

Repeated Cocaine Exposure Alters Behavioral but Not Incentive Sensitization in Collaborative Cross Mice

Repeated exposure to psychostimulant drugs enhances locomotor responses (behavioral sensitization), facilitates the acquisition of drug self-administration, and increases preference for drug paired environments. These effects arise, in part, from neuroadaptations within the mesolimbic dopamine system and contributed to the incentive sensitization theory of addiction. This theory posits that drug induced sensitization of mesocorticolimbic circuitry alters incentive motivational processes and confers heightened salience to drugs and drug-associated cues. Despite this theoretical link, direct comparisons of behavioral sensitization and incentive sensitization remain limited. The substantial phenotypic variation in behavioral sensitization that we previously reported across 50 Collaborative Cross (CC) strains provides a powerful opportunity to evaluate the genetic relationship between these behavioral domains. We developed an incentive sensitization protocol incorporating Pavlovian conditioning in which a visual cue (CS) predicted delivery of a palatable food reward (US), followed by five exposures to either cocaine or vehicle using the same schedule as our behavioral sensitization assay. We then measured acquisition of a lever press response reinforced by the visual cue functioning as a conditioned reinforcer. Testing in more than 550 mice from 48 CC strains revealed significant strain and sex differences in Pavlovian conditioning and identified individual mice and strains that did not acquire the CS-US association; these were excluded from conditioned reinforcement analyses. During conditioned reinforcement testing, preference for the cue-paired lever differed significantly by strain, but no strain by treatment effects emerged. These findings indicate that the incentive salience of the visual cue varies across strains but is not altered by repeated cocaine exposures. Finally, we observed no significant correlation between behavioral and incentive sensitization, suggesting that these processes are dissociable under the conditions tested in this panel of CC mice.

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