21 Tyrosine

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CONTENTS

21.1 INTRODUCTION

21.1.1 Background

Tyrosine is a large neutral amino acid (LNAA) and one of the nonessential amino acids. Nonessential means that the body can synthesize tyrosine in adequate amounts for normal function. It does not mean that this amino acid is not an essential constituent of the proteins, but rather it is not essential to include in the diet because tissues can make their own supply from the essential amino acid phenylalanine, the precursor of tyrosine. Phenylalanine and tyrosine together lead to the formation of thyroxin and epinephrine (Krause and Mahan, 1984). In addition, tyrosine is the precursor from which the pigment of skin and hair is made (Brown, 2001). Thus, most phenylalanine is converted to tyrosine. Excess phenylalanine is normally eliminated from the body by hydroxylation to tyrosine. Formation of L-tyrosine from L-phenylalanine occurs in the liver by the action of the enzyme

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phenylalanine hydroxylase and, to a very limited extent, in the brain by a secondary action of tyrosine hydroxylase on L-phenylalanine. As the enzyme phenylalanine hydroxylase is essential for this reaction, inactivity of this enzyme leads to an accumulation of phenylalanine in the blood and from there the excess is excreted in urine. This inborn error of metabolism, characterized by a virtual absence of phenylalanine hydroxylase activity and an elevation of plasma phenylalanine, is called phenylketonuria (PKU). PKU frequently results in mental retardation. The exact cause of the mental retardation is not known, but it is the consequence of the biochemical defect. Regarding tyrosine, anomalies of tyrosine metabolism are called tyrosinemia, in which the enzyme tyrosine aminotransferase is deficient and may, like PKU, lead to mental retardation and eventually keratitis and dermatitis. Treatment consists of controlled phenylalanine and tyrosine intake.

Essential amino acids must be supplied to the body through the diet. As tyrosine can be a metabolite of phenylalanine, daily requirements have been estimated for these two aromatic amino acids together. The adult minimum daily requirement for phenylalanine and tyrosine is 14 mg/kg body weight and an absolute minimum is 1.10 g (Krause and Mahan, 1984; Bender and Bender, 1997). This amount is readily obtained from four slices of bread and one pint of milk. The daily requirements in infancy and childhood (3 months to 12 years) range from 22 to 125 mg/kg. The reference range for plasma tyrosine is 64 ± 19 mol/l (mean ± SD). The solubility of L-tyrosine is low (0.453g/l in water at 25ºC; Bender and Bender, 1997). Various tyrosine-containing dipeptides, however, are more water soluble than tyrosine itself and are capable of raising serum tyrosine concentration. These dipeptides are L-tyrosyl-L-proline (TYR-PRO), L-tyrosyl-L-alalanine (TYR-ALA), L-alanyl-L-tyrosine (ALA-TYR), and L-tyrosyl-L-tyrosine (TYR-TYR). If given intravenously, they all cause significant increases in serum tyrosine.

The past decade has witnessed a resurgence of interest in the aromatic amino acid requirements. Although tyrosine is indispensable in neonates, it is a dispensable amino acid in healthy adults, because it can be synthesized though hepatic phenylalanine hydroxylation when sufficient phenylalanine is provided in the diet. However, in conditions such as hepatic and renal disease, where aromatic amino acid metabolism is impaired, a preformed balanced source of the amino acid may be required to minimize aromatic amino acid excess and catabolism. Tyrosine requirements have been estimated in adults at fixed and adequate, but not excessive, phenylalanine intakes. The mean daily tyrosine requirement of healthy men receiving an average intake of dietary phenylalanine was estimated to be 6 mg/kg. The safe population estimate of daily intake of tyrosine is 7 mg/kg (Roberts et al., 2001). This is half of the Food and Agricultural Organization/World Health Organization/United Nations University (FAO/WHO/UNU) upper requirements of 14 mg/kg for total aromatic amino acids tyrosine and phenylalanine (Basile-Filho et al., 1998).

21.1.2 Tyrosine-Dependent Control of Brain Catecholamine Synthesis

Along with leucine, isoleucine, methionine, valine, phenylalanine, and tryptophan, L-tyrosine is an LNAA. As a consequence, tyrosine shares a sodium-dependent active transport system in the gut with these other neutral amino acids. Before intracellular metabolism, amino acids must be transported from the interstitial space across the cell membrane. This transport requires the presence of a carrier system in the cell membrane and is mostly an active process because the amino acid concentration gradient between the cell's interior and the bloodstream is often unfavorable. The transport process is usually associated with the operation of a sodium ion pump. At least seven different carriers — A, ASCP, L, Ly, dicarboxilate, N, and β (beta) systems (Skeie et al., 1990) — having overlapping specificity for the different amino acids exist. For uptake into the brain, L-tyrosine shares carrier system L with the LNAAs leucine, isoleucine, valine, phenylalanine, tryptophan, and methionine. The affinity of L-tyrosine for the transport system is higher than the affinities of some of the other LNAAs. As a consequence of this shared carrier system, the concentration of L-tyrosine in relation to the concentration of all the LNAAs determines the uptake into the brain. Thus, the tyrosine:LNAAs plasma ratio is predictive of brain tyrosine concentration. In mice, brain

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tyrosine reaches its maximum concentration 1 h after oral ingestion and returns to the baseline level after 4 h (Topall and Laborit, 1989).

At levels up to 15 g/day, the amount of protein in the diet has been shown to influence the levels of tyrosine in plasma. High protein and high carbohydrate meals also influence the plasma ratios among LNAAs. For example, the tyrosine:LNAAs ratio is low following a meal high in protein, because plasma levels of the neutral branch-chain amino acids (BCAAs) leucine, isoleucine, and valine are increased with high protein intake. The BCAAs are transported into the brain by the same carrier that transports the aromatic amino acids (AAAs). Consequently, competition for entry into the brain between BCAAs and AAAs may influence the rate of synthesis and the level of neurotransmitters. Therefore, although the initial metabolism of BCAAs occurs primarily in the skeletal muscle, BCAAs can influence behavior (Skeie et al., 1990). Thus, following a meal high in protein, tyrosine is at a comparative disadvantage for uptake into the brain. Conversely, after a meal high in carbohydrates, the tyrosine:LNAAs ratio is high because the insulin secreted in response to the carbohydrates also promotes entry of the BCAAs into peripheral tissues. As a result, less competition for tyrosine uptake into the brain from LNAAs exists after a meal high in carbohydrate.

L-Tyrosine thus is a precursor for several biologically active substances, including brain catecholamine neurotransmitters (norepinepherine and dopamine). Urinary excretion products of the catecholamines include methoxyhydroxyphenylethyleneglycol (MOPEG) and homovanillic acid (HVA).

Wurtman (1992) formulated a sequence of biochemical processes necessary for any nutrient precursor to affect the synthesis and release of its neurotransmitter product.

1. Plasma levels of the precursor must be allowed to increase after its administration or after its consumption as a constituent of foods. Indeed, plasma levels of tyrosine vary severalfold after the consumption of normal foods.
2. Brain levels of the precursor must be dependent on its plasma level; that is, there must not be an absolute blood-brain barrier for circulating tyrosine. Such a barrier does not exist. Rather, facilitated diffusion mechanisms operate that allow tyrosine to enter the brain at rates that depend on its plasma level.
3. The rate-limiting enzyme within presynaptic nerve terminals that initiates the conversion of tyrosine to its neurotransmitter product must be unsaturated with its substrate so that it can accelerate synthesis of the neurotransmitter when presented with more tyrosine.
4. The activity of tyrosine hydroxylase cannot be subject to local end-product inhibition, that is, the products of tyrosine hydroxylation and sodium. DA itself may not suppress tyrosine hydroxylation activity. However, tyrosine hydroxylase activity is probably subject to some end-product inhibition when the enzyme protein is in its nonphosphorylated state. But once the enzyme is phosphorylated, when the nerve cells containing it become active it is apparently freed from this constraint.

At present, L-tyrosine or tyrosine-containing diets are known to increase the plasma tyrosine:LNAAs ratio and brain tyrosine levels in animals and humans. This occurrence may be followed by an increase in brain noradrenaline (NA) or dopamine (DA), or both. The ability of tyrosine supplementation to enhance catecholamine (NA and DA) synthesis has been established in a variety of animal and human studies.

21.2 ANIMAL STUDIES

Interest in the amino acid tyrosine centers on its role as a precursor to neurotransmitters, in particular NE and DA. The question is whether elevating tyrosine concentration in brain NE and DA neurons can stimulate neurotransmitter synthesis. The first question is whether plasma levels of tyrosine

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rise after its administration and whether the level of tyrosine in the brain is dependent on its plasma level. Studies on these issues have been mainly conducted on animals, because techniques for determining the concentration of brain neurotransmitters cannot be applied to humans. The usual procedure involves decapitating the animal after stress induction, removing the brain, freezing, and storing until dissection. Brain tissue can than be taken from different regions. At present, an extensive amount of animal data is available on the effects of tyrosine administration on neurotransmitter synthesis, neuroendocrine and autonomic variables, and behavior.

21.2.1 Protein-Rich Meals and Plasma Tyrosine Levels

In rat studies it has been shown that the acute ingestion of a single meal varying in protein content from 6 to 18 to 40% casein results in elevations of the serum tyrosine level from 73 to 121 to 344 nmol/ml, respectively. However, although the *ad libitum* consumption of meals varying in protein content for 3 days caused tyrosine serum levels to rise from 100 to 200 nmol/ml as protein intake increased from 6 to 24% casein, the serum level declined after intake of 40% casein. The increase in tyrosine from 6 to 24% casein was larger than the rise in levels of the competing LNAAs, and the serum tyrosine ratio also rose. In rats fed high-protein (40% casein) diets, the serum tyrosine level and ratio decreased slightly with ingestion of casein diets. All parameters of retinal DA synthesis and release, that is, retinal DA, DOPAC, and HVA levels, reflected the changes in precursor level, peaking at 24% casein intake. The increase in the amount of dietary protein to the normal diet increased retinal tyrosine levels, which in turn increased retinal DA synthesis and release (Gibson, 1988). The finding that after a single meal the serum tyrosine level directly varies with dietary protein only to decline with a 40% casein diet can be explained by adaptation in the liver tyrosine-metabolizing enzyme. Thus, serum tyrosine levels in rats consuming 40% casein diets seem to be related to an increase in the liver enzyme tyrosine aminotransferase (TAT), a major tyrosine-metabolizing enzyme. Increase in the activity of TAT prevents the continued rise in serum tyrosine levels in the case of chronic ingestion of high-protein diets. An additional cause may be the influx of other amino acids, for example, leucine or phenylalanine, which may inhibit or compete for the synthetic enzyme tyrosine hydroxylase.

Several years later, groups of young adult male rats were studied that ingested *ad libitum* diets containing 2, 5, 10, or 20% protein for 2 weeks (Fernstrom and Fernstrom, 1995a). Serum tyrosine levels and serum tyrosine:LNAAs ratio rose as dietary protein content increased from 2 to 10%. In addition, tyrosine levels in the retina, hypothalamus, and cerebral cortex were lowest in rats consuming 2% protein and rose progressively to a plateau in rats ingesting 10% protein. No consistent increase occurred between 10 and 20% protein intake. Tyrosine hydroxylation rate in retina and hypothalamus, but not prefrontal cortex, rose in parallel with the increments in tyrosine serum level between 2 and 10% protein, showing no further increase between 10 and 20% protein. These results indicate that the differences in tyrosine levels in the retina and hypothalamus may influence directly the rate of tyrosine hydroxylation, and thus perhaps the overall rate of catecholamine synthesis. This relationship might provide the hypothalamus, a region that is important in food intake control, with a signal for monitoring and ultimately modulating the chronic level of protein intake.

21.2.2 Neurotransmitter and Behavioral Studies in Animals

Tyrosine may be especially useful in counteracting any stress-related NE depletion and associated behavioral disturbances. The rationale behind this hypothesis is that stress induces brain depletion of catecholamines, especially NE, in animals. As a consequence of the decrease of brain NE levels, behavior deficits may become visible in these stressed animals. Supplementation with tyrosine may increase depleted brain NE levels and thereby counteract stress-induced behavioral impairment. Thus, most animal studies on tyrosine, brain NE, and behavior explore the potentially beneficial

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effects of tyrosine under stressful conditions. Exposure of mice or rats to an acute, uncontrollable stressor such as cold-swim or tail shock can increase brain NE turnover and decrease locomotor and exploratory behavior. Cold-swim stress was used to determine the effects of dietary supplements of L-tyrosine on brain neurotransmitters as well as on aggressive behavior and locomotor activity in young and aged mice presented with or without this type of stress (Brady et al., 1980). Forty-eight minutes before observing aggressive behavior, half the animals were placed in a tank filled with cold water (2 to 6ºC) for 3 min. Nonstressed animals were placed in a mouse cage for only 3 min. In the absence of stress exposure, aggressive behavior in the young mice increased after tyrosine supplementation (a diet consisting of 21% casein supplemented with 4% L-tyrosine). However, no increase in aggressive behavior was seen in the aged mice. The induction of cold-swim stress decreased the aggressiveness of both young and aged mice. Tyrosine prevented the stress-induced decrease of aggressiveness in both groups. In stressed older mice, tyrosine prevented decreases in locomotion. In addition to the behavioral effects, tyrosine was found to increase brain tyrosine and DA. The authors concluded that tyrosine is effective in reducing behavioral deficits of stressed animals. This observed effect may be related to the prevention of NE depletion. The authors explain the increase of aggressive behavior in young, unstressed mice by tyrosine with a reciprocal relationship between DA and (NE + 5-HT) for the facilitation of aggressive behavior. Thus, aggressive behavior may be related to a lower brain NE and 5-HT relative to DA. An enhanced metabolism of 5-HT, indicated by increases in 5-HIAA, was observed in the aging mice. In addition, the DA:(NE+ 5-HIAA) ratios were highly correlated with mean aggression scores in young and aged animals. As the aged mice had the highest levels of NE and 5-HIAA, tyrosine could not facilitate aggression in these older animals but it could in young animals with lower brain NE and 5-HT. This finding suggests that tyrosine increases aggression if DA levels are relatively higher than NE and 5-HT levels.

The other type of stress induction, tail shock, has also been studied in male Sprague-Dawley rats. Animals were subjected to a 60-min period of tail shock or no shock after pretreatment with tyrosine (200 mg/kg, IP). Effects were compared with those in animals pretreated with saline. Norepinephrine and 3-methoxy-4-hydroxy-phenylethylene-glycol sulfate (MHPG-SO_4) levels within the locus coeruleus, hippocampus, and hypothalamus were altered after exposure to shock. Brain NE appeared to be depleted and its turnover increased. Behavioral deficits were observed by using measures of locomotion, standing on hind legs, and hole poking in an open-field apparatus. Animals given tyrosine before shock displayed neither shock-induced NE depletion nor the deficits in locomotion and hole poking. Also, brain MHPG-SO_4 levels tended to be higher than after shock alone. Thus, after tail-shock stress NE is released more rapidly from some neurons and can be restored by synthesis or reuptake. The consequence is that noradrenergic transmission and NE-dependent exploratory behaviors are impaired. Tyrosine prevents both the neurochemical and behavioral deficits in tail-shocked animals, presumably by enhancing NE synthesis (Reinstein et al., 1984).

A similar study was performed in rats given a diet enriched with tyrosine and exposed to tail-shock stress. Animals receiving the tyrosine-enriched diet displayed neither the stress-induced depletion of NE nor behavioral deficits like reduction of exploratory motor activity, of hole-poking, or of the frequency of standing on their hind legs. As tyrosine did not change NE turnover in animals not subjected to stress, one can conclude that catecholaminergic neurons seem to respond to the precursor amino acid only when they are physiologically active (Lehnert et al., 1984).

These studies clearly indicate that stress may deplete NE brain levels and thereby impair behavior. In addition, these effects may be prevented or reversed by tyrosine. It has been proposed that the technique of measuring striatal DA metabolism in untreated animals is too insensitive to demonstrate an increase in DA release, despite it being present. Thus, a more sensitive intracerebral dialysis method that directly assesses DA levels within the intrastriatal extracellular fluid was used to determine whether tyrosine may increase CA brain levels when neurons are not physiologically active, that is, if no stress is induced to accelerate the firing of CA neurons. The effect of the intraperitoneal administration of 50 to 200 mg/kg tyrosine on DA release *in vivo* in anesthetized

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rats on responses of DA neurons in the corpus striatum and the nucleus accumbens has been investigated in some studies. DA release was assessed using brain microdialysis to monitor extracellular fluid from rat striatum and nucleus accumbens. DA concentration from both the striatum and nucleus accumbens increased in response to tyrosine. A larger tyrosine effect was seen in the nucleus accumbens than in the corpus striatum. Tyrosine administration at 50 to 200 mg/kg IP causes a dose-related increase in extracellular fluid DA levels. However, the rise in DA was brief, suggesting that a receptor-mediated feedback mechanism responded to the increased DA release by diminishing neuronal firing or sensitivity to tyrosine. The levels of DOPC and HVA, its major metabolites, were slightly elevated, and this increase was not dose related. Thus, if the measurement of changes in striatal DOPAC and HVA is negative, it need not rule out increases in nigrostriatal DA release. From these findings it can be concluded that tyrosine is able to increase DA release even when no additional treatment is given to accelerate the firing of DA neurons (Acworth et al., 1988; During et al., 1988).

Although tyrosine may enhance DA release in nonstressed animals, there is no indication that the same is true for NE release. However, if the concentration of NE and DA is measured in animals after stress induction, no changes in the DA concentration are found (Weiss, 1991). Therefore, more severe stress seems to be required to alter DA levels in the brain than NE levels. The release of DA may be more related to coping behaviors than to the uncontrollability of the stressor, which appears to be the crucial determinant of the NE response (Lehnert et al., 1984). These data suggest that NE is more easily released than DA in nontreated animals.

21.2.3 Regulation of Blood Pressure in Animals

In animals, tyrosine not only reduces blood pressure in hypertensive rats but also elevates blood pressure in animals with hemorrhagic shock. Thus, tyrosine may normalize blood pressure. In one study, rats were injected with 25, 50, or 100 mg/kg tyrosine after having been bled until 25 to 50% of blood volume was lost (about 45 min). The 50- and 100-mg/kg doses produced significant increases in systolic blood pressure. The 50-mg/kg dose produced an increase after 5 min, the 100-mg/kg dose after 5, 15, and 30 min. Therefore, a higher dose continued to increase blood pressure 30 min after tyrosine administration (Conlay et al., 1981). With respect to hypertension, a 100-mg/kg injection of 15 µg L-tyrosine resulted in a significant reduction in blood pressure in the spontaneously hypertensive rat (SHR). At the same time, an increase in the turnover of NA as indicated by MOPEG-SO_4 was observed. Blood pressure depression was maximal at 2 h following injection, with pressure returning to the preinjection value by 4 h (Yamori et al., 1980). Unfortunately, the use of IV tyrosine to enhance catecholamine release in hemorrhagic shock and other cardiovascular diseases, or as a constituent of nutrient mixtures used for total parenteral nutrition, is limited by the unusually poor solubility of the amino acid in water. Fortunately, as mentioned in the introduction, various tyrosine-containing dipeptides are much more water soluble than tyrosine itself. Within 5 min of administering an IV of these dipeptides (12.5 to 25 mg/kg) to hemorrhaged, hypotensive rats, significant increases in serum tyrosine and significant elevations in systolic blood pressure were observed. The extent of blood pressure increase after 2 h ranged from 50 to 88%. In addition, in SHRs all these dipeptides given intraperitoneally at 100 mg/kg lowered systolic blood pressure. The dipeptide TYR-TYR also reduced blood pressure at 50 mg/kg. These observations suggest that tyrosine-containing dipeptides may be useful in maintaining or elevating blood TYR levels (Maher et al., 1990). These studies indicate that tyrosine may accelerate catecholamine synthesis, depending on the firing frequency, which may be high in hypertension and low in hypotension, of catecholamine-producing cells in the brain stem.

Tyrosine then raises blood pressure by enhancing the peripheral synthesis and release of catecholamines. The data available indicate that the effect of tyrosine on blood pressure is in the range of several hours, peaking at ca. 2 h after administration. As the use of parenteral tyrosine is limited by its poor water solubility, it would be interesting to examine the possibility to use

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tyrosine-containing dipetides pharmacologically. If there were more knowledge of the efficacy of these dipeptides to use as tyrosine substitutes in parenteral solutions, it may be of clinical use, particularly for normalization of blood pressure.

21.2.4 Behavioral Studies in Animals

Exposure to cold stress or other stressors such as tail shock or (simulated) altitude can impair working memory. This may be attributed to a reduced synthesis of brain catecholamines. Some studies have been performed to determine whether tyrosine would protect rats from the adverse effects of cold stress or hypobaric hypoxia (simulated altitude) on working memory. In the cold stress condition, working memory was assessed by a delayed matching-to-sample (DMTS) task, which was administered in a standard operant chamber. There were two response levers on the front wall and a third lever at the rear wall. A light above one of the two response levers was illuminated and the rat had to press the lever beneath it. The light was extinguished and a cue light was turned on above the rear response lever, which started a delay interval of 1, 2, 4, 8 or 16 sec. The first response on the rear wall lever after the delay interval illuminated both lights above the other two response levers on the front wall. The rat then had to push the cued lever previously responded to and a food pellet was delivered. By this procedure, the retention interval for remembering the right lever was varied from 1 to 16 sec. In the hypoxia study, memory was assessed by the Morris water maze with a hidden escape platform. Reference memory was established by allowing each rat 120 sec to escape onto the platform. If the rat failed, it was guided to the platform. After having stayed for 10 sec on the platform, working memory was assessed by determining the latency of reaching the platform on a second trial.

Cold stress was induced by providing an ambient temperature of either 2 or 22ºC. Hypobaric stress was induced at 2 and 6 h of an 8-h exposure to a simulated altitude of 5950 m. During cold exposure, doses of 100 and 200 mg/kg tyrosine significantly improved overall matching accuracy but did not completely reverse the effects of cold exposure. An IP dose of 400 mg/kg of tyrosine, administered 30 min before testing, reversed the memory decrement that was induced by altitude exposure. Thus, supplemental tyrosine is partially effective in ameliorating the effects of stress on working memory performance, possibly by preventing a stress-induced reduction in brain catecholamine levels (Shukitt-Hale et al., 1996; Shurtleff et al., 1993).

21.2.5 Effects of Tyrosine on the Cognitive and Biochemical Consequences of Weight Loss

Animal studies have provided some indications that tyrosine might be a potential therapy for cognitive and mood problems related to maintaining a reduced body weight. It can probably be used to treat eating disorders such as anorexia nervosa and obesity. Chronic voluntary and involuntary weight loss may lead to changes in brain neurotransmission, which may be counteracted by administering tyrosine. Work in rats has shown that catecholamine pathways in the hypothalamus are involved in feeding behavior. Stimulation of α-adrenergic receptors in the area of the paraventricular nucleus of the hypothalamus induces feeding and stimulation of β-adrenergic receptors inhibits feeding behavior. Animals depleted of DA may stop eating and starve to death. This observation appears to be similar to patients with anorexia nervosa. In these patients, cerebrospinal fluid (CSF) levels of tyrosine, NE, and metabolites of NE are decreased. After weight loss, the inability to eat and restore body weight may be related to neurochemical dysfunctions (Avraham et al., 1996). Thus, as a consequence of insufficient NE or DA, appetite in these patients may be suppressed. If weight is returned to normal, NE levels can remain abnormal for a long time after recovery. Studying the effects of malnutrition on catecholamine regulation and cognitive function in animals can shed more light on the pathophysiology of eating disorders in humans and may lead to more successful treatments.

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One method to decrease body weight in mice is to place them in a cage with plexiglass partitions. The mice are separated from each other by plexiglass and can smell and see each other without having any physical contact. This separation stress decreases body weight. Within 14 days, a reduction of 35% in body weight can be observed. Separation-induced behavioral deficits were assessed by measuring the number of spontaneous alternations in the T-maze. Spontaneous alternation is a two-trial phenomenon in which an animal is said to alternate if its choice on the second trial of testing is opposite to that of the first trial. Alternation behavior in the T-maze is considered to be a test of hippocampal function, related to catecholaminergic and cholinergic pathways. A reduction in the number of spontaneous alternations is seen as impaired behavior. Separation reduced the ability of mice to spontaneously alternate in the T-maze when compared with control groups. This reduction was related to depletion of NE and DA. Increasing tyrosine availability by injections (dose of 100 mg/kg) 1 h before testing restored performance to control levels and repleted DA. In addition, tyrosine injections increased MHPG and the MHPG:NE ratio, suggesting an increase of NE. However, tyrosine did not affect body weight (Hao et al., 2001). Another way to decrease weight is by chronically restricting the diet and then studying the resulting cognitive and neurochemical alterations. Young female rats were fed 100, 60, and 40% of the calculated daily nutritional requirements for up to 18 days. For the mice on a 60% diet restriction weight loss was ca. 15%, whereas the mice on the 40% diet restriction experienced a 25% weight loss. Cognitive function was evaluated by an eight-arm maze with water as a reward. In animals on the 40% diet restriction, maze performance was impaired. Tyrosine injections of 100 mg/kg/day restored performance. This was associated with changes in α and β receptor density and increased NE and MHPG. Regarding adrenergic receptors, diet restriction to 40 and 60% increased the number of α-receptors and decreased gradually the number of β receptors in the hypothalamus. Tyrosine treatment reversed these alterations, reducing the number of α-receptors in both 40 and 60% diet-restricted mice and increasing β receptors in the 40% diet-restricted mice. There were no changes in body weight (Avraham et al., 1996).

Thus, at present there is evidence from animal studies that tyrosine restores the neurobiological disturbances caused by diet restriction without causing an increase in body weight. These insights may be directed toward improving the treatment of anorexia nervosa and related eating disorders in humans. Unfortunately, studies on tyrosine administration in human subjects with eating disorders are nonexistent.

21.3 HUMAN STUDIES

Behavioral effects of stress in humans are well documented. The main cognitive effects of stress are (1) attentional narrowing, (2) increased speed in information processing paired with less accuracy, and (3) decrease in the capacity of short-term memory. Whether these behavioral stress effects are associated with NE depletion is still unclear. The physiological effects of stress on the peripheral nervous system can be summarized as being increased heart rate, blood pressure, muscle tonus, skin conductance, and respiration rate. In addition, biochemical changes take place, such as an increase in the concentration of catecholamines (Deijen and Orlebeke, 1994). In humans, NE depletion causes insuppressible eye movements during smooth pursuit and visual search. The finding that catecholamine depletion increases the amplitude and frequency of saccadic intrusions during fixation and pursuit implies that brainstem neurons use catecholamines to suppress saccades (Tychsen and Sitaram, 1989). The well-known association between anxiety and the frequency of eye movements may be circumstantial evidence that stressful events cause NE depletion in human brain.

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21.3.1 Tyrosine/Catecholamine Depletion

Low levels of catecholamines may predispose humans to lowered mood and psychomotor retardation. Acute depletion of the catecholamine precursors phenylalanine and tyrosine can reduce catecholamine synthesis.

An amino acid cocktail has been devised and tested in rats to determine whether it reduces central nervous system (CNS) tyrosine levels. In addition, the effect of this mixture on *in vivo* tyrosine hydroxylation rate was examined. The amino acid cocktail consisted of 10 amino acids lacking tyrosine and phenylalanine. Serum TYR levels, the serum ratio of TYR to the sum of its transport competitors, and CNS TYR concentrations fell within 1 h of intubation and remained low for at least 3 h. *In vivo* tyrosine hydroxylation rate, determined in the hypothalamus and retina 2 h after amino acid administration, also declined. Thus, such a mixture can be used to acutely reduce TYR levels and hydroxylation rate in the CNS. This paradigm has been proved to be a useful tool for studying catecholamine involvement in normal and impaired behavior in humans (Fernstrom and Fernstrom, 1995b). The use of this acute phenylalanine/tyrosine depletion (APTD) paradigm in humans indicated that participants ingest a mixture of essential amino acids that is deficient in the catecholamine precursors phenylalanine and tyrosine. This induces protein synthesis, which diminishes the body's stores of phenylalanine and tyrosine. Because tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, is normally not fully saturated with tyrosine, the reduced availability of tyrosine will likely reduce catecholamine synthesis. Effects of APTD on mood and anxiety have been examined in several human studies. In one study, 5 h after ingesting an amino acid mixture lacking tyrosine and phenylalanine, healthy female participants aged 19 to 39 years underwent a mild threatening psychological challenge, a social stress test. This test consists of preparing and presenting a 5-minute speech followed by 5 min of solving arithmetic problems. Mood scales were administered before ingestion of the amino acid mixture and again before and immediately after the social stress test, which took place 5 h after ingestion. APTD lowered mood and energy and increased irritability scores. Effects were only significant after the psychological challenge. APTD did not attenuate the anxiety caused by the psychological challenge. This study shows that lowered catecholamine synthesis impairs mood, but only after subjects have been exposed to unpleasant events (Leyton et al., 2000). The same paradigm of inducing acute tyrosine depletion has been studied in male and female volunteers who received an amino acid drink lacking tyrosine and phenylalanine (TYR-free) on one occasion and on the other received a balanced amino acid drink (BAL). Plasma prolactin, amino acid levels, mood, and cognitive functions were assessed at different timepoints within a 6-h period following the drinks. As plasma prolactin levels rose 5 to 6 h following the TYR-free drink relative to the BAL-drink, decreased DA neurotransmission within the hypothalamus was inferred. The subjects reported that they felt worse after the TYR-free drink than after the BAL drink. Regarding cognitive functions, ca. 6 h following the TYR-free drink, spatial recognition memory and spatial working memory were impaired. Both types of memory functions are sensitive to frontostriatal dysfunction, particularly dopaminergic pathways. Thus, tyrosine depletion in healthy volunteers may impair executive functions, such as planning and set shifting, involving neuronal networks connected with or situated within the prefrontal cortex (Harmer et al., 2001). It has been suggested that DA plays a major role in executive functions as DA neurons appear to be more vulnerable to TYR depletion than do NA neurons. Administration of a TYR-free amino acid load also reduced DOPA accumulation, especially in the striatum (–44%) and nucleus accumbens (–34%), areas with a predominant dopaminergic innervation. Smaller decreases (–20 to 24%) were detected in the cortex, hippocampus, and hypothalamus. The effect on DOPA was prevented by supplementing the mixture with tyrosine/phenylalanine. However, the TYR-free amino acid mixture did not alter the basal or amphetamine-evoked release of NA in the hippocampus. Therefore, administration of a TYR-free amino acid mixture to rats depletes brain TYR to cause a substantial decrease in brain DA synthesis and release (McTavish et al., 1999).

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21.3.2 Endocrine/Biochemical Studies

At present there is compelling evidence that the synthesis and release of a number of brain neurotransmitters (e.g., acetylcholine, serotonin, and the catecholamines) depends on brain levels of their precursor nutrients, that is, choline, tryptophan, and tyrosine. Wurtman (1981) introduced this idea.

The effects of tyrosine on plasma tyrosine and catecholamine synthesis and release have been examined in many human studies. For instance, an oral load of 100 mg/kg tyrosine significantly increases the plasma tyrosine level. In fasting recumbent normal subjects, the plasma concentration was nearly doubled 1 h after tyrosine ingestion and doubled 2 h after ingestion (Cuche et al., 1985).

In addition to the effects of L-tyrosine alone, the combined effect of tyrosine and concurrent food consumption on plasma tyrosine levels and the plasma tyrosine ratio has been examined. On the first day, 11 subjects consumed three equal portions of a diet containing 113 g of protein at 8 a.m., 12 p.m., and 5 p.m. On the other day, they took 100 mg/kg of L-tyrosine in three equally divided doses before the same meals. Plasma tyrosine levels rose during the day when subjects consumed the diet alone. The concentrations were highest between 1 p.m. and 9 p.m. and lowest at 5 p.m. The consumption of the protein-rich meals caused daytime postprandial plasma amino acid levels to rise. Ingestion of L-tyrosine 1 h before each meal elevated plasma tyrosine levels much more. Tyrosine administration did not change plasma concentrations of the other neutral amino acids that compete with tyrosine for entry into the brain. Peak tyrosine plasma levels of Day 2 (178 nmol/ml) were more than double the peak levels of Day 1 (79 nmol/ml). The plasma tyrosine ratio increased from 0.13 (only diet) to 0.21 on the day subjects received the combination of the diet and tyrosine. Because the amount of tyrosine that enters the brain depends on the plasma tyrosine ratio, the authors concluded that tyrosine administration might thus increase brain tyrosine levels and may accelerate catecholamine synthesis in humans with diseases in which catecholamine synthesis or release is deficient (Melamed et al., 1980).

Another step then is to determine the relationship between the plasma tyrosine level and the CSF concentration of tyrosine. The biochemical relationship between CSF tyrosine and plasma tyrosine was determined in 52 normal individuals. Males showed higher concentrations of plasma tyrosine than did females. In both females and males, CSF tyrosine was significantly related to plasma tyrosine and the plasma ratio of tyrosine to LNAAs. Age does not appear to be related to these biochemical parameters in males or females (Möller et al., 1996). Effects of oral amino acid supplementation on physical and neuroendocrine variables were investigated in male subjects who cycled in four trials until exhaustion. In one of the four conditions, 20 g of tyrosine was administered. Plasma TYR/BCAAs was augmented. Plasma prolactin (PRL) was increased after 30 min of exercise. Tyrosine administration did not alter physical performance (exercise time to physical exhaustion). However, the observed rise in plasma PRL concentration indicates that tyrosine administration affected transport characteristics of the L-carrier and central neurotransmitters systems. Augmented PRL secretion is likely to have resulted from an increased activity of the dopaminergic system induced by supplemental plasma tyrosine. This study provides further evidence that tyrosine enhances DA release, but only from activated neurons (Strüder et al., 1998). From these studies it may be concluded that ingestion of L-tyrosine leads to higher plasma tyrosine levels and is associated with higher CSF tyrosine levels, which in turn may increase levels of brain catecholamines.

21.3.3 Treatment of Depression

Only two studies on the possible use of tyrosine as an antidepressant have been performed. The first study was a single case and provides evidence for an antidepressant effect of tyrosine. In a double-blind, placebo-controlled crossover trial, a depressed woman was administered L-tyrosine 100 mg/kg/day by mouth in three daily doses for 5 weeks. After 2 weeks of tyrosine administration

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the depression decreased. The patient felt an improvement in mood, self-esteem, sleep, and energy level, and she also experienced less anxiety and somatic complaints. Her clinical global impression went from "moderately ill" to "not ill at all." Within 1 week of placebo substitution, the depressive symptoms returned. No unwanted effects of tyrosine ingestion were observed. Ten years later, the same author reported negative findings in a large sample of patients. In this double-blind study, 65 outpatients with major depression were treated with 100 mg/kg/day oral L-tyrosine, imipramine, or placebo for 4 weeks. MHPG excretion rose significantly after tyrosine administration, suggesting an increase in catecholamine turnover. However, HAM-D scores did not show evidence of tyrosine's antidepressant activity (Gelenberg et al., 1980, 1990). In spite of these negative results it may still be possible that a subgroup of depressed patients with low pretreatment tyrosine plasma levels is responsive to tyrosine. However, no data concerning such depressed patients are available.

21.3.4 Treatment of Attention Deficit Disorder

Tyrosine supplementation has also been used to treat attention deficit disorder (ADD) in children and adults. In seven children with ADD, 100mg/kg/day of tyrosine was given for 3 weeks. The treatment effects were evaluated by the parents on the 10-item Connors rating scale and by their teachers on the Connors Teaching Rating Scale. Furthermore, the children were given a vigilance task, the Children's Checking Task. There were no treatment effects (Eisenberg et al., 1988). For the treatment of adults, the daily dose of L-tyrosine given to treat ADD was 150 mg/kg in all studies. The treatment periods in adults ranged from 8 to 16 weeks. Although in some studies treatment effects were seen after ca. 4 weeks, at 6 weeks all patients who responded to L-tyrosine became tolerant to its therapeutic effects (Wood et al., 1985; Reimherr et al., 1987; Eisenberg et al., 1988). It is clear from these findings on ADD that tyrosine has no clinical utility in the treatment of this disorder.

Another way to use tyrosine for treating ADD is to combine it with methylphenidate. Studies of rats have examined whether exogenous tyrosine could potentiate the methylphenidate-induced increase in extracellular DA. Male rats were implanted with microdialysis probes in the right nucleus accumbens. Samples were collected from awake animals beginning 22 h after surgery for 3 consecutive days. On a given day, an animal was infused with methylphenidate, tyrosine, or methylphenidate plus tyrosine. Methylphenidate plus tyrosine significantly increased extracellular levels of DA in comparison to the drug alone. This effect was long lasting and peaked 40 min after the peak induced by methylphenidate alone. Tyrosine alone induced a small but significant increase in extracellular DA in the absence of any treatment to accelerate the firing of DA cells (Woods and Meyer, 1991). Tyrosine or a tyrosine-rich diet given to attention deficit hyperactivity disorder (ADHD) children may thus increase the supply of brain DA. In addition, if supplemental tyrosine does sustain the methylphenidate-induced increase in extracellular DA in humans by preventing the depletion of tyrosine, exogenous tyrosine along with methylphenidate may prolong the effect of such drugs as Ritalin®. Thus, administration of tyrosine in addition to methylphenidate may reduce the side effects of methylphenidate by reducing the frequency of administration. Although these considerations may have implications for treating ADHD, there are no other studies on this topic. It would be worthwhile to carry out clinical studies in patients to evaluate the effects of tyrosine combined with methylphenidate.

21.3.5 Tyrosine and Parkinson's Disease (PD)

To determine whether L-tyrosine administration can enhance DA synthesis in humans, the levels of tyrosine and the major DA metabolite HVA were measured in lumbar spinal fluids of 23 patients with Parkinson's disease (PD) before and following ingestion of 100 mg/kg/day of tyrosine (Growdon et al., 1982). Nine patients received 100 mg/kg probenecid, which blocks the transport of HVA across the CSF-blood barrier and allows it to accumulate in the CSF. L-Tyrosine increased both

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CSF tyrosine levels in all patients as well as HVA levels in patients pretreated with probenecid. Thus, L-tyrosine can increase DA turnover in Parkinson's patients in whom dopaminergic neurotransmission should be enhanced. The question then remains whether L-tyrosine has a therapeutic effect in Parkinson's patients. Daily doses of 4.7, 4.2, and 1.8 g of L-*m*-tyrosine in three Parkinson's patients in addition to a decarboxylase inhibitor did not result in any improvement in tremor, rigidity, or hypokinesia. The treatment duration, however, is not reported (Cotzias et al., 1973). In addition to this pilot-like study, there is one long-term study on tyrosine and PD with positive results. Ten PD patients were tested in an open study. Five patients with ongoing and unsatisfactory L-dopa or DA agonist treatment, or both, shifted to L-tyrosine treatment, and five patients were initially treated with L-tyrosine. Patients were administered a mean daily dose of 2.24 g L-tyrosine for 5 to 36 months (mean treatment duration 14.8 months). A gradual improvement, as assessed by a scale of 0 to 4 concerning rigidity, tremor, akinesia, and gait, was observed over several months, reaching a maximum within ca. 6 months. Tyrosine administration was not associated with side effects and on–off episodes did not occur. The authors conclude that after 3 years of treatment, L-tyrosine treatment resulted in positive clinical results, negligible side effects, and a possible neurons-sparing capability (Lemoine et al., 1989). However, as no comparisons were made with a reference group and no statistical analyses were carried out, the claims of the authors should be confirmed in other placebo-controlled studies. At present, there is no experimental evidence on the positive effects of L-tyrosine in the treatment of PD.

21.3.6 Tyrosine Levels in Aging and Alzheimer's Disease

One study to date provides data of an absence of a relationship among tyrosine, aging, and Alzheimer's disease (AD). This study was directed not on tyrosine but on the 3-nitrotyrosine concentration, which was determined in the CSF of neurologically normal controls and patients with AD. However, at the same time, the CSF concentration of tyrosine was determined. The 3-nitrotyrosine concentration and the 3-nitrotyrosine:tyrosine ratios significantly increased with advancing age. The tyrosine concentration did not change with increasing age. In patients with AD, the 3-nitrotyrosine concentration and the 3-nitrotyrosine:tyrosine ratio was significantly higher than those of controls of similar age and increased with decreasing cognitive functions. Regarding tyrosine, it appeared that the CSF concentration in patients with AD was not different from that of age-matched controls. Thus, an activation of tyrosine nitration, increase in nitrated tyrosine-containing proteins, and its degradation may be involved in brain aging and play an important role in the pathogenesis of AD (Toghi et al., 1999). The tyrosine concentration itself is not related to age and does not seem to play a role in the development of AD.

21.3.7 Tyrosine and Stress-Induced Behavioral Deficits

Tyrosine may be useful in counteracting performance decrement and mood impairments that are caused by stress. The hypothesis advanced is that various stressors may induce brain depletion of catecholamines, especially NE, in animals. Lower brain NE levels are associated with a decreased performance in animals. The administration of tyrosine may reduce or even reverse stress-induced performance decrement and mood deterioration by increasing depleted brain NE levels. In animals, these relationships are supported by the results of many studies. However, in humans it is more difficult to find support for these claims as there is no direct evidence that stress depletes NE in the human brain. However, there is some indirect evidence. For instance, it is generally known that humans under stress are not able to keep their eyes stable and fixed. Under stress, humans are characterized by an increase in involuntary saccadic eye movements. These eye movements seem to be associated with catecholaminergic pathways. There is one study in which ocular motor pathways in humans were studied after catecholamines were experimentally depleted. Subjects received metyrosine (α-methylparatyrosine), a drug that temporarily depletes DA and NE, as

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measured by a reduction in the metabolite 3-methoxy-4-hydroxy-phenylethyleneglycol (MHPG). Metyrosine induced an increase in the amplitude and frequency of saccadic intrusions during fixation and pursuit. The increase in the number of saccadic intrusions can be explained by a modulatory role of catecholamines of the activity of a subpopulation of suppressor motor neurons in the human brain stem (Tychsen and Sitaram, 1989). As stress induces an increase in eye movements and eye movements are related to NE levels, it can be inferred that stress depletes brain catecholamines, especially NE, in humans. The next step is to provide evidence that NE depletion is related to impaired attention. It has been found that central NE is important in maintaining attention. Brain levels of NE can be lowered by clonidine, an α-2-adrenoceptor agonist. In low doses, clonidine acts presynaptically to decrease noradrenergic cell firing and NE release. The reduced NE release can be reversed by idazoxan, a selective α-2-adrenoceptor antagonist. To study the relationship between attention processes and NE levels, subjects were assigned to groups receiving placebo, clonidine, or idazoxan + clonidine. They had to perform, in both a quiet and noisy environment, a two-choice RT task, which was adapted to record lapses of attention (RT > 1.5 msec). It was found that the number of lapses of attention increased after clonidine administration. This effect was reversed, that is, attention was normalized, by coadministration of idazoxan (Smith and Nutt, 1996).

The relation between attention and the inhibition of NE release by clonidine suggests an interrelationship between NE and cognitive processes. Although insight into the mechanisms explaining the relationship between stress, NE, and performance is lacking in humans compared with animals, catecholamines may be a mediating factor between stress and performance in humans. Based on the evidence available, the usefulness of tyrosine in military sustained operations has been proposed. Sustained operations consist of continuous work periods exceeding 12 h. The resulting sleep loss and fatigue can lead to stress, anxiety, deterioration of mood, and performance decrements (Owasoyo et al., 1992). Techniques for coping with combat stress to prevent emotional breakdown mostly rely on such stress-reducing approaches as effective leadership, rest, relaxation, and being in good physical condition. As these techniques are not adequate to deal with combat stress, the military needs more innovative techniques (Salter, 1989). As a consequence, some studies have been performed to study the possible usefulness of tyrosine to reverse performance decrements and mood deterioration in humans. These studies have been largely directed on learning and memory functions, including mood states. One of the first studies on tyrosine and behavior included16 healthy men, aged 18 to 45, who were administered tryptophan (50 mg/kg), tyrosine (100 mg/kg), and a placebo in a single dose, using a double-blind crossover design. Before ingestion, the subject fasted for 12 h. Four tests of sensorimotor performance and two self-reported mood questionnaires were administered 2 h after ingestion of the substances. In this study, no effects of tyrosine were observed (Lieberman et al., 1982). However, subjects in this study did not experience experimental stressors. In later studies, it was recognized that tyrosine would be expected to have positive effects on behavior only under stressful conditions.

The first study in which the behavioral effects of tyrosine were examined in humans subjected to acute stress was conducted in young men exposed to cold and hypoxia. Subjects who were most vulnerable to the stressors exhibited fewer stress symptoms, such as headache, tension, and fatigue, and showed less psychomotor impairment after being supplemented with 100 mg/kg tyrosine (Banderet and Lieberman, 1989).

Since then, these findings have been replicated in healthy volunteers and extended. Tyrosine in oral dose ranges from 85 to 170 mg/kg given 1 to 2 h after stress induction, such as cold stress (4ºC) or noise (90 dB), restored memory performance and mood particularly in individuals who were most affected by the stressors. Tyrosine did not seem to have dose-dependent effects (Deijen and Orlebeke, 1994; Shurtleff et al., 1994). In one of these studies, tyrosine decreased blood pressure in humans. About 15 min after ingestion, diastolic blood pressure was decreased and 1 h after ingestion diastolic blood pressure returned to baseline level (Deijen and Orlebeke, 1994). These studies suggest that tyrosine is only beneficial in counteracting cognitive impairments under stress.

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However, positive effects of tyrosine on neuropsychological test performance have been found without overt exposure to stress. One hour after the administration of 150 mg/kg of L-tyrosine or placebo, healthy volunteers performed a number of tests of a multiple-test battery, assessing working memory, arithmetic skills, and visual and auditory monitoring simultaneously. A comparison was made with the performance on a simple battery, measuring working memory and visual monitoring. Tyrosine was found to prevent decrements of working memory only in the multiple-task condition. Thus, tyrosine may sustain working memory performance when there are competing requirements by other tasks (Thomas et al., 1999). Although no stress was overtly induced in this study, it may well be true that performing more tasks at the same time is a stressful requirement that is comparable with the induction of cold or noise.

In addition to these laboratory-like studies, tyrosine has been tested in real-life stress settings. Behavioral effects of tyrosine were examined during an episode of continuous nighttime work involving one night's sleep loss. Subjects, male U.S. Marines aged 21 to 27 years, performed nine iterations of a battery of performance tasks and mood scales for ca. 13 h, beginning at 19:30 and ending at 08:20. They remained awake throughout the day on which the experiment began and were awake until testing was completed (totaling 24 h). Six hours after the experiment had begun, subjects received 150 mg/kg tyrosine or placebo. Tyrosine reduced the performance decline on a psychomotor task and lapse probability on a vigilance task. These improvements lasted for 3 h (Neri et al., 1995).

In another study, the effects of a protein-rich drink containing 2 g tyrosine on cognitive task performance, mood, blood pressure, and the norepinephrine metabolite MHPG were determined in a group of cadets after a 5-day demanding military combat training course. Subjects received the tyrosine-rich drink for 5 days. Effects were compared with subjects who received a carbohydrate-rich drink with the same amount of calories (255 kcal). Assessments were made both immediately before the combat course and on the sixth day of the course. The group treated with the tyrosine-rich drink performed better on a memory and a tracking task than the group given the carbohydrate-rich drink. In addition, supplementation with tyrosine decreased systolic blood pressure (Deijen et al., 1999). These findings suggest that supplementation with tyrosine or even a tyrosine-rich drink may, under operational circumstances characterized by psychosocial and physical stress, reduce the negative effects of stress and fatigue on cognitive task performance.

21.3.8 Blood Pressure and Cardiovascular Stress

Tyrosine decreased diastolic blood pressure in normotensive young subjects 15 min after ingestion, whereas blood pressure returned to baseline value 1 h after ingestion (Deijen and Orlebeke, 1994). Similar effects were found in normotensive cadets receiving a tyrosine-rich drink during a demanding military combat training course. The group supplemented with the tyrosine-rich drink showed a decrease in systolic blood pressure (Deijen et al., 1999). Thus, tyrosine can reduce blood pressure in healthy, normotensive persons during or after stressful situations. Data from animal studies suggest that tyrosine has a unique regulatory function, lowering high blood pressure while increasing low blood pressure. Decreased blood pressure can be induced experimentally by cardiovascular stress, that is, subjecting them to lower-body negative pressure (LBNP; Dollins et al., 1995). LBNP is a technique used to simulate gravitational stress (orthostasis) by exposing the lower body to subatmospheric pressures. Subjects exposed to LBNP initially respond with decreased blood pressure and increased heart rate. In the course of this cardiovascular stress exposure, consciousness is lost if LBNP is not terminated. After oral administration of 100 mg/kg tyrosine subjects maintained higher pulse pressures. As a result, tyrosine appears to reverse blood pressure alterations and may therefore be protective when cardiovascular parameters in humans are disturbed.

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21.3.9 L-Tyrosine and Skin Pigmentation

L-Tyrosine is one of the agents stimulating natural pigmentation because it is not only the precursor of brain catecholamines but also the precursor compound for the melanogenic pathway. This pathway leads to the formation of melanin, a dark-brown to black pigment that occurs in the skin, hair, pigmented coat of the retina, and medulla and zona reticularis of the adrenal gland. The rate-limiting enzyme in melanogenesis is tyrosinase, which catalyzes the conversion of tyrosine to L-dopa and then dopaquinone. Dopaquinone is then converted either to brownish-black eumelanins or reddish-yellow pheomelanins. Eumelanins are more photoprotective than pheomelanins.

It is assumed that L-tyrosine may induce melanogenesis because the primary substrate for tyrosinase may be limiting. Increasing L-tyrosine from 10 to 200 μ*M* in the medium of melanoma cells results in a 10-fold increase of tyrosinase activity. In addition, 500 μ*M* of L-tyrosine increased ca. 1.6-fold the melanin content of normal human epidermal melanocytes. These are pigment-producing cells located in the basal layer of the epidermis. L-Tyrosine at 1000 μ*M* resulted in a 2.3-fold increase.

These findings suggest that L-tyrosine may be applied to induce tanning or to enhance ultraviolet B-induced tanning. Indeed, 48 m*M* L-tyrosine ethyl ester increased simulated-solar radiation (SSR)-induced pigmentation by 1.35-fold in rat skin. In humans, only19 m*M* L-tyrosine ethyl ester resulted in the same SSR increase as in the rats. However, no L-tyrosine derivatives or formulations have been demonstrated to induce tanning in animal or human skin without ultraviolet radiation (UVR).

Safety is a major concern when using L-tyrosine as a potential tanning agent. However, because natural pigmentation is associated with greatly reduced skin cancer risk, the use of pigmentation stimulators before sun exposure has the potential to reduce both solar radiation-induced damage and skin cancer incidence (Brown, 2001). The development of agents to increase pigmentation of the skin is still continuing. Whether L-tyrosine will become a safe and efficacious compound to enhance skin pigmentation depends on further research on the mechanisms that induce melanogenesis and the willingness of companies to produce and sell it as a tanning agent. The possible clinical use of L-tyrosine in treating psychiatric disorders, reversing behavioral deficits, or protecting against stress or sunburn can be inferred from the summary of studies on the topics in Table 21.1. From this table it is clear that most evidence is on L-tyrosine and the reversal of stress-induced behavioral deficits.

21.4 SAFETY OF TYROSINE AS A DIETARY SUPPLEMENT

21.4.1 Risk Factors

Excess L-tyrosine in low-protein diets may lead to a distinct syndrome of cataracts, skin lesions, and histopathological changes in rats. These changes are the consequence of providing L-tyrosine at levels of 3 to 5% in low-protein diets. The eye lesions appear to be related to the low solubility of the amino acid. These adverse effects of excess L-tyrosine appear to be intensified by adrenalectomy and hyperthyroidism. This syndrome has not been described in rats fed high-protein diets, even when as much as 12% L-tyrosine was added.

In humans, L-tyrosine has been studied extensively as a therapeutic agent in large doses. Doses of 70 to 150 mg/kg body weight are required because of the demonstration that this amount of precursor availability can influence the synthesis and release of brain catecholamines. Administration of 100 mg/kg body weight of L-tyrosine (7 g for a 70-kg individual) with or without food and as single or divided doses doubles the plasma tyrosine concentrations and increases the tyrosine to LNAAs ratio in humans (Cuche et al., 1985). Administration of this amount of L-tyrosine on a single day has not been associated with clinically significant changes in blood pressure, pulse rate, urinary volume, or abnormal neurological or psychological phenomena. Some studies have reported

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TABLE 21.1
Studies on the Clinical Utility of Tyrosine

Disease/Condition	Type of Study	Daily Tyrosine Treatment	Number of Studies	Number and Type of Positive Outcomes	Number of Negative Outcomes
Stress-induced behavioral deficits	Animal	Tyrosine-enriched diet or 100–400 mg/kg IP tyrosine	5	5; reversion of behavioral deficits	0
	Human	85–170 mg/kg	7	7; reversion of behavioral deficits	0
High blood pressure	Animal	15 μg Tyr-containing dipeptides	2	2; blood pressure decrease	0
Low blood pressure	Animal	Tyr-containing dipeptides	1	1; blood pressure increase	0
	Human	100 mg/kg	1	1; blood pressure increase	0
Normal blood pressure	Human	100 mg/kg Tyr (2 g)-rich drink	2	2; decrease of blood pressure	0
Biochemical misbalance by weight loss	Animal	100 mg/kg	2	2; repletion DA and NE normalization adrenergic receptors	0
Physical condition	Human	20 g	1	0	1
Depression	Human	100 mg/kg	2	1; decrease in depression	1
Attention deficit disorder	Children	100 mg/kg	1	0	1
	Adults	150 mg/kg	3	0	3
Parkinson's disease	Human	1.8–4.7 g	2	1; less tremor, rigidity, akinesia	1
Skin pigmentation	Animal	48m*M* L-tyrosine ethyl ester	1	1; pigmentation increase	0
	Human	19 m*M* L-tyrosine ethyl ester	1	1; pigmentation increase	0

gastrointestinal side effects in some subjects receiving 100 mg/kg body weight of L-tyrosine given without food but not with food.

Administration of 100 mg/kg in divided doses for 4 weeks was associated with palpitations in 1 of 21 patients given L-tyrosine as a treatment for major depression. High plasma concentrations of tyrosine are associated with hepatic and renal failure in patients with tyrosinemia I, an autosomal recessive disorder. In tyrosinemia II, the enzyme tyrosine aminotransferase is defective, which can lead to mental retardation. Development of eye and skin lesions may occur in patients with tyrosinemia II. Transitory neonatal tyrosinemia (TNT) in premature and term infants has been associated with impaired intellectual abilities in childhood.

21.4.2 Safe Levels of Human Intake

The usual daily L-tyrosine intake from the diet is about 2.2 g for an individual consuming 100 g protein per day. In one study in which the extremely high dose of 500 mg/kg body weight (35 g for a 70-kg individual) was given, no side effects were reported. Thus, from the information of one subject, L-tyrosine given at ca. 15 times the daily intake does not seem to induce side effects.

However, as noted previously, the occurrence of more severe effects of high doses of L-tyrosine is found in animals receiving low-protein diets. Therefore, humans with low intakes of protein may be more susceptible to possible adverse effects of chronic consumption of L-tyrosine as a dietary supplement.

Evidence of biochemical and behavioral effects in offspring of female rats given L-tyrosine during gestation suggests that women should not take L-tyrosine during pregnancy or lactation. High circulating levels of tyrosine during infancy, called transient neonatal tyrosinemia (TNT),

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resulting from the feeding of high-protein formulas (e.g., inappropriately diluted evaporated milk formulas) may be associated with impaired intellectual performance. Although some investigators have reported normal development of children with TNT, others have reported deficits in intellectual performance (Food and Drug Administration, 1992). Therefore, L-tyrosine should not be given to infants or children as a dietary supplement. Evidence that L-tyrosine increases the cytochrome P450 content in the liver of rats raises the possibility of interactions of tyrosine with some drugs. Likewise, evidence that compounds which stimulate the cytochrome P450-containing drug-metabolizing system also increase the acute toxicity of L-tyrosine in rats also suggests that L-tyrosine should not be used by persons taking pharmaceutical preparations, which stimulate this system.

The safety of continued ingestion of L-tyrosine as a dietary supplement by normal subjects cannot be determined from the data available. The relative insolubility of L-tyrosine raises concern about the possibility of localized adverse effects in the small intestine or in the lens with chronic exposure. Knowledge that greatly elevated plasma concentrations of tyrosine are associated with eye and skin lesions in persons with tyrosinemia II and that these lesions can be reversed by lowering plasma concentrations of L-tyrosine gives cause for concern about chronic high concentrations of plasma tyrosine. Likewise, demonstrations of pharmacological effects on catecholamine synthesis and release in stimulated catecholaminergic neurons in rats and on behavior of humans subjected to stressful situations by L-tyrosine given orally in single doses of 100 mg/kg body weight do not provide evidence of the safety of L-tyrosine at this level of intake.

Studies demonstrating evidence of safety, or lack thereof, with lower oral doses of L-tyrosine are not available. Amino acids used as dietary supplements can interact with prescription drugs such as monoamine oxidase inhibitors and other antidepressants, sympathomimetic amines, and opioids (Food and Drug Administration, 1992).

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