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## Memory Suppressor Genes: Modulating Acquisition, Consolidation, and Forgetting

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### Summary

The brain has a remarkable but underappreciated capacity to limit memory formation and expression. The term memory suppressor gene was coined in 1998 as an attempt to explain emerging reports that some genes appeared to limit memory. At that time, only a handful of memory suppressor genes were known, and they were understood to work by limiting cAMP-dependent consolidation. In the intervening decades, almost 100 memory suppressor genes with diverse functions have been discovered that affect not only consolidation but also acquisition and forgetting. Here we highlight the surprising extent to which biological limits are placed on memory formation through reviewing the literature on memory suppressor genes. In this review, we present memory suppressors within the framework of their actions on different memory operations: acquisition, consolidation, and forgetting. This is followed by a discussion of the reasons why there may be a biological need to limit memory formation.

### Keywords

Memory enhancement; acquisition; consolidation; forgetting; behavioral flexibility; memory accuracy

### Introduction

Molecular and cellular studies of learning and memory over the last five decades have focused nearly exclusively on functions that are required for normal learning and memory. The general approach has been to apply insults to certain molecules or cells to see if this compromises these processes. For instance, genetic approaches that were employed early identified learning and memory mutants in *Drosophila*, including the well-known mutant,

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Declaration of Interests

The authors declare no competing interests.

*rutabaga*. *Rutabaga* was found to encode a  $\text{Ca}^{2+}$ /calmodulin responsive adenylyl cyclase (Levin et al., 1992; Livingstone et al., 1984), a critical molecule supporting many different forms of learning across phyla by acting as a molecular coincidence detector between the stimuli that are associated (Gervasi et al., 2010; Tomchik and Davis, 2009). A second classic example of a molecule required for normal memory formation is the *N*-methyl-D-aspartate (NMDA) ionotropic glutamate receptor, which is crucial for the formation of many different types of memory (Morris, 2013). This receptor also acts as a molecular coincidence detector, sensing the coincident release of neurotransmitter from a presynaptic neuron and the depolarization of the postsynaptic neuron (Bliss and Collingridge, 1993). The cumulative research over the last five decades has identified hundreds of genes and the molecules they encode that are essential for normal learning and memory processes.

However, there is a yin for every yang. Recent research has revealed that the brain is also designed with processes that constrain memory formation, such that reducing the activity of these molecules enhances learning and/or memory performance. Genes that encode molecules limiting memory in a wildtype animal are termed ‘memory suppressor genes’ by analogy to tumor suppressor genes (Abel et al., 1998). Thus, the normal function of these molecules is to suppress a process involved in the formation, storage or recall of memory. The opposite of a memory suppressor gene is a memory enhancer gene, which increases memory formation when its activity is increased. A notable example of a memory enhancer is the NMDA receptor subunit *NR2B*. Overexpression of the *NR2B* subunit in the mouse forebrain enhances long-term memory (LTM) in a variety of tasks, including fear conditioning, novel object recognition, and Morris water maze performance, paralleled by increased hippocampal long-term potentiation (Tang et al., 1999); whereas reduction of the *NR2B* subunit impairs spatial memory and long-term potentiation (Clayton et al., 2002).

The earliest memory suppressor molecules identified include repressors of CREB, such as ApCREB2 in *Aplysia*. Inhibiting ApCREB2 activity by injecting anti-ApCREB2 antiserum into *Aplysia* sensory neurons allows the formation of long-term facilitation (LTF) after only a single application of serotonin, whereas LTF is normally produced only with multiple applications of serotonin. Thus, ApCREB2 suppresses the formation of LTF by repressing CREB function (Bartsch et al., 1995). Studies of CREB repressors such as ATF4 in the mouse (Chen et al., 2003; Yin et al., 1994) provide cross-species support that negative regulators of CREB function as memory suppressor molecules.

Only recently has there been focused and systematic research on memory suppressor genes. This focus is important for several reasons. First, a deep understanding of memory suppressors will pinpoint the neurophysiological processes that limit memory formation. This will reveal the number and type of molecular control points that limit learning and memory. Arguably, understanding the negative regulators of memory is as equally important as understanding the positive ones. Second, identifying memory suppressors is relevant for understanding enhanced and compromised memory that occurs in the human population. Savant syndrome, for example, is characterized by remarkable memory capacity, often occurring in individuals with autism spectrum disorder (ASD) (Treffert, 2009). Conversely, post-traumatic stress disorder (PTSD) presents as maladaptive, abnormally strong memories – potentially arising from the dysregulation of memory suppressor genes and/or their

products. Third, the products of memory suppressor genes offer targets for designing drugs that could act as cognitive enhancers, since identifying antagonists of molecular targets is often easier than identifying agonists.

The formation of memory that becomes retrievable over short- and long-periods of time can be conceptualized as four basic operations: (1) the initial acquisition or encoding of information, (2) the consolidation of memory into a more stable form resistant to disruption, (3) the active forgetting of memory, and (4) the retrieval of memory (Figure 1). In principle, memory suppressors could function by limiting one or more of these four operations. Only the first three – acquisition, consolidation, and forgetting – have been explored using molecular genetics approaches because retrieval remains relatively intractable. Here, we provide a comprehensive review of memory suppressors within the framework of the first three memory operations. Many of the memory suppressors identified in the scientific literature could not be placed into this framework due to the lack of data required for assignment. Nevertheless, we have included them in Supplemental Tables to serve as a comprehensive resource, grouping the genes and gene products into three categories. Table S1 contains suppressors of early memory (effects found at the earliest time point tested within 4hr of training). These are likely to include suppressors of acquisition as well as suppressors of early memory. Table S2 includes genes that suppress late memory (no effects at the earliest time point tested but affecting time points thereafter). This category would contain suppressors of consolidation or promoters of forgetting. Table S3 summarizes memory suppressors that could not be categorized into either of the first two groups. We identify memory suppressors from the enhancement of behavioral memory when the suppressor is inhibited, and we provide a mechanistic basis for the memory enhancement when it is known. Finally, this is followed by a discussion of the reasons why memory suppressors exist.

## Suppressors of Acquisition

We define suppressors of acquisition as those genes or molecules that, when inhibited, result in enhanced memory performance when the animal is tested immediately after training. In the *Drosophila* literature, memory acquisition is frequently measured using multiple, short conditioning trials to monitor how memory performance builds as a function of training trial number (Beck et al., 2000). Moreover, by altering the training trial number across groups to normalize performance immediately after training, researchers have been able to dissociate effects on acquisition from those on memory consolidation or forgetting (Figure 2). However, most rodent learning paradigms measure memory performance hours to weeks after training, so only a few of the memory suppressors identified in mouse studies could definitively be assigned as suppressors of acquisition. Nevertheless, it is likely that many of the early or unassigned genes and their products in Table S1 and S3 act on acquisition.

## GABAergic inhibition limits the potency of learned stimuli

Genes that encode molecules of GABAergic inhibitory systems function as suppressors of acquisition. The  $\gamma$ -amino butyric acid (GABA)<sub>A</sub> receptors are ligand-gated chloride channels that, upon binding of GABA neurotransmitter, hyperpolarize neurons – reducing

their ability to be depolarized and fire action potentials. Resistance to dieldrin (*Rdl*), which codes for a subunit of the GABA<sub>A</sub> receptor, offers the earliest report of a suppressor of acquisition in *Drosophila* (Liu et al., 2007; Liu et al., 2009). *Rdl* is highly expressed in the antennal lobes and mushroom body neurons (MBn; Liu et al., 2007), areas known to be important for *Drosophila* olfactory processing and memory (Davis, 2004) and which are analogous to the mammalian olfactory bulb and primary olfactory cortex (Murthy, 2011). *Rdl* overexpression in the MBn impairs aversive olfactory conditioning, while RNAi-mediated reduction of *Rdl* in the MBn enhances the performance of flies in both aversive and appetitive olfactory conditioning tasks (Liu et al., 2007; Liu et al., 2009). Interestingly, *Rdl* knockdown enhances memory acquisition using short, multiple training sessions like those described in Figure 2, but produces aligned memory retention scores with control flies when knockdown flies are normalized for the enhanced acquisition (Liu et al., 2007). Examining MBn activity in response to olfactory stimuli using the optical Ca<sup>2+</sup> reporter GCaMP indicates that *Rdl* overexpression reduces, while *Rdl* knockdown enhances, odor induced MBn activity (Liu et al., 2007). These observations led to the conclusion that reducing GABA<sub>A</sub> receptor function by knocking down *Rdl* increases the MBn response to odors, which serves as the conditioned stimulus, leading to increased acquisition. In other words, reducing GABA<sub>A</sub> receptor increases the potency of the odors used for conditioning as experienced by the MBn (Figure 3).

Studies of GABA<sub>A</sub> receptor function in the mouse support this general conclusion. *GABA<sub>A</sub> receptor subunit  $\alpha$ 5* (*GABRA5*) knockout (KO) mice acquire spatial memory in the matching-to-place version of the Morris water maze faster than control mice (Collinson et al., 2002). This subunit exhibits preferential expression in the mouse hippocampus, a brain area known to be required for spatial and contextual memory. The same study discovered that the hippocampal neurons in the KO mice exhibit increased paired pulse facilitation, indicating they have a higher amplitude of excitatory synaptic potentials compared to controls. Thus, in both *Drosophila* and mice, reducing inhibitory signaling through GABA<sub>A</sub> receptors leads specifically to enhanced memory acquisition.

Genes encoding metabotropic GABA<sub>B</sub> receptors also function as acquisition suppressors in *Drosophila*. Reducing levels of the *GABA-B-R3* receptor in the dopamine neurons (DAn) responsible for conveying the sugar reward during olfactory appetitive conditioning results in enhanced acquisition of the reward memory (Yamagata et al., 2021). Inhibiting GABA release from the upstream neuron by reducing glutamic acid decarboxylase 1 (*Gad1*) and the vesicular GABA transporter (VGAT) also enhance appetitive memory. Interestingly, these flies exhibit a higher learning maximum, rather than reaching the same ceiling asymptotic level as observed with many other acquisition suppressors. Calcium imaging revealed that GABA-B-R3 acts to limit the responses of reward DAn synapses to sugar ingestion (Yamagata et al., 2021). Thus, the hyperpolarization resulting from both GABA<sub>A</sub> and GABA<sub>B</sub> receptors limit acquisition to balance the strength of memory formed with the stimuli used in olfactory conditioning.

Several other mouse studies have also reported GABAergic genes as memory suppressors, although it is not clear whether they suppress acquisition since measures of immediate memory post-training were not recorded. Knockout of GABA<sub>A</sub> receptor subunits *GABRA4*

(Fan et al., 2020), *GABRA $\alpha$ 2* (Engin et al., 2015), *GABRA $\beta$ 2* (Parker et al., 2011), and heterozygous knockouts of the GABA transporter *GAT1* (Shi et al., 2012) were all reported to lead to enhanced performance in a variety of memory tasks including aversive and appetitive conditioning and spatial memory in the Morris water maze.

### MicroRNAs that constrain the excitability of neurons

MicroRNAs (miRs) are small, non-coding RNAs that regulate gene expression through translational repression and/or through mRNA degradation (Bushati and Cohen, 2007). To identify novel miRs that participate in learning and memory processes, a *Drosophila* miR screen was conducted using a “microRNA sponge” approach to individually inhibit more than 130 miRs, preventing them from binding and silencing their mRNA targets (Busto et al., 2015). This screen identified several miRs that act as memory suppressor genes. One miR identified from the screen, *miR-980*, was shown to suppress memory acquisition.

*MiR-980* inhibition in all neurons, and various subsets of neurons involved in aversive olfactory conditioning (except for GABAergic neurons), led to increased memory scores in the aversive olfactory conditioning paradigm, while *miR-980* overexpression in MBn impaired memory (Güven-Ozkan et al., 2016). When memory acquisition and retention were assayed, *miR-980* inhibition in all neurons was shown to increase memory scores in both experiments. However, when memory retention was tested after normalizing for the increased memory acquisition of *miR-980* knockdown flies (Figure 2), intermediate memory scores (3hrs) were found to be higher than the control, suggesting that *miR-980* may independently constrain memory acquisition and alter consolidation and/or forgetting processes (Güven-Ozkan et al., 2016). To determine how a reduction in *miR-980* might alter neuron function leading to increased memory expression, the authors examined calcium responses of the MBn to odor. The results indicated that reduced *miR-980* led to a stronger odor response in these neurons. Furthermore, current-clamp recordings of the projection neurons that deliver odor information to the MBn, showed that *miR-980* inhibition increases firing frequency compared to control neurons or neurons that overexpress *miR-980*. Thus, *miR-980* suppresses memory acquisition by limiting the excitability of neurons (Figure 3). The gene, *A2bp1*, was identified in this study as a major mediator of the observed *miR-980* effects. *A2bp1* is an autism and epilepsy-susceptibility gene functioning principally via a role in RNA alternative splicing (Lee et al., 2009). The conclusion that *miR-980* functions by limiting neuronal excitability parallels results obtained by reducing GABA receptor function.

### Transcriptional regulation that limits the potency of unconditioned stimuli

Stromalin is a member of the highly conserved cohesion complex that is best known for its role in supporting proper chromosome segregation during mitosis and in regulating gene expression (Peters et al., 2008). A memory suppressor function of Stromalin was first identified in a large, RNAi behavioral screen using *Drosophila* (Walkinshaw et al., 2015). RNAi-mediated depletion of *Stromalin* in MBn or DAN enhanced memory, while overexpression had no effect (Phan et al., 2019). Further experiments (Figure 2) showed that *Stromalin* knockdown specifically increases memory acquisition. The authors focused on the role of Stromalin in DAN to identify the cellular mechanisms of Stromalin’s memory

suppression effects. DAN in the *Drosophila* aversive olfactory conditioning paradigm are known to encode the aversive or foot-shock information. RNAi-mediated reduction of *Stromalin* increases communication between the DAN and their downstream MBn partners, determined by measuring cAMP increases in the MBn in response to DAN activation, while not affecting the calcium responses of the DAN itself to the shock stimulus. Cellular studies revealed that this occurred because of an increase in the number of synaptic vesicles in *Stromalin* knockdown DAN compared to controls. The important conclusion drawn from this study is that Stromalin suppresses memory acquisition by limiting the number of synaptic vesicles in the DAN that convey the unconditioned stimuli (Figure 3).

In an unexpected twist, the authors found that Stromalin's memory suppressor function occurs not during adulthood, when olfactory memory was assayed, but during the development of 3<sup>rd</sup> instar larvae (Phan et al., 2019). This observation was made possible using tools that allow the experimenter to control the timing of RNAi-mediated knockdown. Due to its developmental function that becomes apparent in adult memory tests, the mechanism by which the gene limits synaptic vesicle number was hypothesized to be through the developmental regulation of gene expression from cohesin's known role in gene expression.

One other gene has been found to function during development to limit adult memory formation. Diaphanous homologous protein 1 (*Diap1*) is an actin polymerization regulator, whose reduction *in utero* using RNAi or overexpression of *miR-9* results in adult mice that display improved performance in an auditory fear conditioning task 48hrs after training (Lin et al., 2017). Unlike Stromalin, Diap1's effects are not due to enhancements in memory acquisition, but on LTM. Diap1 appears to limit dendritic branching and synapse formation of developing cortical neurons. Thus, the attractive explanation for the experimental results is that this memory suppressor gene constrains adult memory by restricting the potential to form synaptic connections during development.

### Limiting neurotransmitter function at the synapse

DmSLC22A (CG7442) was also identified from the aforementioned RNAi screen (Walkinshaw et al., 2015). Based on its homology to the mammalian SLC22A family of transporter proteins, it was predicted to be an organic cation transporter, but no substrates were known when its memory suppressor function was discovered. *In vitro* experiments identified DmSLC22A as a transporter for choline and acetylcholine (Figure 3; Gai et al., 2016). RNAi-mediated depletion of *DmSLC22A* in MBn or DAN increases memory scores, whereas overexpression in the MBn impairs memory performance of flies in the aversive olfactory conditioning paradigm. Since the projection neurons that provide olfactory input into the MBn are cholinergic and SLC22A localizes to the dendrites of the MBn, the gene product appears to function by limiting the persistence of acetylcholine at the projection neuron-MBn synapse (Figure 3).

In summary, the known suppressors of acquisition function by: (1) limiting the potency of stimuli through circuit inhibition, (2) capping neuronal excitability, (3) limiting the availability or release of neurotransmitter, and (4) limiting neurotransmitter persistence/function in the synapse (Figure 3).

## Suppressors of Consolidation

Consolidation is the process of converting newly formed memories that are initially sensitive to disruption into long-lasting memories that are stable and resistant to interference (McGaugh and Alpern, 1966; Quinn and Dudai, 1976; Scoville and Milner, 2000; Squire and Davis, 1981). The strength and repetition of the stimuli being learned are the major factors that influence consolidation (Carew et al., 1972; Cepeda et al., 2006; Tully et al., 1994). Thus, consolidation provides a filter to save highly consequential events and/or events likely to be encountered again. Suppressors of consolidation prevent inconsequential information or spurious associations from being encoded into LTM.

### Consolidation suppressors limit cAMP-signaling and CREB regulated gene expression

Early cellular studies with *Aplysia* and genetic studies with *Drosophila* established that the cAMP signaling pathway is critical for acquisition and short-term memory (Brunelli et al., 1976; Byers et al., 1981; Livingstone et al., 1984; Scholz and Byrne, 1988). Research with these same model systems subsequently established that the normal function of CREB is required for consolidation of LTM and the plasticity associated with it (Dash et al., 1990; Kaang et al., 1993; Tully et al., 1994). A suppressor of consolidation associated with CREB function was identified from studies with *Aplysia*. When neutralizing antibodies to the endogenous CREB inhibitor, ApCREB2, are injected into sensory neurons, a single pulse of serotonin, which is normally insufficient to drive long-term changes in plasticity, is able to produce long-term facilitation (Bartsch et al., 1995). Similar results were obtained using RNAi to knockdown *ApCREB2* (Lee et al., 2003). Inhibition of *ATF4* in the mouse, a homologue of *ApCREB2*, was found to enhance spatial memory and long-term potentiation (LTP) (Chen et al., 2003). These and other related studies have established that CREB-dependent transcription is required for LTM and that suppressors of CREB prevent the consolidation of short-term memory (STM) into LTM (Figure 4).

The conceptual model for protein-synthesis dependent consolidation described above supports the notion that natural constraints on CREB activity, such as the activity of the *ApCREB2* gene/protein, or *ATF4*, limit consolidation. Indeed, the CREB repressor *ICER* (Mioduszevska et al., 2003) meets the definition of a memory suppressor gene and it achieves this suppression by altering the CREB-activity threshold for memory consolidation. In mice, loss of *ICER* enhanced fear memory after weak but not strong training (Kojima et al., 2008). This indicates that *ICER* acts to prevent weak events from being encoded into LTM. Consistent with this model, overexpression of *ICER* in the forebrain impaired long-term fear memory but not memory measured one hour after training. Interestingly, elevated cAMP drives the expression of *ICER* (Mioduszevska et al., 2003), indicating that the same signals that promote the activation of CREB also lead to increased CREB-suppressor activity.

How does CREB promote consolidation and how might CREB suppression prevent it? Several studies have found that CREB modulates basal neuronal excitability and the development of LTP. Mice that lack CREB display impaired fear and spatial LTM and a failure to develop hippocampal LTP (Bourtchuladze et al., 1994). Conversely, overexpression of *CREB* in the amygdala increases neuronal excitability (Yiu et al., 2014,

Zhou et al., 2009) and LTM after suboptimal fear conditioning (Josselyn et al., 2001). Similar increases in neuronal excitability occur following *CREB* overexpression in the hippocampus (Barco et al., 2002; Gruart et al., 2012) and the rat nucleus accumbens (Dong et al., 2006). Expression of *CREB* in random subsets of mouse amygdala neurons increases encoding of fear memory in those neurons relative to neurons without ectopic *CREB* expression (Han et al., 2007, Han et al., 2009, Zhou et al., 2009). Together, these data suggest that CREB's role in consolidation may occur by increasing neuronal excitability.

Since CREB abundance and activation provide a threshold for determining the probability that a memory undergoes CREB-dependent consolidation (Figure 4), one would anticipate that genes and gene products that limit this activation, besides the ATF4/ICER proteins discussed above, would function as consolidation suppressors. There exist two obvious control points at which memory suppressors might function. The first is through the negative regulation of cAMP levels from the activity of 3',5'-cyclic phosphodiesterases (PDEs) and the second through negative regulators of PKA (protein kinase A), a cAMP-dependent kinase that stimulates CREB transcriptional activity (Figure 4).

The *Drosophila dnc* gene encodes a cAMP PDE with four mammalian orthologs known as PDE4a-d (Byers et al., 1981; Chen et al., 1986; Davis and Kiger, 1981). Consistent with a memory suppressor function, Scheunemann et al (2018) reported that a partial reduction of *dnc* activity in serotonergic projection neurons (SNP) neurons facilitates LTM following subthreshold training. In wildtype flies, the *dnc* PDE prevents SPN cAMP elevation during a single round of training. However, after multiple spaced training cycles, the PDE is inhibited and elevated cAMP levels promote SPN activity, which ultimately drives LTM consolidation. Nevertheless, the role of *dnc* as a memory suppressor gene is difficult to cleanly unpack since it seems to have neuron-specific roles in memory formation and the complete loss-of-function of *dnc* throughout the organism causes a profound impairment in memory formation (Dudai et al., 1976).

The function of PDE4s as memory suppressors has more robust support from mammalian studies. Injection of the PDE4 inhibitor rolipram (Nemoz et al., 1985; Henkel-Tiggs and Davis, 1990) into the brains of mice enhances contextual long-term fear memory but has no effect on STM (Barad et al., 1998). In addition, rolipram injection specifically during the consolidation period enhances object recognition memory (Rutten et al., 2006) and rescues age-related memory impairments in object recognition (Wimmer et al., 2020). Genetic studies support the role of PDE4s as consolidation suppressors. *PDE4a* KO mice exhibit enhanced passive avoidance (Hansen et al., 2014) and *PDE4d* KO and hippocampal knockdown enhances spatial memory and novel object recognition (Li et al., 2011). Interestingly, inhibition of PDE2 during consolidation promotes novel object location memory when combined with suboptimal doses of a PDE4 inhibitor (Paes et al., 2021), suggesting that multiple PDEs constrain consolidation. Indeed, PDE8b, PDE1b, and PDE7 have been reported to suppress multiple types of memory. (McQuown et al., 2019; Tsai et al., 2012, McQuown et al., 2021).

The evidence is less robust for a potential role of PKA inhibitors in consolidation and indeed, some evidence is contrary to this point of view. Eukaryotic cells express a family



of PKA inhibitors (PKA-I), that include PKI $\alpha$ ,  $\beta$ 1,  $\beta$ 2 and  $\gamma$  (Chen and Sabatini, 2021). Although no systematic studies have been performed to determine whether any of these molecules function as memory suppressors, significant reductions in *PKI $\alpha$*  mRNA levels were observed following neuronal stimulation in the rat hippocampus, raising the possibility that learning relieves PKI $\alpha$  inhibition of PKA and promotes subsequent PKA-dependent consolidation (de Lecea et al., 1998). Contrary to the well-established role for PKA in protein synthesis dependent-consolidation, Horiuchi et al (2008) reported that a partial loss of PKA activity in the MBn leads to enhanced protein synthesis-independent consolidated memory (Horiuchi et al., 2008), and this partial-loss-of function rescues age-related impairments in consolidated memory with no effect on learning (Yamazaki et al., 2010).

### **Small, noncoding RNAs function as consolidation suppressors by regulating protein product abundance**

Cellular systems that silence RNA expression act to restrict consolidation (Figure 4). Disrupting the function of miRs as well as piRNA, another type of small, non-coding RNA that represses target mRNA translation and transcript degradation (Huang et al., 2017), enhances memory. The enzyme Dicer1 is required for the conversion of mature miRNA to pre-miRNA (Bartel, 2007) and loss of *Dicer1* in the mouse brain enhances conditioned fear memory and alters mRNA levels of memory-related genes (Fiorenza et al., 2016; Konopka et al., 2010). There are three piwi-like (*piwil*) genes (O'Donnell and Boekel, 2007) in the mouse that participate in piRNA-mediated mRNA degradation, two of which serve redundantly as memory suppressors. Hippocampal knockdown of *piwil1* and *piwil2* simultaneously in adult mice enhances long-term contextual fear memory, while leaving behavior unaltered during the training phase (Leighton et al., 2019).

The specific piRNAs that mediate piwil-dependent memory suppression remain unknown. However, progress has been made in identifying the miRNAs that suppress consolidation. In *Drosophila*, *miR-92a*, a highly conserved miR across species (Yuva-Aydemir et al., 2015), was identified as a memory suppressor gene in a miR memory screen (Busto et al., 2015). Inhibition of *miR-92a* in the MBn has no effect on learning but enhances one form of consolidated memory known as anesthesia-resistant memory (ARM) (Quinn and Dudai, 1976). This form of consolidated memory is erased by a cold shock to the flies within one hour after acquisition and is distinct from protein synthesis-dependent consolidation. One gene regulated by *miR-92a* that appears to be largely responsible for ARM consolidation encodes the motor protein Khc73 (Güven-Ozkan et al., 2020), whose overexpression also enhances ARM. These observations implicate protein transport in the process of consolidation, which is consistent with the earlier discovery that consolidation is enhanced by the overexpression of kinesin heavy chain in *Aplysia* sensory neurons (Puthanveetil et al., 2008).

*MiR-182* levels are rapidly reduced in the mouse amygdala after auditory fear conditioning, suggesting that this miR may keep consolidation at bay until released by *miR-182* degradation (Griggs et al., 2013). Consistent with this proposition, overexpression of *miR-182* in the lateral amygdala reduces the expression of the plasticity promoting proteins, Rac1 and cortactin, and impairs LTM but not STM after cued fear conditioning. It seems

likely that *miR-182* is a consolidation suppressor, but this provisional conclusion is based on overexpression experiments. A *miR-182* disruption experiment is required to satisfy the defining criteria for a consolidation suppressor.

### Consolidation suppressors that constrain protein synthesis

Translation of pre-existing and newly synthesized transcripts is required for protein synthesis-dependent (PSD) consolidation of LTM (Flexner et al., 1962; Hernandez and Abel, 2008), making the proteins that regulate translation ideal consolidation control points. The translation initiation factor eIF2 $\alpha$  is one such control point whose activity is regulated by several memory suppressor genes. eIF2 $\alpha$  is rapidly dephosphorylated following contextual fear conditioning in the mouse hippocampus, derepressing its activity. This derepression promotes memory formation, since mice with phosphorylation-deficient eIF2 $\alpha$  display enhanced spatial memory, fear memory, taste memory, and elevated late phase-LTP (Costa-Mattioli et al., 2007). Phosphorylation of eIF2 $\alpha$  suppresses memory formation via two distinct mechanisms. First, eIF2-dependent production of memory-supporting proteins is decreased (Boye and Grallert, 2020). Second, the translation of the CREB inhibitor ATF4 is increased (Lu et al., 2004; Vattem and Wek, 2004). The memory suppressor genes *PKR*, *GCN2*, and *PERK* all code for kinases that phosphorylate eIF2 $\alpha$  at the S51 residue, thereby suppressing eIF2 $\alpha$ -dependent consolidation and synaptic plasticity (Costa-Mattioli et al., 2005; Sharma et al., 2018; Zhu et al., 2011).

Other than translation initiation factors, memory suppressors operate at several other points in the translation pathway. The first is through Poly(A)-binding protein (PABP). PABP interacts with and promotes the translation of memory relevant mRNAs (Gray et al., 2000), but is inhibited by interactions with poly(A) binding protein interacting protein 2 (PAIP2A). Fear conditioning drives the degradation of PAIP2A, freeing PABP to form a complex with mRNA and translation initiation factors (Khoutorsky et al., 2013). *PAIP2A*<sup>+/-</sup> mice exhibit normal memory 1 hour after fear conditioning but have significantly elevated memory 1 day later. In mice with the complete loss of *PAIP2A*, 24-hour memory is enhanced after weak training, L-LTP forms more easily and PABP binding to memory related mRNAs is increased. Second, mTOR (mechanistic target of rapamycin) is required for fear memory consolidation through its complex formation with the protein Raptor (Jobim et al., 2012). Fear conditioning promotes the formation of this complex in the hippocampus, overcoming mTOR inhibition by the protein FKBP12 (Hoeffler et al., 2008) in the mouse forebrain enhances contextual long-term fear memories without altering STM. *FKBP12* knock out also increases hippocampal L-LTP. But the enhanced L-LTP is eliminated by protein synthesis inhibition, supporting the proposition that FKBP12 suppresses consolidation by controlling mTOR-dependent protein translation. The net effect of mTOR activation is the regulation S6K1 and 4E-BP, which modulate the activity of translation initiation factors (Hoeffler and Klann, 2010).

### Ras pathway signaling limits consolidation

Ras signaling affects processes throughout the neuron and regulates synaptic plasticity through both pre- and post-synaptic mechanisms (Curtis and Finkbeiner, 1999; Kushner et al., 2005; Platenik et al., 2000; Xing et al., 1996). Although mammalian Ras activating

mutations can lead to either enhancement or impairment of memory depending on the conditions (Fasano and Brambilla, 2011; Kushner et al., 2005), Ras is generally held to be required for PSD-LTM (Mazzucchelli and Brambilla, 2000), in other words, a LTM facilitator.

The positive influence of mammalian Ras on LTM is at least partly due to its effects on learning-induced protein synthesis through the downstream kinase ERK (Peng et al., 2010). However, Ras also has an ERK-independent role in both protein synthesis-dependent and independent consolidated memory in *Drosophila*. In this organism, ERK-independent Ras signaling through Raf suppresses protein synthesis-independent ARM and facilitates PSD-LTM (Noyes et al., 2020). Knockdown of *Ras* in the MBn enhances ARM without altering acquisition, but strongly reduces or eliminates PSD-LTM. Prior behavioral studies had shown that ARM and PSD-LTM are antagonistic (Isabel et al., 2004; Placais et al., 2012). Thus, Ras function within its signaling systems provides a molecular explanation for the antagonism between ARM and PSD-LTM. PSD-LTM in *Drosophila* is analogous to PSD-LTM in mammalian systems, but it remains unclear how ARM relates to mammalian memory. However, many genes that modulate ARM also regulate mammalian memory, including *Ras*, *Raf* (Fasano and Brambilla, 2011; Noyes et al., 2020), Rho Kinase (*ROCK*) (Huentelman et al., 2009; Noyes et al., 2020), *CDC42* (Kim et al., 2014; Zhang et al., 2016) and *PDE4/dnc* (Bolger, 2017; Scheunemann et al., 2012; Scheunemann et al., 2018). Therefore, we speculate that genes discovered in *Drosophila* that promote or inhibit ARM may prove to be suppressors or facilitators, respectively, of mammalian memory. For instance, *Drosophila* ROCK activity enhances consolidated ARM, while its pharmacological inhibition in mice improves memory and rescues memory deficits in disease models (Koch et al., 2018).

Thus, there are multiple mechanisms for filtering information to be consolidated into LTM. The major mechanisms include the control of protein synthesis for PSD-LTM by regulating gene expression through transcription factors such as CREB, or by controlling protein translation through small, inhibitory RNAs and/or translation initiation factors (Figure 4). An offshoot of this involves Ras signaling for ARM in *Drosophila*, whose relationship with mammalian consolidation is currently unknown.

## Suppressors that Act on Forgetting

Forgetting is the temporary or permanent inability to retrieve a previously acquired memory. Although forgetting is often viewed as an impediment, as seen in aging or neurodegenerative diseases, it is a critical process for selecting and maintaining those memories that will drive advantageous behavior. For example, behavioral flexibility requires an individual to forget prior information that would prevent updating of memories with new information. This can be observed experimentally using reversal learning paradigms, in which an organism previously trained to associate a stimulus with particular valence must later learn to associate the same stimulus with a neutral or opposite valence (Izquierdo et al., 2017). Forgetting is also critical for memory generalization, the process that allows memories of specific situations to be used to make predictions about similar, but non-identical situations (Robertson, 2018). In this process, forgetting causes the loss of memory details and allows

the memory to be retrieved using broad similarities rather than the details present during acquisition. The identification of memory suppressor genes has played a central role as an entrée to the molecular mechanisms for active forgetting.

Enhanced consolidation and impaired forgetting both result in increased memory performance at time points after acquisition. There are several observations that support the categorization into either one of the two categories. (1) Impaired forgetting results in slower memory decay over time, whereas enhanced consolidation should produce a normal memory decay rate. (2) In *Drosophila*, many of the studies on forgetting have focused on labile memory in the absence of PSD-consolidation. (3) Effects that occur outside the generally accepted time window for consolidation (e.g., ~1 day for PSD-LTM) suggest that consolidation is not affected.

### AMPA receptor mediated forgetting

Across species, synaptic strength is efficiently modulated by changes in synaptic AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (AMPA) levels (Turrigiano and Nelson, 1998). Insertion of additional AMPARs into post-synaptic sites after learning increases synaptic strength and underlies the formation of some types of memory. Conversely, internalization of surface AMPAR reduces the functional connection between potentiated synapses and is proposed to be one mechanism for forgetting (Figure 5A; Hardt et al., 2014). Some evidence supports this proposal. Postsynaptic levels of the AMPAR subunit Glu2a in the amygdala positively correlate with memory strength after fear conditioning (Migues et al., 2010) and inhibiting hippocampal Glu2a internalization following training suppresses the forgetting of episodic memory (Migues et al., 2016). Although there is some debate on the issue, there is evidence that PKM $\zeta$ -dependent maintenance of hippocampal memory is achieved by sustaining surface levels of synaptic AMPARs (Migues et al., 2010).

Two genes have recently been identified that regulate memory stability presumably through AMPAR internalization. First, reducing expression of the memory suppressor gene, *Caspase-2*, slows the forgetting of spatial memory and impairs the internalization of hippocampal AMPARs by reducing GSK3 $\beta$  activity (Xu et al., 2019). Caspase-2 is also required for the formation of LTD, which is formed by the internalization of AMPARs from the post-synaptic membrane (Malenka, 2003). The second AMPAR-regulating gene to affect memory stability, *syt3*, does not fit the working definition of a memory suppressor, as there is no evidence that loss of the gene function alters memory decay. However, *syt3* KO mice are impaired in a Morris water maze reversal-learning task (Awasthi et al., 2019). These mice fail to forget the previously learned position of a platform after they are repeatedly trained to the platform's new position. Like Caspase-2, Syt3 promotes the endocytosis of AMPAR and is required for LTD formation. Thus, *syt3* may also be a memory suppressor gene functioning by facilitating the endocytosis of AMPARs.

### Dopamine signaling and active forgetting

Research using *Drosophila* has revealed that dopamine (DA), in addition to being critical for the acquisition of memories, is an intrinsic signal that drives forgetting. The ongoing activity

of a subset of DAN is sufficient to cause significant forgetting of labile memories (Berry et al., 2012). Inhibiting these neurons prolongs memory retention while their activation quickly impairs memory performance. These same neurons are required for normal associative olfactory learning and their activation can be substituted in place of an unconditioned stimulus to form an “artificial” memory (Aso and Rubin, 2016; Claridge-Chang et al., 2009). This seemingly contradictory role of DA in learning and forgetting is achieved through two different DA receptors. The D1-like receptor, *dda1*, is responsible for acquisition, registering the DA signal produced by the unconditioned stimulus (Kim et al., 2007; Tomchik and Davis, 2009). Loss of *dda1* in the MBn eliminates associative olfactory memory (Kim et al., 2007). DA-induced forgetting is mediated by DAMB (Berry et al., 2012). Although learning is relatively normal in DAMB mutants, labile memory decay is significantly reduced. Dopamine signaling through DAMB elicits Gαq-dependent increases in cytosolic Ca<sup>2+</sup> and reduction of MBn *Gαq* results in impaired forgetting (Figure 5B; Himmelreich et al., 2017). Interestingly, *Drosophila* DANs may promote memory decay through co-neurotransmitters. Nitric oxide produced in DANs during aversive conditioning signals through guanylate cyclase in MBn, resulting in reduced memory retention (Aso et al., 2019). This possibility is supported by an earlier study showing that RNAi knockdown of a subunit of guanylyl cyclase enhances memory (Walkinshaw et al., 2015).

Evidence has emerged linking the mammalian dopaminergic system to forgetting. Post-training injection of a D1 dopamine receptor antagonist in the rat hippocampus after training enhances 7-day food and cocaine-place conditioning memory (Diaz et al., 2019), raising the possibility that the D1 receptor drives forgetting in mammals. Recent work has tested the role of rat D1 receptors in retrieval-induced forgetting, a phenomenon in which retrieval of a memory promotes the forgetting of other related memories. Pharmacological inhibition of prefrontal cortex D1 receptors eliminates retrieval-induced forgetting while activation promotes it (Gallo et al., 2021). Dopamine has also been suggested to contribute to retrieval-induced forgetting in humans. Study subjects with an allele for catechol-*O*-methyltransferase (COMT) associated with higher prefrontal cortex dopamine levels display higher levels of retrieval-induced forgetting (Wimber et al., 2011) despite exhibiting normal or enhanced performance in other cognitive tasks (Savitz et al., 2006). Intriguingly, dopamine promotes the transient blockade of aversive LTM retrieval in *Drosophila* (Sabandal et al., 2021). This temporary forgetting is dependent on MBn DAMB, which appears to mediate stimuli-induced dopamine release from upstream dopaminergic neurons.

*Scribble*, first identified as a gene of interest in a memory suppressor screen (Walkinshaw et al., 2015), was later discovered to function downstream of DAMB (Cervantes-Sandoval et al., 2016). Knockdown of *Scribble* in the MBn recapitulates the DAMB mutant forgetting phenotype and results from epistasis experiments suggest that the Scribble protein propagates the forgetting signaling from DAMB to downstream proteins. Importantly, these studies provided a link between DAMB and the previously established role for Rac1 in active forgetting (Shuai et al., 2010). Current evidence suggests that Scribble acts as a scaffolding protein, physically interacting with Rac and other Rac signaling molecules (Cervantes-Sandoval et al., 2016).

### Small G-proteins, including Rac1 and CDC42, drive active forgetting

The role of Rac1, a Rho family GTPase, in forgetting has been demonstrated in mice for several types of memory. Hippocampal Rac1 activity is increased following contextual fear conditioning and pharmacological inhibition of this activity enhanced the conditioned fear memory (Jiang et al., 2016; Lv et al., 2019). Importantly, hippocampal injection of the Rac1 inhibitor was delivered after training, indicating that Rac1 activity has a post-acquisition role in producing the increased memory performance. Lv et al (2019) also showed that the expression of a dominant negative (DN) or constitutively active (CA) form of Rac1 in the hippocampus enhanced and impaired long-term contextual fear memory, respectively, with neither insult altering acquisition. Hippocampal inhibition of Rac1 reduces forgetting of episodic memory tested by novel object recognition (Liu et al., 2016) and in a social discrimination paradigm (Liu et al., 2018), while Rac1 activation accelerates memory decay in these same tasks. However, Rac1 has been reported to have roles in other memory forming operations depending on the nature of the genetic insult, the neurons that are affected, and the task being learned (Gao et al., 2015; Haditsch et al., 2009; Oh et al., 2010).

The process of Rac-dependent active forgetting is conserved across animal phyla. *Drosophila* MBn expression of dominant-negative (DN) Rac slows the forgetting of labile memory produced by associative olfactory conditioning while constitutively active (CA) Rac increases forgetting (Shuai et al., 2010). Like Scribble, which scaffolds Rac to downstream signaling components (Cervantes-Sandoval et al., 2016), MBn Rac also regulates behavioral flexibility observed in reversal learning and retroactive interference experiments (Shuai et al., 2010).

While Rac is responsible for active forgetting of labile memories, another small G-protein, Cdc42, drives the forgetting of consolidated memories. A single cycle of aversive olfactory conditioning causes an increase in Cdc42 activity. Inhibition of this activity in the MBn through expression of DN Cdc42 impairs the forgetting of ARM (Zhang et al., 2016). After massed training, consolidated ARM is elevated at later time points compared to single cycle training but initial ARM levels are similar in both training paradigms. Massed training prevents the increase in Cdc42 activity observed following single cycle training. This suggests consolidated ARM is formed at similar levels regardless of the type of training, but the type of training alters the forgetting of ARM through Cdc42 activity.

What molecular processes are altered by Rac1 and Cdc42 activation to cause forgetting? The discovery of Rac1 and Cdc42 as regulators of forgetting implicates actin dynamics as the process that may mediate forgetting. Rac1 and Cdc42 are known to modulate dendritic spine morphology, cellular projections and presynaptic organization via control over actin dynamics (Chen et al., 2012; Duman et al., 2015), consistent with the possibility that undoing structural changes that occur during acquisition may underlie active forgetting. In *Drosophila*, SCAR/WAVE and dia were found to be downstream from Rac, mediating Rac-induced forgetting of labile memories (Gao et al., 2019). The same paper concluded WASp and ARP2/3 are downstream from Cdc42 and mediate Cdc42-induced forgetting of consolidated ARM. In each case, RNAi knockdown of the individual genes led to enhanced memory after acquisition, with epistasis experiments revealing the relative position of each component in the active forgetting pathways. These four genes are well-established

regulators of the actin cytoskeleton (Kovar, 2006; Miki and Takenawa, 2003; Rotty et al., 2013).

It remains unknown how these proteins undo distinct types of memory but their distinct roles in actin dynamics offers a path forward. Dia promotes unbranched actin filaments (Kovar, 2006), while Arp2/3 can nucleate branched filaments (Rotty et al., 2013). But the specific changes in actin dynamics that underlie forgetting may be specific to the developmental stage, behavioral task, and/or organism being studied. Arp2/3 was found to have the opposite effect on associative memory in *C elegans*. In this organism, the memory suppressor gene *mushai-1* reduces the expression Arp2/3, thereby facilitating forgetting (Hadziselimovic et al., 2014). Interestingly, the mouse version of dia, Diap1, is also a memory suppressor gene. Knockdown of *Diap1* in the medial prefrontal cortex produced enhanced conditioned fear memory in adult mice (Lin et al., 2017). However, this effect was produced by development-specific knockdown, while *Drosophila dia* regulates forgetting through increased activity in the adult brain, presumably initiated during acquisition.

In summary, molecules that participate in active forgetting have been identified as memory suppressor genes from genetic screens for enhanced memory performance along with candidate gene approaches. The general principles learned to date include: (1) memory suppressor genes encode molecules that participate in the endocytosis of neurotransmitter receptors so as to reduce excitatory synaptic input, and (2) certain DAN have the responsibility to remove memories by activating specific DA receptors on postsynaptic engram cells, initiating a signaling cascade that seems to terminate in the activation of small G-proteins and the rearrangement of the cytoskeleton in the engram cells. Both mechanisms are attractive as forgetting mechanisms, the first to simply reduce the receptive state of the engram cell and the second to modify or eliminate the structural changes at the synapse that occur with acquisition and consolidation (Figure 5).

## Discussion

The literature discussed above indicates that memory suppressors exist, and they function in at least three of the basic operations that underlie memory formation: acquisition, consolidation, and forgetting. In addition, some of the mechanisms by which they constrain memory formation are summarized in the subtitles above. Future investigations will undoubtedly reveal deeper insights into the various mechanisms that the brain utilizes to suppress memory formation and perhaps elucidate other important principles beyond those discussed here. But a general and important question is why do memory suppressors exist? Why should the brain be designed with biological limits for memory formation?

### Information overload?

One possibility is that memory suppressors may reduce information overload, allowing the brain to function efficiently only with the essential and important information that it needs for optimal evolutionary fitness of its host. This explanation based on limited capacity is intuitively appealing. However, there are rare and exceptional outliers among us that seemingly have remarkable memories in the apparent absence of neurodevelopmental disorders or brain injury that throw this possibility into question (Brandt and Bakker, 2018).

Theoretical and computational modeling of memory capacity also suggest that saturation of memory capacity is unlikely to be a concern (Richards and Frankland, 2017). Therefore, although this explanation cannot be eliminated, there exist sound reasons to search for alternatives.

### **Allow for behavioral flexibility?**

A second possibility is that memory suppression provides for behavioral flexibility in changing environments, allowing individuals to suppress memories that underlie behaviors that are not adaptive or advantageous. A recent review nicely discusses this idea in the context of forgetting (Richards and Frankland, 2017), but the concept can also be applied to suppressors of other memory operations.

For instance, reversal experiments using flies impaired in forgetting show that they have difficulty adjusting their behavior to the altered contingencies, that is, to new rules or environmental conditions (Berry et al., 2012; Cervantes-Sandoval et al., 2016; Shuai et al., 2010). Such observations extend to mice carrying a conditional knockout of LTM suppressor *FK506-binding protein 12* or knockdown of *WT1* (Hoeffler et al., 2008; Mariottini et al., 2019). Therefore, the normal function of active forgetting molecules may facilitate the ability of animals to update memories to new situations.

Extinction experiments with many different memory suppressors (Rin1, GABRA $\alpha$ 5, DREAM, WT1, JIP1-JNK, and Tet2) also reveal that reducing their function limits behavioral flexibility (Bliss et al., 2010; Engin et al., 2015; Fontan-Lozano et al., 2009; Mariottini et al., 2019; Morel et al., 2018; Zengeler et al., 2019). As one specific example, inhibiting the function of the memory suppressor gene, *calcineurin* (Malleret et al., 2001), impairs the extinction of fear memories (Havekes et al., 2008). The repeated exposure of wildtype mice after acquisition to the context originally learned but without the associated foot shock extinguishes their fear responses. Mice defective in calcineurin function fail to extinguish their fear responses, exposing their lack of behavioral flexibility. However, inhibiting some memory suppressor genes, including *NHe5*, *STEP*, *Sharp1&2*, *Cdk5*, *Hdac2*, and *PKR*, enhances both memory and behavioral flexibility as measured by reversal or extinction experiments (Chen et al., 2017; Hawasli et al., 2007; Morris et al., 2013; Shahmoradi et al., 2015; Venkitaramani et al., 2011; Zhu et al., 2011). Why some memory suppressors promote behavioral flexibility while others suppress flexibility remains a mystery. However, such behavior would be consistent with these memory suppressors functioning through acquisition or through limiting the lability of memory.

### **Promote accurate association memories?**

A third possibility is that memory suppressors promote the formation of more accurate associations. Memory suppressor molecules are predicted to allow associations only for those things that reach a threshold for acceptance as an authentic association, reducing the probability of forming relationships between items that are unrelated or only tangentially related. Three types of experimental data support this idea: (1) Conditional knockout mice of *GABRA $\alpha$ 5*, an acquisition suppressor, produces a deficiency in latent inhibition of auditory fear conditioning. Latent inhibition refers to the phenomenon that organisms are



less likely to associate familiar stimuli with an unconditioned stimulus compared to novel stimuli. It is often approached experimentally by pre-exposing the organism to a conditioned stimulus prior to the association trial. This leads to a decrease in the strength of association, presumably reflecting a reduced fidelity of the relationship between the familiar conditioned stimulus and the unconditioned stimulus. The *GABRA $\alpha$ 5* conditional knockout mice form memories that are similar in strength with or without preexposure to the conditioned stimulus (Engin et al., 2015). Thus, these mice fail to devalue the conditioned stimulus after pre-exposure, leading to an erroneously strong association with the unconditioned stimulus. (2) Loss of function in two memory suppressor genes, *Dicer1* and *GABRA4*, prolongs the duration of trace conditioning (Fan et al., 2020; Konopka et al., 2010). Trace conditioning occurs when the conditioned stimulus precedes the unconditioned stimulus with a gap in time. Longer gaps in time between the conditioned stimulus and unconditioned stimulus increases the probability that the two events are unrelated. (3) The *GABRA $\alpha$ 5* conditional knockout mice exhibit difficulties in pattern separation between two similar contexts compared to control animals, such that they erroneously exhibit a fear response to a context similar, but not identical, to the trained context (Engin et al., 2015). Similarly, reduction of GABAergic neuron function and GABA<sub>B</sub> receptor GABA-B-R3 in flies leads to difficulties in odor discrimination (Lin et al., 2014; Yamagata et al., 2021). These are errors in stimulus generalization due to the loss of function of a memory suppressor gene.

### Promote social behaviors?

Dysfunction of some memory suppressors also result in disrupted social behavior. Inhibition of two GABA<sub>A</sub> receptor subunits, *GABRA $\alpha$ 5* and *GABRA4*, produced altered sociability in mice. The *GABRA4* knockout mice exhibit impaired social recognition memory (Fan et al., 2020) and *GABRA $\alpha$ 5* knockout mice display reduced social behaviors, making fewer social contacts with conspecifics as adults and producing fewer ultrasonic vocalizations as pups (Zurek et al., 2016). In flies, the knockdown of *Rdl* alters the mating behavior of females (Ishimoto and Kamikouchi, 2020). Similarly, knockout of the *M1 muscarinic receptor* impairs social recognition (Anagnostaras et al., 2003), *STEP* knockout increases dominance behaviors and impairs social memory (Blazquez et al., 2019; Venkitaramani et al., 2011), while *Lrfd2* knockout decreases social interest and increases social avoidance (Morimura et al., 2017). Sociability is argued to increase fitness (Hawkley and Capitanio, 2015).

A speculative aspect of this explanation extends to human behavior. Humans with savant syndrome are characterized by having significant mental disability but excelling in at least one skill, such as in music, art, calendar counting, mathematics, or in mechanical or spatial skills (Treffert, 2009). Interestingly, regardless of the type of skill they possess, savants always exhibit extraordinary memory (Treffert, 2009). Individuals with savant syndrome usually have some type of neurodevelopmental disorder but can also acquire the syndrome after brain injury. Approximately 50% of savants have autism spectrum disorder (ASD), which is characterized by abnormal social behavior and/or social information processing, and it has been estimated that 10% of individuals with ASD have savant-like skills (Treffert, 2009). Such observations follow the conceptual thread of an increased memory capacity associated with decreased sociability. Nevertheless, some memory suppressors also seem

to function as suppressors of social behavior. *Np65* knockout mice (Li et al., 2019) and *HCNI* knockdown mice display significantly elevated levels of social interaction while also exhibiting enhanced spatial and object recognition memory (Amuti et al., 2016; Li et al., 2019; Nolan et al., 2004; Silveira Villarroel et al., 2018). This indicates the existence of genetic suppressors of sociability, a research area that may have implications for ASD.

## Conclusions

Research on memory suppressors has thus far revealed they function at most operations of memory tested; acquisition, consolidation and forgetting. This organization provides a conceptual framework for future studies. The number of suppressors described in the literature (Table S1–S3) strengthens the case that there is a strong biological need to limit and balance memory formation, but additional research is required to provide an exhaustive list of all their mechanisms of action. In addition, the question of why memory suppressors exist needs further exploration. Currently, there is only limited evidence to support the possibilities that they provide behavioral flexibility, facilitate accurate memories, or modulate social behaviors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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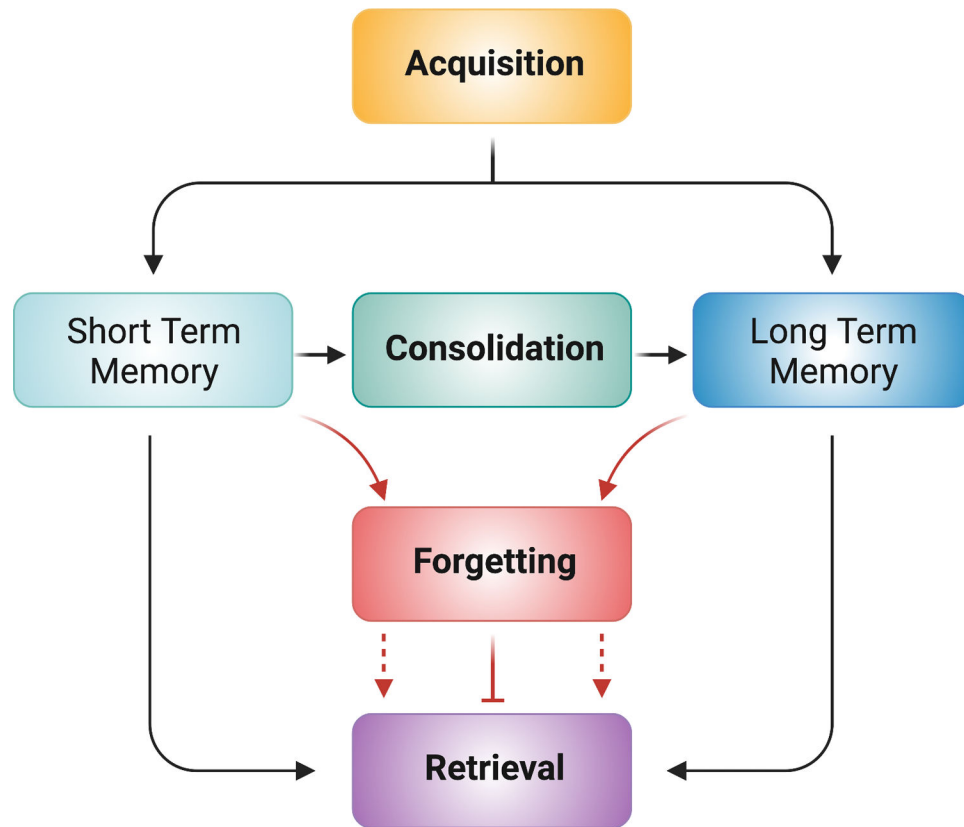
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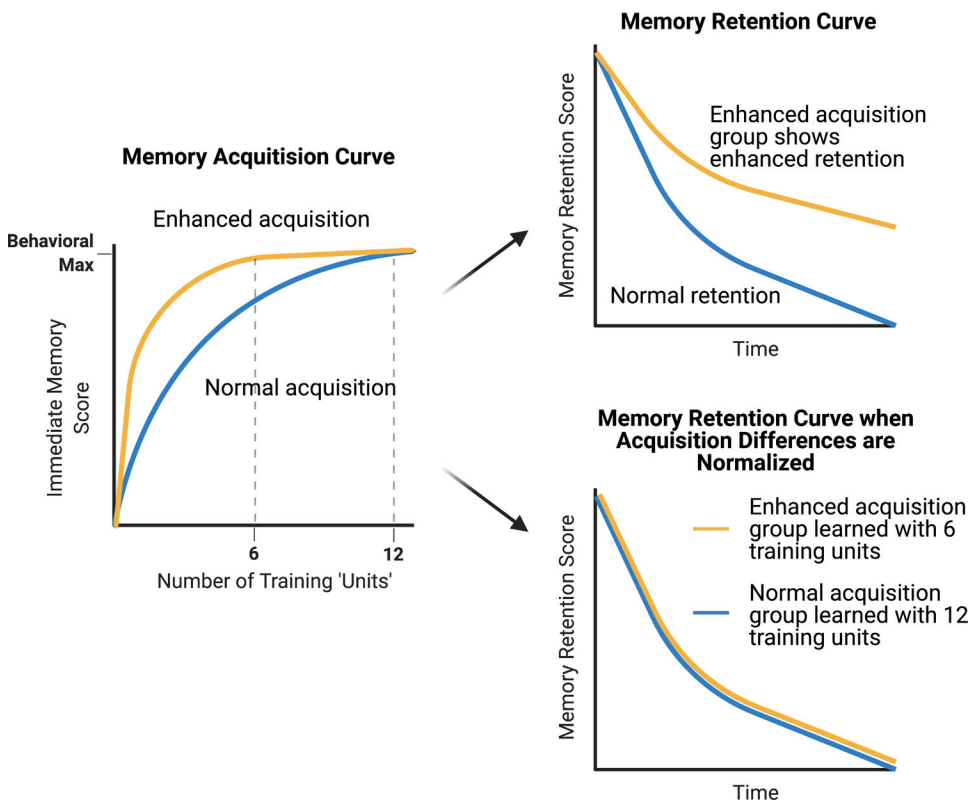
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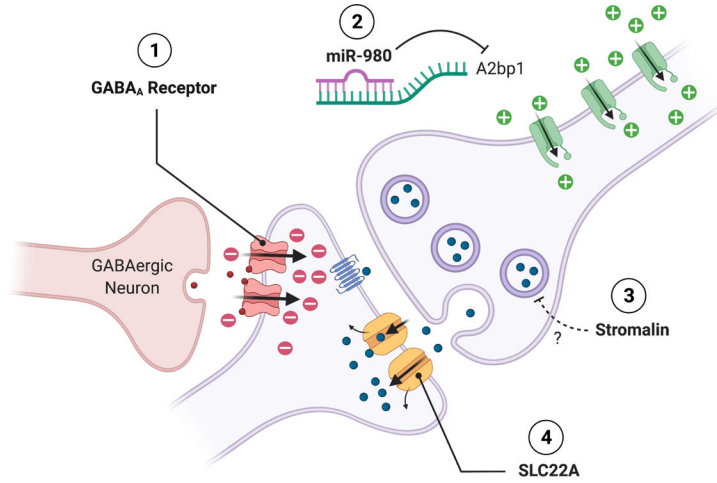
**Figure 1: Memory Operations.**

Acquisition includes the molecular, cellular, and circuit processes during learning that encode memory. Short-term memory is unstable and prone to disruption. Consolidation stabilizes memories into a long-term form for subsequent retrieval. Short-term or long-term memory can be altered by forgetting processes (red lines), leading to a reduction in retrieval (dotted red lines with arrow). Alternatively, transient forgetting processes can temporarily block retrieval (solid red line with blocked end). Retrieval allows for the access of information stored in short- and long-term memory.

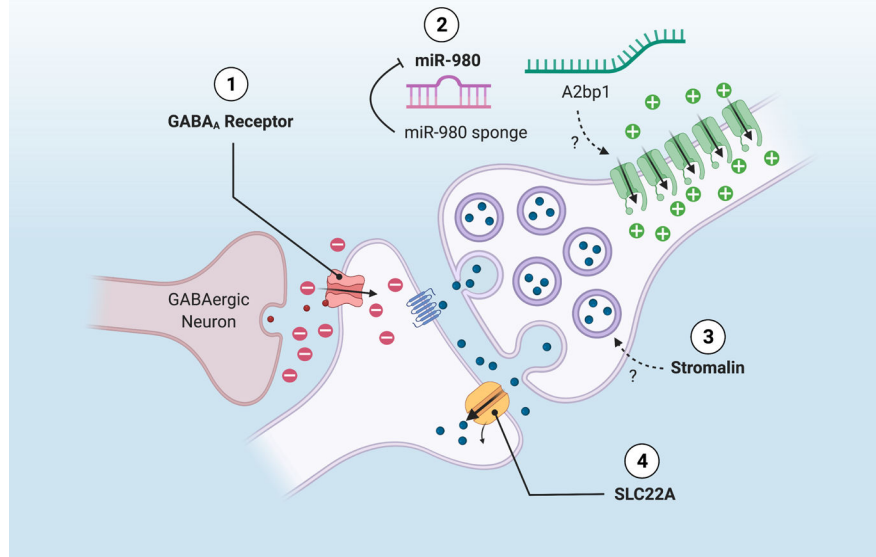


**Figure 2: Normalizing for differences in memory acquisition.** Reducing memory suppressors of acquisition results in enhanced memory acquisition scores (yellow line) compared to wildtype animals (blue line) when short, multiple training sessions ('Units') are applied (left graph). Both groups often reach the same measured level of behavioral performance with sufficient training due to ceiling levels on performance in the memory tasks employed. When these groups are tested for later memory, they often exhibit enhanced retention scores across time (upper right graph). However, a retention curve obtained when groups reach ceiling levels of performance does not discriminate between enhanced acquisition, enhanced consolidation, or reduced forgetting. To tease these scenarios apart, the two groups are trained with different numbers of training 'units', normalizing for differences in acquisition before testing for memory retention (lower right graph). If the retention scores align with one another, this molecule is designated a suppressor of acquisition. If retention scores remain distinct, the molecule is assigned as having a role in acquisition as well as consolidation or active forgetting.



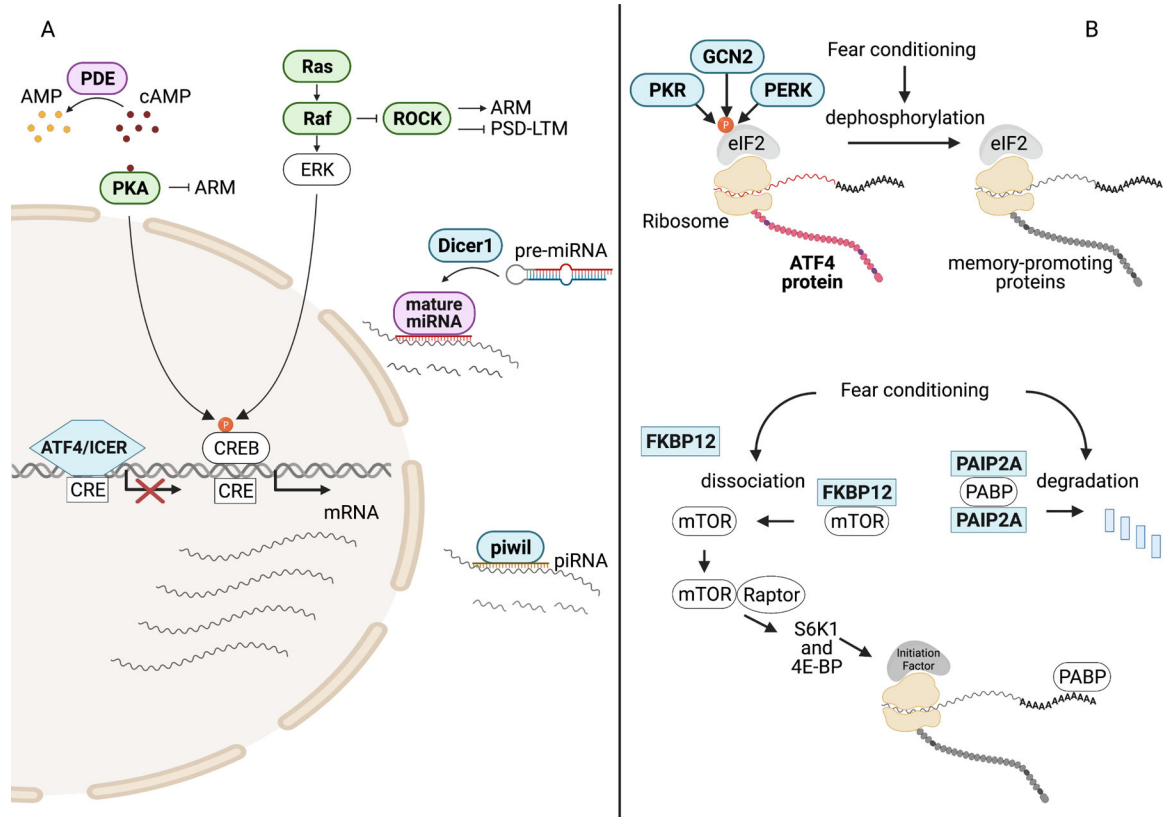


**Removing Memory Suppressors of Acquisition**



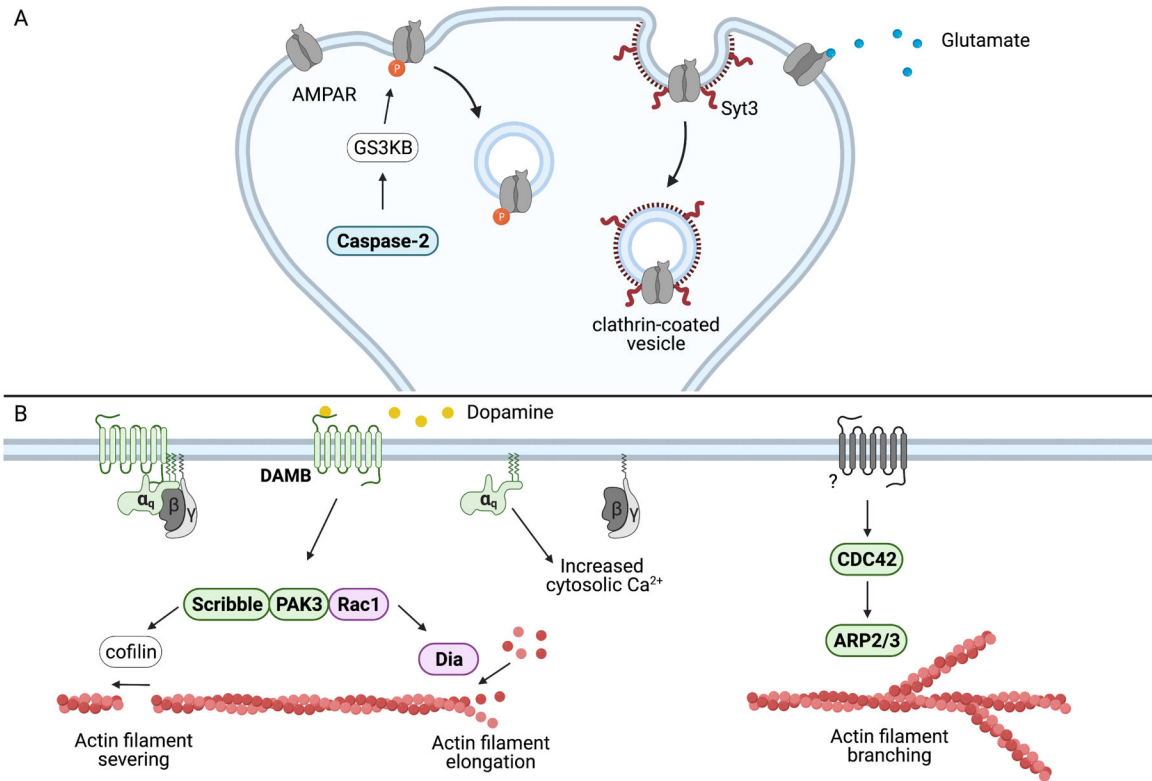
**Figure 3: Memory Suppressors of Acquisition.**

Suppressors of acquisition function in several ways. (1) Inhibiting the neural representation of stimulus strength in the circuit through GABAergic receptor function. Both GABA<sub>A</sub> and GABA<sub>B</sub> receptors suppress acquisition. (2) Capping neuronal excitability by *miR-980* inhibition of A2bp1. (3) Limiting the number of synaptic vesicles through Stromalin regulation of gene expression. (4) Reducing the neurotransmitter persistence in the synapse by the transporter SLC22A. These suppressors of acquisition function by controlling neuronal activity or synaptic strength in the memory-relevant neural circuit.



**Figure 4: Memory Suppressors of Consolidation.**

Memory suppressor genes are in bold and color-coded green (fly), blue (mouse), and purple (both mouse and fly). A) PDEs regulate cAMP levels by converting cAMP to 5'-AMP. Activation of PKA by cAMP promotes consolidation through the phosphorylation of CREB but also inhibits consolidated ARM in *Drosophila* through an unknown mechanism. In *Drosophila*, ROCK activity enhances ARM and inhibits PSD-LTM. ROCK activity is suppressed by ERK-independent Ras signaling. Phosphorylated CREB binds CRE and drives transcription of mRNA required for memory formation. Proteins that inhibit CREB-dependent transcription, like ATF4 and ICER, suppress consolidation. Following transcription, memory-relevant mRNA can be reduced by small, non-coding RNAs (miRNA, piRNA) that either prevent translation or promote mRNA degradation. Dicer is required for the processing of pre-miRNA and piwil is required for piRNA-mediated mRNA degradation. B) Regulation of translation factors by inhibitory proteins through phosphorylation or protein-protein interactions prevents ribosomal translation of mRNA to protein. Phosphorylation of the alpha subunit of eIF2 by PKR, GCN2, and PERK promotes translation of ATF4 and suppresses the synthesis of memory-promoting proteins. Fear conditioning stimulates dephosphorylation of eIF2 $\alpha$  thereby facilitating consolidation. Fear conditioning also promotes consolidation by disinhibiting mTOR and PABP. FKBP12 association with mTOR prevents mTOR/raptor complex formation and subsequent control of translation regulators by mTOR/raptor. PAIP2A complex formation with PABP prevents PABP association with mRNA poly(A) tails. Fear conditioning drives the degradation of PAIP2A, freeing PABP to facilitate translation through its direct interaction with mRNA.



### Figure 5: Memory Suppressors that Act on Forgetting.

Memory suppressor genes are in bold and color-coded green (fly), blue (mouse), and purple (both mouse and fly). A) Caspase-2 activity initiates a multi-step signaling cascade, starting with the cleavage of Rictor in the protein complex mTORC2. This results in the activation of the kinase AKT followed by the kinase GSK3 $\beta$ . Activated dendritic GSK3 $\beta$  phosphorylates the AMPAR subunit GluA2, inducing AMPAR internalization and a weakening of synaptic strength. Syt3 also regulates AMPAR internalization through GluA2, driving clathrin-mediated endocytosis of AMPARs.

B) Dopamine-driven active forgetting in *Drosophila* is mediated by the G $\alpha$ q-coupled DAMB receptor. DAMB signals downstream to a protein complex that includes Rac1. Rac accelerates forgetting in both mice and *Drosophila*. In *Drosophila*, Rac1 propagates the forgetting signal to cofilin that induces actin filament severing and to dia that promotes actin filament elongation. CDC42 drives forgetting of consolidated memory through ARP2/3, a protein that controls the branching of actin filaments. Upstream activators involved in CDC42-facilitated forgetting are not known.