An Emerging Role for Relaxin as a Renal Vasodilator

Jennifer M Sasser,* Marshall D. Lindheimer,‡ and Chris Baylis*†
*Department of Physiology and Functional Genomics, ‡Department of Medicine, Division of Nephrology, University of Florida, Gainesville, Florida; †Departments of Obstetrics & Gynecology and Medicine, and the Committee on Clinical Pharmacology, University of Chicago, Chicago, Illinois


S triking renal and cardiovascular adaptations occur early in human pregnancy, including increases in intravascular volume and cardiac output. Despite these adaptations, and because of a marked reduction in systemic vascular resistance, blood pressure (BP) falls (1,2). One of the earliest and most dramatic changes is the increase in renal plasma flow (RPF) and GFR due to renal vasodilation (3). Animal studies indicate a role for the ovarian hormone relaxin (RLX) (4,5), and the report by Smith et al. (6) in this issue of JASN expands on this literature by reporting on the renal hemodynamic effect of acute RLX infusion in normal men and nonpregnant women.

In human pregnancy, GFR and RPF are maximally increased (50% or more) by midterm, with the rise in RPF exceeding GFR; thus, the filtration fraction decreases. As expected, plasma creatinine declines, such that values >0.8 mg/dl are considered abnormal. Another striking change is the fall in plasma osmolarity (P_{osm}) (3). Both adaptations are hallmarks of an “optimal” pregnancy, and the causes may be linked (1,3). The rat is useful to study mechanisms underlying renal adaptations to pregnancy because, similar to humans, rats exhibit renal vasodilation, hyperfiltration, and a fall in P_{osm} during gestation. Micropuncture studies show that the increase in GFR and RPF is due to parallel reductions in both afferent and efferent arteriolar resistances with no change in glomerular BP (3). Of note, studies using fractional dextran clearances combined with mathematical modeling suggest this to be the case in human gestation as well (3).

The factors responsible for the increased gestational GFR and RPF are not entirely clear, although there is evidence of activation of the vasodilatory nitric oxide–cGMP signaling pathway (3). The renal vasodilatory stimulus is likely maternal in origin, because similar changes are observed in pseudopregnant rats (3) and on a smaller scale during the luteal phase of the menstrual cycle (2,3).

As mentioned above, studies in the rat have identified ovarian RLX as an important mediator of renal vasodilation, hyperfiltration, and osmoregulation. Chronic administration of RLX in virgin female rats causes renal vasodilation, increased GFR, and decreased P_{osm} with no change in BP (7). The RLX-induced increase in GFR and RPF and fall in P_{osm} is independent of other ovarian hormones as this effect was also observed in ovariectomized female and male rats (4,7).

Relaxin appears to be essential for the renovascular adaptations of rat pregnancy. A key study by Novak et al. demonstrated that removal of circulating RLX by ovariectomy or by administration of neutralizing antibodies to rat RLX abolished the rise in GFR and RPF and fall in P_{osm} and prevented the reduction in myogenic activity in small renal arteries in midterm pregnant rats (5).

In women, RLX levels rise during the luteal phase of the menstrual cycle, when GFR is at its maximum, and increase further when stimulated by human chorionic gonadotrophin during early pregnancy (8), concurrent with the rise in GFR and RPF and decline in P_{osm} (3). Women who conceive by ovum donation and had no measurable levels of circulating RLX had less dramatic changes in creatinine clearance and P_{osm} (9). In this issue of JASN, Smith et al. report that RLX acutely administered (5 h) to nonpregnant women and men results in a marked increase in RPF of approximately 50%. Because there was no concomitant fall in BP, this increase suggests a selective renal vasodilation (6). One very surprising finding is that despite this striking increase in RPF there was no increase in GFR. This implies either a large offsetting fall in glomerular BP or decline in glomerular capillary ultrafiltration coefficient (Kf) sufficient to produce filtration pressure disequilibrium (3). Given the constancy of systemic BP, a fall in glomerular BP would have to result from a greater fall in efferent versus afferent arterial resistance, which is a pattern not seen in the pregnant rat (3). An alternative (unlikely) explanation is that RLX lowers Kf sufficiently to produce filtration pressure disequilibrium and thus offset the rise in GFR expected with increased RPF. Whatever the renal hemodynamic changes that prevent the rise in GFR with acute RLX in this study by Smith et al. may be, it is evident that conscious people and rats do not respond similarly. Changes in GFR, RPF, and P_{osm} are detected as early as 1 h after intravenous administration and 6 h after subcutaneous infusion of RLX in the rat (10). Interestingly, in the setting of acute surgical stress and general anesthesia, rats express a renal vasodilatory response to both short-term (2 h) and chronic (7 d) RLX treatment resulting in increased RPF without a rise in GFR (11). Thus, there must be an additional conditioning signal required for expression of the GFR raising effect of acute RLX, perhaps provided by pregnancy in women.
and suppressed by acute surgical stress/anesthesia in rats. How chronic RLX affects renal hemodynamics and osmoregulation in men and women remains to be determined.

One final point worth consideration is the emerging literature on the beneficial actions of RLX in the nonpregnant state. RLX exerts potent antifibrotic action and the RLX knockout mouse develops widespread fibrosis early in life (12). Chronically administered RLX preserves structure and function in the renal mass reduction and chronic angiotensin II infusion models of chronic kidney disease (13, 14). Perhaps most impressively, only 20 d of RLX administration reverses some of the structural damage and functional declines seen in the aging rat (15).

Thus, RLX may play an important physiologic role in the maternal renal adaptations to pregnancy and may also have tremendous therapeutic potential in chronic kidney disease. Definitive answers will only be obtained by careful clinical investigations like the work reported by Smith et al. in this issue of JASN.

References


See the related article, “Influence of Recombinant Human Relaxin on Renal Hemodynamics in Healthy Volunteers,” on pages 3192–3197.