Glutamatergic neurotransmission is associated with release of arachidonic acid (AA) from membrane phospholipids of both neurons and astrocytes. Since free AA has been shown to enhance glutamate-mediated synaptic transmission, it can be postulated that glutamate release and AA formation constitute a positive feed-back mechanism for sustained excitatory neurotransmission.

In the present study, we examined whether the glutamate-evoked release of AA could be modulated by peptides. Using mouse cortical neurons in primary cultures, we show that the release of AA evoked by glutamate is potentiated by vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide (PACAP). This effect is mediated through the activation of PACAP I receptors. However, several arguments show that this potentiating mechanism does not involve the cAMP/PKA pathway. 1) Increasing intracellular cAMP by either choleratoxin, forskolin, or 8-Br-cAMP treatments does not affect the glutamate-evoked release of AA; 2) potentiation of the glutamate response by PACAP is not prevented by the PKA inhibitor 8-Br-RcAMPS. Also, an involvement of the phospholipase C protein kinase C pathways is unlikely since inhibitors of both phospholipase C (i.e. U-73122) and protein kinase C (i.e. Ro Ro 91-8220) do not affect the potentiation of the glutamate response by PACAP. These observations indicate an effect mediated by PACAP I receptors, which does not involve the second messenger pathways classically associated with activation of this type of receptors. Furthermore, results indicate that this potentiating mechanism mediated by PACAP I receptor acts at a level downstream of the glutamate receptor-mediated calcium influx.

Glutamate is the main excitatory neurotransmitter in the cerebral cortex. As glutamate is released into the synaptic cleft, a specific reuptake system present on both neuronal and glial cells adjusts the extracellular concentrations of this neurotransmitter between 0.2 μM and 200 μM (1). Activation of glutamatergic receptors results in both rapid changes of ionic currents and second messenger formation. Among the second messenger pathways stimulated by glutamate, the release of AA has been shown in brain slices (2) and primary cultures of neurons or astrocytes (3–5). The glutamate-evoked release of AA could be of particular relevance to the physiological regulation of the excitatory signaling, since it has been suggested that AA itself could amplify glutamatergic neurotransmission. Indeed, AA enhances glutamate release from presynaptic terminals (6), inhibits glutamate reuptake (7), and enhances NMDA currents (8). Interestingly, certain components of long term potentiation appear to involve AA formation (9).

AA is an unsaturated fatty acid predominantly located in the sn-2 position of membrane phospholipids from where it can be released by various types of phospholipases, mainly by phospholipase A2 (PLA2) or by sn-2 diacylglycerol lipase (for review, see Ref. 10). In neurons, the glutamate-evoked release of AA appears to involve the activation of PLA2 (3, 4, 11). The release of AA is tightly modulated by different mechanisms; in particular, PLA2 activity is regulated by phosphorylation. Thus, both PLA2 activity and the subsequent release of AA are enhanced by the cAMP/cAMP-dependent protein kinases (cAMP/PKA) pathway (12, 13).

In the present study, we addressed the question of whether activation of the cAMP/PKA pathway in neurons would modulate the glutamate-evoked release of AA. For this purpose, we investigated the effect of VIP and PACAP on the glutamate response, since both peptides are potent and efficient stimulators of cAMP formation in cortical neurons (14–17). Both VIP and PACAP interact with the Gs protein-coupled PACAP I and PACAP II receptors. PACAP I receptors are activated by PACAP in the nanomolar range and by VIP in the micromolar range, whereas PACAP II receptors are activated in the nanomolar range by both peptides (18, 19).

Here we report that VIP and PACAP, by activating PACAP I receptors, potentiate the glutamate-evoked release of AA from primary cultures of cerebral cortical neurons. However, the cascade of events that leads to this potentiation is not mediated by Gs proteins, nor by the cAMP/PKA or the phospholipase C (PLC)/PKC pathway. Therefore, our data describe a potentiating effect mediated by the activation of PACAP I receptors, which does not involve second messenger pathways classically associated with the activation of these types of receptors.
Experimental Procedures

Materials

Poly-l-ornithine (M, 30,000–70,000), laminin, Dulbecco's modified Eagle's medium (DMEM; D-7777), bovine pancreas insulin, human apo-transferrin, putrescine, progesterone, fatty acid free bovine serum albumin (BSA; Biomedical, 89-2196), 3 H-5-cyclic monophosphate (8-Br-CAMP), t-glutamate, NMDA, kainate, t-serine, phorbol 12-myristate 13-acetate (PMA), and lanthanum were obtained from Sigma; (15,3R)-1-aminoacyclopentane-1,3,4dicarboxylic acid, 6,7 dioctanoylglycerol-2,3-dione (DNQX) from Tocris Neuramin, Bristol, United Kingdom; 8-Br-cAMPS from Biomol Research Laboratories, PA; adenosine deaminase (EC 3.5.44) and ionomycin from Boehringer, Mannheim, Germany; [3 H]arachidonic acid ([3H]AA, 2.55 GBq; 58 mCi/mmol), 8-Br-cAMP, 3 H-glutamate, NMDA, L-glutamate, NMDA, kainate, 9-(1,4-dihydro-5-H-dibenzo[a,d]cyclohepten-5,10-imino) hydrogen maleate (MK801) and nifedipine from Research Biochemicals Inc., Natick, MA; VIP, PACAP-38 (PACAP), and secretin from Bachem, Bubendorf, Switzerland; U-73122 from Biomolecules Research Laboratories, PA; adenine (EC 3.5.44) and ionomycin from Boehringer, Mannheim, Germany; [3 H]arachidonic acid ([3H]AA, 2.55 TBq; 200 Ci/mmol), [14 C]arachidonic acid ([14 C]AA, 2.15 GBq; 58 mCi/mmol), [131 I]cAMP (59 KBq; 1.6 µCi/mmol), and [myo-2-3 H]inositol with PGT-271 (633 GBq; 17.1 Ci/mmol) from Amersham, Buckinghamshire, United Kingdom; INDO-1 acetoxymethyl ester (INDO-1 AM) from Molecular Probes, OR; Ro 31-8220 was a kind gift from Dr. G. Lawton, Roche Products Ltd (Herts, UK); PD98059 was a kind gift from Dr. A. S. Saltiel, Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI).

Methods

Cell Culture—Cortical neurons devoid of glial cells were prepared as described previously (11). Briefly, the cerebral cortex of 16-day-old Swiss albino mice embryos was dissected by removing the olfactory bulbs, striatum, hippocampus, and meninges. Cells were dissociated mechanically and were plated (80–100,000 cells/ml) on poly-D-lysine culture dishes (1 ml/well) previously coated with 15 µg/ml transferrin, 60 µg/ml laminin, Dulbecco's modified Eagle's medium (DMEM; D-7777), bovine pancreas insulin, human fibroblast growth factor (50 ng/ml), and heparin (50 units/ml) in serum-free DMEM containing [3 H]AA and 0.01% BSA as a lipid carrier. After 15 min in L-H buffer supplemented with IBMX (1 mM) and adenosine deaminase (1 IU/ml), neurons were then exposed for 15 min at 37°C to the agents in a L-H buffer lacking Mg2+ and Ca2+; Refs. 21 and 22) and in the presence of 100 µM 8-Br-cAMP, L-glutamate, NMDA, kainate, and nifedipine (10 µM). Glutamate was added in these experiments because cortical neurons possess metabotropic glutamate receptors, which are negatively coupled to the stimulation of adenyl cyclase (24). In- deed, as cortical neurons were incubated in presence of 100 µM glutamate, the accumulation of cAMP evoked by 1 µM VIP and 100 nM PACAP was still efficient (data not shown). Therefore, we set out to determine whether agents that are known to stimulate cAMP formation were still efficient in the presence of 100 µM glutamate (see “Results”). The reaction was stopped by replacement of the incubation buffer with ice-cold L-H buffer and subsequent sonication. The suspension was boiled for 10 min and centrifuged for 2 min at 9980 × g, and an aliquot of the supernatant was taken to assess cAMP levels using [125] cAMP as a tracer; Ref. 25.

Determination of [3 H]inositol Phosphate Formation—Formation of [3 H]inositol phosphates ([3 H]IPs) was determined under conditions similar to those used for the [3H]AA release measurement (11). Briefly, cells were plated in the presence of myo-[2-3 H]inositol (4 µCi/ml) in 12-well culture dishes. After 5–7 days in vitro, neurons were washed three times with L-H buffer (1 ml/well) at 37°C, then preincubated for 15 min in L-H buffer supplemented with lithium (10 mM) and adenosine deaminase (1 IU/ml), and finally exposed for 15 min to the agents in a L-H buffer lacking Mg2+ and Ca2+; Refs. 21 and 22) and in the presence of 100 µM 8-Br-cAMP, L-glutamate, NMDA, kainate, and nifedipine (10 µM). Isolation of [3 H]IPs by ion-exchange chromatography (Dowex AG 1-X8) was performed as described previously (see Ref. 11).

Determination of Intracellular [Ca2+]i—Determination of [Ca2+]i, was carried out as described previously (11). Briefly, cortical neurons grown on glass coverslips were studied with dual emission microfluorimetry. Cells were loaded with 12 µM INDO-1 AM and then exposed to various agents (in L-H buffer) using a multichannel cell superfusion device. All responses were measured in the absence of Mg2+ and in the presence of t-serine (100 µM). t-Serine was used instead of glycine because it yields full activation of NMDA receptor on perfused neurons and does not activate glycine-strychnine-sensitive chloride channels (26). The concentration of [Ca2+]i (nM) was calculated according to the equation described by Grynkiewicz et al. (27). Under those conditions, 97% of neurons tested responded to 100 µM glutamate.

Statistical Analysis—Results are expressed as means ± S.E. of n independent determinations. Data were statistically analyzed using InStat, GraphPad Software, San Diego, CA.

Results

VIP and PACAP Potentiate the Glutamate-evoked Release of [3 H]arachidonic Acid—As shown previously, glutamate (used at a maximally effective concentration of 100 µM) evoked the release of 3 H]AA from cortical neurons in primary culture (Fig. 1, and see Ref. 11). Although neither VIP (1 µM) nor PACAP (10 nM) significantly affected the basal release of [3 H]AA, they both potentiated the glutamate response by, respectively, 2- and 3-fold (Fig. 1). EC50 values for these potentiating effects were 1 µM for VIP and 0.7 nM for PACAP (Fig. 2), suggesting that these peptides might exert their effect by activating PACAP receptors. In agreement with this hypothesis, the release of [3 H]AA evoked by the concomitant application of VIP (1 µM), PACAP (10 nM), and glutamate was similar to the response obtained with PACAP (10 nM) and glutamate (n = 9; data not shown). Therefore, in the following experiments, potentiation of the glutamate-evoked release of [3 H]AA was investigated using 10 nM PACAP.

The effect of secretin was also studied, because this peptide shares a high degree of sequence homology with VIP and PACAP (18, 19). However, secretin (1 µM) had no effect on either basal [3 H]AA release or on the glutamate response (Fig. 1).

Thin layer chromatography (TLC) was used to verify that glutamate alone or in the presence of PACAP evoked the release of [3 H]AA exclusively. Indeed, in three separate experiments, the increase in [3 H]-labeled product(s) evoked by glut-
activation of adenyl cyclase with forskolin (Fig. 3). Data are the means ± S.E. of n = 9 separate determinations from three independent experiments. Statistical analysis: **, p < 0.01 significantly different from [3H]AA release evoked by glutamate alone (ANOVA followed by Dunnett’s test).

![Figure 1](http://www.jbc.org/)

**FIG. 1.** Potentiation by VIP and PACAP of [3H]arachidonic acid release evoked by glutamate. Cortical neurons were incubated for 15 min in the presence of glutamate (100 μM), secretin (1 μM), VIP (1 μM), or PACAP (10 nM). [3H]AA release was determined as described under “Experimental Procedures.” Data are the means ± S.E. of n = 12 separate determinations from four independent experiments. Statistical analysis: **, p < 0.01 significantly different from [3H]AA release evoked by glutamate alone.

![Figure 2](http://www.jbc.org/)

**FIG. 2.** Concentration-response curves for VIP and PACAP in potentiating the glutamate-evoked release of [3H]arachidonic acid. Cortical neurons were incubated for 15 min with glutamate (100 μM) in the presence of increasing concentrations of either VIP or PACAP. [3H]AA release was determined as described under “Experimental Procedures.” Results are expressed as percent of the release of [3H]AA evoked by glutamate (100 μM) determined in the same experiment (dotted line). Data are the mean ± S.E. of n = 9 separate determinations from three independent experiments.

![Figure 3](http://www.jbc.org/)

**FIG. 3.** Potentiation by PACAP of the glutamate-evoked release of [3H]arachidonic acid: absence of cAMP involvement. For both [3H]AA release and cAMP determination, cortical neurons were preincubated for 15 min with IBMX (1 mM). Neurons were then incubated for 15 min with glutamate (100 μM), PACAP (10 nM), or forskolin (10 μM). CTx (10 μg/ml) was applied to neurons for 6 h prior to the experiment by adding an 100-fold aliquot to the culture medium. IBMX was maintained with agonists and did not affect the release of [3H]AA evoked by glutamate (100 μM) + PACAP (10 nM) (data not shown). [3H]AA release and cAMP accumulation were determined as described under “Experimental Procedures” (by using similar L-H buffer washing procedures). Results for [3H]AA release are expressed as percent of the release evoked by glutamate (100 μM) determined in the same experiment. Data for [3H]AA release and for cAMP accumulation are the mean ± S.E. of n = 9 separate determinations from three independent experiments.

The involvement of PKA is also unlikely. A specific cell membrane permeant inhibitor of PKA activity, i.e. 8-Br-R-p-cAMPS (100 μM) did not affect the release of [3H]AA evoked by either glutamate alone or by the co-application of glutamate plus PACAP (Fig. 4). Furthermore, application of cell membrane permeant PKA activators i.e. 8-Br-cAMP (100 μM) and 8-Br-S-p-cAMPS (100 μM) did not affect the release of [3H]AA evoked by glutamate (1.1 ± 0.19- and 0.98 ± 0.05-fold of the glutamate response, respectively; n = 9).

**Activation of the Phospholipase C-Protein Kinase C Pathway Does Not Potentiate the Glutamate-evoked Release of [3H]Arachidonic Acid—** A few reports have indicated that PACAP can also activate the PLC pathway (28). Indeed, PACAP induced a significant accumulation of [3H]IPs in cortical neurons, this response being additive with the glutamate-induced accumulation of [3H]IPs (Table 1). To assess the possible involvement of the PLC pathway in AA release, we used a potent inhibitor of several types of PLC, i.e. U73122 (29, 30). When added to cortical neurons, U73122 (3 μM) inhibited the PACAP plus glutamate-induced formation of [3H]IPs by 84% (Table 1), indicating that this inhibitor was active on the PLC activity present in cortical neurons. However, PLC inhibition by U73122 (3 μM) did not affect the [3H]AA release evoked by the co-application of glutamate and PACAP (10 nM) (Fig. 4), indicating that PLC activation is not necessary to potentiate the glutamate response.

The involvement of PKC is also unlikely. Indeed, we tested a...
potent inhibitor of PKC activity, i.e. Ro 31-8220, which has a specific effect between 1 and 10 μM on intact cells (31). Ro 31-8220 (10 μM) did not affect the release of [3H]AA evoked by either glutamate alone or by the co-application of glutamate plus PACAP (10 nM) (Fig. 4). Furthermore, activation of PKC by application of the phorbol ester PMA (0.1 μM) did not affect the glutamate-evoked release of [3H]AA (1.03 ± 0.16-fold of the glutamate response, n = 6).

Potentiation of the Glutamate-evoked Release of [3H]Arachidonic Acid by PACAP Occurs when Both NMDA and AMPA/Kainate Receptors Are Activated—The glutamate-evoked release of [3H]AA in primary cultures of cortical neurons is mediated by two receptor subtypes: AMPA/kainate and NMDA (11). Activation of AMPA/kainate receptors with either kainate (100 μM) alone or glutamate plus MK801 (1 μM to block NMDA receptors) evoked the release of [3H]AA; both of these responses were similarly potentiated by PACAP (Fig. 5). Activation of NMDA receptors with either NMDA (100 μM) alone or glutamate plus DNQX (10 μM to block AMPA/kainate receptors) evoked the release of [3H]AA; both responses were also potentiated by PACAP (Fig. 5).

Finally, although metabotropic receptors are not involved in the glutamate-evoked release of AA from cortical neurons in primary cultures (11), we considered the possibility that PACAP could reveal such a coupling. This hypothesis can, however, be ruled out since (1S,3R)-1-aminoocyclopentane-1,3-dicarboxylic acid (1 mM) in the presence of PACAP did not evoke a significant release of [3H]AA (n = 9; data not shown).

PACAP Potentiates the Glutamate-evoked Release of [3H]Arachidonic Acid at a Level Downstream of the Glutamate-induced Ca²⁺ Influx—The glutamate-evoked release of [3H]AA is dependent on the intracellular Ca²⁺ concentration ([Ca²⁺]i) (3, 32, 33). Since activation of glutamate receptors is known to induce Ca²⁺ influx (either through the ionotropic receptors themselves or by opening voltage-sensitive Ca²⁺ channels (VSCCs)), an amplification of these influxes by PACAP could account for its potentiating effect on the glutamate-evoked release of [3H]AA.

In a first step, we studied the overall elevations in [Ca²⁺]i, in INDO-1-loaded cortical neurons. Application of PACAP did not affect basal [Ca²⁺]i, nor did it significantly alter the elevation in [Ca²⁺]i elicited by glutamate (Table II). Since modifications in [Ca²⁺]i, microdomains might not be detected by fluorescent imaging techniques (but could nevertheless be involved in regulation of enzymatic activities; Ref. 34), we considered the possibility that activation of PACAP I receptors could enhance Ca²⁺ influx due to the opening of Ca²⁺ channels. This hypothesis can be ruled out, since in the presence of a broad spectrum VSCC blocker, i.e. lanthanum (2 μM), PACAP similarly potentiated the glutamate-evoked release of [3H]AA (2.3 ± 0.02 μM enhancement of the glutamate response; n = 9). Confirming these results, a specific L-type VSCC blocker, i.e. nifedipine (10 μM) did not significantly affect the release of [3H]AA evoked by glutamate and PACAP (2.65 ± 0.11-fold enhancement of the glutamate response; n = 9).

Taken together, these results suggest that the potentiating mechanism mediated by the activation of PACAP I receptors could be operative at a level further downstream of the glutamate-induced Ca²⁺ influx. To strengthen this hypothesis, we examined whether PACAP would affect the release of [3H]AA evoked by a receptor-independent pathway, such as a large
Modulation of Arachidonic Acid Release by Peptides

Increases in [Ca\(^{2+}\)]

| Agents added | Amount added (\(\mu\)M) | [Ca\(^{2+}\)]
\(_{i}\) (nM) | number of cells |
|--------------|-------------------------|-----------------|-----------------|
| Basal        | 41 ± 1                  | 327             |                |
| PACAP        | 44 ± 4                  | 52              |                |
| Glutamate    | 715 ± 51                | 143             |                |
| Glutamate + PACAP | 855 ± 56               | 132             |                |

In summary, results reported here suggest that the substrate, whose activity is modulated following the activation of PACAP I receptors, is involved at a level downstream of the Ca\(^{2+}\) influx. Whether this substrate is PLA\(_{2}\) itself remains to be demonstrated. This study also shows that activation of PACAP I receptors alone (by VIP or PACAP) is not sufficient to promote the release of AA, whereas it clearly potentiated a Ca\(^{2+}\)-dependent release of AA evoked by either glutamate or ionomycin.

Is VIP a cell-specific neuromodulator of the glutamate signaling? The morphological characteristics and physiological properties of VIP-containing neurons in the neocortex, the region from which the cultures used in this study were prepared, have been characterized in detail (for review, see Ref. 42). In particular, VIP is almost exclusively localized to a homogenous population of bipolar, radially oriented neurons (43). The dendrites of these neurons extend from the pial surface to layer V-VI arborizing to a maximum of 100–120 \(\mu\)m in the horizontal plane. The axons of VIP-containing neurons are...
radially oriented and ramify within the radial domain of the dentritic arborization (43). These morphological characteristics imply that the actions of VIP released from VIP-containing neurons are confined within cortical columnar ensembles (for review, see Ref. 44). Since glutamate is released from activated afferent pathways to a given cortical area, VIP-containing bipolar neurons are ideally positioned to receive laminarily specified excitatory inputs from afferent pathways. Frequent asymmetrical (excitatory) synapses have been identified on VIP-containing neurons (45); furthermore, glutamate (in addition to other depolarizing stimuli) has been shown to evoke VIP release (46). Thus, the activation of excitatory afferents can result in synergistic interactions between VIP and glutamate on potential common target cells within discrete cortical domains.

From the data presented in this study, and from previous observations showing that VIP actually inhibits the glutamate-evoked release of AA from astrocytes in primary cultures (5), it follows that the concomitant release of VIP and glutamate within discrete radially oriented cortical domains will selectively enhance the release of AA within neuronal rather than glial populations of activated cortical columns. This cell type-specific modulation of the glutamate signaling by VIP could result in a transient sharpening of the information flow to target neurons resulting in the enhancement of the signal-to-noise ratio of AA-mediated cellular processes. Indeed, AA has been shown to regulate the efficacy of glutamatergic neurotransmission by several mechanisms. AA increases (i) NMDA receptor mediated currents (possibly by enhancing synaptic release of glutamate (47), (ii) the glutamate concentration in the synaptic cleft (possibly by enhancing synaptic release of glutamate and by inhibiting its reuptake) (48, 7). In line with these observations are the results obtained in the hippocampus showing that certain components of long term potentiation appear to require AA formation (9, 49). Therefore, data reported here suggest that VIP and PACAP could participate in the amplification of glutamate signaling, as already shown for the glutamate-induced c-fos expression (16).

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