Impact of Adolescent Social Isolation Stress on Kappa Opioid Receptor Function and Addictive Behaviors

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Chronic early life stress exposure, such as neglect during childhood, increases the risk of developing alcohol and substance use disorders during adulthood. Similarly, rats reared in social isolation (aSI) during adolescence show increased ethanol intake and cocaine seeking in adulthood compared to group housed controls (aGH). Acute stress elevates dynorphin levels, a kappa opioid receptor (KOR) ligand, which regulates dopamine (DA). The goal of this study was to compare the reinforcing efficacy of cocaine and ethanol in aSI and aGH animals and investigate the underlying mechanisms involved in aSI-mediated augmentation in cocaine seeking and ethanol intake. Furthermore, it is known that KORs and dopamine transporters (DATs) interact. We hypothesize that this interaction is altered by adolescent stress exposure.

Methods: Rats were either housed in groups (aGH; 3 or 4 rats/cage) or individually (1 rat/cage) for six weeks (PND 28 – 74). After the housing manipulation rats were examined for anxiety-like behavior on the elevated plus maze. Some rats were then implanted with jugular catheters and were given access to levers to self-administer cocaine. Rats were tested on progressive and fixed ratio schedules of reinforcement. Cocaine seeking, and consumption was also measured using behavioral economics. A separate group of rats were given access to bottles containing 20% ethanol on an intermittent access schedule. To investigate the KOR function specifically on DA terminals, ex vivo voltammetry in conjunction with optogenetics was used to record the effects of U50,488 (10 – 1000 nM), a KOR agonist, on optically stimulated DA release in slices containing NAc from aGH and aSI rats. To test causality, Cre dependent KOR overexpressing virus was infused into the ventral tegmental area (VTA) of aGH TH:Cre positive rats and ethanol intake was measured. Lastly, KOR and DAT interaction was examined using a combination of cocaine and U50,488 in a systematic way and recording DA release using *ex vivo* voltammetry.

Results: A progressive ratio schedule showed enhanced motivation to ingest cocaine in aSI compared to aGH rats (mean final ratio: aGH, 77; aSI, 268; at 2.25 mg/kg/infusion). Nor-binaltorphimine (nBNI; 10 mg/kg; i.p.), a KOR antagonist, reduced motivation to self-administer cocaine in aSI rats to aGH levels (lever presses/mg of cocaine post nBNI: aGH, 198; aSI, 210). KOR inhibition also reduced ethanol intake in aSI rats. Similarly, overexpression of KORs in DA neurons elevated ethanol intake in aGH rats. The inhibitory effects of U50,488 on optically stimulated DA release were enhanced in the NAc of aSI rats suggesting that chronic stress increases the functional responsiveness of KORs on DA terminals. Activation of KORs increases cocaine potency at the DAT in aGH rats with history of cocaine. Inhibiting KORs decreases cocaine potency in aSI rats naïve and exposed to cocaine; but increases it in aGH rats with a history of cocaine.

Discussion: The KOR inhibition-induced attenuation of ethanol intake and cocaine seeking suggests that KORs contribute to augmented ethanol intake and motivation to self-administer cocaine. In addition, elevated ethanol intake following overexpression of KORs implies that KOR-function drives ethanol intake, at least in part. Furthermore, voltammetry data suggest that chronic stress dysregulates the functional interaction between KORs and DATs.

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