Targeting Arterial Remodeling
A Key Tile in the Mosaic of the Therapeutic Effects of Relaxin in Cardiovascular Disease

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In the present issue of Hypertension, Xu et al1 from the University of Melbourne (Melbourne, Australia), an experienced team of “relaxinologists,” describe the findings of a well-done multidisciplinary experimental study providing evidence that therapeutic administration of human recombinant H2 relaxin has beneficial effects on arterial remodeling in aged spontaneously hypertensive rats (SHRs). This is a major advance to our knowledge of the cardiovascular effects of relaxin, especially considering that the hormone preparation used in this study, similar to that currently used in clinical trials for heart failure,2 has good chances to be adopted as a cardiovascular drug for human use.

Relaxin is known as a cardiovascular hormone and a potent vasodilator. In pioneer studies in rats,3,4 purified luteal rat relaxin was shown to have antihypertensive effects and to blunt the response to vasoconstrictors. Of note, the relaxin-induced decrease in blood pressure was only observed in SHRs and not in normotensive, age-matched animals.5 This peculiar behavior suggested that relaxin could specifically counterbalance the pathogenic mechanisms of hypertension without interfering with the physiological regulation of blood pressure. In 1995, we demonstrated that the vasodilatory effects of relaxin were dependent on the upregulation of endogenous NO biosynthesis by cells of the vascular wall, conferring to this hormone an even higher potency than equimolar concentrations of acetylcholine or sodium nitroprusside.6 Later, evidence was provided that relaxin is a key regulator of pregnancy-induced hemodynamic adjustments, including increased renal blood flow.7 Convincing experimental evidence has been accumulating to consider relaxin a bona fide vascular hormone and possible endogenous agent for vascular health.7

From a clinical viewpoint, the possibility that relaxin may exert long-term vascular effects that go beyond an immediate vasodilator response is a matter of great interest. In 2004, Conrad et al8 demonstrated that chronic administration of steady levels of recombinant H2 relaxin to normotensive rats decreased systemic vascular resistance and cardiac afterload by increasing arterial compliance. This effect was attributable not only to reduction in vascular smooth muscle tone, as expected from the known effects of relaxin, but also to anatomic changes of the vascular wall consistent with extracellular matrix remodeling.8 The novel study from Xu et al1 confirms and extends the previous one by adopting an animal model of arteriosclerosis, namely, aged SHRs, to specifically address the question of whether the observed improvement in arterial compliance on administration of relaxin is directly its vasodilatory action or whether relaxin is able to induce regression of adverse arterial remodeling and stiffness per se. Interestingly, a 2-week therapeutic administration of H2 relaxin to aged SHRs caused a marked, persistent reduction of arterial wall thickening and fibrosis in comparison with the untreated age-matched SHRs, resulting in decreased arterial stiffness and increased compliance.

These key findings clearly indicate that relaxin has the therapeutic property to counteract and even revert vascular remodeling in arteriosclerosis, a finding that could raise the interest of clinicians to verify whether H2 relaxin may behave similarly in patients experiencing cardiovascular disease. Indeed, clues to a positive answer come from the early work of Casten et al,9 who successfully used partially purified porcine relaxin to treat patients with peripheral vascular diseases and obtained impressive amelioration of peripheral arteriopathy and ischemic ulcers, as well as from a more recent observation that recombinant H2 relaxin, given as experimental therapy to a patient with severe idiopathic occlusive peripheral arterial disease of the lower limbs, caused a marked, long-lasting amelioration of both subjective symptoms and objective clinical and instrumental signs.10 Both reports highlight the persistent effects of relaxin even after discontinuation of the treatment, consistent with the possibility that relaxin may have induced anatomic changes of the arterial wall.

Looking over the literature of the last decade on relaxin suggests that it is no longer a “Cinderella hormone,” as defined in late 1990s but is now recognized as a cardiovascular physiological effector with therapeutic potential. Many researchers, including myself, are convinced that the availability of relaxin for human use would add a major weapon for clinicians to fight their never-ending war against cardiovascular disease.

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References


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