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The tryptophan utilization concept in pregnancy

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The decrease in maternal plasma total (free + albumin-bound) tryptophan (Trp) during the third pregnancy trimester is attributed to induction of indoleamine 2,3-dioxygenase (IDO). When measured, free [Trp] is increased because of albumin depletion and non-esterified fatty acid elevation. The Trp depletion concept in pregnancy is therefore not supported because of incorrect interpretation of changes in Trp disposition and also for not addressing mouse strain differences in Trp-related responses and potential inhibition of Trp transport by the IDO inhibitor 1-methyl tryptophan. Application of the Trp utilization concept in pregnancy offers several physiological advantages favoring fetal development and successful outcome, namely provision of Trp for fetal protein synthesis and growth, serotonin for signaling pathways, kynurenic acid for neuroprotection, quinolinic acid for NAD^+ synthesis, and other kynurenines for suppression of T cell responses. An excessive increase in Trp availability could compromise pregnancy by undermining T cell suppression, e.g., in pre-eclampsia.

Keywords: Albumin; Free tryptophan; Non-esterified fatty acids; Pregnancy; Tryptophan

Introduction

L-tryptophan (Trp) is essential for protein synthesis and fetal growth and development. The Trp depletion concept proposes that fetal rejection is prevented by immune activation accelerating maternal Trp degradation along the kynurenine pathway by cytokine induction of indoleamine 2,3-dioxygenase (IDO). In this review, I suggest that Trp is not depleted in pregnancy and propose an alternative interpretation of the mechanisms of the decrease in maternal circulating [Trp] involving modulation of Trp disposition, but not IDO induction. Aspects of Trp metabolism and disposition of particular importance in human pregnancy are discussed and application of the Trp utilization concept to pregnancy is strongly suggested.

Overview of tryptophan metabolism

Normally, very little dietary Trp (<1%) is used for protein synthesis, because, in a person in nitrogen equilibrium, the amount of protein synthesized matches exactly that degraded [1]. The bulk of dietary Trp is metabolized via 4 pathways, the quantitatively most important of which is the hepatic kynurenine-nicotinic acid pathway, accounting for >95% of Trp metabolism [1,2]. This pathway is controlled by the first enzyme, Trp 2,3-dioxygenase (TDO, formerly Trp pyrrolase) [1,2]. TDO is regulated by glucocorticoid induction involving *de novo* enzyme synthesis, substrate activation and stabilization by Trp, cofactor activation by heme and feedback inhibition by NAD(P)H [1,2]. TDO activity can also be inhibited by estrogens and progesterone and this is of particular relevance to Trp disposition in pregnancy [3]. In human, rat, mouse and some, but not all other, animal species, TDO exists in 2 form: the active heme-containing holoenzyme and the inactive heme-free apoenzyme, in roughly equal proportions [4]. With glucocorticoid induction, only one half of the newly synthesised apoenzyme becomes heme-saturated, whereas after activation by Trp or

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heme, most of the enzyme exists as the active holoenzyme. TDO inhibition by progesterone or estradiol involves prevention of conjugation of the apoenzyme with heme and inactivation of the heme cofactor [3].

Trp can also be degraded by the extrahepatic IDO, to a modest extent under normal conditions, but a greater one after immune activation. IDO is induced mainly by interferon-γ [5,6] and to a lesser extent by interferon-α [7] and its activity can be modulated by both pro- and anti-inflammatory cytokines and mediators in various ways (for references, see [8]). The resultant decrease in [Trp] after IDO induction by interferon-γ is thought to underlie the antiparasitic, antibacterial and antiproliferative actions of this major cytokine [9,10].

Is maternal tryptophan availability really decreased in pregnancy?

The human placenta is the richest source of IDO [11] and the decrease in maternal plasma [Trp] recently reported in this journal [12] was attributed to induction of placental IDO during pregnancy, in support of the Trp depletion concept of Munn et al. [13]. This decrease in maternal [Trp] has previously been demonstrated [14-19], mainly in the third trimester and in association with a modest (approximately 35%) elevation of serum neopterin [17], a surrogate marker of interferon-γ activity [20,21]. However, in some of these studies [12,17-19], only total (free + albumin-bound) [Trp] was determined in the maternal circulation. Free Trp, the form immediately available for tissue uptake, is actually elevated in pregnancy [14,16], thus suggesting that Trp availability to the fetus is enhanced. The postulated decrease in maternal (total) Trp availability during pregnancy [12,17,19] would be disadvantageous to the fetus, whose Trp levels are much higher than those in maternal plasma (see below). Thus the increase in maternal free [Trp] is at variance with the reported decrease in total [Trp] as the basis of the above concept. It will be shown in the following section that the decrease in the latter cannot be attributed to IDO (or TDO) induction, unless accompanied by a decrease in free [Trp], hence the importance of accurate interpretation of changes in Trp disposition.

Plasma tryptophan disposition

Only 5% to 10% of circulating Trp is free (i.e., not bound to albumin) and therefore available for tissue uptake. Plasma nonesterified fatty acids (NEFA) are the physiological displacers of albumin-bound Trp. Thus changes in albumin and NEFA can modulate Trp binding and hence availability. Table 1 lists most of the conditions influencing Trp disposition (for details and references, see [22]). Inhibition of TDO or IDO can increase both free and total [Trp] to similar extents without altering Trp binding, expressed as the percentage free Trp ([free Trp]×100/[total Trp]). Conversely, induction or activation of either enzyme will decrease both free and total [Trp] to similar extents without altering Trp binding. Thus interpreting inhibition or activation of TDO or IDO requires demonstration of quantitatively similar changes in both free and total [Trp] in the appropriate direction. Trp binding can be increased or decreased. It is increased if NEFA levels are decreased, e.g., after inhibition of lipolysis by insulin, nicotinic acid and antilipolytic drugs. Here, only free [Trp] will be decreased. Trp binding is decreased if NEFA are increased, e.g., by stimulation of lipolysis (e.g., by catecholamines, sympathomimetic agents and phosphodiesterase inhibitors), or if albumin is decreased, e.g., in liver cirrhosis [23] or pregnancy [3]. Here, only free [Trp] is increased. If displacement of bound Trp by NEFA (or certain

Table 1. Factors influencing plasma Trp disposition

Condition	Free Trp	Total Trp	% Free Trp	Interpretation
1	↓	↓	—	TDO/IDO induction
2	↑	↑	—	TDO/IDO inhibition
3	↓	—	↓	Inhibition of lipolysis
4	↑	—	↑	Decrease in circulating albumin
5	↑	—	↑	Displacement from albumin-binding sites
6	↑↑	↓	↑↑	Strong and sustained displacement

This Table is based on Table 1 in Badawy AA. J Psychopharmacol 2010;24:809-15, with permission from Sage Publications [22].
Trp, tryptophan; TDO, tryptophan 2,3-dioxygenase; IDO, indoleamine 2,3-dioxygenase; ↑, increase; ↓, decrease; —, no change.

drugs, e.g., salicylate) is strong and sustained, total [Trp] is decreased, due to increased tissue uptake and the rapid equilibration between the free and bound fractions. Under these latter conditions, tissue Trp levels (e.g., in liver and brain) are increased, despite the decrease in total Trp [22]. The increased Trp entry into the liver caused by this large and sustained elevation of plasma free [Trp] can lead to increased formation of kynurenine metabolites either by simple increase in the flux of Trp down the pathway or a Trp-mediated activation of TDO [22]). If a NEFA increase occurs in conjunction with an albumin decrease, a greater increase in free [Trp] could be expected, as observed in pregnant rats ([3], see below). Thus a clear interpretation of changes in Trp disposition and availability requires assessment of both free and total [Trp] in the first instance and, if necessary, albumin and NEFA levels and also whether subjects are receiving antilipolytic medication or drugs that can displace albumin-bound Trp. It is also important to emphasise that kynurenine metabolite formation can be enhanced simply if the flux of Trp down the pathway is increased, without TDO or IDO induction.

Tryptophan disposition in rat pregnancy

The changes in pregnant rats [3] summarised in Fig. 1 illustrate many of the aspects of Trp disposition described in Table 1. In rats, maternal Trp availability is enhanced throughout pregnancy [3]. Liver TDO activity is inhibited from day 1 until day 15, returning to normal on day 16 and staying unaltered over the remaining 5 days of pregnancy [3]. The TDO inhibition is maximal on day 9. As expected and shown in Fig. 1, this TDO inhibition leads to proportionate increases in free and total serum [Trp] on days 1-12, without altering Trp binding. On day 16, when TDO inhibition is absent, serum total [Trp] returns to normal. Although free [Trp] should have also returned to normal, it remains elevated, thereby increasing the % free Trp significantly by 33%. On day 16, [NEFA] remain unaltered, whereas [albumin] is decreased by 19%. This level of albumin decrease triggers the release of bound Trp on day 16. The smaller 16% decrease in albumin on day 12 is presumably insufficient to initiate Trp release. On day 20, the albumin decrease (21%) is accompanied by a 76% increase in [NEFA] and their combined effects on Trp binding are reflected in the (large) 122% increase in free [Trp] and 180% increase in the % free Trp. When free [Trp] is very strongly elevated on day 20, total [Trp] is significantly decreased (by 21%), due, as stated above, to increased tissue uptake. These data in pregnant rats (Fig. 1) may help explain the reported decrease in maternal total [Trp] in human pregnancy. In particular, the changes in total [Trp] in rats mirror those observed in humans [17] over the 3 trimesters (see below). Accordingly, the decrease in plasma total [Trp] previously reported in human pregnancy is unlikely to involve IDO (or TDO) induction.

TDO inhibition in pregnant rats is caused by progesterone and estrogens preventing conjugation of the apoenzyme with its heme cofactor and decreasing cofactor availability [3]. Progesterone levels rise in rats very early in pregnancy and, along with those of estrogens start to decline near the time of the TDO recovery (for references, see [3]). Some earlier studies reported TDO enhancement in pregnancy and attributed it to estrogens. However, subsequent studies with estrogens *in vitro* and after administration to rats and humans have clearly established their TDO inhibitory effect (see [3] and references cited therein).

The decrease in serum albumin in pregnant rats (Fig. 1) is due to hemodilution [23], whereas the increase in [NEFA] is caused mainly by enhanced lipolysis caused by increased mRNA expression and activity of adipose tissue lipase [24]. As similar changes in albumin and NEFA levels also occur in human pregnancy, it is very likely that Trp disposition will undergo changes similar to those in rat pregnancy.

Tryptophan disposition in human pregnancy

As stated above, a decrease in maternal plasma total [Trp] [12,14-19] and an increase in free [Trp] [14,16] have been reported. As in rats, the increase in free [Trp] may be due decreased serum albumin and a NEFA elevation. In humans, hemodilution causes a progressive decrease in circulating maternal albumin [25], of approximately 13%, 24% and 31% over the 3 trimesters respectively. Studies in pregnant rats (Fig. 1) show a parallel pattern and that (free) serum Trp is released from binding sites when albumin concentration drops by 19% or more. Plasma [NEFA] are also increased in human pregnancy [26-28], particularly in late pregnancy [27] as is the case in rats (Fig. 1). Accordingly, an increase in maternal plasma free [Trp] would be expected during the second, and more strongly the third, trimester of human pregnancy, in addition to a

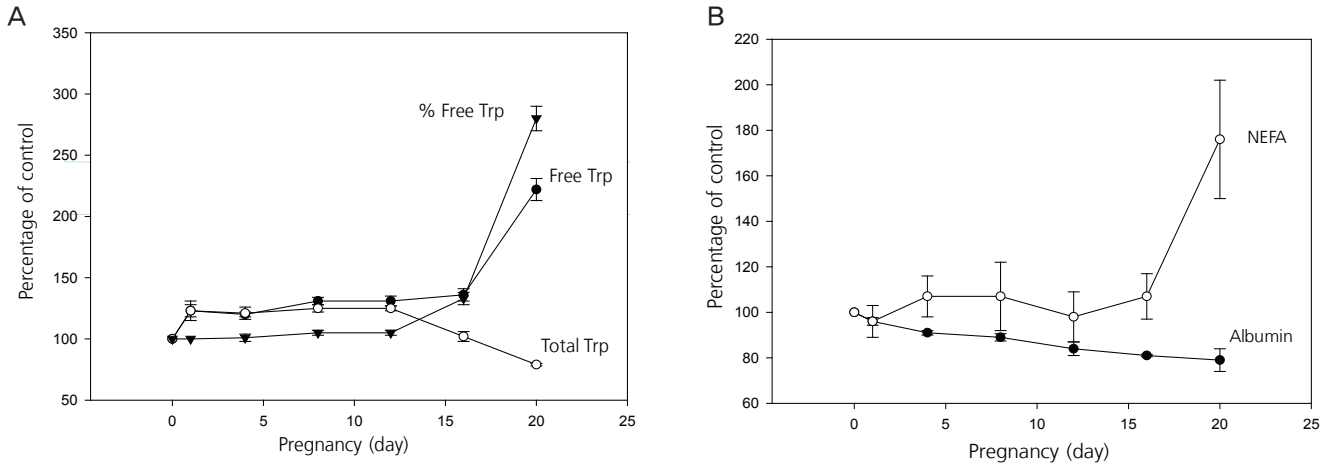

Fig. 1. Effects of pregnancy on tryptophan (Trp) disposition in rats. This research was originally published in reference [3]. Results are expressed as percentages of controls at each time interval during pregnancy for changes in free and total serum Trp concentrations and binding (expressed as the % free Trp) (A) and concentrations of serum albumin and non-esterified fatty acids (NEFA) (B). Details are in Table 1 in reference [3]. From Badawy AA. Biochem J 1988;255:369-72, according to the Creative Commons license [3].

potential increase during the first trimester due to TDO inhibition.

That liver TDO may also influence Trp disposition in human pregnancy is suggested by the only study comparing maternal plasma total [Trp] during the 3 pregnancy trimesters with control non-pregnant women [17]. Plasma total [Trp] was increased significantly by approximately 23% in the first trimester, but decreased by 10% and 25% respectively in the second and third trimesters. The increase in the first trimester was comparable to that in rats on days 4 and 8 (21% and 25% respectively) [3], and is consistent with a TDO inhibition by progesterone and estrogens, whose levels are also increased early in human pregnancy [25]. Also, the decrease in total [Trp] in the third trimester (25%) was comparable to that (21%) on day 20 in rats (Fig. 1). These remarkable similarities between rats and humans reinforce the notion that Trp disposition in human pregnancy is subject to control mechanisms similar to those in rats. Decreases in plasma total [Trp] in late pregnancy >25% and ranging between 34% and 48% have been reported in (most of) the above studies [12,16,18,19].

Human TDO activity, assessed in liver biopsy specimens, is inducible by cortisol [29]. Unlike the elevations of progesterone and estradiol, plasma cortisol levels do not rise early in pregnancy and their elevation in mid and later pregnancy are modest by comparison [25], thus supporting the notion that TDO activity is not induced during pregnancy. Even if TDO was induced by cortisol in the third trimester, any consequent increase in enzyme activity would be neutralised by the inhibitory effects of progesterone and estradiol, both acting to prevent conjugation of newly synthesized apoenzyme with heme.

Comparison of plasma tryptophan disposition in maternal, fetal and newborn humans

A decrease in maternal Trp availability is physiologically disadvantageous to fetal growth and development. Protein requirement and synthesis are increased during pregnancy [30], amino acid transport from mother to fetus is very important [31] and differences in Trp distribution between mother, fetus and newborn infant are in line with these requirements [14,16,32]. Thus, fetal umbilical plasma total [Trp] is twice that in maternal plasma [16], which would not be possible if IDO (or TDO) was induced in mother. Free [Trp] is however similar in mother and fetus, because, albumin binding is low in mother, but high in fetus, possibly also because of increased fetal albumin synthesis [33]. At birth, both free and total infant plasma [Trp] are almost double those in mother [14] and this is followed by a slower decrease in free, as opposed to total, [Trp] during the first 5 days of life. Thus Trp availability and transport to the fetus are both enhanced, with free Trp playing a major role.

Trp distribution between liver, blood, placenta and fetus was studies in pregnant mice on a diet supplemented with Trp at 2

dose levels (2% and 5%) [34]. Placental [Trp] was comparable to that in maternal blood, thus confirming the direct supply route and possibly also suggesting that any potential IDO induction in placenta does not modulate [Trp]. The increase in total (free + albumin-bound) [Trp] in fetus was greater than that in blood or placenta, thus further demonstrating the preferential increase in fetal [Trp] in pregnancy. Whereas pregnancy outcome in mice whose diet was supplemented with 2% Trp was similar to that in un-supplemented controls, The 5% Trp-supplemented diet was, however, associated with lower placental weight and high mortality rates in pups (see further below). It is noteworthy that supplementing healthy women with 5 g of Trp daily does not cause any adverse effects on pregnancy [35].

The tryptophan depletion concept of Munn et al.

The above accounts strongly suggest that: 1) the decrease in maternal total [Trp] is caused by increased tissue uptake by a combination of albumin depletion and NEFA elevation; 2) free Trp availability (to the fetus) in the maternal circulation is increased; 3) accordingly, maternal IDO is not induced and any induction in placenta is insufficient to alter significantly placental [Trp].

Though attractive, the Trp depletion concept [13] applied to other clinical conditions cannot be reconciled with many observations [36] and leaves some important and intriguing questions unanswered [37]. In pregnancy, the concept is based on observations obtained in 2 mouse strains (CBA and C57BL/6J) treated with the IDO inhibitor 1-methyl tryptophan (1-MT). A number of issues arise from the experimental design and assumptions upon which the concept is based. 1) Evidence exists for increased availability of maternal plasma free Trp. 2) In the absence of data on Trp disposition in the mouse study [13], it is not clear where and to what extent the 1-MT-induced IDO inhibition influenced Trp availability in the maternal circulation, placenta or fetus. 3) Whether 1-MT could exert effects on Trp disposition other than by IDO inhibition was acknowledged [13], but untested. 4) The effect of 1-MT on pregnancy in syngeneic C57 × C57 mice was not examined to establish if mouse strains exhibit differences in Trp-related immune responses. 5) The possible role of Trp metabolites was also not addressed, but acknowledged [13]. The following discussion elaborates on these issues.

Munn et al. [13] suggested that the "assumed" maternal Trp depletion is due to IDO induction, presumably by cytokines. Of the 3 relevant studies, two [19,38] measured circulating cytokines and mediators at or near parturition and at 3 days or 6 weeks post-partum, but not during pregnancy. In the third [17], the interferon-γ marker neopterin was decreased during the first trimester, returning to normal during the second, and rising during the third, trimester, by a modest approximately 35%. This suggests a mild degree of immune activation during the third trimester, which should be contrasted with the huge neopterin elevations of 300% to 600% in conditions of heightened immune activation, such as human immunodeficiency virus infection [39,40]. Under these latter conditions and also when liver TDO is strongly induced by glucocorticoids, the decrease in plasma total [Trp] never exceeds 30% [8]. It is therefore unlikely that a modest maternal immune activation in pregnancy can decrease maternal plasma total [Trp] to any significant extent, if at all. This is the more likely, given that the combined IDO activity in extrahepatic tissues is very small, only approximately 5% to 15% of that of hepatic TDO [8]. The larger decreases in maternal total [Trp] of 34% to 48% [12,16,17-19] cannot be explained by accelerated Trp degradation and are therefore most likely the result of increased tissue uptake following release of albumin-bound Trp. Taken together, this suggests that placental IDO induction is unlikely to have influenced maternal Trp availability.

The use of the plasma [kynurenine]/[total Trp] ratio as an expression of IDO induction or activity is not justified without excluding TDO induction [8]. Robust induction of either enzyme should lead to proportionate decreases in both free and total [Trp] (Table 1). As kynurenine undergoes a large renal clearance [41,42], its elevation in plasma can only be seen when the flux of Trp down the pathway after TDO/IDO induction exceeds its renal clearance. Maternal plasma kynurenine is not increased in pregnancy [12,17]. As the decrease in total [Trp] is unlikely to be due to IDO induction, the observed increase in the above ratio [12,17] must be considered fortuitous. This further underscores the importance of accurate interpretation of changes in Trp disposition.

Munn et al. [13] used 1-MT as an IDO inhibitor, but did not study changes in plasma Trp in dams or foetuses. These authors considered the possibility that 1-MT may exert effects additional to IDO inhibition. One such potential effect is inhibition of Trp transport, demonstrated, e.g., in human placenta

[43] and fibroblast cell lines [44]. This potential effect may have contributed to the observed [13] deleterious effects of 1-MT and therefore implies the importance of adequate Trp transport for fetal health. Although 1-MT is a specific inhibitor of IDO [45], but not TDO [46], though it does not inhibit purified IDO1 *in vitro* [47], it is not known if it can activate TDO after administration or influence albumin binding of Trp either directly or by modulating lipolysis. TDO activation is, however, unlikely, as it has been shown in normal mice not to elevate plasma kynurenine nor lower [Trp] [48]. The absence of changes in Trp and kynurenine in this latter study further emphasizes the minimal contribution of IDO to Trp degradation under normal conditions.

The effect of 1-MT on pregnancy in syngeneic C57BL/6J X C57BL/6J mice (hereafter referred to as C57) should be examined in view of significant mouse strain differences in Trp metabolism. Thus, differences in liver TDO activity and its induction by cortisol or activation by Trp exist between various mouse strains [49]. The basal TDO activity in male C57 mice is higher than that in DBA, AKR and C_3H [49], and twice as high as in CBA [50,51], mice. Male C57 mice also show a greater response to induction by cortisol and dexamethasone [49,52]. Compared to males, female C57 mice have a higher basal TDO activity, but a lesser response to cortisol [49]. Ethanol, which activates TDO by a lipolysis-dependent Trp-mediated substrate mechanism, activates TDO in CBA, but not C57, mice [50], thus suggesting that lipolysis-dependent TDO activation is defective in C57 mice. The high TDO activity of C57 mice renders them Trp- and hence serotonin-deficient, which may explain the serotonin deficiency of this alcohol-preferring strain [51]. The higher TDO activity in C57 mice compared with the CBA strain is associated with comparably lower free and total serum [Trp] of 27% and 24% respectively, with no change in Trp binding. If female C57 mice have relatively lower [Trp] than CBA, this may compromise Trp availability to concepti in the former strain and magnify the Trp transport inhibitory effect of 1-MT.

Mouse strain differences in IDO activity and immune responses also exist, with C57 mice showing an enhanced immune sensitivity. Examples include: 1) susceptibility of C57 mice to profound immunodeficiency following LP-BM5 retroviral infection [53], 2) susceptibility of C57 mice over BALB/c to liver injury during Trypanosoma cruzi acute infection [54], 3) C57 peritoneal macrophages differ significantly from those of BALBc mice in their immune response to lipopolysaccharide stimulation and show a greater phagocytic capacity [55]. These and the above aspects of C57 physiology strongly justify the need to assess the effect of 1-MT in syngeneic C57 mice.

Tryptophan and pregnancy complications

There are several pathological determinants of pre-eclampsia (PE) and other pregnancy complications. Of these, the potential role NEFA may be important in relation to the Trp status in pregnancy. Although maternal plasma [NEFA] are increased in normal pregnancy, an excessive elevation is observed in pre-term delivery [27] and PE [28]. This is likely to precipitate oxidative stress [56] and activate the immune system [57,58] possibly via natural killer cells [59]. Immune activation in PE is suggested by the observed [60] 70% increase in neopterin in the maternal circulation, though only 25% in cord blood. However, despite a more enhanced pro-inflammatory environment in PE, maternal [61] and umbilical cord [62] (total) [Trp] is not different from that in normal pregnancy. Also, the absence of a greater decrease in maternal plasma total [Trp] in PE [12] in the presence of the above elevation in maternal neopterin does not support a role for IDO, but suggests that the decrease in maternal total [Trp] in pregnancy is caused by other mechanisms. This further underscores the poor predictive value of maternal total [Trp] as the only indicator of Trp disposition.

That maternal plasma free Trp may play a role in PE is suggested by the greater elevation of [NEFA]. The NEFA elevation is caused by increased levels of circulating catecholamines [63,64], thus enhancing lipolysis by lysophospholipase activation [65]. A greater increase in [NEFA] in PE can induce a stronger displacement of albumin-bound Trp, thus increasing Trp entry into liver and its flux down the kynurenine pathway. In rats, Trp doses of 50 mg/kg body weight do not activate TDO, but stabilise it against degradation [66]. This and smaller doses cause dose-dependent increases in plasma kynurenine and 3-hydroxykynurenine concentrations [67]. Even a 10 mg/kg dose causes significant increases in these 2 metabolites (68% and 29% respectively) in association with a modest 16% elevation of plasma total [Trp] [67]. Thus, kynurenine formation can be enhanced simply by the Trp flux. Whereas maternal total [Trp] is not altered in preeclampsia, kynurenic acid (KA) is elevated [61], as is quinolinic acid (QA) in pre-

eclampsia [61] and toxaemia [62]. Also, an excessive increase in (free) Trp is very likely, as levels of amino acids in maternal and cord blood have been shown to be higher in PE [68] (Trp was not measured in this study).

The tryptophan utilization concept in pregnancy

Strong evidence is accumulating in support of the utilization concept based on the immune activity of kynurenine and its metabolites [36,69,70]. Investigating the Trp utilization concept will be an important task in future studies of pregnancy. I propose that a Trp positive utilization concept operates in pregnancy at multiple levels. 1) Fetal Trp requirements for growth and development are illustrated by the increases in maternal (free) Trp availability and fetal [Trp] discussed above. 2) Serotonin synthesis from Trp ensures an active signaling activity of this indolylamine that is vital for brain development [69] and myometrium contractions [70]. The serotonin source is initially the maternal circulation [71], and later the placenta [72]. Rat plasma and brain levels of serotonin and its major metabolite 5-hydroxyindol-3-ylacetic acid are significantly increased by modest elevation of plasma Trp [67]. These changes would not be expected if maternal Trp degradation was enhanced. 3) The increased flux of Trp into the liver and subsequent transport are reflected in the 2-fold higher [Trp] and 5-fold higher [kynurenine] in fetal umbilical, compared with maternal, plasma [16]. 4) This large kynurenine elevation is akin to kynurenine loading [1] and so should result in advantageous increases in fetal kynurenine metabolites. Of these, KA is the neuro-protective endogenous antagonist of the *N*-methyl-*D*-aspartate (NMDA) types of receptors of the excitatory amino acid glutamate [73]. As this is associated with normal pregnancy, it may be suggested that KA plays an important neuro-protective role in fetal development. 5) Similarly, although QA is the endogenous excitotoxic NMDA receptor agonist [73], it is nevertheless the precursor of NAD^+, and so is important for provision of this important redox co-factor, a shortage of which could compromise cell viability. 6) Increased formation of 2 other kynurenine metabolites (3-hydroxykynurenine and 3-hydroxyanthranilic acid) can suppress T cell proliferation and hence the immune response (see [36] and references cither therein). All these beneficial changes can result simply from the increased flux of free Trp down the kynurenine pathway with no need for IDO or TDO induction. 7) However, if this increased flux of free Trp is excessive, as possibly in PE, it can undermine the suppression of T cell responses [74]. Thus, "T cells could respond with either activation or arrest, depending on the level of Trp they find" [74].

Very little is known about kynurenine metabolite levels in pregnancy. In normal human pregnancy, fetal umbilical venous and arterial plasma [kynurenine] is 4.96 and 4.59 μM respectively, compared with 0.91 μM in maternal plasma [16]. Normal adult plasma [kynurenine] of either gender of USA subjects is 2.15±0.12 μM (mean±SD for n=114) [75], though lower values have been reported. 3-hydroxyanthranilic acid concentration in umbilical blood is 0.26 to 0.27 μM, compared with 0.04 μM in maternal plasma [16] and 0.28 μM in controls [75]. As stated above, maternal plasma total [Trp] is a half of that in umbilical cord [16]. That excess Trp could harm pregnancy is suggested by the poor outcome when mice are maintained on a 5%, but not a 2%, Trp-enriched diet [34]. The 5% Trp diet causes significant decreases in placental, fetal and pup (body) wt and a 25% fetal rejection. In this study [34], only [Trp] was monitored in liver, blood, placenta and fetus. Normal pregnancy in control mice and those on the 2% Trp diet was associated with blood, placental and fetal [Trp] of 100 to 150 μM, 100 to 320 μM and 175 to 360 μM respectively. By contrast, mice receiving the 5% Trp diet exhibited greater elevations of 700 to 900 μM (blood), 770 to 870 μM (placenta) and 1,200 to 1,400 μM (fetus). These latter Trp values are in excess of that (490 μM) in the medium used to demonstrate the ability of excess Trp to reverse the suppression of T cell responses to kynurenines [74]. It is tempting to suggest that another advantage of increased fetal albumin synthesis [33] is to limit availability of excess Trp for kynurenine production.

Conclusion

It is hoped that the present review has clarified the Trp disposition status in human pregnancy. The Trp utilization concept in pregnancy offers exciting prospects for further research, which should include plasma free Trp measurements in assessment of the Trp status, kynurenine metabolite determinations in normal and abnormal pregnancies and a further assessment of mouse strain differences and 1-MT inhibition of Trp transport in pregnancy outcome.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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