

## UROCORTIN REVERSES PARKINSONIAN LIKE EFFECTS OF INTRA-NIGRAL LIPOPOLYSACCHARIDE INJECTION

Amjad Abuirmeileh<sup>1</sup>, Christopher S. Biggs<sup>2</sup>, Rebecca Lever<sup>1</sup> and Peter S Whitton<sup>1</sup>

<sup>1</sup> Department of Pharmacology, The School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK. <sup>2</sup> School of Biosciences, The University of Westminster, 115 New Cavendish Street, London W1W 6UW, UK.

Parkinson's Disease (PD) is an irreversible neurodegenerative disorder with no cure and current treatments which have limited efficacy and unpleasant side effects. The etiology of PD is complex involving apoptotic changes mediated by factors including inflammatory mediators (Hirsh *et al.*, 2006). We have recently observed that the corticotrophin releasing factor-like peptide urocortin (UCN) reverses key features of nigrostriatal neurodegeneration in the 6-hydroxydopamine (6-OHDA) hemiparkinsonian rat, including ipsilateral circling following apomorphine challenge, loss of tissue DA and loss of striatal and nigral tyrosine hydroxylase activity (TH; Biggs *et al.*, 2006). However, while useful, the 6-OHDA model of PD is based upon an highly aggressive pro-apoptotic degeneration. Intranigral lipopolysaccharide (LPS) injection produces a relatively milder, more progressive 'model' of PD, based upon the initiation of pro-inflammatory events. In the present study we have evaluated whether UCN is also effective in the LPS treated rat, as we have found it to be in the 6-OHDA treated animal. A key factor in our use of this model is that UCN has been reported to have anti-inflammatory properties in the periphery (Gonzalez-Rey *et al.* 2005).

Male Wistar rats (250-280g<sup>-1</sup>; n = 4-6 per group) were anaesthetised with isoflurane and 2µg of LPS and / or 2 pmol<sup>-1</sup> of UCN in 2µl<sup>-1</sup> of phosphate buffered saline were stereotaxically injected into the substantia nigra. 14 days later, rats were challenged with 0.5 mg kg<sup>-1</sup> of apomorphine to evaluate ipsilateral circling behaviour after which they were decapitated, the brains rapidly removed and the striata and nigra taken for determination of TH activity and DA content as previously described (Biggs *et al.*, 2006). Data were subjected to one way ANOVA followed by Dunnett's post hoc test.

None of the rats in the study showed any overt changes in behaviour following nigral LPS injection. In rats given LPS alone, apomorphine induced circling behaviour was greatly attenuated by co-injection of UCN (11.2 ± 0.98 vs 3.77 ± 0.6 turns/120 s for LPS and LPS + UCN respectively, p<0.05). In the ipsilateral nigra and striatum of LPS treated rats, tissue DA level was reduced by 59 and 60% respectively and this was reversed in rats co-treated with UCN. Similarly, TH activity was reduced by 55 % and 40% respectively in nigral and striatal homogenates of LPS treated rats and this was significantly attenuated by UCN co-administration.

The current data provide further evidence for a potential neuroprotective role for UCN in models of PD. Given that PD is almost certainly the result of complex multifactorial events, the actions of UCN may be especially fortuitous. By combining both anti-apoptotic and anti-inflammatory properties it may be that UCN combines actions to yield an 'anti-Parkinsonian' like effect. It is our opinion that the development of CNS permeable ligands for the UCN receptor could constitute a significant development in the therapy of PD

Biggs, C.S. *et al* (2006) *Proceedings of the British Pharmacological Society at* <http://www.pa2online.org> Vol. 13 Issue 4 abst 162P

Gonzalez-Rey *et al.* (2006) *Gut*, **55**, 824-832.

Hirsh *et al.* (2005) *Parkinsonism and related disorders*. **11**, S9-S15.