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European Journal of Pharmacology 402 (2000) 209–211

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Rapid communication

Vasodilator effect of urotensin II, one of the most potent vasoconstricting factors, on rat coronary arteries

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Received 14 July 2000; accepted 17 July 2000

Abstract

The effects of human urotensin II on coronary flow were studied in the perfused rat heart. Urotensin II transiently decreased coronary flow, then induced sustained vasodilatation. In the presence of a cyclooxygenase inhibitor, diclofenac, coronary vasodilatation was significantly inhibited. A nitric oxide synthase inhibitor, N^G-nitro-L-arginine (L-NNA), attenuated the urotensin-induced vasodilatation. These data suggest that urotensin II modulates coronary flow through factors such as cyclooxygenase products and nitric oxide to elicit coronary vasodilatation.

Keywords: Urotensin II; Coronary artery; Vasodilatation

Urotensin II is a cyclic peptide composed of 12 amino acid residues initially isolated from the fish neurosecretory system, and the biological activity of urotensin II is dependent on a well-conserved cyclic hexapeptide (Coulouarn et al., 1998). Recently, human urotensin II has been cloned (Coulouarn et al., 1998; Liu et al., 1999) and demonstrated to be the most potent mammalian vasoconstrictor (Ames et al., 1999). The distribution of urotensin II varies among species. It is mainly expressed in the neurosecretory system in fish, while it is found in the mammalian cardiovascular system and motoneurons (Coulouarn et al., 1998). Fish urotensin II showed a complex effect in rat, and was suggested to have an endothelium-dependent and independent action on vessels (Gibson, 1987). The major arteries, such as thoracic aorta, were contracted by fish urotensin II concentration dependently (Gibson, 1987; Itoh et al., 1987) through an increase in Ca^{2+} caused mainly by an influx of extracellular Ca^{2+}. In vivo, however, it decreased blood pressure in rats (Gibson et al., 1986). Although a recent study reported the expression of urotensin II-receptors in the heart (Liu et al., 1999), it is not known whether human urotensin II has a physiological effect in the heart. Therefore, we tried to characterize the effect of human urotensin II on the coronary circulation by using a perfused heart system.

Male Fischer 344 rats (body weight ~250 g) were obtained from Charles River Japan (Atsugi, Japan). The rats were anaesthetized with ether and the heart was rapidly excised. The aorta was dissected free and mounted onto a cannula attached to a Langendorff's perfusion apparatus. Experiments were performed in accordance with the Guide for Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85–23, revised 1996) and under the regulations of the Animal Care Committee of Yamagata University School of Medicine. The heart was immediately perfused at a constant pressure (75 cm H_2O) by Langendorff's method with a modified Krebs–Ringer bicarbonate solution (37 ± 0.5°C). The buffer solution was aerated with a gas mixture of 95% O_2 and 5% CO_2 (pH 7.4). Coronary flow was measured with an electromagnetic flowmeter (MFV 1100, Nihon Kohden, Tokyo, Japan). Intactness of the endothelium in the preparation was confirmed by the presence of vasodilatation caused by 10 pmol acetylcholine. Drugs were injected as a bolus for 10 s or administered by continuous infusion into the rubber tubing connected to the aortic cannula. The volume of a single bolus injection was less than 0.1 ml. Continuous infusion of each inhibitor was started 20 min before application of urotensin II at a rate of 0.057 ml/min by means of a syringe pump (Harvard Apparatus 940e, Millis, MA, USA).

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00506-9

Human urotensin II (0.1 nmol) elicited a biphasic response of coronary flow, namely an initial phase of decreasing coronary flow followed by sustained vasodilatation (Fig. 1). The vasoconstricting effect induced by urotensin II was short lasting (within 1 min) with rapid recovery, and followed by a sustained vasodilatation. The second phase of the response was slow in onset but long lasting, up to 20 min. The maximal flow (114.1 ± 2.7% of the basal flow, $n = 8$) was obtained at ~5 min after injection of urotensin II, then it gradually returned to its basal level. In the presence of diclofenac (10 μM), the vasodilating effect of urotensin II was significantly inhibited (100.7 ± 0.9% of the basal flow, $n = 4$). In addition, there was a significant difference in urotensin II-induced coronary vasodilatation between control and N^G-nitro-L-arginine (L-NNA, 10 μM)-treated groups (103.5 ± 0.8% of the basal flow, $n = 6$).

In this study, we demonstrated for the first time that urotensin II elicits a sustained vasodilatation of the coronary artery in the isolated perfused rat heart, probably due to the urotensin II-induced release of nitric oxide and prostacyclin. This finding is very intriguing because

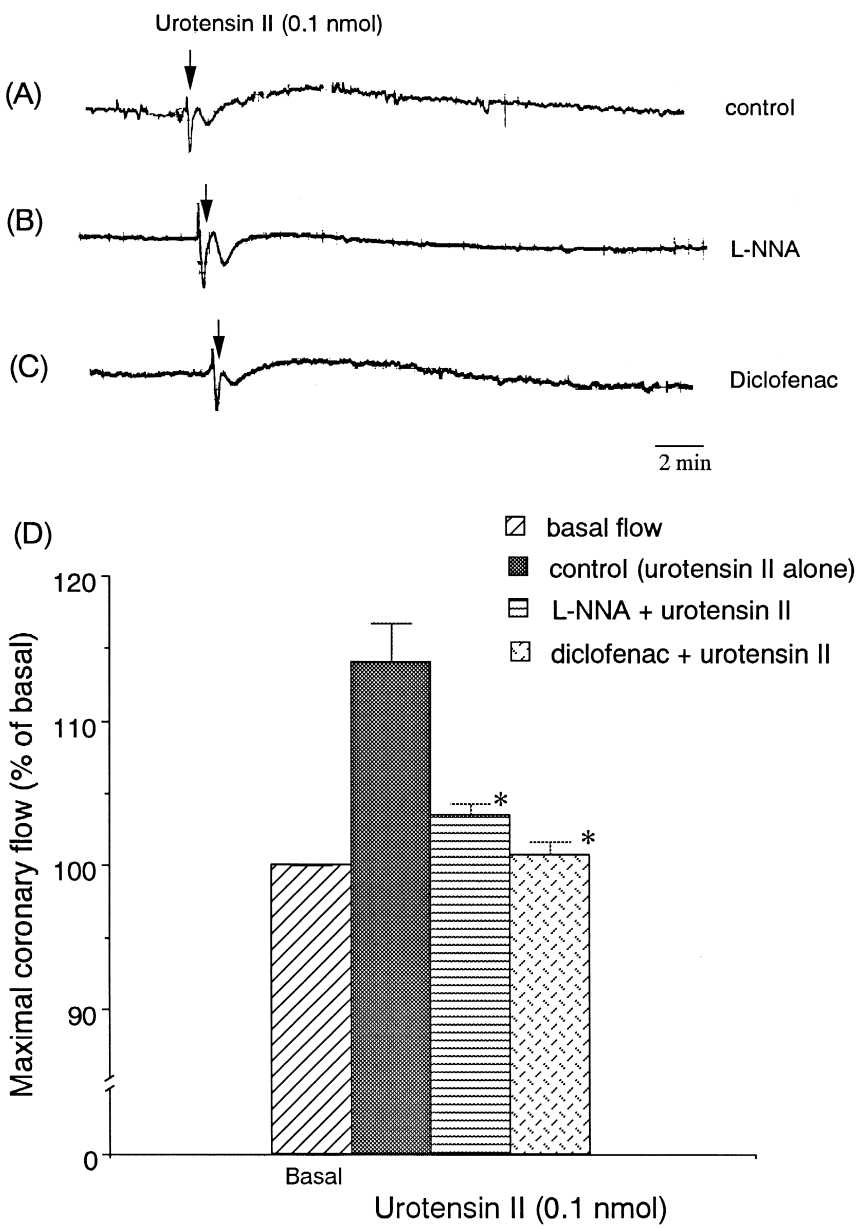

Fig. 1. Effect of human urotensin II on the coronary flow of rat hearts. (A) Transient constrictor response and sustained dilator response induced by urotensin II (0.1 nmol). (B) Influence of nitric oxide synthase inhibitor, L-NNA (10 μM), on the effect of urotensin II. (C) Influence of cyclooxygenase inhibitor, diclofenac (10 μM), on the effect of urotensin II. (D) Summary of the effect of L-NNA and diclofenac on the urotensin II-induced coronary vasodilatation. The data are means ± S.E.M. of the basal coronary flow. * $P < 0.01$ vs. control. Each inhibitor was continuously infused into the rubber tubing connected to the aortic cannula. The infusion of each inhibitor was started 20 min before application of urotensin II.

urotensin II has been recognized as one of the most potent vasoconstricting peptides known so far (Ames et al., 1999). Indeed, human urotensin II markedly increases total peripheral resistance in the anaesthetized monkey. However, the contractile responses to human urotensin-II are complex and modulated by the endothelial factors in pulmonary arteries (MacLean et al., 2000), as shown by the fact that inhibition of nitric oxide synthase uncovers contractile responses to human urotensin-II. Furthermore, fish urotensin II induces endothelium-dependent relaxation and independent contraction in rat aorta (Gibson, 1987). Other vasoconstrictors such as endothelin-1 and angiotensin II cause a strong coronary vascular contraction in the Langendorff-perfused rat heart (Ishihata et al., 1999), although these peptides stimulate the release of nitric oxide and prostacyclin. This vasoconstriction may become an ischemic stress on the myocardium. On the contrary, the major effect of urotensin II on the rat coronary artery was vasodilatation, suggesting that urotensin II may not act as an ischemic cardiodepressant. It remains to be elucidated whether urotensin II is involved in the development of hypertension and/or ischemic heart diseases, and whether urotensin II plays a protective role as a coronary vasodilator in these pathophysiological conditions.

Acknowledgements

This study was supported by the Grant-in-Aid for Scientific Research (C) (No. 11672254 to Dr. A. Ishihata and No. 11670658 to Dr. Yumi Katano) from The Ministry of Education, Science, Sports and Culture, Japan.

References

Ames, R.S., Sarau, H.M., Chambers, J.K., Willette, R.N., Aiyar, N.V., Romanic, A.M., Louden, C.S., Foley, J.J., Sauermelch, C.F., Coatney, R.W., Ao, Z., Disa, J., Holmes, S.D., Stadel, J.M., Martin, J.D., Liu, W.S., Glover, G.I., Wilson, S., McNulty, D.E., Ellis, C.E., Elshourbagy, N.A., Shabon, U., Trill, J.J., Hay, D.W., Ohlstein, E.H., Bergsma, D.J., Douglas, S.A., 1999. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature 401, 282–286.

Coulouarn, Y., Lihrmann, I., Jegou, S., Anouar, Y., Tostivint, H., Beauvillain, J.C., Conlon, J.M., Bern, H.A., Vaudry, H., 1998. Cloning of the cDNA encoding the urotensin II precursor in frog and human reveals intense expression of the urotensin II gene in motoneurons of the spinal cord. Proc. Natl. Acad. Sci. U. S. A. 95, 15803–15808.

Gibson, A., 1987. Complex effects of Gillichthys urotensin II on rat aortic strips. Br. J. Pharmacol. 91, 205–212.

Gibson, A., Wallace, P., Bern, H.A., 1986. Cardiovascular effects of urotensin II in anesthetized and pithed rats. Gen. Comp. Endocrinol. 64, 435–439.

Ishihata, A., Katano, Y., Nakamura, M., Doi, K., Tasaki, K., Ono, A., 1999. Differential modulation of nitric oxide and prostacyclin release in senescent rat heart stimulated by angiotensin II. Eur. J. Pharmacol. 382, 19–26.

Itoh, H., Itoh, Y., Rivier, J., Lederis, K., 1987. Contraction of major artery segments of rat by fish neuropeptide urotensin II. Am. J. Physiol. 252, r361–366.

Liu, Q., Pong, S.S., Zeng, Z., Zhang, Q., Howard, A.D., Williams, D.J., Davidoff, M., Wang, R., Austin, C.P., McDonald, T.P., Bai, C., George, S.R., Evans, J.F., Caskey, C.T., 1999. Identification of urotensin II as the endogenous ligand for the orphan G-protein-coupled receptor GPR14. Biochem. Biophys. Res. Commun. 266, 174–178.

MacLean, M.R., Alexander, D., Stirrat, A., Gallagher, M., Douglas, S.A., Ohlstein, E.H., Morecroft, I., Polland, K., 2000. Contractile responses to human urotensin-II in rat and human pulmonary arteries: effect of endothelial factors and chronic hypoxia in the rat. Br. J. Pharmacol. 130, 201–204.