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Targeting diacylglycerol lipase to reduce alcohol consumption

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Alcohol use disorder (AUD) is associated with substantial morbidity, mortality, and societal cost, and pharmacological treatment options for AUD are limited. The endogenous cannabinoid (eCB) signaling system is critically involved in reward processing and alcohol intake is positively correlated with release of the eCB ligand 2-Arachidonoylglycerol (2- AG) within reward neurocircuitry. Here we show that genetic and pharmacological inhibition of diacylglycerol lipase (DAGL), the rate limiting enzyme in the synthesis of 2- AG, reduces alcohol consumption in a variety of preclinical models ranging from a voluntary free-access model to aversion resistant-drinking, and dependence-like drinking induced via chronic intermittent ethanol vapor exposure in mice. DAGL inhibition also prevented ethanol-induced suppression of GABAergic transmission onto midbrain dopamine neurons, providing mechanistic insight into how DAGL inhibition could affect alcohol reward. Lastly, DAGL inhibition during either chronic alcohol consumption or protracted withdrawal was devoid of anxiogenic and depressive-like behavioral effects. These data suggest reducing 2-AG signaling via inhibition of DAGL could represent a novel approach to reduce alcohol consumption across the spectrum of AUD severity.