ROLE OF NUCLEUS ACCUMBENS SUBREGIONS IN INCUBATION OF METHAMPHETAMINE CRAVING AFTER VOLUNTARY ABSTINENCE

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In humans, drug addiction is characterized by high relapse rates, indeed, cue-induced craving increases during early abstinence and remains elevated for extended time periods. An analogous phenomenon, termed 'incubation of drug craving', has been observed in rats trained to self-administer different addictive drugs and tested for cue-induced drug seeking during abstinence. We recently introduced an animal model to study incubation of drug craving after prolonged voluntary abstinence, mimicking the human condition of relapse after successful contingency management treatment. Here we studied the role of the nucleus accumbens (NAc) in this model.

We trained rats to self-administer a palatable solution (sucrose+maltodextrin 1%, 6h/d, 6d) and methamphetamine (6h/d, 12d). We then evaluated relapse to methamphetamine seeking after 1and 15days of voluntary abstinence, achieved via a discrete choice procedure between the palatable solution and methamphetamine (14d). We used RNAscope in-situ hybridization to quantify the colabeling of the neuronal activity marker Fos, and dopamine Drd1- and Drd2-expressing medium spiny neurons (MSNs) in NAc core and shell during the incubation tests. Next, we determined the effect of pharmacological inactivation of NAc core and shell by either $GABA_A$ and $GABA_B$ agonists (muscimol+baclofen, 50+50 ng/side) or selective Drd1and Drd2antagonists (SCH391661.0 μg/side, raclopride 1.0 μg/side) during the relapse tests.

There are three main findings in our study. First, incubation of methamphetamine craving wasassociated with increased Fos expression in NAc core Drd1- and Drd2-MSNs after 15abstinence days; in contrast we did not found any increased Fos expression in the NAc shell subregion. Second, reversible inactivation of NAc core selectively decreased methamphetamine seeking during late (day 15) but not early (day 1) abstinence. This effect was selective to methamphetamine seeking, muscimol + baclofen injections had no effect on SM1% solution seeking. Third, blockade of Drd1- and Drd2-family receptors in NAc core decreased incubated (day 15) methamphetamine craving after voluntary abstinence.

Together, our results suggest that dopamine transmission through Drd1and Drd2in NAc core is critical to the incubation of methamphetamine craving after voluntary abstinence.