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The Role of Kappa Opioid Receptors in Glutamate Input Selection in the Ventral Striatum

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Review of Brooks and O'Donnell

The ventral striatum is an important controller of motivated behavior. This nucleus receives dopamine afferents from the ventral tegmental area and glutamate afferents from the basolateral amygdala, thalamus, medial prefrontal cortex (mPFC), and ventral hippocampus, which encode emotional, sensory, executive-control, and contextual information, respectively. The ventral striatum integrates information from these inputs, and its principal neurons, GABAergic medium sized spiny neurons (MSNs), send output to the rest of the basal ganglia. The weight given to the different glutamate sources determines the extent to which contextual, emotional, or executive information influences behavior.

MSNs are segregated into direct and indirect pathways based on their projection target. Direct-pathway MSNs express D1 dopamine receptors, and their activation is thought to promote execution of motivated behaviors. In contrast, indirect-pathway MSNs express D2 dopamine receptors, and their activation is thought to inhibit the performance of motivated behaviors (Kravitz et al., 2012). The integration and processing of glutamate and dopamine inputs to D1 or D2 MSNs constitute the basis for a diverse range of actions.

As mentioned above, MSN activity is controlled by afferents that carry different type of information. Most of the time, the activity of the ventral striatum is synchronized with that of the hippocampus. Hippocampal activity sets MSNs into an active, depolarized state that gates other inputs to ventral striatum. This might be the mechanism by which contextual information is constantly updated in the ventral striatum for use during the execution of motor behavior. Notably, inputs from mPFC evoke firing in MSNs only when the neurons are already in a depolarized state (O'Donnell and Grace, 1995). Nonetheless, the mPFC can take control over MSN activity in certain situations. Specifically, burst activity in mPFC afferents induces heterosynaptic suppression of the MSNs' response to subsequent hippocampal or thalamic activation (Calhoon and O'Donnell, 2013). This effect might allow executive information to transiently take control of the behavior by means of an inhibition of less relevant information, enabling efficient decision-making.

Previous work (Calhoon and O'Donnell, 2013) showed that mPFC inhibition of hippocampal inputs is partially mediated by $GABA_A$ receptors. Intra-MSN blockage of $GABA_A$ receptors *in vivo* attenuated, but did not eliminate, the mPFC-induced inhibition of hippocampal inputs (Calhoon and O'Donnell, 2013), suggesting that other inhibitory mechanisms are recruited during this phenomenon. What mediates the rest of the inhibition was left unanswered.

One mechanism by mPFC activity might produce heterosynaptic suppression of hippocampal input is presynaptic inhibition mediated by the kappa opioid receptors (KORs). KORs are G_i-coupled receptors highly expressed in the ventral striatum, and are mainly found presynaptically in both symmetric and asymmetric synapses (Svingos et al., 1999, 2001). KORs in the ventral striatum are part of a retrograde signaling system, in which the endogenous KOR agonist dynorphin is somatodendritically released from D1-MSNs to act on presynaptic KORs (Gerfen and Young, 1988). Most studies have focused on the impact of KORs on dopamine neurotransmission. Indeed, within the ventral striatum, KORs are preferentially localized in close proximity to the dopamine transporter (Svingos et al., 2001), a localization that is consistent with its inhibitory role over dopamine release (Di Chiara and Imperato, 1988; Chefer et al., 2005). However, increasing evidence points to an inhibitory effect of KOR activation on glutamate neurotransmission. KORs are located presynaptically on asymmetric synapses, indicative of glutamate afferents (Svingos et al., 1999). Early studies of striatal synaptosomes showed that KOR agonists decrease glutamate release (Hill and Brotchie, 1995, 1999). Moreover, electrophysiological studies in brain slices showed

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that bath application of U69,593, a KOR agonist, decreased the EPSPs in MSNs via a presynaptic mechanism (Hjelmstad and Fields, 2001, 2003). Finally, a recent study showed that KOR activation inhibits amygdalar, but not hippocampal glutamate inputs on D1 MSNs (Tejeda et al., 2017), indicating that KORs have input- and cell-specific actions. Together, the available data indicate that KORs regulate different afferent inputs and that KOR might influence input integration in the ventral striatum, thus influencing behavior.

To test whether the KOR system contributes to the mPFC inhibition of hippocampal inputs within the ventral striatum, Brooks and O'Donnell (2017) used whole-cell patch-clamp recordings to evaluate EPSPs evoked in MSNs by optogenetic stimulation of hippocampal inputs, before and after burst stimulation of corticostriatal fiber bundles (Brooks and O'Donnell, 2017). With this *in vitro* approach, the authors first replicated their previous *in vivo* findings (Calhoon and O'Donnell, 2013) that burst stimulation of mPFC inputs significantly decreased the amplitude of EPSPs elicited by a hippocampal optical stimulation relative to baseline, and that this effect is partially mediated by $GABA_A$ receptors. They then assessed whether KOR activation inhibits the EPSPs evoked by hippocampal or mPFC input. Consistent with previous reports (Hjelmstad and Fields, 2001; Tejeda et al., 2017), bath application of a KOR agonist significantly decreased the EPSPs after both hippocampal and mPFC stimulation. Most importantly, Brooks and O'Donnell (2017) found that KOR antagonists significantly reduced the magnitude of the mPFC-induced inhibition of hippocampal stimulation. These data demonstrate that KOR activation contributes to the mPFC-induced heterosynaptic inhibition of hippocampal inputs. Moreover, when both $GABA_A$ and KORs were blocked simultaneously, the mPFC-induced inhibition of hippocampal inputs was abolished. These data indicate that mPFC burst activity engages KOR and $GABA_A$ systems to inhibit, through independent mechanisms, input from ventral hippocampus.

The findings of Brooks and O'Donnell (2017) not only replicate their previous *in vivo* study, but also expand the knowledge on the function of KORs acting as a retrograde signaling system on glutamate inputs within the ventral striatum. It would be of interest to address whether the KOR-mediated inhibition of hippocampal activity targets both D1 and D2 MSNs or whether it exhibits cell specificity, as described for KOR control over amygdala inputs within the ventral striatum (Tejeda et al., 2017). The KOR-mediated inhibition of MSN responses to hippocampal inputs triggered by burst stimulation of mPFC inputs likely involves the release of dynorphin from D1 MSNs that act presynaptically on KORs located in ventral hippocampus terminals. The selective removal of KORs from ventral hippocampus terminal would help to elucidate the influence of KORs on the performance of behavioral tasks in which the mPFC-induced suppression of ventral hippocampus responses is relevant.

The findings described by Brooks and O'Donnell (2017) suggest a mechanism by which the KOR system can influence behavior. Increasing evidence links KOR dysfunctions with the development of neuropsychiatric disorders in which behavioral inflexibility is a key component, including drug addiction (Lalanne et al., 2014), obsessive compulsive disorder (Perreault et al., 2007), and schizophrenia (Tejeda et al., 2012). The data suggest that a hyperactive KOR system within the ventral striatum could lead to enhanced mPFC-mediated suppression of hippocampal inputs, an effect that could impede the adaptation to important changes in environmental cues during the decision-making process. Alternatively, a hypoactive KOR system could lead to weaker mPFC-mediated suppression, leading to a loss of behavior execution during critical decision-making instances.

Finally, the results from this study point to the important function of ventral striatum as a switchboard nucleus, in which glutamate inputs are integrated and where MSNs respond according to the hierarchal order of glutamate inputs (Gruber and O'Donnell, 2009), placing the KOR system as a key intermediary of the animal response to environmental cues during the decision-making process.

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