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GluR2 protein–protein interactions and the regulation of AMPA receptors during synaptic plasticity

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AMPA-type glutamate receptors mediate most fast excitatory synaptic transmissions in the mammalian brain. They are critically involved in the expression of long-term potentiation and long-term depression, forms of synaptic plasticity that are thought to underlie learning and memory. A number of synaptic proteins have been identified that interact with the intracellular C-termini of AMPA receptor subunits. Here, we review recent studies and present new experimental data on the roles of these interacting proteins in regulating the AMPA receptor function during basal synaptic transmission and plasticity.

Keywords: AMPA receptor; GluR2; interacting proteins; *N*-ethylmaleimide-sensitive fusion protein; protein interacting with C-kinase 1

1. PROTEINS INTERACTING WITH GluR2

AMPARs interact with a variety of synaptic proteins through the intracellular C-termini of their constituent subunits (Braithwaite *et al.* 2000; Sheng & Lee 2001). These interactions have been the subject of intense study because they are believed to have critical roles in the trafficking, targeting, anchoring and functional regulation of receptors at synapses in the mammalian brain (Braithwaite *et al.* 2000; Lüscher *et al.* 2000; Sheng & Lee 2001). Recent studies show that AMPARs are rapidly inserted into synapses during hippocampal LTP (Hayashi *et al.* 2000; Lu *et al.* 2001; Pickard *et al.* 2001) and are rapidly removed during hippocampal LTD (e.g. Carroll *et al.* 1999; Beattie *et al.* 2000). This has led to considerable interest in determining whether proteins interacting with AMPARs are involved in the expression mechanisms of these forms of synaptic plasticity.

Interactions with the GluR2 subunit are of particular interest because GluR2 (in its edited form) controls the key biophysical properties of AMPAR function: Ca^{2+} permeability, single channel conductance and rectification (e.g. Burnashev *et al.* 1992; Bowie & Mayer 1995; Kamboj *et al.* 1995). The critical importance of the appropriate physiological regulation of GluR2 has been demonstrated in mutant mice that either lack GluR2 (Jia *et al.* 1996) or lack GluR2 editing (e.g. Brusa *et al.* 1995). Furthermore, there is now accumulating evidence that during certain pathological conditions there is a decrease in the GluR2 content of AMPARs which causes increased Ca^{2+} influx through AMPARs and which has been implicated in the subsequent neurotoxicity (Weiss & Sensi 2000). Thus, proteins that specifically bind to GluR2 are candidate mechanisms for the pathophysiological regulation of AMPAR function.

To date, two distinct interaction domains have been identified for the GluR2 C-terminus (figure 1). NSF protein interacts at a site proximal to the fourth transmembrane domain ('the NSF site'; Nishimune *et al.* 1998; Osten *et al.* 1998; Song *et al.* 1998), while at the extreme C-terminus there is a PDZ motif that binds ABP (Srivastava *et al.* 1998), GRIP (Dong *et al.* 1997) and PICK1 (Dev *et al.* 1999; Xia *et al.* 1999). In addition, recent work has shown that the clathrin adaptor complex protein AP2 associates with GluR2 via interactions at the NSF site (Lee *et al.* 2002). Interacting proteins at both the NSF and PDZ sites are involved in a rapid regulation of AMPAR function during synaptic plasticity.

2. THE *N*-ETHYLMALEIMIDE-SENSITIVE FUSION PROTEIN SITE

Most extensively studied is the role of interactions at the NSF site. Blocking these interactions with a peptide, 'pep2m' (KRMKVAKNAQ), causes a rapid run-down in AMPAR-mediated EPSCs at hippocampal CA1 synapses (Nishimune *et al.* 1998; Song *et al.* 1998). Immunocytochemical analyses show that this reduction in transmission is due to a loss of surface-expressed AMPARs (Lüscher *et al.* 1999; Noel *et al.* 1999). A recent study has found that AP2 interacts with AMPARs via this site and has identified distinct roles for NSF and AP2 in the regulation of AMPARs (Lee *et al.* 2002). Collectively these studies show that AMPARs rapidly recycle between intracellular and postsynaptic membranes and, furthermore, that interactions at the NSF site are involved in this rapid regulation.

Although it is known that AMPARs rapidly recycle during basal transmission, it is not clear what process drives the rapid recycling of AMPARs. To investigate this we

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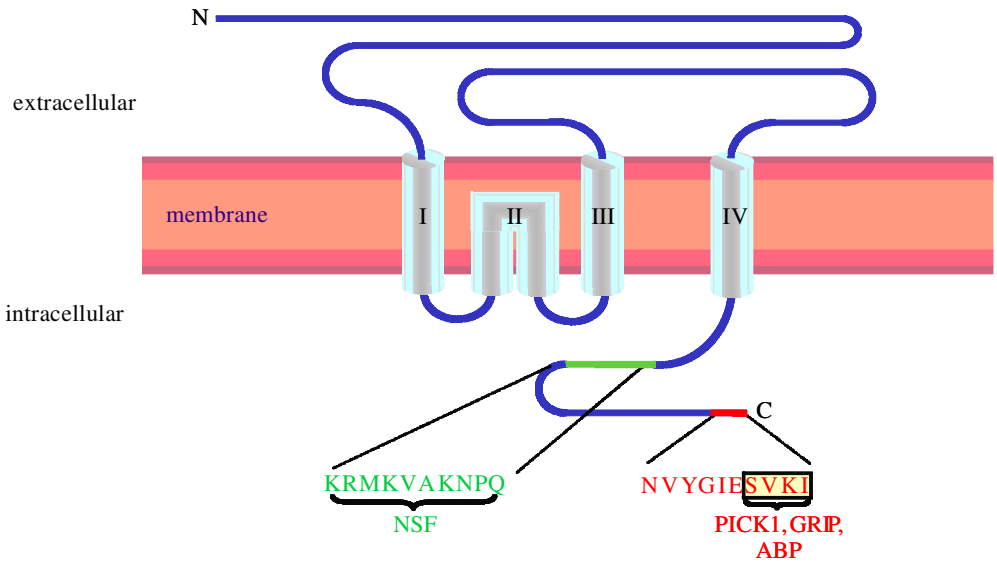

Figure 1. Protein–protein interaction sites on the C-terminus of the AMPAR subunit GluR2. The sites of interaction are shown together with the sequence of each binding domain: the NSF site (green), and the extreme C-terminal PDZ protein binding site (red, PDZ motif highlighted in yellow).

studied whether the run down of AMPAR-mediated EPSCs observed in the presence of pep2m is dependent on synaptic activity (figure 2). As previously shown, infusion of pep2m (100–1000 μM) into CA1 pyramidal neurons in hippocampal slices (Nishimune *et al.* 1998; Lüthi *et al.* 1999) caused a rapid reduction in EPSC amplitude in two independent pathways. Here, we show that the interruption of stimulation at one pathway caused a recovery of EPSC amplitude while continuous stimulation at the other pathway yielded a sustained depression of EPSC amplitude (figure 2*a*). The time-course of this recovery, as estimated by varying the period of stimulation interruption, was slower than the depression caused by pep2m. The activity-dependent depression of transmission by pep2m was consistently observed in a number of cells (figure 2*b*). However, in interleaved control experiments using the inactive peptide pep4c (KRMKVAKSAQ; Nishimune *et al.* 1998) that differs from pep2m by a single amino acid, EPSC amplitude showed no run down in transmission (EPSC amplitude after 10 min of stimulation = 106 ± 4% initial baseline, $n = 10$), and little activity-dependent recovery (EPSC amplitude following 30 min interruption of stimulation = 119 ± 6% of amplitude before stimulus interruption; $n = 10$). These data, together with similar data from another study (Lüscher *et al.* 1999), indicate that synaptic activity drives the rapid recycling of AMPARs. One possible mechanism for this is that binding of glutamate to AMPARs causes a ligand-induced internalization that drives the insertion of replacement AMPARs via a mechanism involving interactions at the NSF site on GluR2. When this mechanism is blocked this reveals a second slower component for the delivery of AMPARs to synapses which is independent of interactions at the NSF site. The mechanism for this is at present unknown; however, one possibility is that this reflects insertion of AMPARs involving a GluR1-dependent process (Passafaro *et al.* 2001).

In addition to regulating AMPAR function during basal synaptic transmission there is also good evidence that interactions at the NSF site are important for the expression of hippocampal NMDA receptor-dependent LTD. This form of LTD involves the rapid internalization of AMPARs (e.g. Carroll *et al.* 1999; Beattie *et al.* 2000). Acute blockade of interactions at the NSF site with pep2m prevents LTD (Lüscher *et al.* 1999; Lüthi *et al.* 1999; Lee *et al.* 2002). Since pep2m also causes a run down in synaptic transmission, one explanation for this is that there is a pool of mobile AMPARs regulated by interactions at the NSF site that are specifically involved in LTD. However, a recent study (Lee *et al.* 2002) has provided evidence that the NSF–GluR2 interaction is primarily involved in the regulation of AMPARs during basal synaptic transmission while the newly identified AP2 interaction at this site is important for AMPAR regulation during NMDA receptor-dependent LTD. Since AP2 is directly involved in clathrin-dependent endocytosis this provides a simple mechanism by which AMPARs are internalized during LTD and indicates that the NSF–GluR2 interaction is primarily involved in the insertion or stabilization of AMPARs.

3. THE PDZ SITE

There has also been much interest in the role of ABP/GRIP and PICK1, proteins that interact at the PDZ binding motif at the extreme C-terminus of GluR2. Interactions at this site have been shown to regulate the surface expression of the GluR2 subunit in cultured hippocampal neurons (e.g. Dong *et al.* 1997; Osten *et al.* 2000; Passafaro *et al.* 2001; Braithwaite *et al.* 2002). At hippocampal CA1 synapses, acute blockade of these interactions by infusing peptides that mimic the extreme C-terminus of GluR2 into neurons causes a PKC-dependent increase in AMPAR-mediated synaptic transmission in a third of neurons and blocks hippocampal NMDA receptor-dependent LTD in all cells (Daw *et al.* 2000; Kim *et al.* 2001). This indicates that GRIP/ABP and/or PICK1 are important for the PKC-dependent regulation of AMPARs during basal transmission and that these interactions regulate receptors during LTD. Furthermore, our data indicated a role for these interacting proteins in LTP of synapses that had pre-

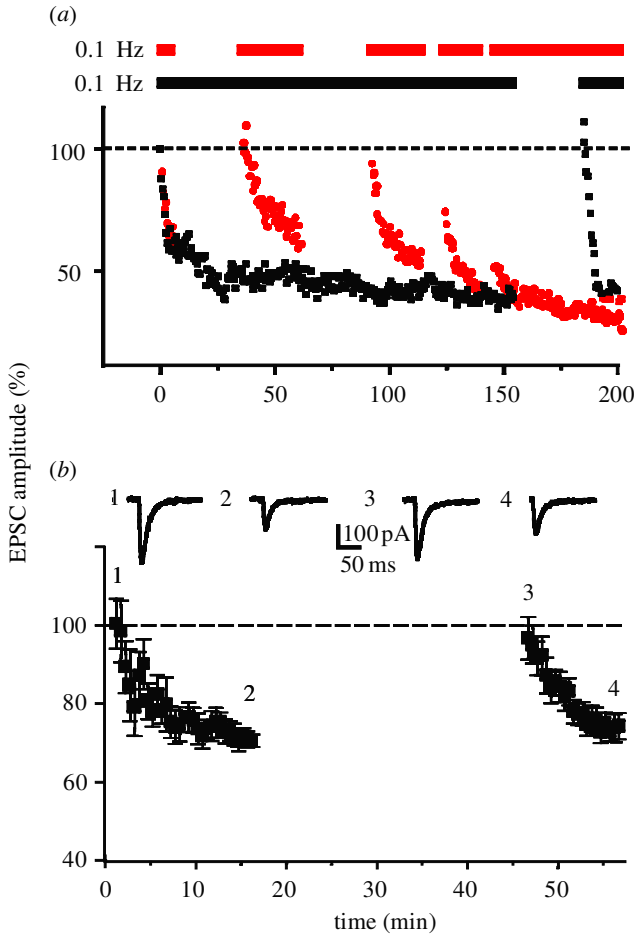

Figure 2. The run-down of AMPAR-mediated synaptic transmission in the presence of pep2m is activity dependent. (*a*) Data from a single experiment showing EPSC amplitude versus time for a whole-cell patch-clamp recording from a CA1 neuron in a hippocampal slice (see Lüthi *et al.* (1999) for methods). AMPAR-mediated EPSCs were evoked by electrical stimulation of two independent pathways onto the same cell (data for one pathway represented by red, one by black; inset top shows the patterns of activity at each pathway). Interruption of stimulation at the red pathway allowed a recovery of EPSC amplitude, while continuous stimulation of the black pathway produced a stable depression. The use of different time intervals for the interruption of stimulation of the red pathway reveals the time-course of this recovery. A subsequent pause in stimulation of the black pathway also allows recovery of EPSC amplitude at this pathway. (*b*) Pooled data ($n = 14$) from experiments with intracellular pep2m showing the consistent effect of pausing stimulation for 30 min on EPSC amplitude following the initial run-down.

viously undergone LTD, so-called 'de-depression' (Daw *et al.* 2000). Based on our findings we proposed a model in which GRIP/ABP binds AMPARs sub-synaptically and together with PICK1/PKC dynamically regulates their surface expression during LTD, and in an LTP-like mechanism during de-depression (Daw *et al.* 2000).

Recent studies have focused on determining the precise roles of each of these PDZ domain-containing proteins in the regulation of AMPAR expression at synapses. In particular there has been a lot of interest in PICK1 since it was originally identified as an interactor for PKCα (Staudinger *et al.* 1995, 1997). In addition, to PKCα and GluR2, PICK1 also interacts with a number of other proteins including mGluR7 (Boudin *et al.* 2000; Dev *et al.* 2000; El Far *et al.* 2000), non-voltage-gated Na^+ channels (Baron *et al.* 2002; Duggan *et al.* 2002; Hruska-Hageman *et al.* 2002) and ephrin receptors (Torres *et al.* 1998). Although PICK1 contains only a single PDZ domain, it can also dimerize via a coiled-coil domain (Perez *et al.* 2001) providing the possibility that PICK1 dimers could target other proteins such as PKCα to AMPARs. Indeed, evidence for such a mechanism is provided by the finding that PKC activators cause the translocation of PICK1 and PKCα to synapses which is accompanied by an increase in the phosphorylation of GluR2 (Chung *et al.* 2000; Perez *et al.* 2001). PICK1 therefore may function as a chaperone bringing activated PKC to AMPARs.

Other studies have now started to address the functional role of PICK1 in regulating AMPARs during synaptic transmission and plasticity. At cerebellar parallel fibre–Purkinje cell synapses, peptides and other reagents that interfere with the PICK1–GluR2 interaction have no effect on basal synaptic transmission, but block cerebellar LTD (Xia *et al.* 2000). This is consistent with previous studies showing that this form of LTD involves the PKC phosphorylation of GluR2 (Matsuda *et al.* 2000) and the internalization of AMPARs (Wang & Linden 2000). This leads to the hypothesis that PICK1 mediates this PKC-dependent internalization (Xia *et al.* 2000).

The functional role of PICK1 at hippocampal CA1 synapses, however, is less clear. Immunocytochemical studies show that overexpression of PICK1 in cultured hippocampal neurons causes a profound loss of surface-expressed recombinant GluR2 (Perez *et al.* 2001) or endogenous GluR2 subunits (L. Cotton, K. Dev and J. Henley, personal communication). This indicates that PICK1 can downregulate AMPAR function at hippocampal synapses. The acute role of PICK1 has also been studied using C-terminal GluR2 peptides in which serine^{880} is phosphorylated or has been substituted for a glutamate. Phosphorylation of serine^{880}, or glutamate substitution that mimics phosphorylation, prevents GRIP/ABP but not PICK1 binding (Chung *et al.* 2000), making these peptides selective inhibitors of the PICK1–GluR2 interaction (Li *et al.* 1999; Daw *et al.* 2000; Kim *et al.* 2001). One study reported that either of these PICK1 selective inhibitors caused an increase in basal synaptic transmission and partially blocked LTD at hippocampal synapses (Kim *et al.* 2001). Based on these and other immunocytochemical findings it has been proposed that PICK1 causes AMPAR internalization during hippocampal LTD (Perez *et al.* 2001; Kim *et al.* 2001), in an analogous mechanism to that proposed for cerebellar LTD (Xia *et al.* 2000). However, we have reported that a C-terminal GluR2 peptide in which serine^{880} is substituted for a glutamate ('pep2-EVKI' [YNVYGIEEVKI]), had no effect on basal synaptic transmission and did not block hippocampal LTD (Daw *et al.* 2000). Figure 3 shows data from this study re-plotted to illustrate the effects of pep2-EVKI infusion on LTD. In two pathway experiments using whole-cell patch-clamp recordings from CA1 neurons in hippocampal slices we compared the effect of the intracellular infusion of pep2-EVKI, which blocks the PICK1–GluR2 interaction, with that of an inactive control peptide pep2-SVKE (YNVYGIESVKE). In the presence of either pep2-

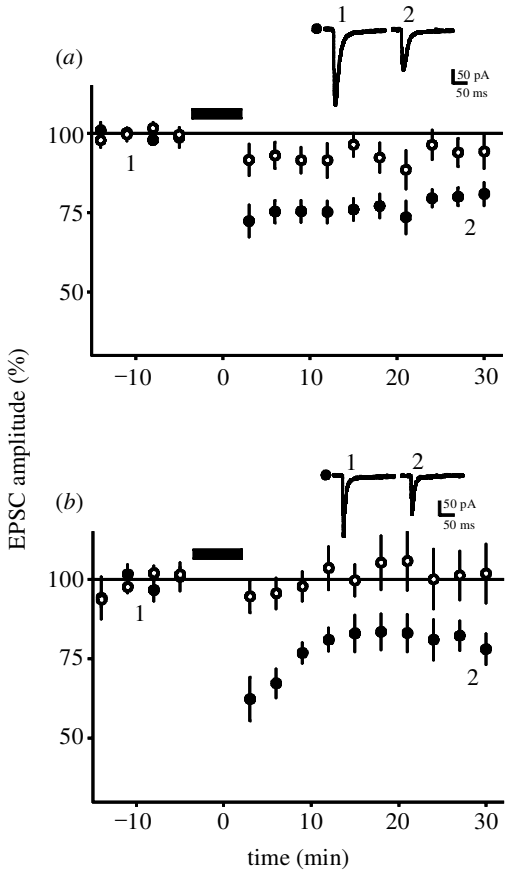

Figure 3. Pep2-EVKI, a peptide that blocks the PICK1–GluR2 interaction, does not block hippocampal LTD (data re-plotted from Daw *et al.* (2000)). (*a*) Pooled data ($n = 8$) from experiments in which 100 μM pep2-EVKI was infused into CA1 hippocampal neurons during whole-cell patch-clamp recordings. EPSC amplitude at two independent pathways was monitored and LTD induced (black bar) in one pathway (black circles) using 300 stimuli at 0.5 Hz paired with a holding potential of −40 mV (peptide was infused into neurons for at least 30 min before applying the induction protocol; see Daw *et al.* (2000) for methods). Inset shows EPSCs from the LTD pathway for an example experiment taken at the times indicated. (*b*) Pooled data ($n = 10$) for similar experiments (interleaved with experiments in (*a*)) in which the inactive control peptide pep2-SVKE was infused into the neurons.

EVKI (figure 3*a*) or pep2-SVKE (figure 3*b*) LTD could be reliably induced. These data indicate therefore that PICK1 is not involved in LTD under our experimental conditions, but rather that the GRIP/ABP interaction is important in regulating AMPARs. The reasons for these discrepancies in the acute effects of blocking PICK1–GluR2 interactions are not clear, and therefore at present the role of PICK1 in hippocampal NMDA receptor-dependent LTD remains a matter for debate. Clearly, considerable work is required to fully elucidate the role of PICK1 in hippocampal synaptic plasticity. This will require electrophysiological studies on the effects of long-term manipulations of PICK1 function on synaptic transmission and plasticity, as well as a more detailed characterization of the effects of PICK1 overexpression on AMPAR subunit surface expression. In addition, the role of PKC in hippocampal LTD and in the regulation of AMPAR surface expression also needs to be clarified. Finally, PICK1 is a promiscuous interactor and the consequences of this multi-functionality need to be addressed when considering the mechanism(s) of AMPAR regulation by PICK1.

The study of the roles of protein–protein interaction involving AMPAR subunits in the dynamic regulation of fast excitatory synaptic transmission is an exciting and emerging area. Although ever-increasing numbers of interacting proteins are being identified, elucidating their individual roles in the processes underlying the expression of LTP and LTD is proving to be a challenging task. Much further work is required to achieve a detailed understanding of the precise functions of these interactions.

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GLOSSARY

ABP: AMPAR-binding protein
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
AMPAR: AMPA receptor
AP2: adaptor protein 2
CA1: Cornu Ammonis 1
EPSC: excitatory postsynaptic current
GluR2: glutamate receptor subunit 2
GRIP: glutamate receptor interacting protein
LTD: long-term depression
LTP: long-term potentiation
NMDA: *N*-methyl-D-aspartate
NSF: *N*-ethylmaleimide-sensitive fusion protein
PDZ: postsynaptic density-95/discs large/zona occludens-1
PICK1: protein interacting with C-kinase 1
PKC: protein kinase C