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The kynurenine pathway; A new target for treating maternal features of preeclampsia?

Stephanie A. Worton[a,*], Susan L. Greenwood[a], Mark Wareing[a], Alexander EP. Heazell[a,b], Jenny Myers[a,b]

[a] Maternal and Fetal Health Research Centre, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom
[b] St. Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

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ABSTRACT

In preeclampsia, vasospasm, oxidative stress, endothelial dysfunction, and immune dysregulation are key mediators of maternal disease. A new time-of-disease treatment is needed with the potential to treat these areas of pathophysiology. A review of the literature has indicated that metabolites of the kynurenine pathway have the potential to; (i) induce vasorelaxation of resistance arteries and reduce blood pressure; (ii) exert antioxidant effects and reduce the effects of poly-ADP ribose polymerase activation (iii) prevent endothelial dysfunction and promote endothelial nitric oxide production; (iv) cause T cell differentiation into tolerogenic regulatory T cells and induce apoptosis of pro-inflammatory Th1 cells. This has led to the hypothesis that increasing Kynurenine pathway activity may offer a new treatment strategy for preeclampsia.

1. Background

Despite advances in clinical care, delivery of the baby and placenta remains the only cure for preeclampsia (PE). Current treatment strategies aim to reduce the risk of maternal complications but do not address the underlying pathophysiology of PE. Although maternal deaths from PE are now rare in high-resource settings [1], concerns about maternal safety are a common indication for delivery [2], which transfers the burden of morbidity to the offspring. Babies born prematurely, often in combination with fetal growth restriction, are at risk of short-term complications, lifelong disabilities, and have a lifetime increased risk of cardiometabolic disease [3].

Thus, there remains a cogent clinical need to identify new treatment strategies for PE. Currently, given the absence of effective prevention or reliable prediction of PE, a clinically useful treatment should be appropriate for intervention at the time of diagnosis. At the stage in pregnancy at which a diagnosis is made, reversing underlying placentation defects is unlikely to be possible. Therefore an attractive therapeutic option is to target drivers of maternal pathophysiology; an intervention to halt or retard disease progression could reduce the incidence of maternal complications, and may safely allow gestation to be extended, thereby reducing prematurity-associated risks to the infant.

Whilst the origins of PE can often be traced to impaired spiral artery remodelling in early pregnancy, this is temporally removed from the onset of the maternal syndrome in the second half of pregnancy [4]. The placenta communicates with the maternal immune system at the maternal-fetal interface and with the maternal endothelium via the release of factors into the maternal circulation. In susceptible individuals, oxidative stress and circulating factors derived from the stressed placenta cause a systemic maternal inflammatory response, immune activation, endothelial cell dysfunction and vasospasm. These pathophysiological entities are closely linked and further drive each other in an escalating cycle which leads to hypertension, hypoperfusion and organ dysfunction; the maternal syndrome of PE. We sought to identify a therapeutic target which can apply the brakes to maternal pathology; based on experimental evidence from other fields, the kynurenine (Kyn) pathway has been identified as a potential candidate to fulfil this role. This pathway first came to our attention during a literature review of putative metabolites that were reduced in a

Abbreviations: Ahr, Aryl hydrocarbon receptor; AT1-AA, Angiotensin II Type 1 receptor autoantibodies; BP, blood pressure; *cis*-WOOH, *cis*-hydroperoxide ((2S,3aR,8aR)-3a-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylic acid); FMD, flow-mediated dilatation; IDO, indoleamine 2,3-dioxygenase; KYN, kynurenine; NAD+, nicotinamide adenine dinucleotide; PARP, poly(ADP-ribose) polymerase; PE, preeclampsia; SHR, spontaneously hypertensive rat; TDO, tryptophan 2,3-dioxygenase; Th, T helper cell; TRP, tryptophan; QA, quinolinic acid

* Corresponding author. Maternal and Fetal Health Research Centre, 5th Floor (Research), St Mary's Hospital, Oxford Road, Manchester, M13 9WL, United Kingdom.
E-mail address: Stephanie.worton@manchester.ac.uk (S.A. Worton).

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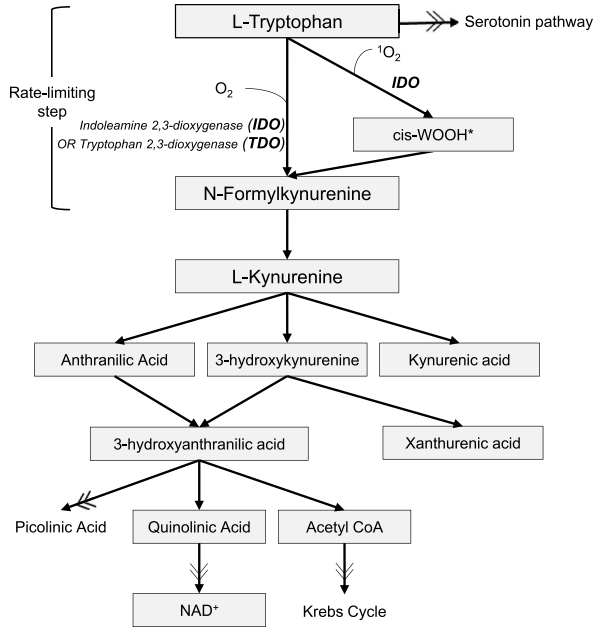

Fig. 1. The Kynurenine pathway. A schematic of the kynurenine pathway of tryptophan metabolism indicating the rate-limiting enzymatic conversion of L-Tryptophan to *N*-formylkynurenine. Feathered arrows indicate several metabolic steps. **cis*-hydroperoxide ((2S,3aR,8aR)-3a-hydroperoxy-1,2,3,3a, 8,8a-hexahydropyrrolo [2,3-b]indole-2-carboxylic acid) [14].

hypothesis-generating comparison of the placental metabolome of women with normal pregnancy or PE [5]; this study found 0.63 fold reduction in placental Kyn levels in PE in comparison to uncomplicated pregnancies. The Kyn pathway has broad physiological roles which may provide an opportunity to target several areas of aberrant pathophysiology observed in PE, notably vasospasm, endothelial dysfunction [6,7], oxidative stress [8,9] and immune activation [10,11](Fig. 2). This led to our hypothesis that intervening in PE to increase activity of the Kyn pathway may ameliorate some features of the maternal pathology. Here, we review evidence regarding functions of the Kyn pathway which underpin our hypothesis.

2. The Kyn pathway

The Kyn pathway is the principal catabolic route for the essential amino acid tryptophan, which results in the *de novo* synthesis of nicotinamide adenine dinucleotide (NAD^+) for use in cellular respiration [12]. The metabolites of the Kyn pathway are shown in Fig. 1. Whilst the Kyn pathway degrades > 90% of Trp, remaining Trp is incorporated in to proteins or converted into the neurotransmitter serotonin and subsequently the neurohormone melatonin. Interestingly, the serotonin/melatonin pathway itself has been extensively investigated as a potential treatment for pregnancy complications including PE (reviewed by Marseglia et al. [13]). The rate limiting step in the Kyn pathway is the conversion of Trp to Kyn which is regulated by hepatic tryptophan 2,3-dioxygenase (TDO) or extrahepatic indoleamine 2,3-dioxygenase (IDO). Hepatic TDO is constitutively expressed, whilst IDO expression and activity is generally responsive to inflammatory stimuli (IFN-γ and TNF) in pathologies such as hypoxia and infection [6,10,14], where IDO is subsequently broadly expressed in the vascular endothelium and a range of immune cells. A notable exception to this is the normal placenta which is the most abundant source of IDO [15].

3. The Kyn pathway in pregnancy

In normal pregnancy, there are high levels of IDO expression and Kyn pathway activity in the placenta (reviewed by Sedlmayr et al. [15]). In the maternal circulation, the ratio of circulating Kyn and Trp (K/T ratio) is significantly increased in normal pregnancy compared to non-pregnant women [16] and urinary excretion of Kyn pathway metabolites are increased accordingly [17]. In PE, despite increased inflammation, which would be expected to stimulate Kyn pathway activity, there is reduced placental IDO expression and activity [16,18], and reduced release of Kyn by cultured placental tissue compared to normal pregnancy [5,16].

Information from several animal models has suggested a role for reduced Kyn pathway activity in PE: (i) Kyn pathway inhibition with low oral doses of the IDO inhibitor 1-me-Trp in wild-type mice increased maternal blood pressure (BP) [19]. (ii) Mice genetically deficient in IDO1 ($IDO^{0/0}$) demonstrate several changes in pregnancy consistent with PE; renal endotheliosis, proteinuria and endothelial dysfunction [20]. In this model there was no significant increase in maternal BP but the usual pregnancy reduction in BP observed in wild type mice was attenuated. (iii) In a recent metabolic screen in catechol-O-methyl transferase knock-out mice, a well-established model of PE, there was a significant reduction in maternal serum Kyn [21].

4. Vasorelaxant effects of the Kyn pathway

Within the last decade a novel role has emerged for a Kyn pathway metabolite as an endothelial-derived regulator of vascular tone [6,22]. Whilst the vasoactive factor was initially reported to be Kyn itself [6], this effect has recently been attributed to the action of *cis*-hydroperoxide ((2S,3aR,8aR)-3a-hydroperoxy-1,2,3,3a, 8,8a-hexahydropyrrolo [2,3-b]indole-2-carboxylic acid) (*cis*-WOOH), a newly-identified intermediary produced by oxidatively-activated IDO [14].

The Kyn pathway is activated in many cellular and animal models of stress and systemic inflammation [6,9,10,14,23]. Hypotension observed in several pathologies (eg: malarial infection) can be attenuated by inhibiting IDO activity [6], indicating that inflammation-induced Kyn pathway activity contributes to the development of hypotension in response to inflammation. This is supported by several observations in humans; Kyn pathway activity, measured by K/T ratio, is inversely correlated with BP in human studies of trauma [23], obesity [24], sepsis [25] and PE [26].

We propose utilising this endogenous vasorelaxant factor in order to purposefully cause maternal vasorelaxation in hypertensive pathologies. In PE, disturbances are evident at all levels of the vascular tree. In resistance arteries (< 400 μm) vasospasm arises due to both an increased sensitivity to vasoconstrictor agents and dysfunction of endothelium-dependent vasorelaxant pathways. These arteries contribute significantly to the determination of peripheral vascular resistance due to their large numbers and ability to regulate large changes in flow to individual vascular beds. *In vitro*, commercially-sourced Kyn or purified *cis*-WOOH cause relaxation in arteries sampled from the microvasculature or macrovasculature across a range of species; pigs, mice, rats, rabbits and humans [6,7,14,22]. Currently, there is only one published report of the direct effects of Kyn on the systemic human vasculature, in which Kyn caused relaxation of pre-constricted omental resistance arteries [7]. In the placental chorionic plate vasculature, high doses of Trp reduce vascular tone via an IDO-dependent mechanism [18]. Kyn, although derived from the vascular endothelium, exerts its vasorelaxant effects independently of the endothelium [6,7,14] which may offer the potential to bypass dysfunctional endothelial pathways in PE to cause vasorelaxation.

In intact animals, intravenous administration of Kyn to spontaneously hypertensive rats (SHR) reduces BP by approximately 40 mmHg [6]. Furthermore, dietary supplementation the Trp-rich grass seed *Phalaris canariensis* (canary seed) caused a sustained BP reduction in both SHR and normotensive rats [27].

5. Antioxidant effects of the Kyn pathway

Oxidative stress and inflammation are increased in pregnancy compared to the non-pregnant state, but this is accentuated in PE (reviewed in Ref. [28]). In PE there is extensive placental oxidative stress, with increased superoxide anions, increased lipid peroxidation, and increased nitrotyrosine residues in both the fetoplacental vasculature and placental villi [29,30]. Markers of oxidative stress are also elevated in maternal serum and urine, changes which precede the onset of clinically detectable disease [31,32]. Oxidative stress is widely accepted to be an important mediator of the maternal syndrome through inflammatory stimulation and endoplasmic reticulum stress which lead to cellular activation, dysfunction and death [33].

The Kyn pathway has a net antioxidant effect which is mediated via a number of pathway constituents. Both Trp metabolising enzymes TDO and IDO utilise superoxide anions (O_2^-) as a co-factor and as a substrate to convert Trp to Kyn, thereby directly scavenging cellular ROS [34]. Whilst other antioxidants, such as superoxide dismutase, convert superoxide to another potentially harmful oxidising compound (hydrogen peroxide), TDO and IDO have the advantage of directly removing a pro-oxidant to generate further powerful antioxidant compounds. Several downstream metabolites have consistently reported antioxidant effects: Kyn [35,36], 3-hydroxyanthranilic acid [35,37], 3-hydroxykynurenine [37], anthranilic acid [35], xanthurenic acid [37,38] and kynurenic acid [37,39]. The phenolic metabolites 3-hydroxykynurenine and 3-hydroxyanthranilic acid are particularly powerful antioxidants and at equimolar concentrations are more potent than Vitamin C and Vitamin E [37].

Whilst the downstream Kyn metabolite quinolinic acid (QA), a *N*-methyl-D-aspartate-agonist, causes lipid peroxidation *in vitro* in neuronal tissues [40], these oxidising effects of QA are neutralised by the activity of either Kyn or kynurenic acid [41] and further offset by activation of the transcription factor Nrf2 [42] which activates the antioxidant response element, a promoter common to > 100genes regulating detoxifying phase 2 enzymes (including superoxide dismutase, heme-oxygenase-1 and glutathione peroxidase [43]). QA is also the most effective substrate for generation of NAD + following activation of poly(ADP-ribose) polymerase (PARP). PARP activation is an important mediator of the deleterious effects of oxidative stress, causing sequential addition of ADP-ribose to cellular proteins, thereby depleting cellular NAD + reserves and leading progressively to cellular dysfunction, apoptosis and necrosis [44]. Importantly, Kyn pathway generation of NAD^+ directly counteracts PARP-mediated NAD + depletion, and in experimental models, IDO induction reduces cell death following PARP activation [9].

6. Pro-endothelial effects of the Kyn pathway

The important role of endothelial dysfunction in propagating the maternal syndrome in PE is widely accepted [28,45,46]. In PE, there are increased circulating levels of many factors which indicate endothelial cell activation, including Factor VIII antigen, plasminogen activator inhibitor-1, vascular cellular adhesion molecule-1, tissue plasminogen activator and von Willebrand Factor [47]. The dysfunctional endothelium drives inflammation by stimulating leukocytes, promoting platelet adhesion, activating complement and coagulation cascades, and releasing cellular debris in to the circulation [47].

Trp catabolism via the Kyn pathway generates QA which combines with nicotinic acid (niacin, vitamin B3) to produce NAD^+. Enhancing NAD + production via supplementation of nicotinic acid is a well-recognised therapeutic strategy to promote vascular health, with over 30 years of use in patients with vascular disease (reviewed by Meyers et al. [48]). Nicotinic acid treatment increases nitric-oxide synthase expression resulting in improved endothelial-dependent vasorelaxation in patients with coronary artery disease [49]. Furthermore, in an animal model of acute vascular inflammation caused by arterial occlusion, nicotinic acid inhibits vascular inflammation and reduces endothelial dysfunction [50]. We postulate that increasing endothelial cell NAD^+ via an alternative mechanism, by increasing Kyn pathway activity, may confer the same benefits.

7. Immunoregulatory effects of Kyn pathway

Adaptations in $CD4^+$ T-cell mediated immunity are important regulators of immune stimulation and regulation in pregnancy. Normal pregnancy is associated with a systemic decline in pro-inflammatory Th1 and Th17 cells [51]. Regulatory T-cells (T_{regs}), which have an important role in modifying the activity of Th1, Th2 and Th17 effector T-cells, are found in high numbers at the fetomaternal interface where they subdue effector responses to induce tolerance of the maternal immune system [52]. In PE, a predominance of Th1 and a reduction in T_{regs} are evident both systemically and at the fetomaternal interface [51] with a net increase in pro-inflammatory cytokines from Th1 (IL6 and TNF-α) and Th17 (IL17) cells [53]. In addition to their inflammatory role, these Th-derived cytokines have more recently been implicated in stimulating the production of auto-antibodies specific to the Angiotensin II Type 1 receptor [51] in PE (AT1-AA; reviewed by Herse et al. [54]). AT1-AA stimulate vasoconstriction and induce an inflammatory transcriptome in both trophoblast and endothelial cells which further fuels escalating production of endothelin-1, anti-angiogenic factors, ROS and TNF-α (reviewed by Harmon et al. [55]).

The immunoregulatory role of the Kyn pathway in pregnancy is well-established. IDO expression and activity in the maternal decidua and in the placenta increase in a gradient towards the maternofetal interface [15], where IDO activity is integral to the immunoregulation of normal pregnancy. In general, the immunoregulatory effects of the Kyn pathway are via both depletion of Trp and utilisation of its downstream metabolites. However, in pregnancy the role of Trp depletion is now considered to be less important than utilisation due to the high availability of free Trp in pregnancy and the inefficiency of expending energy transporting large amounts of Trp into the placenta whilst also trying to maintain a Trp deplete environment [56]. In recent years, there has been increasing recognition of the role of Trp utilisation to produce downstream kynurenines which regulate the immune response. Kyn itself is a physiological ligand for the Aryl hydrocarbon receptor (Ahr) [11], a ligand-activated transcription-factor, although the latest reports indicate that Ahr activation by Kyn is likely to be attributable to trace-extended aromatic condensation products of Kyn [57]. Activation of Ahr in T-cells by Kyn causes their development into T_{regs} [11]. Interestingly, prior to the recognition of Kyn as a physiological Ahr ligand, the only known ligands were external toxins including cigarette smoke. It has been postulated that Ahr activation in cigarette smokers may explain their 33% relative risk reduction for developing PE [58]. Further downstream, Kyn pathway metabolites (specifically 3-hydroxyanthranilic acid and QA) selectively induce apoptosis of Th1 helper cells [59].

8. A new treatment target for PE?

The vasorelaxant, antioxidant, pro-endothelial and immunoregulatory effects of Kyn pathway metabolites reported in the literature has led us to propose the Kyn pathway as a potential new therapeutic target for PE (Fig. 2). The breadth of pathological features across which there is potential to intervene make this an enticing treatment strategy for a heterogenous disease where multiple factors contribute to variable degrees in different women.

Currently, all supporting evidence for this hypothesis is extrapolated from *in vivo* or *in vitro* data obtained from other diseases; clearly, this hypothesis will require extensive investigation. The first step in testing this hypothesis will be to determine whether proposed effects in human cells/tissues occur in relevant *in vitro* models of pregnancy and PE. The most novel and compelling area to achieve potential benefit relates to

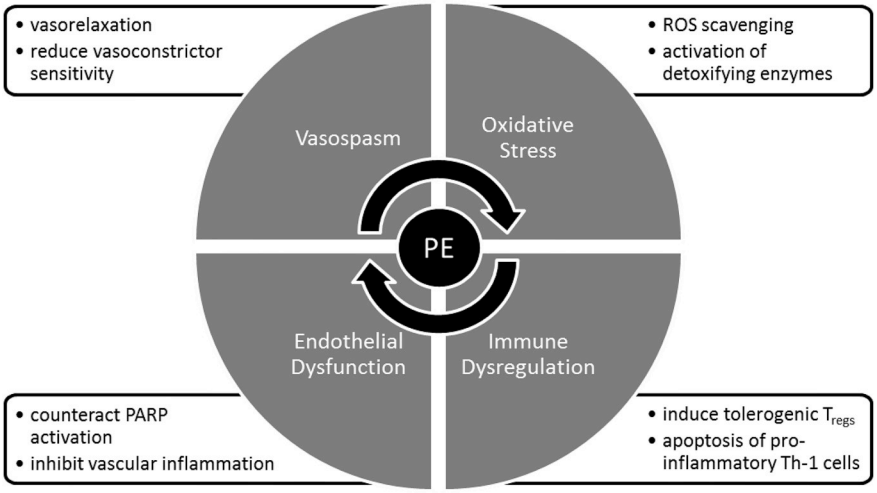

Fig. 2. Potential roles for the Kyn pathway in ameliorating maternal features of PE. Key pathophysiological features of PE (grey boxes) positively feedback to drive escalating maternal disease. The Kyn pathway may offer the opportunity to target each of these areas of pathology via mechanisms described in white boxes. See full text for explanation and references. Abbreviations: PARP, poly-ADP ribose polymerase; PE, preeclampsia; ROS, reactive oxygen species; Th1, T helper cells Type 1; Tregs, regulatory T cells.

the vasorelaxant effects of Kyn pathway metabolites. Currently there is very limited information pertaining to the effects of Kyn in human blood vessels. The vascular effects of Kyn pathway metabolites must be confirmed in arteries obtained from pregnant women and the mechanism of action identified in order to anticipate off-target effects of systemic treatment. It is also essential to confirm that beneficial effects of Kyn are not negated by the extensive vascular dysfunction observed in PE.

The antioxidant and pro-endothelial effects of Kyn pathway metabolites discussed can be addressed initially in macro- and microvascular endothelial cell models of vascular dysfunction, to determine the effect of treatment on markers of endothelial damage and function. However, due to the complexity of immune system interactions *in vivo*, the effects of Kyn pathway manipulations would be more appropriately addressed in a whole animal model.

Extrapolating the findings of *in vitro* studies to whole systems and organisms may be difficult as there is limited information about pathway pharmacokinetics and bioavailability of metabolites in pregnancy. As the potential effects of the Kyn pathway can be attributed to several pathway constituents, even identifying the most appropriate intervention may be challenging. Animal studies indicate that Trp loading induces hepatic TDO activity and increases Kyn pathway flux. However, these metabolites are tightly regulated and increasing pathway flux may not necessarily translate into metabolite bioavailabity within tissues of interest; high dose dietary supplementation with Trp does not result in a detectable serum rise in Kyn [60]. Administration of oral Kyn in pregnant mice does result in a large increase in circulating Kyn; however fetal levels of Kyn were even higher [61].

Observational data from human pregnancy indicate that Kyn pathway metabolites are enriched in the fetal circulation [62]. This has implications for achieving adequate maternal dosage as metabolites will become sequestered by the fetus, but also emphasises the importance of rigorous pre-clinical safety testing. There must be compelling evidence of potential benefit and rigorous investigation of safety in advance of translation to a human treatment being contemplated. In rats, Trp supplementation does not cause fetal malformation or pregnancy loss [60]. However, at high doses (1.43 g/100 g food), there is reduced maternal food intake, reduced maternal weight gain and reduced fetal weight [60]. This is consistent with weight loss observed in non-pregnant animals on high-Trp diets; proposed explanations for reduced consumption include distaste or anorexia, whilst decreased food efficiency ratio is attributed to the increased calorie wastage associated with protein metabolism. These effects of Trp did not occur at lower doses ($\leq$0.29 g/100 g food) [60] –a dose which still exceeds any likely intervention arising from this hypothesis. Essential safety data will include an assessment of acute effects of Kyn pathway metabolites on the fetoplacental circulation (myography), placental transfer and metabolism (placental perfusion), placental function (placental explants) and short- and long-term offspring outcomes (animal studies). Due to the proposed role of Kyn pathway dysregulation in the development of schizophrenia [63] and the linked-regulation of Kyn and serotonin pathways [64], long-term offspring neurological and behavioural studies will be required.

We propose that evidence presented herein warrants a series of pre-clinical investigations to determine whether reported effects of the Kyn pathway in other pathologies can target the vasospasm, oxidative stress, endothelial dysfunction and immune dysregulation which drive maternal features of PE, with the ultimate intention of developing a new therapeutic to ameliorate maternal features of PE.

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Appendix A. Supplementary data

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