

Hypocretin Receptor 1 Regulates Dopamine Transporter Function and Cocaine Seeking

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Persistent drug craving is thought to increase the risk of relapse, thus posing a significant obstacle for the treatment of substance use disorders. Extensive evidence indicates that drug craving increases during periods of abstinence—an effect referred to as incubation of craving. This phenomenon has been modeled pre-clinically as a progressive increase in cue-induced drug seeking after varying periods of abstinence. Although there are no FDA-approved pharmacotherapies to treat cocaine seeking, preclinical evidence suggests that antagonism of the hypocretin receptor 1 reduces motivation for cocaine (Shaw *et al.*, 2019; Brodnik *et al.*, 2020). In the current studies, we examined to what extent hypocretin receptor 1 antagonism early in abstinence reduces cue-induced cocaine seeking and the extent to which this is associated with changes in dopamine transmission.

Methods: Female and male rats underwent intermittent access cocaine self-administration followed by one week of abstinence to induce incubation of cocaine seeking. Cue-induced cocaine seeking tests were conducted on abstinence day 1 (AD1) and abstinence day 8 (AD8). After the seeking test on AD1, rats were treated with a single injection of vehicle or the hypocretin receptor 1 antagonist – RTIOX-276. Eighteen hours after the final seeking test on AD8, rats were sacrificed for Western blotting and fast-scan cyclic voltammetry to examine nucleus accumbens dopamine transmission and dopamine transporter expression.

Results: A single treatment with a hypocretin receptor 1 antagonist on the first day of abstinence blocked incubation of cocaine seeking measured one week later. This effect was associated with normalization of dopamine transmission and biochemical changes in the dopamine transporter.

Discussion: The present findings suggest that hypocretin receptor 1 antagonism early in abstinence provides lasting reductions in cocaine seeking during abstinence via actions on the mesolimbic dopamine system.

Brodnik, Z.D., Alonso, I.P., Xu, W., Zhang, Y., Kortagere, S. & España, R.A. (2020) Hypocretin receptor 1 involvement in cocaine-associated behavior: Therapeutic potential and novel mechanistic insights. *Brain Res*, **1731**, 145894.

Shaw, J.K., Black, E.M., Zhang, Y. & España, R.A. (2019) Chapter 5 - Hypocretin Receptor 1 Regulation of Dopamine Neurotransmission and Motivated Behavior. In Burk, J.A., Fadel, J.R. (eds) *The Orexin/Hypocretin System*. Academic Press, pp. 99-120.