Thyroid Hormone Signaling Regulates Sex-Specific Reward-Associated Behavior and Transcription in the Medial Amygdala.

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Sex differences in reward-associated behaviors are necessary for many species' survival and involve important sex-specific differences in the cellular and molecular response to rewarding stimuli. These sex differences in reward processing are influenced by numerous variables including hormones, the environment and life experiences. Disruptions in the mechanisms regulating reward processing, including changes in gene expression, are associated with numerous psychiatric disorders involving motivation and reward, including substance use disorder. Given the myriad of systems involved in reward processing it is likely that sex-differences in these mechanisms may underly sex-specific vulnerability to psychiatric disorders. Thyroid hormone signaling is a potential candidate for such differences because many sex-specific motivated behaviors are energetically costly (e.g. copulation and aggression). However, very little is known regarding the role of thyroid hormone signaling in regulating reward-associated behaviors.

Methods: To test the hypothesis that thyroid hormone signaling is a key regulator of sex differences in reward, I manipulated expression of the thyroid hormone binding protein, crystallin mu (Crym), in the medial amygdala of mice. Crym interferes with thyroid hormone signaling by sequestering thyroid hormone in the cytoplasm and preventing it from interacting with its receptors, which are known transcription factors. Therefore, Crym is considered a non-canonical transcriptional regulator.

Results: I found that Crym overexpression, through viral mediated gene transfer, induced sex-specific effects on cocaine conditioned place preference, where males but not females increased their preference for cocaine. RNA-seq of the medial amygdala after Crym overexpression revealed that the behavioral effects of Crym overexpression were reflected in Crym-induced transcriptional profiles in males and females. Additionally, rank-rank hypergeometric overlap was used to analyze directional changes in expression between Crym-induced transcriptome-wide changes and a separate RNA-seq data set from male and female mice after a single injection of cocaine. I found that Crym-induced transcriptional patterns closely mirrored those induced by cocaine in males but not females.

Discussion: These data suggest that disruption of thyroid hormone signaling within the medial amygdala influences sex-specific cocaine-induced behaviors through transcriptional changes. I am currently expanding on these findings to investigate sex-specific the epigenetic mechanisms regulated by thyroid hormone signaling in the medial amygdala by direct manipulation of thyroid hormone receptors, analysis of Crym-induced chromatin conformations and determining the behavioral impact of thyroid hormone signaling disruption on other reward-associated behavioral paradigms in both sexes, including cocaine self-administration. Together, these data will provide the first comprehensive analysis of the molecular mechanisms regulating thyroid hormone regulation of sex-specific motivated behaviors.

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