Sex-dependent vulnerability to neurological disorders

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Early life experience, such as maternal environment and stress exposure, has a central role in the susceptibility to psychiatric and metabolic disorders in adulthood (Burghy et al, 2012). Genetic predisposition interacts with dietary habits and psycho-social factors to determine the current obesity pandemia and its comorbid pathologies such as type 2 diabetes.
Neuropeptide Y (NPY) is an abundant and widespread peptide in mammalian nervous system with multiple modulator effects in the regulation of physiological functions including anxiety, stress response and energy balance via the activation of the Y1 receptor (Y1R) subtype.
We recently demonstrated that maternal care induces long term effect on limbic Npy1r gene expression and, thereby, on behavioural and metabolic phenotype in mice. Adult mice raised by low caring dams exhibit lower expression levels of *Npy1r* in the limbic system coupled with anxiety, reduced body weight, decreased amounts of adipose tissue, lowered serum leptin levels, and higher corticosterone levels (Bertocchi et al., 2011). The same phenotype was observed in mice where limbic *Npy1r* gene was deleted (Npy1r^{rfb} mice; rfb, reduced forebrain expression), and became evident only when Npy1r^{rfb} knockouts were raised by high-caring foster mothers (Bertocchi et al., 2011). Importantly, the phenotype observed in Y1R^{rfb} mice was dependent of gender since Y1R^{rfb} females showed an increase in body weight starting at around postnatal day 110 but no differences in anxiety and hypothalamus-pituitary-adrenal axis activity, compared with their control littermates. Preliminary results indicate that conditional gene inactivation of the limbic *Npy1r* gene increases mice vulnerability to metabolic challenges in adult male, but not in female mice. In fact, when Npy1r^{rfb} mice were exposed to a highly palatable high fat diet (HFD) for 3 weeks, Npy1r^{rfb} male, but not female, mice showed a rapid body weight increase, higher calories intake during the first HFD week, and, after treatment, an higher perigonadic fat depot and plasma glycaemia as compared to controls. These data, together with our previous demonstration that ER activate Npy1r gene transcription (Musso et al., 2000), strongly suggest that brain Npy1r represents a key metabolic target gene through which estrogens and their cognate receptors modulate energy metabolism in relation to reproductive activity and stress response. We are currently evaluating whether this gender difference in vulnerability to metabolic challenges and anxiety is caused by hormonal factors and whether the absence of hormonal stimulation abrogates such a status.

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Burghy et al. (2012). Nat. Neurosci 12:1736-41.
Musso et al. (2000). *Neuroendocrinology* 72:360-67.