VK4-40, a Novel D3R Partial Agonist, Attenuates Cocaine Reward and Relapse in Rodents

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Abstract

Background and Purpose. Despite widespread abuse of cocaine, there are no approved treatments for cocaine use disorder. Chronic cocaine use is associated with upregulated dopamine D3 receptor (D3R) expression in the brain, and therefore, most D3R-based medication development has focused on D3R antagonists. However, D3R antagonists do not attenuate cocaine intake under "easy" self-administration conditions when response requirements are low. Here we evaluated a novel, highly selective and metabolically stable D3R partial agonist, VK4-40, for its efficacy in reducing cocaine intake and relapse to drug seeking. Experimental Approach. The impact of VK4-40 on cocaine intake and relapse were evaluated using intravenous self-administration procedures under a fixed-ratio 2 reinforcement schedule and cocaine-primed reinstatement conditions in rats. Optogenetic brain-stimulation reward procedures were used to evaluate the interaction of VK4-40 and cocaine in the mesolimbic dopamine system. Sucrose self-administration and a conditioned place preference paradigm was used to evaluate the abuse potential of VK4-40 alone and other unwanted effects. Key Results. VK4-40 dose-dependently reduced cocaine self-administration and cocaine-primed reinstatement of drug-seeking behavior. In addition, VK4-40 inhibited cocaine-enhanced brain-stimulation reward caused by optogenetic stimulation of dopamine neurons in the ventral tegmental area. VK4-40 alone decreased brain-stimulation reward, and produced neither conditioned place preference nor place aversion. This new D3R partial agonist also failed to alter oral sucrose self-administration. Conclusions and Implications. The novel D3R partial agonist, VK4-40, attenuates cocaine reward and relapse in rodents, without significant unwanted effects. These findings support further investigation of D3R partial agonists as putative treatments for cocaine use disorder.

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