Review TRENDS in Neurosciences Vol.30 No.6



# NMDA and AMPA receptors: old channels, new tricks

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**Learning and memory depend on persistent changes in synaptic strength that require neuronal gene expression. An unresolved question concerns the mechanisms by which activity at synapses is transduced into a nuclear transcriptional response. In the prevailing view, *N*-methyl-D-aspartate (NMDA)- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors have distinct roles in controlling synaptic strength: AMPA receptors effect short-term changes in synaptic strength, whereas NMDA receptors regulate genes that are required for the long-term maintenance of these changes. Here, we review recent data on the roles of these two types of receptor in activity-dependent gene expression. We discuss evidence that signals from NMDA receptors and AMPA receptors are integrated to specify transcriptional responses for particular plasticity related genes.**

## Introduction

Synaptic plasticity, the variable efficacy of neurotransmission at synapses, is thought to underlie the ability of the brain to store memories [1]. The forms of synaptic plasticity that are most likely to be involved in memory storage require gene transcription and protein synthesis to stabilize synaptic changes over time [2]. A fundamental question in neurobiology concerns the mechanisms by which synaptic activation triggers transcriptional changes in the nucleus [2]. Elucidating these mechanisms would provide insight into the biological basis of information storage in the nervous system and might lead to therapeutic strategies for neurological disorders associated with memory loss [3].

Glutamatergic synapses mediate virtually all excitatory neurotransmission in mammalian brains. Glutamate released from presynaptic terminals activates several types of glutamate-gated ion channels on postsynaptic membranes, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and *N*-methyl-D-aspartate (NMDA) receptors. Kainate receptors at the postsynaptic membrane also bind glutamate; however, their roles in synaptic plasticity are understood less well and are not the focus of this review. AMPA receptors are composed of various combinations of four subunits (GluR1–GluR4), and only AMPA receptors that lack the GluR2 subunit are permeable to $Ca^{2+}$ [4]. By contrast, permeability to $Ca^{2+}$ is a feature of all NMDA receptors, which are composed of an essential NR1 subunit and multiple NR2 subunits. In addition to glutamate, NMDA receptors require membrane depolarization to open with high probability because of a voltage-dependent $Mg^{2+}$ block. During bouts of synaptic activity, AMPA receptor-mediated depolarization of the postsynaptic membrane facilitates activation of NMDA receptors, which initiate $Ca^{2+}$-dependent signaling pathways that modulate the surface presence of AMPA receptors. Changes in AMPA receptors at the postsynaptic membrane cause changes in synaptic strength, the best-characterized forms of which are long-term potentiation (LTP) and long-term depression (LTD) [5]. Stability of LTP and LTD over time requires that synaptic signals initiate the synthesis of appropriate gene products [2]. These signals are thought to originate from NMDA receptors, which activate second-messenger pathways that culminate in gene transcription [6]. Thus, a classical model of long-term synaptic plasticity assigns a regulatory role to NMDA receptors and an effector function to AMPA receptors.

Emerging evidence challenges this model by indicating that the contributions of NMDA receptors and AMPA receptors to plasticity processes might not be as segregated as thought previously. Here, we review recent studies that advance the understanding of NMDA receptor-mediated gene transcription and suggest that AMPA receptors might also have important roles in regulating the expression of plasticity related genes. We begin by discussing a growing awareness that the signaling properties of NMDA and AMPA receptors depend on receptor localization and subunit composition. We consider evidence indicating that different subcellular pools of NMDA and AMPA receptors might have distinct functional roles in synaptic plasticity. Then, we examine the coupling of NMDA and AMPA receptors to intracellular signal transduction pathways. Both receptor types signal through $Ca^{2+}$-dependent and $Ca^{2+}$-independent pathways, and we highlight parallels in the coupling of NMDA and AMPA receptors to the mitogen-activated protein kinase (MAPK) cascade. However, the roles of NMDA and AMPA receptors diverge in plasticity mechanisms that require structural changes at the synapse, and we compare their contributions to the formation and stability of dendritic spines. We end by considering the possibility that signals from NMDA and AMPA receptors are integrated to specify transcription

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Available online 6 April 2007.

 0166-2236/$ – see front matter  doi:10.1016/j.tins.2007.03.012

of some plasticity related genes. Transcriptional control of the activity regulated, cytoskeleton-associated (*ARC*) gene might exemplify this mode of regulation.

### Receptor localization and subunit composition

At excitatory synapses, NMDA receptors are embedded in the postsynaptic membrane, where they are organized by a multiprotein structure called the postsynaptic density (PSD). Despite being anchored to the PSD, NMDA receptors are mobile and move laterally between synaptic and extrasynaptic pools [7]. Localization of NMDA receptors might be a key determinant of their signaling capacity. Synaptic NMDA receptors activate MAPK and the transcription factor cAMP–$Ca^{2+}$ response element-binding protein (CREB), induce expression of the gene that encodes brain-derived neurotrophic factor (BDNF), and promote neuronal survival, whereas extrasynaptic NMDA receptors propagate opposing signals that promote cell death [8–10]. Synaptic and extrasynaptic NMDA receptors also exert antagonistic effects on the nucleocytoplasmic distribution of histone deacetylases [11], which are chromatin-modifying transcriptional repressors that are implicated in neuronal survival.

What is the molecular basis for these effects? An important clue might be that the subunit composition of NMDA receptors varies depending on subcellular localization. During synapse development, synaptic NMDA receptors that contain NR2A subunits replace NR2B-containing receptors, which become predominantly extrasynaptic [12]. Therefore, synaptic and extrasynaptic NMDA receptors might propagate distinct signals by associating with different complements of signaling molecules. Indeed, several molecules bind preferentially to NR2A and to NR2B, including $Ca^{2+}$–calmodulin-dependent protein kinase II (CaMKII) [13], synaptic RAS GTPase activating protein (synGAP) [14], and RAS-guanine nucleotide-releasing factor 1 (RASGRF1) and RASGRF2 [15,16].

The subunit-specific signaling model predicts that NMDA receptors that contain NR2A couple to MAPK, CREB and neuronal survival, whereas those that contain NR2B couple to pathways that inactivate MAPK and lead to cell death. However, several lines of evidence indicate that the distinction is not so clear. In young neurons with predominantly ifenprodil-sensitive (NR2B-containing) receptors, treatment with NMDA activates MAPK and induces CREB-dependent gene expression [17]. NR2B-containing NMDA receptors can couple to MAPK by a direct interaction between NR2B and RasGRF1 [15]. In fact, mature synapses contain a mixture of NR2A-containing and NR2B-containing NMDA receptors [7], and either NR2A or NR2B is sufficient to induce MAPK activation in response to NMDA treatment [14]. Finally, transgenic mice that overexpress NR2B have enhanced learning and memory [18], which indicates that NR2B-containing NMDA receptors mediate synaptic plasticity, not cell death. Thus, more work is necessary to clarify the functional differences between synaptic and extrasynaptic NMDA receptors.

AMPA receptors are located diffusely throughout dendrites during development and become concentrated later at postsynaptic sites [19]. AMPA receptors are thought to be more mobile at synapses than NMDA receptors, and their trafficking, which is determined by a balance of endocytosis, exocytosis and lateral diffusion, is essential for synaptic plasticity [5]. Targeting of AMPA receptors to synaptic and extrasynaptic membranes is regulated by at least two families of proteins, PSD-95-like membrane-associated guanylate kinases (PSD-MAGUKs) [20] and transmembrane AMPA receptor regulatory proteins (TARPs) [21]. PSD-MAGUKs, TARPs and other cellular signaling mechanisms allow neurons to regulate the relative levels of synaptic and extrasynaptic AMPA receptors precisely in response to physiological patterns of activity. For example, overexpression of some TARPs selectively increases the number of AMPA receptors at extrasynaptic sites [22,23]. Why is AMPA receptor localization so tightly regulated? Unlike NMDA receptors, AMPA receptors are not thought to have location-specific signaling properties. Instead, regulated trafficking of AMPA receptors to extrasynaptic sites might enable rapid, NMDA receptor-dependent lateral translocation into synapses during LTP [5].

The role of subunit composition of AMPA receptors in plasticity processes is less clear. Similar to NMDA receptors [24], different combinations of AMPA receptor subunits modulate synaptic plasticity reciprocally in some contexts [25]. However, whereas the subunit composition of NMDA receptors governs the initial direction of synaptic plasticity (i.e. either LTP or LTD) [24], signaling by some combinations of AMPA receptor subunits affects events immediately after the induction of plasticity. For example, transient synaptic incorporation of AMPA receptors that lack GluR2 occurs shortly after LTP induction in hippocampal neurons [26]. These $Ca^{2+}$-permeable AMPA receptors are replaced quickly by $Ca^{2+}$-impermeable AMPA receptors, but the temporary source of $Ca^{2+}$ they provide promotes the maintenance of LTP [26] through unidentified signaling mechanisms. The situation is reversed at cerebellar synapses, where activity induces a switch from $Ca^{2+}$-permeable to $Ca^{2+}$-impermeable AMPA receptors in a process that is mediated by proteins that interact with GluR2 [4]. The signaling consequences of switches in AMPA-receptor subtype are not known, and it will be interesting to see whether the subunit-specific rules that govern the sorting of AMPA receptors during synaptic plasticity [27] are paralleled by rules that specify subunit-specific signaling.

### $Ca^{2+}$ signaling

The best-studied modes of signaling by NMDA and AMPA receptors involve the influx of extracellular $Ca^{2+}$. $Ca^{2+}$ enters neurons through NMDA receptors, $Ca^{2+}$-permeable AMPA receptors and voltage-gated $Ca^{2+}$ channels [28]. NMDA receptors are responsible for most $Ca^{2+}$ influx in response to synaptic activity [28]. $Ca^{2+}$ entry through NMDA receptors is crucial for inducing synaptic plasticity and for activating intracellular signaling pathways that culminate in the phosphorylation of transcription factors such as CREB and gene expression [28,29]. The ability of $Ca^{2+}$, a ubiquitous second messenger, to induce specific patterns of gene expression that depends on the type of channel through which it enters [28] indicates that

molecules required for the activation of $Ca^{2+}$-dependent signaling pathways might be tethered near the intracellular mouth of the channel [30]. Indeed, the importance of channel-proximal $Ca^{2+}$ microdomains in activating transcription has been confirmed for several voltage-gated $Ca^{2+}$ channels [30]. Recently, C-terminal splice variants of the NR1 subunit have been shown to differentially induce NMDA receptor-dependent gene expression [17]. In this study, the authors found that the C0 and C1 protein–protein interaction domains in the cytoplasmic tail of NR1 couple NMDA receptors to gene expression directly because their deletion reduces NMDA-induced gene expression without affecting global increases in intracellular $[Ca^{2+}]$ [17]. Mutation of four amino acids in the C0 domain that bind calmodulin reduces gene expression as much as deletion of the entire C0 domain, which indicates that either calmodulin or another protein that binds to these residues might be the local $Ca^{2+}$ sensor that initiates signaling to the nucleus [17,31]. Other reports suggest that components of the transcriptional machinery in dendrites might be activated by rises in $Ca^{2+}$ near synaptic channels. Local elevation of $Ca^{2+}$, presumably near NMDA receptors, activates dendritic pools of the transcription factor nuclear factor-κB (NF-κB), which then translocates to the nucleus to induce transcription [32].

Although the signaling capacity of NMDA receptors is well-known, AMPA receptors are traditionally regarded as passive conduits for current flux across the membrane. However, a growing body of evidence indicates that AMPA receptors also have metabotropic roles as cell surface-signal transducers [33]. Similar to NMDA receptors, the subset of $Ca^{2+}$-permeable AMPA receptors signals to the nucleus to activate CREB [34,35] and other transcription factors [36]. The MAPK cascade is one of the best-characterized signaling pathways that links synapses with the nucleus. NMDA and AMPA receptors couple to the MAPK pathway through similar sets of signaling molecules, including CaMKII and phosphoinositide 3-kinase [37,38], and through interactions between receptor subunits and RASGRFs [15,16,35].

In addition to $Ca^{2+}$-dependent signaling pathways, NMDA receptors activate MAPK, induce phosphorylation of transcription factors and upregulate gene transcription through a $Ca^{2+}$-independent pathway that involves metabotropic glutamate receptors [39]. AMPA receptors also activate MAPK through mechanisms that are independent of ion influx through the channel [35,40,41]. Indeed, $Ca^{2+}$-impermeable AMPA receptors signal through a SRC-family tyrosine kinase [42] and pertussis toxin-sensitive G proteins [43,44]. In these studies, the metabotropic signaling properties of AMPA receptors were investigated by either using heterologous cells that express $Ca^{2+}$-impermeable forms of AMPA receptors [42] or stimulating native AMPA receptors in medium devoid of permeant cations ($Na^+$ and $Ca^{2+}$) [43,44]. Another study compared the effect of Joro spider toxin, a specific antagonist of $Ca^{2+}$-permeable AMPA receptors, with that of NBQX, an antagonist that blocks all AMPA receptors, to identify signaling functions of $Ca^{2+}$-impermeable AMPA receptors [45]. Although stimulation of AMPA receptors with high concentrations of exogenous agonist is necessary to observe activation of some intracellular signaling molecules [42], AMPA-receptor activation by the spontaneous synaptic release of glutamate triggered downstream effects, including regulation of gene expression [45]. Because metabotropic signaling by AMPA receptors has not been demonstrated *in vivo*, it is important that future studies test this in intact animals. Another target concerns the precise mechanisms by which NMDA and AMPA receptors transduce signals independently of ion influx. Although it seems probable that conformational changes that are initiated by agonist binding are sensed by proteins in contact with receptor subunits [33,39], the elucidation of receptor state-dependent links to downstream effectors remains a major challenge.

Despite their similarities, the mechanisms by which NMDA and AMPA receptors couple to the MAPK pathway are likely to be at least partly distinct. For example, AMPA receptor-mediated signaling through $G_i$ results in prolonged activation of MAPK [41], whereas NMDA-receptor stimulation leads to rapid, transient MAPK activation [41,46]. Additionally, NMDA and AMPA receptors induce distinct patterns of transcription factor activation in the nucleus [47]. It is important to determine whether the MAPK pathway induces different patterns of gene expression depending on whether it is activated by NMDA receptors or AMPA receptors (Figure 1).

## Structural plasticity

Gene expression triggered by activation of the MAPK pathway is crucial for human cognitive processes, including long-term memory [48]. Formation of long-term memory is likely to involve persistent changes in the strength of synaptic transmission, such as LTP [1]. NMDA receptors initiate signaling pathways that modulate the number of AMPA receptors at the cell surface to produce short-term changes in synaptic strength. Stabilization of these changes over time requires new gene expression and structural changes in synaptic morphology [49]. Evidence indicates that, in addition to their roles in short-term plasticity, NMDA and AMPA receptors regulate long-term structural plasticity at the level of gene expression, often through pathways that involve MAPK.

NMDA receptor signaling appears to have a major role in dendritic growth and the formation of new synapses. For example, NMDA receptor function and downstream gene transcription are enhanced by EPHB receptor tyrosine kinases [6,50], resulting in the formation of more excitatory synapses [51]. More recently, a novel NMDA receptor-dependent signaling pathway was found to have a major role in translating neuronal activity into changes in dendrite morphology. Working through the MAPK pathway, NMDA receptors enhance CREB-dependent transcription of Wnt-2, a secreted glycoprotein that stimulates dendritic arborization [52]. Although the authors did not examine synapse formation, CREB activity induces formation of 'silent' (NMDA-only) synapses [53], which are ideal substrates for subsequent LTP. Thus, the transcriptional events that are regulated by NMDA receptors might consolidate existing synaptic modifications and also provide neurons with naive synapses that participate in future adaptations of neural circuits [53].

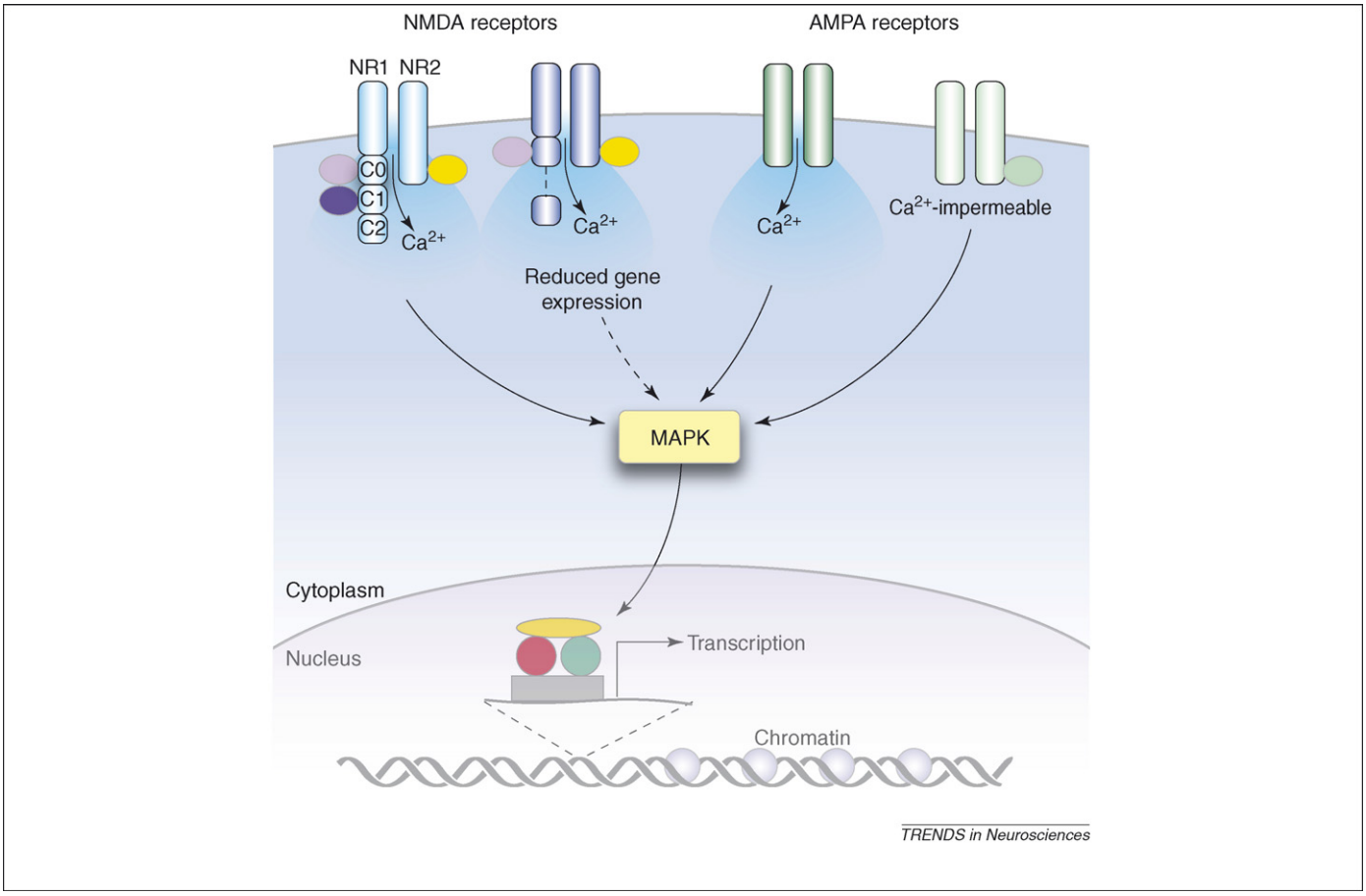


**Figure 1**. NMDA and AMPA receptors activate MAPK. NMDA receptors that contain different splice variants of the NR1 subunit induce different levels of nuclear gene expression. NR1-splice variants are defined by the presence or the absence of C-terminal protein–protein interaction domains (C0, C1 and C2), which concentrate intracellular signaling molecules near the channel mouth. Channels that contain NR1 splice variants and lack C1 do not bind the corresponding signaling molecule(s), resulting in decreased NMDA-receptor-dependent gene expression. MAPK is thought to be a crucial mediator of NMDA-receptor-induced transcription. Different isoforms of the NR2 subunit (not shown) might also exhibit differential coupling to intracellular signaling molecules (see text for details). Although $Ca^{2+}$ is essential for the signaling capacity of NMDA receptors, both $Ca^{2+}$-permeable and $Ca^{2+}$-impermeable AMPA receptors induce nuclear gene expression. Similar to NMDA receptors, AMPA receptors activate MAPK, possibly through signaling molecules that bind to the channel directly. An unresolved issue concerns the mechanisms by which NMDA and AMPA receptors induce distinct, MAPK-dependent transcriptional responses.

AMPA receptors are inserted into synapses during LTP [5] and are, therefore, well-positioned to mediate activity-dependent synaptic stability. In hippocampal slices in culture, activation of AMPA receptors suppresses spine motility [54], and AMPA receptor antagonists prevent the formation of glutamate-induced spine head protrusions [55]. Miniature excitatory synaptic events (minis), which result from activation of postsynaptic receptors by spontaneous, presynaptic glutamate release, are sufficient to stabilize dendritic spines [56]. Minis, which are dominated by the AMPA receptor component under normal experimental conditions, might stabilize spines by either inhibiting dendritic protein synthesis [57] or affecting gene transcription. AMPA receptors also promote spine growth through a novel mechanism that involves the GluR2 subunit [58]. Overexpression of GluR2 increases spine size and density in hippocampal neurons, an effect that requires the extracellular domain of GluR2 but not current flux through the channel. Although the mechanism that underlies this effect is unknown, one possibility is that GluR2 serves as a receptor for an unidentified ligand that stabilizes spines, perhaps by stimulating signaling by metabotropic AMPA receptors [33,58].

These data indicate a model in which NMDA receptors initiate synapse formation at the level of gene expression and AMPA receptors work through diverse mechanisms to promote synapse growth and stabilization (Figure 2).

## Signal integration

The complementary roles of NMDA receptors and AMPA receptors in structural plasticity raise the question of whether they cooperate to regulate neuronal gene expression. The fact that neurons coregulate levels of NMDA and AMPA receptors through homeostatic mechanisms [59] provides insights into this possibility.

LTP and LTD are forms of Hebbian (associative) plasticity, based on positive feedback rules that tend to destabilize neural circuits by driving synaptic strength toward either maximum or minimum values [60]. Neurons counterbalance these effects through homeostatic mechanisms that normalize their excitability. Decreased neuronal activity causes a compensatory increase in the strength of all excitatory synapses, whereas increased neuronal activity has the opposite effect [60]. Compensatory changes in synaptic strength occur in a multiplicative manner that preserves the relative weights of synapses, a

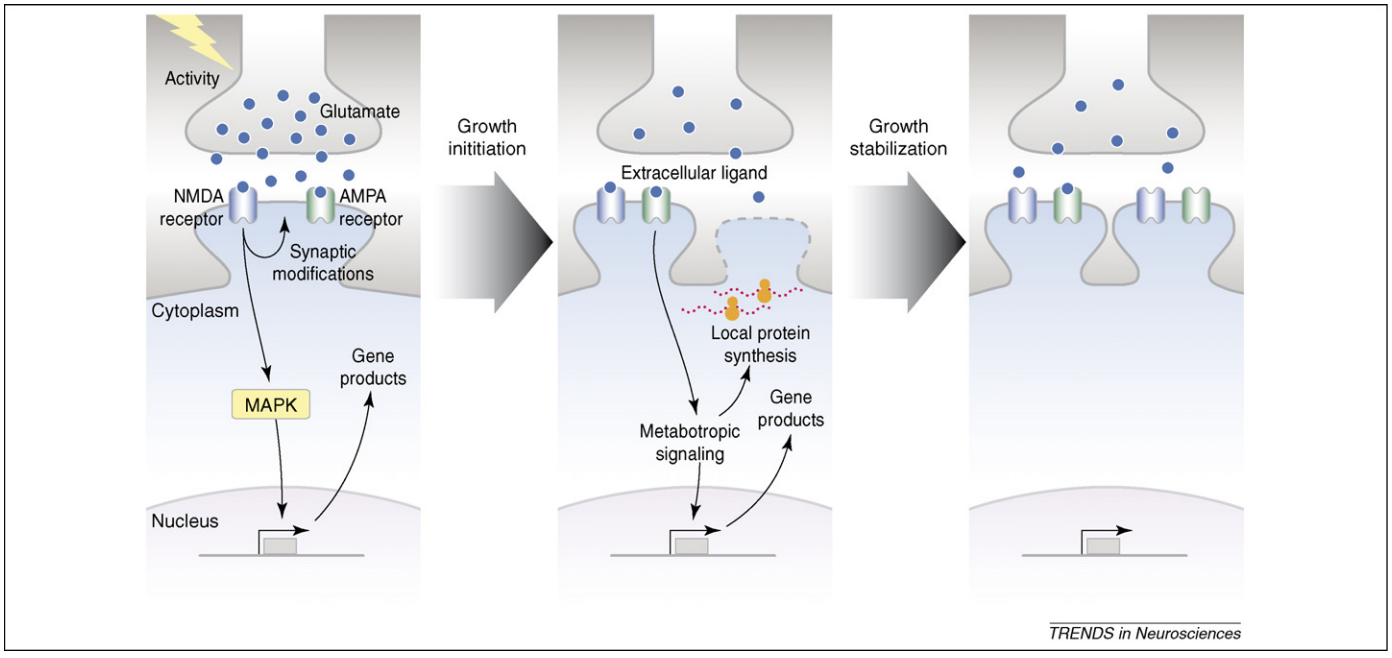


**Figure 2**. NMDA and AMPA receptors regulate synapse formation, growth and stabilization. During bouts of synaptic activity, NMDA receptors initiate signaling cascades that lead to modifications of the activated synapse and activation of MAPK and nuclear gene expression. Nascent gene products promote synapse formation, represented as a second dendritic spine apposed to the presynaptic terminal. In this model, metabotropic signaling by synaptic AMPA receptors regulates transcription and dendritic mRNA translation, thereby promoting the growth and stabilization of the newly formed spine.

phenomenon termed synaptic scaling [61]. NMDA and AMPA receptors are scaled proportionally so that the ratio of currents through these channels is relatively fixed [59]. During LTP, this ratio, which is perturbed transiently by insertion of AMPA receptors into the synapse, is eventually restored by a delayed but proportional potentiation of NMDA receptor-mediated currents [62]. Homeostatic regulation of the NMDA:AMPA ratio might help to preserve the information content of synaptic transmission [60]. Another possibility, which is not mutually exclusive, is that the NMDA:AMPA ratio is crucial for coupling synaptic activity to long-term adaptive responses that require gene expression. In this scenario, transient decreases in the NMDA:AMPA ratio created by the lag in NMDA receptor potentiation might have important implications for synapse-to-nucleus signaling. Regulation of the *ARC* gene provides an interesting example of how such a mechanism might work.

Although neurons maintain low basal levels of *ARC* mRNA, synaptic activity associated with LTP and memory-related behavioral paradigms induces *ARC* transcription robustly *in vivo* [63]. After induction by synaptic activity, *ARC* mRNA translocates to dendrites and localizes near activated synaptic sites [64] where it might be translated [65]. Compelling evidence links *ARC* with synaptic plasticity and memory, including the fact that NMDA receptor activation, which is crucial for induction of LTP, is required for transcription of *ARC* [64]. Recently, it has become clear that AMPA receptors also regulate *ARC* transcription. In cortical neurons in culture and in organotypic brain slices, pharmacological inhibition of AMPA increases activity-dependent *ARC* transcription, measured by quantitative techniques that detect nascent *ARC* transcripts [45]. Selective blockade of $Ca^{2+}$-permeable AMPA receptors has no effect, which indicates that $Ca^{2+}$-impermeable AMPA receptors normally inhibit the expression of *ARC*. Pertussis toxin mimics and occludes the effect of an AMPA receptor antagonist on *ARC* expression, so this effect might involve a pertussis toxin-sensitive G protein [45]. *ARC* expression is, thus, determined by a novel mechanism in which antagonistic signals from NMDA and AMPA receptors are integrated by the pathways that control the transcription of *ARC*. *ARC* regulatory mechanisms are fundamentally distinct from those that control expression of the gene encoding BDNF, which is upregulated by signaling from both NMDA [66] and AMPA receptors [42,67].

Based on the regulation of *ARC* by NMDA and AMPA receptors, a mechanism has been proposed whereby synaptic scaling allows negative-feedback control of *ARC* expression [45]. First, synaptic NMDA receptor activity initiates signaling pathways that stimulate the delivery of AMPA receptors to the surface and induce *ARC* transcription in the nucleus. Then, the decrease in the NMDA:AMPA ratio stops transcription of *ARC*, avoiding excess production. Finally, a delayed potentiation of the activity of NMDA receptors resets this ratio, which allows subsequent expression of *ARC* and synaptic plasticity. In this model, a rapid, transient increase in *ARC* expression is achieved because synaptic activity simultaneously sets into motion signals that induce *ARC* and signals that eventually limit its expression. By dampening NMDA receptor-mediated stimulation of *ARC* expression tonically, AMPA receptors provide ongoing homeostatic regulation of a gene that is crucial for synaptic plasticity [45].

Additional support for a connection between *ARC* and synaptic scaling comes from subsequent reports indicating that *ARC* itself mediates AMPA receptor homeostasis. Overexpression of *ARC* reduces AMPA-receptor-mediated synaptic transmission [68] and inhibits homeostatic

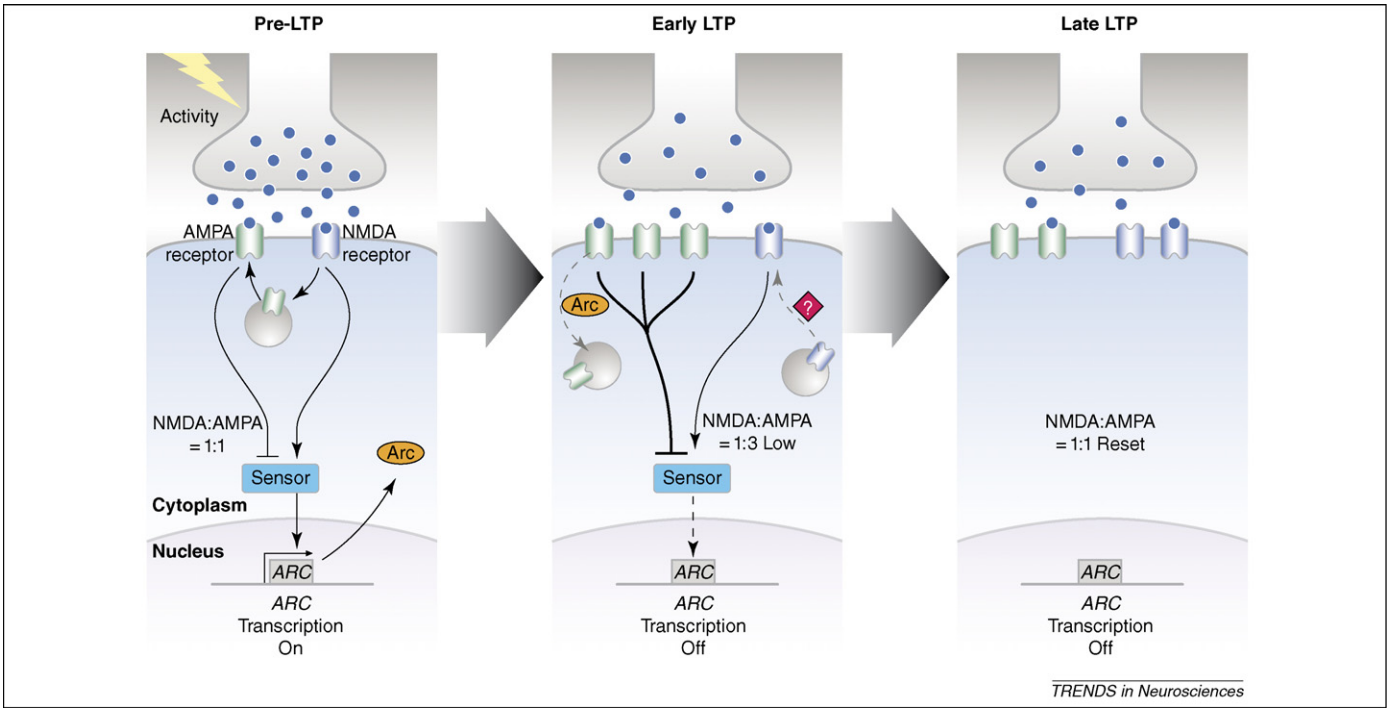


**Figure 3**. Model of the regulation of *ARC* by NMDA receptors and AMPA receptors. During synaptic activity NMDA and AMPA receptors propagate opposing signals that are integrated by a hypothetical 'sensor' and transduced into a transcriptional response. Under basal conditions ('Pre-LTP'), the ratio of the relative activities of NMDA and AMPA receptors, shown here as 1:1, permits robust transcription of *ARC* and production of ARC protein. NMDA receptor activity also initiates signaling pathways that promote the synaptic delivery of AMPA receptors and leads to 'Early LTP'. Insertion of AMPA receptors into the postsynaptic membrane decreases the NMDA:AMPA ratio (1:3) and inhibits *ARC* transcription. ARC promotes the removal of synaptic AMPA receptors and unknown mechanisms (red diamond) potentiate synaptic NMDA receptor currents. The net result of these processes ('Late LTP') is that the NMDA:AMPA ratio is reset (1:1), which enables synthesis of additional *ARC* during subsequent rounds of activity. Note that the synapse becomes stronger, with twice as many AMPA receptors as in the 'Pre-LTP' state. Ratios in this figure illustrate changes in relative activity of the channel rather than experimental measurements of the number of channels.

increases in AMPA receptor function induced by blockade of neuronal activity [69]. Thus, a unified picture is emerging in which synaptic activity of NMDA receptors triggers a dynamic interplay between AMPA receptors and *ARC*, each of which functions to maintain the other within an optimal operating range (Figure 3).

## Future directions

Although the basic cellular events that underlie short-term changes in synaptic strength have yielded to decades of intense scrutiny, the mechanisms that underlie the persistence of these changes are less clear. The results reviewed here represent significant progress in elucidating these mechanisms. A fundamental principle distilled from these data is that AMPA receptors, similar to NMDA receptors, function as signal transducers that mediate long-term, activity dependent synaptic changes. Indeed, NMDA and AMPA receptors share important similarities in this regard. Signals propagated by NMDA and AMPA receptors depend heavily on the position and subunit composition of the receptors and involve both $Ca^{2+}$-dependent and $Ca^{2+}$-independent mechanisms. Although NMDA and AMPA receptors seem to work in complementary ways to regulate structural plasticity at the synapse, they might exert opposing influences on the transcription of some genes that are essential for long-term plasticity. The diversity of signaling mechanisms employed by NMDA and AMPA receptors expands the complexity of adaptive responses of neurons to synaptic activity.

Much work remains to be done, including further characterization of the signaling molecules downstream of AMPA receptors, particularly those that mediate metabotropic signaling. Neuronal maturity appears to be a crucial determinant of the coupling of NMDA receptors and AMPA receptors to signaling molecules [35,70]. The existence of a developmental shift in plasticity mechanisms is important when comparing studies in different experimental systems. With regard to structural plasticity, it is important to define the molecules that are synthesized in response to synaptic activity and how they are involved in mediating morphological changes in distal synapses. Finally, the dual regulation of *ARC* by NMDA receptors and AMPA receptors indicates that *ARC* might be a valuable tool for investigating novel modes of activity dependent gene expression. Elucidation of the underlying mechanisms requires pharmacological, genetic and electrophysiological manipulation of the NMDA:AMPA ratio and correlation with changes in *ARC* expression. Fascinating and complicated, NMDA and AMPA receptors continue to provide memory researchers with fresh challenges.

## Acknowledgements

We thank past and present members of the Finkbeiner laboratory for valuable discussions, G. Howard and S. Ordway for editorial assistance, J. Carroll for preparing the figures, and K. Nelson for administrative assistance. V.R.R. is supported by the NIH-NIGMS UCSF Medical Scientist Training Program and by the Epilepsy Foundation of America. S.F. is supported by the National Institutes of Neurological Disorders and Stroke (NS039074 and NS045191), the National Institute of Aging

(AG022074), the Taube Family Foundation and the J. David Gladstone Institutes.

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