

## REVIEW

# Tyrosine: Food Supplement or Therapeutic Agent?

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*L-Tyrosine occupies a central position in the synthesis of several biologically active molecules, including the catecholamines, thyroxine and melanin. Its conversion to L-DOPA by tyrosine hydroxylase (TH) is the rate-limiting step in the generation of dopamine, epinephrine and norepinephrine, in the adrenal medulla, sympathetic nerve cells and certain neurones of the brain. Under conditions of stress or neuronal stimulation TH activity increases and becomes responsive to increased levels of tyrosine. This has led to studies investigating the potential usefulness of supplementary tyrosine for treating diseases in which catecholamine deficiency may be a feature, such as Parkinson's disease and some types of depression. The usual doses employed have been 30 to 100 mg kg<sup>-1</sup> daily and in preliminary, uncontrolled studies results were encouraging. Tyrosine has also been investigated for its potential use in counteracting performance decrement in military sustained operations, and the effects of stress due to cold, hypoxia, noise or extended wakefulness. The effectiveness of short-term administration at doses of 100 to 150 mg kg<sup>-1</sup> has been demonstrated in controlled trials. Other potential uses include a possible role in facilitating melanogenesis. Very few adverse reactions have been reported in the studies described. However, a report prepared for the US FDA in 1992 on the safety of amino acids as dietary supplements referred to toxicological findings in rats fed high doses of tyrosine, as well as reviewing data in humans. It identified a number of population groups likely to be at increased risk of adverse effects. Finally, the problems of funding definitive research to clarify the benefit/risk of such compounds are discussed.*

**Keywords:** tyrosine, Parkinson's disease, depression, stress, melanin, toxicology, clinical trial, side effects, patent, research.

## INTRODUCTION

Individual amino acids are readily available from most health food shops labelled as food, or dietary supplements. However, although their nutritional roles are well known when consumed in foods, other clinical uses are often recommended in leaflets or other literature with little or no references to supporting data. Unlike many herbal remedies, for which traditional uses are well established, there is no such pool of experience for amino acids, and an evaluation of the published literature is not a practical option for most potential users or advisers. This article attempts to address this deficiency by reviewing the clinical and other studies reported in the literature for tyrosine, an amino acid having a central position in the synthesis of several key biologically active molecules. It also comments on some of

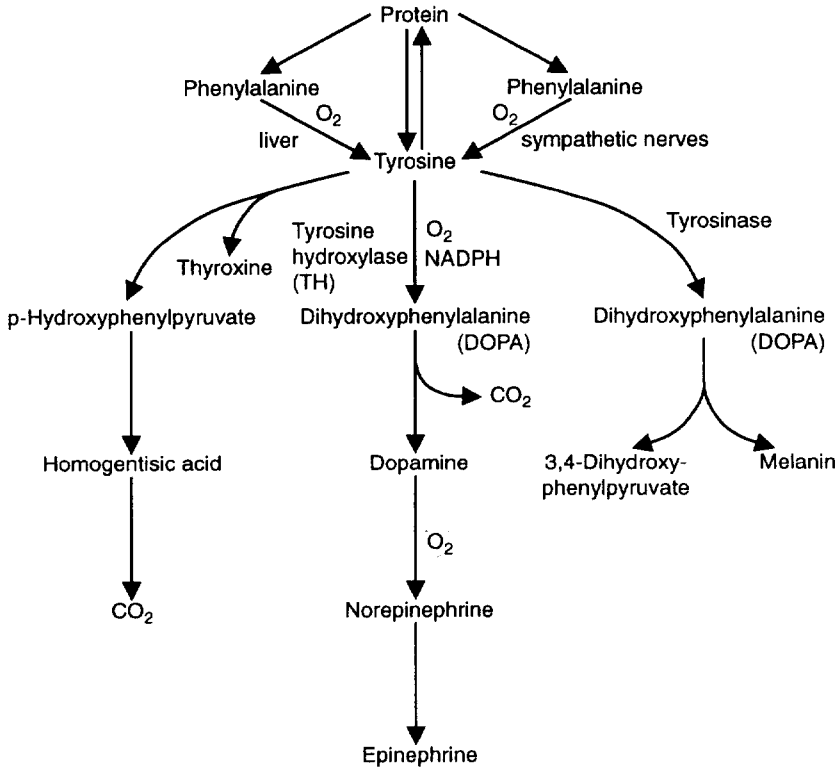


FIG. 1. Metabolism of tyrosine.

the difficulties which may arise in generating the further data needed to confirm or refute its value in the indications discussed.

Tyrosine, occurring naturally as the L-isomer, is present in all naturally occurring proteins and is released from them on digestion. It can also be synthesized to a limited extent in the human body from the essential amino acid phenylalanine, for which the recommended adult daily intake is  $14 \text{ mg kg}^{-1}$  [1]. Tyrosine is well absorbed from the gut, following which a proportion is subject to transamination by the liver. The rate of transamination proceeds rapidly if adequate stores of vitamin  $B_6$  to produce coenzyme are present. In situations where vitamin  $B_6$  status is seriously compromised, less flux through the transaminase pathway would be expected. Tyrosine is the precursor of the catecholamines, dopamine, norepinephrine and epinephrine, and is also the starting point for synthesis of thyroxine and melanin. Excess tyrosine is metabolized to various intermediates, and can by several steps eventually yield carbon dioxide (Fig. 1).

#### SYNTHESIS OF CATECHOLAMINES

The first step in the synthesis of catecholamines is the hydroxylation of tyrosine by the enzyme tyrosine hydroxylase (TH) to produce levodopa (L-DOPA). Other enzymes then convert this to the neurotransmitters dopamine, norepinephrine and epinephrine. However, it is the first step in the process which is rate-limiting and controls the synthesis rate of the entire pathway.

The process occurs in the chromaffin cells of the adrenal medulla, sympathetic nerve

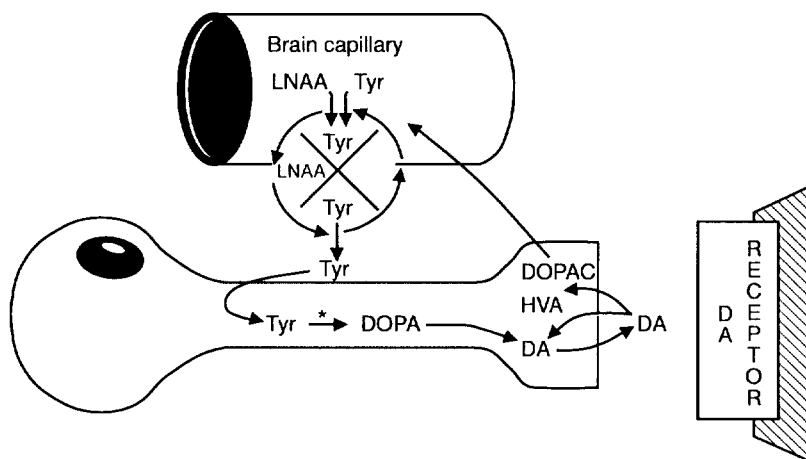


FIG. 2. Tyrosine (Tyr) availability and dopamine (DA) synthesis in neurons. Tyr is converted to DA by a two-step reaction, mediated by tyrosine 3-hydroxylase (Tyr  $\rightarrow$  dihydroxyphenylalanine (DOPA)) and aromatic L-amino acid decarboxylase (DOPA  $\rightarrow$  DA). Monoamine oxidase initiates the catabolism of DA to homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC), the principal DA metabolites in the CNS. \*Rate-limiting step in DA formation, Tyr hydroxylation. Tyr competes with other large neutral amino acids (LNAA) for uptake into brain (after Fernstrom, 1994).

cells, and neurones of various parts of the brain such as the corpus striatum of the mid-brain. In the brain tyrosine uptake occurs via a transport carrier, located at the blood-brain barrier, in competition with other large neutral amino acids (LNAAs) such as tryptophan, phenylalanine, leucine, isoleucine and valine. Hence the amount of this amino acid available to neurones depends both on the blood levels of tyrosine itself and those of its LNAA competitors (Fig. 2) [2].

Administration of single doses of L-tyrosine orally increases plasma tyrosine in normal subjects, a 100 mg kg<sup>-1</sup> dose administered to fasting subjects resulting in a doubling of plasma tyrosine levels [3]. Multiple doses, totaling 100 mg kg<sup>-1</sup> daily, produced two- to three-fold elevations of plasma tyrosine in normal subjects consuming three daily meals containing 113 g protein. They also increased the plasma tyrosine ratio (Tyr/LNAA) which predicts the entry of tyrosine into the brain [4].

Because it is rate-limiting, the TH step is of particular importance and has been the subject of much research (see for example Goldstein and Lieberman [5] and Nagatsu and Ichinose [6]). Human TH exists in four isoforms arising from a single gene. The reaction it catalyzes requires tetrahydrobiopterin (BPH<sub>4</sub>) as a cofactor together with molecular oxygen. The dihydrobiopterin produced in the oxidation of tyrosine is reconverted to BPH<sub>4</sub> by a second enzyme, for which nicotinamide adenine dinucleotide (NADH), or possibly nicotinamide adenine dinucleotide phosphate (NADPH), is the cofactor (Fig. 3).

There are multiple controls on TH, including local availability of substrate (tyrosine), and feedback inhibition by the catecholamines produced. Under normal conditions it has been estimated that the enzyme is 70–80% saturated by substrate [7] so there is limited response to administered tyrosine. This, however, assumes an adequate protein intake to provide the dietary supply of the amino acid or its precursor.

Badawy and Williams [8] found that rat brain catecholamine synthesis was enhanced by small doses of tyrosine given by intraperitoneal injection up to 20 mg kg<sup>-1</sup>, but higher doses had a reduced effect, falling to control values at 50 mg kg<sup>-1</sup> or above. The authors attributed the higher dose effect to substrate inhibition. More recently Nasrin and colleagues

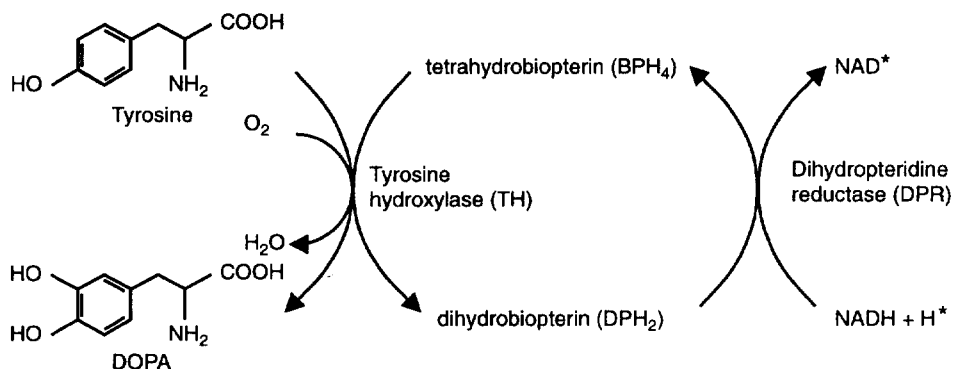


FIG. 3. Hydroxylation of tyrosine.

[9] have reported substrate inhibition *in vitro* with a recombinant human TH isoenzyme at tyrosine levels of 20–50  $\mu\text{M}$ , equivalent to 3.6–9.0  $\mu\text{g ml}^{-1}$ . These are levels in line with those which have been found to occur in cerebrospinal fluid (CSF) of patients receiving 100  $\text{mg kg}^{-1}$  daily or more of tyrosine orally over periods of several days, as described later.

Under conditions of stress or neuronal stimulation TH activity markedly increases and becomes responsive to increased levels of tyrosine [10]. The mechanism for this change is phosphorylation of the enzyme by protein kinases. Long-term stressful stimuli result in enzyme induction via increased TH gene transcription. Both activation processes allow acute and dietary administration of tyrosine to prevent the depletion of brain norepinephrine which would otherwise occur [11]. A response to tyrosine has also been detected under basal conditions using an *in vivo* microdialysis technique [11].

### PARKINSON'S DISEASE

Parkinson's disease (PD) is characterized by a progressive loss of brain nigrostriatal neurones leading to a deficit of the neurotransmitter dopamine (DA). However, clinical symptoms generally do not begin to appear until the degree of cell loss reaches the 70–80% level. Compensating mechanisms must therefore operate, one of which is probably an increased activity of the remaining neurones [12], such that increased activity of TH produces a substrate-dependent condition.

There is no evidence that brain tyrosine levels are depleted in PD, and CSF levels may even be increased [13]. However, this does not mean that there is sufficient tyrosine for optimum activity of the remaining neurones. Mogi and associates [14] demonstrated that although the TH content and overall activity were reduced in PD brains compared to controls, the TH homospesific activity (activity per mg enzyme protein) was significantly increased in PD brains. The critical factor therefore becomes the availability of tyrosine within the cells of the remaining neurones, where the TH has become more active.

Growdon and colleagues [15] have reported that oral administration of tyrosine to PD patients at 100  $\text{mg kg}^{-1}$  daily for 4 to 7 days resulted in significant increases in CSF tyrosine levels (means of 3.5 before and 6.1  $\mu\text{g ml}^{-1}$  after). There was also a significant increase in CSF levels of homovanillic acid (HVA), a metabolite of DA, in those who also received probenidol to block its transport across the CSF–blood barrier. The authors concluded that tyrosine administration can be useful to increase DA turnover and enhance dopaminergic neurotransmission in such patients.

Surprisingly, only two clinical trials of tyrosine in PD patients have been found in the published literature, both uncontrolled.

- (1) In addition to the above mentioned study, Growdon [16] has reported on 39 PD patients with varying severity and duration of disease who received oral doses of tyrosine 50 to 100 mg kg<sup>-1</sup> daily. Ten patients improved as much on tyrosine as they did during subsequent L-DOPA therapy. Benefit was sustained in four patients but lasted only 2 to 4 weeks in the other six patients. The remaining patients did not respond to tyrosine and seven of them were also unresponsive to L-DOPA. Parkinson's disease was less severe and its onset more recent in the 10 patients who responded to tyrosine than in the 24 who did not. The authors concluded that tyrosine administration is likely to be most effective in patients with early, mild PD and should be tested further in this group as an alternative to L-DOPA therapy.
- (2) Lemoine and colleagues [17] treated five recently diagnosed PD patients and five with a mean duration of disease of 3.4 years. The latter group was switched from L-DOPA or other treatment to tyrosine over a short period of up to 1 week. All 10 patients then received gradually increasing doses of tyrosine of 800 mg day<sup>-1</sup> increments until satisfactory clinical results were obtained. Gradual improvement occurred in all patients over several months, reaching an optimum within 6 months, mean dosage being 2.2 g day<sup>-1</sup> (range 1.6 to 4.0 g). At the time of the report patients had received tyrosine for 5 to 36 months and the authors considered it provided better clinical results than other treatments with negligible side effects and no "on-off" episodes. They postulated an advantage of tyrosine over L-DOPA in that the latter is a non-specific precursor which can be taken up by serotonergic as well as dopaminergic neurones, thereby decreasing brain serotonin levels. Their reference to a short lasting trial of tyrosine providing no evidence of benefit was in fact a trial of *m*-tyrosine, a different isomer to the natural L-(*p*)-tyrosine which they used and which is the subject of this review.

Taken together the two clinical studies suggest that, in line with experimental data, supplementary tyrosine administered orally might be beneficial in PD, particularly in the early stages of the disease. However, at least one long-term controlled clinical trial will be needed before this can be confirmed. There is also a need to clarify optimum dosage since the more encouraging results from the two clinical studies emerged from the one in which markedly lower doses were used. On this latter point it should be borne in mind that a number of variable factors are likely to influence response to supplementary tyrosine, including dietary protein consumption, ratio of tyrosine to other LNAAs and availability of coenzyme. There is also the possibility that substrate inhibition, as mentioned earlier, could occur at higher doses, particularly when treatment is continued over several days, when substrate levels may accumulate.

With regard to coenzyme, an alternative therapeutic approach to PD has been to administer supplementary NADH as a means of increasing production of the coenzyme BPH<sub>4</sub>, which is needed along with tyrosine for optimum TH activity [18]. Encouraging results have been obtained in a large open label study, again with most improvement in younger patients with shorter duration of disease. However, the authors admit that the results could be due to a peripheral rather than central effect leading to increased blood levels of L-DOPA, a proportion of which reaches the brain. More recently intravenous infusions of 10 mg NADH have been found to increase the bioavailability of L-DOPA in PD patients receiving conventional pharmacotherapy [19].

Surprisingly, no clinical studies appear to have been conducted on nicotinamide in PD, despite the fact that it is the precursor of NAD and NADH and has been shown experimentally to protect against neuronal injury (either alone or with coenzyme Q10), by nitric oxide [20], malonate [21] and MPTP [22]. Whether a combination of tyrosine with NADH or nicotinamide would be effective in a wider range of patients than either agent alone is open to question and can only be resolved through controlled studies. The same may be said of a possible role for tyrosine as a replacement for L-DOPA in combination

with catechol-O-methyltransferase (COMT) inhibitors such as entacapone and tolcapone, or selective monoamine oxidase (MAO) inhibitors such as selegiline.

It may be asked what advantage tyrosine could have over L-DOPA in the therapy of PD. As mentioned by Lemoine [17], L-DOPA is a non-specific precursor which can lead to decreased levels of brain serotonin by displacing 5-hydroxytryptamine (5-HT) from storage sites. A further cause of serotonin depletion may be due to L-DOPA inhibiting the activity of tryptophan hydroxylase, an enzyme involved in its synthesis from tryptophan [23]. Perhaps the most significant disadvantage of administered L-DOPA is its competition with other LNAAs, including tryptophan and tyrosine, for brain uptake [24] and its action as a feedback inhibitor of TH within neurones. The combined effect is to bypass the activity of the enzyme which provides any remaining physiological control of DA synthesis. The authors of these papers believe that these properties of L-DOPA contribute to its well-known side effects, which contrast with the near absence of side effects reported for tyrosine. These conclusions are also consistent with those of Melamed [25] who described experimental studies showing that, in nigrostriatal dopaminergic neurones, DA derived from exogenous L-DOPA is handled in an entirely different manner to tyrosine-generated dopamine.

## DEPRESSION

The role of DA in the pathogenesis of depression is less clear than in PD, and has been the subject of a review by Brown and Gershon [26]. The authors describe clinical and biochemical evidence of dopaminergic involvement in the disease, and conclude that this is probably significant. However, they believe that the role of DA must be understood in the context of theories involving other neurotransmitters such as norepinephrine, serotonin and acetylcholine.

Tyrosine has been reported to be of benefit in the treatment of amphetamine responsive depression, as discussed in three letters which appeared in the *Lancet* in 1980 and included reference to a supportive double-blind clinical trial [27,28,29]. The correspondence also provides information on the bioavailability and safety of tyrosine when administered orally at a  $100 \text{ mg kg}^{-1}$  dose for a short period of time.

In 1988, Mouret and colleagues [30] reported on 12 patients with what they described as dopamine-dependent depression, diagnosed from sleep recordings (polysomographic) and clinical signs. Treatment with oral tyrosine,  $3200 \text{ mg day}^{-1}$ , resulted in a return to mood from the first day followed by an improvement in sleep parameters. The authors stated that more than 50 patients had been successfully treated for periods ranging from a few months to almost 2 years, and claimed that the treatment was ineffective in other types of depression.

More recently it has been suggested that a low plasma level of tyrosine in users of oral contraceptives, owing to increased tyrosine transaminase activity, may contribute to disturbances of mood in susceptible subjects [31].

In a double-blind study, no evidence of efficacy of tyrosine (at  $100 \text{ mg kg}^{-1}$  daily) was found when compared with imipramine and placebo in 65 outpatients with major depression over a 4-week period [32]. However, the study was not definitive since all three groups improved during treatment with only a trend in favour of imipramine. After 4 weeks, tyrosine depression scores were intermediate to those of imipramine and placebo, though not significantly different from either. Whether tyrosine would show demonstrable efficacy in a larger study, or in patients with less severe symptoms or with a significant element of stress (see later), is not known. It is also possible that the relatively high dose of tyrosine used in the controlled study, compared to the earlier Mouret study, had a negative impact since it would have tended to competitively decrease brain levels of tryptophan. The availability of this amino acid determines the levels of the neurotransmitter, serotonin, and

an inverse relationship has been reported between depression scores and plasma tryptophan/LNAA ratio [33].

One further consideration is the possible influence of thyroid status on response to tyrosine. As mentioned previously, tyrosine is the precursor of thyroid hormones as well as catecholamines, and it is likely that a tendency to hypothyroidism can predispose to depression [34]. It has also been suggested that mobilization of thyroid hormones favours recovery from depression, possibly by increasing the beta-adrenergic receptor response to catecholamines [35].

## STRESS

In 1992, a review article was published [36] which summarized the biochemistry of tyrosine, and the evidence from animal and human studies of its effectiveness in reducing stress-induced performance decrement. The authors concluded that doses of 100 to 150 mg kg<sup>-1</sup>, given orally, could improve performance and mood in military personnel under conditions of battle stress. This was based in particular on two double-blind, controlled studies in normal subjects, subjected to stress induced by cold and hypoxia [37] and physiological stress resulting from lower body negative pressure [38].

Other controlled studies demonstrated that oral tyrosine at these doses reduced performance impairment due to noise [39], cold [40] and extended wakefulness [41].

The results were attributed to the administered tyrosine counteracting the depletion of this precursor by stress-induced increase in neuronal firing rate. There was a remarkable absence of side effects in all the studies, including no significant changes in blood pressure or pulse rate. The lack of cardiovascular effects was possibly due to feedback inhibition of TH, and activation of  $\alpha$ -adrenoceptors which inhibit the release of norepinephrine [42]. The possible involvement of the tyrosine metabolite, tyramine, in the effects produced was discounted by Banderet and Lieberman [37] on the basis that this amine is not detectable in the plasma of animals after they are given large doses of tyrosine [43].

The above studies were all conducted on normal volunteers subjected to various types of "environmental" stress. However, both subjective and objective advantages were recorded for tyrosine compared to placebo, so there is a reasonable possibility of similar benefits in patients exhibiting stress, particularly of an acute nature, as for example in panic attacks.

## MELANOGENESIS

There is a well established link between exposure to UV radiation and skin cancer. However, despite attempts to increase public awareness of the risk, the popularity of sun bathing and the belief that a robust tan looks healthy remain firmly established. Although sunscreens are widely used and may provide some measure of protection there remains a need to consider other approaches to minimize UV exposure which will be acceptable to the public.

As mentioned above, tyrosine is the starting point for the synthesis of melanin, the pigment which provides a physiological defence against UV radiation. The synthesis occurs in the pigment cells (melanocytes) of the skin and involves the oxidation of tyrosine, via L-DOPA, to quinones, which polymerize to give rise to melanin. The biochemical mechanisms involved are complex but have become better understood over the past few years as described in a recent review by Gilchrest and colleagues [44]. Just as TH is the rate-limiting step in the generation of catecholamines, another enzyme, tyrosinase, is rate-limiting in melanin synthesis. Tyrosinase is located in melanosomes, the subcellular organelles in which melanin is deposited. Both enzymes catalyze the hydroxylation of tyrosine, but within the melanosome the level of activity of tyrosinase determines the rate of flux of tyrosine metabolism through the melanin pathway.

A direct effect of UV photons on the DNA of melanocytes results in up-regulation of the

gene for tyrosinase, and increased expression of receptors for the melanogenic factor, melanocyte stimulating hormone (MSH). A further effect of UV radiation on melanocyte membranes releases intermediates which in turn phosphorylate and activate tyrosinase protein. These factors ultimately result in a maintenance or increase in melanocyte numbers and increased melanin pigment in the epidermis.

The above outlined mechanism suggests that, under conditions of UV stress resulting in tyrosinase activation, the availability of its substrate, tyrosine, could be rate-limiting for production of melanin. If this were the case then administration of tyrosine could be expected to speed up the tanning process, thereby providing more rapid protection against adverse UV effects. It might also mean that a moderate tan could be obtained with less UV exposure. Unfortunately, no clinical data have been found in the published literature to confirm or refute this hypothesis, although at least one product is available on the UK market containing L-tyrosine with labeling which strongly implies that it will facilitate tanning. The recommended dose provides 200–600 mg tyrosine daily.

Concerns that L-DOPA, an alternative substrate for tyrosinase, might promote melanoma through stimulation of melanogenesis have been refuted by an epidemiological study [45] and a recent review of the literature [46].

It must be emphasized that there is no evidence that tyrosine will itself reduce the risk of skin cancer nor be of benefit as a treatment. A low supplementary dose during and following UV exposure may contribute to the efficient synthesis of pigment, but until there is some evidence that it is effective and unlikely to be misused, it cannot be recommended for this purpose.

## OTHER CONDITIONS

Tyrosine has been studied in other indications where increased catecholamine synthesis was considered desirable. However, controlled clinical trials have not demonstrated significant efficacy in attention deficit disorder [47], narcolepsy [48], schizophrenia [49] or in the treatment of cocaine dependence [50].

## SAFETY

In clinical studies, with the dosage and duration of treatments used, no significant side effects were reported. However, there are situations in which, on theoretical grounds, tyrosine should not be used, these being:

- use with non-selective MOA inhibitors (risk of severe hypertension);
- use with L-DOPA (possible reduced effectiveness);
- in diabetics (as with other amino acids, due to the patient's metabolic state);
- rare metabolic diseases in which blood levels of tyrosine are already raised.

In addition to the above, a report on the safety of amino acid supplements prepared for the FDA in 1992 [51] recommended, largely on the basis of animal studies in which large doses were used, that the following population groups should not receive tyrosine supplements:

- women immediately prior to or during pregnancy and lactation;
- infants and children;
- those taking medications which stimulate the cytochrome P450 enzyme system.

It also identified the elderly and those on a low-protein diet as being at increased risk of possible adverse effects from chronic consumption. A particular concern from animal studies was the development of cataracts, skin lesions and histopathological changes in rats fed a low protein diet supplemented with 3 to 5% L-tyrosine. The corneal changes regressed on continued treatment. Similar reversible lesions occur in patients with Tyrosinaemia II, when tyrosine plasma concentrations are elevated to approximately seven times normal.



## DISCUSSION

A number of potential therapeutic uses of tyrosine have been identified. In one of these, the early treatment of PD, the biochemical basis of such a role is clear and there are some encouraging preliminary clinical data. In another, the treatment of acute stress, several controlled studies in normal subjects have demonstrated effectiveness, but no clinical trials have been reported. In the case of depression there is some evidence that a particular subgroup of patients may be responsive. Finally, a possible role in promoting the tanning effects of UV exposure is described.

In order to generate the data necessary to establish whether or not tyrosine would be effective and safe in the conditions described, a costly clinical research programme would be needed. This could be undertaken by the pharmaceutical industry, which has the necessary resources and would be able to coordinate pharmaceutical development with the large-scale clinical studies needed to confirm or clarify efficacy, and put safety concerns into perspective. Unfortunately, pharmaceutical companies are unlikely to be interested as they would not have the incentive of patent protection, and would also face competition from the continued availability of similar unlicensed products.

The latter problem arises from the fact that, provided a product can be described as a food supplement and no overt medicinal claims are made on its labeling, it can escape the normal rigors of licensing which apply to a medicinal product. Hence it can generally be assumed that, even where a licensed product is available, there will be an opportunity for a food supplement version to compete with it at a lower price. This exemption is fine up to a point, in that it helps to stimulate academic research and the generation of hypotheses essential for therapeutic advances, but for the reasons given above it acts as a brake on confirmatory studies.

To some extent these difficulties can be offset, at least within the European Community, by the market exclusivity concession in Article 4.8 of the 65/65 EC directive. This prevents a second (generic) applicant from being able to cross-refer to the first applicant's preclinical and clinical data for a period of 6 or 10 years from the first EC marketing authorization (the period depending on the member state concerned). If this is combined with limited lists of reimbursable products, as occurs in several European countries, or subsidized prescription costs as in the UK, there is a reasonable prospect of pharmaceutical investments being commercially viable.

Even so, few companies appear to be moving in this direction as far as readily available naturally occurring substances are concerned, and recent proposals before the European Court of Justice [52] to allow generic approval of new indications authorized within the 6- or 10-year period will not help. Hence selective government and charity funding appears likely to remain the main basis for research activities in the immediate future.

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