Sexual dimorphism in anxiety, depression and diet-induced obesity: relative contribution of brain inflammation*

L. Décarie-Spain[1*], S. Sharma[1], C. Hryhorczuk[1], A. Fisette[1], E. Jacob-Brassard[1], T. Alquier[1] & S. Fulton[1]

[1] Centre de recherche du CHUM, Université de Montréal & Montreal Diabetes Research Centre, Canada

Summary This work emphasizes the urgency for female representation in pre-clinical and clinical research. Specifically, our results evidence a strong divergence in the neurobiological mechanisms underlying anxiety and depression in a context of obesity between males and females, despite a similar behavioural phenotype.

1. Relevance

Obesity increases the odds of developing a major depressive disorder. Mood disorders are twice as prevalent in women as in men. Yet, in the search for novel anti-depressant targets, the use of female rodents is limited. As a jumping board to personalized medicine, biomedical research should validate therapeutic avenues in both males and females.

2. Aims & Objectives

A bilateral relationship ties obesity and depression. A chronic low-grade inflammatory profile is also commonly observed in both conditions. The nucleus accumbens is a core region for hedonia and motivation and alterations in hedonic and motivational functions are characteristic of both depression and obesity. Given these well-established facts, we aimed to verify if anxiety and depressive-like behaviours induced by obesity, in mice, were mediated by inflammation in the nucleus accumbens of male and female mice.

3. Methods

Adult male and female mice fed a low-fat or high-fat diet underwent testing for body composition, metabolic impairments as well as anxiety and depressive-like behaviours. Expression of inflammatory markers were analysed in the plasma and nucleus accumbens. In additional cohorts, a major inflammatory pathway (nuclear factor kappa-B) was downregulated specifically in the nucleus accumbens, via stereotaxic surgery, to investigate this pathway's contribution to anxiety and depressive-like behaviours induced by high-fat feeding.

4. Results

In both male and female mice, saturated high-fat feeding promotes metabolic impairments as well as anxiety and depressive-like behaviours. However, inhibition of inflammation in the nucleus accumbens rescued the behavioural phenotype in males but not females. Their respective nucleus accumbens inflammatory profiles also diverge, with clear activation of astrocytes and microglia in males, while female appear to rely more heavily on peripheral immune cells infiltrating the central nervous system. In addition, alterations in the limbic system of females seem to involve changes in estrogen receptors.

5. Conclusions

Despite similar behavioural presentation, distinct neurobiological mechanisms underlie anxiety and depression in a context of obesity in males versus females. Therapeutic response cannot be extrapolated from one sex to the other. Female representation in pre-clinical and clinical samples is crucial to address the rising problematics of obesity and mental health disorders.

6. Contact details: Léa Décarie-Spain, lea.decarie@gmail.com