Cocaine-taking and -seeking behavior in rats: role of L-DOPA

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Cocaine addiction is a chronic relapsing brain disorder characterized by cycling phases of drug use, withdrawal and relapse. Drug withdrawal is thought to be associated to a condition of hypodopaminergia (Melis et al., 2005) and dopamine (DA) agonists have been suggested as therapeutic tools for the treatment of cocaine addiction (Minozzi et al., 2015). We have recently shown that indirect DA agonists markedly increase cocaine-induced DA release in the medial prefrontal cortex (mPFC) leading to the suppression of cocaine-seeking behavior in rats. Also L-DOPA, the metabolic precursor of DA, prevents cocaine-induced relapse and increases extracellular DA levels in the mPFC (Devoto et al., 2016).

Aims of this follow-up study were to test the effect of L-DOPA on (i) cocaine-taking, (ii) extracellular DA levels in the mPFC during cocaine self-administration, (iii) the motivation to obtain the drug, (iv) cocaine-seeking during the first day of extinction and (v) cue-induced reinstatement of cocaine-seeking.

Male rats were trained daily to self-administer cocaine (0.5 mg/kg/infusion) intravenously for 2 hours under a continuous fixed ratio (FR1) schedule of reinforcement, where each cocaine infusion was associated with a visual cue. At different steps of the study, rats received either an intraperitoneal (ip) injection of L-DOPA (50 mg/kg) together with benserazide (10 mg/kg) or drug vehicle (saline, 2 ml/kg), administered 20 minutes before starting the session.

After 12 days of stable cocaine intake rats were pretreated with L-DOPA to evaluate its effect on cocaine-taking behavior. In a separate group of rats, *in vivo* microdialysis study was performed during cocaine self-administration to verify whether the effect of L-DOPA on cocaine-taking was influenced by changes in extracellular DA concentrations in the mPFC. As next step, animals were shifted from FR1 to progressive ratio (PR) schedule of reinforcement, where the response:infusion ratio increased within the session after each cocaine infusion. After 3 PR sessions, rats were pretreated with L-DOPA and the breaking point (BP), i.e. the maximum effort that an animal expends to receive an infusion of drug, was considered an index of the motivation of animals to work for cocaine. A parallel group of rats, after reaching a stable cocaine intake under FR1 schedule, received an ip injection of L-DOPA before starting the first session of extinction training to evaluate its effect on cocaine-seeking. Finally, at the end of the extinction training, rats were pretreated with L-DOPA and re-exposed to the cocaine-associated cue immediately before starting the session to undergo cue-induced reinstatement testing session.

Data showed that L-DOPA reduced significantly cocaine-taking under FR1 schedule of reinforcement and that this behavioral effect is accompanied by a significant increase of DA level in the mPFC. Pretreatment with L-DOPA significantly decreases the BP and the number of drug infusions. Furthermore, L-DOPA diminished lever-pressing activity on the first day of extinction training and inhibited cue-induced reinstatement of cocaine-seeking behavior.

Overall, our findings suggest that L-DOPA may reduce reinforcing properties of cocaine and its motivational effects and might be effective in reducing the risk to relapse to cocaine-seeking, as shown by its ability to prevent the reinstatement of cocaine-seeking behavior induced by both drug and cue re-exposure.

References

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