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A Molecular Perspective of the Role of Gut Microbiome in Cocaine-Induced Neurobehavioral Plasticity

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The gut microbiome has been proposed to modulate social, communicative, stress-related, and cognitive behaviors. Moreover, an altered gut microbiota (known as dysbiosis) has been associated with different neurological disorders, including drug use and substance use disorders (SUDs). However, determining whether these microbiome changes cause, enhance, or are the consequences of these disorders remains a challenge in the field. Cocaine and other psychostimulants act by blocking catecholamines reuptake. *Citrobacter rodentium* is a mouse proteobacterium that can sense host norepinephrine to colonize the gut, inducing dysbiosis. I used this bacterium as a model to test whether cocaine-induced increase in catecholamines can modify microbiota composition. I found that, indeed, cocaine increased C. rodentium colonization by raising gut norepinephrine levels. Remarkably, *C. rodentium*-colonized mice show increased addiction-like behaviors. These results were also observed in mice colonized with *Escherichia coli HS*, a human commensal proteobacterium. Employing metabolomics, we found that these proteobacteria can deplete glycine from the gut, blood, and cerebrospinal fluid, altering cocaine-induced transcriptional changes in the Nucleus Accumbens. Importantly, systemic glycine administration or bacterial genetic manipulation reversed these microbial-induced host metabolic alterations and prevented the increase in cocaine responses. Altogether, these results propose a novel and defined host-microbiota interactions relevant for SUDs. Drug use and SUDs affect more than 27 million people in the United States; and yet, no successful evidence-based treatments have been developed. Here we introduce the possibility of manipulating intestinal bacteria as potential signaling nodes that can be used to impact the course of psychiatric diseases.