EFFECTS OF A NOVEL SELECTIVE SHORT-ACTING KAPPA OPIOID RECEPTOR ANTAGONIST ON COCAINE INTAKE DURING ESCALATION AND UPON RE-EXPOSURE AFTER WITHDRAWAL

1)Valenza M. 2)Butelman ER. 3)Kreek MJ.

The Rockefeller University

Cocaine addiction is a chronic brain disease characterized by compulsive drug intake and dysregulation of brain reward system. The precise role of escalation of cocaine intake over time remains unclear. Identification of changes in the pattern of cocaine intake during the development of addictive-like states may allow the identification of potential underlying neurobiological changes and eventually of effective treatments. Extended-access chronic self-administration protocols are powerful methodologies to model the advanced stages of addiction. Several protocols have been published in literature; few have duration of drug access greater than 12 hours per day, potentially resulting in limited construct validity.

Here we characterized for the first time the behavioral pattern of intake across all hours of exposure to chronic (14 consecutive days) 18-hour intravenous cocaine self-administration (with 0.5 mg/kg unit dose of cocaine available; FR1 schedule). Rats' hourly pattern of intake changed across the 14 days of cocaine exposure. During the first week of access, rats show a stable intake over the 18-h operant session. However, during the second week of cocaine access, the intake was higher during the last 9 hours of the 18-h sessions, when the rats were in the light (sleep) part of the light/dark cycle, compared to the first 9 hours (dark-active), suggesting that this protocol induces a disruption of the light/dark cycle typically seen in addicted patients.

There are no effective medications for cocaine addiction; therefore new pharmacological approaches are needed. The Kappa opioid receptor (KOPr) signaling tone is upregulated in chronic cocaine exposure and its signaling plays a crucial role in balancing reinforcing, dysphoric and anhedonic effects of chronic drugs of abuse, including cocaine. However, most current knowledge on the pharmacotherapeutic potential of KOPr antagonism is based on molecules (e.g. norBNI, JDTic) with extremely unusual pharmacokinetic and pharmacodynamic properties, including slow onset of KOPr selectivity and durations of action >30-60days. These features complicate experimental designs, interpretation and translation of results into the clinic. Novel, highly selective, centrally penetrating KOPr antagonists with a moderate duration of action (<24h) have been recently synthetized.

Here we investigated the effect of a novel short-acting KOPr antagonist, LY2540240 (kind gift of Eli Lilly & Co.) administered chronically during the second week of chronic extended access cocaine self-administration (18h/day for 14 days), as well as upon a "re-exposure" session (modeling relapse). Chronic LY2540240 prevented escalation of cocaine self-administration, affecting the pattern of self-injections during the 18-h operant sessions. In addition, LY2540240 administration significantly attenuated the increased cocaine intake that vehicle-injected rats showed upon re-exposure.

Our results demonstrate that treatment with a selective short-acting KOPr antagonist may be a novel therapeutic approach to prevent escalation and attenuate relapse-like behaviors, in addition to reducing behavioral and neuroendocrine signs of withdrawal from cocaine.

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