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ScienceDirect
General and Comparative Endocrinology 153 (2007) 241–242
GENERAL AND COMPARATIVE ENDOCRINOLOGY
www.elsevier.com/locate/ygcen

Discussion

New insights into urotensin endocrinology: From fish to man

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The urotensins (UI and UII) were first identified in the caudal neurosecretory system (CNSS) of fish, a unique neuroendocrine structure located in the terminal segments of the spinal cord. More recently, homologues to both peptides have been identified in mammals and, while research continues into the role of the CNSS in fish, interest in the actions of the urotensins in other vertebrates, including man, has grown.

Steve Douglas reviewed the history of UII research in mammals, following the identification of its "orphan" G-protein coupled UT receptor, GPR14. Both UII and UT receptor are localised in regions of the mammalian brain, as well as in non-neural tissues such as cardiovascular and renal tissues. The potent vasoconstrictor actions of UII led to the search for antagonists that might be effective in disease states such as hypertension, congestive heart failure and diabetes mellitus. Current animal studies give cause for optimism that this "from gills to pills" approach will lead to novel and improved clinical tools, such as in patients whose hypertension cannot currently be controlled. For example, UT receptor antagonists have been shown to be highly protective against heart failure in animal models. Continuing on this theme, **Nick Ashton** and **Alaa Abdel-Razik** reported renal effects of UII in the rat. UT receptors are present in renal medulla and UII appears in relatively high concentrations in urine, suggesting that it is actively secreted. Both haemodynamic and tubular actions of UII are indicated, leading to reduced urinary output, and the converse effects were seen with a UT receptor antagonist, urantide.

Isabelle Lihrmann gave a comparative overview of UII, UII-related peptide (URP) and UT receptor distribution throughout the vertebrates. mRNA expression profiles for UII appear to be well conserved throughout the vertebrate series from dipneusts to mammals, with the highest level of expression in spinal cord, localised to motoneurons in the ventral horn. A similar distribution is seen for URP expression, apart from some differential expression in cranial nuclei. The UT receptor is widely expressed in the CNS and peripheral tissues, including skeletal muscle. In addition to central actions of the peptides with respect to cardiovascular control, these findings perhaps support a locomotory role for UII. In addition a role for URP in arousal, via the reticular activating system, was proposed.

Jean-Claude Le Mevel reported investigations into the central actions of UI and UII. The two peptides had differential effects when injected intracerebroventricularly in trout. UI, but not UII, caused increases in blood pressure and ventilatory output. Both peptides enhanced locomotor activity (swimming), though effects of UII were more long lasting. These findings suggest that the urotensins have important regulatory functions within the brain, which may also be of relevance to mammalian studies.

A comparative genomics study by **Herve Tostivint**, examined the relationship between UII/URP and somatostatin (SS)-related peptides, previously considered to be unrelated gene products. These peptides display a similar cyclic structure and precursor organisation throughout the vertebrates. Analysis of predicted gene duplications and chromosomal locations has led to an evolutionary model supporting a single ancestral gene superfamily for UII- and SS-related genes, raising questions regarding the evolution of UII and its function in lower vertebrates.

The CNSS of teleost fish was presented as a model system in which to examine neurosecretory mechanisms and urotensin physiology. In zebrafish (**Caroline Parmentier**), neurosecretory Dahlgren cells display immunoreactivity for both UI and UII. Most cells do not colocalise the two peptides. However, in some, UI and UII are colocalised even at the level of secretory terminals and vesicles. Detailed morphological observations indicate further secretory roles for the CNSS that have yet to be defined. With its characterised genome, the zebrafish provides the genetic tools with which to dissect CNSS function and other functional aspects of urotensin-related physiology. **Sarah Alderman** described a tissue mapping study of the expression patterns of UI, corticotropin-releasing factor (CRF), and CRF-binding protein in adult and developing zebrafish. All three show widespread but highly localised distribution within the CNS, including

0016-6480/$ - see front matter
doi:10.1016/j.ygcen.2007.06.008

areas of co-expression and unique expression. Both CRF and CRF-BP are expressed in the egg, with UI appearing soon after fertilisation, perhaps suggesting a role for these peptides in development.

In another teleost, the European flounder (**Cathy McCrohan**), the CNSS has been shown to synthesise CRF, parathyroid-related protein and acetylcholine, in addition to UI and UII. Dahlgren cells co-express up to three of these peptides. Electrophysiological and molecular studies of these cells reveal remarkable parallels with oxytocin and vasopressin neurons in the mammalian hypothalamus. It is proposed that differential expression of secretory peptides, ion channels underlying electrical activity patterns, and receptors for potential neuromodulators may lead to functional heterogeneity in the Dahlgren cell population, enabling changes in CNSS output during physiological adaptation. These changes have been examined in relation to osmoregulatory and seasonal demands in this migratory, euryhaline species. **Richard Marley** discussed the potential role of nitric oxide (NO) as an intrinsic local neuromodulator in the flounder CNSS. Dahlgren cells show immunoreactivity for nitric oxide synthase (NOS) and NOS mRNA expression is upregulated following acute transfer of fish from freshwater to seawater conditions. Electrophysiological recording combined with pharmacology suggests that NO excites the Dahlgren cells, potentially providing excitatory feedback to enhance secretory output. Again these findings reveal similarities with magnocellular hypothalamic neurons.

In the general discussion of the symposium, participants considered future directions of urotensin endocrinology research. To further our understanding of UII physiology, a need was identified for studies aimed at characterizing the targets of UII-expressing neurons and determining whether UII is released at neuromuscular junctions. Although expression profile studies have now identified a broad UT receptor distribution pattern, the ligand source for many of these targets is not known. Similarly, while the CNSS is the main source of circulating UII in fish (Balment et al., 2005), in tetrapods the main sources of circulating and cerebrospinal fluid UII have not been identified. Though UII and URP are expressed in motoneurons, the pathophysiological significance of UII in musculoskeletal function has not been addressed. Given the newly discovered relationship between UII/URP- and SS-related peptides (Tostivint et al., 2006), and the previous identification of five SS receptor subtypes in vertebrates (Nelson and Sheridan, 2005), the potential existence of additional UT receptors unrelated to GPR14 and also of URP-specific receptors was questioned. In teleosts, studies are needed to identify potential functional interactions between the CNSS, the brain, and the pituitary. While a variety of descending inputs to the CNSS have previously been identified (Winter et al., 2000), there is no anatomical evidence for neuronal fibers ascending from the CNSS to the brain (Andre Calas, personal communication).

The value of the CNSS to further our understanding of urotensin endocrinology in fish and tetrapods was also discussed. Given its accessibility, the CNSS is arguably one of the best model systems to study the morphology and innervation of neurohaemal organs and the regulation of neuropeptide secretion. Yet many fundamental questions regarding the evolutionary and physiological significance of the CNSS remain unresolved and equivocal views regarding the causes and consequences of the disappearance of the CNSS during tetrapod evolution were presented. Unlike tetrapods, the hypothalamic neurosecretory regulation of the adenohypophysis in teleosts is direct and in most species an hypophyseal portal system is absent (Peter et al., 1990). Does the highly organized CNSS of teleosts provide additional flexibility for the neuroendocrine regulation of physiological processes that are otherwise under the control of the more versatile hypothalamo-hypophyseal axis of tetrapods? If so, do the elasmobranchs, chondrosteans, and lungfish, which have a more diffuse CNSS (Onstott and Elde, 1986) but evidence of a hypophyseal portal system (Zambrano and Iturriza, 1973; Peter et al., 1990), represent intermediate forms between teleosts and tetrapods? What are the physiological consequences of the evolutionary loss of the CNSS in terms of urotensin functions? Although complex, these questions may be partially addressed by an analysis of the changes in target tissue receptor distribution and of the local changes in the paracrine and autocrine functions of the urotensins across different vertebrate taxa. Additionally, whether there has been a complete disappearance of the CNSS in the lineages leading to tetrapods is not known and studies are needed to determine whether a vestigial CNSS may be present during embryonic development in land vertebrates. Finally, future investigations are needed to ascertain the embryonic origin of the neurosecretory Dalhgren cells and their relationship to large motoneurons.

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