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NEURAL CIRCUITS

# Shock signals

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In Pavlovian fear conditioning, signals relating to the conditioned stimulus (CS; for example, a tone) and the unconditioned stimulus (US; such as a shock) converge in the lateral amygdala (LA) to enable synaptic plasticity to encode aversive memories. The circuitry through which the US is conveyed to the LA is, however, not well defined. Li and colleagues now demonstrate that protein kinase Cδ-expressing (PKCδ⁺) neurons in the lateral central amygdala (CeL) deliver US information to the LA during fear conditioning.

The authors selectively inhibited PKCδ⁺ CeL neurons bilaterally using targeted expression of tetanus toxin light chain, which inhibits neurotransmitter release. Inhibiting these neurons during fear conditioning — but not during testing — reduced conditioned freezing and signs of conditioning-induced synaptic strengthening in the LA. Therefore, the activity of PKCδ⁺ CeL neurons is necessary for LA plasticity and in turn for fear conditioning.

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Previous research has revealed that nociceptive signals are relayed by the parabrachial nucleus to the CeL, prompting Li and colleagues to hypothesize that CeL neurons — including those expressing PKCδ — may convey the US shock signal to the LA. To investigate this possibility, the authors imaged calcium responses of PKCδ⁺ CeL neurons in mice in a conditioned lick-suppression task, in which water-deprived mice learned to stop licking water from a water spout when presented with a CS that was followed by a tail-shock US. Strikingly, almost half of the imaged PKCδ⁺ CeL neurons responded to the US during conditioning, and the responses of many of these neurons declined with learning,as the animal began to expect the shock. Furthermore, chemogenetic inhibition of PKCδ⁺ CeL neurons acutely reduced tailshock-evoked LA responses. Thus, PKCδ⁺ CeL neurons convey the US to the LA during conditioning.

Moreover, optogenetic stimulation of PKCδ⁺ CeL neurons while a mouse was in a particular part of a chamber induced aversion to that location, both in real time and when tested the day after stimulation. This further supports a role for these neurons in aversive learning.

Using a combination of anterograde and retrograde labelling, the authors mapped the outputs of PKCδ⁺ CeL neurons and screened for regions that received these outputs and that in turn sent projections to the LA. In this way, the authors identified three regions that could feasibly relay the US signal from PKCδ⁺ CeL neurons to the LA: the substantia innominata, the substantia nigra pars compacta (SNc) and the retrorubral field. Notably, previous studies have implicated dopamine release from the SNc in fear learning; the authors hypothesized that the activation of PKCδ⁺ CeL neurons during US exposure might disinhibit dopaminergic release by SNc neurons in the LA, thus potentially driving synaptic plasticity and memory encoding.

This study demonstrates that, in fear conditioning, PKCδ⁺ CeL neurons convey the US to the LA to enable the encoding of aversive memory.

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