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Tyrosine for the Treatment of Depression

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The catecholamine hypothesis of affective illness suggests that depression may reflect a deficiency of norepinephrine (NE) transmission at specific brain loci (1). Consistent with this model, two types of antidepressant drugs currently in use—tricyclics and monoamine oxidase inhibitors—appear to enhance noradrenergic transmission. Tyrosine is the physiological precursor for catecholamine synthesis, and its administration can increase the rates at which brain neurons synthesize both dopamine and norepinephrine (2–5). If a similar sequence occurs in humans, tyrosine administration might be an effective treatment for disorders, such as depression, that may respond to increased central noradrenergic tone. We will describe the results of a double-blind, placebo-controlled, crossover trial of tyrosine in a depressed woman.

Case Report

Ms. A, a 30-year-old woman, had suffered from chronic and recurrent depressions for several years and was diagnosed as having primary depression, unipolar type. As part of a research study, she was treated with an experimental antidepressant, amoxapine; the drug was discontinued after 10 days because she was agitated and tremulous. We discussed the treatment alternatives of a standard antidepressant or a trial of tyrosine with her, and she gave us informed consent for the latter. We then administered 100 mg/kg per day of L-tyrosine by mouth in 3 daily doses for 2 weeks, an identically appearing placebo at the same schedule for 18 days, and finally tyrosine for an additional 5 weeks.

A psychiatrist (A.J.G.), who was "blind" to the therapy, rated Ms. A weekly on the Hamilton Depression Rating Scale and the Clinical Global Impressions (CGI). Ms. A, who was also blind to the treatment, rated herself weekly on the Zung Self-Rating Depression Scale. Venous blood samples were collected throughout the tyrosine and placebo treatments for measurement of tyrosine concentrations.

TABLE 1
Effect of Tyrosine on Depression Scores of One Patient

Trial	Hamilton Scale		Zung Scale	
	Mean Score	t[a]	Mean Score	t[b]
Pretreatment	28	3.566[c]	67	3.256[c]
First tyrosine (6 g/day for 14 days)	7	3.906[c]	39	3.373[c]
Placebo (18 days)	30	3.355[c]	68	6.062[d]
Second tyrosine (6 g/day for 74 days)	4		33	

[a]Baseline to second tyrosine: t=2.131, p<.01 (one-tailed t test, df=8).
[b]Baseline to second tyrosine: t=5.889, p<.001 (one-tailed t test, df=8).
[c]p<.01 (one-tailed t test, df=8).
[d]p<.001 (one-tailed t test, df=8).

Ms. A's depression improved markedly after 2 weeks of tyrosine therapy. She said she felt better than she had in years and showed striking improvement in mood, self-esteem, sleep, energy level, anxiety, and somatic complaints. Her CGI went from "moderately ill" to "not ill at all." Within 1 week of placebo substitution, her depressive symptoms began to return, and by the end of the placebo period her depressive indices were slightly worse than pretreatment levels.

When we reinstituted tyrosine therapy her depression was again completely alleviated. Hamilton and Zung ratings during the pretreatment, tyrosine, and placebo periods are presented in table 1. No adverse effects were noted during either tyrosine or placebo therapy.

Plasma tyrosine concentrations rose within 1 hour after we administered a single dose of L-tyrosine and were elevated throughout tyrosine ingestion. Plasma levels in samples drawn 2 hours after a tyrosine dose ranged between 26.8 and 32.8 μg/ml, with a mean (±SEM) of 29.8±2.4. Plasma levels in samples drawn at similar times after placebo was taken were 14.2±0.8 μg/ml, p<.001.

Discussion

Oral tyrosine administration increased plasma tyrosine levels in Ms. A, as it has in normal subjects without psychiatric disorders (6). In addition, symptoms of depression decreased dramatically during tyrosine administration and recurred when placebo was substituted. We observed no unwanted effects with tyrosine ingestion.

There are a few reports that tyrosine metabolism may be abnormal in depressed patients. Kishimoto and Hama (7) have reported that plasma tyrosine levels were significantly lower in depressed patients than in controls and that plasma tyrosine levels rose when the patients recovered from depression. They made no attempt to alter blood levels by oral tyrosine administration or by dietary manipulations. Ms. A's plasma tyrosine levels at baseline and during placebo therapy

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were normal, and these levels increased during tyrosine ingestion to the same degree as the increases previously observed in normal subjects. Disturbances have also been reported in the blood-brain-barrier transport of tyrosine and tryptophan in patients suffering from manic-depressive illness (8, 9). It is conceivable that Ms. A required higher than normal plasma tyrosine concentrations to achieve enough brain tyrosine to provide sufficient brain tyrosine levels for adequate catecholamine biosynthesis.

Whether tyrosine therapy will be effective in alleviating depression in significant numbers of patients remains to be seen, and if the therapy is effective, it is not certain whether there are clinical or biochemical criteria that may predict response. If tyrosine is demonstrated to be effective and if it actually has few unwanted effects, it might become an attractive alternative to the antidepressants currently available. We are also studying the use of tyrosine in the therapy of other disorders associated with deficiencies in catecholamine release in the same manner that Growdon and Wurtman (10) have studied the use of tryptophan to increase brain serotonin levels and of choline and lecithin to augment cerebral acetylcholine synthesis and release.

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Dangerousness and the Right of a Psychotic Quadriplegic Patient to Refuse Treatment

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Clinicians face many complexities when deciding whether or not involuntary treatment is indicated for a psychotic individual with a severe physical handicap. The literature on this subject is scarce; we found only one report of a similar case (1).

Case Report

Mr. A, a 32-year-old quadriplegic veteran, was admitted to the medical service of the Louisville Veterans Administration Medical Center with bleeding decubitus ulcers and a urinary tract infection. While on the medical service, he was uncooperative and demanding: he appeared to be hallucinating and expressed delusional beliefs. A psychiatric consultation was obtained and Mr. A was transferred to our psychiatric unit.

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Before he was admitted to the hospital, Mr. A lived with a caretaker and the caretaker's family. The caretaker reported that Mr. A's behavior started changing 2 weeks before he entered the hospital, and that Mr. A had told him that the Holy Ghost, Martin Luther King, and John Kennedy had spoken to him.

Upon admission to the hospital, Mr. A's mental status examination revealed auditory hallucinations, loose associations, and ideas of reference. He claimed that messages about him were being broadcast over the television and radio, and he stated that God had personally informed him that he would walk in the future. His sensorium was clear, his orientation was complete, and his intellectual functioning was normal. He denied having suicidal thoughts and intentions but acknowledged smoking marijuana three times a week in recent months. Physical examination revealed considerable paralysis of his arms. He could not grasp objects, but he was able to use his upper extremities to operate an electric wheelchair. His legs were paralyzed, and he was totally dependent on others for bodily care. His history and clinical picture were not compatible with a drug-induced psychosis. Our diagnosis of Mr. A was acute schizophrenic episode and drug dependence (cannabis sativa).

Mr. A demanded to leave the hospital shortly after being