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## **Sex-Differences in Drug Sensitivity: Gonads or Non-coding RNAs?**

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**Background:** Decades of research have documented sex differences in the causes and consequence of drug use disorders, yet the substrates of these differences remain largely unknown.

**Significance:** There is a growing interest in understanding the biological contributions to sex differences in the risk for developing a substance use disorder. These complex behaviors are multifarious, suggesting that unique sex-dependent and non-sex dependent influences determine specific trajectories and warrant distinct treatments. Though gonadal hormones contribute to differences in drug sensitivity, they do not account for the majority of variance between the sexes.

**Hypothesis:** Non-coding RNAs including long-non-coding RNA and antisense RNA determine sex-dependent responses to drugs of abuse in inbred strains.

**Results:** Preliminary data using RNA-Seq in male and female inbred mice suggests that differential expression in several transcripts in limbic structures predict sex differences in the behavioral response to alcohol. While about half of these code for genes, at least as many appear to be regulatory including antisense, pseudogenes and long non-coding RNA (linc rna).

**Discussion:** Better understanding of the factors that influence addiction will depend upon knowledge of the mechanisms of sexually-dimorphic responses to drugs. Now may be a good time to look beyond the gonads for these influences, and in particular to investigate the role of regulatory RNA transcripts.