Recent evidence has emphasized the importance of p38 mitogen-activated protein kinase (MAPK) in the induction of metabotropic glutamate receptor (mGluR)-dependent long term depression (LTD) at hippocampal CA3-CA1 synapses. However, the cascade responsible of mGluR to activate p38 MAPK and the signaling pathway immediately downstream from it to induce synaptic depression is poorly understood. Here, we show that transient activation of group I mGluR with the selective agonist (S)-3,5-dihydroxyphenylglycine (DHPG) activates p38 MAPK through G protein βγ-subunits, small GTPase Rap1, and MAPK kinase 3/6 (MKK3/6), thus resulting in mGluR-dependent LTD. Furthermore, our data clearly show that an accelerating AMPA receptor endocytosis by stimulating the formation of guanyl nucleotide dissociation inhibitor-Rab5 complex is a potential downstream processing of p38 MAPK activation to mediate DHPG-LTD. These results suggest an important role for Rap1-MKK3/6-p38 MAPK pathway in the induction of mGluR-dependent LTD by directly coupling to receptor trafficking machineries to facilitate the loss of synaptic AMPA receptors.

Long term depression (LTD)1 is a persistent activity-dependent decrease of synaptic efficacy that together with the converse process, long term potentiation, has been considered to be crucial for information storage in the brain (1, 2). In the hippocampus, LTD is divided into three categories: homosynaptic, heterosynaptic, and associative LTD (3). The best-characterized form of homosynaptic LTD is induced in the CA1 region of the hippocampus by prolonged low frequency synaptic stimulation via a NMDA receptor-dependent rise in postsynaptic [Ca2+]i, and the activation of serine/threonine protein phosphatases (4). Recent work has shown that mechanistically distinct type of LTD can be induced in the CA1 region by other types of synaptic stimulation or brief pharmacological treatments. For example, a prolonged period of paired-pulse stimulation or a direct application of the selective group I mGluR agonists, such as DHPG, can induce a robust mGluR-dependent form of LTD that is independent of NMDA receptor activation (5). In contrast to the mechanisms of NMDA receptor-dependent LTD, which are fairly well established, the mechanisms of induction and the site of expression of mGluR-dependent LTD are still a matter of some considerable debate. Current studies have reported that the induction of mGluR-dependent LTD does not require extra-cellular Ca2+ (6), Ca2+ release from intracellular stores (7), activation of Ca2+/calmodulin-dependent protein kinase II (8), protein kinase A or protein kinase C (7, 9), or serine/threonine protein phosphatases (9). However, this form of LTD requires activation of Gq-type G proteins (10), a local translation of dendritic mRNA (5, 11), a long-lasting loss of postsynaptic AMPA receptors (12, 13), and activation of protein tyrosine phosphatases (14). In addition, more recent studies suggest that p38 MAPK signaling also serves as a signal mediator in the induction of mGluR-dependent LTD (15, 16). However, it is still unclear how mGluR activation leads to activate p38 MAPK and the signaling downstream of p38 MAPK to mediate mGluR-dependent LTD induction.

In an attempt to address these questions, in this study we have investigated the mechanisms involved in the induction of DHPG-LTD in hippocampal CA1 neurons. We confirm the previously described the role for p38 MAPK in the induction of DHPG-LTD. We show that by releasing Gβγ-subunits, the mGluR5 may activate Rap1 to mediate DHPG-induced p38 MAPK activation and an accelerating loss of surface AMPA receptor by stimulating the formation of GDI-Rab5 complex is a potential downstream processing of p38 MAPK activation to mediate DHPG-LTD.

**EXPERIMENTAL PROCEDURES**

Electrophysiology—Hippocampal slices (400 μm) were prepared from 21–28-day-old young male Sprague-Dawley rats using standard procedures (17, 18), allowed to recover for a minimum of 1 h, and then transferred to a submersion-type recording chamber continually perfused with 30–32 °C oxygenated ACSF solution (in mM: 117 NaCl, 4.7 KCl, 1.2 MgCl2·6H2O, 25 NaHCO3, 1.2 NaH2PO4, 11 glucose). Area CA3 was surgically removed after sectioning. Extracellular and whole cell recordings were carried out with Axoclamp-2B or Axopatch 200B amplifier (Axon Instruments, Union City, CA). The responses were low pass-filtered at 2 kHz, digitally sampled at 5–10 kHz, and analyzed using pCLAMP software (Version 8.0, Axon Instruments). In whole cell recordings, cells were held at −70 mV while series and input resistances were monitored throughout each experiment. The evoked postsynaptic responses were induced in CA1 stratum radiatum by stim-

---

* This work was supported by research grants from the Academic Excellence Program of the Ministry of Education (89-B-FA08-1-4) and National Health Research Institute (NHRI-EX92-9215NI) (Taipei, Taiwan). The costs of publication of this article were defrayed in part by the National Health Research Institute (NHRI-EX92-9215NI) (Taipei, Taiwan). The authors declare no conflict of interest.

‡ To whom correspondence should be addressed: Dept. of Pharmacology, College of Medicine, National Cheng Kung University, Tainan City 701, Taiwan

§ Affiliations: National Health Research Institute (NHRI-EX92-9215NI) (Taipei, Taiwan)

1 The abbreviations used are: LTD, long term depression; MAPK, mitogen-activated protein kinase; mGluR, metabotropic glutamate receptor; DHPG, (S)-3,5-dihydroxyphenylglycine; Gβγ, G protein βγ-subunit; MKK3/6, MAPK kinase 3/6; GDI, guanyl nucleotide dissociation inhibitor; FTI, farnesyltransferase inhibitor; GDP, GTPase inhibitor; CHAPS, 3-[[(3-cholamidopropyl)dimethylam-ino]propane]sulfonic acid; GDP, guanosine 5’-O-(2-thiodiphosphate); AMPA, amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid; MPEP, 2-methyl-6-(phenylethynyl)pyridine; GGTI, geranylgeranyl-transferase inhibitor; FTI, farnesyltransferase inhibitor.

This paper is available online at http://www.jbc.org
ulation (0.02-ms duration) of Schaffer collateral/commissural afferents at 0.033 Hz with a bipolar stainless steel-stimulating electrode. Field excitatory postsynaptic potentials (fEPSPs) were recorded with a glass pipette filled with 1 M NaCl (2.3-megohm resistance), and the initial slope was measured. Whole cell recording of EPCs were made from CA1 pyramidal cells, which were identified under a differential interference contrast microscope. Patch pipettes (3–5 meghoms) filled with the following internal solution were used (in mM): 110 potassium gluconate, 30 KCl, 10 HEPES, 1 MglCl, 0.5 EGTA, 4 NaATP, 0.3 Na3GTP, 7 phosphocreatine, 5 lidocaine N-ethyl bromide quaternary (QX-314), pH 7.3, 290–295 mosmol). The amplitude of evoked EPCs was measured. To ensure stability of the whole cell recordings, electrical stimulation was initiated before the cell was patched. We waited for ~5 min in the cell-attached configuration before break-in to wash off any residual internal solution spilled from the approaching pipette.

Application of Drugs and Proteins—When experiments were performed in the presence of inhibitors, slices were preincubated in the inhibitors for a minimum of 1 h before and then transferred to the recording chamber where they were continually perfused with a solution containing the inhibitors. Drugs were diluted from stock solutions just before application. Stock solutions of PD98059, SP600125, GGTI-298, and FTI-277 were dissolved in Me2SO and stored at ~20 °C. The final Me2SO concentration in the superfusate was <0.1%. At this concentration, Me2SO had no effect on fEPSPs (17, 18). LY341495 and LY367385 were prepared by first dissolving them into an equimolar solution of NaOH as a concentrated stock solution and then diluting to their final concentration in ACSF. Purified bovine brain GDI inhibitors for a minimum of 1 h before and then transferred to the internal solution spilled from the approaching pipette.

Biochemical Measurements of Surface-expressed AMPA Receptors—Bi-otinylation experiments were performed as described previously (18). The microdissected subregions were then incubated with ACSF containing 1 mg/ml Subtil-NHS-IC-LIOT (Pierce) for 30 min on ice. Unreacted biotinyl-tylation reagent was washed once with ice-cold ACSF and quenched by two successive 20-min washes in ACSF containing 100 mM glycine followed by two washes in ice-cold Tri-HCI buffer solution. The microdissected subregions were lysed and ground with a pellet pestle. Samples were sonicated and spun down at 14,000 × g at 4 °C for 15 min. 50-μl lysates of the resulting supernatant were removed to measure total GluR1 and GluR5. 90-μl lysates of the supernatant were incubated with an antibody (1:250, Synaptic Systems). Immunoblots were analyzed by quantitative immunoblotting with polyclonal anti-GluR1 C terminus (1:1000, Upstate Biotechnology).

RESULTS

DHPG-induced an mGluR5-dependent LTD—Using field potential recordings, we first tested for the existence of an mGluR-dependent form of LTD in the CA1 region of hippocampal slices. As reported previously (19, 20), application of DHPG (50 μM) for 5 min resulted in a substantial LTD of fEPSPs (DHPG-LTD). The synaptic responses were depressed to 63.5 ± 5.1% (n = 8; p < 0.05) measured at 40 min after washout of DHPG (Fig. 1A). This LTD was completely blocked by bath application of the broad-spectrum mGluR antagonist LY341495 (10 μM; 9.4 ± 5.3%; n = 5; p < 0.05) (Fig. 1B), suggesting that it is mediated by mGluR. To further investigate which subtype of mGluR mediates this LTD, we next examined the effect of specific antagonists for mGluR1 and mGluR5 on this LTD induction. Application of the highly selective mGluR5 antagonist MPEP (10 μM) (22) completely blocked the DHPG-LTD (96.3 ± 3.8%; n = 5; p < 0.05, Fig. 1C), whereas the highly selective mGluR1 antagonist LY367385 (100 μM) (23) had no effect (58.9 ± 4.5%; n = 5; p > 0.05, Fig. 1D). These results, which are similar to previous findings in juvenile rat hippocampal slices (19, 20), confirm that activation of mGluR5 is required for the induction of DHPG-LTD. p38 MAPK Inhibitor blocks DHPG-LTD—To assess the involvement of p38 MAPK signaling pathway, DHPG-LTD was attempted in the presence of selective p38 MAPK inhibitor, SB203580 (1 μM) (24). As expected, SB203580 fully prevented the induction of DHPG-LTD (104.3 ± 5.3%, n = 8; p < 0.05, Fig. 2A). Similar results were obtained using an antibody that selectively recognizes phosphorylated, activated p38 MAPK (25). As shown in Fig. 2B, phospho-p38 MAPK was readily detected in untreated control slices, and levels were increased to 138.7 ± 5.7% (n = 6) of control in DHPG-treated slices. MPEP (10 μM) but not LY367385 (100 μM) completely blocked the increase in p38 MAPK phosphorylation induced by DHPG (Fig. 2B). Neither MPEP nor LY367385 alone had obvious effect on basal levels of phospho-p38 MAPK. In contrast, inhibition of p42/44 MAPK signaling pathway with PD98059 (50 μM) (26) or c-Jun N-terminal kinase inhibitor SP600125 (20 μM) (27) failed to affect the induction of DHPG-LTD (PD98059, 62.4 ± 5.6%; n = 6; SP600125, 57.3 ± 6.7%; n = 6; p > 0.05) (Fig. 2, C and D). These results strongly support the view that the p38 MAPK is an obligatory component of the biochemical bases that serves the induction of mGluR-dependent LTD (15, 16).

p38 MAPK Activation by mGluR5 Is Mediated by Gβγ—Mice
lacking Gq exhibit impaired DHPG-LTD in the CA1 region (10).

To further determine whether postsynaptic G protein activation mediated DHPG-LTD, we performed whole cell recordings from CA1 pyramidal cells using a potassium gluconate-based pipette solution where GTP was replaced with 1 mM GDP to inhibit the activation of postsynaptic G proteins. Whereas DHPG induced a robust LTD of EPSCs in control recordings with GTP-containing solution (62.3 ± 4.9%, n = 7), only a small initial depression and no persistent depression were observed in recordings where GDP was used in the pipette solution (106.9 ± 5.4%, n = 7; p < 0.05) (Fig. 3, A and B). As previously reported, after rupture with pipette solution containing GDP, EPSCs gradually grew during the first 5–15 min and were stable for the remainder of the experiments. The initial “run-up” effects of GDP might in part be attributed to the effects on GDPβS on AMPA receptor endocytosis (28, 29). Although these results indicate that DHPG-LTD is dependent on the activation of postsynaptic Gq, no role has been found for the common Gq-stimulated signals (i.e. phospholipase C and protein kinase C) following mGluR5 activation in this form of LTD (30). Consequently, another mechanism unrelated to Gq must underlie the mGluR-dependent LTD. Because GDPβS released by G protein-coupled receptor activation has important role in the G protein-mediated signaling and there is growing evidence demonstrating that several G protein-coupled receptors induce p38 MAPK activation through Gq (31–33), we next investigated the role of Gq in the induction of DHPG-LTD. To address it, we loaded Gq (100 nM) directly into the cells. After establishing the whole cell configurations, EPSCs began to decrease and this "run-down" stabilized after ~20 min at ~40% reduction (Fig. 3C1). This manipulation completely blocked the induction of DHPG-LTD (102.9 ± 4.6%, n = 6; p < 0.05), whereas interleaved cells recorded from a similar period of time with the heat-inactivated Gq exhibited stable LTD (63.5 ±
Rap1 Mediates DHPG-induced p38 MAPK Activation—Having confirmed the role of Gβγ and p38 MAPK in DHPG-LTD, we next identified the signaling components involved in Gβγ-mediated p38 MAPK activation. Among many potential intracellular factors involved in p38 MAPK activation, we investigated the potential role of two small GTPases, Rap1 and Ras. In several experimental models, the family of small GTPase plays a key role in the activation of MAPK. Recently, it has been reported that Rap1, a Ras-like small GTPase, contributes to the induction of activity-induced LTD via phosphorylation of p38 MAPK, whereas Ras mediates the signaling activated by Ca2+/calmodulin-dependent protein kinase II that is responsible for long term potentiation (34, 35). To determine whether Rap1 plays any role in mediating DHPG-LTD, we examined the induction of DHPG-LTD in the presence of membrane-permeable geranylgeranyltransferase inhibitor, GGTTI-298, which blocks Rap1 activation (IC50 = 3 μM) by preventing its recruitment to plasma membrane (36). As shown in Fig. 4A, GGTTI-298 (10 μM) abolished the ability of DHPG to induce LTD (97.8 ± 3.6%, n = 6; p < 0.05). In contrast, pretreatment of the slices with Ras farnesyltransferase inhibitor FTI-277 (10 μM) (IC50 = 0.1 μM) (37) failed to affect the induction of DHPG-LTD (66.3 ± 4.5%, n = 6, p > 0.05, Fig. 4B). Similarly, GGTTI-298 (10 μM) largely blocked the increase in p38 MAPK phosphorylation following the DHPG application (Fig. 4C). In contrast, FTI-277 (10 μM) had no effect on the DHPG-induced increase in p38 MAPK phosphorylation. To directly demonstrate that Rap1 participates in the signaling pathway responsible for DHPG-induced activation of p38 MAPK, we investigated the activation of Rap1 by means of a pull-down assay using the glutathione S-transferase-RalRBD fusion protein. Application of DHPG (50 μM) for 5 min induced a large increase in the amount of Rap1-GTP (62.8 ± 5.7%, n = 5, p < 0.05, Fig. 4D). This DHPG-induced Rap1 activation was blocked by the MPEP (10 μM) but not by the LY367385 (100 μM). In contrast to Rap1, we found that the level of GTP-Ras was not changed following DHPG application (105.3 ± 4.9%, n = 4; p > 0.05) (Fig. 4E).

These results indicate that p38 MAPK acts as a downstream target of Rap1 to induce DHPG-LTD.

DHPG-induced Activation of p38 MAPK by Gβγ and Rap1 Occurs at the level of MKK3/6—In vivo, p38 MAPK can be activated by upstream MKK3 and MKK6 (38). Thus, any changes in MKK3/6 phosphorylation should result in changes in p38 MAPK activity. As shown in Fig. 4F, phospho-MKK3/6 was readily detected in untreated control slices and levels were increased to 136.3 ± 6.5% (n = 6) of control following DHPG application. This DHPG-induced increase in phospho-MKK3/6 was fully prevented by pretreatment of the slices with GGTI-298 (10 μM) but not by FTI-277 (10 μM). Thus, MKK3/6 seems to be an immediate upstream signaling component of p38 MAPK to underlie DHPG-LTD.

Involvement of p38 MAPK-stimulated AMPA Receptor Endocytotic Trafficking in the DHPG-LTD—What is the mechanism that couples an activation of p38 MAPK to synaptic depression? It has recently been demonstrated that DHPG-LTD appears to require loss of AMPA receptors from the postsynaptic membrane surface (12, 13) and p38 MAPK has been identified to have the ability to accelerate the endocytosis trafficking by stimulating the activity of GDI in extracting Rab5 from endosomal membranes and forming a GDI-Rab5 complex (39). This complex is required for ligand sequestration into clathrin-coated pits. The potential involvement of p38 MAPK in DHPG-induced loss of surface AMPA receptors was first investigated. In agreement with previous reports (12, 13), application of DHPG (50 μM) caused a significant reduction in surface expression of AMPA receptors (GluR1: 65.6 ± 6.9% of control slices, n = 5; p < 0.05) (Fig. 5A). This DHPG-induced loss of surface AMPA receptors was completely blocked by SB203580 (1 μM) and GGTI-298 (10 μM).

We finally assessed whether p38 MAPK contributes to regulation of endocytotic trafficking of surface AMPA receptors by stimulating the formation of GDI-Rab5 complex. Following application of DHPG, tissue lysates were immunoprecipitated with anti-Rab5 antibody and immunoblotted with an antibody specific for GDI to measure GDI association with Rab5. Fig. 5B demonstrates that DHPG induced an increase in GDI associa-
Inhibition of Rap1 signaling blocks DHPG-induced LTD and p38 MAPK activation. A, summary of six experiments showing preincubation with the Rap1 geranylgeranyltransferase inhibitor GGTTI-298 (10 μM) blocked the induction of DHPG-LTD. B, summary of six experiments showing that the induction of DHPG-LTD was not affected by a Ras farnesyltransferase inhibitor FTI-277 (10 μM). C, representative immunoblot showing that DHPG-induced increase in p38 MAPK phosphorylation was significantly blocked by GGTT-298 but not by FTI-277. Group data showing the normalization of phospho-p38 MAPK to the nonphosphorylated form was determined in each group of five experiments. D, representative immunoblot showing DHPG induced a robust increase in Rap1-GTP levels, which was prevented by pretreatment with MPEP (10 μM) but not by LY367385 (100 μM) (upper panel). Preincubation of these agents did not modify total Rap1 (lower panel). Results from five separate experiments are summarized. E, representative immunoblot showing the effect of DHPG (50 μM) on Ras-GTP level. Quantification of Ras-GTP immunoreactivity over control base-line levels revealed that DHPG has no effect on Ras activation. F, representative immunoblot showing DHPG-induced increase in phospho-MKK3/6 levels was significantly reduced in GGTTI-298-treated slices but not by FTI-277-treated ones. Group data showing the normalization of phospho-MKK3/6 to the nonphosphorylated form was determined in each group of six experiments.

**DISCUSSION**

Our results provide a plausible mechanism of the induction of DHPG-LTD in hippocampal CA1 neurons (Fig. 6). Activation of mGluR5 by DHPG releases Gβγ-dimers, which in turn promotes the exchange of GDP with GTP of Rap1 and activates a sequential kinase cascades that includes MKK3/6 and p38 MAPK. Activated p38 MAPK enhances the activity of GDI in extracting Rab5 from endosomal membranes leading to a reduced expression of postsynaptic AMPA receptors and eventually resulting in the reduction in synaptic strength observed with LTD.

The finding that DHPG-LTD was completely eliminated in mice lacking Gαq strongly suggests that Gαq plays a crucial role in the induction of DHPG-LTD (10). However, recent work has shown that neither the activation of protein kinase C nor inositol triphosphate-mediated Ca2+ release from intracellular stores, a core signaling pathway to the Gαq, activation, is required for DHPG-LTD. This implies that other signaling process downstream of Gαq activation may underlie such LTD. Because in many cases it is the Gβγ-dimers rather than Gα that transmit the signals through G protein-coupled receptors (40), it is likely that the signal from the mGluR to activate p38 MAPK is mediated by Gβγ. This prediction is supported by our finding that intracellular loading of Gβγ mimicked and occluded the DHPG effect. Similarly, in human embryonic kidney 293 cells Gαq-coupled m1 muscarinic receptor was found to stimulate p38 MAPK by Gβγ (31). What is the mechanism that couples Gβγ to the activation of p38 MAPK? Because the structure of p38 MAPK does not contain the specific Gβγ-binding domain (41), it is unlikely that Gβγ activates p38 MAPK through a direct Gβγ/p38 MAPK association. In this case, additional downstream effectors of Gβγ are also required. Gβγ can activate MAPK via Ras in other cell types. For example, it has been shown that Gβγ could recruit phosphatidylinositol 3-kinase to the plasma membrane, enhancing the activity of Src-like kinase, which in turn leads to the activation of the Shc-Grb2-Sos-Ras pathway, resulting in increased MAPK activity (42, 43). In this study, our results suggest that the activation of Rap1 and MKK3/6 is essential for DHPG-induced p38 MAPK activation. Active Rap enhances the levels of active p38 MAPK, consistent with recent findings indicating p38 MAPK as a downstream target of Rap (43) and able to control some forms of LTD (15). Although how Gβγ increases in Rap1 activity remains to be elucidated, these results imply a model where Rap1 can specifically serve as the downstream effector of Gβγ to stimulate MKK3/6 and p38 MAPK activation.

It has recently reported that the expression of DHPG-LTD is associated with a loss of AMPA receptors from postsynaptic membrane surface (12) and that disruption of endocytic processes by injecting D15, which inhibits the association of dynamin with...
amphiphysin, prevents the induction of DHPG-LTD (13). We have confirmed these results and find that DHPG-induced internalization of AMPA receptors requires the activation of Rap1 and p38 MAPK. Indeed, evidence that active Rap1 enhances levels of active p38 MAPK, which in turn leads to the removal of synaptic AMPA receptors, resulting in occluding the induction of LTD, has been provided more recently in a study on cultured hippocampal slices (34). To date, the locus of expression of DHPG-LTD is highly controversial with evidence for both presynaptic (6, 29, 44, 49) and postsynaptic changes (12, 13). Here, we provide evidence that interventions that attenuated the DHPG-induced loss of surface AMPA receptors during the expression of DHPG-LTD are probably one of the steps mediating the signal initiated by activated p38 MAPK and eventually leading to the loss of surface AMPA receptors. The mechanism by which p38 MAPK regulates GDI in the cytosolic cycle of Rab5 and regulates AMPA receptor trafficking remains to be determined. At excitatory synapses, the loss of AMPA receptors can occur either by diminished recycling or by enhanced endocytosis (47). According to this view, it will be important for future studies to identify which of these mechanisms underlie the long-lasting reduction of surface AMPA receptors during the expression of DHPG-LTD.

FIG. 5. DHPG-LTD is accompanied by a loss of surface GluR1 and an increase in the associated of GDI with Rab5. A, representative immunoblot showing the total (T) and biotinylated surface (S) GluR1 from control (Con), DHPG (50 μM), SB203580 (1 μM) with DHPG, and GGTI-298 (10 μM) with DHPG, and GGTI-298-298 (10 μM) with DHPG treatment slices. Group data (n = 5) showing that 30 min following DHPG surface GluR1 levels were significantly reduced, which can be prevented by SB203580 or GGTI-298 pretreatment. B, representative immunoblot showing that DHPG treatment increased the amount of GDI associated with Rab5. Pretreatment with SB203580 (1 μM) significantly reduced the formation of the GDI-Rab5 complex. Densitometric quantitation from five separate experiments is summarized in the histogram plot.

In conclusion, we have provided further evidence for a functional contribution of p38 MAPK in the induction of mGluR-dependent LTD. The p38 MAPK cascade is a major signaling pathway activated by Rap1 and also has been demonstrated to be an important mediator of AMPA receptor trafficking during synaptic plasticity. It remains to be determined whether such p38 MAPK signaling pathway is also responsible for the induction of other forms of LTD.

REFERENCES
1. Siegelbaum, S. A., and Kandel, E. R. (1991) Curr. Opin. Neurobiol. 1, 113–120
2. Katz, L. C., and Shatz, C. J. (1996) Science 274, 1133–1138
3. Linden, D. J., and Conner, J. A. (1995) Annu. Rev. Neurosci. 18, 319–357
4. Bear, M. F., and Abraham, W. C. (1996) Annu. Rev. Neurosci. 19, 437–462
5. Kemp, N., and Bashir, Z. I. (1999) Neuropharmacology 38, 495–504
6. Fitzjohn, S. M., Palmer, M. J., May, J. E., Nesson, A., Morris, S. A., and Collingridge, G. L. (2001) J. Physiol. (Lond.) 537, 421–430
p38 MAPK Mediates DHPG-LTD

12292

10. Klein, S., Luscher, C., Xia, H., Beattie, E. C., van Zastrow, M., Malenka, R. C., and Nicoll, R. A. (1999) Neuron 24, 649–658
29. Watabe, A. M., Carlisle, H. J., and O’Dell, T. J. (2002) J. Neurophysiol. 87, 1395–1403
30. Bashir, Z. I. (2003) Neurosci. Res. 45, 363–367
31. Yamashita, J., Nagao, M., Kizaki, Y., and Itoh, H. (1997) J. Biol. Chem. 272, 2771–2777
32. Seller, L. A., Alderton, F., Carruthers, A. M., Schindler, M., and Humphrey, P. P. (2000) Mol. Cell. Biol. 20, 3974–3985
33. See, M., Lee, Y. I., Cho, C. H., Bae, C. D., Kim, I. H., and Juhn, Y. S. (2002) J. Biol. Chem. 277, 24197–24203
34. Zhu, J. J., Qin, Y., Zhao, M., van Anstel, L., and Maliniw, R. (2002) Cell 110, 443–455
35. Morozov, A., Muzzio, I. A., Bourchouladze, R., Van-Sriend, N., Lapidus, K., Yin, D., Winder, D. G., Adams, J. P., Sweatt, J. D., and Kandel, E. R. (2003) Neuron 39, 309–325
36. Coxon, F. P., Helfrich, M. H., Larjiani, B., Myzyk, M., Dunford, J. E., Marshall, D., McKinnon, A. D., Nesbit, S. A., Herton, M. A., Seabur, M. C., Ebertis, F. H., and Rogers, M. J. (2001) J. Biol. Chem. 276, 48213–48222
37. Lerner, E. C., Qian, Y., Blaskovich, M. A., Fossam, R. D., Vogt, A., Sun, J., Cox, A. D., Der, C. J., Hamilton, A. D., and Sebti, S. M. (1995) J. Biol. Chem. 270, 26882–26886
38. Yamashita, J., Tsujimoto, G., Kizaki, Y., and Itoh, H. (2001) J. Biol. Chem. 276, 23362–23372
39. Cavalli, V., Vilhosio, F., Corti, M., Marcote, M. J., Tamura, K., Karin, M., Arkin, S., and Gruenberg, J. (2001) Mol. Cell 7, 421–432
40. Schwindinger, W. F., and Robishaw, J. D. (2001) Oncogene 20, 1653–1660
41. Martin-Blanco, E. (2000) BioEssays 22, 327–345
42. Lopez-Irasaca, M., Crespo, P., Pellici, P. G., Gatkine, J. S., and Watiker, R. (1997) Science 275, 394–397
43. Sawada, Y., Nakamura, K., Dui, K., Takeda, K., Tobiume, S., Saitoh, M., Morita, K., Komura, I., De Vos, K., Szeht, M., and Ichiho, H. (2001) J. Cell Sci. 114, 1221–1227
44. Faas, G. C., Adwanikar, H., Gerieu, R. W. IV, and Saggou, P. (2002) J. Neurosci. 22, 6885–6890
45. Rammes, G., Palmer, M., Eder, M., Dott, H. U., Ziegglansberger, W., and Collingridge, G. L. (2000) J. Physiol. (Lond.) 546, 455–460
46. Maclin, W. H., Newell, J., Morrice, N. Osborne, A., West, M., and Smythe, E. (1998) Eur. J. Cell Biol. 78, 34–45
47. Carroll, R. C., Beattie, E. C., von Zastrow, M., and Malenka, R. C. (2001) Nat. Rev. Neurosci. 2, 315–324
48. Huber, K. M., Roder, J., and Bear, M. F. (2001) J. Neurophysiol. 86, 321–325
49. Steward, O., and Schuman, E. M. (2001) Annu. Rev. Neurosci. 24, 299–325
50. Steward, O., and Schuman, E. M. (2003) Neuron 40, 347–359