PHARMACOLOGICAL CHARACTERISATION OF THE UROTENSIN-II RECEPTOR LIGANDS URANTIDE AND UFP-803 IN CHO_{hUT} CELLS

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Urotensin II (U-II) is a cyclic peptide that selectively binds and activates the G protein coupled UT receptor. U-II exerts several biological actions especially on the cardiovascular system however its pathophysiological role(s) are still poorly understood. Selective UT ligands particularly antagonists are essential for the investigation of this novel peptide receptor system. Two U-II related peptides urantide (Patacchini *et al.*, 2003) and UFP-803 (Camarda *et al.*, 2006) were recently reported to behave as competitive UT receptor antagonists in the rat aorta bioassay (pA_2 8.3 and 7.5, respectively). Here we evaluate and compare the effects of urantide and UFP-803 in receptor binding ([^{125}I]UII isotope dilution) and functional studies ([^{3}H]IP_x accumulation and calcium mobilization, Fluo-4 AM/ Flexstation II) performed in CHO cells stably expressing ~1pmol/mg protein of the hUT receptor (Song *et al*., 2006).

Table 1: Effects of U-II, urantide and UFP-803 in CHO_{hUT} cells

	Binding	[^{3}H]IP_x assay			Calcium assay		
	pK_i	pEC_{50}	E_{max}	α	pEC_{50}	E_{max}	α
U-II	9.34	9.31	4022±274	1.00	9.08	193±11	1.00
Urantide	9.22	8.69	1454±82	0.36	9.35	120±4	0.62
UFP-803	8.82	8.19	940±22	0.23	8.63	48±5	0.25

Data are the mean ± SEM of at least 4 separate experiments.

Urantide and UFP-803 mimicked U-II with the following order of affinity/ potency U-II > urantide > UFP-803. However, the maximal effects of both urantide and UFP-803 were only a fraction of those induced by UII indicating partial agonism at the human UT receptor. The efficacy of UFP-803 was consistently lower than that of urantide. In conclusion the present data suggest that both urantide and UFP-803 should be classified as UT receptor partial agonists with the latter showing lower potency and efficacy.

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References

Camarda, V, et al. (2006). *Br J Pharmacol* **147:** 92-100.
Patacchini, R, et al.(2003). *Br J Pharmacol* **140:** 1155-8.
Song W, et al. (2006). Naunyn-Schmiedebergs Arch. Pharmacol. **373**:148-157.