ROLE OF DORSOMEDIAL STRIATUM NEURONAL ENSEMBLES IN INCUBATION OF METHAMPHETAMINE CRAVING AFTER VOLUNTARY ABSTINENCE

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Methamphetamine (Meth) addiction is characterized by high relapse rates and this relapse is often precipitated by exposure to drug-associated cues that provoke drug craving. Animal models of relapse show that cue-induced drug seeking progressively increases during extended forced abstinence periods after self-administration of addictive drugs, including Meth. This phenomenon is termed 'incubation of drug craving'1, and was recently observed in an inpatient clinical study2. In rodent studies of incubation of drug craving, cue-induced drug seeking is assessed after experimenter-imposed forced abstinence1. However, in humans, abstinence is often self-imposed, or voluntary, in favor of other non-addictive alternative rewards. Importantly, this self-imposed abstinence occurs despite drug availability in the addict's environment. This important aspect of human addiction (self-imposed abstinence despite drug availability) is not captured by current animal models of drug craving and relapse.

In this work we used a recently developed rat model of incubation of Meth craving after choice-based voluntary abstinence3 which mimicks the human condition of relapse after self-imposed abstinence4.

We used classical pharmacology, in situ hybridization, immunohistochemistry, and the Daun02 inactivation procedure to investigate the role of dorsolateral striatum (DLS) and dorsomedial striatum (DMS) neuronal ensembles in this new form of incubation of drug craving.

We trained rats to self-administer palatable food pellets (6d, 6 h/d) and Meth (12d, 6 h/d). We then assessed relapse to Meth seeking under extinction conditions after 1 and 21 abstinence days. Between tests, the rats underwent voluntary abstinence (using a discrete choice procedure between Meth and food; 20 trials/d) for 19d. We used in situ hybridization to measure the colabeling of the activity marker Fos with Drd1 and Drd2 in DMS and DLS after the tests. Based on the in situ hybridization colabeling results, we tested the causal role of DMS D1 and D2 family receptors, and DMS neuronal ensembles in "incubated" Meth seeking, using selective dopamine receptor antagonists (SCH39166 or raclopride) and the Daun02 chemogenetic inactivation procedure, respectively. Meth seeking was higher after 21d of voluntary abstinence than after 1d (incubation of Meth craving). The incubated response was associated with increased Fos expression in DMS but not in DLS; Fos was colabeled with both Drd1 and Drd2; DMS injections of SCH39166 or raclopride selectively decreased Meth seeking after 21 abstinence days. In Fos-lacZ transgenic rats, selective inactivation of relapse test-activated Fos neurons in DMS on abstinence day 18 decreased incubated Meth seeking on day 21.

Our results demonstrate a crucial role of DMS dopamine D1 and D2 receptors in the incubation of Meth craving after voluntary abstinence and that DMS neuronal ensembles mediate this incubation.

References

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