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Revisiting adrenomedullin in pre-eclampsia

By Michael J. Haas, Senior Writer

A North Carolina team has shown that fetal deficiency in adrenomedullin resulted in mouse placental abnormalities similar to those found in pre-eclampsia, thereby underscoring adrenomedullin's potential as a marker for the indication.[1] Future studies will need to replicate the findings in other animal models and determine whether low adrenomedullin levels are found in all pre-eclampsia cases or just a subset.

Pre-eclampsia involves hypertension and proteinuria and occurs in about 5% of pregnant women. The condition can lead to life-threatening seizures (eclampsia). Pre-eclampsia is thought to involve insufficient remodeling of maternal uterine spiral arteries, which are part of the uteroplacental vasculature that changes to accommodate the need for low-resistance, high-capacity blood flow to the fetus.

The condition is usually not diagnosed until the second or third trimester of pregnancy—long after key steps in placental development have occurred.

> **"Pre-eclampsia is not a single condition with a single etiology. It is unlikely that adrenomedullin or any other single factor is responsible for pre-eclampsia."**
>
> ***—C. David Adair, Glenveigh Medical LLC***

The standard of care for managing the condition includes antihypertensive drugs, magnesium sulfate (to prevent seizures) and steroids to promote fetal lung development before delivery. The only effective treatment is delivery of the baby by induced labor or Caesarean section.

The precise pathogenic mechanisms of pre-eclampsia are not well understood, although prior studies have shown that signaling between the vasodilatory peptide adrenomedullin (ADM; AM) and its receptor, calcitonin receptor-like (CRLR; CALCRL), has a role in placental development[2,3] and have suggested an association between low maternal serum levels of ADM and pre-eclampsia.[4]

Data linking serum ADM levels to pre-eclampsia have been inconclusive because of technical limitations in handling and measuring the peptide.

"Adrenomedullin is very sticky and adheres readily to plastic, glass and other lab equipment, and it has a very short half-life," Kathleen Caron told *SciBX*.

Caron is an associate professor of cell biology and physiology and assistant dean for research at **The University of North Carolina at Chapel Hill School of Medicine**.

Caron has long postulated that ADM has an important role in pre-eclampsia. In 2006 and 2008, she led teams that reported that pregnant, *Adm* heterozygous knockout mice showed abnormal implantation of fertilized eggs, abnormal placental development and restrictions to fetal growth that were eventually lethal.[5,6]

However, the phenotypes observed in those studies confirmed a role for maternal Adm in pregnancy but "were not quite what I would consider pre-eclamptic," she said.

Thus, for the new study, Caron's team speculated that complete Adm deficiency in the mouse fetus might contribute to a pre-eclamptic phenotype in the placenta and thus identify the peptide as a potential marker or therapeutic target in the indication.

The team first crossed *Adm* heterozygous knockout mice to generate offspring that included *Adm* homozygous knockout fetuses. Compared with their wild-type littermates, homozygous knockout fetuses showed two key features of human pre-eclampsia: decreased remodeling of placental vasculature and decreased placental recruitment of the maternal uterine NK cells required for that remodeling.

The team saw similar reductions in vascular remodeling and maternal uterine NK cell recruitment in *Calcrl* homozygous knockout fetuses.

Placentas of mouse fetuses that overexpressed Adm showed normal vascular remodeling and a 30% increase in recruitment of maternal uterine NK cells compared with those of wild-type littermates.

Finally, maternal uterine NK cells from wild-type mice treated with Adm showed increased secretion of cytokines, chemokines and matrix metalloproteases involved in remodeling of placental vasculature compared with untreated cells.

Taken together, the results highlighted a pathogenic role for ADM in pre-eclampsia and the need to re-evaluate the target as a marker for the condition, the team wrote in its report in *The Journal of Clinical Investigation*.

Caron added, "The importance of the baby and fetal tissue to pre-eclampsia has been widely assumed, but few—if any—fetal-derived factors have been identified with such a clear correlation to the pathophysiological manifestation of pre-eclampsia as adrenomedullin."

Caron's team also included researchers from **The University of North Carolina at Chapel Hill** and **Duke University Medical Center** (DUMC).

"This study broadens understanding of the early development of the fetus and placenta and, by explaining some placental features of the disease, confirms that adrenomedullin seems to play a role in pre-eclampsia," said C. David Adair. "It also raises new questions to investigate."

Adair is founder, chairman and CSO of **Glenveigh Medical LLC** and vice chair of obstetrics and gynecology at **The University of Tennessee College of Medicine Chattanooga**.

One of those new questions, he said, is whether the findings in mice are relevant to human pre-eclampsia. He noted that in the team's

experiments, "none of the pregnant females developed the hypertension and proteinuria associated with pre-eclampsia."

In the *JCI* paper, the team wrote that because only one-quarter of the fetuses in a pregnant female were *Adm* homozygous knockouts—all of which died and were reabsorbed at mid-gestation—it was "unlikely that a minority of placentas could induce the presentation of overt maternal pre-eclampsia early in gestation."

Adair said that the explanation is plausible, but he still thinks mice might not make the best models for pre-eclampsia because they have a different type of placenta from that of humans.

Instead, he wanted to see the findings replicated in guinea pigs, whose placental type is more similar to that of humans. However, he acknowledged that pregnant guinea pigs would also carry a minority of *Adm* homozygous knockout fetuses in each litter and so might not develop overt pre-eclampsia.

"The only animals that have single offspring and a placenta comparable to humans are primates, but these are challenging and expensive to use as models for any disease," he said. "There is just not a good animal model for pre-eclampsia."

Caron agreed that studying the *Adm* homozygous knockout phenotype in guinea pigs, nonhuman primates and other species could be useful. "But the drawback is that we do not yet have sophisticated and robust genetic engineering capabilities in these species," she said. "The process of spiral artery remodeling is actually well conserved between all of these species. So there is just as much to learn from studying a mouse as there is from studying any other animal—except maybe humans."

Going pro

If the *JCI* findings do translate into humans, Adair said that the results would be more likely to help diagnose a subset of pre-eclampsia cases rather than all of them.

"Pre-eclampsia is not a single condition with a single etiology," he said. "It is unlikely that adrenomedullin or any other single factor is responsible for pre-eclampsia."

To establish the subset of patients in which ADM might be a marker, the team "could test adrenomedullin in samples from a serum bank and look for correlations between it and abnormalities in placental samples," Adair said. "Or they could run an open-enrollment study in women who are 12–16 weeks pregnant—when we think pre-eclampsia begins—measure their adrenomedullin levels, then follow them over time to see which women develop pre-eclampsia."

Indeed, Caron said, the team now plans to study serum ADM as a marker of pre-eclampsia in pregnant women.

The group plans to use an antibody-based assay for pro-adrenomedullin (pro-AM) marketed by the Brahms GmbH subsidiary of **Thermo Fisher Scientific Inc.** as a research tool to diagnose acute myocardial infarction (MI), acute destabilized heart failure and lower respiratory tract infections. Pro-AM is a stable precursor of ADM, and its serum levels correlate closely with those of the peptide, Caron said.

The assay measures serum pro-AM more accurately and reliably than is possible for serum ADM, thereby allowing the team to determine how closely ADM correlates with pre-eclampsia and whether the peptide could be a prognostic or diagnostic marker of the condition in early pregnancy, she said.

She added, "I think that a reliable assay might allow detection of abnormally low levels of ADM as early as the first trimester."

Caron acknowledged that ADM might be a useful marker only for a subset of pre-eclampsia cases. "But the answer will depend on just how broadly adrenomedullin signaling is interconnected with other genetic factors and pathways in pre-eclampsia," she said. "We—and others—need to test these ideas in large trials."

She also said that her team and collaborators at DUMC have developed screening assays to identify small molecule CRLR agonists as potential therapies for pre-eclampsia.

The findings reported in *JCI* are unpatented and unlicensed. The *Adm* homozygous knockout mouse models are available for licensing, Caron said.

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