Am J Physiol Regul Integr Comp Physiol 294: R915–R916, 2008;
doi:10.1152/ajpregu.00018.2008.

ACE2 and ANG-(1-7) in the gravid uterus: the new players on the block

Jeffrey S. Gilbert, Babbette B. LaMarca, and Joey P. Granger

Department of Physiology and Biophysics and Center for Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, Mississippi

Submitted 9 January 2008; accepted in final form 10 January 2008

THERE HAS BEEN LONG-STANDING interest in the widely recognized role of the renin-angiotensin system (RAS) in electrolyte homeostasis and regulation of hemodynamics in both diseased and nondiseased states (5). While the role of the RAS in the long-term regulation of renal function and arterial pressure has been well defined, the importance of angiotensin peptides in tissues such as the reproductive organs has yet to be fully elucidated. Nevertheless, components of the RAS have been localized to both male and female reproductive tissues and are proposed to play several important roles ranging from ovulation and the acrosome reaction to regulation of uteroplacental blood flow during pregnancy (6, 10).

During normal pregnancy, plasma renin activity, and renin and ANG II concentrations are all increased, yet vascular responsiveness to ANG II paradoxically appears to be reduced (2, 6, 8). In contrast, during preeclampsia there appears to be a marked increase in the sensitivity to ANG II (2, 8), although the mechanisms underlying these observations remain unclear. Gaining a clearer picture of these enigmatic actions of ANG II during pregnancy has remained elusive; however, recent years have seen renewed interest in the role of the RAS in both gestational physiology and the pathophysiology of hypertensive pregnancies.

Recent findings have revealed several novel mechanisms by which the RAS might be involved in the pathophysiology of the hypertension in preeclampsia (2). These include activation and augmentation of signaling through the ANG II type-1 (AT_1) receptor either by heterodimerization with the bradykinin B_2 receptor (1) or stimulation via agonistic AT_1 autoantibodies (11). Another effect recently attributed to the AT_1 receptor, is stimulation of the soluble vascular endothelial growth factor receptor (sFlt-1) expression from trophoblast cells (12). While these findings provide evidence suggesting that the RAS via the AT_1 receptor could be a central mediator of several pathways in preeclampsia, the specific mechanisms underlying these observations still remain unknown.

The recent identification of an additional component of the RAS, ANG converting enzyme-2 (ACE2) (9), has also furthered interest in the potential roles of the ANG peptides in developmental and gestational physiology. The presence of ACE2 in reproductive tissues provides a potential major pathway for the production of ANG-(1-7), a peptide that generally evokes antagonistic effects with respect to ANG II. While ANG-(1-7) has been recognized as a biologically active RAS peptide for some time, the endogenous receptor that it primarily acts through (Mas) has only been recently identified (7). In light of these recent additions to the RAS family, the role of the ANG peptides in gestational biology and the hypertension associated with preeclampsia will undoubtedly be modified as numerous questions remain unanswered. Are the new players, ACE2 and ANG-(1-7), expressed in a fashion consistent with possessing a role in reproduction? If so, what sort of role? Is ANG-(1-7) an important component of paradoxical vascular reactivity of ANG II during pregnancy? Is ACE2 an important regulator of the balance between the systemic and uteroplacental RAS during pregnancy? Does reduced uterine perfusion have an effect on the uteroplacental expression of ACE2 and ANG-(1-7)?

The recent article by Neves et al. (4) provides important initial observations regarding the temporal and spatial regulation of ANG-(1-7) and ACE2 in the rat uterus during early and late gestation that may provide insights to help unravel unanswered questions about the enigmatic actions of ANG II during pregnancy. Although it remains unclear what role ACE2 and ANG-(1-7) play across the term of gestation, the author's findings suggest several interesting possibilities. During early gestation, the reported localization of ACE2 and ANG-(1-7) (4) suggest that, in addition to possibly playing a role in implantation, the RAS may also be important in the regulation or composition of uterine milk, which is important to early embryonic development and survival. Additionally, Neves et al. (4) hypothesize that ACE2 and ANG-(1-7) participate in the regulation of uteroplacental blood flow during late gestation, a concept largely supported by their findings. To address the issue of whether or not ANG-(1-7) concentrations may be decreased in late-gestation hypertensive pregnancy, the authors measured concentrations in normal pregnant and reduced uterine perfusion pressure (RUPP) rats at *day 19* of gestation (4). It is interesting to note that the authors reported chronic RUPP results in the decrease of uterine concentrations of ANG-(1-7), a potent vasodilator (4). While these data suggest that uteroplacental ischemia suppresses ANG-(1-7) formation in the pregnant rat model of RUPP, it remains unclear whether other pathways may be at work causing the decreased ANG-(1-7) concentrations previously reported in preeclamptic women (3). Nevertheless, these data suggest hypoxia may be an important additional factor in the regulation of the uteroplacental RAS during pregnancy.

The study by Neves et al. (4) provides intriguing new insights regarding the functions of the RAS during both normal and pathological pregnancies. While characterization studies such as the present work are important, it is essential to note that these data are correlative and the quantitative contributions of the ACE2 and ANG 1-7 to the physiology and pathophysiology during pregnancy remain unclear. Further studies employing the use of specific ligand or receptor blockers and inhibitors or tissue-specific conditional gene knockouts of ACE2 and ANG 1-7 at different gestational ages are certainly warranted to identify the specific roles of these factors in the hemodynamics of pregnancy as well as other aspects of repro-

Address for reprint requests and other correspondence: J. P. Granger, Dept. of Physiology and Biophysics, Univ. of Mississippi Medical Center, 2500 N. State St., Jackson, MS 39216-4505 (e-mail: jgranger@physiology.umsmed.edu).

ductive physiology. The present work by Neves *et al.* provides the groundwork for follow-up studies that may yield fruitful results in a variety of physiological disciplines and bring new insights to a wide range of questions (from fertilization to parturition) in reproductive biology.

GRANTS

The authors of this article received funding from National Heart, Lung, and Blood Institute Grants HL-51971, HL-38499, HL-90269, and HL-78147.

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