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The gut microbiome as a homeostatic regulator of striatal gene expression in response to opioids

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Background: There is growing evidence that the resident bacteria of the gastrointestinal tract, the gut microbiome, play a key role in brain health and homeostasis. Previous results from our lab have demonstrated that shifts in the gut microbiome affect the rewarding properties of psychostimulants.

Rationale/Significance: Given the diverse effects that the gut microbiome has been shown to have on brain function we set out to determine how depleting the microbiome would alter brain and behavior in models of opioid use disorder.

Hypothesis: We hypothesized that reduction of the microbiome would lead to alterations in behavioral response to opioids as well as changes in gene expression in important limbic brain structures.

Results: Animals lacking a complex microbiome exhibited reduced morphine place preference. Additionally, antibiotic-treated animals self-administered less fentanyl than controls and demonstrated attenuated drug-seeking after abstinence. RNA-sequencing analysis of the nucleus accumbens indicated that morphine administration in control animals lead to regulation of 262 genes. However, treatment of microbiome-depleted animals with morphine lead to significant regulation of 3,006 genes. In addition to marked changes in the number of regulated genes, microbiome-depleted mice also exhibited marked changes in patterns of histone acetylation and methylation in the nucleus accumbens.

Discussion: Our results indicate that the microbiome and its resultant metabolites are key regulators of brain and behavior in response to opioids. Microbiome-depleted animals exhibit decreased opioid seeking, and marked alterations of the brain transcriptome and epigenome. These data suggest that the gut microbiome represents a new and exciting area for translational research.