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Sex differences in susceptibility to addiction: Role for X chromosome inactivation?

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There is a sex-based disparity associated with substance use disorders (SUDs) as demonstrated by clinical and preclinical studies. Females are known to escalate from initial drug use to compulsive drug-taking behavior (telescoping) more rapidly, and experience greater negative withdrawal effects than males. Although these biological differences have largely been attributed to sex hormones, there is evidence for non-hormonal factors, such as the influence of the sex chromosome. However, genetic and epigenetic mechanisms underlying sex chromosome influences on substance abuse behavior are not completely understood. Females have two X chromosomes (XX), and during X-chromosome inactivation (XCI), one X chromosome is randomly chosen to be transcriptionally silenced. However, some X-linked genes escape XCI and display biallelic gene expression. We hypothesized that escape from XCI in females contributes to sex-associated differences in addiction behavior. To test our hypothesis, we utilized a hybrid mouse model with identifiable alleles to identify X-linked genes that escape XCI during chronic exposure to addictive drugs. We bred 2 different mouse strains (C57BL/6 with CAST/EiJ), which maximizes the level of allelic differences detectable by SNPs frequencies. Using this model, combined with an innovative single cell RNA sequencing methodology, we intend to identify genes that escape XCI, as well as the different cell populations that display bi-allelic expression of X-linked genes during chronic cocaine exposure that potentially contribute to sex differences in addictive behavior. These studies will provide a global molecular profile of X-linked genes which escape XCI during chronic exposure to addictive drugs.