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RIM1 $\alpha\beta$ Are Required at the Corticostriatal Synapses for Habit Formation

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Review of Kupferschmidt et al.

Control of instrumental actions relies on a dual system of goal-directed and habit strategies (Liljeholm and O'Doherty, 2012). Goal-directed actions involve anticipation of rewards and are therefore sensitive to changes in the value of the outcome. Habits, in contrast, are well learned actions driven by a stimulus without regard to the outcome (Yin, 2008). Through repetition and learning, goal-directed strategies gradually evolve into less flexible habits (Yin, 2008; Gremel and Costa, 2013). This happens when the sensorimotor association becomes strong enough to overcome the expectancy of the outcome, allowing the brain to complete everyday actions with minimal effort.

The balance between goal-directed and habitual action is regulated by an intricate neuronal network in which the dorsal striatum plays a pivotal role (Liljeholm and O'Doherty, 2012; Corbit et al., 2013). Specifically, the dorsomedial striatum (DMS) regulates goal-directed strategies, while the dorsolateral striatum (DLS) is involved in action learning and

habitual strategies (Yin, 2008; Liljeholm and O'Doherty, 2012; Nazzaro et al., 2012; Gremel and Costa, 2013). Thus, changes in DMS and DLS activity underlie switches from goal-directed to habitual action strategies (Yin et al., 2009; Santos et al., 2015). These changes in activity have been proposed to be regulated by glutamatergic projections from the cerebral cortex, which are the main source of excitatory signals to the striatum (Huerta-Ocampo et al., 2014).

In addition to postsynaptic changes in AMPA and NMDA receptors, which occur in the DLS in the late phases of skill learning and habit formation (Yin et al., 2009), recent findings suggest that presynaptic release dynamics in the dorsal striatum are important predictors for action learning (Kupferschmidt et al., 2017). For example, expression of CB1 cannabinoid receptors (CB1Rs) in cortical neurons projecting to the dorsal striatum are indispensable for habit formation (Gremel et al., 2016), and endocannabinoid-dependent long-term depression (eCB-LTD) of neurotransmitter release might be involved in this dependence (Wu et al., 2015).

Presynaptic release of neurotransmitters relies on a complex machinery that couples local calcium influx to synaptic vesicle fusion. Several proteins coordinate this process, including Rab3 interacting molecules (RIMs), one of the main com-

ponents of the presynaptic active zone (Schoch et al., 2002). RIM proteins are encoded by four genes that give rise to seven isoforms; of these, the α and β isoforms encoded by the *Rims1* gene are the most studied (Kaesler and Südhof, 2005). RIM proteins are expressed ubiquitously in the CNS (Schoch et al., 2006), and they have been proposed to be coordinators of the components involved in short- and long-term synaptic plasticity at the active zone (Schoch et al., 2006). Interestingly, RIM1 deletion has different effects on plasticity at different synapse types (Kaesler and Südhof, 2005). For instance, RIM1 α knock-out enhances short-term plasticity in hippocampal CA3–CA1 synapses (Schoch et al., 2002), whereas it disrupts long-term plasticity while sparing short-term plasticity in dentate gyrus mossy fibers (Castillo et al., 2002). Moreover, it has been shown in *ex vivo* (Chevalleyre et al., 2007; Grueter et al., 2010) and *in vitro* (Alonso et al., 2017) experiments that endocannabinoid-induced long- and short-term depression depends in part on RIM1 α expression.

To determine whether RIM1 influences plasticity at corticostriatal synapses, Kupferschmidt et al. (2019) used *Emx1::Cre;RIM1^{-/-}* mice, in which the RIM1 isoforms α and β were deleted selectively in excitatory neurons in the neocortex (RIM1 $\alpha\beta$ cKO). As expected, this reduced the frequency of spontaneous

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Figure 1. Simplified proposed mechanism for the shift from goal-directed to habitual strategies and the RIM1 $\alpha\beta$ contribution to the corticostriatal network established by Kupferschmidt et al. (2019). **A**, In the presence of a novel stimulus, actions are highly dependent on outcomes, indicative of goal-directed strategies. These are modulated mainly by the neural inputs from associative and limbic areas (like the BLA) to the DMS, while the DLS is disengaged. **B**, After training or action learning, the stimulus becomes the driver of the action, indicative of habits. In this situation, projections from the sensorimotor cortex are strengthened, possibly through the contribution of RIM1 $\alpha\beta$ in the presynaptic modulation of glutamate release. In addition, inputs from the associative cortices to the dorsal striatum (likewise the OFC terminals) are inhibited by eCB-LTD, a process dependent on CB1R. Whether RIM1 $\alpha\beta$ is important in the inputs from cortical structures to the DMS is still unknown.

EPSCs in medium-sized spiny neurons (MSNs), the most abundant neurons in the DLS, without changing the amplitude of spontaneous events, indicating a defect in presynaptic vesicle release (Castillo et al., 2002; Schoch et al., 2006). In addition, responses evoked in MSNs by stimulation of corticostriatal fibers were significantly reduced in mutant mice, suggesting evoked release was also impaired.

To evaluate whether CB1R-dependent synaptic plasticity was also affected in RIM1 $\alpha\beta$ cKO mice, the authors used different strategies to induce short- or long-term depression. First, depolarization-induced suppression of excitation (DSE) was used to induce short-term depression in corticostriatal synapses. Depolarizing neurons to 30 mV for 10 s induced similar amounts of depression in RIM1 $\alpha\beta$ cKO and wild-type mice. Second, DHPG was used to induce long-term depression. Again, the extent of depression was similar in RIM1 $\alpha\beta$ cKO and wild-type mice. Moreover, this effect was effectively blocked by a CB1R antagonist in both mutant and control animals. Therefore, both short- and long-term depression of neurotransmitter release were spared in the RIM1 cKO mice.

Next, Kupferschmidt et al. (2019) investigated how the reduction in basal neurotransmission between the cortex and the DLS in RIM1 $\alpha\beta$ cKO mice affected goal-directed and habit-driven action. To do this, they used a self-paced instrumen-

tal task followed by a valuation test. Food-restricted mice were trained to press a lever to receive a food-pellet reward, using a random-interval reward schedule for several days; this protocol was previously shown to promote habit formation (Gremel et al., 2016). Bias to use a goal-directed or habitual action strategy was assessed after training by giving mice access to either a sucrose solution or food pellets before testing them on the lever-pressing task in the absence of the reward. Importantly, access to the food pellets before testing is expected to devalue the reward, whereas access to sucrose solution is not. If mice are using goal-directed strategies, they should press the lever fewer times in the devalued condition; but if they are using habitual strategies, the number of lever pressings should be indistinguishable in the two conditions. As expected, reward devaluation did not affect lever pressing in control animals, indicating habitual control of actions. In contrast, RIM1 $\alpha\beta$ cKO mice were sensitive to the devaluation, as indicated by fewer lever presses compared with the wild-type and to the sucrose condition. This suggests that habit formation was impaired in these mice.

These findings are exciting for two main reasons. First, according to the “dual-system theory” of instrumental learning, goal-directed strategies, which depend on cortico-DMS synapses, have initial dominance over habits that rely on

cortico-DLS synapses. Therefore, weakening the cortical transmission to DLS might be expected to bias the animals toward the use of goal-directed actions even when interval-schedule reward training is used to promote habits (Nazzaro et al., 2012). Indeed, the findings presented by Kupferschmidt et al. (2019) support this notion, where goal-directed strategies would be set by default when habits cannot be formed. Second, they suggest a RIM1-independent synaptic plasticity at corticostriatal synapses, different to what is observed in other synapses in the CNS. For example, in cultured cerebellar granule cells, using protocols of endocannabinoid-induced depression similar to the one used by Kupferschmidt et al. (2019), CB1R activation induced greater depression of neurotransmitter release in RIM1 α -deficient cells than in wild-type, and this effect was rescued by re-expressing RIM1 α (Alonso et al., 2017). Opposite results were found in hippocampal neurons and a subset of neurons in the core region of the nucleus accumbens (NAc): RIM1 α depletion in these structures caused a reduction in the DHPG-induced eCB-LTD (Grueter et al., 2010). Given that eCB-LTD occurs in corticostriatal synapses and its relevance has been shown in several studies (Nazzaro et al., 2012; Wu et al., 2015), the lack of effect in the RIM1 $\alpha\beta$ cKO mice shown by Kupferschmidt et al. (2019) suggests that, as in short- and long-term potentiation, short- and long-term

depression can be RIM1-dependent or independent, depending on the synapse type. Because RIMs proteins are ubiquitously expressed in the CNS, this also suggests a differential specialization of the neurotransmitter release machinery in different synapse types.

Excitatory synapses in other regions where RIM1 $\alpha\beta$ have a predominant function might contribute to the phenotypes observed here. As stressed above, whereas DLS [which Kupferschmidt et al. (2019) examined] is engaged in later stages of action learning and habit formation, DMS is involved in goal-directed strategies (Liljeholm and O'Doherty, 2012; Gremel and Costa, 2013), and in early phases of training. Both the orbitofrontal cortex (OFC) and the basolateral amygdala (BLA) project to the DMS (Kelley et al., 1982; Gremel and Costa, 2013; Gremel et al., 2016). It has been shown that inhibition of OFC inputs to the dorsal striatum is necessary for habit formation, and this process depends on CB1Rs (Gremel and Costa, 2013; Gremel et al., 2016). The BLA was also shown to be involved in the process of goal-directed action learning; specifically, BLA lesions increase outcome devaluation (Corbit et al., 2013). Therefore, it is possible that the inability to set habitual strategies in the RIM1 $\alpha\beta$ cKO mice arises from defective activation/inactivation balance of DMS by OFC and/or BLA, in addition to the reduction in basal neurotransmission at cortex-DLS synapses reported by Kupferschmidt et al. (2019) (Fig. 1).

By addressing the role of RIM1 $\alpha\beta$ in the corticostriatal synapses, Kupferschmidt et al. (2019) have provided new evidence on the importance of basal corticostriatal neurotransmission in the balance between goal-directed and habitual strategies. Untangling these mechanisms will lead us to a better understanding of

complex diseases, such as obsessive-compulsive disorder or drug-related seeking behavior, where this balance is biased toward habits. Moreover, the authors have presented exciting new data showing that RIM1 can differentially modulate neuronal plasticity, raising new questions about the molecular arrangement of pre-synaptic components at corticostriatal synapses.

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