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The 5-HT1D receptor modulates volitional cocaine-related behaviors

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Cocaine use disorder is a serious public health problem that increasingly results in morbidity and mortality. There are currently no approved pharmacotherapy approaches to treat cocaine use disorder. Psychosocial intervention remains the treatments of choice for cocaine use disorder, but the relapse rate are high even after treatment. Our genetics and genomics work on high-diversity mice discovered an understudied serotonin receptor, the 5-HT1D receptor, as a possible sex-specific modulator of cocaine-related behaviors. Bioinformatics resources indicated that this receptor is specifically expressed in addiction-relevant cell populations within the striatum. However, no direct causal evidence has linked 5-HT1D's with addiction phenotypes to date. We performed cocaine intravenous self-administration in both male and female *Htr1d* knockout mice on a C57BL/6NJ background. This self-administration protocol involved acquisition, a dose- response phase, extinction, and reinstatement in the presence of cues. Male *Htr1d-/-* mice acquired cocaine intravenous self-administration significantly more slowly than their wild-type counterparts. Though dose-response curves yielded no significant differences in the amount of cocaine taken in either sex, the dose-response data demonstrated that female *Htr1d-/-* mice are significantly more "inefficient" than wild-type females, pressing more during time-out for each infusion of cocaine. The same effect was not observed in male mice. Extinction did not differ significantly for either sex, but female and not male *Htr1d-/-* engaged in significantly more cue-paired cocaine seeking lever pressing than their wild-type counterparts. These results demonstrate that the 5-HT1D is a potential pharmacological target involved in specific aspects of volitional cocaine-taking behaviors.