

UROCORTIN ATTENUATES KEY INDICATORS OF NIGROSTRIATAL PATHWAY DESTRUCTION IN A RAT HEMIPARKINSONIAN MODEL

Christopher S. Biggs², Amjad Abuirmeileh¹, Ian C. Locke², Richard A. Knight², Hardial S. Chowdrey² and Peter S. Whitton¹, ¹Department of Pharmacology, The School of Pharmacy, 29-30 Brunswick Square, London WC1N 1AX, UK, ²School of Biosciences, University of Westminster, 115 New Cavendish Street, London W1W 6UW, UK

Recent evidence suggests that the corticotrophin releasing hormone (CRH) related peptide urocortin (Ucn) may confer protection upon a variety of cell types subjected to cytotoxic insults. We have investigated this possibility in the rat 6-hydroxydopamine (6-OHDA) hemiparkinsonian model by examining the effects of Ucn upon two standard indices of nigrostriatal pathway function as well as the appearance of TUNEL positive cells within the substantia nigra.

Male Wistar rats (230-260g) were used throughout and administered pargyline (50mg kg⁻¹) and desmethylimipramine (25mg kg⁻¹; 1.0ml kg⁻¹ body weight, i.p.) prior to intracerebral 6-OHDA injection, in order to protect non-dopaminergic neurons. Data were statistically analysed using one way ANOVA followed by post hoc students t-test (n = 4-6 per group). Fourteen days following stereotaxic surgery, rats given concomitant injections (t=0) of 6-OHDA and Ucn (injection volume 2µl⁻¹) into the right medial forebrain bundle and ipsilateral substantia nigra (SNc) respectively, responded weakly to apomorphine (0.5 mg kg⁻¹) challenge, in marked contrast to those given 6-OHDA and vehicle (p<0.05). In separate experiments, rats received Ucn seven days *following* initial stereotaxic injection of 6-OHDA (t+7) as described previously and these animals exhibited near identical circling intensity to those that received 6-OHDA and Ucn concomitantly, following apomorphine challenge (overall turns: sham = 0; 6-OHDA/vehicle = 20.3 ± 5.3; 6-OHDA/Ucn t=0 = 3.2 ± 0.5; 6-OHDA/Ucn t+7 = 4.4 ± 1.65). In all animals, we estimated tissue dopamine (DA) levels in striata ipsilateral to injection sites and those of 6-OHDA/ Ucn treated rats were comparable with sham injected rats, whilst rats given 6-OHDA and vehicle had considerably lower DA levels (p<0.05), consistent with extensive destruction of nigrostriatal neurons. Striatal DA levels in animals where Ucn injection had been delayed by seven days were only modestly decreased compared to those of animals receiving 6-OHDA and Ucn concomitantly (overall DA µg/mg tissue: sham = 1.01 ± 0.08; 6-OHDA/vehicle = 0.062 ± 0.025; 6-OHDA/Ucn t=0 = 0.86 ± 0.06; 6-OHDA/Ucn t+7 = 0.7 ± 0.2). Finally the appearance of TUNEL positive cells was also significantly reduced (p<0.05) in Ucn treated rats at both t=0 and t+7 (overall mean counts TUNEL positive nigral cells: sham = 1.06 ± 0.65; 6-OHDA/vehicle = 3.31 ± 0.2; 6-OHDA/Ucn t=0 = 1.2 ± 0.56; 6-OHDA/Ucn t+7 = 1.6 ± 0.61). We are aware that TUNEL is not a marker for dopaminergic neurons per se. However, in total our data strongly suggest that Ucn is capable of maintaining adequate nigrostriatal function *in vivo* following a neurotoxic challenge which simulates many aspects of Parkinson's disease, a finding consistent with prevention of neurodegeneration or increasing functional capacity of surviving neurons.