

# L-Tyrosine

## Introduction

L-tyrosine is a conditionally essential amino acid because under normal conditions the body synthesizes sufficient quantities from phenylalanine.<sup>1</sup> For those with phenylketonuria, however, a severe deficiency in the enzyme phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine, making tyrosine an essential amino acid for this population.<sup>2</sup> Tyrosine is incorporated into proteins of all life forms and is a precursor for synthesis of thyroxin, melanin, and the neurotransmitters dopamine and norepinephrine.<sup>1,2</sup> Food sources of tyrosine include fish, soy products, poultry, eggs, dairy products, lima beans, almonds, peanuts, sesame seeds, pumpkin seeds, wheat germ, oats, avocados, and bananas.<sup>1,3</sup> Clinical conditions for which tyrosine supplementation may be of therapeutic benefit include depression, hypertension, stress, cognitive function and memory, Parkinson's disease, phenylketonuria, and narcolepsy.

## Pharmacokinetics

Absorption pharmacokinetics of a single oral dose of L-tyrosine was studied in 12 normal fasting subjects (ages 18-21). Six subjects in each group fasted overnight then were given either 100 or 150 mg/kg tyrosine and continued to fast for another eight hours. Peak plasma tyrosine levels were attained at two hours post-ingestion and remained elevated above baseline for 6-8 hours. For those taking 100 mg/kg tyrosine, plasma levels rose from 69 nmols/mL ( $\pm 3.9$ ) to 154 nmols/mL ( $\pm 9.5$ ); for those receiving 150 mg/kg tyrosine, plasma levels rose to  $203 \pm 31.5$  nmols/mL. No side effects were noted. The flow of tyrosine across the blood-brain barrier and brain tyrosine levels are dependent on the ratio of plasma tyrosine to the total plasma concentrations of other large neutral amino acids (phenylalanine, tryptophan, methionine, valine, leucine, and isoleucine) that compete for neuronal uptake in the brain.<sup>4</sup> Animal studies demonstrate brain tyrosine levels enhance neurotransmitter synthesis,<sup>5,6</sup> and research in humans seems to indicate the same.<sup>7</sup>

L-tyrosine is absorbed from the small intestine and transported to the liver via the portal circulation. L-tyrosine not utilized by the liver enters the systemic circulation and is distributed to various body tissues<sup>1</sup> where it is utilized in three different metabolic pathways: (1) absorbed into the tissues and incorporated into proteins and peptides; (2) used as precursors in smaller amounts for thyroxin, melanin, and neurotransmitter synthesis; or (3) deaminated to form the gluconeogenesis substrate, p-hydroxy phenylpyruvic acid. In the latter process, the enzyme catalyzing this reaction (tyrosine transaminase) exhibits a marked diurnal variation in liver concentrations, causing a similar degree of diurnal variation in plasma tyrosine levels in normal humans.<sup>8</sup>





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### Mechanisms of Action

Although tyrosine has numerous mechanisms of action, perhaps the most clinically significant is its role as a precursor for norepinephrine and dopamine synthesis. By improving the rate of neurotransmitter synthesis,<sup>5,6</sup> tyrosine stimulates the central nervous system and acts as an antidepressant.<sup>9,10</sup> Tyrosine also serves as a precursor for melanin, the pigment responsible for skin and hair color that provides protection against harmful ultraviolet rays,<sup>11</sup> and for the thyroid hormone thyroxine.<sup>3</sup> Enkephalins, pentapeptides with opioid pain-killing activity, contain tyrosine in their structure.<sup>12</sup> In addition to its function as a precursor, tyrosine stimulates growth hormone<sup>13</sup> and is involved in adrenal and pituitary function.<sup>3</sup> It also appears to function as an adaptogen by relieving physical symptoms of stress, such as high blood pressure, anxiety, and mood swings.<sup>14,15</sup> Because of its phenolic structure, tyrosine is a powerful antioxidant, scavenging and neutralizing numerous free radicals and inhibiting lipid peroxidation.<sup>14,15</sup>

### Clinical Indications

#### Depression

One hypothesis of depression etiology is the catecholamine hypothesis, based on a deficiency or malfunction of norepinephrine in the brain. The role of tyrosine as a precursor for norepinephrine and dopamine synthesis has prompted research on its efficacy as an antidepressive agent. Tyrosine may be particularly helpful in a subset of depressed patients with a deficiency in brain norepinephrine who fail to respond to conventional antidepressant medication except amphetamines.<sup>16</sup>

Most clinical trials examining tyrosine supplementation in depressed patients have been small in size and yielded mixed results. In 1980, Gelenberg et al published a single case, using a placebo-controlled, double-blind, crossover model, involving a woman who was unable to take conventional antidepressant medications due to side effects. Administration of 100 mg/kg oral tyrosine daily for two weeks resulted in significant symptom improvement, while one week of substitution with placebo caused a return of depressive symptoms. Under blinded conditions, tyrosine therapy was started again and the woman experienced marked improvement

in depressive symptoms. Plasma tyrosine levels two hours post-dose were approximately double those seen with placebo administration and no side effects were noted.<sup>10</sup>

The same researchers conducted a subsequent double-blind, placebo-controlled trial involving 14 patients suffering from major depression (five or more symptoms of depression present for at least two weeks) of at least moderate severity. Six patients received 100 mg/kg oral tyrosine daily and eight received placebo for four weeks. Four of six patients (67%) receiving tyrosine achieved scores of 10 or less (lack of clinically significant depression) on the Hamilton Depression Scale (HAM-D), indicating improvement in depressive symptoms. Only three of eight patients (38%) in the placebo group reported improvement. The patient sample size was too small to warrant an analysis of statistical significance.<sup>17</sup>

A larger randomized, prospective, double-blind trial, including 65 patients (ages 18-75) with major depression, compared the efficacy of tyrosine to imipramine or placebo for four weeks. Patients in the tyrosine group (n=21) received 100 mg/kg daily, the imipramine group (n=22) received 2.5 mg/kg daily, and the control group (n=22) received a placebo. Although patients taking tyrosine had increased fasting plasma tyrosine levels as well as increased urinary excretion of a norepinephrine metabolite, no statistically significant improvement in HAM-D scores was noted in the tyrosine group. This may have been a result of the 26-percent dropout rate (17 of 65 patients dropped out – four in the tyrosine group, eight in the imipramine group, and five in the placebo group) and the resulting small patient sample size.<sup>18</sup>

#### Effects of Stress

Several clinical trials have demonstrated tyrosine administration ameliorates some effects of stress, including hypertension. Some studies were conducted by the U.S. military to identify agents that would help military personnel cope with combat stress. In one double-blind, placebo-controlled, crossover trial, 23 male military personnel (ages 18-20) were given 50 mg/kg tyrosine or placebo and then exposed to three levels of environmental stress – exposure to 58°F/15°C and either 4,200 or 4,700 meters simulated altitude or

exposure to 71°F/22°C and 550 meters simulated altitude (normal control) for 4.5 hours. Forty minutes after stress initiation subjects received a second 50 mg/kg dose of tyrosine or placebo. At the end of the stress period, tyrosine administration had significantly reduced headache, coldness, stress, fatigue, muscle aches, and sleepiness compared to controls, regardless of which simulated high altitude subjects were exposed to. Improvements were noted in mood/mental states (happiness, mental clarity, hostility, and tension) and cognitive tests (math skills, coding map compass, and pattern recognition) in the tyrosine group.<sup>19</sup> A second study conducted by Massachusetts Institute of Technology and U.S. Air Force researchers demonstrated a similar affect when subjects were exposed to -50 mm Hg lower body negative pressure (LBNP) for 30 minutes. LBNP is a technique used to induce cardiovascular stress via application of a simulated gravitational load to the lower body. Tyrosine was administered in 50 mg/kg doses an hour before and after initial stressor exposure. Improvements were noted in pressure tolerance, pulse pressure, and feelings of “vigor.”<sup>20</sup>

In a study of 16 healthy young adults (mean age=27), 100 mg/kg tyrosine given prior to auditory stressor exposure resulted in significant improvement in the Stroop color-identification test and the Digit Span test evaluating short-term memory. In addition, a significant decrease in diastolic blood pressure was observed in the tyrosine group compared to placebo.<sup>21</sup> Other studies have also noted decreased blood pressure in stressed subjects receiving tyrosine therapy.<sup>22,23</sup>

In The Netherlands, 21 Royal Military Academy cadets were given tyrosine and evaluated on computerized memory and tracking tasks, mood questionnaire, and blood pressure during an extremely demanding two-week combat course. In double-blind fashion the tyrosine group (n=10) received 2 g tyrosine in a 500-mL protein-rich orange juice drink daily, and the placebo group (n=11) received a 500-mL carbohydrate-rich orange juice drink daily for the first six days of the combat training. Testing was conducted before combat training and the post-test commenced on the sixth day of training. The tyrosine group performed better on memory comparison and tracking tasks and had lower blood pressure readings than the placebo group. Mood

questionnaires did not reveal statistically significant improvement in the tyrosine group, although only 13 of 21 participants completed the questionnaire.<sup>22</sup>

Another double-blind study similar in sample size investigated the effects of tyrosine on cognitive performance in U.S. Marines during periods of extended nighttime wakefulness. Results demonstrated 150 mg/kg oral tyrosine given in the middle of the testing period resulted in improved performance (smaller performance decline) during the sleep deprivation period. Better performance was observed on tracking tasks and running memory tasks, and subjects also reported reductions in sleepiness and fatigue intensity. No side effects were noted in those taking tyrosine.<sup>23</sup> Two additional small studies conducted by other branches of the U.S. military indicate tyrosine administration at doses of 150 mg/kg prior to exposure to prolonged cold temperatures mitigates working memory deficits.<sup>24,25</sup>

### Attention Deficit Disorder

L-tyrosine has been studied as a potential therapeutic agent for attention deficit disorder (ADD) based on evidence suggesting dopaminergic central nervous system malfunctioning in individuals with ADD. In two studies of 34 and 12 patients with tyrosine dosages ranging from 30-150 mg/kg daily, significant symptomatic improvement in ADD symptoms was initially noted. However, tolerance to tyrosine developed after 6-10 weeks and symptoms returned, indicating no long-term benefit to tyrosine supplementation in this patient population.<sup>26,27</sup>

### Phenylketonuria

Individuals with phenylketonuria (PKU) are unable to convert phenylalanine to tyrosine, making tyrosine an essential amino acid for this population. Untreated patients who consume phenylalanine develop very high levels and are at risk for severe mental retardation.<sup>28</sup> Current treatment includes a phenylalanine-restricted diet and tyrosine-enriched amino acid mixtures to enhance neurological function.<sup>29</sup> Additional free tyrosine can be given but should be used judiciously, as tyrosine levels fluctuate throughout the day. Conversely, research in The Netherlands indicates it may be more beneficial to decrease the tyrosine in enriched amino acid mixtures to no more than six percent



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by weight and discontinue or decrease the amount of extra free tyrosine administered. When supplementing with tyrosine, blood levels should be closely monitored for diurnal variation.<sup>2</sup>

### Parkinson's Disease

Although tyrosine use in Parkinson's disease (PD) is not well researched, studies on animals, post-mortem Parkinson's patients, and dopamine metabolites in live Parkinson's patients indicate it may be of therapeutic benefit.<sup>30,31</sup> Post-mortem examination reveals hyperactivity of surviving neurostriatal neurons. It is thought tyrosine supplementation may enhance the synthesis and release of dopamine from these hyperactive neurons. Tyrosine may actually prove superior to L-dopa (conventional Parkinson's treatment) because it is normally present in the diet and side effects tend to be minimal.<sup>30</sup> Evaluation of tyrosine's effect in 23 PD patients demonstrated 100 mg/kg tyrosine daily raised plasma and cerebral spinal fluid tyrosine and homovanillic acid (a major dopamine metabolite) levels, indicating increased catecholamine synthesis and release.<sup>30</sup> In a small (n=10), long-term French study (English full text unavailable), five PD patients received tyrosine and five received L-dopa. Three years of tyrosine therapy resulted in better clinical results and fewer side effects than L-dopa treatment; study details and dosages were not available.<sup>32</sup>

### Narcolepsy

In a small, six-month pilot trial in eight narcoleptic patients an average daily dose of 100 mg/kg tyrosine resulted in complete elimination of daytime sleep attacks and cataplexy. The open-label design with lack of a control group limits this study's value.<sup>33</sup> A randomized double-blind, placebo-controlled trial of L-tyrosine in 10 narcoleptic patients with cataplexy (mean age=42) yielded different results. Patients were randomized to receive either 3 g tyrosine three times daily (~125 mg/kg daily for 160-lb adult) or placebo for four weeks and then switched to the other treatment with no washout period. Measurements included a multiple sleep latency test, patient symptom assessment, and psychometric tests. Three subjects in the tyrosine group reported improvement and rated themselves less drowsy, less tired, and more alert when on tyrosine; but improvement was

mild and not clinically significant. No significant differences were reported on other assessments compared to the placebo group.<sup>34</sup>

### Drug-Nutrient Interactions

The use of L-tyrosine with L-dopa may decrease the effectiveness of L-dopa because they compete for absorption in the small intestine. If taken concomitantly it is recommended that dosages be separated by at least two hours.<sup>3</sup> In persons taking thyroid hormone medications, tyrosine administration may boost thyroxin levels because it is a thyroid hormone precursor.<sup>2</sup>

### Side Effects and Toxicity

Tyrosine is generally safe with infrequent reports of side effects. Occasional nausea, diarrhea, headaches, vomiting, or insomnia are reported by those taking higher doses of tyrosine (>150 mg/kg daily).<sup>3</sup> Insomnia can be prevented by avoiding supplementation in the evening. Tyrosine has FDA GRAS status (generally recognized as safe), although safety studies in pregnancy have not been conducted. Therefore, patients who are pregnant or wish to become pregnant should consult a health care practitioner regarding tyrosine supplementation.

### Warnings and Contraindications

Patients with Grave's disease (hyperthyroidism) should use caution when supplementing with tyrosine because it can boost thyroid hormone levels.<sup>2</sup>

### Dosage

As reported in the literature, the typical daily dosage of oral tyrosine is 100-150 mg/kg body weight.

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