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Prewired for Addiction: Amygdala GABA Dysregulation Predicts Cocaine Vulnerability

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Cocaine use disorder (CUD) persists as a major public health issue, with effective treatments remaining elusive. Elucidating the neurobiological substrates underlying individual susceptibility to addiction is imperative for the development of targeted interventions. This study employs a cutting-edge polygenic trait prediction approach to uncover preexisting differences in GABAergic and glutamatergic neurotransmission within the central amygdala (CeA) that may predispose individuals to cocaine addiction.

Utilizing the RATTACA method, we genetically profiled rats to predict high or low susceptibility to cocaine addiction-like behaviors prior to any drug exposure. Basal GABAergic and glutamatergic transmission in the CeA were assessed using whole-cell patch-clamp electrophysiology. Additionally, we examined the effects of ex vivo cocaine application on these neurotransmitter systems.

Our data indicate that rats predicted to have high addiction susceptibility exhibit significantly elevated GABA release in the CeA compared to low-susceptibility counterparts. Remarkably, ex vivo cocaine application resulted in a reduction of GABA release exclusively in the high-susceptibility group, highlighting a preexisting hyperresponsiveness of CeA GABAergic neurons to cocaine. Baseline glutamatergic transmission showed no significant differences between groups. Cocaine increased spontaneous excitatory postsynaptic currents (sEPSCs) in both high and low susceptibility rats without altering kinetics, suggesting a presynaptic mechanism of action. These novel insights reveal that inherent alterations in CeA GABAergic transmission are associated with heightened vulnerability to cocaine addiction. The selective sensitivity of GABAergic neurons to cocaine in high-susceptibility rats underscores the importance of GABAergic dysregulation in addiction pathology. Identifying preexisting neurobiological differences advances research and guides personalized treatments for CUD and related disorders.