Glutamate receptors modulate multiple signaling pathways, several of which involve mitogen-activated protein (MAP) kinases, with subsequent physiological or pathological consequences. Here we report that stimulation of the N-methyl-D-aspartate (NMDA) receptor, using platelet-activating factor (PAF) as a messenger, activates MAP kinases, including c-Jun NH2-terminal kinase, p38, and extracellular signal-regulated kinase, in primary cultures of hippocampal neurons. Activation of the metabolotropic glutamate receptor (mGluR) blocks this NMDA-signaling through PAF and MAP kinases, and the resultant cell death. Recombinant PAF-acetylhydrolase degrades PAF generated by NMDA-receptor activation; the hetroazepine BNS0730 (an intracellular PAF receptor antagonist) also inhibits both NMDA-stimulated MAP kinases and neuronal cell death. The finding that the NMDA receptor-PAF-MAP kinase signaling pathway is blocked by mGluR activation indicates that mGluR blocks the extracellular signal-regulated kinase (ERK), p38, and c-Jun NH2-terminal kinase (JNK) in the excitotoxic death of hippocampal neurons in vivo but not treated with Ara-C. Repeated exchanges of culture media containing Ara-C. After 4 days in vitro, cultures were treated with 10 μM Ara-C. After 4 days in vitro, Ara-C was removed and cells moved to a solution of 0.1% papain in L-15 + bovine serum albumin for 20 min (under oxygen) and then triturated with a Pasteur pipette. Cells were plated at 500,000 cells/ml in minimal essential medium plus 10% fetal calf and horse serum supplemented with insulin, transferrin, and selenium and with glucose and glutamine and then maintained in 37 °C, 5% CO2 incubators (5). After 1 day in vitro, cultures were treated with 10-5 μM Ara-C. After 4 days in vitro, Ara-C was removed and cells moved to fresh minimal essential medium lacking serum. All experiments were carried out on cultures after 12 days in vitro.

Preparation of Astrocytes—Cultures were grown in flask and were not treated with Ara-C. Repeated exchanges of culture media containing fetal calf and horse serum were carried out on the cultures weekly. Once culture flasks reached confluence, cells were lifted from the flasks and counted. This work was supported by National Institutes of Health Grant NS23002. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Glutamate receptors participate in neural development, plasticity, learning, memory, and pathology, (e.g. excitotoxicity and neurodegenerative diseases.) Overactivation of the glutamate ionotropic receptors leads to excitotoxic cell death. NMDA receptor antagonism results in prominent neuroprotection in vivo and in vitro. The signals generated by these receptors activate the stress-sensitive MAP kinases JNK and p38 that are implicated in neuronal apoptosis (1). A role for JNK in the excitotoxic death of hippocampal neurons in vivo has been recently illustrated using JNK3 mice (2). However, the specific messengers and potential antagonist drugs involved in these signaling pathways are not understood. The bioactive phospholipid, platelet-activating factor (PAF), is a candidate mediator of excitatory amino acid signaling because it is a retrograde messenger of long-term potentiation (LTP) (3, 4) that enhances glutamate release (5), is generated by NMDA receptor activation (6), and participates in memory formation (7–9). PAF is synthesized through several pathways (10). The PAF precursor is enriched in arachidonate at the C2 position. The Ca2+-dependent PAF remodeling pathway engages a phospholipase A2, followed by acetylation to give rise to PAF (11). Neuronal stimulation, such as at the onset of seizures or from ischemia, promotes the rapid release of arachidonic acid (12, 13), reflecting synaptic phospholipase A2 activation (14, 15). The cytosolic form of phospholipase A2 is important in post ischemic neuronal cell death as is shown using knockout cPLA2 mice (16). Also, a secretory PLA2 may contribute to excitotoxicity (17, 18). Again, the signaling events are not clear. In brain ischemia and seizures, there is also PAF accumulation (19, 20), which in turn, contributes to increased glutamate release (5) and COX-2 transcription (21, 22), both enhancing brain injury. Therefore, PAF is a neuronal injury mediator, and consequently, PAF antagonists elicit neuroprotection (23, 24). Both PAF (25–27) and glutamate (28–30) activate MAP kinases. These studies directly implicate PAF as a second messenger in a glutamate-induced signaling pathway. We used primary rat hippocampal neuronal cultures to determine whether the injury/inflammatory messenger PAF is a mediator of NMDA activation of JNK, p38, and ERK MAP kinases. Furthermore, we have explored whether metabolotropic receptor activation affects NMDA receptor signaling to stress-sensitive MAP kinases and have examined the consequences of glutamate receptor interplay through PAF signaling on neuroprotection.

EXPERIMENTAL PROCEDURES

Primary Rat Hippocampal Neuronal Cultures—Culture plates were coated with Matrigel (Collaborative Research). Hippocampi from 1–3 day old rat pups were pooled in oxygenated Liebovitz’s (L-15) medium plus 0.05% bovine serum albumin. Hippocampi were then moved to a solution of 0.1% papain in L-15 + bovine serum albumin for 20 min (under oxygen) and then triturated with a Pasteur pipette. Cells were plated at 500,000 cells/ml in minimal essential medium plus 10% fetal calf and horse serum supplemented with insulin, transferrin, and selenium and with glucose and glutamine and then maintained in 37 °C, 5% CO2 incubators (5). After 1 day in vitro, cultures were treated with 10-5 μM Ara-C. After 4 days in vitro, Ara-C was removed and cells moved to fresh minimal essential medium lacking serum. All experiments were carried out on cultures after 12 days in vitro.
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dissociated with trypsin/EDTA treatment, centrifuged to a cell pellet, and then diluted in culture medium and replated for experimental use. These cultures were then washed repeatedly with serum-containing medium until reaching confluence before using for experiments as described previously (31).

In Vitro Immunocomplex Protein Kinase Assay—Cell cultures were exposed to agonists and/or antagonists in Locke’s solution without MgCl₂ and supplemented with 1 μM glycine to optimize the activation of the NMDA receptor. Exposure of cells to PAF was carried out in serum-free culture medium as indicated in the figure legends. To terminate exposure, medium was removed; cells were then washed with cold PBS, scraped in homogenization buffer, homogenized, and centrifuged at 2800 × g for 15 min at 4 °C and the supernatants used for the assay. The bioactive phospholipid PAF is a candidate mediator of glutamate receptor signaling because it is a retrograde messenger of LTP (3, 4) that enhances glutamate release (5), is generated by NMDA receptor activation (6), and participates in memory formation (8). PAF is synthesized through several pathways (10). The PAF precursor is enriched in arachidonate at the C₂ position. The Ca²⁺-dependent PAF remodeling pathway engages a phospholipase A₂, followed by acetylation to give the bioactive phospholipid PAF. Antagonists remained during PAF exposure. Activation of ERK, JNK, and p38 kinases was determined using different substrates (Fig. 1, C–F). Autoradiogram on each figure is a representative gel. Line graphs show the quantification of the autoradiograms. C and E, concentration response curves for PAF activation of ERK (panel C) and JNK and p38 kinases (panel E). D and F, antagonism of PAF activation of MAP kinases. Data have been normalized to activation elicited by 100 nM PAF, which has been set as 100%. As indicated some cells were pretreated with BN50730 (1 μM), CNQX (5 μM), or MK-801 (300 nM). Pretreatment time with antagonists was 30 min for BN50730 and 10 min for CNQX or MK-801 before addition of PAF. Antagonists remained during PAF exposure. Activation of ERK, MAP kinase (panel D), JNK and p38 kinases (panel F) was then measured. G, PAF and NMDA activate MAP kinases in neurons but not in astrocytes. Primary cultures of astrocytes were prepared as described under “Experimental Procedures.” Neurons and astrocytes were exposed to 100 nM PAF or NMDA at the indicated concentrations as described for Fig. 2, A–D. H, antagonism of NMDA activation of stress-sensitive MAP kinases in hippocampal neurons. Neurons were treated with NMDA (100 μM) for 15 min at room temperature. Where indicated, cells were pretreated for 30 min at 37 °C with recombinant PAF-acetylhydrolase (rPAF-AH, 20 μg/ml, Icos Corp.). Each point was obtained from pooling two wells from five to seven separate experiments.

RESULTS AND DISCUSSION

Using primary rat hippocampal neuronal cultures in the absence of MgCl₂ and in the presence of 1 μM glycine (see “Experimental Procedures”), NMDA (100 μM) prominently activates ERK (10-fold), JNK (8-fold), and p38 (7.5-fold) (Fig. 1, A and B). At submaximal concentrations, NMDA (50 μM) promotes the rapid activation of these MAP kinases, peaking at 15 min. p38 MAP kinase and JNK activation are transient, whereas ERK activation is somewhat sustained after removal of NMDA stimulus (Fig. 1B). The non-competitive NMDA receptor antagonist MK801 (300 nM), effectively blocked NMDA stimulation of the protein kinases (Fig. 1A). To test the involvement of PAF as a mediator of NMDA signaling, the synthetic tetraazepine, BN50730 (1 μM), an intracellular PAF receptor antagonist (22, 34), was used and was found to block NMDA stimulation of the protein kinases to an extent similar to that of MK801 (Fig. 1A).

The bioactive phospholipid PAF is a candidate mediator of excitatory amino acid signaling because it is a retrograde messenger of LTP (3, 4) that enhances glutamate release (5), is generated by NMDA receptor activation (6), and participates in memory formation (8). PAF is synthesized through several pathways (10). The PAF precursor is enriched in arachidonate at the C₂ position. The Ca²⁺-dependent PAF remodeling pathway engages a phospholipase A₂, followed by acetylation to give rise to PAF (11). Brain stimulation, such as at the onset of seizures or from ischemia, promotes the rapid release of arachi-
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Fig. 2. Glutamate prominently activates stress-sensitive MAP kinases in neurons (A), the antagonist MK 801, but not BN50730, elicits inhibition (B) and, to a limited extent, glutamate exerts activation in astrocytes (C). Glutamate activation of MAP kinases requires the inhibition of the metabotropic receptor to unmask BN50730 inhibition (D). Striped bars, ERK; white bars, JNK; and black bars, p38. Cells were exposed to glutamate (50 μM) and/or antagonists, as described for NMDA in Fig. 1. MCPG, (+)-MCPG (10 μM); TPA, 12-O-tetradecanoylphorbol-13-acetate (50 ng/ml); LPS, lipopolysaccharide (50 ng/ml); and IL-1β- interleukin-1β (20 ng/ml), which were added to astrocytes for 1 h at 37 °C before terminating for kinase activity assay. Values are averages from four to six separate experiments. For panel D, * = p < 0.05 by Student’s t test compared with glutamate alone condition.

Fig. 3. 1S,3R-ACPD, a metabotropic receptor agonist, inhibits NMDA activation of stress-sensitive MAP kinases. Striped bars, ERK; white bars, JNK; and black bars, p38. A, 1S,3R-ACPD (10 or 50 μM) added at the beginning of the 15 min incubation with or without NMDA (50 or 100 μM). The metabotropic receptor antagonist (+)-MCPG (10 or 50 μM) dose-dependently reverses inhibition of NMDA stimulus by 1S,3R-ACPD. (+)-MCPG was added 10 min before 1S,3R-ACPD; 30 s later, NMDA was added. Values are averages ± S.E. from four to five independent experiments. B, 1S,3R-ACPD (25 μM) has no effect on kainate (KA, 100 μM)-induced activation of MAP kinases. The AMPA/ kainate receptor antagonist CNQX (5 μM) inhibits kainate activation of kinases. Values are averages of three to five independent experiments. In gel, kinase assay was performed by resolving 65 kD protein kinases. Values are averages of three to five independent experiments. Extract using MBP as ERK (panel C) and GST-cJun (1–169) as JNK substrate (panel D). For panel A, * = p < 0.05 by Student’s t test compared with NMDA + t-ACPD condition.

sensitive MAP kinase activation, the hydrolysis of this lipid to lyso-PAF should inhibit this action of NMDA. PAF acetylhydrolase catalyzes this hydrolysis (36). Plasma-type recombinant PAF acetylhydrolase prevents PAF-induced inflammatory responses in non-neural cells (36, 37) and elicits neuroprotection against NMDA in primary hippocampal neuronal cultures. Preincubation of hippocampal neurons with plasma-type recombinant PAF acetylhydrolase (rPAF-AH) greatly reduced the NMDA-mediated activation of MAP kinases (Fig. 1H).

All of the above findings were made using either NMDA or PAF as an agonist. Therefore, the effects of glutamate itself were investigated. It was surmised that glutamate-mediated activation of stress-sensitive MAP kinases should have at least a component that utilizes PAF as a mediator. Surprisingly, glutamate was found to activate MAP kinases through a mechanism insensitive to the PAF receptor antagonist, BN50730 (Fig. 2). MAP kinases from hippocampal astrocytes are weakly activated by glutamate although they are more responsive to phorbol-12-myristate-13-acetate (TPA), lipopolysaccharide (LPS), and interleukin 1β (IL-1β) (Fig. 2C). The NMDA receptor antagonist MK801 effectively blocks glutamate activation of MAP kinases at either 50 or 100 μM. Therefore, although NMDA activates MAP kinases through a BN50730 sensitive route (Fig. 2A), glutamate, an agonist of the NMDA receptor and non-NMDA glutamate receptors, does not display BN50730 sensitivity. The failure of the PAF receptor antagonist BN50730 to block glutamate-stimulated activation of stress-sensitive MAP kinases (Fig. 2D) suggests that glutamate and PAF utilize separate pathways for the activation of these protein kinases, or that glutamate, by activating the
metabotropic receptor is inhibiting the NMDA-stimulated signaling pathway that involves PAF. To address this dilemma, we investigated the significance of metabotropic and AMPA/kainate receptors. Fig. 3A shows that 1S,3R-ACPD, a selective glutamate metabotropic receptor agonist, when added together with NMDA, inhibits NMDA-induced activation of ERK, JNK, and p38. (+)-MCPG, a mGluR antagonist, reverses the 1S,3R-ACPD effect (Fig. 3A) and allows for BN50730 to significantly block glutamate-activation of the MAP kinases (Fig. 2D). Kainic acid also activates the MAP kinases; however, 1S,3R-ACPD fails to affect this pathway (Fig. 3B). The 1S,3R-ACPD effect on ERK and JNK was further confirmed using in-gel kinase assays (Fig. 3, C and D). Quantitative analysis of in-gel kinase assays showed that NMDA increases the 42- and 44-kDa ERK isoforms by 340 and 210%, over controls (Fig. 3C). The JNK isoforms were increased 240 and 180% for the 54 and 46 kDa, respectively (Fig. 3D). 1S,3R-ACPD potently inhibited these effects of NMDA, as assayed by in-gel kinase (Fig. 3, C and D), in agreement with the data obtained by immunoprecipitation (Figs. 1, 2, and 3, panels A). We interpret the effect of 1S,3R-ACPD as a metabolotropic receptor-mediated attenuation of the NMDA inductive signal. By inhibiting mGluR, we postulated that the attenuation exerted by this glutamate receptor on the NMDA inductive signal might be removed. To test this prediction, hippocampal neurons were preincubated with the competitive metabotropic receptor antagonist, (+)-MCPG, followed by glutamate. Fig. 2D shows that, indeed, under these conditions, the BN50730-sensitive component of glutamate action is partially unmasked.

Glutamate is an endogenous agonist for metabotropic receptors. Because the cumulative MAP kinase signal stimulated by glutamate is presumably the sum of NMDA, AMPA/kainate, and metabotropic receptor activation, we tested whether 1S,3R-ACPD would inhibit MAP kinase signal stimulated by glutamate. Using 50 μM glutamate to stimulate MAP kinases, we found that 50 μM 1S,3R-ACPD inhibited 33.4 ± 0.3%, 29.7 ± 7.4%, and 21.1 ± 4.3% of ERK, JNK, and p-38 activation, respectively. In comparison, using the same platings of hippocampal neurons, we found that MAP kinase activation stimulated by 50 μM NMDA was inhibited by 50 μM 1S,3R-ACPD to the extent of 88.1 ± 0.3%, 86.7 ± 3.7%, and 69.9 ± 7% for ERK, JNK, and p38, respectively. It should also be noted that the metabotropic receptor antagonist (+)-MCPG also slightly inhibited glutamate-stimulated activation of the MAP kinases (Fig. 2D). However, (+)-MCPG is a mixed Group I/II mGlu receptor antagonist, so the inhibition observed in our current studies may be because of inhibition at Group I mGlu receptors, which, when activated, increases neuronal excitation (38).

The major route of MAP kinase activation under the experimental conditions used here is via the NMDA receptor. It should be pointed out that the conditions used during exposure of the hippocampal neurons to either NMDA, glutamate or 1S,3R-ACPD in this work were optimized for the activation of the NMDA receptor, with glycine present and magnesium absent in the Locke’s exposure solution (see “Experimental Procedures,” Fig. 1A).

The ubiquitous MAP kinases are components of signal transduction pathways involved in cell proliferation and differentiation. The hippocampal neurons used in the present experiments are post-mitotic; thus, the PAF-mediated protein kinase activation represents cell signaling through which the bioactive lipid elicits other responses. For example, increases in synaptic efficacy in the hippocampus in the form of LTP are accompanied by activation of p42 MAP kinase (39). The NMDA-mediated signaling through PAF leading to stress-sensitive MAP kinase activation may also participate in cell survival. To test this hypothesis, morphological evaluation of neuronal cell injury and nuclear damage with DAPI staining were used (Fig. 4, A–C). Although NMDA-treated hippocampal cultures showed a majority of cell bodies brightly stained in the nucleus with DAPI, control cultures and cultures treated with BN50730 plus NMDA showed far fewer damaged cells. Image analysis over multiple experiments demonstrated a significant protective effect of BN50730 against NMDA-induced cell damage, as measured by DAPI staining (Fig. 4D). These results were correlated in the same cultures used for DAPI staining with measurement of LDH release, which showed neuroprotection by BN50730.
against NMDA toxicity (Fig. 4E). Neuroprotection was also observed when 1S,3R-ACPD or rPAF-AH was added (Fig. 4F). The NMDA receptor antagonist MK801 (used as a positive control) was effective in exerting neuroprotection to about 92%. When glutamate was used as an agonist, no neuroprotection by the PAF receptor antagonist BN50730 was observed except in the presence of the metabotropic glutamate receptor antagonist, (+)-MCPG (Fig. 4F).

In agreement with these observations, agonists of glutamate metabotropic receptors exert neuroprotection in neuron injury models (40). However, other studies have indicated the neurotoxic effects of mGluR agonists (41–43). In this regard, we have evaluated a number of mGluR agonists to 1S,3R-ACPD, comparing the ability to inhibit NMDA-stimulated activation of the MAP kinases. At a concentration of 50 μM, the group I mGlu receptor agonists DHPG and HPG, and the mixed group I and II agonist 1S,3R-ACPD inhibited 50 μM NMDA-stimulated MAP kinase activation with a rank order efficacy of DHPG > 1S,3R-ACPD > HPG, and the resulting inhibition measured at 97% for DHPG, 96% for ACPD, and 57% for HPG. Using antibody to JNK3, the kinase found predominantly in neurons (44), we found that 50 μM NMDA activated both JNK-1 and JNK-3, with activation inhibited by DHPG, 1S,3R-ACPD, and HPG for both forms of the kinase (data not shown). It was of interest to observe that under identical stimulus conditions, 50 μM CPG, an mGluR1 antagonist and mGluR2 agonist, failed to inhibit NMDA-stimulation of MAP kinases (data not shown). Although 1S,3R-ACPD provided significant neuroprotection against NMDA toxicity (Fig. 4F), DHPG and HPG, which inhibited MAP kinases, were not neuroprotective. In fact, at 50 μM, DHPG and HPG were slightly neurotoxic in their own right (30–40% above controls). This reflects the complexity of the multiple subtypes of metabotropic glutamate receptors of different neurons in culture. This is combined with the possible multiple and contradictory effects that these metabotropic receptors may have on ionotropic subtypes of glutamate receptors in neurons.

Previous findings that, in general, activation of group I metabotropic receptors increases neuronal excitability and activation of group II or III diminishes synaptic excitation (38, 45–47) might explain the toxicity of DHPG and HPG in our experience with group II agonist 1S,3R-ACPD. Furthermore, 1S,3R-ACPD attenuated DNA fragmentation induced by NMDA but potentiated that induced by kainate. In the present work, we found no toxic effect of 1S,3R-ACPD, and we found that it had no inhibitory action on KA-stimulated MAP kinase activation (Fig. 3B).

PAF itself increases glutamate release and electrophysiological activity at the synapse (3, 5). Treatment of neuronal cell lines with PAF has been implicated to be neurotoxic; however, unlike in the present study, long-term treatment with PAF was necessary for expression of this toxicity (50). In other studies, PAF antagonists have demonstrated neuroprotection against excitotoxic and ischemic injury (24, 51). Fig. 5A outlines the sequence of events that may be triggered by NMDA-induced Ca2+ influx. PAF synthesis, likely through a phospholipase A2, will lead to MAP kinase activation and cell death. The importance of the cytosolic form of phospholipase A2 has been shown to be important in postischemic neuronal cell death as demonstrated using knockout cPLA2 mice (16). Also, a secretory PLA2 may contribute to excitotoxicity (17, 18). Again, the signaling events are not clear. ERK may potentiate cPLA2 activation through phosphorylation. rPAF-AH neuroprotection (Fig. 4F) may reflect diverting PAF to its biologically inactive metabolite, lyso-PAF (Fig. 5A).

In brain ischemia and seizures, there is also PAF accumulation (19, 20) and, in turn, PAF accumulation contributes to increased glutamate release (5) and COX-2 transcription (22), both enhancing brain injury. Therefore, PAF is a neuronal injury mediator, and consequently, PAF antagonists elicit neuroprotection (23, 24). Both PAF (25–27) and glutamate (28–30) activate MAP kinases. These studies directly implicate PAF as a second messenger in a glutamate-induced signaling pathway.

Agonists of glutamate metabotropic receptors may attenuate inductive signals generated by another receptor (NMDA) and, as a consequence, lead to the selective termination of NMDA-mediated inductive responses (Fig. 5). In this instance, one signaling route, which is mediated by PAF, is terminated. Initial observations made by Koh et al. (40) that trans-ACPD elicits neuroprotection upon NMDA-induced damage of neurons in culture are thus confirmed here. 1S,3R-ACPD selectively inhibits MAP kinase activation mediated by NMDA but not by K+ (Fig. 5A). Glutamate, by activating NMDA and non-NMDA receptors activates an inhibitory signal acting on the pathway stemming from the NMDA receptor (Fig. 5B). This inhibitory signal is the result of metabotropic receptor activation. Thus, (+)-MCPG unMASKS the mGluR receptor action (Fig. 5C).

The use of cells expressing specific receptor subtypes will help to define whether the inhibition of signals emanating from the NMDA receptor by mGluR activation originates at the level
of the receptor itself, inhibition of PAF synthesis or enhancement of its degradation, or at the PAF receptor. Also, other converging and diverging signals, such as NO, may modulate the events described here. Ultimately, the activation by PAF of stress-sensitive MAP kinases may lead to transcriptional activation of genes related to cell survival. For example, the PAF antagonist BN50730 inhibits COX-2 transcription in transfected cells (21) as well as in vivo during kainate-induced hippocampal damage (22). In conclusion, we have identified a pathway from NMDA through PAF that activates stress-sen-
sitive kinases and leads to hippocampal neuronal cell death. This pathway contributes to the networks of signals that promote survival/death. We demonstrate that by activating the metabolotropic glutamate receptor, this signaling pathway is inhibited. We further show that neuronal cell death involves a mechanism that displays morphological changes, characteristic of apoptosis. Our results indicate that mGluR and NMDA receptor interplay is an important effector in neuronal death signaling. Moreover, agonists of mGluR that inhibit NMDA signaling through PAF may be useful to ameliorate excitotoxicity and neurodegeneration as are strategies to selectively block the PAF receptor or to degrade PAF as it accumulates.

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