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ADDICTION

Under a stressful influence

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Epidemiological studies indicate an association between stress and increased alcohol consumption; however, the neuronal mechanisms underlying this association are not known. In a new paper in *Neuron*, Ostrumov *et al.* show that, in rats, stress promotes alcohol use through actions on GABAergic signalling in the ventral tegmental area (VTA).

The authors showed that rats that underwent acute restraint stress 15 hours before introduction to ethanol self-administered considerably more ethanol in this session than controls; moreover, this increase in alcohol use was maintained over 7 days. VTA dopamine (DA) neurons are activated in response to ethanol and release DA in the nucleus accumbens (NAc), and this DA release has previously been shown to be associated with self-administration of alcohol. In this study, ethanol-induced DA release (assessed using microdialysis) was reduced in the stressed rats. *Ex vivo* electrophysiological recordings showed that stress blunts the ethanol-induced increase in firing rate of VTA DA neurons that was observed in slices from non-stressed animals but that this firing was restored by application of the GABA type A receptor ($GABA_AR$) antagonist picrotoxin. These data suggest that stress may reduce ethanol-stimulated DA release by modulating GABAergic signalling in the VTA.

In slices from stressed, but not control, rats, ethanol induced large increases in the firing rate of VTA GABA neurons synapsing onto VTA DA neurons. This, as well as previous studies showing that stress leads to a shift towards excitatory GABA signalling, led the authors to hypothesize that stress may cause GABA to excite VTA GABA neurons. In support of this, repeated stimulation of $GABA_ARs$ decreased and increased the firing rates of VTA GABA neurons in slices from control and stressed rats, respectively. In addition, patch-clamp recordings revealed that the concentration of intracellular chloride ions in VTA GABA neurons is higher in stressed animals than in controls. Thus, stress may alter the chloride gradient of VTA GABA neurons such that GABA excites these cells.

Previous work has shown that stress leads to dephosphorylation of the potassium–chloride symporter KCC2 and thus reductions in the extrusion of chloride ions. Here, Ostrumov *et al.* demonstrated using Western blots that the ratio of phosphorylated to dephosphorylated KCC2 in the VTA was indeed lower in stressed animals than in controls. Treatment of slices from stressed rats with the KCC2 activator CLP290 restored the chloride gradient in VTA GABA neurons and restored the ethanol-induced increase in the firing rate of VTA DA neurons to control levels. Last, the authors showed that infusion of CLP290 into the VTA of stressed rats just before the first ethanol exposure prevented the escalation of ethanol intake.

This study reveals a mechanism through which stress can promote the self-administration of alcohol. Specifically, the authors propose that stress leads to accumulation of chloride ions in VTA GABA neurons in the presence of ethanol, causing an excitatory shift in the effects of GABA, a paradoxical excitation of VTA GABA neurons and thus a reduction in the ethanol-stimulated release of DA in the NAc.

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ORIGINAL ARTICLE Ostrumov, A. *et al.* Stress increases ethanol self-administration via a shift toward excitatory GABA signaling in the ventral tegmental area. *Neuron* http://dx.doi.org/10.1016/j.neuron.2016.09.029 (2016)

> “stress may cause GABA to excite VTA GABA neurons”

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