REGIONALLY-SELECTIVE VASODILATOR ACTIONS OF CORTICOTROPIN RELEASING FACTOR (CRF) 2 RECEPTOR LIGANDS IN CONSCIOUS RATS

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Hypotensive effects of the CRF2 receptor-selective ligands, human and mouse urocortin 2 (UCN 2) in rats (Chen *et al*., 2003; Mackay *et al*., 2003), and vasorelaxant actions of stresscopin related peptide (SRP i.e. human UCN 2) in human isolated vessels (Wiley & Davenport, 2003) have been reported, but their *in vivo* haemodynamic actions are not known. Our aim was to compare the regional haemodynamic effects of mouse UCN 2 and SRP in conscious rats.

Under anaesthesia (fentanyl and medetomidine, 300 μg kg^{-1} of each i.p. reversed with nalbuphine and atipamezole, 1 mg kg^{-1} of each s.c.), 12 male, Sprague-Dawley rats (400-450g) had pulsed Doppler flow probes and, at least 14 days later, intravascular catheters, implanted. On the day following catheterisation, measurements of mean arterial blood pressure (BP), heart rate (HR) and renal (R), mesenteric (M) and hindquarters (H) vascular conductances (VC) were made. Rats were randomised to receive i.v bolus doses (3, 30, 300 and 3000 p mol kg^{-1} in ascending order) of mouse UCN 2 or SRP on Day 1 and the other peptide on Day 3, with control injections of saline (0.1ml) on Day 2.

Resting cardiovascular variables (mean ± s.e. mean), prior to the administration of the first dose of UCN 2 or SRP were not different (HR 340±11, 366±12 beats min^{-1}; BP 110±2, 109±2 mmHg; RVC 81±4, 80±4; MVC 102±9, 99±6; HVC 35±1, 43±5 ([kHz $mmHg^{-1}$]10^3), respectively). At the two lower doses, neither UCN 2 nor SRP had any significant cardiovascular effects. At doses of 300 and 3000 p mol kg^{-1},

Table 1. Cardiovascular effects of UCN 2 or SRP (p mol kg^{-1}) in conscious rats. Values (mean ± s.e.mean; n=12) represent the areas under or over the curves (AUC, AOC) between 0 and 30 min for HR (beats), BP (mmHg min), and VC (% min).

UCN2	**HR**	**BP**	**RVC**	**MVC**	**HVC**
300	+334±127	-154±33	-51±17	+397±58	+345±122
3000	+2452±316	-387±63	-216±54	+1188±231	+1018±142
SRP	**HR**	**BP**	**RVC**	**MVC**	**HVC**
300	+797±174	-153±27	-70±18	+418±62	+137±12
3000	+1836±234	-770±39	-201±46	+1172±127	+1760±326

both peptides caused dose-dependent tachycardia, hypotension, and increases in MVC and HVC, but not RVC (Table 1). The effects of 300 p mol kg^{-1} SRP on HR, and 3000 p mol kg^{-1} SRP on BP and HVC were greater than those of the corresponding dose of UCN ($P<0.05$, Wilcoxon's test).

The results indicate that the hypotensive effects of selective CRF2 receptor ligands are due to preferential mesenteric and hindquarters vasodilatation, as are those of CRF administered under the same conditions (Bennett *et al*., 2002). Thus, it seems likely that the cardiovascular effects of peripherally-administered CRF are mediated by CRF2 receptors.

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