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Acute Reinforcement, But Little Adaptive Behavior With Ketamine

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Introduction: Ketamine, a bona fide NMDA antagonist, is approved as antidepressant with a fast onset. Ketamine is also recreationally abused for its dissociative effects. Concerns over ketamine abuse could impede clinical use, yet its addiction liability has not been directly investigated.
Aims: To assess the abuse potential of ketamine in a mouse model, in comparison to the well-studied psychostimulant cocaine.
Methods: We used a novel genetically encoded sensor for dopamine (DA) to measure DA levels in the nucleus accumbens (NAc) of mice in response to ketamine injections. We also assessed behavioral reinforcement and drug-adaptive plasticity *ex vivo*.
Results: A single intraperitoneal injection of ketamine (30 mg/kg) induced DA transients comparable in magnitude to cocaine (15 mg/kg) but of shorter duration. Ketamine reinforced lever pressing for intravenous infusion and led to conditioned place preference, although the effect size was smaller than with cocaine. Acute hyperlocomotion was comparable between ketamine- and cocaine-treated mice, however, unlike cocaine, ketamine did not induce behavioral sensitization. In parallel, drug-evoked synaptic plasticity of excitatory afferents onto D1-MSNs, a hallmark of early neural adaptation to all addictive drugs, was not observed with ketamine.
Conclusions: We conclude that ketamine at doses typically used in recreational setting is reinforcing but does not potentiate accumbal afferents, likely by inhibiting NMDA receptors, thus limiting drug-adaptive behavior.

Keywords: addiction, dopamine, ketamine, self-administration, synaptic plasticity