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Contributed Mini Review

Memory allocation at the neuronal and synaptic levels

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Memory allocation, which determines where memories are stored in specific neurons or synapses, has consistently been demonstrated to occur via specific mechanisms. Neuronal allocation studies have focused on the activated population of neurons and have shown that increased excitability via cAMP response element-binding protein (CREB) induces a bias toward memory-encoding neurons. Synaptic allocation suggests that synaptic tagging enables memory to be mediated through different synaptic strengthening mechanisms, even within a single neuron. In this review, we summarize the fundamental concepts of memory allocation at the neuronal and synaptic levels and discuss their potential interrelationships. [BMB Reports 2024; 57(4): 176-181]

INTRODUCTION

Memory is an internal representation of past experiences, which induces physical changes in neuronal ensembles, known as memory traces or engrams (1). However, the physical substrate of memory remains a topic of discussion, highlighting the need to understand where and how memory is allocated to a particular form during formation.

The lateral amygdala (LA) plays an important role in the storage of auditory fear-conditioned memories (2, 3) and has been a target in memory allocation studies (4-6). The LA mediates the association between conditioned stimuli (CS), such as a tone, and unconditioned stimuli (US), such as foot shock (7), with approximately 70% of LA principal neurons (PNs) responding to both tone and shock (8). However, only 10-30% of PNs are involved in the auditory fear memory trace (4, 8, 9), indicating that a specific mechanism selectively chooses a small population of neurons to be part of the engrams in a process known as neuronal allocation (Fig. 1A).

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Since Donald Hebb proposed the Hebbian theory, synaptic plasticity has long been considered an underlying mechanism of learning and memory, suggesting that if cell A is repeatedly fired with cell B, because they are sufficiently close, the two cells will be wired together (10). Although the nature of engrams is still being debated, numerous studies have shown that synaptic potentiation between engram cells correlates with memory (11). Therefore, similar to neuronal allocation, understanding synaptic allocation that determines which synapses are potentiated through learning, is necessary for explaining memory allocation (Fig. 1B).

In this review, we focus on the basic concepts of neuronal and synaptic allocation in memory allocation and discuss how synaptic signals contribute to neuron-wide activation and synapse-specific changes.

NEURONAL ALLOCATION AND CREB

Neuronal allocation determines which neurons will encode memory. Previous studies have demonstrated that the transcription factor CREB regulates the likelihood of recruitment to memory traces (4, 6, 12). Immediate early genes, such as Arc, have been used as molecular markers to identify neuronal ensembles participating in the fear memory trace (13). Neurons expressing virally-induced CREB have been shown to result in higher levels of Arc expression than the neighboring neurons that do not express CREB (4), suggesting that CREB expression biases neurons to engage in fear memory traces. Conversely, the selective erasure of these neurons impairs fear memory expression (5). These results suggest that the CREB-expressing neurons involved in fear memory traces are necessary for memory recall.

CREB-dependent memory allocation is associated with neuronal excitability. Previous studies have shown that neurons with higher CREB levels exhibit higher intrinsic excitability, thereby engaging in fear memory traces (6). Neuronal excitability is determined by the membrane properties. In cases where Kir2.1, an inwardly rectifying K+ channel, is expressed along with CREB, the increase in neuronal excitability caused by CREB is eliminated (12, 14). This suggests that the CREB-mediated increase in neuronal excitability is caused by a decrease in the after-hyperpolarization current. Artificially enhancing neuronal excitability using optogenetic or chemogenetic tools was shown to be sufficient for recruiting a biased memory ensemble (12). Thus,

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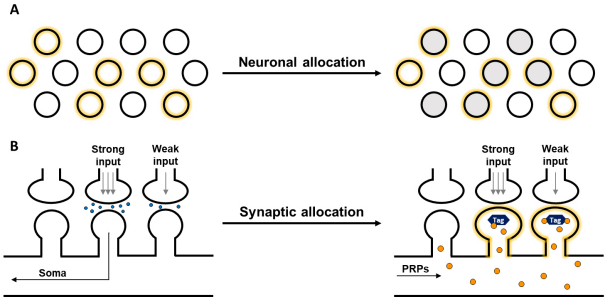

Fig. 1. Schematic illustration of neuronal and synaptic allocation. (A) Neuronal allocation. In this process, relatively more excitable neurons (yellow halo) are more likely to become memory engrams (gray). (B) Synaptic allocation (STC hypothesis). Synaptic input (gray arrows) via neurotransmitter (blue circles) release activates specific synapses, which are selectively tagged, leading to the capture of plasticity-related products (PRPs, orange circles) and the subsequent induction of long-lasting synaptic potentiation (L-LTP). PRPs induced by strong stimuli can be shared with nearby synapses, resulting in the potentiation of synapses initially tagged by weak stimuli.

in addition to CREB, the recruitment of the memory ensemble may be affected by other pathways that increase neuronal excitability. Furthermore, CREB overexpression induces morphological changes in synapses (15). The finding that CREB overexpression increases spine density in the LA suggests an alternative mechanism for how CREB mediates memory allocation.

CREB-dependent memory allocation has been observed not only in the LA but also in the hippocampal and cortical areas (16, 17). Overexpression of CREB in dentate gyrus (DG) neurons during contextual fear conditioning was shown to be sufficient for forming a biased memory ensemble similar to that observed in the LA (16). Selective silencing of CREB-expressing neurons in the insular cortex caused deficits in conditioned taste memory, providing further evidence that high CREB levels can determine neuronal allocation (17). In studies conducted on the piriform cortex, increasing excitability using channelrhodopsin2 was shown to be sufficient for allocating specific neuronal ensembles to both appetitive and aversive memories (18). Hence, elevated neuronal excitability is likely to be considered as a global mechanism explaining how the subpopulations of neurons become involved in memory storage.

CREB ACTIVATION: SYNAPSE TO NUCLEAR GENE EXPRESSION

CREB is a transcription factor that responds to diverse external stimuli and regulates the expression of several genes (19). For CREB, the nuclear transcription factor, which plays a key role in neuronal allocation, synaptic inputs must be transferred to the nucleus where CREB functions (20, 21). Phosphorylation of CREB at Ser133 enables the binding of the transcriptional coactivator CREB-binding proteins (CBPs), and together, they act as transcriptional activators (22). Several kinases mediate CREB phosphorylation, one of which is the cAMP-dependent protein kinase (PKA) (23, 24). Upon the activation of G protein-coupled receptors (GPCRs) by neurotransmitters (particularly via Gs signaling), cAMP levels are increased by adenylyl cyclase (AC), leading to PKA activation.

Intracellular Ca^{2+} levels also induce CREB activation (25). Membrane depolarization caused by synaptic inputs triggers calcium influx through voltage-gated calcium channels (such as CaV [L-type] channels) or ionotropic receptors (such as NMDAR) (25). In response to synaptic activity, the increased submembrane Ca^{2+} binds to calmodulin (CaM) and activates Ca^{2+}/CaM-dependent protein kinases, which then move to the nucleus, leading to CREB phosphorylation (26). A previous study elucidated how CaMK cascades transfer local calcium signals to the nucleus to induce CREB phosphorylation and trigger gene expression (27). The results showed that γCaMKII serves as a carrier for Ca^{2+}/CaM near the CaV channel into the nucleus. The phosphorylation of γCaMKII by α/βCaMKII captures Ca^{2+}/CaM, while the dephosphorylation of γCaMKII at another site by calcineurin (CaN, Ca^{2+}/CaM-dependent phosphatase) exposes nuclear localization signals (NLSs) that trigger nuclear translocation. Finally, Ca^{2+}/CaM is transferred to the nucleus and activates CaMKK and CaMKIV, leading to CREB phosphorylation.

The extracellular signal-regulated kinase (Erk) and Jacob, a synapto-nuclear messenger, pathways represent another NMDAR-dependent Ca^{2+} signaling mechanism that carries synaptic signals to the nucleus (28). In the absence of synaptic activation, Jacob localizes to the synaptic spines, where it associates with αCaMKII and GluN2B-containing NMDAR. Caldendrin prevents the nuclear trafficking of Jacob by hiding the NLS from importin-α binding (25). Upon Ca^{2+} influx through GluN2B-containing NMDARs, calpain is activated, leading to the cleavage and subsequent release of Jacob and αCaMKII. This process ultimately results in the phosphorylation of Erk1/2 (29, 30). Active Erk1/2, in turn, phosphorylates the S180 residue of Jacob. Following phosphorylation, Jacob forms a trimeric signalosome complex with the intermediate filament internexin, preserving its phosphorylation during transportation to the nucleus. Lastly, importin binds to the NLS of Jacob and transports the signalosome along microtubules to the nucleus, promoting CREB phosphorylation (30).

Ultimately, activated CREB initiates the synthesis of plasticity-related proteins (PRPs). PRPs refer to various proteins synthesized in response to input stimuli and contribute to long-term memory formation. The comprehensive understanding of their identity and function remains a significant challenge, but it could encompass various synaptic structural proteins, neurotransmitter receptors, or other transcription factors. The known CREB target genes include genes that are involved in synaptic plasticity, synaptogenesis, and neurotransmitter/ neuropeptide receptor signaling (31). This implies that CREB plays a pivotal role in the synthesis of PRPs required for memory consolidation.

SYNAPTIC ALLOCATION AND SYNAPTIC TAGGING AND CAPTURE (STC) HYPOTHESIS

General memory storage is accompanied by synaptic strengthening via long-term potentiation (LTP) (32). Notably, LTP occurs at each synapse, even within a single neuron. Stimulation of single spines in hippocampal CA1 pyramidal neurons induces the selective enlargement of stimulated spines (33). Furthermore, studies using the dual-eGRASP technique have shown that among the synapses of CA1 engram cells, those receiving inputs from CA3 engram cells specifically exhibit increases in both spine volume and density (34). These findings suggest that the synapses receiving inputs for a particular memory are selectively potentiated. Therefore, memory storage requires not only an overall increase in neuronal excitability but also synapse-specific modifications.

Frey and Morris proposed the synaptic tagging (or capture) hypothesis to explain the mechanisms underlying synapse-specific LTP and its modifications (35). In this study, hippocampal neurons were treated with anisomycin, a protein synthesis inhibitor, to prevent late LTP (L-LTP), which relies on *de novo* protein synthesis. Anisomycin prevented L-LTP induction during treatment; however, induced input-specific L-LTP if *de novo* protein synthesis was achieved by other stimuli before anisomycin administration. These results suggest that previously synthesized proteins were shared at the corresponding activated synapses by a protein-synthesis-independent transient synaptic tag, allowing L-LTP to manifest even in the presence of anisomycin. Therefore, the initial hypothesis posited that certain activated synapses are tagged during LTP induction, subsequently capturing PRPs to maintain LTP, resulting in synaptic plasticity. A similar transition between early and late states induced by previous stimulation is also observed in the context of long-term depression (LTD) (36). Late LTP can also permute early LTD to late LTD, a phenomenon termed cross-tagging (36).

The input-specific synaptic plasticity proposed by the STC hypothesis suggests the possibility of specific synapses to store memory, even within a single neuron, and may offer supporting evidence for synaptic allocation.

MECHANISM OF STC

What are the synaptic tags, and how do they capture PRPs? According to the STC hypothesis, the synaptic tag is 1) localized to input-specific synapses, 2) transiently present, and 3) independent of *de novo* protein synthesis (35, 37). The tag may refer to either the molecular complex responsible for PRPs capture or a synaptic change occurring in an activity-dependent manner. We review several previous studies to reveal the underlying mechanisms of STC.

Several pharmacological studies have provided evidence supporting the STC hypothesis. As previously stated, CaMKII carries the Ca^{2+}/CaM formed in the activated synapse, and CaMKK activates CREB. Moreover, synaptic tagging is blocked when CaMKII is selectively inhibited by low concentrations of KN-93 (2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl) amino-N-(4-chlorocinnamyl)-N-methylbenzylamine), a CaMK inhibitor (38). In contrast, the CaMKK inhibitor STO-609 (7H-benzimidazo(2,1-a)benz(de)isoquinoline-7-one-3-carboxylic acid) only impairs PRP synthesis and L-LTP maintenance (38). These results align with the distinct functions of these kinases, with CaMKII primarily responding to synaptic activity, and CaMKK governing gene expression in the soma.

Synaptic plasticity elicited by LTP is accompanied by morphological changes in dendritic spines, known as structural plasticity (39). The actin network plays a vital role in structural plasticity by facilitating local protein trafficking and recruitment of AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor). Early LTP (E-LTP) induced by weak tetanus can be altered into L-LTP by following strong tetanus, which is explained by the sharing of PRPs. This transition is hindered when actin polymerization is inhibited by actin assembly inhibitors (40). These results suggest that the dynamic actin network is a part of the synaptic tag setting during E-LTP (41).

The classical mechanism underlying hippocampal LTP involves the insertion and redistribution of AMPAR in an NMDAR-dependent manner (42). Tetrameric AMPAR consists of four subunits, namely GluA1-4, each of which regulates the function and trafficking of AMPAR differently through the interaction between the C-terminal domain and intracellular molecules (43). The protein kinase C (PKC) isoform, protein kinase Mξ (PKMξ), is a critical protein that controls the number of AMPARs (especially for GluR2-containing AMPARs) at postsynaptic density in response to NMDAR activation (44). PKMξ mRNA is localized to the synaptodendritic domain, and its translation is facilitated by signaling molecules (*e.g.*, CaMKII, phosphoinositide 3-kinase [PI3K], PKA, etc.) activated by LTP induction (45, 46). Therefore, the synthesis of PKMξ is limited to the recently activated synapses and increases the number of AMPARs in the synapse. Interestingly, when the PKMξ complex is isolated from the synaptic AMPAR, the exposed free GluR2 C-terminus acts as a synaptic tag capturing the PKMξ complex, allowing increased AMPAR and LTP to persist within the synapse (47); this process is named synaptic auto-tagging because PKMξ itself mediates and maintains synaptic tagging.

Calcium-permeable (CP)-AMPAR has recently been implicated in hippocampal LTP (48, 49). Synaptic activity triggers the insertion of CP-AMPARs with subsequent calcium transients via these receptors potentially initiating local *de novo* protein synthesis, leading to the establishment of L-LTP (48). Therefore, CP-AMPARs act as synaptic tags by inducing input-specific LTP.

Most proteins synthesized in the soma are packaged in cargo and transported along microtubules and actin filaments through interactions with molecular motors such as kinesin and dynein (50). Regulation of the local protein transport can also be activity-dependent. For example, KIF17, a member of

the kinesin-2 family that delivers GluN2B-containing vesicles, is locally degraded and synthesized in response to NMDAR-dependent activity, indicating that its cargo transport is controlled in an activity-dependent manner (51). Presumably, this local activity-dependent transport system is part of the STC process, in which the newly synthesized protein moves from the soma to the activated synapse, where they are captured by synaptic tags.

Although the previously mentioned synaptic tags stabilize synaptic potentiation in active synapses, there are also inverse synaptic tags that selectively weaken inactive synapses (52). The neuronal immediate early gene Arc/Arg3.1 is rapidly expressed in an activity-dependent manner (53). Within inactive synapse, βCaMKII is exposed in a form unbound to calmodulin, displaying a high affinity for Arc/Arg3.1 (52). The interaction between βCaMKII and Arc/Arg3.1 causes the endocytosis of AMPAR and weakens the corresponding synapses.

Numerous molecules are complexly intertwined, leading to input-specific synaptic changes recognized as synaptic tags at postsynaptic densities. These tags facilitate the capture of newly synthesized PRPs from the soma or induce local *de novo* protein synthesis to maintain LTP. Several studies have proposed potential synaptic tags, but further research is required to integrate these mechanisms and gain a comprehensive understanding of input-specific synaptic plasticity.

NEURONAL AND SYNAPTIC ALLOCATION

Notably, both neuronal and synaptic allocations play crucial roles and share certain mechanisms. For instance, CaMKII is activated by synaptic input mediates signaling pathways to the nucleus to induce CREB phosphorylation while acting as a synaptic tag to induce local synaptic plasticity. Additionally, CREB, a central hub for activity-driven gene expression (54) induces the synthesis of other transcription factors and PRPs that are captured by the activated synapse to stabilize LTP. CREB overexpression, which biases neuronal allocation, may be due to the increased availability of PRPs, enabling preferential maintenance of potentiated synapses (55).

Furthermore, a CREB-dependent increase in neuronal excitability occurs during learning (6, 12). Many studies have suggested that increased neuronal excitability creates a temporal window during which two distinct memories can be encoded and linked within a shared ensemble (56-62). Notably, even within overlapping ensembles, each memory retains a unique identity (63). This study used two tones (2 and 7 kHz) to form two distinct auditory fear memories. When auditory fear conditioning was performed at 5-h intervals, overlapping ensembles were recruited to the LA but not in the auditory cortex, which transmits auditory information to the LA (57, 63). Remarkably, complete retrograde amnesia or engram-specific optogenetic depotentiation of one memory induces tone-specific memory impairment without disrupting the other linked memories. This suggests that even within individual neurons, distinct subsets of synapses are allocated to specific memories by each input, highlighting the cooperative relationship between neuronal and synaptic allocation. Moreover, this mechanism offers insights into how the brain achieves its enormous memory capacity.

CONCLUSION

In this review, we briefly examined neuronal and synaptic allocation, how they have been studied in different areas, and how they are related (Fig. 2). The outlined studies identified several shared key molecules and signaling pathways in neuronal and synaptic allocation that respond to presynaptic inputs and participate in synaptic plasticity, alongside PRPs, all of which contribute to memory formation and maintenance. These studies consistently provide compelling evidence for the interconnectedness of these processes; however, a direct linkage between these two aspects remains elusive. Many neuronal allocation studies have utilized artificial manipulation techniques to determine whether neurons are involved in memory tracing in a specific manner. In the case of synaptic allocation, a majority of experiments have been conducted under *in vitro* or *ex vivo* conditions, with few instances of *in vivo* studies (64). In the natural state, the neuronal subpopulation participating in memory formation is determined by the competition between dynamic neuronal states influenced by presynaptic inputs or past experiences, rather than by CREB overexpression or artificial synaptic activation. Therefore, further research is impera-

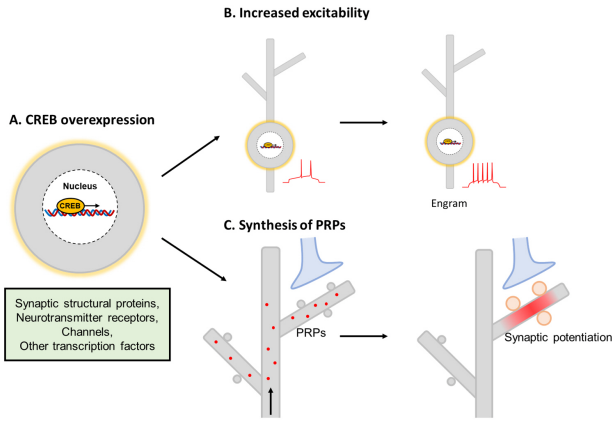

Fig. 2. Schematic Illustration of putative effects of CREB overexpression on neuronal and synaptic allocation. (A) CREB mediates the expression of synaptic structural proteins, neurotransmitter receptors, ion channels, and other transcription factors. Thus, overexpression of CREB (yellow halo) results in (B) increased excitability, such that when a presynaptic action potential occurs, CREB-overexpressing neurons are more likely to fire and subsequently become engram cells. CREB overexpression also facilitates (C) the synthesis of PRPs (red circles) and increases their availability, enabling the preferential maintenance of potentiated synapses (orange).

tive to understand how neuronal activation and synaptic plasticity determine memory storage. It is also essential to develop methodologies for labeling and real-time monitoring of neuronal and synaptic alterations during memory allocation in real-world learning.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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