Epigenetic Editing of Cdk5 Leads to Sexually Dimorphic Stress Responses

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Women are more prone to disorders such as PTSD and depression. Yet, most preclinical psychopathological research solely uses male subjects, and there is a paucity of sex-specific studies. Thus, I investigated sex-specific responses to chronic unpredictable mild stress (CUMS) and fear conditioning (FC). Additionally, I examined the role of epigenetic regulation of cyclin-dependent kinase 5 (Cdk5), implicated in stress, fear, and depression. Section one of this study used data pre-collected from mice exposed to CUMS or targeted epigenetic repression of Cdk5 in the nucleus accumbens. I scored four tests modeling behaviors linked to stress disorders and measured Cdk5 protein levels. Results showed Cdk5 repression decreased compulsive- and depressive-like behaviors in female, but not male, mice (compulsive: $p = 0.0177$; depressive: $p = 0.0027$), and anesthesia/surgery increased anxiety- and depressive-like behavior in male mice only (anxiety: $p < 0.0001$; depressive: $p = 0.0035$). These results suggest that targeted Cdk5 repression has potential for female-specific therapeutics. Section two used data pre-collected from mice exposed to FC, with or without targeted epigenetic activation of Cdk5 in the hippocampus. Results showed, during long-term fear retrieval, females, but not males, exhibited darting behavior—rapid locomotion in response to fear ($p = 0.0446$). Overall, this study elucidated sex-specific stress responses linked to epigenetic regulation and suggested Cdk5 repression for potential female-specific therapeutics. Beyond the intricacies of Cdk5, this study shows disregarding sex in neuropsychiatric research is detrimental to understanding stress disorders. Researchers must prioritize sex differences, laying the foundation for more effective and equitable treatments.

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