Identification of a unique corticostriatal pathway involved in cue-controlled heroin seeking

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Our aim is to identify circuits in the brain involved in conditioned heroin-seeking following long-term abstinence and to determine their overlap or uniqueness with respect to the brain circuitry mediating conditioned natural reward (sucrose) seeking. To that end, we apply a so-called reinstatement model in which rats are trained for several weeks to self-administer heroin (100 µg/kg/injection) or sucrose in association with a compound visual cue at an active nose poke hole (alias pellet receptacle). After an extinction period of three weeks, the rats are placed in the cages with or without the compound stimulus for 90 minutes. Re-exposure to the cue successfully reinstates heroin and sucrose seeking behavior to comparable levels. Within the brains of these rats, cue exposure induces site-specific and even opposing changes in heroin versus sucrose-trained rats in the expression of the activation marker zif268 (quantitative immunocytochemistry) in sub regions of the prefrontal cortex and striatal complex. This implicates the presence of corticostriatal circuits that are uniquely involved in cue-controlled drug (heroin), but not natural reward seeking. Detailed analysis of cell location and optical densities further confirms that the cue-induced changes in heroin vs sucrose trained rats may take place in distinct subsets of striatal neurons. In this respect, activity mapping techniques reveal that these cue-activated changes, at least in part, have spatial non-overlapping distributions. With respect to the causal relationship of the identified brain structures with conditioned drug versus natural reward seeking, experiments involving pharmacological blockade of the identified brain regions, are currently in progress. Further characterization of these corticostriatal neurons may ultimately lead to the discovery of new pharmacological targets for the treatment of drug addicts.

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