TRPV1 mRNA Expression Within The CNS Of Two Rat Strains Differing In Nociceptive Responsivity

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Introduction: The Wistar-Kyoto (WKY) rat is a stress-hyperresponsive strain that exhibits a hyperalgesic phenotype, compared with the Sprague-Dawley (SD) strain[1,2]. Given the well-established role of the transient receptor potential vanilloid receptor 1 (TRPV1) in modulating peripheral[3,4] and central[5,6] pain processing, we hypothesised that differences in the expression of TRPV1 within the CNS may account for the differential nociceptive responsivity in WKY vs. SD rats. The aim of the present study was to complete a comparative analysis of TRPV1 mRNA expression within the CNS of WKY and SD rats that had received intra-plantar injection of either saline or the noxious chemical formalin.

Methods: Adult male WKY or SD rats weighing 280-320g received intra-plantar injection of either saline(SAL) or formalin (2.5%, 50µl)(FORM) (n=10-12 rats per group for behaviour and n=6 for post-mortem analysis) under brief isoflurane anaesthesia (3%) and nociceptive behaviour assessed for 30 minutes using EthoVision XT software to generate composite pain scores (CPS). Rats were killed by decapitation at the end of the formalin trial period and total RNA was extracted from spinal dorsal horn and frozen punches of periaqueductal grey (PAG), rostroventral medulla (RVM), hippocampus (HIPP), amygdala (BLA) and prefrontal cortex (PFC). qRT-PCR was used to determine the expression of mRNA coding for TRPV1. Data were analysed by two-way ANOVA followed by Fisher's LSD post-hoc test. $P<0.05$ was considered statistically significant and data are presented here as mean ± SEM.

Results: WKY rats exhibited significantly higher formalin-evoked nociceptive behaviour than SD counterparts, indicating a hyperalgesic phenotype (CPS: SD-FORM: 0.84±0.09 vs. WKY-FORM: 1.14±0.04; $P<0.01$). TRPV1 mRNA levels were significantly higher in the dorsal PAG (SD-SAL: 100±14.2% vs. WKY-SAL 55.3±6.8%; $P<0.05$), and lower in the lateral PAG (SD-SAL: 100±5.38% vs. WKY-SAL: 183±23.4%; $P<0.05$) of saline-treated SD rats compared with WKY counterparts. There were no significant differences in TRPV1 mRNA expression in the ventrolateral PAG between the two strains. Formalin treatment was associated with a significant reduction in TRPV1 mRNA expression in the dorsal PAG of SD rats only (SD-SAL: 100±14.42% vs. SD-FORM: 63±7.84%, $P<0.05$). In contrast, formalin injection was associated with increased TRPV1 mRNA expression in the ventral PAG of SD rats only (SD-SAL: 100±9.65% vs. SD-FORM: 209±35.4%; $P<0.001$). Formalin administration was associated with reduced TRPV1 mRNA expression in the PFC of SD rats only (SD-SAL: 100±20.32% vs. SD-FORM: 52±7.73%; $P<0.05$), and in the BLA of both WKY (WKY-SAL: 98±6.57% vs. WKY-FORM: 36±6.04%; $P<0.01$) and SD (SD-SAL: 100±15.8% vs. SD-FORM: 54±7.08%; $P<0.05$) rats. TRPV1 mRNA expression in the ventral hippocampus did not differ between the two strains, but there was a significant formalin-induced reduction in mRNA expression in SD rats (SD-SAL: 100±26.76% vs. SD-FORM: 43±4.68%; $P<0.05$). TRPV1 mRNA expression in the spinal dorsal horn did not differ between the two strains irrespective of SAL/FORM treatment.

Conclusion: These data provide evidence for rapid, dynamic formalin-evoked alterations in TRPV1 gene expression in pain-related brain regions of SD and WKY rats. Further studies

are required to determine whether these alterations underlie differential formalin-evoked nociceptive behaviour in the two rat strains.

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Ethics approval: All animal experiments were performed in accordance with Animal Care and Research Ethics Committee, National University of Ireland, Galway, Irish Department of Health and Children, and the European Communities Council directive 86/609 guidelines on the use of animals in scientific research under the license no: B100/3613.

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