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Neuronal Basis of Behavioral Responses to Reward-Predictive Cues

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Abstract Cue-evoked reward-seeking behaviors require recognition of learned cues that predict reward availability and selection of appropriate motor responses to the cues. Multiple brain areas such as the nucleus accumbens (NAc), dorsomedial prefrontal cortex (dmPFC), basolateral amygdala and ventral tegmental area contribute to the performance of cue-evoked reward-seeking behavior. However, less is known about function of the neuronal circuits consisting of those brain regions. Recent study has reported the importance of projections from the dmPFC to the NAc core in behavioral and NAc neuronal responses to reward-predictive cues in a discriminative stimulus (DS) task in which an intermittently presented cue directs rats to make an operant response for reward. Here I review the neuronal mechanism underlying cue-evoked reward-seeking behaviors focusing on behavioral, anatomical and electrophysiological evidence for the significance of dmPFC projections to the NAc core in cue responding in the DS task.

Key words: anterior cingulate cortex, basolateral amygdala, discriminative stimulus, nucleus accumbens, prelimbic cortex

Introduction

Central nervous system has an ability to predict forthcoming events based on environmental cues and select an appropriate motor response to obtain a reward. Neuronal circuits underlying the ability involve the nucleus accumbens (NAc), dorsomedial prefrontal cortex (dmPFC), basolateral amygdala (BLA) and ventral tegmental area (VTA). However, it remains to be determined how cue and reward information are integrated in the neuronal circuits. Previous studies have reported that cue-elicited phasic changes in firing of NAc neurons can facilitate appropriate responding to reward-predictive cues.[1)2)] dmPFC, BLA and VTA neurons also respond to reward-predictive cues during many reward-seeking behaviors,[3-6)] and dopamine is thought to enhance the glutamate-induced excitation of NAc neurons.[7)8)] Anatomically, the NAc that has long been considered a "limbic-motor interface"[9)] receives glutamatergic inputs from the dmPFC and BLA in addition to dopaminergic projections from the VTA.[10)11)] Thus, a convergence of inputs from the dmPFC, BLA and VTA to the NAc is considered as a neuronal basis underlying a processing of cue information in reward-seeking behaviors. In this review, I focus on a role of dmPFC projections to the NAc in behavioral responses to reward-predictive cues and explore the functional significance of a proposed neuronal circuit consisting of the NAc, dmPFC, BLA and VTA.

Role of dmPFC projections to the NAc in cue-evoked reward-seeking behaviors

Cue-elicited firing changes of NAc neurons has a pivotal role in cue responding during a discriminative stimulus (DS) task in which an intermittently presented cue (DS) directs rats to make a lever pressing for sucrose.[1] Microinjection of $GABA_A$ (muscimol) and $GABA_B$ agonists (baclofen) (M/B) into the dmPFC, which is a major source of glutamatergic afferents to the NAc, impairs behavioral responding to reward-predictive cues and also significantly reduces the magnitude of the DS-elicited excitatory and inhibitory responses of NAc core neurons (Fig. 1).[12] Previous works demonstrate that inactivation of the VTA in a similar DS task also selectively reduces the magnitude of cue-evoked NAc neuronal firing[13] and that both VTA inactivation and injection of dopamine antagonists into the NAc reduce cue responding.[13][14] As dopamine alone does not directly excite NAc neurons,[8] it is possible that dopamine increases incentive cue responses by facilitating glutamate-mediated excitatory inputs arising from afferents to the NAc. Therefore, dmPFC neurons could be a crucial source of the excitatory afferents underlying the NAc dopamine-dependent cue responses.

Unilateral dmPFC inactivation reduces ipsilateral NAc core DS-evoked excitations to the same extent as bilateral dmPFC inactivation, despite the fact that the behavioral impairment in cue responding caused by unilateral inactivation was much less pronounced.[12] These results are not compatible with the idea that cue-evoked excitations of NAc neurons are resulted from cue responding behavior due to other circuits and in fact represent strongly that ipsilateral dmPFC projections to the NAc core drive cue-evoked excitations that are required for the behavioral responses to reward-predictive cues.

Neuronal circuits of cue-evoked reward-seeking behaviors

The projection from the dmPFC to the NAc core is essential for NAc neurons to fire

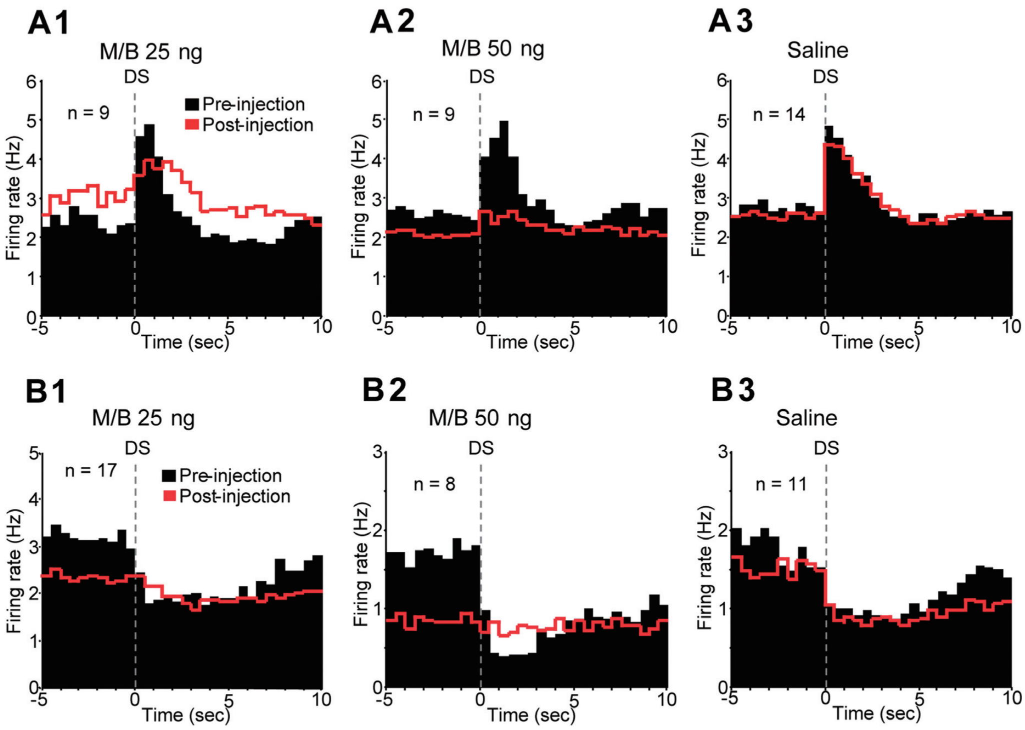

Fig. 1 Inactivation of the dmPFC reduces the DS-evoked excitation and inhibition of NAc neurons. Averaged perievent time histograms (PETHs) of pooled DS-excited (A1, A2, A3) and DS-inhibited (B1, B2, B3) neurons before (black) and after (red) 25 ng of M/B, 50 ng of M/B, and saline injections, respectively. Injections of 25 and 50 ng of M/B into the dmPFC reduce the DS-evoked excitation and inhibition of NAc neurons, whereas saline injections have no effect on the firing. Histograms are all time locked to DS presentation. Bin width of PETHs is 0.5 sec. Data are from Ishikawa A et al. (2008)[12]

maximally in response to reward-predictive cues presented during an operant task and the dmPFC facilitates the behavioral response to these cues.[12] Since the BLA, VTA, and dopamine receptor activation within the NAc are also required for cue responding, a simple circuit model has been proposed.[14] When a reward-predictive cue is presented, glutamatergic neurons in the dmPFC[5,6] and BLA[3] are excited and release glutamate in the NAc. VTA neurons are also excited[4] and release dopamine in the NAc core.[15] BLA neurons signal an event of potential emotional significance,[16] and dmPFC neurons signal the action to be selected to obtain the reward.[17] VTA neurons signal that a reward-predictive cue is being encountered.[18] When all of these inputs converge in the NAc core, just those neurons that receive convergent input from the cue-excited neurons in the dmPFC, BLA and VTA fire and increase the probability of the specific behavioral response necessary to obtain reward.

Summary

Recent behavioral and electrophysiological works have scrutinized the significance of major limbic inputs to the NAc in reward-seeking cue responding.[12,19] The projection from the dmPFC to the NAc core is thought to signal cue-associated motor response to obtain a reward, whereas BLA neurons projecting to the NAc core could signal an event of emotional salience. Proposed neuronal mechanism underlying appropriate behavioral responses to reward-predictive cues is an integrated function in the convergent input from glutamatergic (dmPFC and BLA) and dopaminergic (VTA) afferents to the NAc core, where interaction of glutamate and dopamine simultaneously released within the NAc is required to completely perform the cue-evoked reward-seeking behaviors.[14]

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