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The serotonin-immune axis in preeclampsia

Serena Gumusoglu[*],
University of Iowa Carver College of Medicine, Department of Obstetrics and Gynecology, Iowa City, Iowa, USA;

Sabrina Scroggins,
University of Iowa Carver College of Medicine, Department of Obstetrics and Gynecology, Iowa City, Iowa, USA;

Julie Vignato,
University of Iowa College of Nursing, Iowa City, Iowa, USA;

Donna Santillan,
University of Iowa Carver College of Medicine, Department of Obstetrics and Gynecology, Iowa City, Iowa, USA;

Mark Santillan
University of Iowa Carver College of Medicine, Department of Obstetrics and Gynecology, Iowa City, Iowa, USA;

Abstract

Purpose of Review: To review the literature and detail the potential immune mechanisms by which hyperserotonemia may drive pro-inflammation in preeclampsia and to provide insights into potential avenues for therapeutic discovery.

Recent findings: Preeclampsia is a severe hypertensive complication of pregnancy associated with significant maternal and fetal risk. Though it lacks any effective treatment aside from delivery of the fetus and placenta, recent work suggests that targeting serotonin systems may be one effective therapeutic avenue. Serotonin dysregulation underlies multiple domains of physiologic dysfunction in preeclampsia, including vascular hyporeactivity and excess platelet aggregation. Broadly, serotonin is increased across maternal and placental domains, driven by decreased catabolism and increased availability of tryptophan precursor. Pro-inflammation, another hallmark of the disease, may drive hyperserotonemia in preeclampsia. Interactions between immunologic

[*]The corresponding author can be contacted at: serena-gumusoglu@uiowa.edu.

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dysfunction and hyperserotonemia in preeclampsia depend on multiple mechanisms, which we discuss in the present review. These include altered immune cell, kynurenine pathway metabolism, and aberrant cytokine production mechanisms, which we detail. Future work may leverage animal and *in vitro* models to reveal serotonin targets in the context of preeclampsia's immune biology, and ultimately to mitigate vascular and platelet dysfunction in the disease.

Summary: Hyperserotonemia in preeclampsia drives pro-inflammation via metabolic, immune cell, and cytokine-based mechanisms. These immune mechanisms may be targeted to treat vascular and platelet endophenotypes in preeclampsia.

Keywords

Preeclampsia; serotonin; immunology; inflammation; pregnancy; obstetrics

1. Introduction

Preeclampsia is a severe hypertensive complication of pregnancy associated with acute maternal risk and long-term risk to resultant children. While the incidence of preeclampsia is high and continues to grow (currently 3–10% worldwide), there are no effective treatments or cures for this often-devastating gestational disorder. This is in part because preeclampsia is a complex, multisystem progressive disorder, involving immune, neurological, and cardiovascular dysregulation [1–3].

Neurological and neurodevelopmental problems occur at increased rates in preeclamptic women and in their children, respectively, implicating neurobiological systems in preeclampsia dysfunction [1]. For instance, women with severe preeclampsia may develop posterior reversible encephalopathy syndrome (PRES) and associated neurological deficits, while their children face increased rates of autism [odds ratio=1.50 (95% CI, 1.26–1.78)], ADHD [odds ratio=1.31 (95% CI, 1.19–1.44)], and other neurodevelopmental disorders [1, 4, 5]. History of maternal mood or anxiety disorder is also associated with a 2.12-fold increased risk of preeclampsia [6]. Serotonin dysregulation may explain this bi-directional risk, as serotonin systems are abnormal in both preeclamptic women and in mood disorder patients. Further, serotonin-linked behaviors and psychopathologies are disproportionately impacted in children from preeclamptic pregnancies [1, 7, 8]. Similarly, immune dysregulation occurs in both mood and gestational hypertensive disorders [9, 10]. This suggests overlapping mechanisms and highlights the need to understand preeclampsia, at least in part, as a disordered serotoninergic and immunologic state.

Disrupted serotonin-immune interactions may unite the multiple domains of dysfunction in preeclampsia and explain resulting maternal and fetal vulnerabilities. Here, we review multiple mechanisms of serotonin-mediated immune disruption in preeclampsia. Understanding preeclampsia as an immune disorder, driven at least in part by serotonergic dysfunction, may highlight novel avenues for its treatment.

2. Serotonin

Italian scientist Vittorio Erspamer discovered serotonin, an amine that caused contractions in the intestines, dubbing it “enteramine” [11]. Contemporary science maintains that serotonin is primarily found in the gastrointestinal tract, where it acts as a local hormone, though it is also localized to the nervous system, circulating platelets, and pulmonary epithelium [12]. More recent studies have also extended the biological role of serotonin to include immunoregulation, as we will discuss here.

Serotonin-immune interactions are integral in its very synthesis. Serotonin synthesis begins with tryptophan, an essential amino acid found in dietary proteins, which contributes either towards the serotonin or kynurenine pathways. In the kynurenine pathway, tryptophan is metabolized by indolamine-2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) in an O_2-dependent manner. IDO is a rate-limiting enzymes in the kynurenine pathway and is produced in response to inflammation, acting as an immunosuppressor [13]. The serotonin pathway begins with tetrahydrobiopterin (BH4)-dependent conversion of tryptophan by tryptophan hydroxylase (TPH) into 5-hydroxytryptophan (5-HTP). 5-HTP is then decarboxylated to serotonin (5-HT) by dopa decarboxylase (DDC) in a pyridoxal phosphase (PLP)-dependent manner. 5-HT can further be inactivated or excreted by conversion into 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase A (MAO-A).

In circulation, serotonin is readily bound up by intravascular platelets, which express the serotonin transporter (SERT). Binding of serotonin by platelets leaves little free serotonin in the blood, and release from activated platelets (e.g., upon aggregation) elicits local vasoconstriction [14]. The use of tryptophan in serotonin or kynurenine synthesis is balanced by a variety of factors, including by melatonin, the end-product of the serotonin synthesis pathway, and by IDO itself [15].

Serotoninergic cell bodies in the midbrain and brainstem raphe nuclei also release serotonin and project to a variety of targets in the central nervous system (CNS), including the spinal cord, forebrain, and locally. Though only approximately 5% of the body’s serotonin is synthesized in the brain [16], serotonin axons are distributed throughout the brain, implicating this system in many brain networks and physiological functions (e.g., sleep-wake regulation, feeding, stress reactivity, learning and memory, mood, and more [17]). The role of serotonin also involves CNS response to peripheral [18] and central inflammation, as we discuss in further detail below.

Serotonin’s vascular role is complex—it causes vasodilation or vasoconstriction depending on the nature and conditions of a particular vascular bed, the receptor expression profile, administration route, and underlying sympathetic tone [19]. The distribution and function of serotonin receptors also varies widely. There are seven known serotonin receptors ($HTR_{1–7}$) with 14 subtypes, all of which except HTR_3 (a serotonin-gated ion channel) are protein-coupled. HTR signaling thus strongly implicates regulators of protein-coupled signaling [e.g., the regulator of G protein signaling (RGS) family] in downstream cascades. Given this heterogeneity, target- and tissue-specific study of serotonin interactions in normal and diseased physiology is critical.

Among its many complex physiologic roles, serotonin's role in the immune system was only identified in recent decades [20]. As reviewed elsewhere, serotonin is immunomodulatory and serotonin receptors and serotonin cascade molecules/enzymes are expressed by many types of immune cells including dendritic cells, mast cells, NK cells, T cells, B cells, neutrophils, macrophages, and monocytes [21]. Platelet delivery of serotonin to sites of immune response or injury is also well described, and direct serotonergic modulation of monocytes and lymphocytes is an emerging area of discovery [21]. These mechanisms have significant implications for preeclampsia, a disease featuring profound vascular and immune dysregulation leading to significant pathologic effects in pregnancy and development.

3. Serotonin in pregnancy and embryogenesis

The serotonin system is required for multiple aspects of normal pregnancy, maternal behavior, and placental and fetal development [22–25]. Serotonin receptors are broadly expressed in female reproductive tissues. For instance, the genes encoding the serotonin transporter (*SLC6A4*) and receptors *HTR2B*, *HTR1F*, and *HTR1D* are expressed in breast tissues. *HTR7* is expressed in the ovaries, and a variety of serotonin receptors (*HTRA4, HTRA1, HTR3A, HTRA2, HTR2B, HTR1F*), *SLC6A4* (at low levels in trophoblast cells), and *MAOA* are expressed in the placenta [26, 27]. These expression patterns indicate some functional importance for serotonin systems in reproductive tissues and biological processes, though differences between tissues also demonstrate unique roles of serotonin that are dependent on target tissue type. For instance, early embryonic blood flow via placental vascular beds is regulated by serotonin transporters at the trophoblast cell membrane, and serotonin regulates trophoblast viability and proliferation via HTRA2 [24, 28].

Platelet serotonin levels increase during pregnancy then decrease following delivery in response to fetal requirements, a phenomenon that has been linked to risk for pre- and postpartum mood disorders [29]. Both maternal and placental serotonin are early and critical sources of serotonin for developing mammalian offspring. Embryogenesis, including formation of the fetal CNS and gut, is regulated by maternal serotonin. *Tph1*-null dams, which are hyposerotonemic, produce morphologically abnormal pups, and maternal but not offspring SERT Ala56 genotype, which causes hyperserotonemia, alters placental and offspring brain serotonin [30, 31]. Work by Bonnin and Levitt revealed that maternal immune activation disrupts placental tryptophan metabolism, leading to altered fetal brain serotonergic circuit formation. Bonnin and Levitt further demonstrated that the placenta is the primary source and regulator of fetal forebrain serotonin, which is synthesized from maternal tryptophan [22, 32]. Their data underlies the importance of pregnancy and placental mechanisms in driving crucial serotonin production during development. During the postpartum period, maternal serotonin is likewise critical to caregiving and attachment behaviors, which also shape offspring neurodevelopment [25]. Clearly, dysregulation of serotonin in pregnancy at multiple levels can lead to pathologic states.

4. Serotonin dysregulation in preeclampsia

Serotonin dysregulation in maternal circulation, placenta, and cord blood is well documented in clinical preeclampsia (Fig. 1). Broadly speaking, increased tryptophan

availability, decreased kynurenine pathway activity (e.g., decreased synthesis by indoleamine 2,3 dioxygenase), and decreased degradation of serotonin by MAOA drives increased free 5-HT in maternal circulation in preeclampsia [12, 13, 33–37] and gestational hypertension [38, 39]. As in circulation, IDO [33, 34] and kynurenine are decreased in the preeclamptic placenta; unlike in maternal circulation, placental tryptophan is decreased [33]. Transcriptomics further suggest significant preeclampsia impacts on tryptophan metabolism gene networks in the placenta [26]. Placental serotonin is significantly increased (up to 9.6-fold) in preeclampsia [37] in a dose-responsive manner, with serotonin levels positively correlated with blood pressure and disease severity [8]. Given that *in situ* quantitation suggests significant serotonin decrements with preeclampsia in placental villus syncytiotrophoblasts [46], where 5-HT is synthesized, extracellular serotonin is likely driving placental hyperserotonemia in preeclampsia, as in maternal circulation.

While previous studies are under-powered, warranting replication, reports generally demonstrate increased serotonin and impaired serotonin catabolism by MAOA across maternal and placental domains in preeclampsia [8, 40, 41]. For instance, placental serotonin is significantly increased from 174.01 ± 9.74 ng/gm to 324.16 ± 15.34 ng/gm in one study of preeclamptic women, while MAOA activity (units/mg protein localized to the mitochondrial fraction) is decreased, from 33.93 ± 2.97 to 19.43 ± 2.03 units [8]. However, serotonin transporter expression and function at the placental interface remains unchanged [41–43]. Carrasco *et al.* reported equivalent levels of serotonin uptake by placental syncytiotrophoblasts from normal and preeclamptic subjects but increased serotonin metabolism in preeclamptic placental homogenate [41]. These results demonstrate that increased plasma-free serotonin in preeclampsia is likely due to reduced MAOA activity rather than reduced serotonin uptake by placental cells in preeclamptic patients.

Despite conclusions around maternal-placental serotonin function, direct examination of cord blood is required to better understand serotonin levels and metabolism in fetal domains. Indeed, whole cord blood 5-HT is increased in severe preeclampsia [44], while 5-HT catabolism by MAOA is impaired in preeclamptic umbilical artery samples [44, 45]. Examination of enzymatic activity and bound versus free serotonin remain necessary.

While existing findings paint a somewhat mixed view of fetal conditions, what is clear is that serotonin supplies to the fetus are increased in preeclampsia, as in maternal circulation and placenta, while serotonin degradation is decreased. A clearer understanding of umbilical vein versus artery supplies will be important for clarifying disruptions to arterial supplies, a read-out of fetal metabolism and immunologic response, or venous supplies, a read-out of placental function. These details are important in understanding the relationship of serotonin-immune interaction in disease states such as preeclampsia.

5. Mechanisms of dysregulated serotonin-immune interaction in preeclampsia

As with serotonin biology dysfunction, immune biology dysfunction is also well-documented in preeclampsia, as has been expertly reviewed elsewhere [10, 47–49]. Broadly, preeclampsia can be understood as a pro-inflammatory condition in which the

maternal response to the immunologic challenge of pregnancy is allogenic placental-fetal rejection. Serotonin is strongly implicated in the pro-inflammatory processes that occur in preeclampsia and may thus contribute to the immune pathology seen in preeclampsia. Serotonin-immune interaction disruptions may drive preeclamptic abnormalities in kynurenine pathway metabolism, T cell function, and cytokine production, as we review here (Fig. 2).

5.1. IDO-mediated metabolism in preeclampsia

One of the mechanisms by which serotonin and inflammatory systems interact is via the kynurenine pathway. Pro-inflammatory cytokines such as IFN-γ, the principal effector of IDO [50], alter IDO activation, thereby limiting tryptophan availability for kynurenine synthesis and driving serotonin synthesis. In the IDO knock-out animal, impacts of pro-inflammation on serotonin synthesis are absent [51]. Decreased serotonin-to-tryptophan in the context of pro-inflammation may restore inflammatory homeostasis, as serotonin alters the inflammatory milieu [9]. Notably, the IDO knock-out model also recapitulates essential features of clinical preeclampsia, including pregnancy-induced hypertension and proteinuria, as well as intrauterine growth restriction [13]. IDO is also dysregulated in clinical preeclampsia (Fig. 2b), as discussed above and may serve as a key switch in serotonin-immune signaling, which is necessary for the maintenance of balanced immunoreactivity and a healthy pregnancy. Dysregulation of this immunogenic switch may result in inadequate inflammatory mediation, as occurs in preeclampsia.

5.2. Immune cells and serotonin interaction in preeclampsia

Interactions between serotonin and the immune system are enabled by the cellular and molecular profiles of immune cells. Platelets are the primary source of serotonin to immune cells such as macrophages and monocytes, which take up serotonin. Many immune cells, including monocytes, mast cells, and T cells, also have the molecular machinery required to synthesize and catabolize serotonin [9]. Furthermore, seminal early work found that exogenous systemic serotonin suppresses inflammatory processes, including IgM and IgG antibody production, via peripheral and not CNS mechanisms [52]. Serotonin release from mast cells, basophils, or platelets, which is triggered by injury or inflammation, can initiate immune cascades and processes including HTR_{1A}-mediated chemotaxis (e.g. for eosinophils, dendritic cells, mast cells) and cellular phagocytosis [53].

Data also support the conclusion that serotonin signaling is necessary for normal dendritic cell function; Li et al. demonstrated decreased IL-12 production by dendritic cells lacking TPH1, which was restored by serotonin stimulation. These authors also reported decreased CD4+ T cell production of IL-17 and IFN-γ after T cell priming by TPH1-deficient dendritic cells [54], further pointing to the functional significance of serotonin-immune cell interactions.

Serotonin-immune interactions in the context of other inflammatory diseases may inform an understanding of these dynamics in preeclampsia. For example, in inflammatory conditions such as asthma and arthritis, T cell function and cytokine production are modulated by serotonin, which is elevated as it is in preeclampsia [55]. *Ex vivo* studies of T cells

from patients with multiple sclerosis, an autoimmune disease, demonstrate that serotonin modulates T cell proliferation and pro-inflammatory cytokine release (e.g., IL-17), as well as regulatory T cell frequency [56]. T cell function may be modulated by serotonin via a number of mechanisms. Via one direct mechanism, serotonin stimulates T cells via receptors including HTR_7, driving T cell activation, differentiation, and cytokine release. In the context of increased tryptophan, suppression of T cell regulatory pathways necessary for fetal tolerance is impaired [57]. This mechanism may underlie pro-inflammatory disease processes in preeclampsia, in which tryptophan is increased. Collectively, these findings reveal direct impacts of serotonin on T cell behavior and function across pro-inflammatory conditions including preeclampsia.

5.3. Cytokine release and serotonin in preeclampsia

Serotonin is required for normative cytokine production and activation of inflammatory processes. Serotonin impacts acute and more chronic, reactive production of cytokines including IFN-γ, IL-1B, IL-8, IL-12, TNFα, IL-17, and IL-6 [9, 58]. Mice lacking TPH1 have decreased dendritic cell activation, cytokine production, and pro-inflammatory reactivity [54]. Serotonin antagonism in pro-inflammatory mouse models of heart disease and asthma decreases inflammation and improves outcomes [55], while SERT knockout mice have abnormal pro-inflammatory responses to immune perturbation [59]. These findings suggest that manipulations of the T cell serotonin response (e.g., via HTR_7 blockade) in the setting of preeclamptic hyperserotonemia may mediate inflammation-linked pathology in preeclampsia. However, to further clarify underlying mechanisms, there remains a need to examine how specific types of immune cells and transgenic manipulations of serotonin targets in these cells contribute to preeclampsia pathogenesis.

6. Additional serotonergic mechanisms in preeclampsia

Canonical serotonergic vascular mechanisms also interact with immune biology in ways which may explain elements of preeclampsia pathoetiology. Given that umbilical vessels lack direct innervation, vasoactive factors such as serotonin regulate umbilical smooth muscle and contractility [60]. Kynurenine is similarly vasoactive, with metabolism of tryptophan to kynurenine by IDO causing vascular relaxation and hypotension. This relaxation is exacerbated by IDO induction by pro-inflammation in endothelial cells [61].

Serotonin and serotonin synthesis pathways play essential roles in regulating blood flow, and thus immune cell trafficking, to/from the feto-placental unit. Vascular hyporeactivity to serotonin occurs in the uterine, placental, and other vessels of preeclamptic patients [62–64], and the peripheral blood flow response to serotonin infusion is blunted in preeclamptics relative to non-pregnant controls [65]. However, exogenous serotonin administered to venous chorionic rings from preeclamptic women reveals 1.7-fold increased sensitivity to 5-HT, as well as earlier instantiation of rhythmic contractions of a higher amplitude, relative to healthy control rings [66]. Collateral vessels, which have enhanced vasoreactivity to serotonin [67], may also play a role in serotonin response heterogeneity. Preeclampsia results in placental ischemia and hypoxia [68], particularly in late gestation, conditions that drive collateral vessel formation [69]. Little is known about the impacts of serotonin on

lymphatic trafficking. Chen et al. reported much lower levels of serotonin in lymph than in portal blood [70], though additional studies are needed to clarify the potential impact of serotonin on immune cell trafficking via lymphatic vessels.

Mixed vasoreactivity findings may be driven by receptor expression variability across tissues and pathological states. For instance, preeclampsia is associated with increased vascular expression of HTR_{1B} and $HTR_{1D,}$ which, when agonized, lead to vasoconstriction [71, 72]. In the preeclamptic placenta, HTR_7 expression, which regulates smooth muscle relaxation [73], is increased 8-fold relative to control placenta [74]. These various receptors have differing developmental roles—for example, HTR_{2A} is critical to placentation and trophoblast cell viability, migration, and invasion processes, as well as vasoconstriction, and may thus play more of a role in early than late placental vascular pathology in preeclampsia [75, 76]. Additionally, HTR_7 is a critical regulator of macrophage effector functions and brain development [77].

Platelets are critical players in mechanisms of inflammatory effector cell activation, delivering serotonin to circulating and resident immune cells at sites of inflammation. The body's largest pool of circulating serotonin exists in dense granules stored in blood platelets, which, upon aggregation, induce serotonin release into local vasculature via calcium-dependent signaling cascades. Endothelial cell damage in preeclampsia promotes platelet aggregation and thus serotonin release and vasoconstriction, which in smooth muscle and in the human uterine artery is largely HTR_2-mediated [78]. This exacerbated serotonin release by platelets alters local vascular function directly, by stimulating vascular smooth muscle contraction and endothelial cell activation, and indirectly, by potentiating other vasoactive factors (e.g., thromboxane A2, prostaglandins, etc.) and adrenergic innervation of smooth muscle, causing vasodilation [19, 79].

Increased platelet aggregation and serotonin release feeds-forward to further increase serotonin release via platelet HTR_2 mechanisms. Furthermore, prostaglandin up-regulation and thus renin-angiotensin activation in umbilical and placenta vessels by serotonin mechanisms, which might otherwise compensate for impaired placental perfusion, fails due to loss of HTR_1 in damaged vessels [12, 80]. These conditions collectively promote vasoconstriction by HTR_2-mediated mechanisms, which are largely unopposed by HTR_1-mediated vasodilation in damaged vessels [81]. Unchecked, preeclamptic hyperserotonemia thus drives further endothelial cell damage, platelet aggregation, and ultimately turbulent blood flow and microvascular damage in the placenta and systemically, phenomena that further increase inflammation.

In HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, a severe variant of preeclampsia, platelet count decreases while the neutrophil-to-lymphocyte ratio increases due to increased neutrophils, indicative of circulating immune dysfunction [82]. Platelets are also critical to dendritic and natural killer cell function; platelet deficits in HELLP syndrome may thus contribute to deficient immunomodulation [83].

Hyperserotonemia-related platelet aggregation and resulting vasoconstriction may also drive placental spiral artery pathology, including the inflammatory, invasion, and remodeling

deficits which are hallmarks of preeclampsia [84]. Serotonin also regulates trophoblast viability, though in excess, as in SERT-deficient animals [28, 76], it also causes impaired trophoblast proliferation and cell death [28]. This cellular dysfunction and death can further drive local inflammation. Hyperserotonemia may therefore interact both directly (e.g., via vasoactive mechanisms) and indirectly (e.g., via inflammatory mechanisms) with placental vascular function to drive placental dysfunction in preeclampsia.

In addition to platelet and broader vascular mechanisms, serotonin may also interact with maternal inflammatory mechanisms to drive preeclampsia via CNS mechanisms. Hyperserotonemia can cause blood-brain barrier dysfunction, brain edema, and neurotoxicity, likely via oxidative stress and NO-related pathways [85]. These pathologies may underlie susceptibility to eclamptic seizure and PRES. Critically, serotonin does not cross the blood brain barrier and as such peripheral and central serotonin systems are generally independent in the intact system. However, peripheral inflammation can trigger central dorsal raphe serotonin activity and serotonin release [18], demonstrating systemic links between peripheral inflammation and CNS serotonergic tone. Underlying mechanisms, whether direct via the nervous system or indirect via messenger cascades, remain unclear. One possibility is that vagus nerve tone, which is diminished with sympathetic activation under conditions of stress or pro-inflammation, communicates from the periphery to the CNS to regulate serotonin transmission. CNS inflammatory cells such as microglia also release inflammatory factors in response to perturbation, changing local tryptophan metabolism dynamics [86]. How these dynamics interact with broader preeclampsia physiology remains unclear, however.

Also in the brain, serotonin fibers from the raphe directly synapse onto vasopressin (AVP) neurons in the supraoptic nucleus and nucleus circularis, which express HTR_{1B}. Vasopressin (AVP), a hormone synthesized in the hypothalamus, regulates systemic blood pressure and water reabsorption by the kidney. It is also elevated, as early as the first trimester, in women who develop preeclampsia [87], and chronic infusion of AVP into pregnant mice is sufficient to causes key phenotypes of preeclampsia (e.g., gestational hypertension, renal glomerular endotheliosis, proteinuria, fetal growth restriction, pro-inflammation, and placental pathology and oxidative stress) [87, 88]. Serotonergic neurons inhibit downstream vasopressin neurons, which project to the anterior hypothalamus and elsewhere. These links are not unidirectional—amygdala AVP projections to serotonergic neurons in the dorsal raphe via glutamate intermediates [89] also stimulate serotonergic neurons via HTR_{1A} [90]. Increased CNS AVP in the context of preeclampsia may therefore facilitate further hyperserotonemia. This functional neuroanatomy provides a known biological substrate for direct CNS interaction between AVP, a key regulator of preeclampsia biology and clinically-relevant preeclampsia biomarker [87, 88], and serotonin. The role of brain immune cells, such as microglia, in these circuits remains unclear. There is cause to predict, however, that systemic inflammation, as in preeclampsia, might lead to microglia activation, which alters the formation of neural systems [91].

6.1. Unanswered mechanistic questions

Despite significant growth in scientific understanding of the mechanisms underlying serotonin dysregulation in preeclampsia, gaps remain. Animal models for the study of preeclampsia (e.g., the AVP model, RUPP model, etc.) will serve a particularly important role in addressing these mechanistic gaps [87, 92] in determining whether serotonin dysregulation is necessary and/or sufficient to achieve specific preeclampsia endophenotypes.

Future studies may target intracellular signaling cascades. Given that most serotonin receptors are G-protein coupled, intracellular serotonin signaling is reliant on regulators of G-protein signaling (RGS), including RGS2. RGS2, which is expressed in reproductive tissues and immune cells [93] and is an early response gene in activated T lymphocytes [94], regulates intracellular serotonin signaling via Gαq [95] and is an endogenous inhibitor of AVP signaling [3]. RGS2 overexpression drives aggressive behavior in mice, a phenotype mediated by increased serotonergic tone and neurotransmission in the dorsal raphe and ventrolateral hypothalamus [96]. Decreased RGS2 expression, meanwhile, decreases $HTR_{1A,B}$ expression in the raphe, increases anxiety- and depressive-like behavior, and decreases sociability [97]. In humans, *RGS2* variants predict social anxiety and clinical serotonergic drug response [98] and are associated with preeclampsia [99]. In addition to serotonergic behavioral deficits, RGS2-deficiency is further associated with reduced T cell proliferation and IL-2 production [100]. Despite these roles at the crux of serotonin-immune and neurobiological mechanisms, there remains much to be understood about the precise role of RGS2 in regulating hyperserotonemia physiology in preeclampsia.

The potential role of genetics in specific aspects of serotonin-immune signaling is also unclear. Genes encoding transporters at the placenta, for example, may encode placental response potential to drugs and endogenous factors such as serotonin cascade molecules and immune factors [101]. Some work has indicated that polymorphic variants of *HTR2A* and *SLC6A4* are not associated with hypertension in pregnancy [102], though additional targets and gene-by-environment interactions remain unexplored.

Epigenetic and posttranslational modifications may also link serotonin dysregulation to immune dysfunction in preeclampsia. This is particularly relevant to SERT, as its function, kinetics, and membrane insertion are regulated by post-translational modifications, which may be altered in preeclampsia [103]. Recent work has also demonstrated that serotonin directly targets histones via post-translational “serotonylation,” a process by which serotonin alters recruitment of chromatin-remodeling complexes and transcription factors [104]. Extravesicular serotonylation in the cell nucleus and soma may explain gene expression changes in response to serotonin dysregulation in immune and other cells.

7. Conclusions

Despite causing significant maternal-fetal morbidity and mortality, the pathoetiology and clinical interventions for preeclampsia are poorly developed, with treatment presently limited to delivery. However, decades of research on serotonin and immunologic dysfunction offer some significant insights to move the field forward. Given the significant bi-directional

clinical association between psychiatric disorders and preeclampsia, consideration of serotonin-related therapy for either/both may prove to alter clinical outcomes of these common co-morbidities in pregnancy. As we discuss here, preeclamptic hyperserotonemia is likely a significant driver of immune dysfunction in preeclampsia, interacting with placental, vascular, and platelet pathology to drive maternal disease (Fig. 2a). Further investigation of serotonin-immune interactions in preeclampsia may offer some hope for the many women who succumb to preeclampsia annually, as well as their clinical providers, families, and children.

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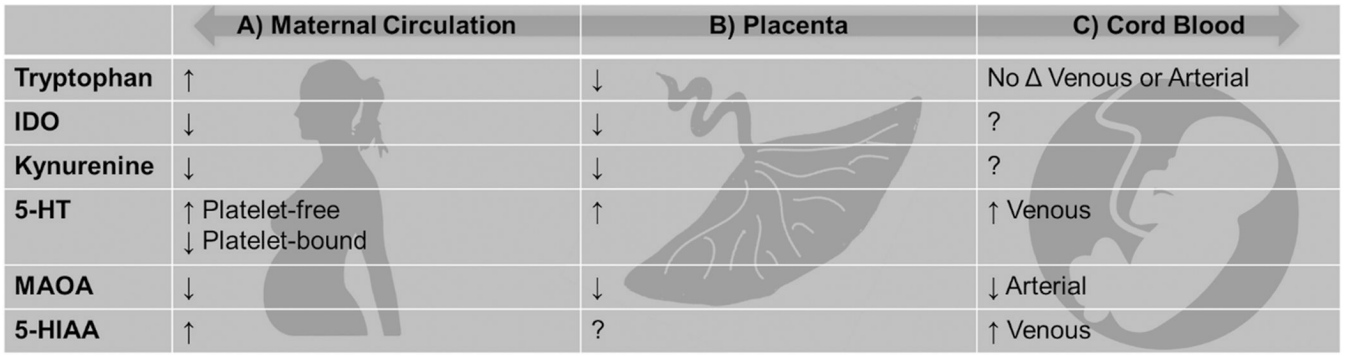

Fig. 1. Serotonin is dysregulated across maternal, placenta, and fetal domains in preeclampsia.

A) Plasma tryptophan is increased in preeclampsia, while the kynurenine-to-tryptophan ratio is decreased [12] in some but not all patients [33] and kynurenine synthesis by indoleamine 2,3 dioxygenase is decreased [13, 34]. Increased tryptophan ultimately increases maternal plasma 5-HT in preeclampsia [35–37] and gestational hypertension [38, 39], though whole serum 5-HT is decreased in preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome. Decreased MAOA in plasma and platelets further leads to blunted production and urine excretion of 5-HIAA [35]. In the preeclamptic placenta, tryptophan [33], IDO [33, 34], and kynurenine [33] are decreased, demonstrating tryptophan preference for the serotonin over kynurenine pathway. **B)** Placental serotonin is significantly increased in preeclampsia [37], increases which are positively correlated with blood pressure and disease severity [8]. Placental MAOA (protein and enzymatic activity) is decreased in preeclampsia, possibly contributing to increased placental serotonin [40], with greater MAOA deficits associated with more severe disease (preeclampsia versus eclampsia) [8]. Decreased serotonin catabolism in placental syncytiotrophoblasts also contributes to increased placental serotonin [41]. Despite increased serotonin in preeclampsia, fetal serotonin transport may be unaffected. Placental serotonin transporter (SERT) gene (*SLC6A4*) and protein expression [42, 43], as well as functional 5-HT transport by syncytiotrophoblasts [41], are unchanged in preeclampsia. **C)** Umbilical artery or vein tryptophan is unchanged in preeclampsia, though whole cord blood 5-HT is increased in severe cases while 5-HIAA-to-5-HT ratio is decreased [44]. Conversely, umbilical vein 5-HT and 5-HIAA are decreased in gestational hypertension [38], likely due to impaired 5-HT catabolism by MAOA [44, 45]. 5-HIAA is increased in umbilical cord blood in both mild disease (gestational hypertension) [38] and in severe preeclampsia [44]

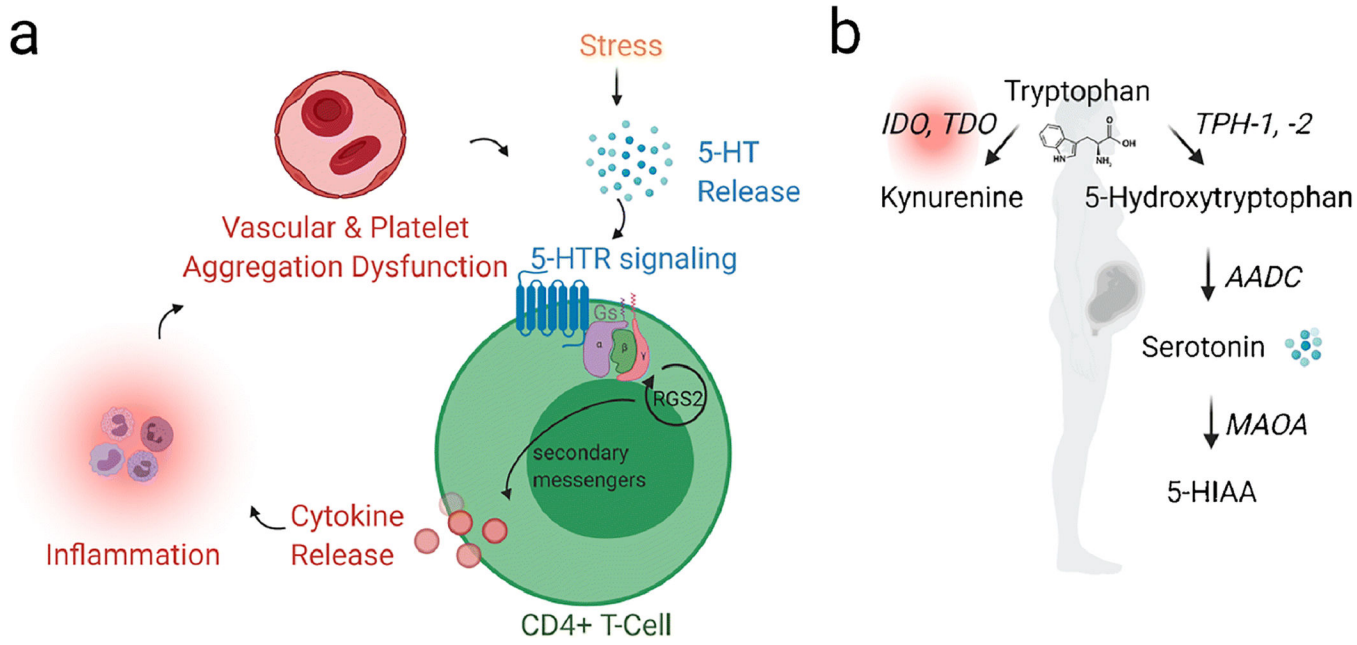

Fig. 2. Hypothesized mechanism by which hyperserotonemia drives pro-inflammation in preeclampsia.

A) Persistent serotonergic disruptions in the context of preeclampsia—namely, hyperserotonemia across maternal, placental, and fetal domains—may be due to initiating factors such as physiologic stress. Serotonin binds T cells and initiates downstream cascades through serotonin receptors (5-HTR), which are G protein-coupled receptors. Regulators of G-protein signaling (RGS), such as RGS2, modulate intracellular cascades and therefore inflammatory protein production. Inflammatory proteins including cytokines have impacts on vascular and platelet function and can contribute to further dysfunction in the setting of preeclampsia. Vascular and platelet dysfunction also feed-forward to increase circulating serotonin and signaling at the level of the T cell. B) Decreased maternal and placental IDO expression, which is modulated by inflammation, pushes tryptophan towards increased serotonin production in preeclampsia