EFFECTS OF NEUROPATHIC INJURY ON THE EXPRESSION PROFILE OF PACAP FAMILY MEMBERS IN THE RAT BRAIN

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BACKGROUND

Increasing evidence supports the idea that neuropathic injury can trigger an array of disruptions in emotional coping behaviours in a cohort of vulnerable patients. These patients exhibiit abnormalities in social behaviour, sleep patterns and feeding habits, which can culminate in depression. Despite the efforts, there is still a gap in our understanding of the causes underlying the development of these comorbidities. In earlier works, we have developed and characterised a model of chronic constriction injury (CCI) of the sciatic nerve in rats. The model well-reproduces several of the 'behavioural disabilities' observed in humans, with an incidence of about 30%. The peptide pituitary adenylate cyclase-activating polypeptide (PACAP), its homologue vasoactive intestinal peptide (VIP) and the related receptors PAC1, VPAC1 and VPAC2 are strongly implicated in regulating social behaviours and sleep patterns, making them attractive targets to study in relationship to the disabilities caused by nerve injury. In this study, our aim was to profile the PACAP system in brain regions involved in the development of such disabilities with the purpose of identifying a possible association between perturbations of the PACAPergic system and the occurrence of behavioural disabilities in selected cohorts of animals.

METHODS

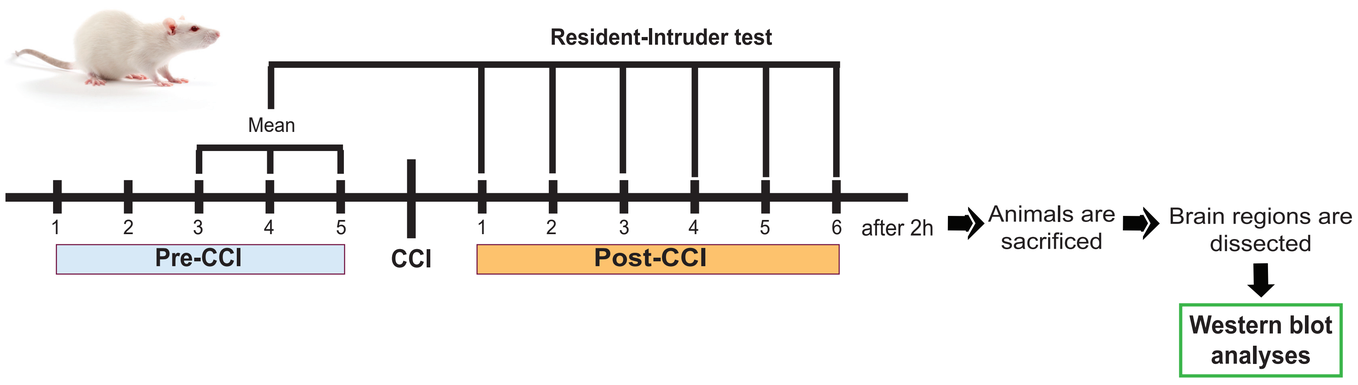
Male Sprague Dawley rats were characterised using the Resident-Intruder social interaction testing. Based on the changes in dominance behaviour following the CCI surgical procedure, animals were indicated as either having Pain alone, Transient Disability and Persistent Disability.

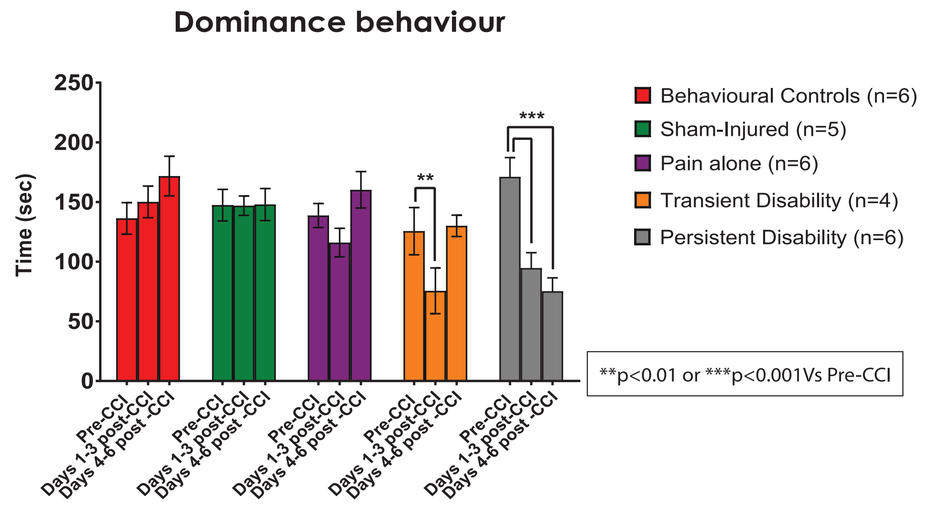
Dominance behaviour is a robust territorial behaviour that a rat in his home cage develops *Vs* a novel non-littermate rat (*the intruder*) to demonstrate his position in the social hierarchy within that cage. Observable behaviours include standing above, leaning on the supine *intruder*, offensive sideways lateral attacks and biting.

Pain alone - No change in dominance behaviour post-CCI compare d to pre-CCI.

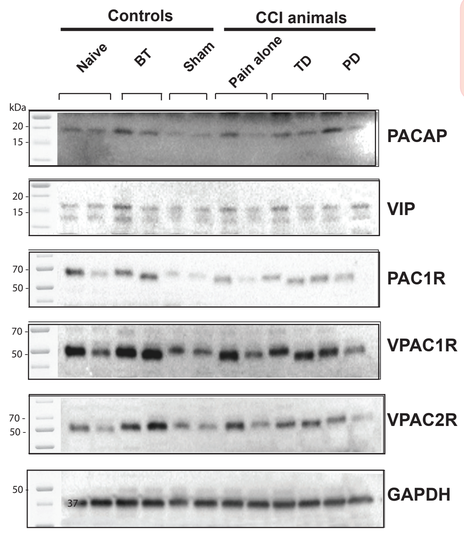
Transient Disability - >30% decrease in dominance behaviour post-CCI with recovery within 5 days

Persistent Disability - >30% decrease in dominance behaviour post-CCI.

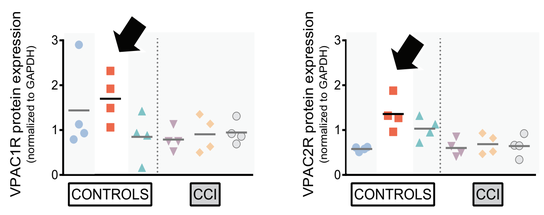




(1) - PACAP system in the Dorsal Hippocampus

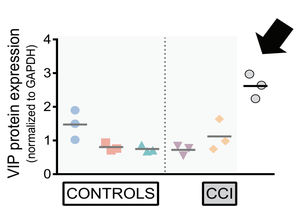


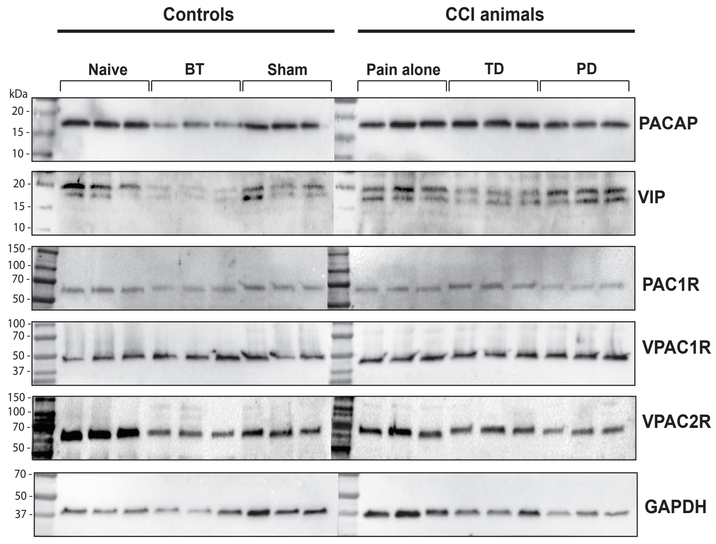
Representative blots showing that VPAC1R and VPAC2R protein expression levels are increased as an effect of the social interaction testing (Resident-Intruder test) and reversed by the nerve injury. *(n=4 per group)*

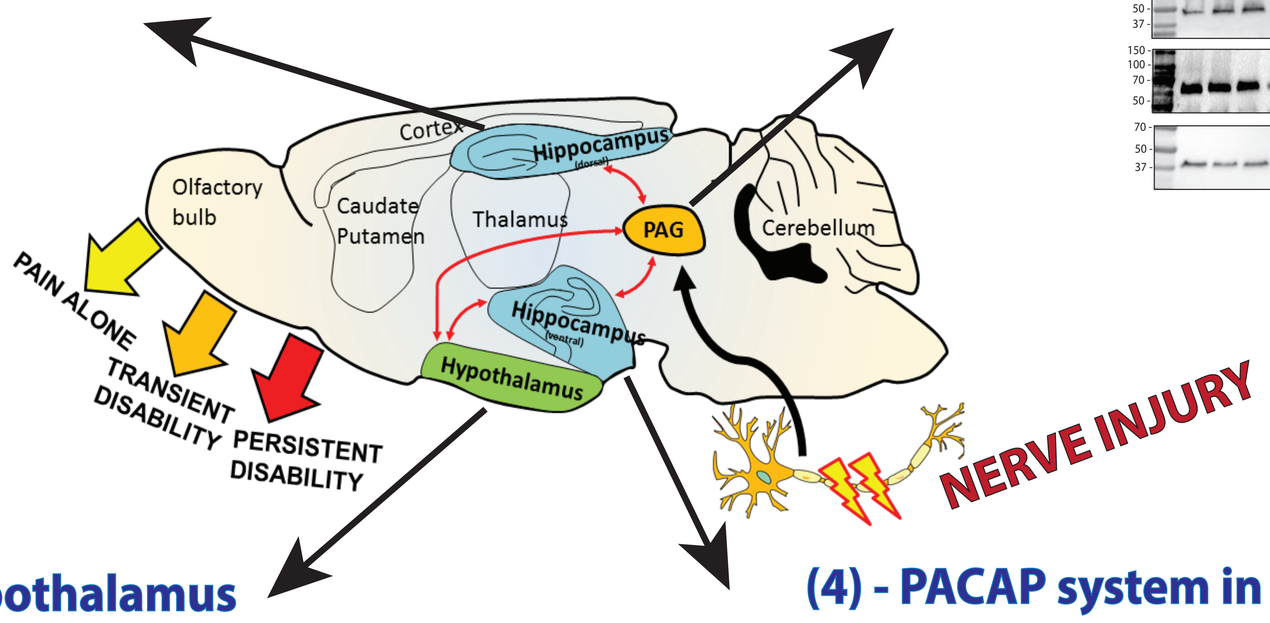


(2) - PACAP system in the Periaqueductal grey

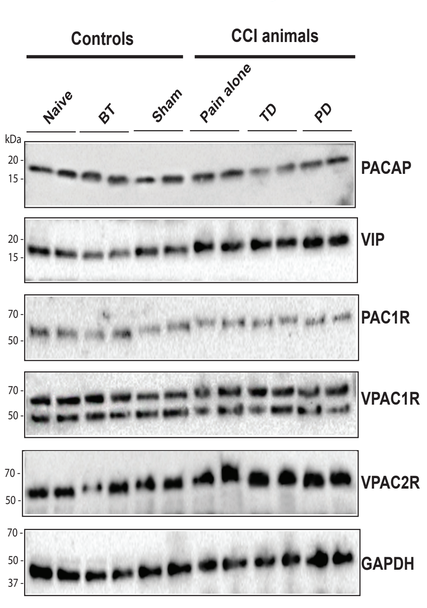
Western blots depicting a selective increase in VIP protein expression in the animal group that had undergone CCI surgery and developed "Behavioural Disability". *(n=3 per group)*



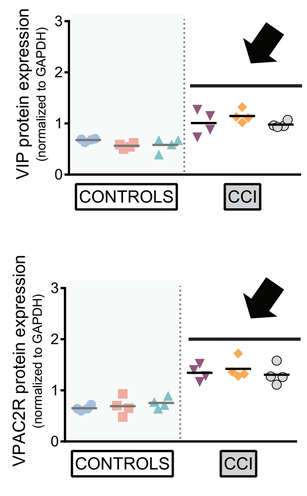




(3) - PACAP system in the Hypothalamus

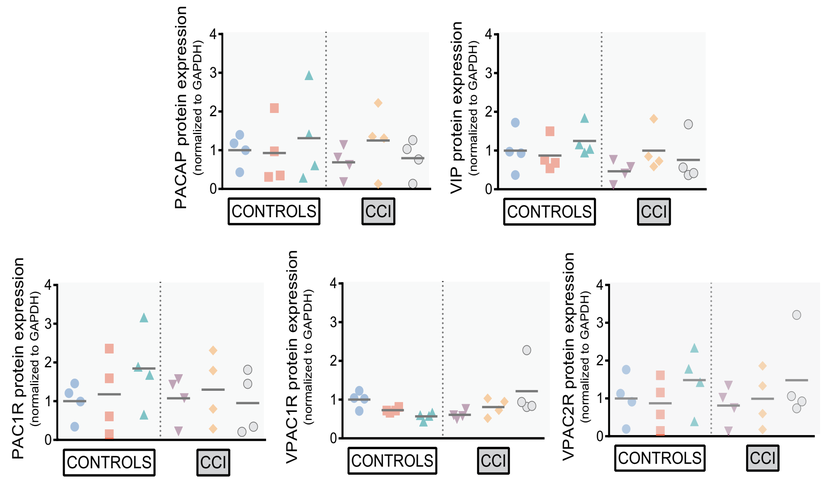


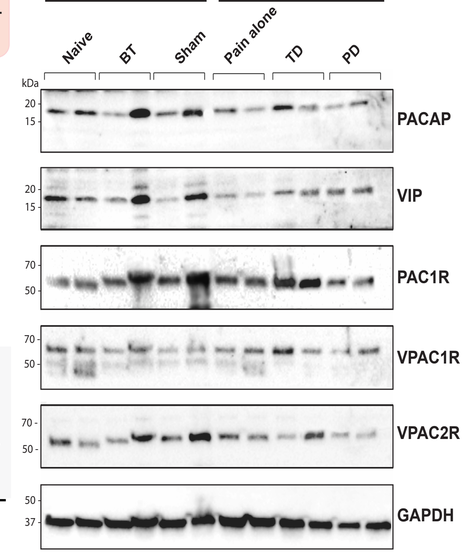
Representative Western blots showing increased VIP and VPAC2R protein expression levels in CCI rats, regardless of the behavioural phenotype. *(n=4 per group)*



(4) - PACAP system in the Ventral Hippocampus

Western blots analyses demonstrated that the expression levels of none of the PACAP family members were altered by the nerve injury alone or in combination with the associated behavioural disabilities in the ventral hippocampus. *(n=4 per group)*





FINAL REMARKS

The present findings suggest that the PACAP system may be involved in the complex behavioural disabilities triggered by nerve injury. We observed regional-specific changes in the expression of PACAP, VIP and related receptors, which may account for specific dysfunctions in cyrcadian rythmicity, coping mechanisms and mood. Specifically, the enhanced VIP/VPAC2R axis in the hypothalamus of nerve-injure rats may be a pre-requisite for the development of sleep disturbances, whereas the select increase of VIP expression in the periaqueductal grey of disabled rats points to a role of PACAP system in regulating passive coping behaviours. Finally, the increased expression of VPACRs in the dorsal hippocampus highlights the sensitivity of this peptidergic system towards social stressors.