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Regulation of AMPA Receptors by Phosphorylation*

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The AMPA receptors for glutamate are oligomeric structures that mediate fast excitatory responses in the central nervous system. Phosphorylation of AMPA receptors is an important mechanism for short-term modulation of their function, and is thought to play an important role in synaptic plasticity in different brain regions. Recent studies have shown that phosphorylation of AMPA receptors by cAMP-dependent protein kinase (PKA) and Ca^{2+} - and calmodulin-dependent protein kinase II (CaMKII) potentiates their activity, but phosphorylation of the receptor subunits may also affect their interaction with intracellular proteins, and their expression at the plasma membrane. Phosphorylation of AMPA receptor subunits has also been investigated in relation to processes of synaptic plasticity. This review focuses on recent advances in understanding the molecular mechanisms of regulation of AMPA receptors, and their implications in synaptic plasticity.

KEY WORDS: AMPA receptors; protein kinase C; protein kinase A; Ca^{2+}/calmodulin-dependent protein kinase II; synaptic plasticity; protein phosphatases.

INTRODUCTION

Glutamate mediates most excitatory neurotransmission in the central nervous system, through its action on two distinct categories of glutamate receptors: metabotropic glutamate receptors, that are coupled to G proteins and generate intracellular second messengers, and ionotropic glutamate receptors, which have receptor-associated cation channels, that open upon receptor activation by agonists. Ionotropic glutamate receptors exhibit great diversity, and are further classified in three different classes, according to the receptor affinity for different agonists and to the receptor electrophysiological characteristics: α-amino-3-hydro-5-methyl-4-isoxazole propionate (AMPA) receptors, kainate (KA) receptors and *N*-methyl-D-aspartate (NMDA) receptors. AMPA and kainate receptors activate and desensitize rapidly in response to glutamate, thus mediating fast depolarization of the postsynaptic membrane. On the other hand, NMDA receptors show voltage-dependent magnesium blockade. Since AMPA and NMDA receptors are frequently colocalized in the postsynaptic neuron, the rapid and brief activation of AMPA receptors facilitates the unblock of NMDA receptors, and their slow activation. In the early nineties, the glutamate receptor subunits were cloned (reviewed in reference 1); different subfamilies of sequence-related receptor subunits were found to comprise the previously identified pharmacological classes of glutamate receptors. This article focuses on AMPA receptors; four homologous subunits (GluR1–4), which have been cloned and characterised, assemble in various combinations to form AMPA receptors.

GluR subunits have a large extracellular N-terminal domain, and an intracellular C-terminal domain (Fig. 1). In between, there are three transmembrane domains (M1, M3 and M4), and the ion pore domain, a re-entrant hairpin loop that originates at the intracellular side of the membrane and forms the channel domain (2). Receptor subunits oligomerize into tetrameric or pentameric

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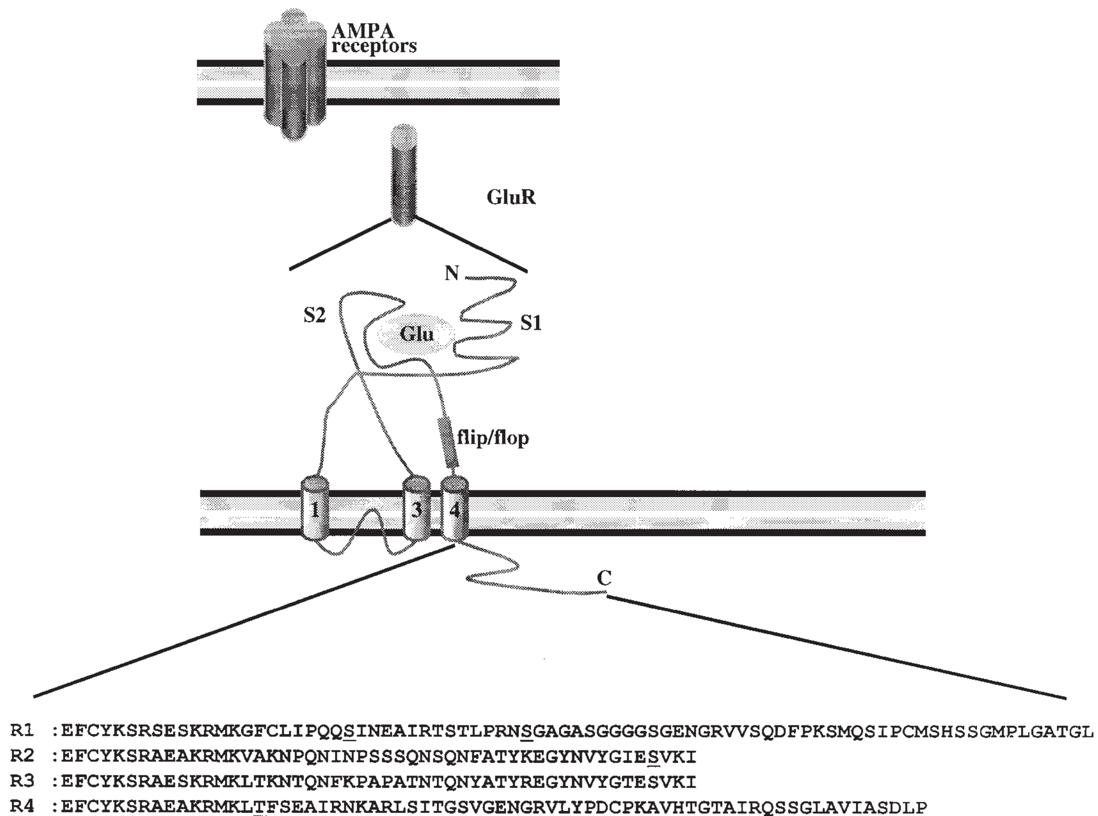

Fig. 1. AMPA receptor topology model and comparison of the C-terminal region of GluR subunits. Identified phosphorylation sites are underlined.

assemblies, with the transmembrane segments of each subunit forming a barrel-like structure that separates the ion-conducting pore from the surrounding lipids (3). The agonist binding site of ionotropic glutamate receptors is formed by two non-contiguous extracellular segments, S1 and S2, localized in the N-terminal domain and in the extracellular segment between transmembrane domains M3 and M4, respectively (4). S1 and S2 domains have homology to the bacterial amino acid binding proteins, and form a bilobed structure at whose interface the receptor agonists bind. The structure of the ligand binding core of the ionotropic glutamate receptors has been confirmed by mutagenesis studies (5) and by the crystal structure of the receptor agonist binding site complexed to kainate (6).

In addition to the existence of several genes for glutamate receptors, the receptors' diversity is increased by post-transcriptional events, such as alternative splicing and RNA editing. In what concerns AMPA receptors, alternative splicing generates the flip and flop versions of AMPA receptor subunits, with different desensitization characteristics and different expression patterns (7,8), and the GluR2c and GluR4c are forms of the AMPA receptors alternatively spliced at the C-terminal. RNA editing occurs for GluR2–4, at the ion pore domain of the receptor (GluR2) or at a site adjacent to the flip/flop domain (GluR3/4). GluR2 RNA editing at the Q/R site on the ion pore domain of the receptor is extensive in the adult brain (>90% of GluR2 molecules are edited), and has drastic functional effects, since the edited R form of GluR2 is calcium-impermeable (9).

Taking advantage of the wide variety of glutamate receptor subunits, the activity of glutamate receptors may be regulated by the subunit composition of the receptors. In fact, in different brain regions receptors are composed of different subunit combinations and have distinct funcional characteristics (10). On a shorter time scale, the activity of glutamate receptors has been found to be regulated by receptor phosphorylation, and a possible role for AMPA receptor phosphorylation in synaptic plasticity has been proposed (reviewed in references 11–14). Much attention has been given to the identification of phosphorylation sites on glutamate receptor

subunits and to the characterization of the functional consequences of glutamate receptor phosphorylation. It is known from various studies, which combine site-directed mutagenesis approaches to biochemical analysis, that AMPA receptors are phosphorylated at serine and threonine residues, and functional studies have supported a role for the phosphorylation of some of these sites in the regulation of receptor activity.

Regulation of AMPA Receptor Activity by Phosphorylation

Accumulated evidence shows that the activity of AMPA receptors is regulated by protein kinases and phosphatases. Early studies performed in cultured horizontal retinal cells showed that dopamine and cAMP enhance ionic conductances gated by kainate (15). In cultured hippocampal neurons, a similar potentiation by protein kinase A (PKA) of the current induced by activation of the non-NMDA glutamate receptors was shown (16,17). Single-channel analysis revealed that PKA increases the opening frequency and the mean open time of the non-NMDA type glutamate receptor channels in hippocampal neurons (17). Interestingly, both studies that used hippocampal neurons (16,17) found that a competitive inhibitor of PKA can depress the kainate currents, suggesting that AMPA receptors are basally regulated by endogenously active PKA in hippocampal neurons. Moreover, the PKA-mediated regulation of AMPA/kainate currents is dependent on anchoring of PKA to post-synaptic densities by A-kinase anchoring proteins (AKAPs), since disruption of the interaction between PKA and AKAPs prevents the modulatory effect of PKA in hippocampal neurons (18). In an heterologous expression system, cAMP potentiated the current and also the flux of calcium through activated GluR1/GluR3 receptor channels (19), and the phosphorylation of GluR1 on serine residues increased upon cell treatment with the adenylyl cyclase activator forskolin, both in cortical neurons and in transfected cells (20). Taken together, these results indicate that PKA regulates AMPA receptor responsiveness. Subsequent work found evidence of direct phosphorylation of AMPA receptors subunits by PKA, both in vitro and in vivo (see next section).

The role of protein kinase C (PKC) in the regulation of AMPA receptors was first investigated in cultured hippocampal neurons, perfused with the catalytic fragment of PKC (21). The responses to kainate and AMPA were potentiated by PKC, and inhibited by perfusion of a PKC inhibitory peptide (21). In cultured amacrine cells, calcium influx through AMPA receptors, evoked by kainate, was potentiated by PKC activation, and inhibited by a selective inhibitor of PKC (22). Both these studies suggest that basal phosphorylation by PKC may regulate AMPA receptor activity, and that PKC activation potentiates AMPA receptors. However, in oocytes expressing several different combinations of AMPA receptor subunits, activation of PKC inhibited kainate-induced currents (23). The phosphorylation of GluR1 was increased by phorbol ester treatment of cultured cortical neurons (20) or of cultured hippocampal neurons (24), and several PKC phosphorylation sites have been identified in AMPA receptor subunits (see next section).

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is a major constituent of postynaptic densities at glutamatergic synapses, and it becomes constitutively active upon autophosphorylation, after binding to Ca^{2+}/calmodulin. AMPA receptors are a relevant substrate of CaMKII in the postsynaptic density (25), in cultured hippocampal neurons (24), and in transfected HEK 293 cells (26). CaMKII enhances kainate-induced ion currents conducted by native AMPA receptors in cultured hippocampal neurons (25) and in isolated rat spinal dorsal horn neurons (27), and by recombinant GluR1 expressed in heterologous systems (28). Moreover, GluR1 is phosphorylated by CaMKII during long-term potentiation (LTP) in the hippocampus (29,30), and postsynaptic expression of a constitutively active form of CaMKII in hippocampal slices enhanced synaptic transmission through AMPA receptors, and prevented further LTP induction (31,32), suggesting that CaMKII and LTP enhance synaptic transmission by the same mechanism.

Neurons have high levels not only of protein kinases by also of protein phosphatases. Various studies showed that the activity of glutamate receptors is regulated by phosphatase activity. Okadaic acid (16,21), microcystin-LR (25) and caliculyn A (33), which inhibit protein phosphatases 1 and 2A, enhance kainate currents in cultured hippocampal neurons (16,21,25) and in hippocampal slices (33). In cultured retina cells, okadaic acid was also shown to enhance the kainate-evoked $[Ca^{2+}]_i$ increase, and the immunosuppressant FK 506, which inhibits calcineurin, was found to potentiate by ~30% the kainate-induced Ca^{2+} influx (22). The AMPA receptor activity in the striatum is modulated by protein phosphatase 1 in a DARPP-32 regulated manner. This protein is present in large amounts in the striatum, and its inhibitory effect on PP1 activity depends on D1 receptor activation and subsequent phosphorylation by PKA (34).

Phosphorylation Sites on AMPA Receptors

The identification of the phosphorylation sites on AMPA receptor subunits was initially controversial, in part due to previous receptor topology models, based on the acetylcholine receptor topology, that proposed the C-terminal of the receptors to be extracellular, and considered the loop between M3 and M4 to be the major intracellular segment of the receptor subunits. Based on this model, several phosphorylation sites on the M3–M4 loop were reported (e.g. 28). However, immunucytochemistry experiments and studies of receptor glycosylation lead to the proposal of a new transmembrane topology model for glutamate receptors, with an intracellular C-terminal, and an extracellular loop between M3 and M4 (Fig. 1; reviewed in reference 2). Analysis of the phosphorylation of chi-meric GluR1 demonstrated that GluR1 phosphorylation sites all reside in the intracellular C-terminal (35). Site-directed mutagenesis and phosphopeptide analysis lead to the identification of the two major phosphorylation sites on GluR1: Ser 845, that is phos-phorylated by PKA, and Ser 831 that is phosphorylated by PKC (35). Moreover, phosphorylation of Ser 845 by PKA underlies the potentiatory effect of PKA on GluR1 currents in transfected HEK 293 cells, since the effect is not observed for a Ser 845 mutant (35). Recent work demonstrated that PKA phosphorylation of Ser 845 in GluR1 regulates the open channel probability of AMPA receptors (36).

Other studies found that CaMKII also phosphorylates Ser 831 in GluR1 (37,26). When cells expressing GluR1 were perfused with CaMKII, the Ser 831 to alanine mutant failed to show potentiation of the GluR1 current (26), indicating that the potentiatory effect of CaMKII on GluR1 currents is mediated by phosphorylation of Ser 831 by CaMKII. CaMKII phosphorylation of Ser 831 in GluR1 increases the single-channel conductance of the receptor (38), and possibly increases AMPA receptor conductance during LTP (39). It is interesting to note that GluR1 phosphorylation on Ser 831 and on Ser 845 seems to potentiate AMPA receptors through distinct molecular mechanisms, since phosphorylation of Ser 831 by CaMKII changes channel conductance (38), whereas phosphorylation of Ser 845 by PKA alters the open channel probability of AMPA receptors (36). The identification of the phosphorylation sites on GluR1, followed by demonstration of the functional relevance of phosphorylation of those sites, and of the molecular mechanisms through which phosphorylation leads to receptor potentiation, provided conclusive proof that the effects of protein kinases on receptor activity are due to changes on receptor phosphorylation.

Generation of phospho-specific antibodies against the GluR1 phosphorylation sites (37), which recognize GluR1 only when Ser 845 or Ser 831 are specificaly phosphoryated, proved useful to study the phosphorylation of GluR1 in vivo. Using the phosphorylation site-specific antibodies, it was found that, in hippocampal slices, phorbol esters and forskolin increase the phosphorylation of Ser 831 and of Ser 845, respectively (37). Moreover, the phosphospecific antibodies were used to show that induction of LTD in the CA1 region of hippocampus causes a persistent decrease in phosphorylation of Ser 845 but not of Ser 831 in GluR1 (40). A recent study shows that LTP and LTD are associated with phosphorylation and dephosphorylation, respectively, of distinct GluR1 phosphorylation sites, and that the modulated site depends on the history of the synapse (30). The modulation of AMPA receptors by dopamine, in the striatum, has also been studied making use of GluR1 phosphospecific antibodies. D1 dopamine receptor activation in the striatum enhances AMPA receptor-mediated currents, and promotes phosphorylation of Ser 845 on GluR1 (41,42).

The C-terminus of GluR1 shows very low homology to the other AMPA receptor subnits (Fig. 1), but other AMPA receptor subunits are substrates for protein kinases. GluR4, the most rapidly desensitizing AMPA receptor subunit, is phosphorylated on Ser 842, within its C-terminal domain, in vitro and in vivo (43). Ser 842 is the major phosphorylation site on GluR4; it is phosphorylated by PKA, PKC and CaMKII in vitro, and it is phosphorylated by PKA in transfected HEK 293 cells. Thr 830 is also a potential PKC phosphorylation site on GluR4 (43). GluR2 was found to be phosphorylated on Ser 880 by PKC, in vitro and in transfected cells (44). GluR2 interacts with glutamate receptor interacting protein (GRIP, 45), a PDZ domain-containing protein, that plays a role in clustering of AMPA receptors at excitatory synapses (45). The C-terminal region of GluR2 is responsible for the association with GRIP, and Ser 880 is critical for the GluR2-GRIP interaction (45). Recently, it has been found that phosphorylation of GluR2 on Ser 880 reduces the affinity of GluR2 for GRIP, in vitro and in transfected cells (44), suggesting that GluR2 phosphorylation may affect GluR2 distribution and/or clustering in the postsynaptic membrane. The disruption of the interaction between GluR2 and GRIP by GluR2 phosphorylation apparently leads to disruption of AMPA re-

ceptor GluR2 clusters following LTD induction in cerebellar Purkinje neurons (46).

Interactions between AMPA Receptors and Intracellular Proteins

The cytoplasmatic C-terminal of AMPA receptor subunits has a role in synaptic clustering, and in the formation of supramolecular signaling complexes via inteactions with other postsynaptic proteins. In the last few years, a number of proteins which bind directly to AMPA receptors have been identified (reviewed in reference 47). PDZ-domain containing proteins were found to interact with the xS/TxV motif at the extreme C-terminal of short forms of AMPA receptors subunits (Fig. 1). Such proteins, like GRIP (45) and ABP (48), may function as scaffolds, since they have multiple domains that could bind structural proteins, and thus provide a mechanism for clustering receptors in the plasma membrane (49), as well as recruit functional mediators (50) and serve a role in receptor regulation. Interestingly, the interaction of GluR2 with GRIP is negatively regulated by GluR2 phosphorylation (44).

Protein Interacting with C-Kinase (PICK1) is another protein that has been shown to bind to the C-terminal of GluR2/3/4c subunits of AMPA receptors through its PDZ domain (51). PICK1 binds PKCα, also through the PDZ domain, suggesting that GluR2/3/4c and PKCα may compete for interaction with PICK1. Additionally, PICK1 can dimerise, and PICK1 dimers could aggregate AMPA receptors. Indeed, it has been shown that PICK1 induces clustering of AMPA receptors in heterologous expression systems (51). On the other hand, PICK1 dimers could target PKCα to AMPA receptors, thus providing a mechanism for selectively phosphorylating AMPA receptors.

Early studies found that the potentiation of AMPA/kainate receptors on hippocampal neurons requires anchoring of protein kinase A by A-kinase-anchoring proteins (AKAPs, 18). AKAP79 and yotiao are AKAPs that localize to the neuronal postsynaptic membrane (for a review see reference 52), and simultaneously bind PKA and phosphatases. Yotiao has been shown to associate with NMDA receptors, and to bring together PKA and protein phosphatase 1 (53). Targeting of the enzymes near their substrate is proposed to enhance phosphorylation-dependent receptor modulation. Likewise, AKAP79 binds PKA, PKC and cacineurin (54). It is proposed that it may associate with AMPA receptors and play a role in the regulation of their function (52), but AKAP79 association with AMPA receptor subunits remains to be demonstrated.

Yet another possibility is that AMPA receptors may associate directly with kinases. It has been shown that CaMKII interacts with NMDA receptors directly (55,56), and that activation of CaMKII by stimulation of NMDA receptors increases this interaction (56). AMPA receptors have been reported to interact with a protein tyrosine kinase called Lyn (57), and to initiate a mitogen-activated protein kinase (MAPK) signaling cascade that results in increased transcription of brain-derived neurotrophic factor (BDNF). On the other hand, BDNF was shown to inhibit AMPA-mediated currents in developing sensory relay neurons (58). Although the molecular mechanims responsible for this effect were not investigated, it is unlikely that tyrosine phosphorylation of the receptor is involved (59).

Other non-PDZ domain-containing proteins interact with AMPA receptors. Several groups have reported that the N-ethylmaleimide sensitive fusion protein (NSF), an ATPase that plays a role in membrane fusion processes, interacts with GluR2 and GluR3 AMPA receptor subunits, and that the interaction may regulate the membrane insertion/stabilisation of AMPA receptors containing GluR2/3 subunits (reviewed in reference 47). AMPA receptor-interacting proteins seem to be implicated in processes that go from regulation of post-translational modification of the receptors, to regulation of receptor targeting, trafficking and surface expression.

Phosphorylation of AMPA Receptors by PKA and CaM-Kinase II in the Hippocampus: Role in Synaptic Plasticity

Modulation of postsynaptic AMPA receptors in the hippocampus by phosphorylation is thought to play a role in the expression of synaptic plasticity, and may be involved in the storage of information in the brain (e.g. references 29,30,40,60,61). Strong, brief (≤2 sec), high frequency (≥50Hz) synaptic stimulation induces LTP in the hippocampus, whereas weak, prolonged (≥30 sec), low frequency (<10Hz) stimulation leads to LTD. These two forms of synaptic plasticity depend upon a $[Ca^{2+}]_i$ rise in the post-synaptic cell, which shows distinct features depending on the pattern of pre-synaptic stimulation (62). Differences in the $[Ca^{2+}]_i$ response are thought to activate distinct biochemical cascades.

Particular emphasis has been given to the phosphorylation of AMPA receptors in relation to synaptic plasticity in the hippocampus, particularly in the CA1

subregion, because they mediate rapid excitatory transmission in the CNS. In this regard studies have concentrated in the phosphorylation of the GluR1 subunit since it is one of the most abundantly expressed subunits in the hippocampus and, in combination with GluR2, is thought to constitute the majority of AMPA receptor complexes present in this region (63). High frequency pre-synaptic stimulation increases the post-synaptic $[Ca^{2+}]_i$, which is thought to activate Ca^{2+}/calmodulin-dependent protein kinase II (62,64). The active, autophosphorylated, form of CaMKII can translocate to the post-synaptic density (65), where it can phosphorylate various proteins, including AMPA receptors (26). Indeed, high frequency pre-synaptic stimulation of hippocampal Schaffer collaterals increased the phosphorylation of GluR1 subunits on Ser 831, the CaMKII phosphorylation site (30). The other phosphorylation site on GluR1, Ser 845, is thought to be phosphorylated by PKA under basal conditions and, therefore, may not participate in LTP (18,61,66,67).

Whereas LTP results from strong, brief NMDA receptor activation, LTD arises from weak or prolonged NMDA receptor activation (68,69). In contrast to what has been found for LTP, LTD induction requires activation of a protein phosphatase cascade (70,71). In LTD, evoked both by chemical means and by low frequency stimulation, there is a reduction in the phosphorylation of the GluR1 subunit on the PKA phosphorylation site (Ser 845) (30,40,61). Dephosphorylation of the PKA site on GluR1 is a plausible mechanism for LTD expression, since it has been shown that changes in the phosphorylation of Ser 845 affect significantly glutamate evoked currents mediated by AMPA receptors (35). Interestingly, LTD induction in potentiated synapses dephosphorylates the CaMKII site of GluR1, probably by activating PP1/2A, but does not affect significantly Ser 845 phosphorylation. Also, synaptic de-depression in the CA1 region of the hippocampus, by high frequency stimulation, phosphorylates the PKA site on the GluR1 without affecting phosphorylation of Ser 831. Therefore, the phosphorylation or dephosphorylation of GluR1, induced by high and low frequency stimulation, respectively, occurs on distinct sites, depending on the history of the synapse (30). Phosphorylation of the GluR1 receptor subunits on Ser 831 and Ser 845 affects the electrophysiological properties of the receptors and, therefore, may contribute to the change in synaptic efficacy. However, phosphorylation of these sites may also regulate synaptic strength by affecting trafficking and synaptic targeting of AMPA receptors.

Modulation of AMPA Receptors by Protein Kinase C in Long-Term Depression in the Cerebellum

Long-term depression (LTD) of synaptic transmission at the parallel fiber-Purkinje cell synapses has been proposed to underlie several forms of motor learning in the cerebellum. Purkinje neurons, which convey the output signals originated in the cerebellar cortex, receive excitatory inputs from climbing fibers (CFs), originated in the inferior olive, and from parallel fibers (PFs), which are the axons of cerebellar granule neurons. Each Purkinje neuron establishes a strong synaptic contact with a single climbing fiber but receives inputs from many parallel fibers.

Cerebellar LTD was first reported in studies performed in the intact cerebellum (72), but the molecular mechanisms involved in this form of synaptic plasticity have been studied mostly in slice and dissociated cell culture preparations (for reviews see references 73 and 74). Activation, at low frequency, of PF and CF inputs to a Purkinje neuron, for several minutes, decreases PF-Purkinje neuron synaptic drive but does not affect the efficacy of the CF-Purkinje neuron synapse. The activation of non-NMDA receptors, most likely AMPA receptors (75–77), by glutamate released at both synapses depolarizes the plasma membrane, thereby activating voltage gated Ca^{2+} channels (VGCC) which allow the entry of Ca^{2+} into the cell (e.g. references 78 and 79). Furthermore, mGluR1 receptors, coupled to the activation of phospholipase C, are also present at the synapses between PF and Purkinje cells (80) (Fig. 2). Activation of these receptors leads to the production of diacylglycerol (DAG), which activates protein kinase C, and inositol 1,4,5-trisphosphate, which mobilizes Ca^{2+} from intracellular stores, further contributing to a local rise in the cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$). Protein kinase C, present in large amounts in Purkinje cells (81), is activated by DAG and by Ca^{2+} entry through VGCC, and this may increase the phosphorylation of AMPA receptors, either directly or indirectly. Studies performed in dissociated cultured Purkinje cells showed that the $[Ca^{2+}]_i$ rise also contributed to LTD by activating phospholipase A_2 (73). This enzyme gives rise to arachidonic acid which co-activates some PKC isoforms (82) and, therefore, may contribute to maximal PKC activity at the synapse. However, the role of phospholipase A_2 in LTD in the cerebellum remains to be investigated in the intact tissue. Also, although Ca^{2+} release from internal stores may also contribute to LTD, this is still not clearly established (74).

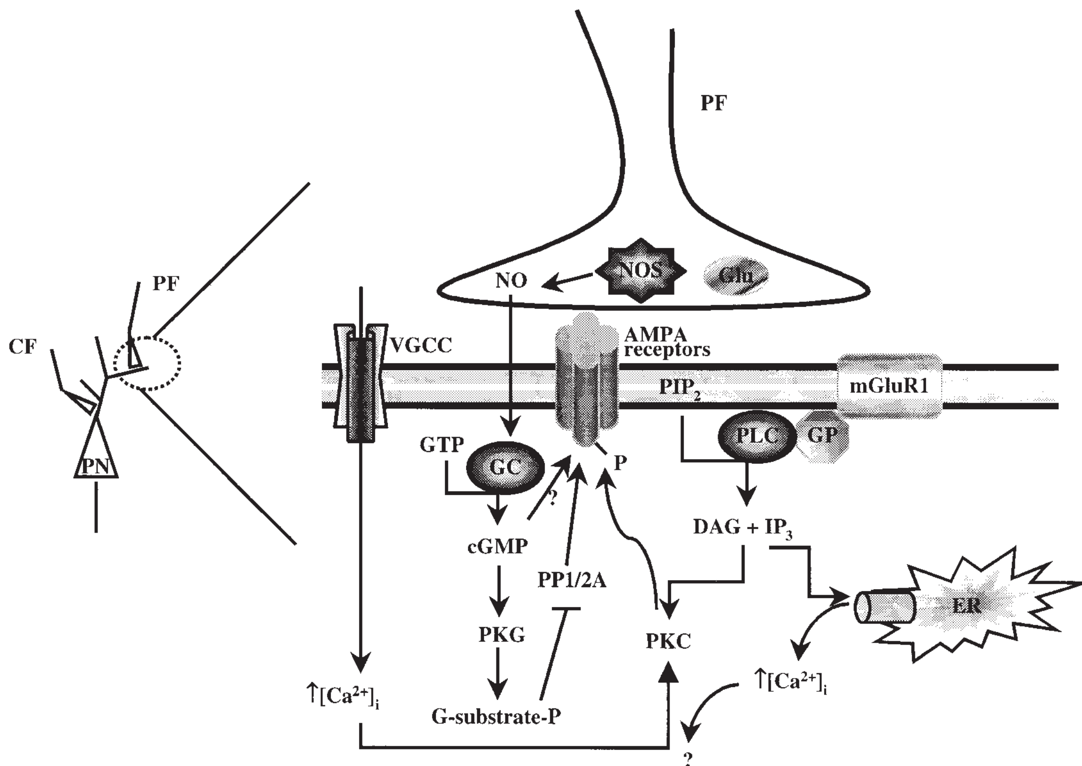

Fig. 2. Molecular mechanisms involved in the regulation of AMPA receptor activity during LTD in the cerebellum. LTD is generated at the parallel fiber (PF)-Purkinje cell (PC) synapse, by synchronous activation of the PF and climbing fiber (CF) inputs to a Purkinje neuron. The following abbreviations are used: DAG, diacylglycerol; ER, endoplasmic reticulum; GC, guanylate cyclase; Glu, glutamate; GP, G protein; IP_3, inositol 1,4,5 trisphosphate; NO, nitric oxide; NOS, nitric oxide synthase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PKG, cGMP-activated protein kinase; PLC, phospholipase C; PP1/2A, protein phosphatase 1/2A; VGCC, voltage gated Ca^{2+} channels.

Phosphorylation of AMPA receptors by PKC on Purkinje neurons may decrease the response of these cells to glutamate released by cerebellar granule neurons at the PF-Purkinje cells synapses. Accordingly, phorbol esters were found to decrease the response to glutamate or AMPA in cerebellar Purkinje neurons (83,84). Furthermore, phorbol esters, together with AMPA, evoke LTD in cultured mouse Purkinje neurons (85).

Several studies using cerebellar slices suggested that the release of nitric oxide (NO) and the consequent production of cGMP by guanylate cyclase are important for the induction of LTD in the cerebellum (see reference 74 for a review). Since the neuronal isoform of NO synthase (nNOS) has not been identified in Purkinje cells (86), NO may be produced by nNOS expressed by neighboring PFs (87), in response to a rise of the $[Ca^{2+}]_i$. NO is thought to activate guanylate cyclase in Purkinje cells (88,89), giving rise to cGMP and therefore stimulating cGMP-dependent protein kinase (PKG) (84,90). One of the PKG substrates is substrate G, which is expressed in the cerebellum and inhibits protein phosphatase 1/2A (PP1/2A) activity in its phosphorylated form (91,92). Therefore, the NO pathway may contribute to cerebellar LTD by inhibiting the dephosphorylation of AMPA receptors. Alternatively, cGMP may have a direct inhibitory effect on AMPA receptor activity, as recently reported in cultured hippocampal neurons (93).

PKC phosphorylation of GluR2, an AMPA receptor subunit largely expressed at the PF-Purkinje neuron synapses (e.g. reference 77), was recently shown to decrease the affinity of the receptors to the anchoring protein GRIP in cultured cerebellar Purkinje neurons. Under stimulating conditions that induce cerebellar LTD, GluR2 phosphorylation on Ser 880 caused a disruption of receptor clusters followed by their internalization (44,46). These results suggest that AMPA receptor phsophorylation followed by endocytosis underlie the induction of LTD at PF-Purkinje neuron synapses.

Phosphorylation of AMPA Receptors by PKA in the Neostriatum

The activity of the GABAergic medium-sized neurons (MSNs), the most common cell type in the neostriatum, is controlled by two major inputs: a glutamatergic input from the cortex and a dopaminergic input from the substantia nigra. Glutamatergic and dopaminergic nerve endings terminate on the same spines of MSNs (94,95), and anatomical studies have localized both ionotropic glutamate receptors and dopamine receptors to dendrites of these cells (96–98). Ionotropic glutamate receptors mediate fast excitatory synaptic transmission from cortical afferents to MSNs (99–101) whereas the activation of G-protein coupled receptors by dopamine released from substantia nigral afferents modulates intracellular cAMP levels (102).

Studies performed in dissociated neostriatal neurons and in striatal slices showed that dopamine tightly controls the activity of AMPA receptors by activating D1 receptors, coupled to the stimulation of adenylyl cyclase (34,41,42,101) (Fig. 3). Under resting conditions the receptor channel is kept in the dephosphorylated ('low activity') state by protein phosphatase-1 (PP-1), which is constitutively active. PP-1 is anchored near the AMPA receptors by spinophilin, a PP-1 binding protein that is highly enriched in dendritic spines (103). Activation of dopamine D1 receptors converts AMPA channels to the phosphorylated ('high activity') state by a dual mechanism, involving a direct phosphorylation of the receptor subunits by protein kinase A and the inhibition of PP-1 activity by the dopamine and cAMP-regulated phosphoprotein DARPP-32 (34,41,42). In its phosphorylated form DARPP-32 inhibits the catalytic activity of PP-1, thereby contributing to the maintenance of AMPA receptor activity (104). Activation of D1 receptors in cultured striatal neurons and neostratal slices increases the phosphorylation of GluR1 AMPA receptor subunits at the PKA phosphorylation site (Ser 845), as determined by Western blot (41,42). In vivo studies showed that phosphorylation of GluR1 at Ser 845 is also strongly increased in the neostriatum in response to the psychostimulants cocaine and methamphetamine, suggesting that AMPA receptor currents may be rapidly enhanced in response to dopamine release by psychostimulant drugs.

It has been suggested that activation of D1 receptors in the neostriatum stimulates the direct pathway, a neuronal circuit where the internal segment of the globus pallidus receives input from the caudate and putamen and sends a projection directly to the thalamus.

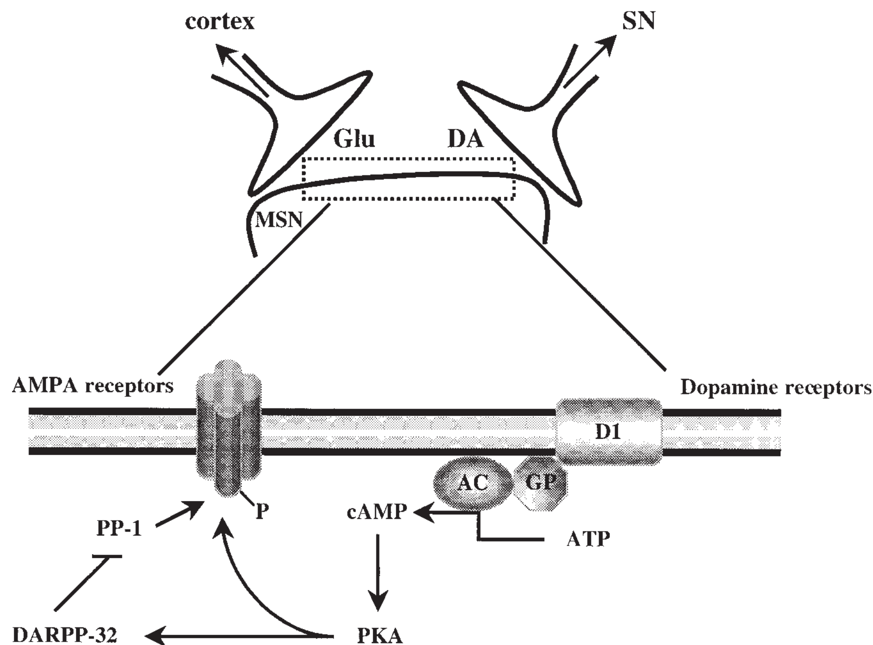

Fig. 3. Regulation of AMPA receptors by type 1 dopamine receptors (D1) in the striatum. The activity of the medium-sized neurons (MSNs) is controlled by a glutamatergic input from the cortex and a dopaminergic input from the substantia nigra (SN). The following abbreviations are used: AC, adenylate cyclase; DARPP-32, dopamine- and cAMP-regulated phosphoprotein; GP, G-protein; PKA, cAMP-dependent protein kinase; PP-1, protein phosphatase-1.

Activation of this pathway disinhibits thalamic neurons thereby facilitating movement (105,106). The functional interaction between glutamate and dopa-mine systems in the neostriatum has an important clinical significance, since imbalances in dopaminergic and glutamatergic synaptic transmission have been implicated in several neurological disorders, including Parkinson's disease, Huntington's disease and shizophrenia (105,107,108).

NOTE ADDED IN PROOF

It was recently demonstrated that AKAP79 recruits PKA to AMPA receptor complexes through direct interaction between AKAP79 and SAP97, a PDZ domain-containing protein that binds AMPA receptors (Colledge et al. 2000. Neuron 27:107–19).

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