Sex-specific behavioral epigenetics in animal models of stress-related psychiatric disorders

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Current pharmacological research in psychiatry encourages sex-specific therapeutic intervention. This reflects the rate of successful treatment for environmental- and genetic-related psychiatric diseases in men and women. Males and females use distinct brain circuits to cope with similar challenges. The hippocampus is a crucial target of stress and sex hormones, because of its neuroanatomical connectivity and expression of steroid hormone receptors. We explored sex and genotype differences on hippocampal transcriptome and behavior in response to stress and estradiol in heterozygous BDNF Val66Met (HET-Met) mice, a model of genetic sensitivity to stress. RNA sequencing of ribosome-bound mRNA from hippocampal CA3 neurons demonstrated a sexually dimorphic transcriptome, with HET-Met female mice displaying greater gene expression change than HET-Met males, when compared to their respective wild-type mice. Interestingly, genes common to both sexes were regulated by genotype in opposite direction. HET-Met mice of both sexes showed a pre-stressed translational phenotype, in which the same genes that were induced as a function of genotype, without applied stress, were also induced in wild-type mice by an acute stressor. Pre-stressed gene networks included epigenetic modifiers and glucocorticoid-binding genes. Thus, the translational response to stress in CA3 neurons was sex- and genotype-specific. Behaviorally, males of either genotype did not exhibit cognitive deficits. In females, spatial memory was affected only in HET-Met mice, regardless of stress exposure. This effect was not observed in ovariectomized HET-Met females, suggesting that circulating ovarian hormones induce cognitive impairment in Met carriers. Ovariectomized HET-Met mice also displayed anxiety- and depressive-like behavior when treated with estradiol. This was associated with changes in unique gene networks in the ventral hippocampus of estradiol-treated Met carriers. We found that estradiol add-back in ovariectomized HET-Met mice affected the Extra Sex Combs and Enhancer of Zeste complex, ESC/E(Z), a gene-silencing epigenetic cluster altered in women suffering from premenstrual dysphoric disorder (PMDD). Tissues isolated from HET-Met mice and women with PMDD were compared using RNA-seq data, revealing gene expression similarities that transcended species and cell types. These findings shed light on sex-specific epigenetic targets for the treatment of mental illnesses.