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Molecular and Cellular Mechanisms of Memory Allocation in Neuronetworks

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Abstract

Determining how neuronal networks encode memories is a key goal of neuroscience. Although neuronal circuit processes involved in encoding, storing and retrieving memory have attracted a great deal of attention, the processes that allocate individual memories to specific neurons within a network have remained elusive. Recent findings unraveled the first insights into the processes that modulate memory allocation in neuronetworks. They showed that neurons in the lateral amygdala compete to take part in auditory fear conditioned memory traces and that the levels of the transcription factor CREB (cAMP-response element binding protein) can affect the probability of a neuron to be recruited into a given memory representation. CREB-mediated transcriptional regulation involves several signaling pathways, known to mediate nuclear responses to diverse behavioral stimuli, along with coordinated interactions with multiple other transcription activators, co-activators and repressors. Moreover, activation of CREB triggers an autoinhibitory feedback loop, a metaplastic process that could be used to allocate memories away from cells that have been recently involved in memory. Beyond CREB, there may be a host of other processes that dynamically modulate memory allocation in neuronetworks by shaping cooperation and competition among neurons.

Keywords

Memory allocation; Competition; cAMP-response element binding protein (CREB); Activity-regulated cytoskeleton-associated protein (Arc); Metaplasticity

1. Memory allocation: a competitive process

Memory depends on specific sets of connected neurons which together support the ‘memory trace’ (McGaugh, 1972; Thompson, 2005). Electrophysiological and cellular imaging studies demonstrated that only a portion of neurons are involved in a given memory (Repa et al., 2001; Rumpel, LeDoux, Zador, & Malinow, 2005). Despite numerous studies on the nature and properties of memory traces, little is known about how memories are allocated into specific subsets of neurons in a given neuronetwork.

Activity-dependent competitive refinement of connections is a general feature of neural circuits in the central nervous system. Competition between bilateral monocular neural activities is critical for segregating projections from the two retinae into distinct laminae in the lateral

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geniculate nucleus and then into distinct columns in the visual cortex (Wiesel & Hubel, 1965; Cabelli, Hohn, & Shatz, 1995). Competition also sharpens the topographic mapping of retinal axons onto their central targets. In addition, competitive maintenance of long-term potentiation (LTP) of synaptic pathways has been described; when one of two previously potentiated synaptic pathways is stimulated again, further potentiation comes at the expense of the maintenance of potentiation in the other pathway (Miller, 1996; Fonseca, Nagerl, Morris, & Bonhoeffer, 2004).

Several studies have indicated that only a portion of eligible neurons participate in a given memory (see for example, Guzowski, McNaughton, Barnes, & Worley, 1999; Repa et al., 2001; Rumpel et al., 2005; Wilson & McNaughton, 1993). For example, plasticity within the lateral amygdala (LA) is essential for auditory conditioned fear memories (LeDoux, 2000; Fanselow & Gale, 2003), and although ~70% of LA neurons receive the necessary sensory input, only one-quarter exhibit auditory fear conditioning-induced synaptic plasticity (Repa et al., 2001; Rumpel et al., 2005). Why are some neurons, rather than their neighbors, recruited in storing a given memory? A recent study from our laboratory suggests that neurons compete with each other to take part in fear memory traces and that the transcription factor cAMP-response element binding protein (CREB) plays a crucial role in determining which neurons will participate in a memory representation (Han et al., 2007).

2. Role of CREB in competitive memory allocation

CREB, a member of a family of structurally related transcription factors, is widely expressed in the brain and its activity is induced in response to calcium, neurotrophin, and cytokine signals as well as a variety of cellular stresses (Silva, Kogan, Frankland, & Kida, 1998; Shaywitz & Greenberg, 1999; Mayr & Montminy 2001; Lonze & Ginty, 2002; Carlezon, Duman, & Nestler, 2005). Membrane depolarization or/and an elevation of cAMP strongly induce the phosphorylation of CREB at serine 133, and thereby activate CREB-dependent transcription (Sheng, Thompson, & Greenberg, 1991; Gonzalez & Montminy, 1989). A large body of evidence indicates that CREB-dependent transcription is essential for both long-lasting forms of synaptic plasticity and long-term memory, but not short-term plasticity or short term memory (e.g., Silva et al., 1998; Shaywitz & Greenberg, 1999; Mayr & Montminy 2001; Lonze & Ginty, 2002; Carlezon, Duman, & Nestler, 2005). Genetic and pharmacological studies in several species demonstrate that CREB has a seemingly universal role in memory, tested in a wide range of tasks that span emotional, spatial and social memory (e.g., Yin, Del Vecchio, Zhou, & Tully, 1995; Bartsch, Casadio, Karl, Serodio, & Kandel, 1998; Josselyn et al., 2001; Wallace, Stellitano, Neve, & Duman, 2004; Jasnow, Shi, Israel, Davis, & Huhman, 2005). In addition, several lines of evidence have implicated CREB in the competition between neurons necessary for refining retinogeniculate axons and establishing ocular dominance within the visual cortex in the developing brain (Pham, Impey, Storm, & Stryker, 1999; Pham, Rubenstein, Silva, Storm, & Stryker, 2001; Pham et al., 2004; Mower, Liao, Nestler, Neve, & Ramoa, 2002).

To determine whether CREB had a role in memory allocation, amygdala cells were transfected with a virus over-expressing either CREB or its dominant-negative form (Han et al., 2007) (Fig. 1). To visualize the memory trace, nuclear-localized transcripts of the neuronal activity-dependent gene *Arc* (activity-regulated cytoskeleton-associated protein; also termed *Arg3.1*) were detected with high-sensitivity fluorescence in situ hybridization (FISH). Neuronal activity induces a rapid and transient increase in *Arc* transcription, and thus nuclear-localized *Arc* RNA can serve as a molecular signature of a recently (5-15 min) active neuron (Guzowski et el., 1999). Only neurons active during the memory test have *Arc* RNA localized in the nucleus which can be detected with high-sensitivity FISH five minutes after the fear memory test (Guzowski et el., 1999). Arc is a particularly good marker for memory activation because not

only is its expression associated with memory formation, but Arc expression is also needed for memory (Tzingounis & Nicoll, 2006).

Neurons infected with a virus overexpressing CREB in the lateral amygdala preferentially expressed *Arc* after recall of a memory for auditory fear conditioning (Fig. 1A). Moreover, in comparison with their noninfected neighbors, neurons infected with a dominant-negative form of CREB ($CREB^{S133A}$), in which serine 133 is replaced by alanine, have a much lower probability of having *Arc*-positive nuclei (Fig. 1A). Importantly, the overall proportion of *Arc*-positive neurons was constant regardless of CREB manipulation (Fig. 1B), suggesting that neuronal selection during memory formation is competitive rather than cell-autonomous. Importantly, a number of controls showed that the ability of CREB to bias memory allocation *a)* was not the result of a specific narrow set of training conditions, *b)* was not due to CREB function directly inducing *Arc* transcription, *c)* is dependent on training and learning, and *d)* is not due to changes in the threshold for *Arc* expression.

Taken together, these findings provide a novel approach to study memory allocation, and show that neuronal competition, which has previously been demonstrated to have an important role during brain development, is also an essential part of memory formation. Furthermore, the findings provide the first mechanistic insights into memory allocation: they show that CREB plays a crucial role in the selection of neurons to be recruited into a memory representation.

3. What are the mechanisms underlying CREB-mediated competitive memory allocation?

How do neurons with higher levels/activity of CREB gain a competitive edge during memory allocation? CREB regulates a diverse array of genes, and many CREB targets (e.g., c-fos, JunD, C/EBPβ, Egr1, Nurr1, etc.) are themselves transcription factors that regulate other genes. Multiple CREB target genes could contribute to the coordinate regulation of the memory allocation process. Much effort has been invested on identifying the CREB ‘transcriptome’ or ‘regulon’, a complex that includes all genes regulated by CREB (Cha-Molstad, Keller, Yochum, Impey, & Goodman, 2004; Impey et al., 2004; Zhang et al., 2005). Among this cohort of players, we will highlight a subset of CREB target genes and processes that could be involved in CREB-mediated competitive memory allocation.

Changes in neuronal excitability could directly affect memory allocation, since neurons with higher excitability would be more easily activated by learning and therefore would be more likely to be recruited into memory representations. Indeed, several lines of evidence indicate that CREB plays an important role in controlling the excitability of neurons (Marie, Morishita, Yu, Calakos, & Malenka, 2005; Dong et al., 2006; Han et al., 2006). Viral overexpression of CREB in the locus ceruleus (LC) of rats had no significant effect on neuronal firing at baseline, but enhanced the excitatory effect of forskolin (an activator of adenylate cyclase) on LC neurons, suggesting that the cAMP signaling pathway in these neurons was sensitized by CREB (Han et al., 2006); This is especially significant because this signaling pathway is known to be engaged during learning. Moreover, LC neurons expressing constitutively active CREB fired significantly faster and their resting membrane potential was more depolarized compared with control cells. Conversely, downregulating CREB activity in LC neurons decreased the firing rate and hyperpolarized the neurons. In addition, expression of active CREB in the rat nucleus accumbens (NAc) medium spiny neurons (MSNs) increases their excitability, whereas dominant-negative CREB has the opposite effect (Dong et al., 2006).

CREB could also affect the numbers of “silent” or “naïve” synapses (those expressing NMDA but not AMPA receptors) in each neuron, and thus affect where memories are more likely to be stored: neurons with higher CREB levels and therefore more naïve synapses would be more

likely to store the memory than those with lower CREB levels and consequently fewer naive synapses. Neurons infected with a virus expressing constitutively active CREB showed an enhancement of *N*-methyl-D-aspartate (NMDA) receptor-mediated synaptic responses and LTP relative to their non-infected neighbors (Marie et al., 2005), a result consistent with the idea that CREB affects the number of silent synapses ready for synaptic changes, such as LTP. Importantly, additional electrophysiological and morphological studies provided compelling evidence for the idea that higher CREB levels lead to the generation of 'silent synapses', containing NMDA- but not $AMPA^-$ receptors, which are thought to provide an ideal substrate for the storage of memory traces (Marie et al., 2005).

The CREB target genes that are responsible for changes in either excitability or silent synapse numbers described above are not known. Likely candidates for CREB-mediated changes in neuronal excitability include voltage-dependent ion channels as well as second messenger systems that modulate these channels. Current-clamp recordings suggested that CREB-induced increases in neuronal excitability were mediated, at least in part, by an enhancement of Na^+ conductances and an inhibition of K^+ conductances (Dong et al., 2006). Consistent with these findings, a microarray analysis found that CREB expression in the NAc stimulated the transcription of a voltage-dependent sodium channel subunit, 1β, and inhibited the transcription of a voltage-dependent potassium channel subunit, Kv1.4 (McClung & Nestler, 2003). Additionally, adenylate cyclase VIII (ACVIII) appears to be a direct target for CREB (Lane-Ladd et al., 1997). Active CREB induces ACVIII promoter activity, whereas dominant-negative CREB inhibits it, both *in vitro* and *in vivo* in the brain (Chao et al., 2002). Since activation of the cAMP pathway increases neuronal excitability (Wang and Aghajanian, 1987; Alreja and Aghajanian, 1995; Ivanov and Aston-Jones, 2001), these observations support the hypothesis that increased CREB activity, through the consequent induction of ACVIII, increases neuronal excitability.

4. Potential molecular pathways regulating memory allocation

The finding that neurons with higher levels of CREB activity become memory attractors, while those with low levels are less likely to participate in a given memory trace, suggest that some or all of the cooperating and antagonizing signaling pathways known to regulate CREB activity (Fig. 2) might also affect the competitive memory allocation process.

CREB is crucial for translating diverse behavioral stimuli into transcriptional responses in the nucleus. Several intracellular signaling pathways are involved in transmitting information initiated by activation of membrane receptors to CREB in the nucleus (Fig. 2). Multiple kinases, including protein kinase A (PKA), Ca^{2+}/calmodulin-dependent kinase IV (CaMKIV), mitogen- and stress-activated protein kinase (MSK), and mitogen-activated protein kinase (MAPK)-activated ribosomal S6 kinases (RSKs), have been shown to phosphorylate CREB at serine 133 and thereby activate CREB-dependent transcription in response to a variety of stimuli. However, specific kinases and signaling pathways appear to respond primarily to subsets of these stimuli (Shaywitz & Greenberg, 1999;Mayr & Montminy 2001;West, Griffith, & Greenberg, 2002;Lonze & Ginty, 2002).

Phosphorylation of CREB at serine 133 triggers the recruitment of the transcriptional coactivator CREB-binding protein (CBP), which induces transcription via its intrinsic and associated histone acetylase activities and/or by interacting with the core transcriptional machinery (Vo & Goodman, 2001; Lonze & Ginty, 2002). In contrast, CaMKII phosphorylates CREB at serine 142, which promotes the dissociation of CREB dimers and thus reduces CREB-mediated gene transcription (Matthews et al., 1994; Wu & McMurray, 2001). Calcium-dependent activation of protein phosphatases PP1 and PP2A leads to the dephosphorylation of CREB at serine 133 (Shaywitz & Greenberg, 1999; Lonze & Ginty, 2002). Phosphodiesterase

type IV (PDE4), which degrades cAMP, can also regulate CREB-dependent transcription. Dynamic regulation of these signaling pathways, stimulating and antagonizing CREB activity, might fine tune the process that allocates memories in neuronetworks.

The CREB family of transcription factors comprise CREB, CREM (cAMP response element modulatory protein) and ATF-1 (activating transcription factor 1), which can form both homo- and heterodimers to bind to the same *cis*-regulatory element, cAMP response element (CRE), a sequence identified in the promoters of many inducible genes (De Cesare et al. 1999; Mayr and Montminy 2001; Shaywitz and Greenberg 1999). CREB and CREM genes can be alternatively spliced to encode both transcriptional activators and repressors (Foulkes, Borrelli, & Sassone-Corsi, 1991; Walker, Girardet, & Habener, 1996). In addition, ATF-4 (CREB-2), an unconventional member of the CREB family, has been reported to negatively regulate CRE-mediated transcription and long-term memory (Bartsch et al., 1995; Chen et al., 2003). Thus, CREB-mediated memory allocation could be regulated at the level of alternative splicing of CREB family members as well as by their physical interactions and competition for binding sites on target promoters.

Multiple lines of evidence indicate that epigenetic alterations, including DNA methylation and histone modifications are actively engaged in neural plasticity, learning, and memory via regulation of gene expression critical for these processes (Levenson & Sweatt, 2005; Feng, Fouse, & Fan, 2007). In resting neurons, neural plasticity genes, many of which are direct targets of CREB (e.g., BDNF), are associated with more inactive chromatin structures, in which histones are deacetylated or methylated on certain lysine residues (e.g., lysine 9 of histone H3) and/or DNA is more methylated (Martinowich et al., 2003; Chen et al., 2003). Upon induction of neural plasticity, calcium signaling activates the CREB kinase RSK2, CREB, and CBP. These events lead to chromatin remodeling and to a more open chromatin structure that allows for long-lasting expression of plasticity genes and consequently to long-term memory storage. Recent studies have demonstrated that increased histone acetylation, caused by environmental enrichment or by inhibitors of histone deacetylases (HDACs), induce sprouting of dendrites, an increase in the number of synapses and increased access to long-term memories (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). Moreover, a recent study has shown that HDAC inhibitors enhance memory processes by the activation of key genes regulated by the CREB-CBP transcriptional complex (Alarcon et al., 2004; Korzus et al., 2004; Vecsey et al., 2007). HDAC inhibitors seem to potentiate CREB activity by prolonging serine 133 phosphorylation in response to cAMP stimuli, suggesting a potential role for HDAC complexes in silencing CREB activity (Canettieri et al., 2003).

Promoters harboring CRE sites are subject to combinatorial regulation by CREB and other transcription factors and coactivators, which themselves are under control of various signaling pathways. Moreover, their transcriptional activities are influenced by nearby chromatin structure. Therefore, integration of multiple signals can occur in the context of CREB target genes, which themselves could control memory allocation. This perspective illustrates a novel mechanism by which diverse signaling and chromatin-modifying activities act coordinately to dynamically allocate memories in neuronetworks.

5. Metaplasticity in memory allocation

It is possible that the acquisition of a memory changes the activity of CREB (activation followed by repression due to the transcription of CREB repressors such as inducible cAMP early repressor, ICER), which then decreases the probability that the cells engaged in the first memory participate in a second memory some time later. Memories created very close in time are a special challenge because of the high likelihood that there will be common attributes and overlapping contexts. Dynamic memory allocation to different sets of neurons may increase

capacity for, and decrease interference between, the encoding of these multiple distinct attributes that together constitute an epoch. These considerations support the existence of a form of 'metaplasticity', by which predisposition of neurons to participate in a memory trace can be dynamically adjusted according to the history of neuronal activity (Abraham & Bear, 1996), thus resulting in the effective separation of distinct memories.

Besides CREB and related transcriptional processes that could serve to separate memories by transcribing inhibitors (requiring tens of minutes), there may be other processes that could affect memory allocation more quickly. For example, feedback inhibition in neuronal circuits could affect the allocation of two subsequent memories within a given episode by immediately decreasing the probability that cells engaged by one aspect of an episode, are again recruited into encoding a closely related aspect of the same episode seconds/minutes later.

Recently, Guzowski et al. demonstrated that the coupling between cell firing and *Arc* transcription, which is required for memory consolidation (Guzowski et al., 2000), is plastic, not static, because it is influenced strongly by recent behavioral history (Guzowski et al., 2006). They showed that the number of *Arc*-positive CA1 neurons in the hippocampus decreased dramatically in rats exposed repeatedly to an environment (25 min between exposures in a single day), although the firing properties of CA1 neurons did not change across these repeated sessions. Intriguingly, if after repeated exposures to the same environment rats were exposed to a novel environment, the percentage of *Arc*-positive CA1 neurons was that predicted if the reduction of *Arc* transcriptional responsiveness was limited to the cell population repeatedly activated in a repeatedly exposed environment (Guzowski et al., 2006). These results indicate that the altered association and *Arc* transcription observed with repeated exposures is cell and experience specific and not a generalized inhibition of *Arc* transcription in all CA1 neurons. But, what could be the underlying mechanisms for this inhibition?

It is possible that cell-intrinsic oscillating feedback loops control the intracellular levels of CREB and thereby modulate dynamically memory allocation in neuronetworks. Studies of the CREB transcriptome suggest the existence of a negative feedback loop under transcriptional control (Fass, Butler, & Goodman, 2003; Impey et al., 2004). For example, one of the genes most highly induced by activation of CREB is *ICER*, which is a potent inhibitor of CREB function (De Cesare & Sassone-Corsi, 2000; Fass, Butler, & Goodman, 2003). In addition, calcium-dependent activation of protein phosphatases PP1 and PP2A, which leads to the dephosphorylation of CREB at serine 133, might also contribute to this intracellular negative feedback loop (Shaywitz & Greenberg, 1999; Lonze & Ginty, 2002).

6. Reconsolidating the allocation of stored memories

Transgenic studies with inducible CREB mice showed that CREB plays a key role in the reconsolidation as well as consolidation of memory (Kida et al., 2002). It would be exciting to examine whether reconsolidation, just as consolidation, involves the re-allocation of memories, and whether CREB plays a role in this process. The levels and activities of CREB in each neuron might differ dramatically during acquisition and retrieval. Therefore, reactivation of memory circuits during retrieval and subsequent reconsolidation could alter the set of neurons dedicated to the storage of a particular memory. Putative memory reallocation processes could have an important role in the slow reorganization of cortical-dependent remote memories, where fine-tuning storage sites may underlie the emergence of statistical regularities underlying semantic memory (Frankland & Bontempi, 2005). It is conceivable that memory *relocation* processes play a role during the prolonged periods required to consolidate memories in the neocortex, when these memories are thought to be interleaved with previous related memories into integrated semantic-like representations. New memories may force the relocation of previous related memories so that the two are seamlessly integrated within neocortical

networks. In another words, memory allocation and memory reconsolidation processes may work together to generate semantic-like integrated knowledge structures in neocortical networks.

7. Concluding remarks

Recent findings show that competition between neurons, which has been demonstrated to be necessary for refining neural circuits during development, may be important for selecting the neurons that participate in encoding memories in the adult brain. They also suggest that CREB mediates the competition between neuronal cells that leads to the formation of memory traces. Yet, there are both competing as well as cooperating pathways regulating CREB activity in neurons (Shaywitz & Greenberg, 1999; Mayr & Montminy 2001; Lonze & Ginty, 2002; Carlezon, Duman, & Nestler, 2005) and both of these could also affect memory allocation. Thus, the many dynamic signaling processes that converge on CREB could play a role in modulating and fine-tuning where memories are stored in neuronetworks.

Much remains to be done regarding the molecular and cellular basis of memory allocation processes. Identification of critical CREB target genes and the mechanism(s) by which their expressed products control competitive memory allocation is a key goal for future studies. It also remains to be determined whether CREB plays a role in the allocation of memory in brain regions other than the amygdala. For example, it was shown that ~40% of CA1 hippocampal neurons are recruited during spatial learning (Guzowski et al., 2006) and it would be of interest to examine whether CREB-mediated competition also affects which CA1 neurons encode a given spatial memory. In addition, the mechanism(s) by which neurons with higher CREB activity keep other neurons from participating in a given memory trace will be undoubtedly the target of future studies.

The studies reviewed above are the first of what will definitely be an exciting new line of research probing the molecular and cellular mechanisms that determine the addresses of memories in neuronetworks. The combination of approaches that made this study possible represent a new trend in the study of memory where powerful new tools are allowing us to probe deeper into the mechanisms that process and store information in the brain.

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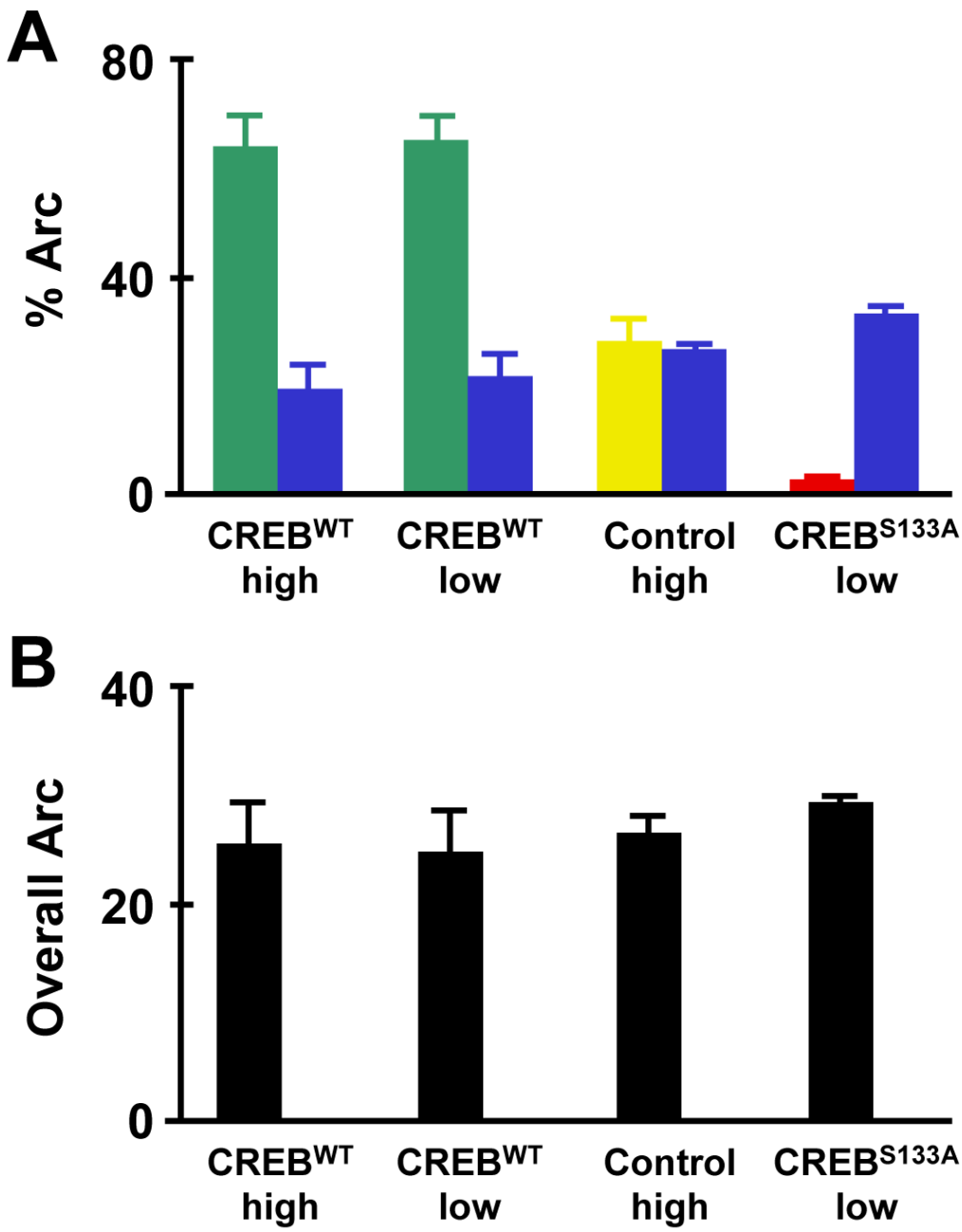

Fig. 1.

Relative CREB activity influences the competitive recruitment of neurons into a memory trace. (A) Distribution of *Arc*-positive neurons varied according to CREB manipulation. *Arc*-positive nuclei were more likely to be in neurons infected with a virus overexpressing wild-type CREB ($CREB^{WT}$) (green bars) than in noninfected neighbors (paired blue bars), whether the mice were trained with high or low shock intensities. In contrast, *Arc*-positive nuclei were equally likely to be in neurons with (yellow bar) and without (paired blue bar) a control virus that does not express CREB. *Arc*-positive nuclei were less likely to be in neurons with decreased CREB function (neurons infected with a virus overexpressing $CREB^{S133A}$; red bar) relative to noninfected neighbors (paired blue bar). (B) Irregardless of the conditions listed above, the

percent of cells expressing *Arc*-positive neurons remained constant, regardless of virus used (control, $CREB^{WT}$, $CREB^{S133A}$) or training intensity (high or low) (modified from Han et al., 2007).

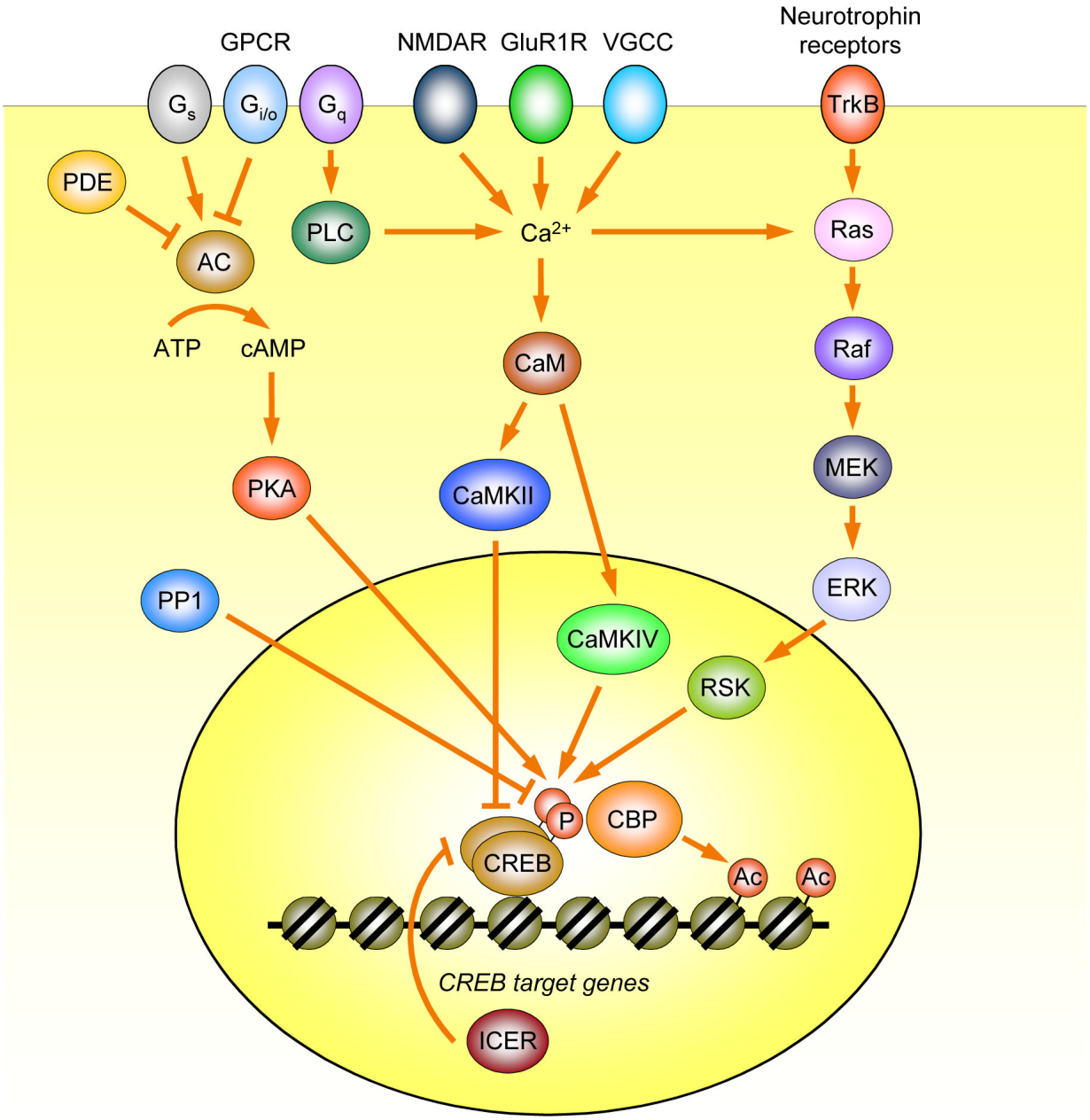

Fig. 2.

Signaling pathways regulating CREB-dependent transcription. Pathways and cross-interactions depicted here are grossly simplified. Arrows and barred lines indicate activation and suppression, respectively. In principle, each of the molecules in these pathways can contribute to the competitive memory allocation process. Abbreviations: Ac, acetylation of histone tails; AC, adenylate cyclase; CaM, calmodulin; CamKII, calcium/CaM-dependent protein kinase II; CaMKIV, calcium/CaM-dependent protein kinase IV; CBP, CREB-binding protein; CREB, cAMP-response element binding protein; ERK, extracellular signal-regulated kinase; GluR1R, glutamate receptor subunit GluR1 homomeric AMPA receptor; GPCR, G protein-coupled receptor; ICER, inducible cAMP early repressor; MEK, mitogen-activated

protein kinase or extracellular signal-regulated kinase kinase; NMDAR, *N*-methyl-D-aspartate receptor; P, phosphorylation of CREB on Ser133; PDE, phosphodiesterase; PKA, protein kinase; PLC, phospholipase C; PP1, protein phosphatase 1; RSK, ribosomal S6 kinase; TrkB, tyrosine kinase receptor B; VGCC, voltage-gated calcium channel.