Role for NPY in the gender-specific gastrointestinal and feeding responses to stress

Sarah Forbes¹, Herbert Herzog², Helen Cox¹

¹Wolfson Centre for Age-Related Diseases, King’s College London, SE1 1UL, London, United Kingdom, ²Neuroscience Programme, Garvan Institute of Medical Research, NSW 2010, Sydney, Australia

Exposure to an acute stress inhibits gastric emptying and stimulates colonic transit in the gastrointestinal tract (GI), in addition to reducing food intake, via modulation of central neuropeptide Y (NPY) pathways. Stress-responses are gender-dependent, with several stress-related GI pathologies such as irritable bowel syndrome and eating disorders, more prevalent in females (Drossman et al., 1993; Blehar, 1995). Interestingly the anxiogenic-like phenotype of NPY⁻/⁻ mice is more pronounced in males (Karl et al., 2008) raising the possibility that stress-induced GI and feeding responses are sexually dimorphic through interactions with NPY. The aim of this study was to determine GI transit rates, food intake and corticosterone levels after an acute restraint (AR) or novel environment (NE) stress in adult male and female NPY⁻/- and WT mice.

All mice had a mixed 129/SvJ/C57BL/6 background and were aged 10-16 weeks. Small intestinal transit (SIT) was determined in vivo 30 min after intra-gastric administration of a charcoal marker (10% plant charcoal in 5% gum acacia), and corticosterone levels were determined under basal or restrained conditions (30 min) and in male WT mice treated with the Y₂ antagonist BIIE0246 (60µg/100µl i.p.). Faecal pellet output (FPO) and food intake were established after 15 min and 4 hr, respectively, in a novel environment and the rate of colonic faecal pellet propulsion (FPP) was measured in vitro over 20 min in the presence or absence of BIIE0246 (1µM) in WT mouse tissue. Additionally the role NPY plays in the peripheral modulation of GI motility through Y₂ receptors and stress-induced changes in GI Y₂ receptor expression were semi-quantified using RT-PCR. Female NPY⁻/- mice, compared with female WT and male NPY⁻/- mice, displayed the slowest SIT (% small intestinal length) after restraint (41.4±1.9 vs. 43.2±9.5 and 55.8±4.3, female and male NPY⁻/- SIT P<0.05, n=4-5), but the highest faecal pellet output (FPO, Pellets/15 min) (10.0±2.0 vs. 3.1±0.4 and 7.7±0.5, respectively, P<0.05, n=6-8) and reduction in food intake (g) during or after both stressors (0.12±0.04 vs. 0.72±0.06 and 0.27±0.03 (AR stress), 0.12±0.04 vs. 0.5±0.1 and 0.24±0.05 (NE stress), P<0.05, n=3-8). Male NPY⁻/- mice had significantly higher levels of corticosterone (ng/ml) than male WT mice under basal and stress stimulated conditions (714.2±123.4 vs. 129.5±20.5 and 278.8±27.5, respectively, P<0.05, n=3-6). Additionally peripheral Y₂ receptor antagonism in WT males showed a tendency to increase SIT in vivo (68.3±2.9 vs. 57.3±6.2, P>0.05, n=4) and colonic transit (% colonic length) in vitro (13.06±1.7 vs. 8.1±1.07, P<0.05, n=8) compared to vehicle-treated male WT mice, whilst genetically ablating NPY led to a trend in this direction in both parameters (SIT: 71.3±8.02 vs. 57.3±6.2, P>0.05 and FPP: 10.6±1.7 vs. 8.4±0.9, P>0.05, n=4-5), however chronic stress did not appear to affect Y₂ receptor expression in any group. The results of this study indicate that NPY may exert moderate peripheral inhibitory effects on GI transit through the Y₂ receptor but it possesses a significant role in the gender-dependent susceptibility to stress-induced GI and feeding responses.


Funded by the BBSRC.