Gene-environment interactions in eating disorders and obesity and their relationship with the reproductive functioning

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Abstract

This thesis investigates gene-environment interplay underlying molecular basis of eating disorders and obesity. We focused the attention on the role of epigenetic mechanisms controlling expression of relevant feeding-modulating homeostatic and hedonic genes, analyzed also in the attempt to suggest nutritional intervention by gut microbiota modulation. The major finding was the selective regulation of genes belonging to the endogenous cannabinoid system in different conditions. We observed epigenetic regulation of cannabinoid receptor type type I gene (*Cnr1)* in hypothalamus and nucleus accumbens of the activity-based model of anorexia nervosa (ABA), namely a significant reduction of gene expression correlated with higher DNA methylation at specific CpG sites in ABA rats compared to controls. Consistent hypermethylation was observed at *Cnr1* in a subset of restricted human subjects where, with different environmental cues (i.e. hyperactivity, stressful events and dieting history) relevant for the epigenetic regulation of the gene. In an animal model of obesity, we reported

the exactly opposite direction of changes for *Cnr1* in the hypothalamus, that were confirmed in human subjects. We also explored effects of dietary intervention with selected probiotic strain in the *anx/anx* mice model of anorexia, observing a reverted expression of the central *Cnr1* gene, as well as tendency to lower inflammatory markers in the colon. The transcriptional regulation of relevant endogenous system genes, such as those belonging again to the endocannabinoid but also to the opioid system, was also analyzed in an animal model of Diet Induced Obesity. A selective epigentic regulation was observed for *Cnr1* and mu opioid receptor gene just at the beginning of the development of the obese phenotype. Finally, we also investigated the transcriptional regulation of endocannabinoid system components in an animal model of binge eating behavior where the selective altered gene expression of the enzyme responsible for endocannabinoids degradation, fatty acid amide hydrolase, was observed in the hypothalamus of rats displaying binge behavior compared to controls. These changes were correlated with altered histone acetylation at gene promoter. Our findings suggest novel biomarkers for eating disorders and obesity, and due to the reversible nature of the epigenetic hallmark, open avenues for environmental strategies of intervention.