Unveiling the Vasodilatory Actions and Mechanisms of Relaxin

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R elaxin is a 6-kDa peptide hormone that is secreted from the corpus luteum of the ovary and circulates in the blood during pregnancy in several species, including humans, rats, and mice (see Appendix for relaxin ligand and receptor nomenclature). Hisaw and colleagues, who discovered the hormone, provided the first evidence, albeit structural in nature, that the vasculature is a relaxin target. In ovariectomized monkeys administered relaxin, they noted marked morphological changes in the endothelial cells of endometrial blood vessels consistent with hypertrophy and hyperplasia, as well as enlargement of arterioles and capillaries.

Functional evidence for a vasodilatory role of the hormone was initially reported by St-Louis and Massicotte, who demonstrated that chronic infusion of purified rat or porcine relaxin decreased systolic blood pressure in female spontaneously hypertensive rats but not Wistar-Kyoto rats. In another study, the same group of investigators showed that short-term administration of purified rat relaxin decreased mean arterial pressure in female spontaneously hypertensive rats as early as 8 hours after initiating the infusion, and the vasococonstrictor responses to norepinephrine and arginine vasopressin were blunted in the mesenteric circulation of these animals perfused in situ. Subsequently, some doubt about the physiological importance of the vascular role of relaxin was raised, when Ahokas et al found that the gestational decline in systolic blood pressure and decrease in vascular reactivity to angiotensin II were comparable in gravid spontaneously hypertensive rats as with and without circulating relaxin. Further supportive evidence for vascular effects of relaxin was garnered by Bani-Sacchi et al, who reported that, in the Langendorff preparation, relaxin acutely increased coronary blood flow in rat and guinea pig hearts. This group also showed that the vasodilatory action of relaxin in the coronary circulation was prevented by N^G-monomethyl-L-arginine, an NO synthase (NOS) inhibitor.

More recent understanding of relaxin as a vasodilatory hormone has stemmed, in part, from investigations of the maternal renal and cardiovascular adaptations to pregnancy, in which relaxin is emerging as an important player. The overall objective of this Brief Review is 2-fold: first, to highlight the vasodilatory actions of relaxin, particularly in the context of pregnancy; and, second, to outline current understanding of the mechanisms underlying the vasodilatory attributes of relaxin with emphasis on the role of arterial gelatinases.

Maternal Systemic Circulation During Pregnancy

The maternal circulation is profoundly vasodilated throughout gestation. In human pregnancy, systemic vascular resistance (SVR) plummets, and cardiac output reciprocally rises by ≈50% reaching a nadir and peak, respectively, by the end of the first or beginning of the second trimester (reviewed in Reference 10). Comparable vasodilation occurs in the systemic circulation of chronically instrumented, conscious pregnant rats. Interestingly, the systemic hemodynamic changes in human gestation are observed in the luteal stage of the menstrual cycle when SVR decreases and cardiac output increases (relative to the follicular phase), albeit to lesser degrees than those observed during pregnancy. Perhaps not coincidentally, relaxin is also secreted from the corpus luteum during the luteal phase of the menstrual cycle, producing low (compared with pregnancy levels) but detectable serum concentrations.

Concurrent with the alterations in systemic hemodynamics, global arterial compliance (AC) increases during human gestation, reaching a peak by the end of the first or beginning of the second trimester. Consistent with this finding are other measures indicative of increased AC, augmentation index, carotid-radial, and carotid-femoral pulse wave velocities, that significantly decrease starting in early pregnancy. Once again, the gestational decrease in augmentation index is anticipated in the luteal phase of the menstrual cycle. Comparable increases in global AC are observed during pregnancy in chronically instrumented, conscious rats. In the face of the profound increases in stroke volume and cardiac output and the decrease in SVR, the simultaneous increase in global AC is critical to cardiovascular homeostasis during pregnancy by maintaining efficient ventricular-arterial coupling and diastolic perfusion pressure.

Renal vascular resistance also declines in early pregnancy and is a major contributor to the overall reduction in maternal
Table. Relaxin Administration in Rats Mimics Maternal Vasodilation of Pregnancy

<table>
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<th>Systemic hemodynamics and arterial mechanical properties</th>
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<td>Long-term relaxin administration in conscious male and female normotensive control and hypertensive rats: ↓ SVR, ↑ CO, ↑ global AC, ≈ MAP</td>
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Renal circulation

| Long-term relaxin administration in conscious male and female intact or ovariectomized rats: ↓ RVR, ↑ RPF, ↓ GFR, ↓ myogenic reactivity of small renal arteries, ≈ MAP |
| Long-term relaxin administration ↓ renal vasoconstrictor response to angiotensin II infusion in conscious female rats |
| Long-term relaxin administration in anesthetized male rats: ↑ RBF, ≈ GFR, ≈ MAP |
| Short-term relaxin administration in conscious female rats: ↓ RVR, ↑ RPF, ↑ GFR, ≈ MAP |
| Short-term relaxin administration in anesthetized male rats: ↑ RBF, ≈ GFR, ≈ MAP |

Long-term relaxin administration is shown in day(s); short term relaxin administration is shown in hour(s). SVR indicates systemic vascular resistance; CO, cardiac output; global AC, global arterial compliance; MAP, mean arterial pressure; RVR, renal vascular resistance; RPF, renal plasma flow; RBF, renal blood flow; SHR, spontaneously hypertensive rats. See text for citations.

Relaxin Administration Mimics Maternal Vasodilation of Pregnancy

The short- and long-term effects of relaxin administration on systemic hemodynamics and global AC in rats are summarized in the Table.26–28 Chronic administration of relaxin attenuated the renal vasoconstrictor response to an intravenous infusion of angiotensin II,26 a phenomenon also noted during rat gestation.29–31 Consistent with the renal vasodilatory action of relaxin is that myogenic reactivity was inhibited in small renal arteries isolated from relaxin knockout mice.24 This finding is identical to the inhibition of myogenic reactivity noted previously in small renal arteries isolated from midterm pregnant compared with virgin rats33 and in small renal arteries isolated from wild-type mice compared with relaxin knockout mice.24

In normal human subjects, short-term intravenous infusion of relaxin for 6 hours increased RPF by 60% but, surprisingly, not GFR.34 The renal vasodilatory effect was observed in both men and women and as soon as 30 minutes after starting the infusion. There was no significant change in blood pressure.34 During 26 weeks of subcutaneous relaxin infusion in patients with mild scleroderma, the predicted creatinine clearance rose by 15% to 20%, and diastolic blood pressure fell slightly but significantly during the study.35,36 Thus, the renal vasodilatory action of relaxin initially described in conscious rats is likely to translate to humans, although GFR was inconsistently increased among the various studies in rats (Table) and humans.

Relaxin Immunoneutralization or Elimination From the Circulation Prevents Maternal Vasodilation of Pregnancy

Relaxin is critical to the alterations in systemic hemodynamics and global AC during midterm pregnancy in conscious rats.15 The ≈25% increase in cardiac output and global AC and decrease in SVR typically observed during midterm pregnancy were completely prevented by daily administration of rat relaxin neutralizing antibodies beginning on gestational day 8.15 In preliminary studies, relaxin immunoneutralization only partly inhibited the ≈45% increase in cardiac output and decreased SVR and increased cardiac output, as well as improved renal function, as reflected by decreases in serum creatinine and blood urea nitrogen. They further showed that relaxin decreased pulmonary capillary wedge pressure and N-terminal pro-brain natriuretic peptide, findings not predicted from the studies in normal healthy rats, although differences in the circulating concentration of relaxin reached or the pathological setting of congestive heart failure may explain the decrease in preload.22 Thus, the systemic vasodilatory actions of relaxin initially described in conscious rats are likely to translate to humans.

Evidence shows that, in addition to large arteries, small arteries contribute to global AC.23 Small renal arteries dissected from female rats after 5 days of relaxin administration demonstrated increases in passive compliance compared with arteries from vehicle-infused rats.16 Moreover, small renal arteries harvested from relaxin knockout mice were stiffer than those from wild-type animals.24 These results suggested that alterations in vascular structure, that is, cellular components or extracellular matrix, contribute to the relaxin-induced increase in global AC.16,25

The short- and long-term effects of relaxin administration on renal hemodynamics in rats are also summarized in the Table.26–28 Chronic administration of relaxin attenuated the renal vasoconstrictor response to an intravenous infusion of angiotensin II,26 a phenomenon also noted during rat gestation.29–31 Consistent with the renal vasodilatory action of relaxin is that myogenic reactivity was inhibited in small renal arteries isolated from relaxin knockout mice.24 This finding is identical to the inhibition of myogenic reactivity noted previously in small renal arteries isolated from midterm pregnant compared with virgin rats33 and in small renal arteries isolated from wild-type mice compared with relaxin knockout mice.24

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global AC and decrease in SVR during late gestation in rats, suggesting that other (possibly placental) hormones may contribute at this stage of pregnancy (unpublished data). Whether relaxin might contribute to the gestational changes in systemic hemodynamics and global AC during human pregnancy is currently under investigation.

Relaxin is also critical to the changes in renal hemodynamics during midterm pregnancy in conscious rats. The gestational increase in RPF and GFR and decrease in renal vascular resistance normally observed during midterm pregnancy were completely prevented either by ovariectomy or by daily administration of rat neutralizing antibodies beginning on gestational day 8. These interventions also prevented gestational inhibition of myogenic reactivity in small renal arteries isolated from the same rats. In infertile women with ovarian failure who became pregnant through egg donation, in vitro fertilization, and embryo transfer, the gestational rise in GFR was significantly attenuated in the first trimester (later stages of pregnancy were not investigated). Because these women lacked ovarian function and a corpus luteum, circulating levels of relaxin were undetectable as reported previously, thus implicating relaxin in the initiation of gestational renal hyperfiltration. However, unlike the gravid rat in which the gestational increase in GFR was totally dependent on circulating relaxin (vide supra), a partial increase in GFR persisted in human pregnancies despite the absence of circulating relaxin (and other corpus luteal products).

Molecular Mechanisms of Renal Vasodilation and Hyperfiltration During Administration of Relaxin or in Pregnancy

An emerging view is that the molecular mechanisms of relaxin vasodilation vary according to the duration of hormone exposure, that is, there are sustained and rapid vasodilatory responses to relaxin.

**Sustained Vasodilatory Responses**

**Nitric Oxide**

In conscious rats chronically treated with relaxin or the vehicle for relaxin, acute intravenous infusion of N^G^-monomethyl-L-arginine, an NOS inhibitor, leads to a convergence of GFR, RPF, and renal vascular resistance in the 2 groups of animals (Figure). That is, rats administered relaxin responded more robustly to NOS inhibition showing a greater decrease in GFR and RPF and an increase in renal vascular resistance compared with those animals administered vehicle. Consequently, NOS inhibition completely blocked relaxin-mediated renal vasodilation and hyperfiltration. Consistent with these in vivo investigations, the inhibition of myogenic reactivity in small renal arteries isolated from rats that were chronically treated with relaxin was restored to the robust levels observed in arteries from vehicle-infused animals after the addition of NOS inhibitors to the bath or by removal of the endothelium. Importantly, a critical role for NO in the renal vasodilation, hyperfiltration, and reduced myogenic reactivity of small renal arteries was already established for pregnant rats, again by the application of NOS inhibitors or endothelial removal. The 24-hour urinary excretion of nitric oxide metabolites and cGMP did not increase in relaxin-treated rats despite the proven functional role of NO in relaxin-induced vasodilation of the renal circulation. Thus, ironically, the increase in urinary and plasma cGMP and nitric oxide that were observed during rat pregnancy and which motivated further investigation of these molecules, may not be of vascular origin or of hemodynamic relevance.
**Endothelial Endothelin B Receptor**

The mechanism for the NO-dependent vasodilatory changes in the renal circulation by relaxin administration or pregnancy does not appear to be attributed to increases in endothelial NOS protein. Although a role for the other renal NOS isoforms cannot be excluded and requires further investigation, the possibility was explored that NOS, presumably endothelial NOS, might be activated by endothelin (ET), thereby mediating the NO-dependent renal vasodilatory changes during pregnancy or by relaxin administration. This hypothesis was based on previous studies that established a role for the endothelial ETB receptor in the maintenance of low renal vascular tone in the nonpregnant condition most likely by tonic stimulation of NO (reviewed in References 17, 18, and 45). Thus, it was proposed that, during pregnancy, relaxin accentuates this vasodilatory pathway in the renal circulation.

Analogous to NOS inhibition, in conscious rats chronically administered relaxin or vehicle for days, acute intravenous infusion of the ETB receptor antagonist, RES-701-1, led to a convergence of GFR, RPF, and renal vascular resistance in the 2 groups of animals and, consequently, complete blockade of relaxin-mediated renal vasodilation and hyperfiltration. That is, rats administered relaxin responded more robustly to ETB receptor blockade, showing a greater decrease in GFR and RPF and an increase in renal vascular resistance compared with those animals administered vehicle. In similar studies, a critical role was established previously for the endothelial ETB receptor in mediating relaxin vasodilation and hyperfiltration during pregnancy in conscious rats.

Consistent with these in vivo investigations, the inhibition of myogenic reactivity in small renal arteries isolated from relaxin-administered nonpregnant or midterm pregnant rats was restored to robust levels after the addition of RES-701-1 or the mixed ETA/B antagonist, SB209670, but not the ETA antagonist, BQ123, to the bath. Additional studies suggested that the NO-cGMP signaling pathway specifically mediated the vasodilatory role of endogenous ET in the renal circulation during pregnancy.

**Arterial Gelatinases**

Given the essential, albeit perhaps paradoxical role for ET in the relaxin vasodilatory pathway, a logical hypothesis was that relaxin upregulates the endothelial ETB receptor. However, this idea needs further investigation, because Dschietzig et al reported compelling evidence in favor of the hypothesis, whereas our group was unable to find any supportive evidence. In light of this impasse, an alternative hypothesis was formulated based on the confluence of several findings: (1) the crucial role of relaxin, the endothelial ETB receptor, and NO in pregnancy (relaxin)-mediated renal vasodilation as described above; (2) the ability of relaxin to upregulate matrix metalloproteinase (MMP) 2 and 9 activity (so called gelatinases A and B, respectively) at least in various nonvascular cell types; and (3) the potential for MMPs such as MMP-2 and -9 to process big ET at a gly-leu bond to ET1-32, a novel ET fully capable of activating ET receptors (References 48–51 and citations therein). Thus, it was reasoned that relaxin might upregulate MMP-2 or -9 activity in the renal vasculature during pregnancy, thereby mediating renal vasodilation, hyperfiltration, and inhibited myogenic reactivity in an ET- and NO-dependent manner (Figure). This alternative pathway for ET formation was especially compelling, because phosphoramidon, which blocks the traditional ET-converting enzyme and ET1-21 formation, failed to affect the renal vasodilatory responses of relaxin, although the dose used completely blocked the slow pressor response to a bolus of big ET.

To test this new hypothesis, a specific inhibitor of gelatinase activity was used, cyclic CTHHWGFTLC (cyclic CTT), which preferentially inhibits the activity of MMP-2 relative to MMP-9. Because cyclic CTT is 10 times more potent than STTHWGFTLS, the latter was used as a control peptide. Analogous to NOS inhibition, in conscious rats chronically administered relaxin or vehicle for days, acute intravenous infusion of the ETB receptor antagonist, RES-701-1, led to a convergence of GFR, RPF, and renal vascular resistance in the 2 groups of animals and, consequently, complete blockade of relaxin-mediated renal vasodilation and hyperfiltration. To corroborate these findings, a general and well-established inhibitor of MMP activity that is structurally distinct from cyclic CTT was used next, GM6001. GM6001, but not its vehicle dimethyl sulfoxide, also reversed relaxin-mediated renal vasodilation and hyperfiltration.

The myogenic reactivity bioassay was also used. Small renal arteries from midterm pregnant or relaxin-treated nonpregnant rats showed inhibition of myogenic reactivity that was restored to the robust (virgin) phenotype by the addition of cyclic CTT, but not STTHWGFTLS; GM6001, but not dilute dimethyl sulfoxide vehicle; tissue inhibitor of metalloproteinase (TIMP), TIMP-2, but not heat inactivated TIMP-2; and MMP-2 neutralizing antibody, but not control IgG antibody to the bath or into the lumen of the arteries. Importantly, phosphoramidon did not affect the inhibited myogenic reactivity. Therefore, these results obtained from the myogenic reactivity bioassay in vitro were consistent with those observed in vivo (vide supra), and, together, they supported a pivotal role for gelatinase (most likely MMP-2) in the renal vasodilatory responses to relaxin and pregnancy. They also implicated local, arterial gelatinase activity rather than circulating enzyme.

Although these studies established the essential role of arterial MMP-2 in the renal vasodilatory pathway of relaxin and pregnancy, they did not address whether MMP-2 activity itself was being regulated. To address this question, gelatinase activity was measured in small renal and mesenteric arteries and aortas isolated from relaxin-treated nonpregnant or midterm pregnant rats. An ~40% increase in both pro-MMP-2 and active MMP-2 activity, as well as pro-MMP-2 protein and mRNA, was observed relative to arteries harvested from virgin control or vehicle (for relaxin) -infused rats. Interestingly, pro-MMP-9 activity was also consistently increased in small renal arteries from midterm pregnant rats, although its activity was markedly less than MMP-2. This increase in maternal systemic arterial gelatinase activity after relaxin administration or during pregnancy has been corroborated by other reports. There were no significant differences in TIMP-1 or TIMP-2 activity, although there was considerable variability in the reverse zymography assay.
MMP-2 was localized to both the endothelium and vascular smooth muscle of the small renal arteries by immunohistochemistry, but further investigation is required to determine in which of these cell type(s) it is upregulated by either relaxin or pregnancy.

Interestingly, MMP-9 rather than MMP-2 activity was elevated in small renal and mesenteric arteries harvested from rats after short-term subcutaneous administration of relaxin for 4 to 6 hours by osmotic minipump (Reference 50 and Figure). These small renal arteries exhibited inhibition of myogenic reactivity that was restored to robust levels by a specific MMP-9 rather than an MMP-2 neutralizing antibody introduced into the artery lumen. MMP-9 was immunolocalized to the vascular smooth muscle. It should be pointed out that MMP-9 can also cleave big ET to ET1-32 at a gly-leu bond. Of note, cyclic CTT failed to restore myogenic reactivity in this setting, suggesting that, in this tissue and at the dosage used, it is specific for MMP-2. Finally, the endothelial ETB receptor and NO were also involved in the inhibition of myogenic reactivity in arteries isolated from rats after 4 to 6 hours of relaxin administration.

Functional evidence was obtained for arterial MMP-2 being in series with, and upstream of, the endothelial ETB receptor and NO rather than as part of a separate and parallel vasodilatory pathway. Inhibited myogenic reactivity was not observed in small renal arteries isolated from relaxin-treated or midterm pregnant ETB receptor–deficient rats, thus corroborating the studies using pharmacological inhibitors of the ETB receptor. Nevertheless, arterial MMP-2 activity was increased. This dissociation of increased arterial MMP-2 activity from the functional end point, that is, inhibited myogenic reactivity, which was not observed because of genetic disruption of the ETB receptor, strongly suggested that MMP-2 was in series with, and upstream of, the endothelial ETB receptor and NO (Figure).

Why does ET preferentially interact with the endothelial ETB receptor rather than the ETB or ETA receptor on vascular smooth muscle? We hypothesize that the molecular constituents of the relaxin vasodilatory pathway are colocalized in the caveolae of the endothelium: relaxin/insulin-like family peptide receptor (RXFP) 1 and ETB Receptors, pro-MMP-2, TIMP-2, membrane-type MMP, and endothelial NOS, a hypothesis that needs testing.

**Emerging Role of Angiogenic Growth Factors**

Using RXFP1 and RXFP2 knockout mice, a preliminary report indicated that the major relaxin receptor, RXFP1, mediates the arterial responses to relaxin (Reference 58; see the Appendix). Unexpectedly, RXFP1 receptor mRNA and protein expression in vascular smooth muscle greatly exceeded those of endothelium (unpublished data). This finding suggested that other factors (eg, angiogenic growth factors) are secreted by the vascular smooth muscle on RXFP1 activation and diffuse to the endothelium, where they stimulate gelatinase(s) expression, thereby activating the endothelial ETB receptor-NO vasodilatory pathway. Note, however, that this reasoning may be flawed because it was formulated based on relative receptor abundance. It is possible that the endothelial RXFP1 receptor, albeit of vastly lower expression than vascular smooth muscle, is the receptor of physiological relevance to the sustained relaxin vasodilatory pathway. Nevertheless, given that relaxin has been shown to increase vascular endothelial growth factor (VEGF) expression at least in several nonvascular cell types and is angiogenic (reviewed in References 45 and 59), whether relaxin can increase VEGF or placental growth factor (PGF) activity in arteries was considered. To date, functional approaches have been taken to address this hypothesis, and the data show that the VEGF receptor tyrosine kinase inhibitor, SU5416, and specific VEGF and PGF neutralizing antibodies each prevented the inhibition of myogenic reactivity by relaxin in mouse and rat small renal arteries and in human subcutaneous arteries. Furthermore, SU5416 prevented relaxin-mediated decreases in renal vascular resistance and increases in RPF and GFR in chronically instrumented, conscious rats. Thus, emerging evidence suggests that angiogenic growth factors may play a role in the relaxin vasodilatory pathway, but the precise molecular underpinnings await elucidation.

**Rapid Relaxation Responses**

Recently, Fisher et al demonstrated that relaxin also induces a rapid relaxation response (ie, within minutes) in isolated human arteries and in an endothelium-dependent fashion. Interestingly, this effect was observed in vessels obtained from gluteal biopsies and not from pulmonary tissues. In a preliminary report, the molecular underpinnings of this rapid vasodilatory action of relaxin were investigated. The phenomenon was observed in small renal arteries isolated from rats and mice but not in mesenteric or coronary septal arteries. Rapid relaxin relaxation was also shown in isolated human subcutaneous arteries. Brief exposure of cultured human endothelial but not vascular smooth muscle cells to relaxin increased NO production as measured by the fluorescent probe 4-amino-5-methylamino-2′,7′-difuorofluoroscein. These rapid responses to relaxin were inhibited by L-arginine analogs, phosphatidylinositol 3-kinase inhibitors, and pertussis toxin but not by the VEGF receptor tyrosine kinase inhibitor SU5416. Increased phosphorylation of Akt was demonstrated. These studies suggest that relaxin rapidly dilates arteries from select vascular beds across a range of species, and one mechanism involves Goi/o protein coupling to phosphatidylinositol 3-kinase, Akt, and endothelial NOS but not VEGF receptor transactivation.

**Summary**

Relaxin administration to nonpregnant rats and humans mimics the vasodilatory phenomena of pregnancy. Moreover, relaxin immunoneutralization or elimination from the circulation during pregnancy prevents maternal systemic and renal vasodilation and renal hyperfiltration and increases global AC. The molecular mechanisms of relaxin vasodilation depend on the duration of hormone exposure, that is, there are rapid and sustained vasodilatory responses. Our current understanding is that the vasodilatory responses of relaxin are transduced by its major receptor, RXFP1. As revealed recently, the rapid vasodilatory responses of relaxin are mediated by Gxi/o protein coupling to phosphatidylinositol 3-kinase/Akt (protein kinase B)–dependent phosphorylation and
activation of endothelial NOS. Sustained vasodilatory responses depend on vascular placental and/or endothelial growth factors and increases in vascular gelatinase(s) activity. Gelatinases process big ET at a gly-leu bond to form ET_{1-32}, which activates the endothelial ET_{1/NO} vasodilatory pathway (Figure). Investigation of potential therapeutic applications of relaxin will be aided by thorough understanding of the mechanisms underlying its vasodilatory actions.

**Perspectives**

The rationale for investigating vasodilation of pregnancy is to unveil the pivotal vasodilatory hormones and their intermediary signaling molecules. In turn, such knowledge will advance our understanding of this remarkable pregnancy adaptation and potentially lead to novel therapeutic strategies for the prevention and treatment of preeclampsia and for diseases associated with vasoconstriction in the nonpregnant population.

Highlighted in this Brief Review is the emerging evidence that supports a major role for relaxin in the maternal cardiovascular and renal adaptations to pregnancy. Furthermore, the new and emerging concept that relaxin exhibits both rapid and sustained vasodilatory responses is presented, the molecular underpinnings of which differ according to duration of hormone exposure. The sustained vasodilatory action is likely to be important when relaxin circulates for long periods of time during pregnancy and in the luteal phase of the menstrual cycle. However, chronic administration of relaxin also exerts sustained vasodilatory actions in males, in which most investigators agree relaxin does not circulate.

It is possible that the arterial-derived relaxin ligand-receptor system acts through both the rapid and sustained vasodilatory pathways in males (and in females during the follicular phase of the menstrual cycle). For example, minute-to-minute fluctuations in prorelaxin, the major form expressed in arteries, has been shown to be as active as actions of relaxin will be aided by thorough understanding of the mechanisms underlying its vasodilatory actions.

**Appendix: Relaxin Ligand and Receptor Nomenclature**

Humans have 3 relaxin genes, designated relaxin 1, 2, and 3. Rats and mice each have 2 relaxin genes, designated relaxin 1 and 3. Human relaxin 2 and rat and mouse relaxin 1 gene products are true orthologs insofar as they are secreted by the corpus luteum during pregnancy and circulate. Humans, rats, and mice have 1 receptor, the so-called Lgr7 (leucine rich repeat-containing G protein–coupled) receptor, recently renamed RXFP1, that binds relaxin. Although relaxin 2 may also bind to the Lgr8 receptor (RXFP2), albeit with reduced affinity, the preferred ligand for Lgr8 is Ins-3. Recently, 2 new receptors have been described for relaxin-3: GPCR135 and 142 (Reference 71; although GPCR142 is a pseudogene in rats).

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**Disclosures**

K.P.C. discloses use patents related to relaxin.

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