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EMOTION

Exciting extinction

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Just as it is essential for animals to rapidly form associations (fear memories) between threats and the cues that predict them, it is important to temper the expression of fear behaviour in response to the cue once the threat is removed. Luo and colleagues now reveal an unexpected role for $GABA_B$ receptor ($GABA_BR$)-mediated presynaptic excitation in habenula neurons in fear memory extinction in mice.

$GABA_B$Rs have been linked to the control of anxiety and fear and are expressed at high levels along the axons of cholinergic neurons projecting from the medial habenula (MHb) to the interpeduncular nucleus (IPN); however, little is known about the contribution of this pathway to fear-memory formation or extinction. Here, the authors used a transgenic strategy to selectively ablate MHb cholinergic neurons in mice that were then conditioned to associate an auditory tone with a footshock. Although the mice lacking MHb cholinergic neurons formed a fear memory (reliably freezing in response to the tone during conditioning), when compared with control mice they exhibited delayed extinction of the fear response in a subsequent phase in which the tone was presented repeatedly without a footshock. Conversely, optogenetic activation of MHb–IPN projections in wild-type mice boosted the rate of fear extinction.

To determine the contribution of the presynaptic $GABA_B$Rs present on MHb neurons to fear extinction, the authors genetically inactivated *Gabbr1*, which encodes an essential $GABA_BR$ subunit. This impaired fear extinction, as did the infusion of a $GABA_BR$ antagonist into the IPN. Activation of $GABA_B$Rs using the agonist baclofen increased the rate of fear extinction.

Presynaptic $GABA_B$Rs were thought to have predominantly inhibitory effects on synaptic transmission. However, when the authors recorded from IPN neurons in brain slices, they were surprised to find that application of baclofen increased the amplitude of the excitatory postsynaptic currents and the number of action potentials evoked in these neurons in response to stimulation of MHb-neuron terminals. Further experiments showed that baclofen-induced $GABA_BR$ activation resulted in an increase in presynaptic Ca^{2+} influx, which might facilitate synaptic transmission. Blocking or genetically inactivating R-type Ca^{2+} channels abolished the effect of baclofen on presynaptic Ca^{2+}, suggesting that these channels are involved in the potentiation of fear extinction triggered by $GABA_BR$ activation.

These findings show that $GABA_BR$ activation in MHb cholinergic neurons can facilitate fear extinction through a previously unknown capacity to potentiate synaptic transmission. Given that dysfunctional fear extinction is thought to contribute to human disorders such as phobias and post-traumatic stress disorder, these findings may point to new candidate targets for therapeutic intervention.

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ORIGINAL ARTICLE Zhang, J. *et al.* Presynaptic excitation via $GABA_B$ receptors in habenula cholinergic neurons regulates fear memory expression. *Cell* http://dx.doi.org/10.1016/j.cell.2016.06.026 (2016)

FURTHER READING Tovote, P., Fadok, J. P. & Lüthi, A. Neuronal circuits for fear and anxiety. *Nat. Rev. Neurosci.* **16**, 317–331 (2015)