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Review

Central and peripheral cardiovascular, ventilatory, and motor effects of trout urotensin-II in the trout

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ABSTRACT

Urotensin-II (U-II) was originally considered to be exclusively the product of the caudal neurosecretory system (CNSS) of teleost fish, but it has now been demonstrated that U-II is widely expressed in peripheral tissues and nervous structures of species from lampreys to mammals. However, very little is known regarding the physiological effects of this peptide in its species of origin. In the present review, we summarize the most significant results relating to the cardiovascular, ventilatory, and motor effects of centrally and peripherally administered synthetic trout U-II in our experimental animal model, the unanesthetized trout *Oncorhynchus mykiss*. In addition, we compare the actions of U-II with those of other neurohormonal peptides, particularly with the actions of urotensin-I, a 41-amino acid residue peptide paralogous to corticotropin-releasing hormone that is co-localized with U-II within neurons of the CNSS.

Contents

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1. Introduction

Urotensin-II (U-II) is a cyclic neuropeptide originally isolated from the caudal neurosecretory system (CNSS) of the teleost fish, *Gillichthys mirabilis*, on the basis of its smooth muscle-stimulating activity [6,48]. It has now been demonstrated that U-II is widely expressed in peripheral tissues and nervous structures of species from lampreys to mammals, and that evolutionary pressure has acted to conserve the cyclic region of the peptide (Cys-Phe-Trp-Lys-Tyr-Cys) while the N-terminal region is highly variable [15,16,38]. U-II has been identified as a specific natural ligand of the orphan G-protein-coupled receptor GPR14 (now renamed UT receptor) in mammals [1,39,44,46] and in teleost fish [41]. However, very little is known regarding the physiological effects of this peptide in its species of origin. In teleost fish, the CNSS is the major site of U-II expression, but U-II and the UT receptor have been also detected in several peripheral tissues including the heart, the gills, and the kidney, in close association with vascular elements and in several brain regions [31,41,58]. These data indicate that, in teleost fish, in addition to being a potent vasomodulatory [12,36] and osmoregulatory peptide [3,42] in the periphery, U-II may also act as a neurotransmitter or a neuromodulator in the central nervous system loci [29,30,36].

The present review summarizes the most significant results obtained relating to the cardiovascular, ventilatory and motor effects of centrally and peripherally administered synthetic trout U-II in our experimental animal model, the unanesthetized trout *Oncorhynchus mykiss*. In addition, we compare the actions of U-II with those of other neurohormonal peptides, particularly with the actions of urotensin-I (U-I), a 41-amino acid peptide, with similarity in structure to corticotropin-releasing hormone (CRH) [4,15,33,40] that is co-localized with U-II within neurons (Dahlgren cells) of the CNSS [6,32,41].

2. Central nervous system effects

Fish do not possess large and expanded cerebral hemispheres with a developed neocortex [45]. Consequently, these animals offer the opportunity to insert directly, under visual control, an intracerebroventricular (ICV) micro-guide between the two habenular ganglia towards the third ventricle until its tip is positioned between the two preoptic nuclei [37]. The method is rapid and accurate since no stereotaxic placement and no post-injection confirmation of the injected site is required.

2.1. Cardiovascular actions

After ICV injection of graded doses of trout U-II (5, 50 and 500 pmol) in the unanesthetized trout, the lowest dose of 5 pmol produces no change in either blood pressure or heart rate, 50 pmol U-II provokes a slight but significant increase in heart rate (HR) while only the highest dose of the peptide (500 pmol equivalent to ~2 nmol/kg) causes a significant and long lasting hypertensive response without changing HR [36]. The absence of bradycardia in response to an increase in blood pressure stands in sharp contrast to the results obtained following peripheral injection of the peptide (see Section 3), and suggests that the cardio-inhibitory baroreceptor reflex is altered following the injection of the high dose of the peptide. In normotensive and hypertensive unanesthetized rats and in unanesthetized sheep, ICV administration of U-II causes pressor and tachycardic responses through activation of the sympathetic system (for review see [56]) suggesting that in these species the baroreflex response is also impaired. Studies conducted on unanesthetized sheep to test this hypothesis demonstrated that, after ICV infusion of U-II (0.2 nmol/kg for 1 h), the baroreflex response is effectively blunted since no changes occur in the cardiac sympathetic nerve activity in spite of an increase in blood pressure [23]. In trout, comparisons may also be made between the central cardiovascular actions of trout U-II and trout U-I. Even at the very low dose of 5 pmol, U-I induces a large and prolonged hypertensive response that is due to an increase in cardiac output. HR does not change following the ICV injection of U-I, suggesting that, as for the central actions of a high dose of U-II (500 pmol), the cardiac baroreflex is impaired [43]. In summary, U-II and U-I at a low equimolar picomole dose of 5 pmol, exert differential effects on blood pressure, but neither peptide produces any change in the HR of the trout. It should also be noted that the central cardiovascular actions of U-II are relatively weak compared with the central actions of angiotensin II, which involve a pronounced tachycardic effect and a potent decrease in the cardiac baroreflex sensitivity [28,37], and endothelin I that involve a strong hypertensive action and reduced cardiac baroreflex response [35].

2.2. Ventilatory actions

In trout equipped only with a cannula inserted within the mouth to detect the change in buccal ventilatory pressure and with two electrocardiographic electrodes, we found that ICV injection of low doses of U-II (1 and 5 pmol) had no significant action upon the ventilatory amplitude (VA) and the ventilatory frequency (VF). However, U-II at a dose of 50 pmol produces a gradual increase in both VA and VF so that there is an overall twofold elevation in the total ventilation (VA × VF), indicating that U-II elicits a hyperventilatory response compared with vehicle injection [29,30]. The minimal effective dose for a twofold increase in the total ventilation after U-I ICV injection is 5 pmol, suggesting that brain structures controlling ventilation are more sensitive to U-I than to U-II. However, while the