REVIEW ARTICLE

Tryptophan as an evolutionarily conserved signal to brain serotonin: Molecular evidence and psychiatric implications

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Abstract
The role of serotonin (5-HT) in psychopathology has been investigated for decades. Among others, symptoms of depression, panic, aggression and suicidality have been associated with serotonergic dysfunction. Here we summarize the evidence that low brain 5-HT signals a metabolic imbalance that is evolutionarily conserved and not specific for any specific psychiatric diagnosis. The synthesis and neuronal release of brain 5-HT depends on the concentration of free tryptophan in blood and brain because the affinity constant of neuronal tryptophan hydroxylase is in that concentration range. This relationship is evolutionarily conserved. Degradation of tryptophan, resulting in lower blood levels and impaired cerebral production and release of serotonin, is enhanced by inter alia inflammation, pregnancy and stress in all species investigated, including humans. Consequently, tryptophan may not only serve as a nutrient, but also as a bona fide signalling amino acid. Humans suffering from inflammatory and other somatic diseases accompanied by low tryptophan levels, exhibit disturbed social behaviour, increased irritability and lack of impulse control, rather than depression. Under particular circumstances, such behaviour may have survival value. Drugs that increase brain levels of serotonin may therefore be useful in a variety of psychiatric disorders and symptoms associated with low availability of tryptophan.

Key words: Serotonin, tryptophan, depression, psychopathology, evolution, indole 2,3-diamino oxygenase

Introduction
During the last five decades, more than 25,000 reports have appeared on the possible involvement of cerebral serotonin (5-hydroxytryptamine, 5-HT) in a wide variety of psychiatric disorders. Dysfunctional 5-HT transmission has been associated with depression, panic, anxiety, postpartum blues and depression, obsessive-compulsive disorders, attention deficit hyperactivity disorder, autism, eating disorders, schizophrenia and borderline personality disorders (see, e.g., Maes et al. 2001, 2002; Van Praag 2001, 2004; Jans et al. 2006; Maron and Shlik 2006; M’Bailara et al. 2006). The central serotonergic system has also been implicated in many physiological processes and behaviours such as sleep (Jouvet 1999), thermoregulation (Lin et al. 1998), satiety (Leibowitz and Alexander 1998), neurogenesis (Banasr et al. 2004), stress response (Meijer and de Kloet 1998; Leonard 2005) and aggression (Popova 2006). The present overview emphasizes the non-specificity hypothesis about brain 5-HT (and tryptophan) and psychopathology. Accordingly, a strict (or deterministic) pathogenic role of low 5-HT levels in most if not all the mentioned psychiatric conditions, seems unlikely. In far the most psychiatric disorders brain 5-HT dysfunction and associated genes are modulating or worsening a wide variety of psychiatric conditions, instead (e.g. Levinson 2006; Jans et al. 2006; Maron and Shlik 2006; Riedel 2004; Riedel et al. 2002).

We propose that low levels of brain 5-HT are not only found in (mental) disorders, but may occur in various physiological conditions. This idea will also be discussed from an evolutionary point of view. The synthesis of brain 5-HT, and therefore its function, depends on the availability of the essential amino acid tryptophan (Fernstrom 2000). Blood plasma levels of tryptophan vary under a variety of conditions, such as starvation, infection and stress. Consequently, tryptophan may fulfil an important role as a signalling molecule in the communication of the organism with its environment. Thus, an organism...
may perceive whether plasma tryptophan levels lie outside the physiological range through cerebral 5-HT function. We speculate about the possible survival value of this mechanism for an organism. Some consequences of this point of view for the clinical indications of 5-HT-potentiating drugs, such as the antidepressants of the selective serotonin reuptake inhibitor (SSRI)-type, will also be discussed.

Phylogenetic perspectives of 5HT neurons

Specific 5-HT-containing neurons and ascending 5-HT projections probably arose early in phylogeny (Jacobs and Azmitia 1992; Azmitia 2001). In snails, leeches and molluscs, specialized 5-HT-containing neurons have been identified (Weiger 1997). In vertebrates, 5-HT-containing cell bodies are clustered in nuclei, containing a few thousands up to 100,000 cells. Ascending serotonergic projections almost exclusively stem from the dorsal and median raphe nuclei clustered around the midline of the brainstem (B7 and B9; Dahlstrom and Fuxe 1964). From these nuclei, ascending axons project to many regions in the brain and spinal cord, including the hippocampus, hypothalamus, amygdala, basal ganglia and the neocortex. According to the common anatomical features in vertebrates, 5-HT must have widespread effects on the state of the central nervous system and may secondarily influence a wide variety of behaviours in the organism.

Blockade of the 5-HT transporter with an SSRI during early development in mice resulted in abnormal adult behaviour (Ansorge et al. 2004), and 5-HT-depletion of the pregnant mother (lacking TPH-1) limited normal development of the cerebral 5-HT in the offspring (Cote et al. 2007). These findings suggest that 5-HT may also function as a morphogen during early development of neural wiring (Fukumoto et al. 2005; Nakamura et al. 2006). Such function may also be maintained in the adult, as 5-HT affects brain plasticity via the induction of neurotrophins (Mattson et al. 2004). It should however be mentioned here that the morphogen-like signalling function of 5-HT may in particular depend on the synthesis of 5-HT through tryptophan 5-hydroxylase (TPH, subtype 1).

Tryptophan and 5-HT synthesis

Tryptophan is an essential amino acid in higher organisms, but its abundance in proteins is relatively low (Bender 1983). It is conceivable that the availability of tryptophan is a limiting factor in the synthesis of several compounds such as proteins, nicotine amide and 5-HT. The cerebral influx of tryptophan is determined by the ratio of plasma tryptophan and other large neutral amino acids with which it competes for transport over the blood–brain barrier (Fernstrom 2000). Figure 1 shows an overview of the here discussed metabolic pathways.

In both mammalian and non-mammalian species, a direct relation between tryptophan levels, cerebral synthesis and metabolism of 5-HT has been observed. For instance, tryptophan loading increases the formation of brain 5-HT and its main metabolite

![Figure 1. Overview of the metabolic fate of tryptophan en serotonin (5HT). The emphasis is on the differential dependence of the cerebral 5HT formation via TRP type 1 and 2 and on the tryptophan influx from the circulation. Transport is indicated with gray arrows. Metabolic conversions are indicated with black arrows. Broken arrow indicates that 5HT synthesis is dependent from free (cerebral) tryptophan.](image-url)
5-hydroxyindole acetic acid (5-HIAA) in fish (Koutoku et al. 2003) and it reduces cortisol secretion during stress in a dose-dependent manner (Lepage et al. 2002), features strikingly similar to those seen in mammals. The consequences of tryptophan loading on the cerebral synthesis and metabolism of 5-HT have, however, best been documented in mammals. In various species, administration of tryptophan leads to acute increases of cerebral 5-HT and/or 5-HIAA (Bender 1983). Conversely, rapid tryptophan depletion, through the ingestion of food or beverages devoid of tryptophan, resulted in impaired cerebral 5-HT formation in all mammals studied, including humans. In humans, plasma levels of tryptophan can thus be reduced to approximately 10% of baseline levels a few hours after ingestion of such a beverage (Delgado et al. 1994; Jans et al. 2006). In the vervet monkey, CSF levels of 5-HIAA are diminished following dietary tryptophan depletion (Young et al. 1989). Microdialysis studies on rats demonstrated that dietary depletion of tryptophan diminishes cerebral 5-HT release in both acute and chronic designs (Fadda et al. 2000).

These observations together, point to a direct relationship between the availability of tryptophan, neuronal release and metabolism of 5-HT. Apparently, this relationship is evolutionarily conserved.

Regulation of 5-HT synthesis

The rate-limiting step for the cerebral biosynthesis of 5-HT is the enzyme tryptophan 5-hydroxylase (TPH). Recently, two different forms of TPH have been identified. TPH1 is expressed in peripheral tissues, the pineal gland, and in many brain regions. TPH2 is expressed in virtually all brain areas and is responsible for the majority of the cerebral 5-HT production (Walther et al. 2003; Zill et al. 2004, 2007). In vitro the human brain isoform TPH2 has a significantly lower affinity for tryptophan than TPH1 (McKinney et al. 2005). The in vitro \( K_m \) value for tryptophan of the TPH2 enzyme is in the range of the free concentration of tryptophan of the intact organism (McKinney et al. 2001, 2005). This implies that the production of cerebral 5-HT is directly dependent on the non-protein-bound concentrations of tryptophan in blood and brain. In contrast, the closely related TPH1 isoform has a lower \( K_m \) value, so within physiological ranges the production of 5-HT by this isoform is maximal. From an evolutionary perspective one can envision that if such substrate-dependence were harmful to the organism, “evolutionary pressure” should have led to the formation of a tryptophan hydroxylase with high substrate affinity. On the contrary, in the brain the low affinity TPH subtype (TPH2) is the most abundant isoform present. We propose therefore that variations in blood levels of tryptophan are perceived via the rate limiting enzyme TPH2, which is confined to cerebral 5-HT neurons, and that the relatively low affinity of TPH2 for tryptophan has been conserved throughout evolution.

Inducible tryptophan degradation

In mammals less than 1% of dietary tryptophan is converted to 5-HT and only 10% of that conversion takes place in the brain. The quantitatively most important catabolic pathway of tryptophan is the so-called oxidative or kynurenine pathway, metabolizing about 99% of dietary tryptophan (Bender 1983). End products such as nicotinamide adenine dinucleotide and \( \text{H}_2\text{O}_2 \) are formed via tryptophan oxygenase (TO) which is found mainly in the liver. This pathway is most prominent under non-challenged conditions. However, oxidative catabolism of tryptophan is susceptible for various internal and external stimuli, such as hormones, stress and immune-activation.

The human liver TO is induced by the administration of large amounts of tryptophan and following high levels of adrenal stress hormones, including cortisol (Bender 1983; Renkawitz et al. 1996). In volunteers, administration of cortisol results in a reduction of plasma tryptophan levels (Maes et al. 1990). In rats undergoing immobilization stress, a decrease in plasma tryptophan levels of 20% was observed (Martin et al. 2000). In most organisms, low levels of brain 5-HT enhance corticoid release, thus rendering the animal more responsive to stress (Lucki 1998). But, increased excretion of cortisol or corticosterone is also induced by 5-HT-releasing drugs, such as fenfluramine, and by anxiolytic drugs (summarized in Bechtholt et al. 2007). In summary, there is a complex mutual interaction between glucocorticoid levels and cerebral 5-HT function. Although it is clear that long-term exposure to high corticosteroid levels induces enhanced tryptophan catabolism, the ultimate effect of increased circulating glucocorticoids on the release of 5-HT is difficult to predict. Transient depletions may therefore have different effects than lasting depletion of tryptophan and subsequently on cerebral serotonin.

Extra-hepatic catabolism of tryptophan along the oxidative pathway occurs via the enzyme indoleamine 2,3-dioxygenase (IDO). Under normal conditions IDO activity is minimal, but the enzyme becomes induced through pro-inflammatory cytokines such as interferon (Stark et al. 1999) and in the placenta (Kudo and Boyd 2000). High IDO activity has been observed in activated macrophages of the
Receptor regulation of 5-HT neuronal activity

The multitude of functions of the cerebral serotonin system is consistent with the large number of brain areas innervated by serotonin and the varying distribution patterns of the multiple serotonin receptor subtypes within the brain.

Serotonergic neurons display spontaneous firing activity (0.2–1.0 Hz; Vandermaelen and Aghajanian 1983), which is regulated by both homo- and hetero-receptors. In the raphe area 5-HT1A receptors are located on the soma and dendrites of serotonergic neurons (but not exclusively, see Kirby et al. 2003) where they are involved in feedback regulation of neuronal firing (Sprouse and Aghajanian 1987), 5-HT release (Sharp et al. 1989; Bosker et al. 1994, 1996) and synthesis (Hutson et al. 1989). In axon terminal areas 5-HT release and synthesis is also controlled via 5-HT1B receptors (Engel et al. 1986; Middelmiss et al. 1988; Limberger et al. 1991; Hjorth et al. 1995). Other 5-HT receptors subtypes have been implicated in 5-HT neural activity, but their role as auto-receptor is not very well established. Feedback inhibition likely serves to limit excessive firing of 5-HT neurons, but its precise physiological role is not well established. It is conceivable, however, that a decrease of 5-HT release will lead to an increased firing rate of 5-HT neurons, leading to a faster exhaustion of the transmitter pools, in particular when the synthesis becomes limited.

Hetero-receptor regulation is achieved by converging projections to 5-HT neurons. Several pathways have been identified, including projections from prefrontal cortex, central amygdala and hypothalamic nuclei (e.g., Bosker et al. 2001a,b). Most of these projections are excitatory, presumably glutamatergic acting through NMDA, kainate and AMPA receptors (see, e.g., Liu et al. 2002). Noradrenaline and dopamine also play a role, through a1,2-adrenoceptors (Hopwood and Stamford 2001) and D2 receptors (Ferre et al. 1994), respectively. Moreover, serotonergic neurons are a minority in the raphe nuclei. Inter-neurons of the dorsal and median raphe nuclei are predominantly inhibitory (GABA), acting via both GABA_A and GABA_B receptors (Judge et al. 2004). Finally, a considerable number of cells in the dorsal raphe that express NK1 receptors also contain glutamate (Commons and Valentino 2002). The endogenous NK1 receptor agonist substance P increases the firing rate of dorsal raphe glutamatergic neurons that activate serotonergic neurons (Liu et al. 2002). This suggests that NK1 agonists make use of a glutamatergic mechanism to control the activity of 5-HT neurons in the dorsal raphe. Valentino and Commons (2005) also suggest that 5-HT neuronal activity in dorsal raphe nucleus is controlled by CRH1 and CRH2 receptors via opposite actions on GABA. According to these authors, the abundant expression in dorsal raphe nucleus of NK1 receptors in the vicinity of neurons that co-localize 5-HT and CRH suggests that the dorsal raphe nucleus is an important locus for 5-HT-CRH-NK interactions.

The regulatory effects of the various 5-HT-receptors, together with the converging neuronal innervation, indicate that the activity of the serotonergic raphe neurons depends both on auto-inhibition, local inhibition and on excitatory input from brain regions involved in higher functions and from “lower” cerebral neurons. A decrease in circulating tryptophan and 5-HT synthesis results in less peripheral immune system and in activated microglia of the brain. Induction of IDO has been observed in human, rodents and a few other species (Cannazza et al. 2001). Catabolism of tryptophan by IDO causes accumulation of the NMDA receptor antagonist kynurenine in the brain. This might cause a dysbalance of glutamatergic neurotransmission, thus contributing to the development of disorders such as depression and schizophrenia (Muller and Schwarz 2006). In diseases such as AIDS and cancer, high formation of endogenous interferon-γ is concomitant with low plasma levels of tryptophan (Iwagaki et al. 1997). In inflammatory brain diseases including Alzheimer’s dementia, microglia concomitant with IDO will become activated, leading to an increased degradation of tryptophan, thereby reducing local synthesis of 5-HT (Versijpt et al. 2005). Therapeutic intervention with pro-inflammatory interferon-γ in patients suffering from hepatitis-C or cancer leads to increased excretion of tryptophan catabolites and consequently to low blood levels of tryptophan (Russo et al. 2005). A function of the induction of IDO in the immune cells is to deplete tryptophan locally, so protein synthesis of pathogens (bacteria, viruses) and tumours will be decreased. Placental IDO protects the foetus from pathogens and the immune rejection by the mother (Munn et al. 1998). During or just after delivery low tryptophan may evoke emotional instability, such as postpartum blues.

The organism may thus perceive activation of immune activity or sustained exposure to glucocorticoids through cerebral 5-HT neurons, as the result of induction of tryptophan catabolism by immune cells or in the liver, respectively. Considering the balanced ingestion and catabolism of tryptophan, the in vivo availability of tryptophan is in a pseudo-steady state, implicating that any (physiological) change has direct or indirect consequences for cerebral 5-HT function.

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auto-inhibition. At low tryptophan levels the average release of cerebral 5-HT over time may at least in part be compensated initially by an increased 5-HT cell firing, but the 5-HT pool may become exhausted soon thereafter.

**Behavioural aspects of tryptophan**

Delineation of a specific function of the 5-HT system in behaviour is mainly based on mammalian research, but there are also reports on non-mammalian species, including fish and reptiles (Weiger 1997). Modulation by 5-HT has been shown in feeding, sleep, and sexual and aggressive behaviour (Winberg et al. 1993). In rats, mice, monkeys and humans the behavioural consequences of low brain 5-HT content have been studied extensively. Increased feeding behaviour 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 (McGuire and Troisi 1998). In general, tryptophan loading or feeding in animals results in a reduction of aggressive behaviour, drowsiness, sleepiness and satiety (Fernstrom 2000; Luciana et al. 2001). In pigs subjected to social stress, the resulting cortisol peak was unaltered after tryptophan loading, but plasma levels returned faster to pre-stress levels (Koopmans et al. 2005). In all mammalian species studied, aggressive behaviour was negatively correlated to brain 5-HIAA and 5-HT content. This relation is also present in non-mammalian species such as the rainbow trout (Winberg et al. 1993). In rats, depletion of hippocampus 5-HT induces an increased killing behaviour towards mice, that was dose-dependently decreased by 5-HT agonists and 5-HT reuptake blocking agents (Molina et al. 1987). Depletion of 5-HT also increases conspecific and predatory behaviour in rodents. 5-HT-depleted rats show increased frequency and duration of offensive behaviours with an intruder rat in the cage. In the vervet monkey increased 5-HT (induced by tryptophan or fenfluramine) suppresses aggressive behaviour and promotes dominant behaviour (Fairbanks et al. 2001). In other monkey species there was an inverse relationship between aggression and CSF 5-HIAA as well (McGuire and Troisi 1998). This trait was not only significant at an inter-individual level but also at an inter-species level (Westergaard et al. 1999). Furthermore, 5-HIAA in CSF has positively been correlated to social rank (McGuire and Troisi 1998). These data together suggest that in animals aggressive behaviour becomes often facilitated when the central 5-HT tone is reduced. Moreover an organism may strive to a maximally active cerebral 5-HT transmission for wellbeing.

In humans the behavioural consequences of low 5-HT have systematically been assessed through the effects of the acute transient tryptophan depletion paradigm (e.g., Young and Leyton 2002; Booij et al. 2002, 2003; Jans et al. 2006). Most emphasize the effects on mood in depressive patients and depression vulnerable subjects. Initially, it was reported that patients and healthy human subjects showed mild deteriorating effects on mood, hostility and irritability (for review, see Young and Leyton 2002). Meta-analysis showed that the effects on mood were seen in particular in patients with pre-existing psychopathology, recurrent depressive episodes, female gender, prior exposure to SSRI treatment and previous suicidal thoughts/ attempts, all being independent predictors. Also, chronicity of depression and familiar and genetic vulnerability were powerful predictors (Booij et al. 2002; Jans et al. 2006). A recent study in healthy volunteers demonstrated that tryptophan depletion induced a shift away from cooperative behaviour associated with more long-term gain in favour of short-term profit (Wood et al. 2006). Support for non-specificity of transient tryptophan depletion was demonstrated in patients suffering from bulimic, depressive and anxiety disorders (e.g., Goddard et al. 1994; Kent et al. 1996; Weltzin et al. 1995; Smith et al. 1998). Interestingly, acute depletion of tryptophan improves focused attention (Riedel 2004; Riedel 2002). Others have observed improvements in simple motor speed/attention tests and decision making following tryptophan depletion (Hughes et al. 2003; Talbot et al. 2006).

These and many other examples (see, e.g., the recent comprehensive review of Jans et al. 2006) suggest that low 5-HT alone is insufficient to cause psychopathology. Accordingly, emerging behavioural and psychopathological responses during a transient decrease of circulating tryptophan depend on (existing) subject characteristics and propensities.

In humans, the consequences of long-term depletion of tryptophan cannot be systematically studied with a tryptophan-deficient diet, because of ethical restrictions. However, some somatic diseases and also pregnancy allow the assessment of behavioural effects following persistently reduced tryptophan levels. For instance, low tryptophan can be the result of an inflammatory response or a peripheral tumour consuming tryptophan. We studied patients with hepatitis-C, during a treatment with interferon-α, or with carcinoid tumours. The latter are slowly progressive intestinal tryptophan-consuming tumours. In only a few cases depression was noted; in far the majority (80%), lack of impulse control...
and irritability was the main feature (Russo et al. 2004, 2005). The latter symptoms did indeed correlate with lowered plasma tryptophan levels. In the carcinoid patients there were no serious cognitive impairments, but an increased ability to rapidly shift attention was observed (Russo et al. 2003a). The reviewed studies illustrate that low brain 5-HT resulting from acute and the long-term tryptophan depletion, does not lead to major cognitive and functional impairments.

In psychiatric patients low cerebral 5-HT levels have been associated with aggressive suicide attempts, impulsive arsonism, and outwardly directed hostility in personality disorders (Asberg et al. 1976; van Praag 2001, 2004), rather than with depressive symptoms. In a double-blind cross-over design study in 100 volunteers, consumption of 1 g of tryptophan after each meal for 12 days increased dominant behaviours. Furthermore, quarrelsome behaviours significantly decreased (Moskowitz et al. 2003). In another study, high stress prone subjects showed attenuation of post stress cortisol peak after a meal that increased brain tryptophan levels (Markus et al. 2000). Recent genetic studies have demonstrated an association between several psychiatric diagnostic categories and certain polymorphisms of genes associated with serotonin functions, including those of TPH1, TPH2, 5-HT receptors, and the 5-HT transporter (Zhang et al. 2005). These polymorphisms, however, seem to account for a small proportion of patients with these diagnoses. In somatic patients we observed that the change (decrease) rather than baseline plasma levels of tryptophan triggered aggressive and impulsive behaviour (Russo et al. 2005). Low tryptophan during pregnancy or following delivery are seen in far the most women, but only a fraction of the subjects appeared to experience a “postpartum blues” (Maes et al. 2001, 2002; M’Bailara et al. 2006), possibly because of protection by the high levels of progesterone and oestradiol during pregnancy. Evidence for a genetic association between genes of the 5-HT pathway and aggressive behaviour has recently been summarized (Popova 2006). These observations together tend to support the idea that regardless of psychiatric diagnosis (van Praag 2001) symptoms such as the lack of impulse control and (auto) aggression are associated with persistent low tryptophan and consequently low cerebral 5-HT.

Such a conclusion, however, is in apparent contrast with some recent studies showing an association of trait aggressive behaviour (reviewed by Olivier 2004) or of a decreased dominant behaviour in male subjects (aan het Rot et al. 2006) on a tryptophan supplementation diet. Another recent study emphasized gender differences in the (positive) relationship between plasma free tryptophan levels and hostility (Suarez et al. 2006).

All these behavioural observations together suggest that there is no simple relationship between tryptophan levels and related behavioural consequences: such behaviour may depend also on the history and inclinations of the subject. In addition, in long-term studies 5-HT receptor regulation may also influence the emerging behaviour during high or low availability of tryptophan. We suggest, therefore, that additional parameters, including characteristics of subjects or patients have to be taken into account to understand the relationship between low tryptophan and psychopathology.

**Comments**

**Tryptophan as signal**

The levels, biosynthesis and neuronal release of 5-HT are highly dependent on the blood levels of the essential amino acid tryptophan and this dependence is maintained during the evolution of animal species. If this mechanism was harmful to the organism, it would have disappeared during evolution. Under physiological circumstances, over 90% of ingested tryptophan is degraded. By increasing its rate of degradation, tryptophan in the circulation can rapidly be depleted. Enhanced catabolism of tryptophan and consequently lowered levels of cerebral serotonin occur by the induction of tryptophan-degrading enzymes in the liver (i.e. by glucocorticoids), the placenta and in the immune system (i.e. by cytokines). These inductive processes are found in many animal species. These issues together lead us to the suggestion that tryptophan has a signalling function to inform the organism via its influence on cerebral 5-HT synthesis (Table I).

Figure 2 gives a schematic overview of the various functional aspects described in this report.

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<th>Table I. Arguments supporting that tryptophan has signalling capacity.</th>
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<td>In all animal species the cerebral formation and release of serotonin depends on influx tryptophan in physiological ranges. The tryptophan dependent synthesis of serotonin is mediated by only one of two isoforms of tryptophan hydroxylase (TPH2) present in the brain. The low functional affinity of TPH2 for tryptophan hydroxylation is conserved during evolution and thus unlikely to be harmful, but must be beneficial for an organism. Tryptophan is an essential and the least abundant of amino acids, so its levels are highly susceptible for changes in catabolism. There are several inducible metabolic routes for tryptophan that once activated, lead to changes in cerebral 5HT release. Low tryptophan and low serotonin affect inter-subject interactions and may thus have survival value, e.g., to limit con-species distributions of pathogens.</td>
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**Functional aspects**

The next question is what could be the survival value of a signalling function of tryptophan for an organism. We have already emphasized that there was no clear deficiency in human functioning following transient or persistently low tryptophan levels: in fact some neuropsychological tasks were performed better. The emergent behaviour in psychiatric patients following low tryptophan may better be considered as the result of pre-existing and latent pathology and other motivations of the subject. The activity of 5-HT neurons and associated release of 5-HT is the consequence of precursor availability, auto-regulation and neuronal input from several higher brain centres. So it is conceivable that external factors or challenges in combination with existing information (stored in the brain) determine emergent behaviour and that the magnitude of response to external stimuli depends on the state of cerebral 5-HT neurotransmission. In short: cerebral 5-HT modulates, rather than induces, intended behaviour.

We illustrate this idea with differential social behaviour observed during low tryptophan levels. Humans and animals become often more responsive to external stimuli and there is the tendency towards aggression. Since animals do not possess senses to detect an infectious environment, they cannot actively avoid contact with infected littermates. During serious and chronic infections, tryptophan levels decrease, because of the induction of IDO, and the affected subjects become irritated and social interaction will be avoided actively, passively, or both. Accordingly, tryptophan depletion may reduce the con-specific spreading of an infectious agent. Humans treated with a pro-inflammatory interferon also become more irritable, showing diminished impulse control and symptoms of depression. Interferon treatment is of course a non-natural condition, but is nevertheless similar to the infectious state.

The possibility that low tryptophan and 5-HT affects non-specificity various psychiatric conditions may also be seen in the light of recent genetic reports. For instance, Caspi and co-workers reported an association between a genetic polymorphism of the promoter gene of the 5-HT transporter and the precipitation of depression following severe life events (Caspi et al. 2003). The specific allele is, however, not associated with the prevalence of depressive disorder. Low 5-HT may aggravate various underlying or existing psychopathologies. We speculate that the psychopathology associated with somatic disease is a remnant of the natural reaction of an organism to immune activation, as affected subjects avoid close inter-individual contact. Thus, a consequence of alterations in cerebral 5-HT transmission is a change of social behaviour.

**Psychopharmacological implications**

SSRIs have particularly been developed to modify the cerebral 5-HT transmission and are among the most prescribed drugs in depression. It may be questioned what is the best indication for SSRIs. Meta-analyses point to the modest efficacy of SSRIs in depression (e.g., Moncrief and Kirsch, 2005) suggesting that there is no firm aetiological relation between 5-HT (deficiency) and depression. In addition, antidepressants, including the SSRIs, are used in a wide variety of psychiatric disorders and conditions, including anxiety, phobia and pain (see
Introduction). Moreover, low 5-HT has been associated with apparently unrelated neuro-psychiatric disorders. The conventional rationale for SSRIs is that they are prescribed in disorders characterized by low brain 5-HT. Taking into account the studies reviewed, one indication for SSRIs should be disorders associated with low cerebral 5-HT and low tryptophan availability. Psychiatric disorders due to low tryptophan and/or responding to antidepressant medication do not necessarily match present diagnostic systems. The consequence of our suggestion is that if the indications of SSRIs were be limited to conditions with low levels of brain 5-HT, it would predict a better therapeutic response. Certain subgroups may be identified, in which SSRI treatment is appropriate. For instance patients marked by tryptophan depletion, which has been observed, for instance, in diseases accompanied by inflammatory responses. Also in genetically susceptible individuals 5-HT-ergic drugs may be prescribed. Such patients could be identified by tracing polymorphisms of the 5-HT transporter and TPH2. Furthermore, SSRIs or tryptophan could be administered to improve social interaction of for instance aggressive subjects. This could help subjects to implement new coping strategies in their behavioural repertoire. Indeed, tryptophan supplementation proved to be useful in treating aggressive inpatients (Young and Leyton 2002). In somatic patients suffering from the behavioural consequences of increased tryptophan catabolism, serotonergic medication may be appropriate (Musselman et al. 2001). It was recently proposed to administer tryptophan to these patients (Turner and Blackwell 2005). However, some caution has to be taken into account. Induction of the tryptophan catabolic pathway releases several neurotoxic compounds such as quinolinic acid. In rodents, brain quinolinic acid production is demonstrated after IDO induction but not under physiological circumstances (Saito and Heyes 1996). Tryptophan supplementation might not be beneficial in circumstances of induced IDO activity. We have, for instance, circumvented such risk by successfully applying mirtazapine to treat psychopathology of interferon-treated patients (Russo et al. 2003b). Finally, prescription of SSRI had positive effects on social function in volunteers (Knutson et al. 1998). Therefore, psychiatric patients could benefit from these drugs, regardless of their diagnosis, because social functioning is an important treatment issue in many patients. More emphasis on the role of SSRIs in social functioning might also contribute to the integration of pharmacological and non-pharmacological treatment.

Final comments

The presently described evolutionarily conserved tryptophan-5-HT link could have a function in shaping adaptive behaviour. We have emphasized that low brain serotonin levels per se do not necessarily lead to a single psychiatric diagnostic entity, as illustrated in Figure 2. The emergent pathology may for instance depend on the duration of low tryptophan levels. The behavioural effects of acute low tryptophan levels, as studied with the acute tryptophan depletion test, are likely to be associated with current and/or underlying psychopathology. Lasting low tryptophan levels may – ultimately – evoke behaviour aimed at survival of the organism. Such a hypothesis dissociates an often assumed deterministic – relationship between low serotonin and certain diagnostic categories, such as anxiety and depression. We realize that the present hypothesis does not take into account the rich pharmacology of the cerebral 5-HT system, considering the high number of 5-HT receptors, as summarized in part here. So, specific receptor blocking or activating agents could – in addition – refine pharmacological interventions. Central in these considerations is the notion that cerebral 5-HT neurons are regulated by a multitude of processes acting in parallel: there are the neuronal inputs of higher centres, such as the cerebral cortex and limbic areas, and, in addition, the here emphasized biosynthetic regulatory mechanisms. The consequences of low serotonin depend – in our view – primarily on the neuronal input and from the information thus generated in these brain centres, which intensity may-in addition – be modulated by the composition of the diet.

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Statement of interest

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