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Synaptic Plasticity onto Dopamine Neurons Shapes Fear Learning

Highlights

- Stress priming enhances fear learning by engaging VTA synaptic plasticity
- Increase of AMPA receptor surface expression and function onto Thorase$_{DA}$KO neurons
- Impair induction and expression of LTD and LTP on Thorase$_{DA}$KO neurons
- Ab initio synaptic plasticity onto DAT^{+} neurons increases associative fear learning

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In Brief

Pignatelli et al. highlight a fundamental, novel role for synaptic plasticity within DAT^{+} neurons in shaping adaptive responses when it comes to assigning motivational value to events that are intrinsically aversive or conditioned to be unpleasant.

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Synaptic Plasticity onto Dopamine Neurons Shapes Fear Learning

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SUMMARY

Fear learning is a fundamental behavioral process that requires dopamine (DA) release. Experience-dependent synaptic plasticity occurs on DA neurons while an organism is engaged in aversive experiences. However, whether synaptic plasticity onto DA neurons is causally involved in aversion learning is unknown. Here, we show that a stress priming procedure enhances fear learning by engaging VTA synaptic plasticity. Moreover, we took advantage of the ability of the ATPase Thorase to regulate the internalization of AMPA receptors (AMPARs) in order to selectively manipulate glutamatergic synaptic plasticity on DA neurons. Genetic ablation of Thorase in DAT$^+$ neurons produced increased AMPAR surface expression and function that lead to impaired induction of both long-term depression (LTD) and long-term potentiation (LTP). Strikingly, animals lacking Thorase in DAT$^+$ neurons expressed greater associative learning in a fear conditioning paradigm. In conclusion, our data provide a novel, causal link between synaptic plasticity onto DA neurons and fear learning.

INTRODUCTION

Dopamine (DA) neurons play a fundamental role in regulating learning and memory of behavioral responses that need to be stored and remembered in order to differentiate stimuli that are predictive of positive or threatening outcomes (Bromberg-Martin et al., 2010; Cohen et al., 2012; Keiflin and Janak, 2015; Kim et al., 2015; Kim et al., 2004; Schultz, 2007; Wise, 2004). More than 10 years have passed since the discovery of experience-dependent plasticity onto DA neurons triggered by rewarding or aversive salient experiences (Dong et al., 2004; Saal et al., 2003; Ungless et al., 2001). However, whether synaptic plasticity on DA neurons is engaged in the process of remembering what is positive or negative for an organism is still unknown. In the current study, we focused on DA neuron synaptic plasticity, aiming at clarifying whether it plays a causal role in the establishment of aversive learning contingencies. With this question in mind, we performed a stress priming procedure to test the possibility that stress-induced synaptic plasticity within the ventral tegmental area (VTA) is capable of affecting the emotional weight of a subsequent aversive experience. Subsequently, in order to gain selective access to DA neuron synaptic plasticity, we purposely decided to use a "bottom-up" approach, by first genetically manipulating glutamatergic synaptic transmission onto DA neurons and then by interrogating the system at the behavioral level, to test for causality between synaptic plasticity and the occurrence of a specific aversive behavioral outcome.

RESULTS

Stress-Induced Synaptic Plasticity in the VTA Affects the Associative Strength of a Subsequent Fear Conditioning

Several lines of evidence showed that a single stress exposure is capable of causing long-lasting neuroadaptive changes onto VTA dopamine neurons, suggesting that acute stressors can affect the responsivity of VTA dopamine neuron to future emotionally charged experiences (Lammel et al., 2011, 2012; Saal et al., 2003). In order to directly test the former possibility, we decided to use a modified version of the stress-enhanced fear conditioning paradigm (Perusini et al., 2016).

In stress-enhanced fear learning, mice were exposed to a stress priming procedure consisting of seven shocks (experimental group) or context exposure without shocks (control group) (Figure 1A). 24 hr after the stress priming procedure, mice were trained in a cue fear conditioning, a paradigm that uses the same stress modality of the stress priming. In particular, mice were placed in a testing chamber (context A), and after 2 min of acclimation period, they received a white noise, which co-terminated with a foot shock. After 24 hr, context-induced fear