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EFFECTS OF ORAL L-TYROSINE ADMINISTRATION ON CSF TYROSINE AND HOMOVANILLIC ACID LEVELS IN PATIENTS WITH PARKINSON'S DISEASE

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Summary

To determine whether l-tyrosine administration can enhance dopamine synthesis in humans as it does in rats, we measured levels of tyrosine and the major dopamine metabolite, homovanillic acid, in lumbar spinal fluids of 23 patients with Parkinson's disease before and during ingestion of 100 mg/kg/day of tyrosine. Nine patients took 100 mg/kg/day of probenecid in six divided doses for 24 hours prior to each spinal tap; 14 patients did not receive probenecid. L-tyrosine administration significantly increased CSF tyrosine levels in both groups of patients ($p<.01$) and significantly increased homovanillic acid levels in the group of patients pretreated with probenecid ($p<.02$). These data indicate that l-tyrosine administration can increase dopamine turnover in patients with disorders in which physicians wish to enhance dopaminergic neurotransmission.

L-tyrosine administration to rats increases the rate at which brain neurons synthesize and release catecholamine neurotransmitters (1,2,3). If a similar sequence occurred in humans, l-tyrosine administration might be useful for treating diseases characterized by deficient catecholaminergic neurotransmission (4). We have previously shown that single oral doses of l-tyrosine (100-500mg/kg) significantly increased plasma tyrosine levels in normal fasting subjects for at least 8 hours (5), and that multiple doses of l-tyrosine (1 total of 100 mg/kg/day) produced similar 2-3 fold elevations in plasma tyrosine among normal subjects consuming 3 daily meals containing 3,000 Kcal and 113 g of protein (6). In both instances, l-tyrosine administration increased the plasma tyrosine ratio (defined as the ratio of the plasma tyrosine concentration to the sum of the concentrations of other large neutral amino acids that compete with tyrosine for transport across the blood-brain barrier); hence the tyrosine probably also increased (7) the entry of tyrosine intothe brain and its availability for catecholamine synthesis. We now describe changes in levels of tyrosine, homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) within the spinal fluid (CSF) occurring in human subjects during tyrosine administration. All subjects had Parkinson's disease and were given tyrosine as a part of a larger clinical study to examine the amino acid's utility in treating this disorder.

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Material and Methods

Twenty-three patients with well-established Parkinson's disease participated in this study. They were hospitalized in the Clinical Research Center at the Massachusetts Institute of Technology or in the Clinical Studies Unit at the Tufts-New England Medical Center. All gave written consent according to the provisions of a protocol approved by the human review committees at both institutions. All patients had discontinued anti-Parkinsonian medications (levodopa and anti-cholinergic drugs) for at least 4 days prior to the initial lumbar puncture. Spinal fluid samples were obtained from the lumbar subarachnoid space by conventional lumbar puncture techniques. Patients then took 100 mg/kg of l-tyrosine daily in 3 equally divided doses for 4-7 days and underwent a second lumbar puncture 2 hours after a dose of tyrosine. Nine patients received 100 mg/kg of probenecid (6 equally divided doses for 24 hours before each spinal tap) in order to block the transport of HVA and 5-HIAA across the CSF-blood barrier and allow them to accumulate in the CSF. Fourteen additional Parkinsonian patients did not receive probenecid. All spinal taps were performed between 9 and 11 A.M.: patients remained flat in bed for 8 hours prior to each lumbar puncture to minimize variation in metabolite levels caused by physical activity. The first 4 ml of CSF were used for routine clinical determinations and the 5th through 8th ml of CSF were immediately frozen and stored until analysis. CSF tyrosine levels were measured by a fluorometric technique (8); HVA and 5-HIAA levels were measured by high pressure liquid chromotography using electrochemical detection (9). Probenecid levels were measured by high pressure liquid chromotography with UV detection (10).

Results

Tyrosine administration significantly increased CSF tyrosine levels in patients who received probenecid. (Table I)

TABLE I

CSF Tyrosine Levels with Probenecid Pretreatment Before and During L-tyrosine Administration in 9 Patients with Parkinson's Disease

Patient	CSF Tyrosine (µg/ml)	
	Before Tyrosine	During Tyrosine +
1	1.6	3.8
2	1.4	3.2
3	6.1	5.8
4	5.5	10.2
5	5.7	12.5
6	1.2	4.0
7	3.8	6.5
8	2.4	3.4
9	3.4	3.4
Mean ±Standard Deviation	3.5±1.9	5.9±3.4 *

+ CSF was obtained 2 hours after a tyrosine dose

* Mean CSF tyrosine level increased significantly during tyrosine administration ($p<.01$, paired t test)

The mean (± standard deviation) baseline CSF tyrosine level was 3.5 ± 1.9μg/ml; this increased to 5.9 ± 3.4 μg/ml during tyrosine administration ($p<.01$). Tyrosine administration produced a similar increase in CSF of patients who were not pretreated with probenecid, mean concentrations rising from 3.5 ± .8 μg/ml to 6.1 ± 2.0 μg/ml. (Table II) The mean CSF tyrosine level in the group that received probenecid did not differ significantly from that in the group without probenecid.

TABLE II

CSF Tyrosine Levels Before and During Tyrosine Administration in 14 Patients with Parkinson's Disease Who Did Not Receive Probenecid

Patient	CSF Tyrosine (μg/ml)	
	Before Tyrosine	During Tyrosine +
10	3.2	7.4
11	3.6	5.2
12	3.4	5.0
13	4.1	6.5
14	3.3	5.6
15	3.6	4.4
16	2.9	4.8
17	2.5	6.3
18	3.6	10.9
19	2.6	4.8
20	5.2	4.9
21	2.2	4.7
22	3.8	4.3
23	2.9	9.9
Mean ± Standard Deviation	3.5±0.8	6.1±2.0 *

+ CSF was obtained 2 hours after a tyrosine dose
* Mean CSF tyrosine level increased significantly during tyrosine administration ($p<.001$, paired t test)

Tyrosine administration significantly increased CSF levels of HVA but not 5-HIAA in patients who received probenecid. HVA levels before tyrosine administration ranged between 61.2 and 155 ng/ml with a mean of 93.5 ± 36.5 ng/ml. HVA levels during tyrosine administration ranged between 61.2 and 224.2 ng/ml with a mean of 126.5 ± 53.1 ng/ml ($p<.02$). Mean probenecid levels did not differ significantly between the first and second CSF samples. Analysis of co-variance to control for minor fluctuations in CSF probenecid concentration indicated that the increase in HVA levels after tyrosine administration was still significant ($p<.02$). Tyrosine administration did not significantly affect the concentrations of monoamine acid metabolites in the 14 patients who did not receive pretreatment with probenecid.

TABLE III
HVA and 5-HIAA Levels in CSF of Parkinson's Disease Patients Before and During Tyrosine Administration

Patient	Before Tyrosine+			During Tyrosine+		
	HVA (ng/ml)	5-HIAA (ng/ml)	PROBENECID (µg/ml)	HVA (ng/ml)	5-HIAA (ng/ml)	PROBENECID (µg/ml)
1	62.3	58.4	14.2	110.3	67.1	15.5
2	127.6	14.5	7.4	170.6	21.2	8.1
3	69.8	69.2	28.6	87.8	74.9	14.9
4	87.1	52.8	23.9	113.2	58.7	27.2
5	130.9	85.9	7.1	224.2	94.2	6.8
6	61.2	120.3	3.3	61.2	100.9	2.3
7	52.4	43.3	19.5	115.9	154.6	23.5
8	155.1	140.3	28.9	176.4	96.5	12.9
9	94.9	137.7	21.4	78.5	100.5	17.9
Mean ± Standard Deviation	93.5±36.5	76.3±39.4	17.1±9.6	126.5±53.1*	85.4±36.6	14.3±7.9

+ Patients received probenecid (100 mg/kg) during the 24 hours prior to each lumbar puncture.
* There was a significant increase in HVA levels during tyrosine administration ($p<.02$, paired t test).

Discussion

These data indicate that tyrosine administration significantly increases CSF levels of both tyrosine and HVA in patients with Parkinson's disease. L-tyrosine enters the brain by an uptake system located at the blood-brain barrier that it shares with other large neutral amino acids (11). We have previously shown that the ingestion of 100 mg/kg of l-tyrosine by normal human subjects increases the ratio of plasma tyrosine to the sum of these competing amino acids, and thereby facilitates tyrosine's entry into the brain (5,6). Although we could not measure tyrosine levels in the brain directly, tyrosine levels did increase significantly in lumbar CSF during tyrosine administration whether or not subjects also received probenecid. CSF tyrosine levels may reflect brain extracellular tyrosine content (12), although the relationship between amino acid concentrations in plasma, brain, and CSF are complex (13). Cisternal CSF levels of another large neutral amino acid, tryptophan, have been found to correlate well with brain tryptophan levels in rats (14); infusions of tryptophan increased lumbar CSF, ventricular CSF and brain cortical levels of tryptophan in humans (15).

Tyrosine is the physiological precursor of the catecholamines and its administration can increase the rate at which neurons synthesize catechols (1,16,17). Tyrosine administration does not increase levels of the catecholamines but it does stimulate their synthesis and release, as measured by increases in the accumulation of the major dopamine and norepinephrine metabolites HVA and 3-methoxy-4-hydroxyphenylglycol sulfate (MOPEG-SO_4) (2,3). Most evidence for this relationship comes from animal experiments showing that

catecholaminergic neurons are especially sensitive to tyrosine availability when they are firing rapidly and their tyrosine hydroxylase is activated. Thus Gibson and Wurtman (16) reported that probenecid administration significantly increased the brain level of MOPEG-SO_4 in rats; tyrosine administration alone did not affect brain MOPEG-SO_4 levels (unless animals were stressed) but the combination of tyrosine and probenecid together produced significantly higher levels of MOPEG-SO_4 than either drug alone. Scally et al (3) gave probenecid or haloperidol to rats pretreated with tyrosine; they found that dopamine turnover was increased in striata of animals pretreated with haloperidol but not in striata of those receiving tyrosine without haloperidol. We recently found that a partial lesion of one nigrostriatal tract that increased the firing frequency (i.e. dopamine turnover/neuron) of surviving neurons (18), caused its rate of dopamine synthesis to become tyrosine dependent (19); contralateral nigrostriatal neurons, presumably firing at normal rates, were unresponsive to administered tyrosine. This may constitute a good experimental model for Parkinson's disease, inasmuch as nigrostriatal dopaminergic neurons degenerate in this disorder and the firing rates of the surviving neurons apparently increase (20,21). The present data provide indirect biochemical support for the hypothesis that dopamine synthesis is precursor-dependent in Parkinson's disease, since HVA levels in CSF increased during tyrosine administration in 7 of 9 patients who received probenecid. Tyrosine administration alone did not increase CSF HVA levels, perhaps because the CSF-blood barrier transport system can easily absorb the increase in HVA induced by tyrosine.

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