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RESEARCH PAPER

Discovery of new antagonists aimed at discriminating UII and URP-mediated biological activities: insight into UII and URP receptor activation

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BACKGROUND AND PURPOSE

Recent evidence suggested that urotensin II (UII) and its paralog peptide UII-related peptide (URP) might exert common but also divergent physiological actions. Unfortunately, none of the existing antagonists were designed to discriminate specific UII- or URP-associated actions, and our understanding, on how these two endogenous peptides can trigger different, but also common responses, is limited.

EXPERIMENTAL APPROACH

Ex vivo rat and monkey aortic ring contraction as well as dissociation kinetics studies using transfected CHO cells expressing the human urotensin (UT) receptors were used in this study.

KEY RESULTS

Ex vivo rat and monkey aortic ring contraction studies revealed the propensity of [Pep^4]URP to decrease the maximal response of human UII (hUII) without any significant change in potency, whereas no effect was noticeable on the URP-induced vasoconstriction. Dissociation experiments demonstrated the ability of [Pep^4]URP to increase the dissociation rate of hUII, but not URP. Surprisingly, URP, an equipotent UII paralog, was also able to accelerate the dissociation rate of membrane-bound ^{125}I-hUII, whereas hUII had no noticeable effect on URP dissociation kinetics. Further experiments suggested that an