Relaxin is a vasodilator hormone

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Relaxin is a polypeptide hormone structurally related to insulin and the insulin-like growth factors (IGFs). There are two biologically active human relaxins, H1 and H2. Both are expressed in the decidua, placenta, and prostate gland. In corpus luteum, which is the main source of circulating relaxin, only the H2 form is expressed. The two isoforms differ in the half-life of their mRNAs (7). Relaxin interacts with two orphan G protein-coupled receptors, LGR7 and LGR8, which mediate the action of relaxin through a cAMP-dependent pathway distinct from that of insulin and IGFs (8). Relaxin has long been known to be involved in the preparation of the female body for pregnancy by relaxing the pelvic ligaments, inhibiting spontaneous uterine contractions, ripening the uterine cervix, and stimulating the mammary gland (13). Locally produced relaxin may be involved in initiating the degradation of the fetal membranes at term, and increased relaxin expression has been associated with preterm premature rupture of the fetal membranes (10). More recently a plethora of nontraditional effects has been reported, including regulation of the growth of breast cancer cells, a chronotropic action on the heart, inhibition of histamine release, depression of platelet aggregation, and regulation of pituitary hormone secretion. In addition, relaxin has emerged as a potentially important vasodilator (1).

In this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, Dr. Conrad and collaborators (12) present a study of relaxin, which is a continuation of nearly 20 years of research on the vasodepressor factor(s) of pregnancy. Having excluded prostaglandins as the mediator, the group first showed that nitric oxide and endothelin were involved in the vasodepressor responses (4). They then provided evidence that endothelin and nitric oxide acted sequentially in reducing myogenic activity in small arteries from pregnant rats (6). Real breakthroughs were the observations that relaxin is a potent vasodilator in conscious rats, that relaxin is essential for renal vasodilation during pregnancy, and that vasodilation in pregnancy can be prevented by infusion of anti-relaxin antibodies (3, 11).

In the present study, Novak et al. (12) couple the relaxin-dependent vasodilation to the previous demonstration of endothelium-dependent vasodilation during pregnancy. They show that the ability of relaxin treatment to blunt myogenic responses is dependent on the endothelium, functional endothelin B (ETB) receptors, and the production of nitric oxide. Their study objects are small arteries isolated from the kidney and the mesenteric bed. Their results are consistent with their conclusion that myogenic responses are clearly attenuated in small renal arteries from relaxin-treated rats. Removal of endothelium, blockade of the ETB receptors, and inhibition of nitric oxide synthase activity by $N^\text{G}$-nitro-L-arginine methyl ester all reverse the effect of relaxin. Attenuation of myogenic responses was also noted in mesenteric vessels. Relaxin also resulted in a blunting of the response to angiotensin II. In contrast to the blunting of the myogenic response, the vascular response to phenylephrine was unaltered during relaxin treatment, underscoring the differences in responses to the sympathetic nervous system and local and circulating hormones. Thus the present study lends further support to the view that relaxin is responsible for the vasorelaxation and decrease in myogenic activity during pregnancy and provides evidence in vitro that the cellular pathway involves endothelin-mediated release of nitric oxide from the endothelium.

A few caveats remain in the interpretation of the data. The vessels studied by the authors are renal interlobar arteries and mesenteric arteries with an unpressurized diameter of 100–200 μm. Although the pressure in vessels of this size has been shown to be lower than arterial pressure, the true regulation of peripheral resistance and of renal blood flow occurs in much smaller arterioles. We still do not know the pathway by which relaxin initiates the endothelin/nitric oxide pathway, but the mechanism may be similar to that described in rat coronary endothelial cells, where relaxin upregulates nitric oxide synthase II mRNA and protein and stimulates intrinsic nitric oxide generation (5).

The possible impact of the new results on relaxin extends far beyond that of interesting phenomena in isolated arteries. Not only does the vasodilator princi-
ple of pregnancy seem to have been identified, but, inasmuch as new vasodilator pathways are prime targets for drug development, we will probably soon see development of relaxin agonists and antagonists that will be helpful tools in the further study of the physiology and pathophysiology of relaxin, and which may prove helpful in the treatment of human disease. Lately, a third relaxin gene has been reported in human (H3) and mouse (M3), where it is expressed at high levels in the brain, suggesting a new role for relaxin in signaling processes (2). With good reason, the recent demonstration of relaxin receptors was accompanied by a commentary with the title, “This hormone has been relaxin too long!” (9).

REFERENCES