

same response may be applied to G protein-linked receptors, particularly those without introns. It is postulated that many of the genes encoding the G protein-linked receptor family evolved from a single precursor gene (possibly an opsin gene) that lost its introns approximately 1 billion years ago²³. Since then, gene duplication events have resulted in many related genes. These intronless genes are so small that they are more likely to be functional, when duplicated, than large intron-containing genes and have, therefore, diverged into a large, related family of functional receptors. These events would, therefore, allow an increase in the diversity of receptors available and correspondingly in the level of complexity possible, particularly in the brain, conferring an evolutionary advantage. So, why have G protein-linked 5-HT₁-like receptors diversified so extensively? Answer: because they can!

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LETTERS

Is the relaxin system a target for drug development? Cardiac effects of relaxin

In a recent issue of *TiPS*, Kakouris and colleagues¹ reported that human relaxin gene 2 product causes concentration-dependent positive chronotropic and inotropic effects by acting directly on specific receptors in the rat isolated atria. On the basis of these findings, together with the demonstration of specific high-affinity binding sites for relaxin in the rat heart² as well as of the increase in serum relaxin concentrations during the first trimester of human pregnancy³, Kakouris and colleagues¹ imply that relaxin may be responsible for the elevation of cardiac output during pregnancy. The authors also suggest¹ that 'the relaxin system (receptors, degradation mechanisms, cell signalling, etc.) could be a novel target for the development of potential inotropic agents'.

We believe that these assertions are, to say the least, premature, for several reasons. First, the highly preferential venodilator effect of relaxin leading to decreased venous blood velocity⁴ will tend to reduce circulating blood volume, venous return and, consequently, cardiac output. Secondly, the ensuing tachycardia with relaxin might partly offset the potential advantage of its cardiotoxic action. Thirdly, it should be noted that while 'the binding of ³²P relaxin... was seen clearly in the heart atria, ... the ventricles did not show detectable binding'² (see also Fig. 1 in Ref. 2). Indeed, our recent observations dealing with the cardiac effects of 5-HT have

established that the increase in contractility induced by this amine in the atrium of both pigs^{5,6} and humans⁷ is not observed in the ventricular myocardium.

We therefore suggest that, although relaxin may elevate cardiac output by increasing heart rate, it is unlikely that relaxin would do so via a positive inotropic effect on the ventricular myocardium. This signifies that the approach of developing potential inotropic agents via the relaxin system will probably not be very rewarding.

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