Amino Acids (2011) 41:1195–1205
DOI 10.1007/s00726-010-0752-7

INVITED REVIEW

Tryptophan metabolism, from nutrition to potential therapeutic applications

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Received: 16 July 2010 / Accepted: 9 September 2010 / Published online: 25 September 2010
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Abstract Tryptophan is an indispensable amino acid that should to be supplied by dietary protein. Apart from its incorporation into body proteins, tryptophan is the precursor for serotonin, an important neuromediator, and for kynurenine, an intermediary metabolite of a complex metabolic pathway ending with niacin, CO_2, and kynurenic and xanthurenic acids. Tryptophan metabolism within different tissues is associated with numerous physiological functions. The liver regulates tryptophan homeostasis through degrading tryptophan in excess. Tryptophan degradation into kynurenine by immune cells plays a crucial role in the regulation of immune response during infections, inflammations and pregnancy. Serotonin is synthesized from tryptophan in the gut and also in the brain, where tryptophan availability is known to influence the sensitivity to mood disorders. In the present review, we discuss the major functions of tryptophan and its role in the regulation of growth, mood, behavior and immune responses with regard to the low availability of this amino acid and the competition between tissues and metabolic pathways for tryptophan utilization.

Keywords Tryptophan · Metabolism · Nutrition · Immune response · Mood disorders

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Introduction

Tryptophan is an indispensable and essential amino acid that has to be supplied by ingested proteins. Among the 20 amino acids that constitute proteins, tryptophan is one of those found in the lowest proportion in proteins and plasma. The relatively low amount of tryptophan found in the body is a singular trait for this amino acid known to be involved in several physiological functions. Indeed, besides its incorporation into body proteins, tryptophan is also the precursor for serotonin and niacin synthesis. The diversity of physiological functions as well as the low content in the body increases the potential risk for creating situations of unbalanced tryptophan homeostasis. In this way, the contribution of the different metabolic pathways of tryptophan may be very different according to the physiological and pathological statuses. Consequently, exogenous tryptophan supplies may be relevant to overcome the adverse effects induced by metabolic competitions for tryptophan utilization. The objective of the present review is to examine the metabolism and the physiological functions of tryptophan. We focus on major aspects of tryptophan metabolism, such as its role in the regulation of growth and feed intake, the impact on mood and behavior, and the modulation of immune responses.

Physiological metabolism of tryptophan

Tryptophan is one of the 20 amino acids constituting proteins. Unlike other amino acids, tryptophan circulates in blood and plasma mainly bound to albumin (Pardridge 1979). Only 10–20% of tryptophan is present as free form in the plasma. Factors such as non-esterified fatty acids or some drugs modify the binding of tryptophan to albumin.

Whether or not tryptophan binding to albumin may modify the availability of tryptophan for tissue metabolism remains controversial (Smith and Pogson 1980; Pardridge 1983).

Tryptophan is the precursor of serotonin (5-HT or 5-hydroxytryptamine), an important neuromediator regulating gastrointestinal functions, mood, appetite and hemodynamics. Tryptophan conversion into serotonin occurs in two steps: the conversion of tryptophan into 5-hydroxytryptophan by tryptophan hydroxylase (TPH; EC. 1.14.16.4) and the decarboxylation of 5-hydroxytryptophan into serotonin. This last step is vitamin B6 dependent. Two isoforms of TPH are known: TPH1 in enterochromaffin cells and TPH2 in neurons. Tryptophan is also the precursor of *N*-formylkynurenine that is converted into kynurenine by the kynurenine formamidase (EC. 3.5.1.9). *N*-formylkynurenine and kynurenine are the first metabolites of a complex metabolic pathway ending in quinolinic acid, niacin, kynurenic and xanthurenic acid. Two enzymes are able to catalyze the conversion of tryptophan into *N*-formylkynurenine: tryptophan 2,3-dioxygenase (TDO; EC. 1.13.11.11) and indoleamine 2,3-dioxygenase (IDO; EC. 1.13.11.52). These two enzymes differ in their tissue localization, structure, substrate specificity, cofactor requirement and function (Table 1). Whereas IDO is widespread in numerous tissues, TDO is mainly located in the liver.

One important physiological function of tryptophan is its use in protein synthesis. Since mammals cannot synthesize tryptophan, the proportion that is metabolized into serotonin and kynurenine is lost for protein synthesis. The average tryptophan protein content in the body is 1.2 g for 100 g of protein, which is much lower than other indispensable amino acids such as lysine (7.6), leucine (7.1) and threonine (4.0) (Mahan and Shields 1998). The estimations of tryptophan that is incorporated into body proteins are scarce and vary within a great range. The reasons for this discrepancy may be attributed to the physiological status, growing period versus adulthood, and the methodology used for the estimation, tryptophan load versus dietary supply within a nutritional range. In young growing pigs, 54% of ingested tryptophan was retained in body protein when tryptophan was supplied below the requirement. This proportion decreases when tryptophan supply exceeds the requirement, because catabolism increases (Sawadogo et al. 1997). In adult humans, there is almost no net tryptophan deposition into protein because of steady-state nitrogen balance. However, assuming that an adult human synthesizes and degrades 300 g of protein per day (Garlick et al. 1980) and that tryptophan body protein content is around 1–1.2 g/100 g of protein (Mahan and Shields 1998), approximately 3–3.6 g of tryptophan is incorporated into and released from proteins each day. The daily nutritional recommendation of tryptophan for an adult comprises between 350 and 400 mg/day (Lazaris-Brunner et al. 1998), which is much lower than the amount of tryptophan incorporated into protein. In fact, dietary tryptophan allows replacing the amount of tryptophan irreversibly lost through catabolism and intestinal degradation by bacteria. Studies involving labeled tryptophan quantified the extent of tryptophan conversion into labeled CO_2 and urinary metabolites following a tryptophan load (Leklem 1971). In those studies, it was thus not possible to evaluate the proportion of tryptophan that was incorporated into protein, since a load of a single amino acid caused catabolism rather than the incorporation of this amino acid in protein. However, these data indicated that tryptophan was mainly degraded through the kynurenine pathway. Whereas 90% of tryptophan that is degraded would be converted into kynurenine, less than 1% of ingested tryptophan would be used for serotonin synthesis (Wolf 1974).

Table 1 Comparison of TDO and IDO characteristics

	Tryptophan 2,3-dioxygenase (TDO; EC. 1.13.11.11)	Indoleamine 2,3-dioxygenase (IDO; EC. 1.13.11.52)
Substrates	L-tryptophan	L- and D-tryptophan 5-Hydroxytryptophan 5-Hydroxytryptamine (serotonin)
Cofactors	Molecular oxygen (heme)	Superoxide anion
Tissue distribution	Liver (skin)	Ubiquitous
Functions	Degradation of tryptophan in excess	Immune regulation
Regulation	Tryptophan, glucocorticoids	IFN-γ, LPS, virus, bacteria

IFN-γ interferon γ, *LPS* lipopolysaccharide

Tryptophan metabolism within specific organs and tissues

Liver

The enzyme TDO is assumed to be normally restricted to the liver in mammals (Fig. 1) (Bertazzo et al. 2001; Knox and Auerback 1966), although it has been also identified in the skin of rats (Naito et al. 1989) and in the cortex of humans (Miller et al. 2004). This enzyme is rate limiting for the entry of tryptophan in the complex kynurenine pathway.

Because of its low affinity for tryptophan, TDO is active when tryptophan concentrations exceed the requirement for

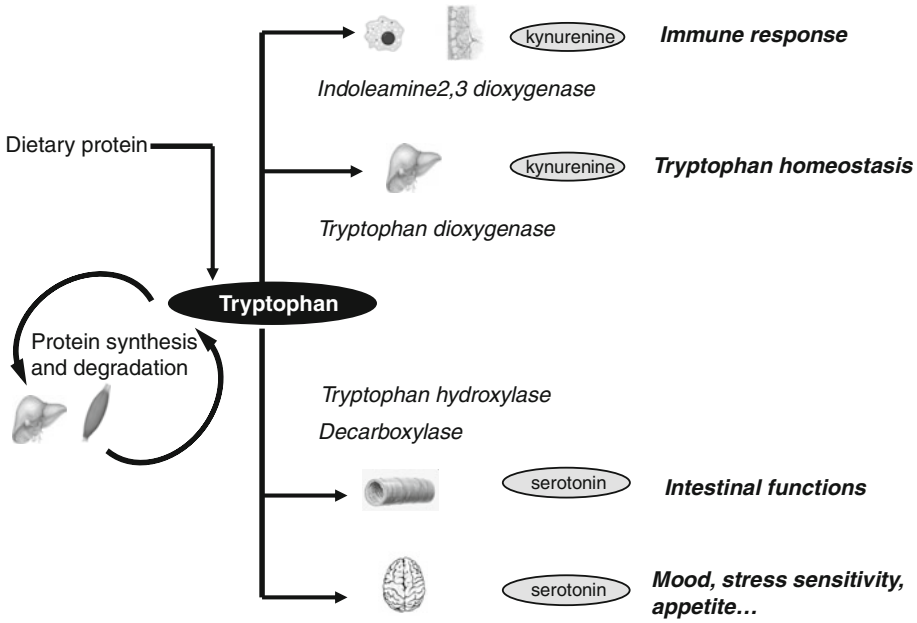

Fig. 1 Simplified scheme of tryptophan metabolism and functions within different tissues

protein and serotonin synthesis (Murray 2003). TDO is subjected to regulation by several factors, such as its own substrate (Knox and Mehler 1951), glucocorticoids and glucagon (Knox and Auerback 1966; Schutz and Feigelson 1971). This implies that the liver, through TDO activity, is responsible for the degradation of tryptophan at excess level and controls plasma tryptophan homeostasis through preventing potential toxic accumulation of tryptophan in the plasma and tissues. The activity of liver TDO is suppressed when extrahepatic IDO activity is induced during inflammatory events (Takikawa et al. 1986).

Tryptophan extracted by the liver is not necessarily degraded into kynurenine. It is also incorporated into constitutive and exported proteins. Acute phase proteins, C-reactive protein, haptoglobin and fibrinogen, for instance, are synthesized by the liver as a result of inflammatory challenges such as infection or trauma. Because these proteins have a high content of tryptophan (Reeds et al. 1994), the synthesis of acute phase proteins during inflammation may require a substantial amount of tryptophan. Preston et al. (1998) suggested that in cancer patients suffering from an inflammatory response, tryptophan would be the limiting amino acid for fibrinogen synthesis. This hypothesis was supported by the low tryptophan plasma concentration in these patients compared to the other amino acids, suggesting that, despite TDO inactivation, the liver could be involved in the clearance of plasma tryptophan during inflammatory states.

Brain

Tryptophan is transported into the brain by a transporter located in capillaries of the blood–brain barrier (BBB). This transporter is shared with large neutral amino acids (LNAA) and is saturated at physiological amino acid plasma concentrations (Pardridge 1998). The LNAA comprise leucine, valine, isoleucine, the three branched chain amino acids (BCAA), tyrosine, phenylalanine and methionine. Consequently, tryptophan entry into the brain is influenced by the ratio between tryptophan and amino acids sharing the same transporter and, particularly, BCAA, which are present in higher proportion than tryptophan in plasma.

Tryptophan binding to albumin is also suspected to influence tryptophan transport into the brain. However, Pardridge (1983) estimated that tryptophan association with albumin has only a minor influence on tryptophan transport across BBB, since the tryptophan–albumin complex dissociates many times during the transit of plasma through the brain capillaries.

In the brain, tryptophan is the precursor for serotonin synthesis (Fig. 2). Tryptophan hydroxylase, the rate-limiting enzyme of serotonin synthesis, is not saturated at physiological brain tryptophan concentrations (Ruddick et al. 2006; Silber and Schmitt 2010). Therefore, brain serotonin synthesis is assumed to be proportional to tryptophan transport into the brain (Pardridge 1998). This explains the dose-dependent enhancement of brain serotonin levels by increasing dietary and plasma tryptophan concentrations or by increasing the tryptophan–LNAA ratio (Henry et al. 1992, 1996; Sarwar and Botting 1999). On the contrary, tryptophan deficiency impairs serotonin synthesis in the brain (Henry et al. 1996). Experimental serotonin depletion in the brain can be achieved by the acute tryptophan depletion (ATD) method. Subjects ingest a tryptophan-free mixture of amino acids, which leads to

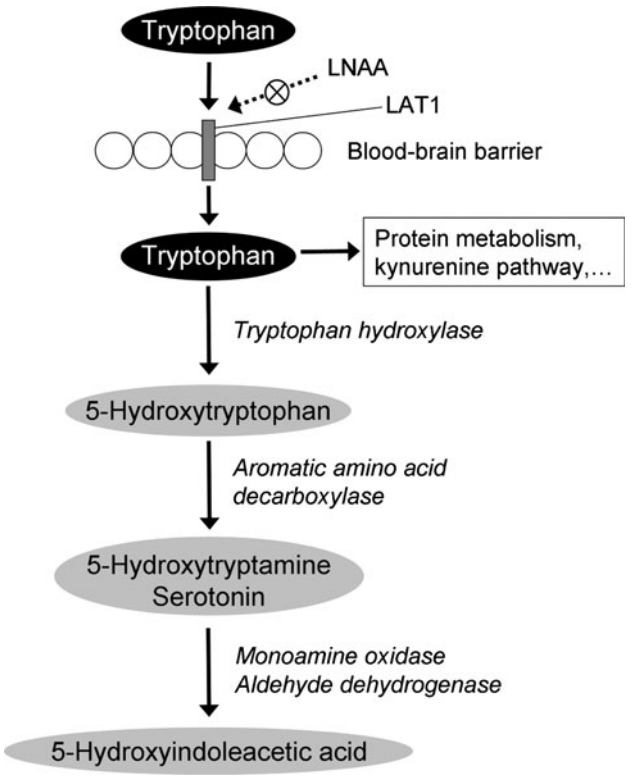

Fig. 2 Tryptophan transport across the blood–brain barrier and serotonergic pathway in the brain. LNAA: large neutral amino acids; LAT1: large neutral amino acid transporter. *Circled times on discontinuous arrow* inhibition

enhanced protein synthesis and thus depletes tryptophan from plasma and tissue. Accordingly, ATD causes a dramatic fall of plasma tryptophan–LNAA ratio and leads to a decrease of brain serotonin synthesis, levels and function (Nishizawa et al. 1997; Carpenter et al. 1998; Lieben et al. 2004). Within the brain, serotonin is released from synaptic vesicles into the synaptic cleft where it can bind to its specific receptors. A reuptake mechanism removes serotonin from the synaptic cleft into the presynaptic neuron where it is metabolized by monoamine oxidase (MAO) and aldehyde dehydrogenase to 5-hydroxyindoleacetic acid that is finally excreted by the kidneys.

In the brain, tryptophan can be degraded into kynurenine, since IDO is expressed by astrocytes, microglia, brain-infiltrating macrophages and dendritic cells (Ruddick et al. 2006). Within the brain, IDO activation has been shown to down-regulate neuroinflammation (Smith et al. 2007). Nevertheless, some of the metabolites produced from kynurenine such as quinolinic acid, a *N*-methyl-D-aspartate receptor agonist, as well as 3-hydroxykynurenine, 3-hydroxyanthranilic acid and picolinic acid, are neurotoxic and are associated with central nervous system diseases (Smith et al. 2007). These metabolites of the kynurenine pathway can pass the BBB during systemic infection or can be produced locally (Kwidzinski and Bechmann 2007).

Gastrointestinal tract

Several amino acids are massively extracted by the gut (van der Schoor et al. 2002). For tryptophan, there is no estimation of the contribution of gut to tryptophan metabolism except in neonatal piglets. Tryptophan supplied intravenously (jugular vein) or enterally did not modify the oxidation of ^{14}C-phenylalanine used as an indicator for amino acid. This indirect estimation of gut contribution to tryptophan metabolism indicated that tryptophan was not extensively used by the gut (Cvitkovic et al. 2004).

About 95% of serotonin body content is present in the gut where it acts as a major neuromediator involved in motility and secretory mechanisms. The TPH1 isoform of tryptophan hydroxylase is located in enterochromaffin cells where tryptophan is converted into serotonin. IDO is also expressed in the intestine of many species (Yamamoto and Hayaishi 1967; Yamazaki et al. 1985; Shimizu et al. 1978), where its expression and activity are high compared to other tissues even in healthy conditions (Takikawa et al. 1986). The role of IDO in the intestine is not well known; however, the regulatory effect of IDO on T cells and immune response suggests that IDO may be involved in the control of inflammatory response in the gut. Additionally, in dogs, kynurenic acid inhibits intestinal motility and may exert an anti-inflammatory effect through the inhibition of xanthine oxidase (Kaszaki et al. 2008).

Immune cells

Tryptophan degradation can be detected in various cells including antigen-presenting cells such as macrophages, fibroblasts and placental trophoblasts. Inflammatory cytokines, released by activated immune cells, stimulate IDO expression and activity. Although interferons α and β (Mellor et al. 2005), and tumor necrosis factor α (O'Connor et al. 2009) can induce tryptophan degradation, interferon γ seems to be the most important cytokine linked to this catabolism (Popov and Schultze 2008). More recently, it has been discovered that, besides macrophages, another type of antigen-presenting cells called dendritic cells (DC) also express IDO. Among DC, some specifics subsets were found to be able to express IDO, either constitutively or after induction.

Physiological functions of tryptophan and consequences of an unbalanced tryptophan metabolism

Growth and feed intake

The relationship between tryptophan and protein synthesis and accretion has been extensively studied in pigs, because

tryptophan is one of the growth-limiting amino acids in raw materials used for diets formulated for growing pigs, especially in corn-based diets. Pigs exhibit very high growth rates. In this species, amino acids and particularly essential amino acids are mainly incorporated into body proteins. This metabolism, dominated by protein synthesis and accretion, could influence the allocation of dietary tryptophan between protein synthesis and other utilizations of tryptophan.

In farm animal nutrition, tryptophan requirement is defined as the amount of tryptophan required to maximize growth rate. Accordingly, a state of deficiency commences when dietary tryptophan content does not permit the highest growth rate. A moderate tryptophan deficiency is able to significantly reduce growth rate, which is the common feature of the so-called limiting indispensable amino acids, i.e., lysine, threonine, methionine and valine. In pigs, the effect of tryptophan deficiency on growth is mainly caused by a reduction of appetite and feed intake (Eder et al. 2001; Henry et al. 1992, 1996), which is not a common response of other limiting amino acids except for valine. Ettle and Roth (2004) showed that piglets were able to detect tryptophan deficiency and develop an aversion against a tryptophan-deficient diet. The depressive effect of tryptophan deficiency on feed intake was enhanced by increasing the level of dietary protein, and particularly by increasing LNAA (Henry et al. 1996). Competition between tryptophan and LNAA in being carried across the BBB has been extensively considered to explain the depressive effect of low tryptophan intake on appetite. The physiological basis of depressed feed intake can be explained by a phenomenon of imbalance detected at the brain level that corresponds to disproportionate amino acid concentrations in the free pool of plasma and brain. This occurs for low tryptophan supply and because of a relative excess of LNAA compared to tryptophan. In pigs, Zhang et al. (2007) showed that ghrelin mRNA expression in the gut and secretion in plasma were depressed when pigs were fed a low tryptophan diet. The correction of tryptophan deficiency restored feed intake together with a greater expression of ghrelin mRNA in the stomach and duodenum. Tryptophan could be also involved in the modulation of insulin secretion and sensitivity (Ponter et al. 1994a, b), and thus in the postprandial anabolic response.

Mood disorders, behavior and stress

The central serotonergic system plays a major role in the regulation of many physiological and behavioral processes such as mood, cognition, activity, sleep and appetite. A disturbed brain serotonergic function by inadequate tryptophan availability is therefore recognized as a contributing factor in affective disorders, anxiety, aggression, stress, eating disorders and others.

Clinical studies provide evidence that altered tryptophan levels can affect mood states. Beneficial effects of increased tryptophan levels are observed in patients with mild to moderate depression (Young and Leyton 2002). Placebo-controlled studies have demonstrated the ability of tryptophan to potentiate the antidepressant action of MAO inhibitors and it was shown in a longitudinal study that tryptophan supply showed better effects than placebo and effects equivalent to amitriptyline (Thomson et al. 1982). However, in healthy subjects, the majority of the literature indicates that tryptophan loading has only minor or no effects on mood (Silber and Schmitt 2010). The effects of tryptophan loading on mood factors may therefore depend on increased serotonin vulnerability in subjects with presumably suboptimal central serotonergic function. On the other hand, tryptophan deficiency induces changes in anxiety and depression-like behavior in rats (Blokland et al. 2002), and increases anxiety and irritability in humans suffering from psychiatric disorders (Russo et al. 2003).

ATD lowered mood in subjects with a family history of major depression, in drug-free patients with major depression in remission and in remitted patients who used serotonergic antidepressants. As with tryptophan loading, ATD had little or no effect on healthy subjects (Young and Leyton 2002; Booij et al. 2003; Fusar-Poli et al. 2006). Mood-lowering responses were also found in subjects with a genetic serotonin vulnerability, i.e., with a polymorphism of the serotonin transporter gene (Walderhaug et al. 2007). Using neurophysiological methods, such as functional magnetic resonance imaging, it was shown that ATD substantially modified emotional processing in many brain structures implicated in unipolar depression and increased responses, specifically to negative stimuli, in areas implicated in the processing of emotionally valenced verbal information (Fusar-Poli et al. 2006; Roiser et al. 2008).

Different animal studies have also shown that tryptophan loading can attenuate aggressiveness (Gibbons et al. 1979; Shea et al. 1990; Highley and Linnoila 1997). In laboratory test situations with humans, a gradation of aggressive responses was found with tryptophan-supplemented groups showing the lowest and depleted groups showing the highest aggression (Pihl et al. 1995; Bjork et al. 2000). It was also demonstrated that tryptophan administration can alter dominant behavior. In healthy human subjects, a significant decrease in quarrelsome behavior and a significant increase in dominant behavior relative to placebo were found (Moskowitz et al. 2001).

Tryptophan loading and depletion experiments also provide evidence for the role of serotonin in cognitive functions. Cognitive improvements in long-term memory for verbal and abstract information, as well as memory

scanning ability, have been shown in vulnerable and clinical subjects supplemented with tryptophan. As with mood disorders, the results are less consistent in healthy volunteers (Silber and Schmitt 2010). Conversely, ATD impairs episodic memory (memory for events and experiences) and recall, as well as recognition in visual verbal learning tests (Mendelsohn et al. 2009). Differences between genders are reported with females showing a positive bias in the processing of emotional stimuli after tryptophan loading (Silber and Schmitt 2010) and a higher vulnerability to ATD effects on episodic memory (Sambeth et al. 2007).

The brain serotonergic system is also involved in controlling hypothalamic-pituitary-adrenal (HPA) stress axis regulation (Markus 2008). It was shown that increases in plasma tryptophan–LNAA ratio enhance negative mood and dampen the cortisol response after acute stress exposure in healthy and vulnerable subjects (Markus et al. 2000; Firk and Markus 2009). Animal studies also reveal that, in pigs, tryptophan loading (3–4 times the dietary tryptophan recommendation) may lead to reduced basal and stress-induced plasma cortisol concentrations, thus lowering the stress response of the HPA axis (Koopmans et al. 2005, 2006; Guzik et al. 2006).

In summary, studies on mood disorders and cognition reveal differential effects of tryptophan loading and depletion between healthy and vulnerable subjects, which may depend on the individual's "initial state" of the serotonergic system. The brain serotonergic system may be particularly sensitive to tryptophan supply in times of scarcity, and moving serotonin toward the optimal level may then have beneficial effects. In healthy subjects, further increases of brain serotonin may then have no or even negative effects.

Pregnancy and the postpartum period

The enzyme IDO is expressed in human developing placenta (Kudo et al. 2004; Yamazaki et al. 1985) and in trophoblasts of gestating mice (Tatsumi et al. 2010). Administration of 1-methyl-tryptophan, an IDO inhibitor, caused allogenic fetal rejection (Munn et al. 1998). The activation of IDO produces locally a tryptophan depletion preventing the fetal allograft rejection by maternal T lymphocytes. It has been postulated that the role of IDO is to generate a local tryptophan depletion leading to the inhibition of the proliferation of maternal T cells in the placenta, inducing an immunological tolerance between the mother and the fetus (Kudo et al. 2004; Mellor and Munn 2001).

The expression of IDO in the placenta is assumed to have no consequence on tryptophan systemic availability. However, a continuous decline of plasma tryptophan associated with a continuous increase in kynurenine concentrations was observed during pregnancy in humans (Schröcksnadel et al. 2003). At the same time, the plasma kynurenine–tryptophan ratio, used as an indicator of tryptophan degradation, increased. Moreover, the early postpartum period is characterized by an increase in inflammatory response that may be associated with an increase in tryptophan catabolism through the IDO pathway (Maes et al. 2002). Such changes in tryptophan metabolism were suspected to be responsible for the central nervous system and postpartum mood disorders. For example, some studies indicated that postpartum mood disturbances were correlated with low tryptophan and high kynurenine plasma concentrations (Maes et al. 2002; Kohl et al. 2005). Changes in plasma tryptophan in the late stage of gestation and around delivery are suspected to change brain serotonin metabolism because of lower availability of tryptophan in the brain. However, no data supported the idea that additional tryptophan may be beneficial for the onset of late pregnancy and postpartum well-being.

Inflammatory states

Depletion of plasma tryptophan or increased kynurenine–tryptophan ratio are reported during viral, bacterial and parasitic intracellular infections (Murray 2003; Boasso et al. 2007; Moreau et al. 2005; Silva et al. 2002) or experimentally induced inflammation (Melchior et al. 2004). Increased tryptophan utilization is also reported during other situations of long-lasting immune activation such as autoimmune diseases (Scott et al. 2009), inflammatory diseases (Wolf et al. 2004), cancer (Denz et al. 1993) and major trauma (Pellegrin et al. 2005). In most of these reports, the rise of metabolic intermediates such as kynurenine and quinolinic acid demonstrates the involvement of the tryptophan degradation pathway. Simultaneously, an over-expression of IDO is observed (Wolf et al. 2004, Brown et al. 1991; Widner et al. 2000), suggesting that IDO is responsible for tryptophan degradation.

The IDO-induced removal of tryptophan by the host immune activation could have two functions: microbial amino acid deprivation and immune tolerance (Fig. 3). Local tryptophan depletion resulting from IDO activation in macrophages would be a mechanism controlling bacteria, virus and parasite proliferation (MacKenzie and Hadding 1998; MacKenzie et al. 2007; Pfefferkorn 1984). In in vitro models of *T. gondii* and *S. aureus* infections, interferon-γ-stimulated lung cells are able to restrict the proliferation of microorganisms via tryptophan depletion by IDO (Heseler et al. 2008). This observation has led to the hypothesis that host tryptophan modulation in the micro-environment of parasites results in an arrest of microbial biosynthesis, conferring a competitive advantage to the host (Pfefferkorn 1984). Consequently, tryptophan depletion has been first

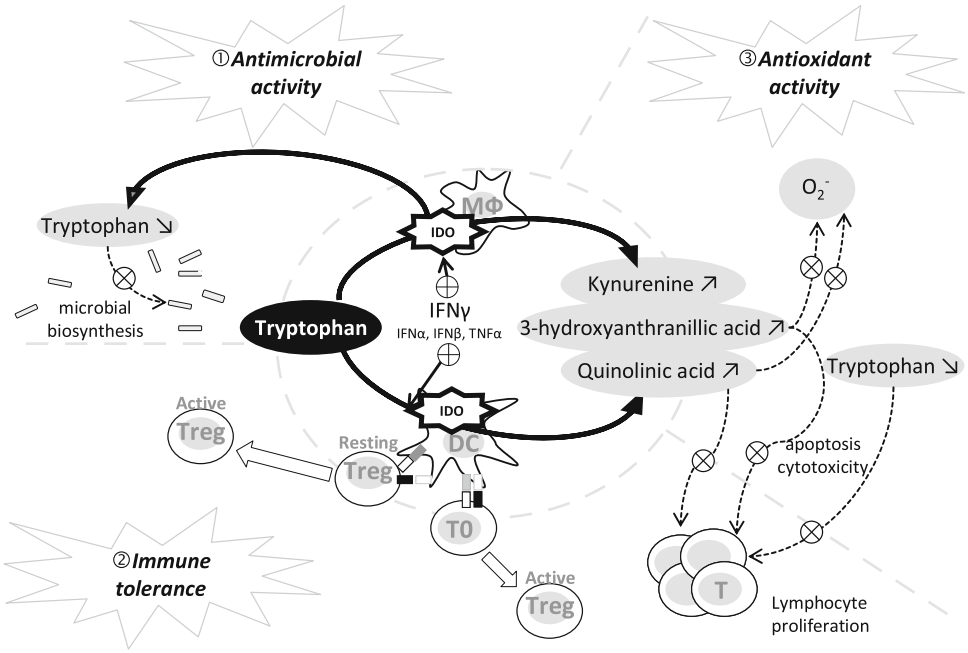

Fig. 3 Roles of tryptophan catabolism by IDO during inflammation. IDO activity is induced by cytokines IFNα, IFNβ and TNFα. Tryptophan depletion caused by IDO induction reduces microbial proliferation ① and regulates T cell activity ②. The production of tryptophan metabolites contributes also to T cell regulation through inhibiting their proliferation ② and exerts antioxidant activity ③. IFNγ, α, β: interferon-γ, -α, -β; TNFα: tumor necrosis factor-α; MΦ: macrophage; DC: dendritic cell; T0: naive T cell; Treg: regulatory T cell. *Circled plus on continuous arrows* induction; *circled times on discontinuous arrows* inhibition

regarded as a defense mechanism induced in immunocompetent cells during immune activation. However, the increase in tryptophan utilization during chronic immune activation of non-pathogenic origins suggests a broader spectrum of IDO action (Schröcksnadel et al. 2006).

The discovery of the protective role of IDO during human gestation by preventing fetal allograft rejection by maternal T lymphocytes suggests that IDO can regulate T cell activity (Munn et al. 1998). It has been postulated that the role of IDO is to inhibit proliferation of T cells through different mechanisms. First, the depletion of tryptophan in the cellular environment by IDO-expressing macrophages results in a blockade of activated T cells at the G1 phase of the cellular cycle, thus preventing lymphocyte proliferation (Munn et al. 1999). Additionally, catabolites such as kynurenine, 3-hydroxyanthranilic acid and quinolinic acid can induce apoptosis by exerting cytotoxic properties on T cells (Fallarino et al. 2002). Besides macrophages, DC also express IDO, which is associated with the acquisition of a regulatory phenotype, leading to immune tolerance. They can induce the maturation of immature T cells into regulatory T cells or activate resting memory T cells bearing a regulatory phenotype (Sharma et al. 2007). This remarkable property is independent of the tryptophan levels in the environment, since kynurenine pathway enzymes downstream of IDO can initiate tolerogenesis by DC independently of tryptophan deprivation (Belladonna et al. 2006).

Finally, IDO induction during immune activation may protect cells from oxidative damage. Indeed, IDO activity consumes superoxide anions (Hayaishi 1996) and thus is probably an antioxidant defense, since superoxide anions are precursors for other oxygen reactive species. It has been demonstrated that over-expression of IDO decreases superoxide anion-dependant oxidative damage to cellular proteins in vitro. Moreover, 3-hydroxyanthranilic acid and 3-hydroxykynurenine that are produced from tryptophan along the IDO–kynurenine pathway seem to have antioxidant properties (Christen et al. 1990). In rats, Bitzer-Quintero et al. (2010) showed that tryptophan supplied at twice the daily requirement reduced tissue lipid peroxidation, whereas Forrest et al. (2004) demonstrated that tryptophan loading in humans induced oxidative stress and lipid peroxidation. These contradictory results underline the complexity of tryptophan metabolism and the diverse properties of metabolites produced from this amino acid. Therefore, recommendations on tryptophan supplementation should be done with caution, even if animal studies indicated that dietary tryptophan influenced positively the inflammatory response and animal health. Indeed, pigs suffering from an experimentally induced lung inflammation had lower acute phase protein concentration compared to pigs fed a diet moderately deficient in tryptophan (Le Floc'h et al. 2008). In a porcine model of induced colitis, Kim et al. (2010) showed that a moderate tryptophan loading reduced colitis symptoms through down-regulating inflammation and restoring local immune response. It can be hypothesized that the putative mechanisms involved in the control of inflammatory response by tryptophan could be different, whether considering a supply within the nutritional range or a tryptophan loading. However, both mechanisms probably concern the IDO pathway. When tryptophan is supplied at a low and inadequate level, the correction of the deficiency would restore the control of inflammatory response by T cells. This could explain why

long-lasting IDO activation in turn maintains inflammation caused by tryptophan depletion. In situations where an excess of tryptophan is provided (Kim et al. 2010), tryptophan itself or some of its metabolites with antioxidant properties may be produced in large concentrations and may exert an anti-inflammatory effect, whereas greater excess of this amino acid may be considered as risky because of inducing an oxidative stress.

Conclusion

Tryptophan has important functions for the regulation of growth, mood, behavior and immune responses. Evidence is now accumulating on the detrimental consequences of tryptophan deficiency during inflammatory states and mood disorders. Situations where tryptophan can be deficient need to be identified to prevent associated disorders through an adequate nutritional provision. Moreover, some data also indicate that large doses of tryptophan may have pharmacological virtues in reducing stress and inflammatory responses and in ameliorating mood disorders. However, the mechanisms, safety and efficiency of such tryptophan loading are still controversial even if experimental data indicate that high tryptophan intake has no serious detrimental effect in humans and animals (Garlick 2004). Indeed, although tryptophan itself and some of its metabolites have potential interesting curative properties, some other metabolites of tryptophan are known to be toxic or to increase oxidative stress. Further studies are required to study the different steps of the complex metabolism of tryptophan and its regulation at different levels of integration, from the cell to the whole organism. With the same objective, the interactions between the different pathways in different physiological or pathological states also merit consideration. This knowledge will open new horizons to specific supply or depletion of certain products within the tryptophan metabolic pathways that could have beneficial effects on inflammatory and stress responses.

Conflict of interest The authors declare that they have no conflict of interest.

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