Amino Acids, Brain Metabolism, Mood, and Behavior

Simon N. Young

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9.1 INTRODUCTION

The regulation of flux down metabolic pathways is controlled in a number of ways. One of the less common methods in mammalian metabolism is through precursor availability; that is, the flux down the pathway depends on the concentration of the substrate of the first and rate-limiting enzyme in the pathway. Interestingly, this method of control occurs in several metabolic pathways involved in converting essential amino acids into psychoactive metabolites in the brain. Essential amino acids are transported into the brain by an active transport system, and the amount transported into the brain depends, in part, on the availability of the amino acids in blood. Therefore, both dietary intake and ingestion of purified amino acids can influence the concentration of metabolic products in the brain. In some circumstances, this can alter aspects of mood and behavior. This chapter (1) reviews some of the biochemical mechanisms involved in converting dietary amino acids into psychoactive metabolites, (2) summarizes what is known about the effects of amino acids on human mood and behavior, and (3) discusses how the sale of amino acids is regulated.

9.2 TRYPTOPHAN AND SEROTONIN

9.2.1 BIOCHEMICAL ASPECTS

One minor pathway (quantitatively) of tryptophan metabolism is its conversion to serotonin (5-hydroxytryptamine, 5-HT). Most of this conversion takes place in neurons and mast cells in the intestine, but it also occurs in the brain. Serotonin does not cross the blood-brain barrier and must be synthesized from tryptophan in the brain. Tryptophan is transported across the blood-brain barrier by a system of capillaries that actively transports all large neutral amino acids (LNAAs; tryptophan, phenylalanine, tyrosine, leucine, isoleucine, valine, methionine, threonine, serine, and cysteine). The affinity of various amino acids for the transporter is such that there is competition between individual amino acids (Pardridge, 1986). Therefore, the amount of tryptophan in the brain depends not only on the amount of tryptophan in plasma but also inversely on the levels of the other LNAAs in plasma (Wurtman et al., 1981). Tryptophan is the only amino acid present in plasma partly in free solution, but mostly bound loosely to albumin. Only a small part of the albumin-bound tryptophan is available to the brain, and brain tryptophan levels tend to follow the free (non-albumin-bound) plasma level. Tryptophan can be displaced from its binding site on albumin by free fatty acids, thereby increasing free plasma tryptophan levels. Thus, an increase in plasma fatty acid levels can increase brain tryptophan, and, as a consequence, serotonin levels (Sainio et al., 1996).

In the brain, the conversion of tryptophan to serotonin occurs only in serotonergic neurons. The first and rate-limiting enzyme in this pathway is tryptophan 5-hydroxylase, which converts tryptophan to 5-hydroxytryptophan (5-HP). Tryptophan hydroxylase uses molecular oxygen and also tetrahydrobiopterin (BH4) for activity. Tryptophan, oxygen, and BH4 are abnormally present in the brain at concentrations that do not saturate the active site of tryptophan hydroxylase. As a result, alterations in the level of any of these compounds will alter the rate of serotonin synthesis. The concentration of tryptophan in the brain is usually about equal to its \( K_m \) for the enzyme. (That is, the concentration of tryptophan is such that the enzyme acts at half its maximum velocity.) Thus, decreases in brain tryptophan will cause a lowering of serotonin synthesis, and increases will increase the rate of serotonin synthesis up to a maximum of twofold (Wurtman et al., 1981).

The conversion of 5-HP to serotonin occurs by the action of aromatic amino acid decarboxylase, which has a high activity. Therefore, in the brain, the level of 5-HP is low because 5HTP is rapidly converted into serotonin. 5-HTP, like tryptophan, is an LNA that when given orally can be transported into the brain and converted into serotonin. 5-HTP is present in the diet in small amounts in some types of beans. However, because aromatic amino acid decarboxylase is present in the liver and kidney as well as in the brain, most 5-HTP ingested orally will be converted to serotonin peripherally and will not alter brain serotonin levels. When used clinically, 5-HTP is
usually given with an inhibitor of aromatic amino acid decarboxylase that does not cross the blood-brain barrier, therefore inhibiting its conversion to serotonin in the periphery but not in the brain.

In the brain, serotonin is broken down by a two-step pathway, initiated by monoamine oxidase, to 5-hydroxyindoleacetic acid (5-HIAA). In the pineal, serotonin (formed there) can be converted to melatonin by the action of serotonin-N-acetyltransferase and hydroxyindole-O-methyltransferase. Although the pineal is located in the center of the brain in humans, neuroanatomically it is part of the peripheral nervous system. Neural connections from the brain to the pineal occur only through the superior cervical ganglion. Furthermore, the pineal does not have anything similar to the blood-brain barrier. However, melatonin released by the pineal can act on the brain and some of the effects of tryptophan may be mediated in part by melatonin. Melatonin shows a marked diurnal rhythm. At night, the activities of serotonin-N-acetyltransferase and melatonin synthesis are high, whereas in the day activities of both enzymes are low. However, melatonin synthesis also depends in part on serotonin availability, and providing tryptophan will increase melatonin levels somewhat during both the day and night (Huether et al., 1992).

9.2.2 Mood and Behavioral Aspects

9.2.2.1 Rationale for Acute Tryptophan Depletion Studies

Most theories that relate serotonin to psychopathology suggest that low serotonin levels or function is involved [see, e.g., Meltzer and Maes (1995)]. Most of the evidence for these theories is indirect. For example, studies of various measures related to serotonin (e.g., levels of the serotonin metabolite 5-HIAA in cerebrospinal fluid) suggest that lowered serotonin synthesis or function occurs in some depressed patients. However, an association does not necessarily imply cause and effect. Does low serotonin cause depression, does depression cause low serotonin, or are low serotonin levels an epiphenomenon? Furthermore, although some antidepressant drugs potentiate serotonin function, this does not necessarily imply that low serotonin function causes depression. (For example, anticholinergic drugs have a therapeutic effect in Parkinson’s disease, although low dopamine, not high acetylcholine, is involved in the etiology of Parkinson’s disease.)

Decreasing serotonin synthesis by lowering tryptophan levels has been used to test some of the hypotheses relating low serotonin function to various types of psychopathologies [reviewed by Young and Leyton (2002)]. The acute tryptophan depletion (ATD) technique makes it possible to reduce brain levels of serotonin in humans to see what symptoms may emerge. This can be done under controlled conditions in a laboratory setting, and the subjects’ biochemistry can be normalized (by giving tryptophan) before they leave the laboratory. Because the depletion is short term and done under close supervision, risks associated with trying to elicit symptoms similar to those that occur in psychiatric disorders are minimized. To date, no adverse effects of ATD have been reported in more than 100 published studies.

In the ATD technique, subjects ingest an amino acid mixture containing all the essential amino acids except tryptophan (T- mixture). The control is a similar amino acid mixture containing the correct amount of tryptophan for a good protein source (nutritionally balanced or B mixture). Normally, when people ingest a protein meal, the protein is broken down into individual amino acids in the gastrointestinal tract. The amino acids are absorbed into the bloodstream. Then, most of the amino acids are incorporated into labile protein stores in the liver and muscle, which prevents free amino acids levels in plasma from rising too much. The B and T- mixtures also induce protein synthesis. However, as the T-mixture contains no tryptophan, tryptophan that is incorporated into protein comes from free tryptophan stores in the blood and tissues. As tryptophan is incorporated into protein, plasma levels of the amino acid fall dramatically. When a human ingests a 100-g T-mixture (the amount of amino acids in ca. 1 lb of steak) plasma tryptophan falls by 70 to 90% within 5 h. This decline in tryptophan availability is accompanied by a decline in serotonin synthesis, as indicated by a decline in the levels of 5-HIAA in the cerebrospinal fluid (Carpenter et al., 1998).
Positron emission tomography, which measures the rate of serotonin synthesis, showed that the ATD procedure lowered the rate of serotonin synthesis in the human brain by 90% or more (Nishizawa et al., 1997). The decline in serotonin synthesis was greater than that in plasma tryptophan because the amino acid mixtures also contain LNAAs, which tend to inhibit transport of tryptophan into the brain. This is true for both B and T- mixtures; therefore, there will presumably be a small decline in brain serotonin synthesis with the control B mixture.

9.2.2.2 Practical Aspects of Acute Tryptophan Depletion

The procedure in ATD studies varies somewhat, but most commonly 100 g of a tryptophan-deficient amino acid mixture is provided to subjects. The amino acids induce protein synthesis, and as tryptophan is incorporated into protein its level in the plasma and tissues declines. The greatest depletion occurs after 5 to 7 h when plasma tryptophan reaches 10 to 30% of its baseline level. At this point, suitable measurements can be made and then the subjects are repleted with tryptophan by allowing them to eat normally, or better by giving them a tryptophan supplement (Young and Leyton, 2002).

In ATD studies, the control treatment is usually a similar amino acid mixture that contains 2.3 g of tryptophan. The relative amounts of the different amino acids in the control mixture are based on the amino acid content of human milk, which is presumably optimized for human metabolism. The control mixture raises plasma tryptophan, but the plasma ratio of tryptophan to the other LNAAs declines because of the higher level of other LNAAs in the mixture. This implies a small decline in brain tryptophan, and thus the control treatment is a conservative one.

9.2.2.3 Effects of Acute Tryptophan Depletion

The effect of ATD on mood depends on the individuals being studied [detailed reviews in Moore et al. (2000) and Young and Leyton (2002)]. In about half the studies that used healthy volunteers, a modest lowering of mood was reported (relative to the effects of the control amino acid mixture). Women are more likely to show a lowering of mood than men. This may reflect their greater susceptibility to depression, as epidemiological studies show a greater incidence of depression in women than in men. Healthy male volunteers with a family history of depression usually show a greater lowering of mood than those with no family history of the disease, also suggesting that the effects of ATD may depend on a susceptibility to depression. In depressed patients who have recently recovered and are on antidepressant drugs, a dramatic lowering of mood, sometimes described as the reappearance of clinical depression, is often seen with ATD, but this lowering of mood remits when tryptophan levels return to normal. The effect of ATD on mood in depressed patients is usually seen when patients are treated with specific serotonin reuptake inhibitors but not with noradrenaline reuptake inhibitors (Delgado et al., 1999). Therefore, the effect of ATD in newly recovered depressed patients who are still being treated may be more relevant to the mechanism of action of the antidepressant than to the etiology of depression. In formerly depressed patients who have recovered and are off antidepressant drugs, a lowering of mood in the clinical range is seen in a minority of subjects. There is a suggestion that a marked mood response in these patients may predict future relapse (Young and Leyton, 2002). Overall these results suggest that (1) reductions in brain serotonin can contribute to lowered mood, (2) a reduction in serotonin by itself is not enough to lower mood, (3) a reduction in serotonin is probably involved in the etiology of depression in some depressed patients, and (4) reduced serotonin synthesis counteracts the antidepressant action of serotonin reuptake inhibitors.

The effect of ATD on anxiety is different from its effect on mood. ATD by itself does not increase anxiety in either healthy subjects or subjects with a history of anxiety disorders. However, ATD often increases anxiety in people with a history of mood disorders, but this increase in anxiety is seen only in conjunction with a lowering of mood. Although ATD does not alter baseline levels
of anxiety, it often increases anxiety in response to an anxiogenic challenge (Anderson and Mortimore, 1999). The anxiogenic challenges include both psychological (e.g., public speaking) and biological challenges. The main biological challenges that have been used are treatments that induce panic attacks in both patients with panic disorder and healthy individuals. These include breathing elevated levels of carbon dioxide, infusing cholecystokinin-4, and administering various anxiogenic drugs. In about half the studies on healthy individuals, ATD increased the anxiety seen in response to an anxiogenic challenge. However, the effect of ATD on anxiety is more reliable in patients with anxiety disorders than in those without these disorders. Therefore, although susceptibility to anxiety may play some role in the effect of ATD, an enhancement of anxiety is usually seen only when there is an anxiogenic challenge. That ATD has no effect, in the absence of an anxiogenic challenge, on patients with anxiety disorders is in sharp contrast to its effect on mood. The data suggest that low serotonin may have a direct effect on mood, but it probably has only has a modulatory effect on anxiety.

A wealth of animal data supports the idea that a low level of serotonin in the brain predisposes an animal to aggression, a finding that is supported by correlational data in humans. [For example, aggressive individuals tend to have low levels of 5-HIAA in their cerebrospinal fluid (Miczek et al., 2002).] In human participants, the effect of ATD has been studied by a variety of laboratory tests of aggression. For example, in one test, participants play a game against an opponent (which, unknown to the participants, is a computer program) in which they can win money or prevent their opponent from winning. The measure of aggression is the number of times the participants prevent their opponent from winning money. Obviously, this type of test suffers from a certain artificiality, but practical and ethical considerations preclude the direct study of ATD on aggressive behavior. In the majority of studies, ATD increased aggressive types of responses, and the effect was often greater or seen only in subjects with preexisting hostile traits. Increases in self-rated hostile or irritable moods have also been seen in patients with conditions often associated with irritability or impulsivity, such as bulimia and premenstrual syndrome (Young and Leyton, 2002). In one study on healthy individuals with a genetic predisposition to alcoholism (often associated with impulsivity or aggression), ATD increased commission errors in a go/no no task; that is, when asked to press a button in response to some stimuli but not others, individuals tended to press the button when they should not. This is taken as an indication of impulsive behavior. Overall, the results suggest that low serotonin can contribute to aggressive behavior in humans and possibly other types of impulsive behavior as well. The effect on aggression is unlikely to be mediated by only an increase in impulsivity, as ATD can also increase hostile mood.

ATD seems to have some subtle cognitive effects, but it is difficult to discern a pattern from the results that have been reported. In a small number of studies, ATD had no effect on hunger or food intake, but in one study ATD was associated with an increase in caloric intake in women with bulimia (Moore et al., 2002). Finally, in one study, ATD had no effect on pain responses in the cold pressor test, but completely abolished the analgesic effect of morphine in that test (Moore et al., 2000). This supports the idea that the analgesic effect of morphine in the cold pressor test is mediated by enhanced release of serotonin, possibly in the spinal cord.

Evidence to date from ATD studies supports the idea that a low level of serotonin in the brain may lower mood and increase irritability or aggression, particularly in those with a susceptibility to depression or aggression. Low serotonin may also increase anxiety in response to stress. Further studies are needed on the other effects of ATD, including its effects on cognition, pain responses, food intake, sexual activity, and any other aspect of central nervous system (CNS) function thought to be mediated by serotonin.

### 9.2.2.4 Metabolic Considerations in the Clinical Use of Tryptophan

Because of the theories that relate low serotonin function to a variety of different types of psychopathology, tryptophan has been tested for its therapeutic action in a number of conditions [reviewed...
by Young (1986). The daily dietary intake of tryptophan for an adult is ca. 1 g. In clinical use, the
dose of tryptophan ranges from 1 to 12 g/day. Tryptophan is metabolized relatively quickly and
plasma tryptophan levels return to normal levels within 8 h of a single 3-g dose. Therefore, to keep
the rate of serotonin synthesis maximized throughout any 24-h period, tryptophan should be given
as a divided dose, three times per day. Clinical trials, which failed to find effects of tryptophan
administration on behavior, used single daily dosing, which probably ensured that serotonin syn-
thesis was increased for less than half of each day.

The most convenient way to give tryptophan is with meals, which tends to minimize nausea,
one of the side effects sometimes seen. Some articles suggest that tryptophan should be given only
with carbohydrate and not with protein. The argument is that other LNAAs in protein will inhibit
the transport of tryptophan into the brain. On the other hand, carbohydrate will cause release of
insulin. Insulin lowers the level of the branched-chain amino acids leucine, isoleucine, and valine
in plasma by stimulating their net uptake into muscle. As the branched-chain amino acids are all
LNAAs, this will stimulate tryptophan uptake into the brain. However, this argument does not take
into account the dynamic aspects of tryptophan metabolism throughout the day. When a single
dose of tryptophan is given, there is a large increase in plasma tryptophan. This probably increases
brain tryptophan enough to saturate tryptophan hydroxylase with tryptophan. Therefore, a modest
decrease in uptake of tryptophan into the brain will not decrease the rate of serotonin synthesis. If
protein had been ingested later, between doses, when tryptophan levels in plasma had fallen from
their peak, this might have decreased serotonin synthesis. Thus, ingesting tryptophan with meals
is better both because it minimizes side effects and maximizes the rate of serotonin synthesis
throughout the day.

9.2.2.5 Side Effects in the Clinical Use of Tryptophan

Side effects associated with tryptophan use are in general infrequent and mild (Young, 1986).
Nausea and lightheadedness are the most common. In the largest and longest comparison of
tryptophan and placebo, tryptophan (1 g TID) produced no more side effects than placebo (Thomson
et al., 1982). However, tryptophan can interact with other drugs that influence serotonin function.
For example, when tryptophan is added to monoamine oxidase inhibitors, it potentiates their side
effects. In rare cases, the combination of tryptophan and another drug that potentiates serotonin
function can cause the serotonin syndrome (Mason et al., 2000). Symptoms of the serotonin syndrome
are variable but include (1) cognitive and behavioral, (2) autonomic nervous system, and
(3) neuromuscular effects. The cognitive and behavioral changes can include confusion and agita-
tion, as well as anxiety and hypomania, or in severe cases coma. Among the symptoms of autonomic
system disturbances, diaphoresis (profuse sweating) and hyperthermia are common. Among the
neuromuscular symptoms, myoclonus, hyperreflexia, and muscle rigidity are the most frequently
reported. Treatment of the serotonin syndrome is usually symptomatic, but a serotonin receptor
antagonist such as methysergide might help. Although deaths have been reported from the serotonin
syndrome, these have always been due to drugs other than tryptophan. There are no reports in the
literature of fatalities due to tryptophan use (when the pure drug was taken).

In late 1989, an epidemic of a new disorder appeared in the U.S called the eosinophilia myalgia
syndrome (EMS; Belongia et al., 1992). EMS is an inflammatory syndrome characterized by
eosinophilia, myalgia, perimyositis, fasciitis, and neuropathies. In the U.S., there were more than
1500 cases and 38 deaths. EMS occurred in various European countries and Japan also, but there
were not as many cases as in the U.S. EMS was found to be associated with the ingestion of
tryptophan from several lots made by a single manufacturer after various changes in the manufac-
turing process. Various trace contaminants in those batches are suspected as the cause, but there is
no definitive evidence as to which compounds caused EMS. Since the initial epidemic, no cases
of EMS have been associated with the use of tryptophan.

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9.2.2.6 Tryptophan in Mood Disorders

Four placebo-controlled studies conducted in the 1960s demonstrated that tryptophan potentiates the antidepressant effect of monoamine oxidase inhibitors [reviewed by Young (1991)]. However, this combination is rarely used, and when used is only in treatment-resistant patients, because tryptophan also potentiates the side effects of monoamine oxidase inhibitors. This is the only clear conclusion from studies on the use of tryptophan in depressed patients. Unfortunately, the literature contains many studies with small sample sizes and lack of placebo control. The finding that tryptophan is not significantly different from a standard antidepressant in a small trial does not mean that it would have been better than placebo. Because of the variability in response to antidepressants and the relatively small difference between the effects of placebo and standard antidepressants, results of small trials are difficult to interpret. A small number of studies suggest that tryptophan may cause a small augmentation in the effects of tricyclic antidepressants, specifically serotonin reuptake inhibitors and electroconvulsive therapy. However, the majority of studies of this type have not found that tryptophan potentiates the antidepressant effect of these drugs, and in cases in which a statistically significant effect was seen it was not always clinically significant (Young, 1986).

The antidepressant effect of tryptophan when given by itself is also controversial. My own interpretation of the literature is that tryptophan is an antidepressant in mild to moderate depression, but there is no evidence for efficacy in severe depression (Young, 1986). In the largest and best-designed study to date, tryptophan was compared with placebo and the tricyclic antidepressant amitriptyline as given by general practitioners to mildly or moderately depressed outpatients for 12 weeks. Tryptophan was equivalent in its therapeutic effect to amitriptyline and significantly better than placebo (Thomson et al., 1982).

Three small studies indicate that tryptophan has a therapeutic effect in acute mania, although the magnitude of the effect is certainly not sufficient to treat a seriously disturbed manic patient. Various clinical reports also suggest that tryptophan may augment the mood-stabilizing effect of lithium in patients with bipolar mood disorder (Young, 1986).

9.2.2.7 Tryptophan, Impulsivity, Irritability, and Aggression

Two small placebo-controlled studies have reported a therapeutic effect of tryptophan in pathological aggression (Young, 1986). In one study, tryptophan decreased the incidence of uncontrolled behaviors, and in the other tryptophan decreased the amount of neuroleptics needed to control the patients. In a study on patients with premenstrual dysphoric disorder (premenstrual syndrome), tryptophan (given intermittently for a few days before and during the premenstrual phase) decreased irritability and well as improved mood.

A recent study looked at the effect of tryptophan on social interaction in healthy subjects in everyday life (Moskowitz et al., 2001). The method used in this study was a form of ecological momentary assessment, a type of methodology developed by social psychologists. Subjects filled in a one-page questionnaire describing their behaviors after each important social interaction throughout the day. Behavior was assessed on two independent axes, agreeable-quarrelsome and dominant-submissive. These behaviors varied greatly from one interaction to another, but mean values were relatively constant over a sufficient number of interactions, ca. 12 days of measurements. In the study, 100 healthy people received tryptophan or placebo, each for 12 days. Tryptophan decreased quarrelsome behaviors and increased dominance. Thus, although there is a popular but mistaken belief that dominance can be enhanced only through aggression, in this study tryptophan promoted more constructive behavior by increasing dominance while decreasing quarrelsome behaviors. The study is also of interest because some psychoactive drugs, for example, antidepressants, seem to have little effect in healthy people. In the study described previously, tryptophan
altered normal behavior in everyday life, suggesting that serotonin function is relevant to more than just psychopathology.

9.2.2.8 Tryptophan and Sleep
Many studies have looked at the effect of tryptophan on sleep [reviewed by Hartmann and Greenwald (1984)]. Overall, these studies indicate that tryptophan, in the dose range of 1 to 5 g taken ca. 45 min before bedtime, can decrease the time taken to fall asleep without altering sleep architecture. Tryptophan is effective in healthy people with long sleep latencies and in patients with mild insomnia. It is not as effective as benzodiazepines in patients with moderate or severe insomnia. However, tryptophan has fewer side effects than benzodiazepines and does not have any detrimental effects the following day. Given that tryptophan can increase melatonin, and that melatonin also has a hypnotic effect, it is unclear to what extent the effect of tryptophan is mediated by an increase of serotonin in the brain or by an increase of melatonin in the pineal gland.

9.2.2.9 Effect of Tryptophan on Pain
The effect of tryptophan has been tested acutely by using experimental pain and in patients suffering from various types of pain (Young, 1986). Some studies found a beneficial effect of tryptophan and others did not. Because of the variety of conditions studied, it is difficult to come to any firm conclusion. However, the situation in which tryptophan has shown a therapeutic effect most frequently is chronic pain associated with deafferentation or neural damage.

9.2.2.10 Tryptophan and Food Intake
The reason why tryptophan availability alters serotonin synthesis in not known, but one theory is that it is part of a mechanism that regulates food intake. However, in a small number of studies tryptophan failed to alter total food intake or macronutrient selection (Young, 1986).

9.3 PHENYLALANINE, TYROSINE, AND CATECHOLAMINES

9.3.1 Biochemical Aspects
There are many similarities between the roles of tryptophan and tyrosine in regulating the synthesis of their respective neurotransmitter products, but there are also some important differences. Phenylalanine and tyrosine are precursors of the catecholamines dopamine and noradrenaline. The conversion of phenylalanine to tyrosine occurs mainly in the liver, but tyrosine hydroxylase in the brain can also form tyrosine from phenylalanine. The metabolic pathway from tyrosine to dopamine is similar to that from tryptophan to serotonin. Tyrosine is hydroxylated to form dihydroxyphenylalanine (DOPA), which is decarboxylated to produce dopamine. Tyrosine hydroxylase, like tryptophan hydroxylase, is the rate-limiting enzyme in this pathway and requires molecular oxygen and also BH4 for activity. Tryptophan hydroxylase is ca. 50% saturated with tryptophan, whereas tyrosine hydroxylase is probably ca. 75% saturated with tyrosine. Furthermore, tyrosine hydroxylase (unlike tryptophan hydroxylase) is regulated in part by product inhibition, that is, it is inhibited by its products dopamine and noradrenaline. These two facts led to the idea that catecholamine synthesis would not be influenced by substrate availability. However, sufficient evidence has accumulated to indicate that under some circumstances changes in tyrosine levels can alter catecholamine synthesis. Increases in catecholamine synthesis due to tyrosine administration seem to occur most often when firing of catecholamine neurons is activated and demand for catecholamine synthesis is greatest (Wurtman et al., 1981).

DOPA is decarboxylated to dopamine by aromatic amino acid decarboxylase. DOPA, like 5-HTP, is an LNAA and is transported into the brain. Also, like 5-HTP, it occurs in some foods,
mainly a few varieties of beans, but when ingested as part of the diet does not affect the brain because it is decarboxylated in the periphery and catecholamines do not cross the blood-brain barrier.

In dopaminergic neurons, dopamine is converted by pathways involving monoamine oxidase to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). In noradrenergic neurons, dopamine is converted to noradrenaline by dopamine-β-hydroxylase. The main catabolic product of noradrenaline in the brain is 3-methoxy-4-hydroxyphenylethylene glycol (MHPG).

Tyrosine administration can increase catecholamine synthesis somewhat, but given that tyrosine hydroxylase is close to saturation with tyrosine, there is greater scope for decreasing catecholamine synthesis by lowering tyrosine levels. Acute phenylalanine/tyrosine depletion (APTD) works in the same way as ATD, except that the amino acid mixture is deficient in phenylalanine and tyrosine instead of tryptophan. In monkeys, APTD decreases levels of HVA and MHPG in the cerebrospinal fluid, suggesting that it decreases synthesis of both catecholamines.

9.3.2 Mood and Behavioral Aspects

9.3.2.1 Effects of Acute Phenylalanine/Tyrosine (APTD) Depletion

Relatively few APTD depletion studies have been carried out to date [reviewed by Booij et al. (2003)], and therefore the conclusions given here must be considered tentative. In healthy individuals, APTD may cause small changes in mood, including a decreased feeling of well-being and alertness and an increase in anxiety but not the increase in irritability seen with ATD (which is thought to be related more specifically to serotonin). However, APTD did not modulate the increase in anxiety seen with pentagastrin, a drug that can cause panic attacks. APTD did cause small declines in various measures of memory. APTD has also been reported to decrease intake of alcohol in healthy subjects undergoing a taste test (in which the real measure was the amount ingested). Furthermore, several studies indicate that APTD decreases the psychostimulant effect of amphetamine (thought to be related to enhanced dopamine function) but not the anorexic effect of amphetamine (thought to be related to noradrenergic function). An intriguing preliminary report indicates that APTD temporarily reverses some of the symptoms of manic patients (McTavish et al., 2002). The results suggest that (1) APTD probably decreases dopaminergic function but not noradrenergic function, (2) lowered dopamine decreases mood and arousal, and (3) decreasing dopamine function may be therapeutic in mania.

9.3.2.2 Effects of Tyrosine on Behavior

Many of the considerations that apply to the clinical use of tryptophan also apply to tyrosine. Doses several times the dietary intake are appropriate and should be given in divided doses throughout the day. Doses that have been used range up to 10 g/day. The small number of studies done have mostly used few participants and been of relatively short duration. Side effects have not been studied systematically but seem to be few, as with tryptophan. Tyrosine seems to have little effect on mood in healthy subjects and in some studies had no therapeutic effect in depressed patients. However, at least three studies have reported some antidepressant effect (e.g., van Praag, 1990).

One important role of catecholamines is to regulate blood pressure. Effects are complex and in animals tyrosine can raise blood pressure in hypotensive animals and lower it in hypertensive animals (Ekholm and Karpapanen, 1987). The former effect has been attributed to an acceleration of catecholamine synthesis in sympathoadrenal cells and the latter to potentiation of CNS noradrenergic function. However, in humans, tyrosine supplements failed to affect mild essential hypertension.

In rats, tyrosine supplementation reverses the decline in brain noradrenaline and reverses some of the behavioral deficits seen in stressed animals. Several studies have looked at the effects of tyrosine on performance in healthy humans undergoing stressful activities. Tyrosine decreased
lowered mood, performance deficits, and memory deficits in subjects exposed to cold or hypoxia. It improved various aspects of cognition in subjects exposed to a loud noise or while multitasking. It reversed the decline in vigilance and performance associated with a period of extended wakefulness and improved memory and decreased systolic blood pressure in cadets undergoing combat training (Deijen et al., 1999).

9.4 METHIONINE AND S-ADENOSYL METHIONINE

9.4.1 BIOCHEMICAL ASPECTS

S-Adenosylmethionine (SAMe) is the major methyl donor in tissues, including the brain, and is involved in more than 35 methylation reactions (Bottiglieri and Hyland, 1994). SAMe is formed from methionine by the action of methionine synthase, also known as 5-methyltetrahydrofolate homocysteine methyltransferase, on homocysteine. Methionine synthase is a vitamin B12-dependent enzyme that obtains methyl groups from 5-methyltetrahydrofolate. The enzyme is normally saturated with its cofactors, but not with methionine. Administration of methionine increases the level of SAMe in the rat brain (Rubin et al., 1974), but the implications of this are not well understood.

9.4.2 MOOD AND BEHAVIORAL ASPECTS

Views of the human psychopharmacology of methionine are colored by the knowledge that in 10 studies carried out several decades ago, methionine exacerbated symptoms of schizophrenic patients (Cohen et al., 1974). The doses used, from 5 to 20 g/day, were high, and in most studies methionine was given with other psychotropic agents, including monoamine oxidase inhibitors. The mechanism for this adverse effect is unknown, but it has essentially prevented consideration of the use of methionine for other purposes. When methionine is given to healthy subjects, it is usually innocuous. In metabolic studies it has been given at doses up to 5 g/day for periods of weeks with no reports of adverse effects. Furthermore, methionine has been used at a dose of 1 g/infant/day as a urinary acidifier (for treating diaper rashes).

The fact that methionine can increase brain SAMe raises the question of whether it has antidepressant properties. SAMe was better than placebo in treating depression in about a dozen studies carried out several decades ago (Bottiglieri and Hyland, 1994). Furthermore, it had few side effects. The dose of SAMe used is usually ca. 1 g/day, suggesting that if methionine is also an antidepressant it should be effective at doses lower than those that had an adverse effect in patients with schizophrenia. To date, there have been no reports on the putative antidepressant effects of methionine.

9.5 HISTIDINE AND HISTAMINE

9.5.1 BIOCHEMICAL ASPECTS

Histidine loading increases brain histamine levels by somewhat more than twofold in rodents, suggesting that histamine is regulated more than catecholamines or serotonin are by precursor availability. However, in the rat, histidine increases brain histamine but it does not increase, or only increases very slightly, the level of the main histamine metabolites tele-methylhistamine and tele-methylimidazoleacetic acid. Furthermore, when brain histamine is depleted with an inhibitor of histidine decarboxylase, histidine still raises brain histamine levels (Prell et al., 1996). This suggests that histidine loads may cause nonspecific decarboxylation of histidine (probably by aromatic amino acid decarboxylase) and that the histamine formed may not all be present in histaminergic neurons. Therefore, histidine loading will not necessarily enhance brain histamine function, even if brain histamine levels are elevated.
9.5.2 MOOD AND BEHAVIORAL ASPECTS

Histamine-releasing neurons project from the hypothalamus to most areas of the brain. In keeping with this broad anatomical distribution, histamine has been implicated in a variety of CNS functions, including arousal, anxiety, pain perception, and control of food intake. A few studies have looked at the behavioral effects of histidine in rodents. A variety of effects have been noted, but no consistent pattern has been reported. There is certainly need for studies looking at the effect of histidine loading in humans.

9.6 THREONINE AND GLYCINE

9.6.1 METABOLIC ASPECTS

Glycine is a nonessential amino acid that is also a neurotransmitter in the spinal cord. In the CNS, glycine is synthesized from glucose, serine, or threonine. Glycine is formed by the action of serine hydroxymethyltransferase (SHMT) on serine. This enzyme employs folic acid. The one-carbon unit removed from serine during the formation of glycine becomes one of the major sources of methyl groups in mammalian metabolism and is used in the formation of SAMe. SHMT also acts on threonine to form glycine (and is sometimes referred to as threonine aldolase). The enzyme is fully saturated with serine, but it is not fully saturated with threonine. Also, unlike serine, threonine is an essential amino acid that is transported into the central nervous system by the transport system that is active toward all large neutral amino acids. As might be expected in these circumstances, giving a rat threonine will increase brain and spinal cord glycine levels (Maher and Wurtman, 1980).

9.6.2 MOOD AND BEHAVIORAL ASPECTS

In the spinal cord, glycine is an inhibitory transmitter controlling muscle tone. This has led to a few small open and placebo-controlled trials of threonine (4 to 7.5 g/day) in treating spasticity (e.g., Growdon et al., 1991) in some studies associated with other conditions such as multiple sclerosis or amyotrophic lateral sclerosis. In some studies, a modest but definite therapeutic effect was found, but it was not always considered clinically significant. Fortunately, the modest therapeutic effect was accompanied by minimal side effects. In the brain, glycine acts to modulate the activity of a particular class of glutamate receptors called the NMDA receptors. The lack of side effects may reflect the finding from animal studies that threonine increases glycine levels more in the spinal cord than in the brain.

9.7 EFFECTS OF PROTEIN AND CARBOHYDRATE MEALS ON BRAIN NEUROTRANSMITTER PRECURSOR LEVELS

All the precursor amino acids discussed are LNAAs. Therefore, their concentration in the brain will depend on the plasma ratio of the individual amino acid levels to that of the sum of the other LNAAs. Administering the amino acids in purified form does not alter the level of the other LNAAs and the brain level of the relevant amino acid rises. After ingestion of protein, the situation is more complex and depends in part on the relative amount of the individual amino acids in the protein (Young, 1996). Tryptophan is among the least abundant amino acids in most proteins, and after ingestion of a protein meal the plasma ratio of tryptophan to the other LNAAs usually declines. Tyrosine is more abundant in most proteins, as is its precursor phenylalanine. Therefore, a protein meal raises the plasma ratio of tyrosine to the other LNAAs. Threonine is also a relatively abundant amino acid and its plasma ratio also rises. Methionine and histidine are less abundant. However, there is one report that the plasma ratios for methionine, brain methionine, and brain SAMe rise after rats ingest a protein meal (Rubin et al., 1974). The reason for this is not clear, but it is a topic that needs further investigation.
Protein meals have a variable effect on the brain levels of different LNAAs, but the effect of a carbohydrate meal is the same for all the amino acids discussed (Young, 1996). Carbohydrate causes the release of insulin, which stimulates the net uptake of the branched-chain amino acids leucine, isoleucine, and valine into the muscle. All branched-chain amino acids are LNAAs, and therefore the plasma ratio for tryptophan, tyrosine, methionine, histidine, and threonine tends to rise after a carbohydrate meal.

One unanswered question is why protein and carbohydrate meals should have effects on neurotransmitter precursor levels and therefore potentially on neurotransmitter function. One suggestion related this phenomenon to the alteration that occurs in serotonin function and the regulation of macronutrient intake (Wurtman and Wurtman, 1988). Pharmacological enhancement of serotonin function in rodents decreases food intake, but the greatest effect seems to be on selection of carbohydrate. Thus, the theory suggests that a carbohydrate meal will raise brain serotonin, which will decrease carbohydrate intake at the next meal. A protein meal will lower serotonin, which will increase intake of carbohydrate at the next meal. In this way, intake of protein and carbohydrate will be regulated within certain limits. Unfortunately, the weight of evidence is against the idea that this mechanism operates in humans. First, real meals do not contain pure protein or carbohydrate. Therefore, a relevant question is what happens to the plasma tryptophan ratio with mixed macronutrient meals. Data show that adding as little as 4% protein to a carbohydrate meal prevents any increase in the plasma tryptophan ratio (Teff et al., 1989a). Even foods popularly regarded as carbohydrate have a protein content this much or more. For example, in orange juice 4% of the calories come from protein, and in bread the figure is more than 10%. Second, meals can certainly alter serotonin levels in rodents, but the extent to which this occurs in humans is uncertain. The amount of food ingested every day, as a percentage of body weight, is much higher for rats than for humans. As a result, the changes in plasma amino acid ratios after ingesting food are greater in rats than humans. In humans, a carbohydrate meal might raise the plasma tryptophan ratio by 20%. This might result in an increase in brain tryptophan of 10% and an increase of brain serotonin synthesis of 5%. A study of human cerebrospinal fluid tryptophan and 5-HIAA after the subjects ingested protein or carbohydrate meals found that the meals did not cause any significant changes in the levels of the two compounds (Teff et al., 1989b). This suggests that any effect of meals on brain serotonin is less than the normal variability in the neurotransmitter. The large changes in tryptophan availability associated with ATD caused no important effects on food intake, and it is highly unlikely that the much smaller change associated with ingesting a meal would have any important action. Third, there is no evidence that humans can regulate their macronutrient intake in the same way that rodents can.

Meals certainly can have effects on mood and behavior in humans, and these sometimes differ depending on the macronutrient content of the meals. For example, carbohydrate meals tend to have a sedative effect, which may be experienced as calmness or tiredness, depending on the individual (Spring et al., 1983). Tryptophan can also have a sedative effect, but this does not necessarily imply that the effect of the carbohydrate meal is mediated by an increase in brain serotonin. As argued previously, the effect of the carbohydrate meal on brain serotonin, if any, would be very much smaller than that of tryptophan. Furthermore, carbohydrate meals are known to have effects unrelated to serotonin. For example, glucose enhances memory, an effect thought to be related to an increase in the release of acetylcholine (Gold, 1995). There may also be other unknown effects. Thus, the fact that the synthesis of a variety of psychoactive substances is determined in part by availability of their amino acid precursors, which in turn is altered by dietary intake, seems to have no known physiological significance.

9.8 ARE AMINO ACIDS FOODS OR DRUGS?

The question of whether amino acids are foods or drugs is one in which opinion and politics play a role as great as science. Different countries regulate amino acids differently. For example, in the
U.S. they are treated as dietary supplements whereas in many European countries and Canada they are regulated as drugs. Part of the problem is that there is no clear delineation between a food and a drug; there is a continuum and governments need to put a dividing line somewhere along this continuum. I consider some of the factors involved.

Traditionally, isolated compounds most often have been regulated as drugs. For example, a cup of coffee is never regulated as a drug. However, caffeine can be extracted from coffee and taken as a tablet. A 200-mg tablet of caffeine is in many countries regulated as a drug, but a cup of coffee containing 200 mg of caffeine is not. By using precedents like this, amino acids would be treated as drugs.

The safety of anything taken in tablet form depends in part on the manufacturing process. For example, the epidemic of eosinophilia-myalgia syndrome (EMS) was associated with a trace contamination of tryptophan produced by bacteria and then purified (but apparently not sufficiently). Safety is certainly a factor in food production, but the issues associated with production of purified amino acids are closer to those of compounds that are unambiguously drugs than those associated with food production.

One important consideration in assessing the status of purified amino acids is the motivation people have for taking them. They are taken usually to overcome some unwanted aspect of mental functioning (e.g., the use of tryptophan to treat depression) or to enhance some aspect of normal functioning (e.g., the use of tyrosine to enhance functioning in stressful situations). In this respect, they fit the definition of a drug as something used to treat or prevent a disease or disorder. When amino acids are regulated as drugs, they can only be sold when regulatory agencies have been persuaded of their efficacy in treating a specific disorder and of their safety. When they are regulated as dietary components, the manufacturer is not usually able to make claims about their effects. In these circumstances, sales of amino acids depend on beliefs about their effect, which may or may not be true. These beliefs are taken from publications (print or electronic) that are, of course, not regulated. Although the manufacturer of an amino acid cannot make any claim as to its effect, there is nothing to stop the owner of a store from placing bottles of amino acids next to sources of information that are totally erroneous about their effect. Although a listing of myths concerning the action of amino acids is beyond the scope of this chapter, a brief survey of Web sites produced the “information” that tryptophan raises serotonin the way nature intended and is often needed by aging individuals. It is useful for treating weight reduction, chemical addiction, alcohol withdrawal, Down’s syndrome, chronic fatigue syndrome, migraine, anxiety, and senile dementia. This type of misinformation suggests that in countries in which amino acids are not regulated as drugs, they are widely used in treating disorders for which they have no effect (but still may produce side effects).

The belief that amino acids should not be classified as drugs is usually derived from the fact that they are considered natural treatments. The word natural implies that the metabolic effects of pure amino acids are similar to those of foods containing protein. This, of course, is incorrect. When protein is ingested, after absorption of the amino acids there is synthesis of labile protein stores, which attenuate the rise of plasma amino acid levels. No such effect occurs after ingesting a pure amino acid, and the increase the plasma level is much greater. Furthermore, for all the amino acids discussed, the increase in the other LNAAs attenuates any increase in their level in the brain after ingesting a protein. This does not occur when a single amino acid is taken. For tryptophan, the tendency for brain tryptophan and serotonin to decline after a meal containing tryptophan (i.e., protein) is in sharp contrast to the large increase in brain tryptophan and serotonin after ingesting tryptophan tablets. Even for tyrosine, the increase in its concentration in the brain after a protein meal is very much lesser than after taking tyrosine tablets. Thus, ingestion of purified amino acids cannot be considered a natural or dietary treatment. Although the issues discussed suggest that purified amino acids are more similar to drugs than foods, the decision on how to regulate them is ultimately a political one.
9.9 CONCLUSIONS

Several amino acids are precursors of psychoactive substances, and giving those amino acids has useful therapeutic effects in some circumstances. Although tryptophan is available as a drug for treating depression or as a hypnotic in some countries, there is currently little research on other indications of tryptophan or on uses of the other amino acids. Research on the psychopharmacological effects of amino acids peaked in the 1970s and 1980s but is no longer popular. This is partly because most uses of amino acids cannot be patented, leading to a lack of interest from pharmaceutical companies, and is partly related to fashion among researchers. This is unfortunate, as there are many promising areas for future investigation. Two examples are the potential use of methionine as an antidepressant and the use of tryptophan in treating aggression.

The psychopharmacological use of amino acids is not a fashionable topic for researchers, but the use of amino acid depletion strategies to investigate the role of neurotransmitters in the etiology of various mental symptoms is an active area of research and promises further insights into the psychopathology of mental disorders.

One area in need of attention is the wide divergence between the results of research and popular beliefs about the effects of amino acids. There is no simple solution to the mass of misinformation available. Books such as this one will help, but they will never, unfortunately, receive the same exposure as misinformation available on the Web.

REFERENCES


