Self-Administration in Genetically Modified Mice: A Streamlined Platform for the Identification of Addiction Biomarkers, Therapies and Disease Mechanisms

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There is an urgent need for therapeutics to address the ongoing addiction epidemic. We have developed a multidimensional pre-clinical platform to expedite the identification of novel anti-addiction agents and to further the understanding of the mechanisms underlying substance use disorders. This platform assesses drug use in genetically modified mice via biochemical, behavioral and serial brain imaging methods. Most importantly, the behavioral arm uses a streamlined intravenous self-administration approach as a phenotypic screen to assess the large and rapidly growing number of transgenic mouse lines, drugs of abuse, and pharmacotherapies. In a 10-12-week paradigm, mice with indwelling jugular catheters progress through the self-administration phases of acquisition, maintenance, extinction and re-instatement in a systematic manner that permits comparison of behavioral parameters across reinforcing drugs, transgenic mouse lines and treatment groups. Results are collected in a relational database to simulate the organizational approach of clinical trials and to provide an upgradable large data set for comparisons and statistical follow up. As proof-of-concept, in neuron-specific knockout mouse lines, we are currently clarifying the role of the critical G-protein-coupled receptor (GPCR) regulatory protein β-arrestin2 in the behavioral effects of cocaine. *We have found that loss of β-arrestin2 has opposing effects when it occurs in dopamine receptor D1R- versus D2R-expressing neurons.* D1R β-arrestin2 KO animals exhibited heightened maintenance cocaine intake, while D2R β-arrestin2 KO animals showed relative deficits in self-administration acquisition and reduced maintenance cocaine intake. These data suggest that modulation of β-arrestin2 downstream of GPCR activation may be a promising new strategy to addiction pharmacotherapy. By incorporating serial, noninvasive micro-positron emission tomography/computed tomography (PET/CT) imaging over the course of the self-administration paradigm to assess brain metabolic and dopamine receptor changes, we are working to not only identify novel therapeutic targets, but also define the genetic and neurometabolic signature of addiction.