Chapter 9
Tryptophan dependency of brain serotonin is evolutionary conserved and of functional significance

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Abstract

Introduction: The cerebral 5-HT system is phylogenetically old and shows remarkable anatomical resemblance among species. The goal of this review is to investigate the physiological role of 5-HT in the accomplishment of behavioral states.

Tryptophan and 5-HT: In higher organisms, tryptophan is an essential amino acid and is also the least abundant of the natural amino acids. Its catabolism is, among others, increased by inflammation and by stress hormones. Fluctuations of plasma tryptophan levels have direct consequences on brain 5-HT synthesis and release and this relation is seen in all species studied.

Behavioral consequences of low tryptophan and 5-HT levels: In humans, decreased brain 5-HT neurotransmission is associated with impulsive aggression. In animals ranging from fish to primates, 5-HT turnover is inversely related with social rank and aggressive behavior.

Conclusions and hypothesis: The precursor dependency of 5-HT production and its behavioral consequences probably have a survival value. We hypothesise that the tryptophan-dependency of 5-HT function is related to adaptation to adverse circumstances. Deficient 5-HT neurotransmission has been associated with many psychiatric conditions, but may be etiologically linked to none of them. Restoring 5-HT transmission by medication may be effective in patients exhibiting depletion of tryptophan.
Introduction

Over the last 5 decades a large body of data has been published implicating the serotonin (5-hydroxytryptamine, 5-HT) system in a wide variety of psychiatric disorders, including depression, panic disorder, generalized anxiety disorder, obsessive compulsive disorder, eating and borderline personality disorders (Nutt et al. 1999). Data of postmortem studies, cerebrospinal fluid (CSF) studies and platelet studies have converged to the suggestion of a deficient 5-HT neurotransmission and possibly also of a reduced function of postsynaptic 5-HT receptors in the central nervous system (CNS) in these psychiatric disorders (Anand et al. 1994, Kahn et al. 1988). For instance, a reduced content of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA, the main metabolite of 5-HT) has been reported, though inconsistently, in several psychiatric disorders. Little, if any, evidence is as yet available to propose that 5-HT dysfunction is related to a particular disorder. Rather, current evidence suggests that low brain 5-HT is related to specific symptoms. Accordingly, aggressive suicide attempts, impulsive fire setting, personality disorders with outward directed hostility have been associated with reduced CSF 5HIAA (Asberg et al. 1976, Roy et al. 1986). Perhaps the most consistent observation in humans is a correlation between low brain 5-HT function and impulsive aggressive behavior. Therefore, a dimensional hypothesis has been put forward suggesting that low cerebral 5-HT function correlates with inward or outward directed hostility (van Praag et al. 1987).

It has been well established in mammalians (including rodents and humans) that the synthesis of brain 5-HT and so the function of this neurotransmitter depends on the availability of the amino acid precursor tryptophan. Tryptophan is in most organisms an essential amino acid and among the least abundant amino acids. Consequently, this amino acid may easily become exhausted during low food intake or increased catabolism, with possible consequences for cerebral 5-HT transmission. Conversely, during high food intake or reduced catabolism brain 5-HT activity may become activated. The question that will be addressed in this review is what the function of 5-HT could be both in physiological and pathological circumstances and how this function is influenced by the precursor
amino acid tryptophan. Apparently, the organism perceives whether tryptophan levels lie outside the range ensuring normal 5-HT function. We hypothesize that the relationship between accessibility of tryptophan and 5-HT function in the brain, and possibly also in peripheral tissue, is conserved during the evolution of species and must therefore have survival value for the organism. Our arguments are based on the following observations:

1st: the brain 5HT-system is a phylogenetically old and thus evolutionary conserved system; 5-HT exerts a modulatory effect on many behavioral and other functions.

2nd: in all thus far studied species the enzyme complex directly responsible for the biochemical synthesis of 5-HT in the brain (tryptophan hydroxylase) has high Km-values in the range of the physiologically effective (i.e. free, that is non-protein bound) concentration of tryptophan. This means that a direct quantitative relation exists between the concentration of tryptophan and 5-HT in the brain.

3rd: tryptophan levels (and consequently brain 5-HT function) are to a significant degree determined by inducible catabolism.

In this review evidence is gathered for these considerations. Then, the behavioral consequences of modulation of the 5-HT system are addressed. Finally, conclusions are drawn about the physiological function of the system.
Neuronal localization of 5-HT and synthesizing enzymes have been recognized in virtually every organism studied thus far. 5-HT functions as a neurotransmitter in even the most primitive nervous system (Weiger 1997). For instance, in snail, leech and mollusks specialized 5-HT containing neurons have been identified. In the best-understood molluscan nervous system (Aplysia californica) an important projection of the 5-HT fibers projects to the muscles of the buccal mass (mediating swallowing and biting) and to the lips and is involved in feeding. In fish (e.g. platy fish, stingray, Senegal bichir, rainbow trout) several clusters of 5-HT containing neurons in the brain have been described, including the spinal cord, rhombencephalon, mesencephalon, prosencephalon, pituitary and retina. The distribution of 5-HT cells in the brain stem shares many similarities with that of other vertebrates, but there were also 5-HT-containing cells outside the raphe nuclei in the lateral tegmentum. 5-HT fibers and terminals arising from posterior tubercle/tegmental origin have been described in several fishes. It appears that the feature ascending projections of the 5-HT system arose early in phylogeny (Margolis et al. 1985, Ritchie et al. 1983). In conclusion, 5-HT functions as a neurotransmitter in the most primitive organisms possessing a CNS. In addition, to its function as neurotransmitter 5-HT is a morphogen, that is already active during early development of peripheral organs and cerebral wiring in a wide variety of animal species. Such function is likely to be maintained in the adult, as 5-HT affects brain plasticity via the induction of neurotrophins (Herlenius & Lagercrantz 2001). In vertebrates 5-HT cell bodies are clustered in the brainstem raphe nuclei. Although only a few thousands of these cells exist, ascending axons project to many regions in the brain. Among these are the hippocampus, hypothalamus, amygdala, basal ganglia and the cortex. These projections show remarkable anatomical similarity among species (Azmitia et al. 1991, Jacobs & Azmitia 1992). According to these common anatomical features in vertebrates, it has been concluded that 5-HT exerts widespread effects on the state of CNS that secondarily alter all behavioral interactions between the organism and its environment (Weiger 1997). To define the function of the 5-HT system more specifically, extensi-
ve research has been done. It has been shown that diverse functions such as feeding, sexual and aggressive behavior, blood pressure regulation and intestinal motility are modulated by 5-HT (Grahame 1988). For instance, increased feeding of rodents has been observed after depletion of 5-HT, whereas drugs that enhance the release of 5-HT (e.g. fenfluramine) or block the uptake of the amine (e.g. sertraline) reduce food intake (Weiger 1997). In fact, 5-HT restricts feeding behavior through interference with several processes, for review see (Lucki 1998). These and several other studies clearly show the modulatory effects of manipulation of 5-HT neurotransmission on several behaviors.
Tryptophan and 5-HT formation

Tryptophan is an essential amino acid in all mammalian species and its abundance in proteins is among the lowest as compared to the other amino acids (Bender 1983). It is therefore likely, that tryptophan limits the synthesis of several compounds such as proteins, coenzymes, and 5-HT. The availability of tryptophan in the mammalian brain is not only related to cerebral demand, but is determined by the ratio of plasma tryptophan and the other large neutral amino acids with which it competes for transport over the blood brain barrier as well. Competing amino acids are phenylalanine, tyrosine, threonine, leucine, isoleucine and valine. In the brain, the rate-limiting step for the production of 5-HT is the enzyme tryptophan 5-hydroxylase (TPH; EC 1.14.16.4).

In several non-mammalian species a relation between brain tryptophan levels and the cerebral production of 5-HT has been observed. Acute oral exposure of the medaka fish to 1 to 4 g tryptophan induces in a dose dependent manner the formation of brain 5-HIAA (Koutoku 2003). Feeding of the rainbow trout (Oncorhynchus mykiss) with tryptophan enriched diet increases the brain content of 5-HT, 5-HIAA and reduces cortisol secretion during stress (Lepage et al. 2002, Aldegunde et al. 2000, Ruibal et al. 2002), features strikingly similar to those seen in mammals.

In mammals the consequences of tryptophan loading or tryptophan-enriched diets on the cerebral synthesis and metabolism of 5-HT have well been documented. In mice, rats, hamsters, pigs and a number of monkeys and, finally, in humans, tryptophan loading results in acute increases of 5-HT and 5-HIAA. Moreover, a strong correlation between tryptophan levels in plasma and cerebrospinal fluid 5-HIAA levels in rats has been reported. Tryptophan loading in humans increases CSF 5-HIAA levels (Bender 1983). Thus, a direct relation exists between plasma tryptophan concentration and brain 5-HT levels in all tested species.

Conversely, rapid tryptophan depletion, through the ingestion of an amino acid beverage devoid of tryptophan, resulted in impaired cerebral 5-HT formation in all mammals studied, including humans. In test subjects, plasma levels of tryptophan could thus be reduced to approximately 10% of baseline levels a few hours after ingestion.
of such a beverage (Delgado et al. 1994). Microdialysis studies on
rats indicated that dietary depletion of tryptophan diminishes cere-
bral 5-HT release in both acute and chronic phases (Fadda et al.
2000). In vervet monkeys, CSF levels of 5-HIAA are diminished fol-
lowing dietary tryptophan depletion (Young et al. 1989).
TPH and regulation of 5-HT production

As TPH catalyzes the rate-limiting step in the biosynthesis of 5-HT, its properties in relation to regulation of 5-HT production has been subject to detailed analyses (McKinney et al. 2001, Kowlessur & Kaufman 1999, Friedman et al. 1972, Kappock & Caradonna 1996, Hamdan & Ribeiro 1999). Several studies have indicated that the Km-value for tryptophan of TPH, measured in vitro, is equal to or higher than the expected concentrations of tryptophan in the intact organism. Thus, it seems that the enzyme may be unsaturated with tryptophan in vivo. However, the kinetic values of TPH are highly dependent on experimental conditions, including pH, cofactors, and enzyme phosphorylation status (McKinney et al. 2001). Moreover, the local concentration of tryptophan in 5-HT neurons may be different from the CSF-values, which have been used in these studies. Thus, it is difficult to conclude on this issue based on enzymological studies alone. More importantly, as detailed above, a strong correlation exists between brain 5-HT-levels and plasma concentration of tryptophan, indicating that the brain 5-HT biosynthetic capacity normally is functionally unsaturated with tryptophan and this phenomenon may be dependent on the properties of TPH or additional factors.

Interestingly, the dependency of 5-HT biosynthesis of plasma tryptophan levels appears to be conserved throughout evolution (Table 1), further indicating that it may be of functional importance. For substrate binding to an enzyme such as TPH, one can imagine different types of "evolutionary pressure" to maintain maximal reaction rates, substrate specificity and possibilities for regulation, in addition to the physiological aspects discussed above. Possibly, the resulting substrate affinity of TPH has emerged as a compromise between multiple factors.
Table 1: Km and brain tryptophan levels in several mammals.

<table>
<thead>
<tr>
<th>organism</th>
<th>$K_m$ $\mu$mol/L</th>
<th>tryptophan $\mu$mol/L</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>human</td>
<td>50</td>
<td>5-25</td>
<td>(12)</td>
</tr>
<tr>
<td>rat</td>
<td>34</td>
<td>20</td>
<td>(40)</td>
</tr>
<tr>
<td>mouse</td>
<td>45</td>
<td>20</td>
<td>(34)</td>
</tr>
<tr>
<td>rabbit</td>
<td>50</td>
<td>9</td>
<td>(41)</td>
</tr>
<tr>
<td>chicken</td>
<td>49</td>
<td>19</td>
<td>(41)</td>
</tr>
<tr>
<td>guinea pig</td>
<td>40</td>
<td>20</td>
<td>(42)</td>
</tr>
</tbody>
</table>
Inducible tryptophan catabolism

In mammals about 1% of dietary tryptophan is converted to 5-HT and only 10% of the conversion to 5-HT takes place in the brain. A quantitatively more important metabolic pathway of tryptophan is its conversion to kynurenine (Bender 1983). About 99% of dietary tryptophan is metabolized along this so-called oxidative or kynurenine pathway. Usually, nicotinamide adenine dinucleotide (NAD) and H2O are formed via tryptophan oxygenase (EC 1.13.11.11) which is found mainly in the liver. Elevation of the oxidative tryptophan catabolism in the liver can be induced by a variety of external and internal mechanisms. Thus, the tryptophan oxidase activity of the liver is induced by administration of large amounts of tryptophan or by adrenal stress-hormones such as cortisol (Bender 1983). Acute exposure to cortisol prepares the individual, among others, for an ongoing immune challenge, including migration of leukocytes to potential infected locations and setting up negative feedback for the immune system. In stressful circumstances, brain 5-HT release is acutely increased (Hajos et al. 2003). In the periphery 5-HT has a role in blood clotting and vasoconstriction where it is released from blood platelets in case of vascular damage. Furthermore, in rodents, chronic treatment with the SSRI fluoxetine attenuated several immunological reactions after lipopolysaccharide challenge (Yirmiya et al. 2001). It seems that in adverse conditions the 5-HT system first is activated but shortly thereafter its activity extinguishes through precursor exhaustion. In rats undergoing immobilization stress, a decrease in plasma tryptophan levels of 20% was observed (Martin et al. 2000). In volunteers, administration of cortisol also results in a reduction of plasma tryptophan levels (Maes et al. 2000).

figure 1, metabolic pathways of tryptophan.

1%

5-HT ↔ TRP ↔ proteins

↓99%

kynurenine →→ NAD + H2O
Tryptophan catabolism along the oxidative pathway may also occur via the enzyme indoleamine 2,3 di-oxygenase (IDO, EC 1.13.11.17) (33). IDO activity under normal conditions is minimal, but the enzyme is highly inducible in a variety of tissues by pro-inflammatory cytokines such as interferons (Stark et al. 1998). High IDO activity has been observed in activated macrophages and microglia. IDO activity has been demonstrated in a variety of species (Cannazza et al. 2001, Malina et al. 1995, Ragazzi et al. 2002) and induction of IDO has been observed both in human and in rodents. In diseases such as AIDS and cancer, the formation of endogenous interferon-γ appears to be increased, with a concomitant decrease of plasma tryptophan levels (Iwagaki et al. 1997). Therapeutic intervention with pro-inflammatory interferon in patients suffering from hepatitis leads to increased tryptophan catabolism and consequently low blood levels of the amino acid (MacKenzie et al. 1999). Another link between immune activation and the 5-HT system is cortisol secretion, which is regulated by central 5-HT pathways (Grohmann et al. 2003). In turn, during induction of tryptophan catabolism down the oxidative pathway, cerebral 5-HT formation is also impaired due to decreased availability of vitamin B6 and folates which are both needed as a co-factors in the 5-HT formation (Bender 1983). The main consequence of tryptophan depletion is decreased protein synthesis which is related to anti-tumor, antiviral and antibacterial effects (MacKenzie 1999).
Behavioral aspects of tryptophan modulation

In several non-mammalian species, e.g. in lizards, cichlid fish, rainbow trout and damselfish, the relation between brain 5-HIAA levels and social rank has been established (Winberg et al. 1993, Maler & Ellis 1987, Winberg et al. 1993b). Submissive behavior in the arctic char was related to enhanced cerebral release of 5-HT (Winberg et al. 1993b). The male gymnotid fish uses high frequency electric discharges as an aggressive signal to other males. Intraventricular injection of 5-HT decreases this response (Maler & Ellis 1987). It has been shown in non-mammalian species that exposure to tryptophan affects both behavior (see also previous section) and the synthesis of 5-HT.

In mammals including rats, mice, monkeys and humans, the behavioral consequences of low brain 5-HT content have been studied extensively. In all these species, aggressive behavior was negatively correlated to brain 5-HIAA and 5-HT content. In rats, depletion of hippocampal 5-HT (by the local injection of 5,7 dihydroxytryptamine) induces an increased killing behavior towards mice. This behavior was dose-dependently decreased by 5-HT agonists (5-methoxy-N,N-dimethyltryptamine, 8-OH-DPAT), or 5-HT reuptake blockers which are widely used as, among others, antidepressants (Molina et al. 1987).

Depletion of 5-HT increases conspecific and predatory behavior in rodents. After depletion of 5-HT, rats show increased frequency and duration of offensive behaviors when an intruder rat is placed in the cage; ventral and dorsal raphe systems may have differential modulations in aggressive behaviors. In the vervet monkey (Cecopithecus aethiops sabaeus) increased 5-HT functions (induced by added tryptophan or fenfluramine) suppress aggressive behavior and may promote dominant behavior. It was also noted that the effects of tryptophan depended on the social circumstances (Brammer et al. 1991). Also, in another monkey species an inverse relationship was established between expressed aggression and cerebrospinal fluid levels of 5-HIAA. This trait was not only significant on an inter-individual but also on an interspecies level, suggesting that expression of
aggressive behavior may well be interrelated with central 5-HT tone. Furthermore, 5-HIAA in cerebrospinal fluid was positively correlated with social rank (Westergaard et al. 1999). In healthy human subjects, mild effects induced by acute transient tryptophan depletion have been reported on mood, hostility and irritability (Young et al. 1985, Leyton et al. 1999). In some somatic diseases with low and lasting tryptophan levels, depression may not be the prominent psychopathology, rather lack of impulse control and irritability are the main features (Russo et al. 2003, Russo et al. 2003b). In patients suffering from carcinoid tumors - these neuroendocrine malignancies consume tryptophan - increased ability to rapidly shift attention was observed (Russo et al. 2003c). Improvement in simple motor speed/attention following tryptophan depletion was observed, thus emphasizing that low brain 5-HT does not necessarily lead to functional impairment (Hughes et al. 2003). Low cerebral 5-HT levels have been associated with aggressive suicide attempts, impulsive arsonism and with outwardly directed hostility in personality disorders (Asberg et al. 1976) rather than with depressive symptomatology. In fact, symptoms related to lack of impulse control and (auto) aggression are associated consistently with low tryptophan, regardless of psychiatric diagnosis (van Praag et al. 1987).
Conclusions and hypothesis

Taken together, we propose that tryptophan is a signaling nutrient that modulates multiple CNS functions via 5-HT neurons. This information may have a survival value for the organism, as the dependency of 5-HT synthesis on tryptophan supply is evolutionary conserved. Moreover, the anatomical resemblance of the central 5-HT system between species is remarkable. For these reasons, it seems plausible that its function is similar among species, suggesting a role for the 5-HT system in the adaptation to adverse circumstances. If such a dependency was harmful to the organism, it is expected to be eliminated during the evolution of species e.g. by the emergence of a variant of the enzyme TPH with a higher affinity for tryptophan.

We made the following speculation about the possible survival value of the tryptophan-5-HT-interrelationship. For survival, food intake is crucial. Tryptophan is an essential amino acid and its availability is the lowest among the natural amino acids. A diet restricted in protein content will reduce its peripheral levels faster than most other amino acids. As maintenance of all essential physiological functions are based on adequate protein synthesis, regular intake of amino acids is necessary for optimal survival. Shortage of tryptophan in plasma may thus be a sensitive indicator of food shortage, enabling physiological and behavioral adaptations. Low tryptophan and low 5-HT are associated with outward oriented behavior, characterized by irritability, impulsive reactivity and aggression. To survive food shortage and starvation, an organism may firstly try to reduce food consumption and activities, but has finally to exert fierce behavior to find food, either by more thorough searching or by battling with competitors. Low brain 5-HT may facilitate such behavior. Not only during low food intake but also during disease low tryptophan/brain 5-HT may have survival value. For instance, plasma tryptophan stores are depleted during inflammation, due -at least in part- to increased tryptophan catabolism. To avoid predation, the diseased subject may firstly hide. However, if the disease lasts to long, the subject may have to take the risk to gather or catch food for survival. Such risky behavior may be facilitated when a certain level of aggression is reached. Low 5-HT, as induced by low tryptophan, may facilitate such behavior. Again, lowering brain 5-HT can be seen as a
survival mediating process. The negative effects of tryptophan depletion on the expression of affiliative behavior in infective circumstances may have consequences for disease spreading. Subjects may become irritated and thus social interaction will be avoided. It is noted that no animal possesses senses to detect an infectious environment. Again, such behavior might be beneficial for survival of the species. Finally, activation of survival facilitating mechanisms may become essential following exposure to severe stress. Stress enhances the secretion of corticosteroids and these induce oxidative tryptophan catabolism in the liver. The resulting low brain 5-HT may initiate and facilitate behavior recovery after a period of inactivity seen in many experimental depression models, based on exposure of male rodents to defeat stress (Summers & Greenberg 1995). The adaptation hypothesis can also be illustrated in higher species. For instance, migration behavior in monkeys has been associated with low 5-HT (Trefilov et al. 2000). This can also be considered as adaptation to unfavorable circumstances.

We propose that tryptophan has a signaling role in physiology that is mediated by 5-HT. High tryptophan levels may induce the feeling of relatively well-being in the organism, diminishing the urge to search for food and enhance dominant behavior. The physiological consequences of tryptophan depletion are not only limited to acute effects, but are also apparent in response times of several hours or days. The consequence is not only induction of aggressive behavior related to low central 5-HT activity, but also modification of immune reactivity and preparation of the body to vascular responses. Stress reactions are remarkably similar among species varying from mollusks to primates, suggesting the involvement of evolutionary conserved mechanisms. Perception of stress may have evolved in a stage of the evolution where there was no discrimination between internal and external stimuli (Sawada et al. 1991). At the beginning of compromising conditions, the organism requires rest and shelter for recovery, but when such condition may last too long, the chances of survival may become increased by more aggressiveness in an (perhaps ultimate) attempt to obtain food. It is therefore not surprising that 5-HT modulates a wide range of cerebral processes that continue to function in its absence (Lucki 1998). It seems that the 5-
HT system informs the brain on basal circumstances being good or bad. Thus instead seeing low tryptophan as a risk factor of psychiatric pathology, we consider it as a physiological signal to the brain. But considering the evolutionary perspective of this relationship, low brain 5-HT may well be associated with unpleasant conditions of the organisms. In humans, this may manifest itself by symptoms such as depression, aggression, impulsivity and (perhaps as the ultimate consequence of these) suicide.

Today, the key feature of antidepressants is the modification of monoamine, notably 5-HT, neurotransmission. Modern drug developments have only contributed to decrease side effects and improvement of tolerance, but have little, if anything contributed to a higher therapeutic efficacy (Payk 1994, Bosker et al. 2003). As antidepressants these drugs are far from ideal. For instance, Kirsch et al. performed a meta-analyses of the efficacy data submitted to the U.S. Food and Drug Administration of the 6 most widely prescribed antidepressants approved between 1987 and 1999. It appears that more than 80% of the effect of these antidepressants has to be attributed to placebo effects (Kirsch et al. 2002). Currently, antidepressants are not only prescribed for depression but also for a wide variety of psychiatric disorders such as anxiety disorders (Wagstaff et al. 2002, Westenberg et al. 1987), eating disorders (Kaye et al. 1998) and personality disorders (Rinne et al. 2002). The observation that SSRI's have small advantage over placebo and lack specificity for a particular psychiatric disease fits with a role of 5-HT in the adaptation to adverse circumstances. The possible implication is that 5-HT is not etiologically linked to any particular psychiatric disease in the general population. However, in a genetic subgroup, a relation between depressive symptoms and the 5-HT system might exist. In primates, a functional polymorphism in the promoter region of the 5-HT transporter gene exists. The short allel is related to decreased production of the transporter. A recent study showed that early childhood abuse was related to psychiatric symptoms only in patients with 1 or 2 copies of the short allel (Caspi 2003). This suggests that gene environment interactions determine the output of the 5-HT system and the vulnerability of an individual to develop symptoms during compromising experiences. It is therefore possible that
fluctuation of plasma tryptophan level alone is not sufficient to cause psychopathology and that interaction with genetic make up takes place. These factors have to be taken into account in further studies into the behavioral pattern associated with tryptophan depletion. Our proposal makes it comprehensible that the output of the 5-HT system is changed in diverse psychiatric patients because (psychiatric) illness can be considered as an adverse condition. Consequently, 5-HT may play an etiological role in the development of psychiatric symptomatology in somatic patients. Thus, the effects of SSRI's should be studied in somatic patients not only suffering from classical depression but also from irritability and aggression. However, it may well be possible that in severe tryptophan depleted subjects, the availability of 5-HT is too low for adequate reuptake inhibition and other therapeutics will be more effective. These include postsynaptically acting 5-HT antagonistic drugs and IDO inhibitors. Regular monitoring of plasma tryptophan levels may help to optimise the therapeutic use of current antidepressants.

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References


