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RESEARCH HIGHLIGHT

A distinct signaling pathway in parvalbumin-positive interneurons controls flexible memory updating

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Creating stable memories is critical for survival, as a means to find scarce resources (e.g., food/water) and avoid dangerous situations. However, the dynamic nature of an environment also requires that memories be updated with new information in order to respond to changing reward and threat contingencies. Thus, optimal brain circuits require both stability and flexibility to efficiently create memories and to update them according to ongoing changes in the environment [1]. The vast majority of research on memory processes has focused on forming stable memories that drive behavior, while much less is known about how these memories are updated when new information is provided.

In their recent *Neuropsychopharmacology* article, Xu et al. [2] identify a specific molecular interaction in the mouse medial prefrontal cortex (mPFC) that helps maintain the persistence of a memory despite new conflicting information. This process occurs during initial learning, is mediated by the ErbB4- NRXN1β interaction in mPFC, and selectively increases excitatory connections onto parvalbumin-positive (PV+) neurons. To block this interaction, the authors developed a novel small peptide, called ErbB4-16P, that directly inhibited ErbB4- NRXN1β interaction while maintaining other ErbB4-mediated actions. By blocking this ErbB4-NRXN1β interaction, the authors blocked the corresponding increase in excitatory connectivity on PV+ interneurons and were able to induce more flexible behavior when mice learned a new reward contingency. Specifically, the authors trained mice to associate odor A with a reward and odor B with no reward. They then performed similar training with two new odors (by rewarding odor C, but not odor D), which the mice quickly learned. When the authors reversed this contingency, and began rewarding odor D, instead of odor C, the control mice took longer to learn this association than during initial learning of odors A and B, showing an interference from the initial training. However, when the authors specifically disrupted the ErbB4-NRXN1β signaling pathway, the mice were able to rapidly learn the new association. Specifically, the improved performance on the reversal task was due to reduced responses to the no-longer-rewarded odor (i.e., correct rejections of incorrect stimuli). Together, these experiments demonstrate that the ErbB4- NRXN1β signaling stabilizes learned information, drives increased excitatory connections onto PV+ interneurons, and contributes to proactive interference to learning new information.

Several aspects of this study are remarkable. First, by disrupting the ErbB4-NRXN1β binding, the authors were able to enhance reversal learning without impacting the initial learning of the reward association. Traditional theories have suggested there is a tradeoff between the stability and flexibility of a memory, where stronger memories are more difficult to update with new information. However, the data presented by Xu and colleagues suggest that these two processes are not entirely opposing, and may be mediated by distinct molecular pathways and circuit properties. Critically, the data suggests that there may be approaches to produce strong, stable memories that are also flexible and can be updated quickly given new information. It is important to note that this flexibility to learn new associations was beneficial in this particular task, but it is unclear if this flexibility would have maladaptive repercussions in other tasks that more closely mimic real-world foraging environments. For instance, it may be beneficial for an animal to continue sampling from previously rewarded stimuli if changes in reward contingency are rare. The authors also did not explore the long-term stability of the reward associations over weeks to months. Thus, it is unclear if blocking the ErbB4-NRXN1β interaction could have led to more subtle effects on stability that were not evident in the first few days of training, but manifested over weeks.

Another remarkable aspect of this study was that the effect was specific to PV+ interneurons and the excitatory connections onto them in the mPFC. PV+ interneurons have been implicated in many cognitive processes including learning and memory and network oscillations, but very few of these functions have been specifically driven by distinct molecular and circuit interactions. While it is not surprising that neuronal activity and learning drive increased excitatory connections onto PV+ neurons, the specificity of this interaction has important implications for the circuit mechanisms that may mediate this enhanced reversal learning. PV+ interneurons have previously been shown to mediate competition for memory ensembles in the amygdala [3] which may help to explain how this effect manifests. Under normal conditions, an excitatory memory ensemble strengthens its connection with PV+ interneurons through ErbB4- NRXN1β signaling, enhancing feedback inhibition that may reduce activation of competing ensembles, which helps to reactivate this ensemble during memory retrieval. By disrupting this plasticity, there is reduced network inhibition, which allows for new ensembles to be engaged and new learning to occur. This appears similar to what Rashid et al. [3] reported when examining competing ensembles in the amygdala. In that case, inhibiting PV+ interneurons supported new learning to occur by allowing different principal neurons to encode the new memory, rather than the previously active ensemble (that encoded a prior

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memory). Thus, we speculate that inhibiting the ErbB4-NRXN1β interaction may reduce the inhibitory tone during reversal learning and drive improved reversal learning.

From a clinical perspective, this work is exciting because it implies that specific molecular interactions could be targeted to enhance the flexibility of memories. In particular, a lack of memory flexibility is a critical component of post-traumatic stress disorder and enhancing the ability to reverse previously learned associations may provide key therapeutic effects for people struggling with this disorder [4]. In addition, reversal learning is impaired with aging and leads to deficits in performance on reversal tasks [5]. For both of these disorders, the work by Xu and colleagues provides new hope that a molecular pathway can be targeted to enhance the flexibility of memory updating, without impacting the stability of prior memories. While there is much work to be done to translate these findings to clinical populations, the authors have already demonstrated a key behavioral effect with a small peptide that has important therapeutic implications for supporting memory flexibility.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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