Vasopressin: the missing link for preeclampsia?

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PREECLAMPSIA is a disease of pregnancy annually affecting more than 6.5 million pregnancies worldwide characterized by hypertension, multiorgan dysregulation, and maternal-fetal mortality (22). Although the ultimate etiology of preeclampsia is still unknown, the concepts that 1) the fetal-placental unit represents an allogenic, transplanted tissue to the mother, and 2) that preeclampsia is initiated through a rejection-type reaction have been forwarded by leaders in the field based on significant epidemiological and basic science data (13, 15, 17, 21). Dysregulation of the normal maternal immune tolerance to the fetus has been implicated as an initiator, as the immunological changes observed in the placenta of preeclamptic pregnancies is very similar to those observed in rejected organ transplants (13). Complementary studies of immunological tolerance also support these concepts. In humans, a 30% decreased risk of preeclampsia is observed with couples having a second child compared with those who change paternity in the second pregnancy (7, 24). Mouse models demonstrate that the disruption of immune tolerance mechanisms is sufficient to replicate human preeclampsia phenotypes (8, 19). Resulting immune rejection reactions are thought to lead to poor placental implantation, poor placental perfusion, and, by mechanisms not yet clearly delineated, the clinical symptoms of preeclampsia (15).

Numerous factors have been implicated in the midgestational progression of preeclampsia, including cytokines like tumor necrosis factor-α, anti-angiogenic factors like soluble fms-like tyrosine kinase, and microparticles secreted by the syncytiotrophoblasts (9, 15). Unfortunately, although these mediators appear to be mechanistically involved in the pathogenesis of preeclampsia (and may represent therapeutic targets to treat the disorder), the dysregulation of these markers in maternal plasma is observed only shortly before the onset of clinical symptoms near the end of the second trimester of gestation (11). The delay between the initial (presumably immune rejection/poor implantation) event and the activation of other immune/angiogenic mecha-
nisms to elicit the clinical presentation of preeclampsia implies the existence of another unidentified mechanism to link these processes across the first trimester. That uterine artery dysfunction appears already in the first trimester (14) supports the concept that a vascular modulator may be involved in this “missing link” mechanism.

**Role for Arginine Vasopressin**

Arginine vasopressin (AVP) is a vascular modulator, and a role for AVP in normal and abnormal pregnancies has been considered since at least the early 1950s (10). Elevated AVP secretion during preeclampsia was only recently documented, though, after assays allowing easy assessment of copeptin (a stable protein by-product of AVP synthesis and release) became commercially available (12). In 2011, Zulfikaroglu et al. (25) described for the first time an association between preeclampsia and elevated copeptin levels in the third trimester of pregnancy after symptoms were already present (25). In 2012, Foda and Abdel Aal (2) confirmed in a small cohort that at parturition (well after the onset of symptoms), copeptin is elevated in preeclamptic pregnancies. In 2014, our group (20) demonstrated that copeptin levels are elevated already by the sixth week of gestation, well ahead of the onset of clinical symptoms of preeclampsia. Later in 2014, Yeung et al. (23) also demonstrated in a large and racially/ethnically diverse population that copeptin is indeed elevated during preeclampsia in the second trimester (again, before the onset of clinical symptoms). Collectively, these studies have independently confirmed an increase in copeptin (and by extension, AVP secretion) during, and preceding, preeclampsia in various subject populations that span the globe.

**Mechanistic Links**

We recently demonstrated that chronic low-dose infusion of AVP into wild-type mice throughout gestation is sufficient to induce all of the cardinal maternal and fetal symptoms of preeclampsia (20), and ongoing work is aimed at optimizing the model and identifying the receptors involved. In humans, four major classes of mechanisms have been implicated in the midgestational pathogenesis of preeclampsia: vascular, immune, angiogenic, and renal. In the nonpregnant state, vasopressin has been associated with each of these mechanisms through actions at its four receptor subtypes (V1A, V1B, V2, and CUL5) (1, 3, 4, 16, 18). Furthermore, the rs4606 single nucleotide polymorphism in the regulator of G protein signaling-2 (RGS2) gene, which acts as an endogenous brake on AVP signaling, results in decreased RGS2 function and correlates with human preeclampsia and its sequelae (5, 6). Thus AVP is sufficient to initiate preeclampsia symptoms in mice, and its receptors are known to interact with the identified major midgestational mechanisms of preeclampsia in human patients.

**Hypothesis and Questions Moving Forward**

We now know that 1) AVP hypersecretion precedes preeclampsia symptoms, 2) AVP infusion is sufficient to initiate...
these symptoms, and 3) in the nonpregnant state AVP interacts with all of the mechanisms implicated in midgestational preeclampsia. We therefore hypothesize that AVP may represent a critical mechanistic link in the early pathogenesis of this disorder (Fig. 1).

We propose five groupings of ongoing questions: 1) Is copeptin a useful biomarker for the very-early pregnancy diagnosis of preeclampsia in all populations? What other factors (history of preeclampsia, comorbidities) alter this relationship? 2) Why is AVP secretion increased during preeclampsia? Is this solely from the brain? Does poor placenta stimulate AVP? If so, does it work via an osmotic or nonosmotic stimulus? Does inhibition of AVP secretion prevent preeclampsia? 3) Where, and through which receptors, does AVP act to initiate the phenotypes of preeclampsia? Are effects of AVP (vascular, immune, angiogenic, renal) the result of a single common mechanism, or through distinct mechanisms? 4) When does AVP act to initiate preeclampsia phenotypes? When would interference with AVP signaling be therapeutically beneficial? 5) Does the copeptin peptide itself have any pathological effect during pregnancy, either through a receptor-based mechanism, or via an immune response?

In summary, AVP and copeptin may represent the “missing link” between poor implantation and other later-appearing and well-recognized mechanisms of the pathogenesis of preeclampsia. We propose that new, extremely early gestation diagnostics to predict the development of preeclampsia will likely come from increased understanding of the regulation and role of AVP in this disorder. Preventative, and possibly corrective, therapeutics for preeclampsia may also therefore result from increased understanding of the actions of AVP and copeptin during early pregnancy.

REFERENCES


