



SUMMARY AND COMMENT | PSYCHIATRY

ON THE HORIZON

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# Learn to No Longer Be Afraid: Role for L-Dopa?

Jonathan Silver, MD reviewing Haaker J et al. Proc Natl Acad Sci U S A 2013 Jun 25.

Dopamine strengthens the learning of extinction behaviors.

The patient undergoing behavioral treatment of a fear response learns a new adaptive response to the same stimulus. This new, inhibitory, extinction memory competes with, and does not erase, the fear memory, which can therefore recur. Researchers examined how the dopamine precursor, L-dopa, affects the return of fear in humans and in a mouse model.

A classic conditioning foot-shock model induced a conditioned response in mice, which then underwent extinction, followed by a single dose of L-dopa or saline. When the mice were placed in the conditioning cage (i.e., context) 1, 7, and 30 days later, L-dopa was associated with less spontaneous recurrence of fear, an attenuated return of contextual fear after shock reinstatement, greater immediate early gene (IEG) expression in the infralimbic cortex, and lower IEG expression in the centromedial amygdala.

In 40 men who learned a conditioned response to tactile pain, L-dopa (150 mg) compared with placebo decreased skin conductance response to the context-conditioned stimulus. In resting-state functional magnetic resonance imaging, placebo patients with renewed fear showed deactivation of the left ventromedial prefrontal cortex; L-dopa cancelled this deactivation.

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Extinction of the fear response raises dopamine activity in the ventromedial prefrontal cortex. The authors suggest that strengthening the extinction memory with L-dopa boosts consolidation, unhooking the extinction memory from any specific context. Thus, L-dopa after a treatment session may be effective. Although L-dopa is specific, stimulants could have similar effects.

However, could dopamine antagonists inhibit learning of the extinction memory in fearful patients? Perhaps, antipsychotics in patients with post-traumatic stress disorder (or with paranoid fear) interfere with learning compensatory strategies. We may need one treatment to decrease fear (NEJM Psychiatry Jun 28 2013) and an opposite therapy to improve new learning and strengthen treatments affecting the underlying biologic process. How do we decide which therapies to use?

Editor Disclosures at Time of Publication

### CITATION(S):

Haaker J et al. Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear. Proc Natl Acad Sci U S A 2013 Jun 25; 110:E2428.

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