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Synaptic AMPA Receptor Plasticity and Behavior

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Abstract

The ability to change behavior likely depends on the selective strengthening and weakening of brain synapses. The cellular models of synaptic plasticity, long-term potentiation (LTP) and depression (LTD) of synaptic strength, can be expressed by the synaptic insertion or removal of AMPA receptors (AMPARs), respectively. We here present an overview of studies that have used animal models to show that such AMPAR trafficking underlies several experience-driven phenomena—from neuronal circuit formation to the modification of behavior. We argue that monitoring and manipulating synaptic AMPAR trafficking represents an attractive means to study cognitive function and dysfunction in animal models.

Introduction

The adult human brain contains over 100 billion neurons, with each interconnected by thousands of synapses. A single experience may therefore be translated into the activation of a nearly infinitely large diversity of possible neuronal circuits. How can an experience lead to changes in circuits underlying adaptive behavior? It is thought that experiences can modify synapses, favoring some neuronal pathways within a circuit and weakening others (Hebb, 1949). Identifying how and where in the brain synapses are modified by experience that leads to changes in behavior are major goals of modern neuroscience.

Plasticity at synapses can be regulated at the presynaptic site by changing the release of neurotransmitter molecules or postsynaptically by changing the number, types, or properties of neurotransmitter receptors. Studies using in vitro synaptic plasticity models have identified the regulated trafficking of postsynaptic AMPA-type glutamate receptors as a prevalent mechanism underlying activity-induced changes in synaptic transmission (for a detailed description read Bredt and Nicoll, 2003; Malinow and Malenka, 2002; Newpher and Ehlers, 2008). Importantly, techniques and reagents have been generated that can be used in more intact systems to examine if similar synaptic plasticity mechanisms participate in behavioral modification (Ahmadian et al., 2004; Hayashi et al., 2000; Luthi et al., 1999). Such tools recruit the power and specificity of molecular biology to address the role of synaptic modifications in behavior. Here we first highlight selected relevant background regarding AMPAR trafficking mechanisms and then review recent studies that have begun to elucidate how these mechanisms mediate aspects of adaptive behavior.

Mechanism of AMPAR Trafficking during Synaptic Plasticity

Excitatory synapses contain AMPA-type receptors (AMPAR) to transmit signals and NMDA-type receptors (NMDAR) to trigger long-term changes in synaptic transmission:

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long-term potentiation (LTP) and long-term depression (LTD). While many mechanisms can regulate the onset or magnitude of LTP and LTD, in many cases, there appears to be one common mechanism controlling the postsynaptic expression: the addition and removal, respectively, of synaptic AMPARs (Barry and Ziff, 2002; Bredt and Nicoll, 2003; Collingridge and Singer, 1990; Malinow and Malenka, 2002; Scannevin and Huganir, 2000).

Four different genes (*GluR1*, *GluR2*, *GluR3*, and *GluR4*) encode AMPAR subunits (Hollmann and Heinemann, 1994; Wisden and Seeburg, 1993). GluR1, GluR4, and GluR2L (a long splice form of GluR2) have a long cytoplasmic carboxy-terminal tail (c-tail), while GluR2, GluR3, and GluR4c (a short splice form of GluR4) have short and structurally similar c-tails. Hippocampal pyramidal neurons of mature rats express mainly GluR1, −2, and −3 (Zhu et al., 2000), which form channels consisting of four subunits with a preferred configuration of two identical heterodimers (Mansour et al., 2001): GluR1/2 and GluR2/3 (Wenthold et al., 1996).

The rules for synaptic AMPAR trafficking are hypothesized to depend on subunit composition: (1) synaptic strengthening involves activity-dependent addition of long-tailed (e.g., GluR1-containing) AMPARs to synapses; (2) synaptic weakening occurs through activity-dependent endocytosis of either long-tailed or short-tailed AMPAR from synapses; (3) short-tailed AMPARs constitutively traffic into synapses independent of activity and without changing synaptic strength. Below, we indicate the support for these views, along with the techniques and reagents generated.

Synaptic Strengthening by AMPAR Trafficking

The functional incorporation of long-tailed AMPARs into synapses was demonstrated by electrophysiological tagging-type experiments (Hayashi et al., 2000). Normally, CA1 pyramidal cells predominantly express heteromeric receptors. GluR1 overexpression produces homomeric GluR1/1 receptors, which, unlike endogenous GluR2-containing receptors, are inwardly rectifying (i.e., allow little outward current at positive membrane potentials). In neurons overexpressing GluR1, LTP increases synaptic rectification, indicating synaptic insertion of GluR1 homomeric receptors (Hayashi et al., 2000; Kakegawa et al., 2004). Coexpression of recombinant GluR1 and GluR2 leads to the formation of heteromeric GluR1/2 receptors, which are also only driven into synapses by mediators of LTP (Shi et al., 2001), suggesting that GluR1/1 behaves like GluR1/2 with respect to activity-induced synaptic trafficking. These (and other: Harms et al., 2005; Kolleker et al., 2003; Larsson and Broman, 2008; Plant et al., 2006; Zhu et al., 2000) experiments suggest that activity-driven synaptic incorporation of AMPARs is mediated by long-tailed AMPARs.

An issue arises as to how much trafficking behavior is affected in an overexpression context. Recombinant overexpression of an AMPAR subunit largely replaces endogenous subunits, leading to only a modest increase in total dendritic AMPAR levels without affecting the dendritic levels of other receptors (H.W.K. et al., unpublished data). This observation suggests that the mechanisms underlying receptor trafficking from dendrite to synapse that one sees with transfected AMPARs are likely the same ones that are regulating endogenous AMPARs. Under some conditions, LTP induction can lead to an increase in rectification that is contributed by endogenous AMPARs (Guire et al., 2008; Plant et al., 2006) (likely to consist of homeric GluR1/1 s [Wenthold et al., 1996]) and may require the Ca^{2+} permeability of GluR2-lacking receptors. However, these findings are not universally accepted (Adesnik and Nicoll, 2007; Gray et al., 2007).

The mechanism by which GluR1-containing receptors are driven to synapses during LTP is not fully elucidated, but it is likely that, during induction, a number of GluR1-interacting proteins together form a complex to create an extra “slot”: a term coined to indicate a synaptic place-holder for receptors (Malinow, 2003). We speculate that the formation, stability, and functionality of a slot will depend on AMPAR-binding proteins (for a list of potential slot proteins, see supplemental Figure 2 of Kopec et al., 2007) and phosphorylation events. Several activity-driven phosphorylation events at the GluR1 c-tail (PKA at S845 [Roche et al., 1996], CaMKII at S831 [Barria et al., 1997; Mammen et al., 1997], PKC at S818 and S831 [Boehm et al., 2006b; Roche et al., 1996]) facilitate synaptic AMPAR delivery (Esteban et al., 2003; Song and Huganir, 2002). Using phospho-specific antibodies, AMPAR phosphorylation states can be monitored in neuronal tissue to assess changes in potentiation of synaptic transmission (Lee et al., 2000).

Activity-dependent AMPAR trafficking can be specifically blocked by expression of the full GluR1 c-tail (Shi et al., 2001; Watt et al., 2004). LTP-like stimuli lead to an enrichment of this cytosolic c-tail fragment at the synapse (Kopec et al., 2007), suggesting it can occupy “slot” complexes and compete with full-length GluR1 for synaptic incorporation during LTP. Importantly, expression of the GluR1 c-tail for days does not affect membrane potential or input resistance, action potential generation, basal AMPAR or NMDAR transmission, or other forms of plasticity that are independent of GluR1 (Shi, 2001; Shi et al., 2001; Watt et al., 2004). This construct therefore serves as a plasticity blocker specific for GluR1 synaptic trafficking.

Synaptic Weakening by AMPAR Trafficking

LTD of synaptic strength is expressed by the removal of synaptic AMPARs (Malinow and Malenka, 2002; Sheng and Hyoung Lee, 2003). Removal of GluR2-containing receptors from synapses can be accomplished by their phosphorylation at S880 by PKC (Chung et al., 2000; Matsuda et al., 2000; Perez et al., 2001; Seidenman et al., 2003). Furthermore, phosphatase activity (known to be necessary for LTD [Mulkey et al., 1993]) can lead to dephosphorylation of GluR1 at S845 or S831, which are associated with GluR1 removal from synapses (Kameyama et al., 1998; Lee et al., 2000). Weakening of synaptic strength through LTD-like mechanisms can therefore be studied by biochemical analysis of brain tissue for phosphorylation of GluR2(S880) and dephosphorylation at GluR1(S845) or (S831).

To block LTD, a fragment of the GluR2 c-tail can be introduced into neurons. The full-length GluR2 c-tail (Shi et al., 2001) or a fragment of this tail that disrupts binding to NSF (Luscher et al., 1999; Luthi et al., 1999) inhibits LTD, but also decreases basal synaptic transmission by preventing the constitutive AMPAR replacement process (described below). However, infusion of a peptide that only spans nine amino acids near the end of the GluR2 c-tail harboring three tyrosine residues (GluR2-3Y) specifically abolishes the regulated NMDAR-dependent endocytosis of synaptic AMPARs without affecting basal synaptic transmission or LTP (Ahmadian et al., 2004). This GluR2-3Y peptide therefore serves as a plasticity blocker for the activity-dependent removal of synaptic AMPARs.

Synaptic Trafficking in the Absence of Plasticity

In the absence of neural activity, AMPARs can go into synapses without changing the magnitude of synaptic transmission (Kakegawa et al., 2004; Shi et al., 2001), suggesting a mechanism for a one-for-one exchange of receptors from extrasynaptic to synaptic sites. In brain slice preparations, only AMPARs lacking GluR1 incorporate passively into synapses (Shi et al., 2001). Studies conducted on either dissociated cultured neurons (Bats et al., 2007; Ju et al., 2004; Passafaro et al., 2001) or hippocampal slices from GluR2-deficient

mice (Panicker et al., 2008) indicate that activity-independent incorporation of AMPARs can occur in a manner that is independent of c-tails. However, several results suggest this is not the case in wild-type tissue or in vivo. For instance, mutations in AMPAR constructs that prevent PDZ domain interactions successfully impede AMPAR synaptic incorporation in wild-type tissue but not in GluR2-lacking tissue (Shi, 2001). In addition, long-tailed receptors do not incorporate into synapses in wild-type slices in the absence of plasticity-inducing stimuli (Kolleker et al., 2003; Shi et al., 2001; Zhu et al., 2000), but do incorporate into synapses in dissociated neurons (Bats et al., 2007; Ju et al., 2004; Passafaro et al., 2001). More importantly, since the mechanisms of AMPAR trafficking in wild-type slices, in particular the control by the c-tails, has been confirmed in vivo (as described below), it is likely that these aspects of receptor trafficking to synapses is aberrant in dissociated or GluR2-deficient neurons.

The passive replacement of synaptic long-tailed recombinant AMPARs (that were driven to the synapse by activity) by endogenous AMPARs has been observed in slice cultures. This process does not require activity and may take up to 20 hr (McCormack et al., 2006; Zhu et al., 2000). The function of GluR1-lacking (e.g., GluR2/3) receptors to replace constitutively synaptic AMPARs may be important to maintain synaptic strength in the absence of activity and in the face of protein turnover. The exchange of GluR1/2 receptors by GluR2/3 receptors may also stabilize synaptic strengthening. Recent findings that several synaptic components more stably tether GluR2/3 than GluR1 subunits (Cingolani et al., 2008; Saglietti et al., 2007; Silverman et al., 2007) support this notion. Stabilization of synaptic strength through AMPAR replacement may represent a molecular mechanism for consolidation of encoded memories. However, the degree or relevance of constitutive cycling by only GluR1-lacking receptors has not yet been fully established. First, acutely isolated brain regions (such as the hippocampus) contain considerable amounts of GluR1 at synapses (Petralia and Wenthold, 1992), leading to the surprising conclusion that these brain regions continuously undergo LTP-like processes. In addition, some studies (Gold et al., 1996; Pellegrini-Giampietro et al., 1994; Sans et al., 2003) suggest low levels of GluR3 and GluR1/2 as the dominant AMPAR in neurons of the hippocampus (but see Wenthold et al., 1996), thus potentially reducing the functional significance of subunit-specific trafficking in this brain region. It may be that continuously ongoing synaptic plasticity in the hippocampus decreases the necessity of AMPAR replacement for maintaining synaptic stability in the face of protein turnover. In cortex, where synaptic strengthening is sparser and memories are encoded for longer periods of time, GluR1 and GluR3 are expressed in equivalent amounts (Gold et al., 1996). It will be important to establish the relative endogenous levels of AMPAR subunits in neurons and synapses from different brain regions and how this relates to the neuron's capacity to encode and store information.

From Brain Slices to Behavior

In the previous sections, the discussion of AMPAR-mediated synaptic plasticity was limited to those aspects that are relevant for probing and manipulating behavior.

Experiments conducted at the CA3-CA1 synapse in hippocampal brain slices suggest a model for synaptic plasticity in which AMPARs are divided into two functionally different subclasses: those that contain long-tailed subunits (e.g., GluR1) and those that lack such subunits. Neuronal activity can lead to synaptic strengthening through the incorporation of GluR1-containing AMPARs at the postsynaptic membrane. GluR1-lacking receptors constitutively traffic in and out of the synapse in order to maintain synaptic strength when activity is absent. While AMPAR trafficking is likely not the only molecular mechanism for behavioral plasticity, a number of studies, discussed in the next sections, suggest that

monitoring and manipulating AMPAR trafficking is an attractive approach to identify synapses that undergo experience-dependent changes to modify behavior.

Experience-Dependent AMPAR Trafficking

The role of AMPAR trafficking in experience-dependent plasticity has been studied in the rodent barrel cortex, the sensory projection of whiskers. Whisker stimulation has been suggested to induce an LTP-like increase in synaptic strength in the neocortex in vivo (Finnerty et al., 1999; Hardingham et al., 2003). Similar to LTP in hippocampal slices, experience-driven synaptic strengthening in barrel cortex pyramidal neurons is dependent on synaptic GluR1 delivery (Takahashi et al., 2003). Following in vivo viral expression of GluR1 in layer 2/3 pyramidal neurons of the barrel cortex, synaptic transmission onto these neurons mediated by AMPARs showed increased rectification, indicating synaptic incorporation of GluR1. This was observed only in animals whose whiskers were spared (permitting experience), but not in whisker-deprived animals. Overexpression of GluR1 increases the proportion of homomeric GluR1, which (in contrast to endogenous GluR2-containing AMPARs) are calcium permeable and therefore may influence plasticity. However, similar experiments in the mouse barrel cortex showed that endogenously expressed rectifying receptors (i.e., most likely homomeric GluR1) are incorporated into synapses upon experience-dependent synaptic strengthening (Clem and Barth, 2006), indicating that these observations were not an artifact of GluR1 overexpression. In addition, viral expression of the GluR1 c-tail blocked synaptic plasticity (while sparing basal transmission in animals with whiskers trimmed), suggesting that experience drives endogenous GluR1-containing AMPARs into synapses (Takahashi et al., 2003).

Constitutive AMPAR cycling, as judged by synaptic trafficking of recombinantly expressed GluR1-lacking AMPARs, was shown to be independent of whisker input (Takahashi et al., 2003). In addition, whisker deprivation after permitting experience-driven synaptic GluR1 delivery showed that GluR1 insertion is transient, suggesting that GluR1-containing AMPARs delivered to synapses in vivo are replaced by GluR1-lacking AMPARs through constitutive cycling within 24 hr (McCormack et al., 2006; Takahashi et al., 2003). Alternatively, whisker deprivation, which leads to a retuning of sensory circuits (Lendvai et al., 2000), may cause active removal of GluR1-containing AMPARs (Wright et al., 2008). This latter view is suggested by studies in which monocular deprivation causes a weakening of synapses in neurons of the visual cortex that coincides with a decrease in GluR1(S845) phosphorylation and an increase in GluR2(S880) phosphorylation (Heynen et al., 2003). Visual experience, in turn, results in a gradual potentiation of synaptic responses in these neurons, which could be blocked by expression of the GluR1 c-tail (Frenkel et al., 2006). In summary, these experiments indicate that the rules for subunit-specific AMPAR trafficking, as laid out based on experiments in hippocampal slice cultures, also apply to experience-dependent synaptic plasticity in the developing neocortex.

Experience-driven AMPAR trafficking has also been examined by comparing the biochemical composition of synapses obtained from awake and sleeping animals (Vyazovskiy et al., 2008). The rationale is that the brain records new experiences when awake and not when asleep. In accordance with the subunit-specific rules of AMPAR trafficking, biochemical analysis revealed that the levels of total and phosphorylated GluR1 are significantly higher in synapse-enriched fractions from cortical or hippocampal neurons of awake animals compared with those isolated from sleeping animals. GluR2 levels remained unaltered—an observation that can be explained by a replacement of GluR1/2 heteromers by GluR2/3 heteromers during sleep. If GluR2/3 is more stable at synapses, sleep may serve to stabilize synaptic modifications by allowing constitutive cycling to replace synaptic GluR1-containing AMPARs by those lacking GluR1.

AMPAR Trafficking in Hippocampus-Dependent Learning and Memory

The role of LTP-like trafficking mechanisms in learning a specific contextual setting was studied using a single-trial hippocampus-dependent conditioning paradigm (Whitlock et al., 2006). In rats trained to avoid a fearful context, a significant proportion of electrodes in an electrode array positioned in their hippocampus (~30% compared with ~10% in control animals that were exposed to the new context without receiving a shock) measured enhanced transmission 30 min after learning. This was accompanied with increased GluR1 phosphorylation and increased levels of GluR1 and GluR2 subunits in synaptosomal fractions from nearby hippocampal regions. These data suggest that contextual fear conditioning leads to synaptic AMPAR trafficking in hippocampal neurons. A recent study suggests that hippocampal spines that are activated during fear conditioning also recruit GluR1-containing AMPARs in the hours after learning (Matsuo et al., 2008). However, it remains unclear whether these spine-localized AMPARs are incorporated into synapses or reside extrasynaptically. In the study by Whitlock et al., biochemical analysis showed that the amounts of synaptically localized GluR1 (and GluR2) returned to control levels in the subsequent hours after learning. Interestingly, at the same time course the proportion of electrodes measuring potentiation remained unchanged, while the proportion of electrodes measuring depression gradually increased (Whitlock et al., 2006). This observation may suggest that (in addition to the replacement of GluR1-containing receptors) some sort of compensatory regulation of total synaptic AMPARs exists; an initial potentiation of a subset of synapses through addition of GluR1-containing AMPARs is over time gradually compensated by a depression in nonpotentiated synapses. This homeostatic process, which differs from the global scaling of synapses following persistent increases or decreases in neuronal activity (Davis, 2006; Turrigiano, 2008), may be conducted by Arc/Arg3.1 and/or PSD95. Arc is an immediate-early gene whose transcription increases following neuronal activity and specifically removes GluR2/3-containing AMPARs from synapses (Rial Verde et al., 2006; Shepherd et al., 2006)—just those receptors that are not at synapses as a consequence of potentiation (e.g., lacking GluR1). Also, PSD-95, a prominent PSD scaffolding protein that can control the strength of a synapse, dynamically redistributes over synapses in vivo and is more stably captured at synapses that receive experience-dependent input (Gray et al., 2006). PSD-95 may therefore preferentially support the stability of AMPARs within potentiated synapses.

The study by Whitlock and coworkers (Whitlock et al., 2006) elegantly showed that learning leads to synaptic strengthening in the hippocampus, but it does not provide evidence that LTP-like mechanisms participate in or are required for the modified behavior. One useful approach to study the requirement of AMPAR trafficking in hippocampus-dependent learning has been to generate animal models that are deficient in the expression of an AMPAR subunit. A mouse lacking the gene encoding the GluR1 subunit (and therefore will predominantly express GluR2/3 heteromeric AMPARs) was generated (Zamanillo et al., 1999). While basal AMPAR- and NMDAR-mediated transmission in hippocampal slices from such mice were normal (but see Andrasfalvy et al., 2003), LTP induced by a brief burst of activity was deficient. This finding is consistent with the view that synaptic trafficking of GluR1-containing AMPARs is necessary for the induction of LTP. In line with the inability of hippocampal neurons to display AMPAR trafficking that depends on a brief burst of activity, GluR1-deficient mice exhibit impaired hippocampus-dependent spatial working memory (SWM) (Reisel et al., 2002; Schmitt et al., 2004; Schmitt et al., 2003) and one-trial spatial memory (Sanderson et al., 2007).

Interestingly, performance of GluR1-deficient mice in the Morris water maze test or related tests for hippocampus-dependent spatial reference memory (SRM) is not impaired (Schmitt et al., 2003, 2004; Zamanillo et al., 1999). While SRM requires NMDAR function (Morris

et al., 1986; Tsien et al., 1996) (but see Bannerman et al., 2008, 1995; Saucier and Cain, 1995), SRM is slowly and gradually acquired, requiring multiple days of repetitive learning trials. Therefore, gradual learning processes may recruit a form of NMDAR-dependent plasticity that does not depend on GluR1 trafficking. Alternatively, SRM could involve AMPAR-trafficking; only in the absence of GluR1, plasticity may be largely devoid of its early component. In the absence of GluR1, the repetitive learning protocols may lead to the formation of new slot complexes lacking an AMPAR. Such empty slots may be sufficiently stable for them to be slowly occupied by AMPARs through constitutive GluR2/3 cycling. Interestingly, stimulation of GluR1-deficient hippocampal slices with theta burst frequencies induced a delayed (30–40 min) form of LTP that could represent such a process (Hoffman et al., 2002). In this scheme, GluR1 is crucial for fast learning, but with protracted conditioning, memories could still be formed, albeit with a delayed onset (H.W.K. and R.M., unpublished data).

Together, the analysis of the behavior of mice lacking subunits of AMPARs has underscored the importance of subunit-specific AMPAR-dependent synaptic plasticity in learning and memory. However, mice lacking AMPAR subunits can be problematic. Interpretation of studies may be confounded by potential compensatory mechanisms that arise when a subunit is absent throughout development, particularly given the strong homology within long-tailed and short-tailed subunits. In addition, the AMPAR subunit usage varies between different brain regions and different cell types. For instance, interneurons preferentially express long-tailed AMPARs (Geiger et al., 1995; Jonas et al., 1994; Petralia et al., 1997), and in GluR1-deficient mice the synaptic input of interneurons will be more severely affected compared with pyramidal cells. Indeed, conditional removal of GluR1 from only a subset of interneurons is sufficient to produce a deficit in spatial working memory (Fuchs et al., 2007). Also, animals lacking GluR2 (which we would presume hampers constitutive trafficking, since GluR3/3 do not traffic to synapses [Shi et al., 2001]) display reduced synaptic transmission (Mainen et al., 1998; Meng et al., 2003) and show major motor abnormalities that preclude behavioral studies (Gerlai et al., 1998; Jia et al., 1996). The generation of mice bearing more subtle mutations (e.g., small, conditional, or neuronal subtype specific deletions or mutations) in genes encoding AMPAR subunits might be preferred. However, caution is indicated, since two seemingly similar mutations of GluR1 that prevent PDZ interactions (removal of the last seven amino acids, and replacement of a single residue within that region) were shown to produce opposite effects. The first has no effect on LTP (Boehm et al., 2006a; Kim et al., 2005), while the latter blocks LTP (Boehm et al., 2006a; Chang and Rongo, 2005; Hayashi et al., 2000). It may be that a point mutation may introduce a steric hindrance and disrupt a multiprotein slot formation required for LTP, while removal of seven amino acids will not.

To study the importance of GluR1 phosphorylation in contextual learning and memory, a mutant mouse was generated that expresses GluR1 lacking PKA and CaMKII phosphorylation sites: GluR1(S831A,S845A) (Lee et al., 2003). In hippocampal slices of these mice, basal transmission is normal, NMDA-dependent LTP is either unaffected or partially reduced dependent on the stimulation protocol, while NMDAR-dependent LTD was absent (Hu et al., 2007; Lee et al., 2003). These results suggest that GluR1 phosphorylation at these sites facilitates but is not necessary to induce LTP, while NMDAR-dependent LTD requires GluR1 dephosphorylation. These phospho-mutant mice exhibited normal Morris water maze learning, but rapid acquisition of new platform location was affected: they could remember the new location shortly after learning (2–4 hr), but at later time points (8 or 24 hr after learning) retention of memory was poor (Lee et al., 2003). This learning deficit critically depended on the PKA phosphorylation site, but not on the site phosphorylated by CaMKII (Crombag et al., 2008). A similar phenotype was found in transgenic mice in which NMDAR-dependent LTD, but not LTP, was blocked by inhibition

of PP2a phosphatase activity (Nicholls et al., 2008), suggesting that this form of LTD is required to modify previously made associations. Alternatively, GluR1 c-tail phosphorylation may increase the stability of GluR1 (and associated slots) in synapses, and thereby also increase the likelihood that they are replaced by GluR2/3 AMPARs for consolidation of new memories.

The Effects of Emotions on AMPAR-Dependent Learning

The brain is equipped with the ability to modulate the acquisition of memories, presumably in order to distinguish between trivial events and important experiences. The emotional charge of an experience has long been appreciated as a mechanism to facilitate learning and memory in order to shape our behavior and optimize the chances of survival (Christianson, 1992; McGaugh, 2000; Richter-Levin and Akirav, 2003). Emotional arousal can lead to the release of endogenous stress hormones, like norepinephrin (NE), in the brain, which may prime synapses for improved plasticity (McGaugh and Roozendaal, 2002). Several molecular mechanisms by which NE can prime neurons have been described, including the activation of PKA (Pedarzani and Storm, 1993) and CaMKII (Wang et al., 2004). Both the injection of NE in mice, as well as exposure of mice to acute emotional stress (predator urine) transiently increases GluR1 phosphorylation at the PKA site and to a lesser extent the CaMKII site (Hu et al., 2007; Vanhoose and Winder, 2003). To determine the role of GluR1 phosphorylation in NE-modulated memory formation, GluR1(S831A,S845A) phospho-mutant mice and wild-type mice were subjected to a hippocampus-dependent contextual fear conditioning protocol. While both mice performed equally in basal conditions, only the wild-type mice displayed improved memory when mice were injected with NE just prior to this learning paradigm (Hu et al., 2007). In a manner that parallels the in vivo results, the threshold for LTP is lowered by NE in hippocampal slices from wild-type mice (Hu et al., 2007; Katsuki et al., 1997), but much less so in slices from GluR1 phospho-mutant mice (Hu et al., 2007). These experiments show that NE release leads to phosphorylation of GluR1 and thereby lowers its threshold for trafficking to the synapse; this appears to be an important molecular mechanism by which emotional or aroused states can facilitate memory formation.

Prolonged or elevated levels of psychological stress can also negatively affect learning and memory through the increased release of the stress-hormone glucocortisol (McGaugh and Roozendaal, 2002; Roozendaal, 2002). Rats that were trained to find a submerged platform in a water maze spatial task were unable to remember the platform location when glucocortisol release was induced by acute stress (foot shock) shortly before the testing stage (de Quervain et al., 1998). Both acute stress and the administration of glucocortisol can inhibit LTP (Shors et al., 1989; Xu et al., 1997) and facilitate LTD (Xu et al., 1997; Yang et al., 2005) in hippocampal neurons. To establish whether AMPAR trafficking is involved in the stress-induced impairment in memory retrieval, the GluR2-3Y peptide that specifically blocks activity-dependent removal of synaptic AMPARs was administered during the stress-induction phase (Fox et al., 2007; Wong et al., 2007). Blocking GluR2 removal during stress fully rescued the rat's ability to find the hidden platform in the Morris water maze test (Wong et al., 2007). These experiments indicate that acute stress can weaken memories via the removal of synaptic AMPARs. In these studies, the membrane-permeant GluR2-3Y peptide was administered systemically, so that it remains unknown which brain regions are involved in the modification of the behavior.

Stressful experiences in early life can have negative effects on brain development and subsequent adult behavior (Anisman et al., 1998; Hall, 1998). Social isolation of neonatal rats for 4 days (6 hr per day) resulted in a glucocorticoid-dependent impairment of synaptic AMPAR trafficking (as judged by electrophysiological tagging of AMPARs) and LTP in the

barrel cortex. These impairments led to a permanent disruption of the cortical whisker-barrel map and reduced performance in whisker-dependent behavior (T. Miyazaki et al., unpublished data). One may speculate that stress hormone-mediated irregularities in AMPAR plasticity underlie neurological dysfunctions following traumatic events, such as posttraumatic stress disorder, major depressive disorder, and general anxiety disorder.

AMPAR Trafficking in Amygdala-Dependent Learning and Memory

Classical conditioning is a type of associative learning in which a subject learns that one stimulus predicts another. The ability to associate a fearful or rewarding event (unconditioned stimulus) with an acoustic cue (conditioned stimulus) is thought to involve an LTP-like process occurring at the synapse between the auditory thalamus and the lateral amygdala (LA) (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997; Sigurdsson et al., 2007; Tye et al., 2008). Using knockout mice, a recent study examined the role of GluR1 and GluR3 in amygdala-dependent auditory fear conditioning (Humeau et al., 2007). GluR1- and GluR3-deficient mice only express GluR2/3 s or GluR1/2 s, respectively, in amygdala principal neurons, and the decrease in total AMPAR levels may be the cause of reduced basal transmission in amygdala neurons of both these mice (Humeau et al., 2007). In GluR1-deficient mice, no LTP was observed in transmission from thalamus to lateral amygdala, whereas LTP in GluR3-deficient mice is unaffected. In accordance, GluR1-deficient mice have complete absence of rapid fear responses during fear conditioning and have no long-term memory of conditioned fear (Humeau et al., 2007).

In contrast, GluR3-deficient mice did acquire fear associations and were able to recall these associative memories after 24 hr (Humeau et al., 2007), suggesting that the lack of replacement of GluR1/2 s by GluR2/3 s in these mice did not affect the storage of fear memories. In wild-type animals, such a receptor replacement process may however contribute to the long-term stabilization (consolidation) of newly acquired memories. For instance, memories based on synaptic strengthening through GluR1/2 incorporation may be less susceptible to degradation once they are replaced by GluR2/3 s (e.g., Myers et al., 2006).

These studies on mice with AMPAR subunit deficiency show that expression of GluR1, but not GluR3, is crucial for amygdala-dependent learning. This finding supports an earlier study in rats showing that AMPAR trafficking is required in amygdala-dependent learning in a wild-type background (Rumpel et al., 2005). The ability to form auditory fear memories was tested while GluR1-dependent synaptic plasticity in a subset of LA neurons was blocked by bilateral injection of a virus expressing the GluR1 c-tail (Rumpel et al., 2005). Remarkably, animals, in which this plasticity blocker was expressed in as few as 10%–20% of LA neurons, displayed a significant reduction in auditory fear conditioning. These experiments indicate that postsynaptic trafficking of GluR1-containing AMPARs is crucial to the formation of associative memories. Furthermore, this study suggests that while memory formation may be distributed over many neurons and synapses, there is little robustness in the system to plasticity blockade in a small fraction of the units. Of note, it appears that disrupting plasticity in a minority of elements in a circuit is more detrimental than outright removal of a large set of neurons in that circuit (Moser et al., 1995). The brain appears to be capable of making a selection from the available neurons that are most amenable to plasticity for creating a memory trace (Han et al., 2007), but if only a few of the selected neurons fail to produce GluR1-dependent synaptic strengthening, the ability to form a memory seems to be compromised. Such experiments, in which AMPAR trafficking is modified in a subset of neurons, display the power of using virally delivered blocking constructs to reveal important neural mechanisms in brain function.

To show that GluR1 is driven into amygdala synapses by fear conditioning, LA neurons of juvenile rats were infected in vivo with a virus expressing GluR1, and animals received a paired auditory stimulus and electric shock. Subsequent electrophysiological recordings from infected neurons in slices displayed increased synaptic levels of GluR1-containing AMPARs (as assessed by rectification measurements) compared with those from control animals where fear and cue stimuli were unpaired (Rumpel et al., 2005; Yeh et al., 2006). The formation of an association between a fearful stimulus and an auditory cue drove synaptic GluR1 trafficking in about one-third of LA neurons (Rumpel et al., 2005), a proportion of neurons observed to undergo modification across different experiments with fear-conditioned animals (Han et al., 2007; Repa et al., 2001). Notably, not all synapses on a plastic neuron undergo modification (Rumpel et al., 2005). Each neuron may therefore participate in the formation of large number of different memories, allowing a combinatorial storage of memories.

AMPAR Trafficking and Addiction

The mesolimbic reward system is specialized in steering reward-seeking and motivational behavior through the regulated release of dopamine. This system can be hijacked by drugs of abuse (e.g., cocaine, heroine, nicotine, amphetamine), which artificially increase the dopamine levels. Such abnormal persistent levels of dopamine can modify neurons and circuits in the reward system and cause addiction (Hyman, 2005). Addictive behavior can be modeled in rodents and is hypothesized to result from changes in synaptic circuits in several brain regions that receive input from midbrain dopamine neurons (Hyman et al., 2006; Kauer and Malenka, 2007). An accumulating number of studies suggest that changes in behavior caused by addictive drugs can be mediated by synaptic plasticity through AMPAR trafficking in the mesolimbic reward system.

The ventral tegmental area (VTA) of the midbrain contains dopaminergic neurons that mediate reward-seeking or motivational behavior. In dopaminergic VTA neurons of rats that are exposed to cocaine or other addictive drugs, LTP is facilitated (possibly through reduced GABA-R-mediated inhibition) ([Liu et al., 2005]) leading to an increased synaptic AMPAR/NMDAR ratio (Saal et al., 2003; Ungless et al., 2001), and elevated synaptic levels of rectifying AMPARs (Bellone and Luscher, 2006). Cocaine-induced synaptic potentiation and increased rectification could be reversed by treatment of the rats with a drug that activates metabotropic glutamate receptors (mGluRs) (Bellone and Luscher, 2006). The activation of mGluRs leads to a form of LTD, whose expression in the VTA requires the de novo synthesis of GluR2. This suggests that mGluR activation, in addition to synaptic weakening, also stimulates the replacement of synaptic GluR2-lacking AMPARs by those containing GluR2 (Mameli et al., 2007).

What are the behavioral consequences of this cocaine-driven AMPAR trafficking in dopaminergic VTA neurons? Increasing the expression level of GluR1 in VTA neurons by viral injection intensified the sensitivity to the drug (Carlezon et al., 1997). In apparent contradiction, in GluR1-deficient mice where cocaine-induced synaptic potentiation in VTA neurons is abolished, behavioral sensitization to cocaine was unaffected (Dong et al., 2004). To study the relation between GluR1-mediated synaptic potentiation in VTA dopaminergic neurons and addictive behavior more specifically, mouse lines were generated in which either GluR1 or GluR2 was selectively deleted from dopamine neurons of the midbrain (Engblom et al., 2008). In contrast to wild-type mice or mice lacking GluR2, mice that lacked GluR1 in dopamine neurons showed a specific deficit in the extinction of conditioned place preference, a measure for the persistence of cocaine-seeking behavior. These experiments support the notion that GluR1-dependent synaptic strengthening in VTA

neurons is not involved in the etiology of addictive behavior, but instead can be beneficial for the recovery from drug addiction.

In the above studies, animals received drugs through passive administration. However, it was recently found that while natural rewards as well as cocaine can potentiate synapses in VTA neurons, this synaptic potentiation and concurrent rise in AMPAR/NMDAR ratio persisted following drug abstinence only when cocaine is self-administered (Chen et al., 2008). Self-administration of a natural reward or passive cocaine infusion led to a reversible increase in AMPAR/NMDAR ratios (Chen et al., 2008). These experiments suggest that the synaptic AMPAR trafficking in VTA neurons is not solely the consequence of the pharmacological effects of cocaine. Other, neural circuit based mechanisms must be at play. Drug self-administration likely represents a preferred strategy to model addiction in humans.

VTA neurons provide dopaminergic input to another part of the mesolimbic reward system: the nucleus accumbens (NAc). Exposure to cocaine for multiple days leads to behavioral sensitization, which correlates with an LTD-like removal of AMPARs in NAc neurons (Thomas et al., 2001). Behavioral sensitization could be blocked by systemic or intra-NAc infusion of the membrane-permeable GluR2-3Y peptide, suggesting that this drug-induced change in behavior depends on the removal of synaptic AMPARs within NAc neurons (Brebner et al., 2005). It is still not known if LTP-like processes coexist in NAc; experiments with GluR1 c-tail could elucidate this possibility.

Withdrawal from cocaine after prolonged use leads to a gradual increase in cocaine craving (Grimm et al., 2001), which correlates with a gradual increase in GluR1 levels (but not GluR2 or GluR3) (Churchill et al., 1999) and increased rectification values in NAc neurons (Conrad et al., 2008). These changes in relative AMPAR subunit levels were also observed in a form of synaptic plasticity that is caused by a prolonged blockade of neuronal activity (Thiagarajan et al., 2005). Enhanced synaptic content of calcium-permeable GluR2-lacking AMPARs may sensitize the NAc neurons to cocaine-associative cues that promote craving and relapse. The relevance of changes in synaptic AMPAR composition to the drug-seeking behavior was underscored by demonstrating that injection of a compound that specifically blocks GluR2-lacking AMPARs into the NAc could inhibit the cue-induced cocaine-seeking (Conrad et al., 2008). In addition, cocaine-induced drug seeking could be blocked by delivery of antisense oligonucleotides to GluR1 mRNA into NAc (Ping et al., 2008). These studies suggest that synaptic plasticity in NAc neurons critically contributes to the formation of a neuronal circuit that mediates addictive behavior.

Relapse following drug addiction also involves changes in AMPAR trafficking in the medial prefrontal cortex (mPFC) (Van den Oever et al., 2008), which is also a target of VTA dopamine neurons. In rats re-exposed to cues that were previously associated with heroin self-administration, GluR2-containing AMPARs were removed from synapses in mPFC neurons. This synaptic depression could be blocked by mPFC injections with the GluR2-3Y peptide, causing attenuation in cue-induced relapse to heroin seeking (Van den Oever et al., 2008).

In summary, the studies above have made important first steps in unraveling the complex neuronal circuitry comprising multiple brain regions that is involved in controlling the different behavioral aspects of addiction. By setting forward promising approaches based on the selective targeting of drug-induced changes in synaptic AMPAR trafficking, a road is paved for further research that may lead to a better understanding of how to treat people suffering from drug addiction.

Conclusions

Studies in hippocampal slices have identified molecular mechanisms by which changes in synaptic strength can be expressed, i.e., through the synaptic trafficking of AMPARs. Based on these observations, a number of studies have now shown that similar events occur and underlie in vivo forms of plasticity. Although it is clear that different synapses throughout the brain employ various types of plasticity, the collection of studies presented in this review imply that several forms of experience-dependent behavioral modifications rely on synaptic plasticity through AMPAR trafficking.

While the in vivo studies have allowed us a first glimpse at the role AMPAR trafficking plays in synaptic plasticity during animal behavior, many questions and challenges remain. For instance, it will be important to determine if AMPAR trafficking and other forms of synaptic plasticity orchestrate the formation or rewiring of neuronal circuits. Do changes in synaptic AMPAR content only play a role in acquiring associative memories or are they also involved in maintaining them? Which molecular mechanisms control the long-term storage of memories, and do AMPARs play a part in this? Our hypothesis that replacement of GluR1 containing AMPAR by GluR2/3s might help to consolidate memories awaits confirmation in animal models.

AMPAR trafficking has been used to examine behavioral plasticity in normal animals and those that model addiction. There is growing evidence from brain slice preparations that abnormalities of AMPAR trafficking may contribute to dysfunction in neurological diseases such as Alzheimer's disease and schizophrenia (Almeida et al., 2005; Hsieh et al., 2006; Kamenetz et al., 2003; Li et al., 2007; Ting et al., 2007). Future investigations will need to address to what extent defects in AMPAR trafficking form a basis for cognitive dysfunction.

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