Agonistic Autoantibodies to Angiotensin II Type I Receptor Contributes Partly to Placental Ischemia-Induced Cerebrovascular Abnormalities

Junie Paula Warrington¹, Fan Fan¹, Babbette B. LaMarca¹, Ralf Dechend², Gerd Wallukat², Richard J. Roman¹, Heather A. Drummond¹, Joey P. Granger¹, Michael J. Ryan¹

¹University of Mississippi Medical Center
²Experimental and Clinical Research Center, Berlin, Germany

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Preeclampsia

• Occurs in 5-8% of pregnancies in the U.S. and 15% of African American pregnancies

• Characterized by new onset hypertension (≥140/90) AND proteinuria OR in absence of proteinuria, any of:
  - Low platelet (< 100,000 per µL)
  - Renal insufficiency – serum creatinine > 1.1 mg/dL
  - Impaired liver function
  - Pulmonary edema
  - Cerebral or visual symptoms

Guidelines from: Hypertension in Pregnancy Task Force; The American College of Obstetricians & Gynecologists; 2013
Link between placental ischemia and maternal vascular dysfunction

- Placental Ischemia
- Release of Placental Factors
  - sFlt
  - TNFα
  - AT1-AA
- Maternal Endothelial Cell Activation
  - ↓NO
  - ↑ET-1
- Abnormal Spiral Artery Remodeling
- Vascular Dysfunction
- Maternal endothelial cells
The effects of these placental factors on cerebrovascular function in preeclampsia are not well established.
Preeclampsia is associated with cerebrovascular complications

• ~40% of preeclampsia/eclampsia related deaths are due to cerebrovascular events (stroke and edema).

• Patients present with neurological symptoms such as headaches, blurred vision, nausea, drowsiness, and seizures (eclampsia).

• Preeclampsia patients have higher risk of developing stroke during pregnancy and the postpartum year

• **While there is strong evidence for cerebrovascular abnormalities in preeclampsia, the underlying mechanisms remain unclear**
Cerebral Blood Flow (CBF) autoregulation in preeclampsia
Clinical studies suggest that CBF autoregulation is impaired in preeclampsia

- Women with pre/eclampsia have impaired dynamic cerebral autoregulation.
  
  Obstet Gynecol, 2013; 122(5):1064-9
  Cerebrovasc Dis, 2006, 22:204-208

- Pregnant women with preeclampsia in a previous pregnancy have poorer dynamic CBF autoregulation.
  
Cerebral Blood Flow Autoregulatory Index

Warrington JP, et al.; *Physiological Reports*, 2014; 2(8)
Placental ischemia induces cerebral edema in the anterior brain

Warrington JP, et al.; *Physiological Reports*, 2014; 2(8)
Placental ischemia increases BBB permeability to Evans blue dye

Cerebrum

Anterior Cerebrum

Warrington JP, et al.; Physiological Reports, 2014; 2(8)
Does AT1 receptor activation by AT1-AA contribute to cerebral edema, increased BBB permeability, and impaired CBF autoregulation?
AT1-AA and AT1R activation are associated with preeclampsia

- AT1-AA is an agonistic autoantibody that activates the AT1 receptor

- AT1-AA is increased in preeclamptic women
  
  *J Soc Gynecol Investigation; 2003; 10(2):82-93*

- AT1-AA is increased in placental ischemic rats
  
  *Hypertension; 2008; 52(6):1168-72*

- Infusion of AT1-AA into pregnant rats induces vascular dysfunction and hypertension
  
  *Hypertension; 2009: 54(4):905-9*
Does blockade of the AT1 receptor improve cerebral edema and BBB permeability?

- Blockade of the AT1 receptor using Losartan attenuates placental ischemia-induced increases in blood pressure.

  *Hypertension*, 2008; 52(6):1168-72
  *Physiological Reports*, 2015; 3(20)
Reduced Uterine Perfusion Pressure (RUPP) model of placental ischemia

AT1R blockade reduces mean arterial pressure in placental ischemic rats
AT1R blockade prevents increases in brain water content in placental ischemic rats
AT1R blockade prevents increases in BBB permeability in placental ischemic rats
While blocking the AT1R improved cerebrovascular abnormalities, it is not known whether AT1-AA infusion into normal pregnant rats leads to impaired CBF autoregulation.
AT1-AA infusion increases mean arterial pressure in pregnant rats

Day 11: Arrival
Day 12: Mini-pumps (1:40)
Day 18: Carotid Surgery
Day 19: BP & Harvest

![Graph showing mean arterial pressure (MAP) comparison between NP and NP + AT1-AA]
CBF autoregulation methods

Anesthetized:
- Ketamine (30 mg/kg, i.m)
- Inactin (50 mg/kg, i.p)

Continuous monitoring MAP, exhaled CO₂, body temperature

Graded phenylephrine Infusion

Arterial PCO₂ maintained at 35 +/- 2 mmHg.

CBF: Laser Doppler Flowmetry Through cranial window
AT1-AA infusion in pregnant rats leads to impaired CBF autoregulation
Summary

• AT1R blockade:
  • Reduces cerebral edema associated with placental ischemia
  • Prevents placental ischemia-induced increases in BBB permeability

• AT1-AA Infusion:
  • Impairs CBF autoregulation
Perspectives

Increased AT1-AA and activation of the AT1 receptor play a significant role in placental ischemia-induced cerebrovascular complications associated with preeclampsia.
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