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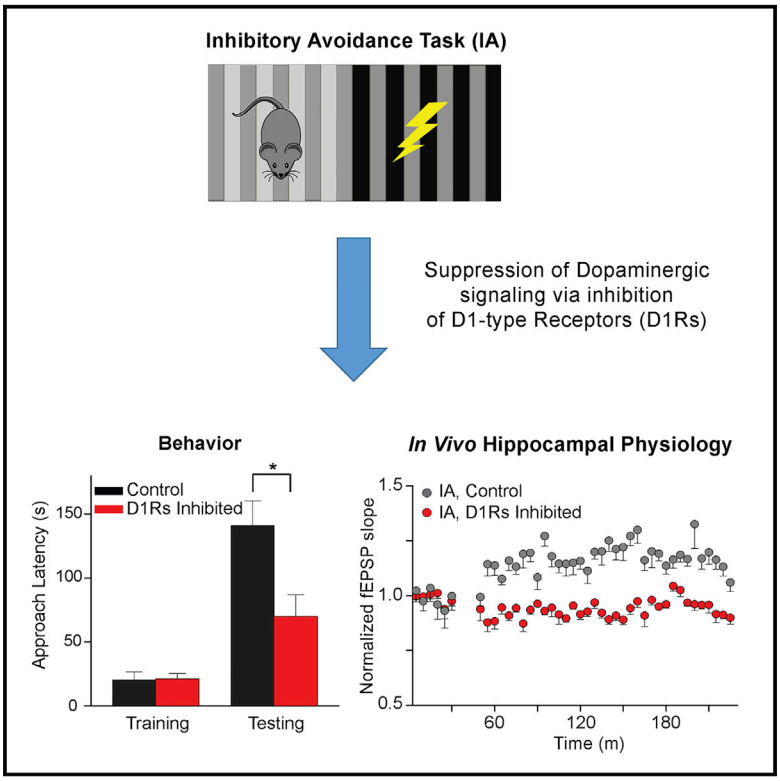
Dopamine Regulates Aversive Contextual Learning and Associated In Vivo Synaptic Plasticity in the Hippocampus

Graphical Abstract



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In Brief

The role of dopamine in signaling rewards is well known, but here Broussard et al. show that dopamine D1-like receptor activity in the hippocampus is necessary for retention of aversive memories. The results indicate dopaminergic innervation and function within the hippocampus underlying long-term synaptic potentiation associated with aversive memory retention.

Highlights

- Molecular approaches verified dopamine innervation of the hippocampus
- Inhibitory avoidance (IA) learning induces ex vivo and in vivo LTP in the CA1
- D1-like dopamine receptor inhibition prevents IA induction of LTP
- Dopamine activation enhances and inhibition prevents long-term retention of IA

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Dopamine Regulates Aversive Contextual Learning and Associated In Vivo Synaptic Plasticity in the Hippocampus

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SUMMARY

Dopamine release during reward-driven behaviors influences synaptic plasticity. However, dopamine innervation and release in the hippocampus and its role during aversive behaviors are controversial. Here, we show that in vivo hippocampal synaptic plasticity in the CA3-CA1 circuit underlies contextual learning during inhibitory avoidance (IA) training. Immunohistochemistry and molecular techniques verified sparse dopaminergic innervation of the hippocampus from the midbrain. The long-term synaptic potentiation (LTP) underlying the learning of IA was assessed with a D1-like dopamine receptor agonist or antagonist in ex vivo hippocampal slices and in vivo in freely moving mice. Inhibition of D1-like dopamine receptors impaired memory of the IA task and prevented the training-induced enhancement of both ex vivo and in vivo LTP induction. The results indicate that dopamine-receptor signaling during an aversive contextual task regulates aversive memory retention and regulates associated synaptic mechanisms in the hippocampus that likely underlie learning.

INTRODUCTION

Dopamine (DA) neurons arising from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) contribute during the formation of rewarded behaviors (Bayer and Glimcher, 2005; Schultz, 1986, 1998). DA neurons fire phasic bursts in response to unpredicted reward, and their phasic firing begins to track neutral stimuli that predict those rewards (Hollerman and Schultz, 1998). This firing characteristic of DA neurons suggests that they are highly effective at pairing neutral stimuli to unconditioned stimuli, and this property provided evidence that DA signals are a neural substrate of reward prediction (Berridge and Robinson, 1998; Dayan and Balleine, 2002; Montague et al., 2004; Schultz et al., 1997).

Recent studies indicate that DA neurons have a more heterogeneous response profile (Henny et al., 2012). For example, dorsal VTA neurons are typically inhibited by footshocks, but ventral VTA neurons may be phasically excited by noxious stimuli (Brischoux et al., 2009; Bromberg-Martin et al., 2010; Zweifel et al., 2011). Aversive events have been shown to increase the firing rate of a subset of VTA DA neurons and, as a result, increase DA release in target areas, such as the striatum or medial prefrontal cortex (Budygin et al., 2012; Dong et al., 2010; Lammel et al., 2011). Recent studies indicate that a DA neuron's response to negative or positive stimuli is largely dependent upon the neuron's presynaptic inputs, and the dopaminergic signal influences separate brain regions depending on valence (Lammel et al., 2011, 2012, 2014). These findings suggest that DA signaling may encode beyond prediction errors and contribute to synaptic plasticity required for updating memory of environmental salience, and that these DA signals act upon specific neural targets.

One such potential target is the hippocampus. Earlier evidence indicated that dopaminergic projections originating primarily from the midbrain (including the VTA, substantia nigra, and retrorubral field) project directly to the hippocampus (Gasbarri et al., 1994a, 1994b, 1996). Quantitative real-time PCR confirmed that D1 and D5 receptors are found in the hippocampus, including the CA1 (Mu et al., 2011). Physiological evidence demonstrated that D1 and D5 receptors are important for controlling spike timing dependent plasticity within the hippocampus (Yang and Dani, 2014). Also, there is functional evidence that indicates that drugs of abuse, such as nicotine (Tang and Dani, 2009; Zhang et al., 2010) and methylphenidate (Jenson et al., 2015), recruit dopaminergic neurotransmission to influence synaptic plasticity within the hippocampus. Dopaminergic neurotransmission in the hippocampus during specific time