Sex-Dependent Changes of miRNA Levels in the Hippocampus of Adrenalectomized Rats following Acute Corticosterone Administration

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Abstract

We explored sex-biased effects of the primary stress glucocorticoid hormone corticosterone on the miRNA expression profile in the rat hippocampus. Adult adrenalectomized (ADX) female and male rats received a single corticosterone (10 mg/kg) or vehicle injection, and after 6 h, hippocampi were collected for miRNA, mRNA, and Western blot analyses. miRNA profiling microarrays showed a basal sex-biased miRNA profile in ADX rat hippocampi. Additionally, acute corticosterone administration triggered a sex-biased differential expression of miRNAs derived from genes located in several chromosomes and clusters on the X and 6 chromosomes. Putative promoter analysis unveiled that most corticosterone-responsive miRNA genes contained motifs for either direct or indirect glucocorticoid actions in both sexes. The evaluation of transcription factors indicated that almost 50% of miRNA genes sensitive to corticosterone in both sexes was under glucocorticoid receptor regulation. Transcription factor-miRNA regulatory network analyses identified several transcription factors that regulate, activate, or repress miRNA expression. Validated target mRNA analysis of corticosterone-responsive miRNAs showed a more complex miRNA-mRNA interaction network in males compared to females. Enrichment analysis revealed that several hippocampal-relevant pathways were affected in both sexes, such as neurogenesis and neurotrophin signaling. The evaluation of selected miRNA targets from these pathways displayed a strong sex difference in the hippocampus of ADX-vehicle rats. Corticosterone treatment did not change the levels of the miRNA targets and their corresponding tested proteins. Our data indicate that corticosterone exerts a sex-biased effect on hippocampal miRNA expression, which may engage in sculpting the basal sex differences observed at higher levels of hippocampal functioning.

Author keywords
Adrenalectomy; corticosterone; glucocorticoid receptors; hippocampus; miRNAs; sex bias