinson's disease was made. With the commencement of L-DOPA with benserazide therapy, the tremors were controlled, and the difficulty in taking the first step was eased, permitting him to work in his office. However, after half a year of this therapy, gait distrubances again became aggravated, but the treatment needed to be continued. He required the assistance of a family member to visit our clinic.

In May 1982, a visit was made due to an aggravation of the symptoms. At the time of examination, he assumed a Parkinsonian posture with Myerson's sign (+), but both tremors and rigidity were well controlled by the L-DOPA with benserazide. His gait was remarkably disturbed with a frozen gait (+++) and hesitation (+++). He could not walk through a narrow space between two chairs. On a spacious flat surface he barely managed to take his first step after more than 10 min. However, on a partition floor, he almost walked normally and was able to go up and down stairs (paradoxical kinesia). Hardly any disturbances in the upper extremities were observed. In addition to the foregoing sympotoms, dysarthria (++) and salivation (++) were present.

At the time of his visit, the patient was taking L-DOPA at 300 mg/day and benserazide at 75 mg/day. The symptom that troubled the patient the most was his inability to walk. When 1,200 mg/day of DL-threo-DOPS was administered in addition to L-DOPS and benserazide, a dramatic improvement was observed in his frozen gait. In 7 to 10 days from the initial administration he was able to walk almost normally. On the 10 th day after the beginning of DL-threo-DOPS, he could stand up from a chair, take his first step smoothly, walk almost normally, and stop and go smoothly as instructed. Moreover, he could walk through a narrow space between two chairs without hesitation. Thus, the administration of DL-threo-DOPS appeared to completely emancipate the patient from frozen gait which he had suffered for several years. His articulation became clearer, and the masked face showed a slight improvement.

When DL-threo-DOPS was suspended after 10 days of administration, the frozen gait returned to almost the former level on the third day, even though he continued to receive L-DOPA and benserazide.

Free 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine, in CSF was measured by high pressure liquid chromatography (YANACO L-2000) before and 10 days after DL-threo-DOPS administration. Sep-

aration was achieved on an ODS column using a mobile phase of sodium citrate -citrate buffer (pH 4.3), containing 1 % tetrahydrofran, 10 % methanol and 0.15 mM EDTA. CSF levels of MHPG were 34.2 ng/ml before DL-threo-DOPS treatment and 43.6 ng/ml after DL-threo-DOPS treatment (27.5 % increase).

DISCUSSION

DL-threo-DOPS has successfully been used by Suzuki *et al.* for postural hypotension in familial amyloid polyneuropathy (6). Narabayashi *et al.* have recently reported that DL-threo-DOPS improved the freezing phenomenon in nine Parkinson's disease cases (3). Narabayashi *et al.* (3) thought that the frozen gait of long standing Parkinson's disease was a symptom that was probably attributable to a brain deficiency of not only dopamine but also norepinephrine. The levo isomer of DL-threo-DOPS, through the action of decarboxylase, is transformed into norepinephrine, but with the combined use of benserazide, a peripheral decarboxylase inhibitor, DL-threo-DOPS probably can not be transformed peripherally into norepinephrine. During the administration of DL-threo-DOPS, there was no change in blood pressure, and following administration, hypertension was not observed. However, the CSF-MHPG level 10 days after DL-threo-DOPS was 27.5 % higher than before administration. This indicates that L-threo-DOPS could pass through the blood-brain barrier and changed into norepinephrine. It is well-known that MHPG is the best index of norepinehrinergic neurons in the CNS (4, 5).

As the freezing phenomenon does not respond to long-term L-DOPA therapy but appears to be improved by DL-threo-DOPS, for at least a short period, Parkinson's disease may be a disorder not only of dopamine deficiency, but also may involve the entire catecholamine metabolism. In our case and the nine cases reported by Narabayashi *et al.* (3), side effects which would constitute a clinical problem were not observed during the administration of DL-threo-DOPS, and no remarkable changes in laboratory data were found after the administration of DL-threo-DOPS. These observations suggest that DL-threo-DOPS may be beneficial in the treatment of the freezing phenomenon of Parkinson's disease patients of long standing.

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