A ROLE FOR THE ARACHIDONIC ACID CASCADE IN FAST SYNAPTIC MODULATION: ION CHANNELS AND TRANSMITTER UPTAKE SYSTEMS AS TARGET PROTEINS

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ABSTRACT

Recent evidence indicates that arachidonic acid (AA) and its metabolites play a fast messenger role in synaptic modulation in the CNS. 12-Lipoxygenase derivatives are released by *Aplysia* sensory neurons in response to inhibitory transmitters and directly target a class of K^+ channels, increasing the probability of their opening. In this way, hyperpolarization is achieved and action potentials are shortened, leading to synaptic depression. Other types of K^+ channels in vertebrate excitable cells have been found to be sensitive to arachidonic acid, lipoxygenase products, and polyunsaturated fatty acids (PUFA). In the mammalian CNS, arachidonic acid is released upon stimulation of N-methyl-D-aspartate (NMDA)-type glutamate receptors. We found that arachidonic acid inhibits the rate of glutamate uptake in both neuronal synaptic terminals and astrocytes. Neither biotransformation nor membrane incorporation are required for arachidonic acid to exert this effect. The phenomenon, which is rapid and evident at low μM concentrations of AA, may involve a direct interaction with the glutamate transporter or its lipidic microenvironment on the outer side of the cell membrane. Polyunsaturated fatty acids mimic arachidonate with a rank of potency parallel to the degree of unsaturation. Since the effect of glutamate on the synapses is terminated by diffusion and uptake, a slowing of the termination process may potentiate glutamate synaptic efficacy. However, excessive extracellular accumulation of glutamate may lead to neurotoxicity.

K^+ CHANNEL MODULATION BY ARACHIDONIC ACID CASCADE AND POLYUNSATURATED FATTY ACIDS

12-Lipoxygenase Metabolites Open S-type K^+ Channels in Aplysia Sensory Neurons

The neuropeptide Phe-Met-Arg-Phe-NH_2 (FMRFa) has an inhibitory action on the

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sensory neurons of the marine mollusk *Aplysia californica*. FMRFa-induced inhibition is, at least in part, achieved through the activation of a class of background K^+ channels termed the S-type K^+ channels (S channels). Functional analysis of single S channels with the patch-clamp technique has shown that FMRFa increases the probability of channel opening and acts through a diffusible second messenger (Belardetti et al., 1987). Lipoxygenase derivatives of arachidonic acid are produced by sensory neurons upon FMRFa stimulation and are able to mimic, at the cellular level, the inhibitory action of the peptide and, at the molecular level, the increased opening of the S channels. Moreover, FMRFa action is inhibited by both phospholipase and lipoxygenase inhibitors. These findings led to the conclusion that lipoxygenase metabolism of arachidonic acid acts as a second messenger of FMRFa action (Piomelli et al., 1987). 12-Lipoxygenase metabolites are significantly more effective than other lipoxygenase derivatives in modulating sensory cell resting and action potentials and S channel opening. Particularly potent is 12-HPETE, which opens S channels in both intact cells and excised patches that lack the intracellular medium. This observation suggests that 12-HPETE acts directly on the S channel molecule. 12-HPETE is effective at nanomolar concentrations when applied from the outer side of the membrane, whereas it acts in the micromolar range from the inner side (Buttner et al., 1989). Interestingly, if 12-HPETE is applied together with the heme-containing compound hematin, it becomes much more effective in opening S channels from the inner side of the membrane (Belardetti et al., 1989). Nonenzymatic metabolism of 12-HPETE is observed in this experiment, with formation of downstream products, possibly mimicking the cytochrome P_{450} pathway, leading to hepoxilins (Pace-Asciak, 1984). Hepoxilin A_3 can be formed from 12-HPETE in the nervous system of *Aplysia* (Piomelli et al., 1989). On the other hand, neither arachidonic acid nor the reduced product 12-HETE is effective in opening the S channels in excised patches, suggesting that 12-lipoxygenase metabolism at some intracellular location is required for the modulatory action. Therefore, in the case of S channel modulation, arachidonic acid acts as a precursor and 12-HETE as a by-product. 12-HPETE and/or a downstream derivative is the putative bioactive messenger.

Other K^+ Channels Are Opened by Lipoxygenase Derivatives, Arachidonic Acid, and PUFA in Vertebrate Cells

Since the discovery that K^+ channels represent a molecular target for the activity of arachidonic acid derivatives, much information has accumulated about the modulation of ion channels (including Na^+ channels, Ca^{2+} channels, Cl^- channels and gap-junctions) by these agents in various excitable and non-excitable cells of vertebrates and invertebrates (see Ordway et al., 1991, for a review). In many of the studies arachidonic acid was utilized as the test compound. The fatty acid was applied to the cells in the external medium, and the authors postulated subsequent membrane penetration and metabolic conversion to bioactive products. However, a distinction among the observed effects of arachidonic acid should be made. In some cases arachidonic acid metabolism through lipoxygenase pathways is required for ion channel modulation. In addition to *Aplysia* S channels, at least two other types of K^+ channels are opened by lipoxygenase products: K_{Ach} channels in heart myocytes (Kurachi et al., 1989; Kim et al., 1989) and K_m channels in hippocampal neurons (Schweitzer et al., 1990). On the other hand, some of the actions of arachidonic acid are not blocked by cascade inhibitors and are mimicked by other fatty acids, in particular polyunsaturated fatty acids. In excised patches, the effects of fatty acids persist, in contrast to what is observed in *Aplysia* S channels, indicating that arachidonic acid and PUFA themselves may directly modulate channel function (Kim and Clapham, 1989; Ordway et al., 1989). Finally, some of the actions of arachidonic acid have been blocked by free radical

scavenger enzymes, such as superoxide dismutase (SOD), and may be achieved indirectly following protein kinase C activation (Keyser et al., 1990).

A point of convergence among the effects reported for lipoxygenase products, arachidonic acid, and PUFA is the general trend for these agents to modulate K^+ channels in terms of increased opening. In physiological situations, K^+ channels act for the most part by extruding K^+ ions from the cells and increasing internal electronegativity. They participate in the setting of the resting potential of the cells and in the shaping of the action potential of excitable cells. In particular, they control the repolarization and the after-potential hyperpolarization phases. By increasing the contribution of K^+ channels to the resting or action potential, lipoxygenase derivatives and fatty acids appear to provide a general modulatory function that opposes electrical excitation. This idea seems to be supported by evidence for an inhibitory action of arachidonic acid and PUFA on Na^+ and Ca^{2+} channels, which, in turn, contribute to cell depolarization and increased excitation (Ordway et al., 1991).

GLUTAMATE UPTAKE MODULATION BY ARACHIDONIC ACID IN NEURONS AND ASTROCYTES

Arachidonic Acid Is Released upon Glutamate Receptor Stimulation in Neurons but Not in Glial Cells

Studies from different laboratories indicate that in mammalian CNS, the arachidonic acid cascade is coupled to excitatory amino acid receptors, in particular to the NMDA subtype. Following pre-incorporation of [^{3}H]arachidonic acid in membrane phospholipids and application of glutamate or NMDA, radiolabeled material is released into the extracellular medium in both striatal neurons (Dumuis et al., 1988) and cerebellar granule cells (Lazarewicz et al., 1990) in primary culture. Most of the released material has been identified as arachidonic acid itself. In cortical slices without pre-labeling, NMDA receptor stimulation leads to 12-HETE formation (Wolfe et al., 1990). Arachidonic acid release is induced by Ca^{2+}dependent activation of PLA_2, probably due to Ca^{2+} entry via the NMDA receptor-channel (Lazarewicz et al., 1990).

In parallel neuronal-enriched and astrocyte-enriched primary cultures from rat cerebral cortex, we found that administration of the Ca^{2+} ionophore, ionomycin (1 μM, 5 min), was followed by an indiscriminate influx of Ca^{2+}, which resulted in a massive release of [^{3}H]arachidonic acid-derived material. However, glutamate (0.1-1 mM, 15 min) and NMDA (100 μM, 15 min) selectively induced [^{3}H]arachidonic acid release only from the neuronal cultures. These data indicate that both neuronal and glial cells possess the enzymatic machinery to trigger arachidonate release, but only neurons respond to glutamate with an extracellular liberation of arachidonic acid. In particular, NMDA receptors at glutamatergic synapses are probably located only in the postsynaptic dendrites. Therefore, the possibility exists that arachidonic acid is liberated by postsynaptic neurons in the synaptic and perisynaptic space to act as an intercellular communicator.

Arachidonic Acid Reduces the Rate of Glutamate Uptake in Both Neurons and Astrocytes

The activity of glutamate at the synapses is terminated by diffusion and uptake via high-affinity transport systems located in neuronal terminals and perisynaptic astrocytes. We have used both synaptosomes and cultured astrocytes from rat cerebral cortex to investigate the modulatory role of arachidonic acid on glutamate uptake. As shown in Figure 1, a substantial reduction in the V_{max} of basal glutamate uptake, as well as a

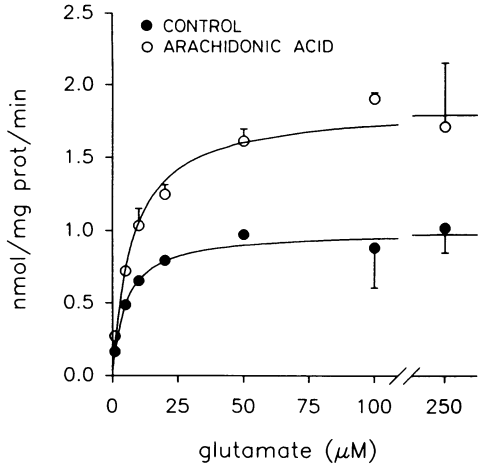

Figure 1. Arachidonic acid-induced inhibition of high-affinity glutamate uptake in cortical synaptosomes. Assay carried out for 1 min at 25°C in absence or presence of 100 μM AA. Estimated parameters: K_m (μM): 7.47 ± 1.88 (CONTROL) vs 5.11 ± 1.34 (AA) (n.s.); V_{max} (nmol/mg prot/min): 1.84 ± 0.21 (CONTROL) vs 0.99 ± 0.11 (AA) ($P<0.05$, F-test).

trend toward reduction in the K_m value, was seen in the presence of arachidonic acid. Arachidonic acid acts rapidly: significant inhibition is seen 30 s after its application and maximal inhibition is reached within 5-10 min. The threshold effective concentration is 1 μM (5-6% inhibition) whereas maximal inhibition (40-50%) is seen at 100 μM. This profile is consistent with a fast messenger role for arachidonic acid. Synaptosomal and astrocytic glutamate transport systems are affected in identical fashion by the fatty acid. Under arachidonate modulation, the uptake function proceeds at reduced speed and the effect, being noncompetitive in nature, cannot be overcome by the increasing concentration of glutamate accumulating in the extracellular space.

Arachidonic Acid Does Not Require Biotransformation or Membrane Incorporation to Act on Glutamate Uptake

Based on the observation that arachidonic acid inhibits glutamate uptake, a series of questions arises about the mechanisms of such action. First of all: is arachidonic acid the actual effector? Both synaptosomes and astrocytes have been reported to be capable of transforming arachidonic acid via the cyclooxygenase and the lipoxygenase pathways (Birkle and Bazan, 1987; Murphy et al., 1988). We have explored this point by incubating either synaptosomes or cultured astrocytes with 100 μM cold arachidonic acid plus 1 μCi [^{3}H]arachidonic acid under the same conditions (time, temperature, buffers, mechanical operations) utilized for the glutamate uptake assay. Biological preparations were then sonicated and both intracellular and extracellular media extracted and processed by reversed-phase high performance liquid chromatography (RP-HPLC) coupled to UV and radiochemical detectors (see Powell, 1985, for method, with slight modifications). As shown in Figure 2, only one major peak was detected; the retention time matched that of arachidonic acid. Automatic integration showed no other peak with an area ≥ 1% of the peak area of arachidonic acid peak area. Moreover,

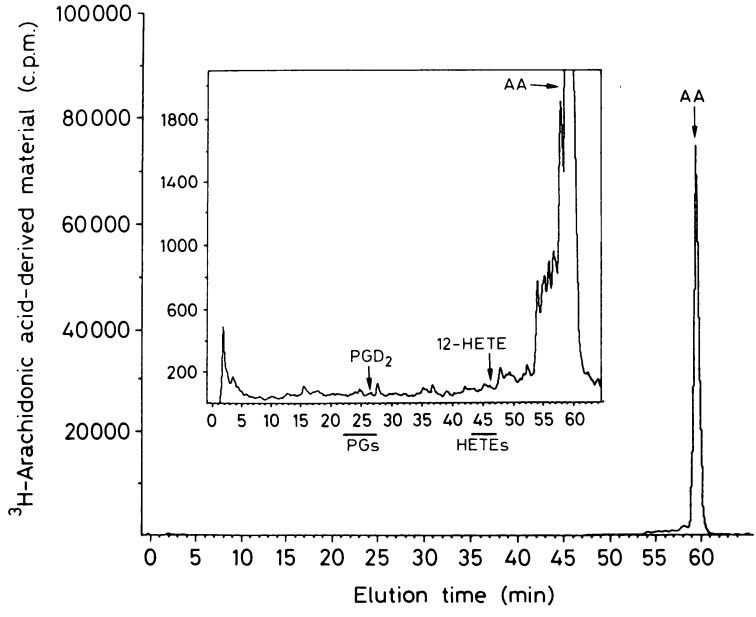

Figure 2. Reversed-phase HPLC chromatogram of [^{3}H]arachidonic acid-derived material following 10 min incubation with intact astrocytes. Insert: same chromatogram at 50-fold higher magnification. Arrows: retention times of standard [^{3}H]PGD$_2$, 12-HETE, AA. Solid lines below insert: elution periods for PGs (PGD$_2$, PGE$_2$, PGF$_{2\alpha}$, 6-keto-PGF$_{1\alpha}$, TXB$_2$) or 5,11,12,15-HETEs. Shoulder at left of AA peak due to nonmetabolic oxidation.

almost no changes were found in the total radioactivity recovered in the time-frames of elution of major cyclooxygenase products, i.e., prostaglandins (PGs) and thromboxane (TX), and lipoxygenase products, i.e., HETEs, in comparison with blank samples incubated in the absence of biological tissue (see Table 1). Therefore, we concluded that arachidonic acid is not significantly transformed into its metabolic products in synaptosomes and astrocytes during the glutamate uptake assay.

Table 1. Time-frame distribution by RP-HPLC of [^{3}H]arachidonic acid-derived material incubated in absence or presence of cortical synaptosomes or astrocytes

Elution Period (min)	Blank	Synaptosomes	Astrocytes
	(% of [^{3}H]AA-derived radioactivity ± SD)		
0 - 15	1.72 ± 0.26	1.64 ± 0.13	2.04 ± 1.10
15 - 30*	1.79 ± 0.59	2.06 ± 0.35	1.61 ± 0.84
30 - 43	2.46 ± 0.37	2.51 ± 0.55	2.95 ± 0.37
43 - 48**	2.11 ± 0.51	1.78 ± 0.18	3.29 ± 0.61
48 - 62***	91.23 ± 1.22	91.11 ± 2.38	89.56 ± 2.41
62 - 65	0.61 ± 0.16	0.68 ± 0.48	0.64 ± 0.08

*Elution period for major cyclooxygenase derivatives (PGs, TX); **elution period for lipoxygenase HETEs derivatives; ***elution period for arachidonic acid. Data are the average ± SD of two experiments in duplicate.

Recently, arachidonic acid was shown to modulate ion channels via free radical formation; the effect was prevented by the addition of the scavenger enzyme, superoxide dismutase (Keyser and Alger, 1990). We investigated this possibility with regard to the glutamate uptake assay and found the opposite result. As shown in Figure 3, arachidonic acid-induced inhibition of glutamate uptake in synaptosomes is not counteracted in the presence of superoxide dismutase. However, when the action of arachidonic acid was tested in the presence of the free fatty acid binding-protein albumin (BSA), inhibition was completely prevented. Moreover, if BSA was added when uptake was already inhibited by arachidonate, it could completely reverse the fatty acid effect. Since BSA chelates only free fatty acids and does not cross cell membranes, we conclude that arachidonic acid requires neither incorporation into the target membrane nor intracellular metabolic transformation to exert its inhibitory effect: it probably acts in its free form at some site on the outer side of the membrane.

PUFA but Not 12-Lipoxygenase Metabolites Mimic the Arachidonic Acid Effect

Arachidonic acid is the major product of glutamate-induced PLA_2 activation (Dumuis et al., 1988). However, 12-lipoxygenase metabolism and 12-HETE formation have also been reported in response to glutamate and NMDA (Wolfe et al., 1990). Therefore, we tested the effect of 12-lipoxygenase metabolites, namely 12-HPETE and 12-HETE, on glutamate uptake and found that they do not exert a significant effect. 12-HPETE at 1-2 μM has some inhibitory efficacy in astrocytes but not in synaptosomes. However, this effect is not always reproducible and does not show clear dose dependency. 12-HETE at 1-10 μM is devoid of any effect on glutamate uptake in both astrocytes and synaptosomes.

Theoretically, excitatory amino acids, by inducing PLA_2 activation, may release other unsaturated fatty acids present at position 2 in membrane phospholipids, such as oleic or docosahexaenoic acid. We have tested the effects of several long-chain saturated and unsaturated fatty acids on glutamate uptake. Figure 4 shows their efficacy in inhibiting glutamate transport in comparison to that of arachidonic acid. It is clear that both saturated (stearic acid) and trans-unsaturated (elaidic acid) molecules are completely ineffective, whereas all *cis*-unsaturated fatty acids, starting with oleic acid, reduce glutamate uptake. A pattern of potency increasing with the degree of unsaturation is similarly observed in synaptosomes and astrocytes. Linolenic acid (18:3), eicosapentaenoic acid (20:5), and docosahexaenoic acid (22:6) are the only unsaturated fatty acids that inhibit glutamate uptake to an extent comparable to that of arachidonic acid. This observation indicates that the effect has a certain specificity and that some structural and/or chemico-physical properties are required for its achievement.

Possible Molecular Sites and Mechanisms of the Action of Arachidonic Acid

Several different mechanisms of action can be hypothesized to explain the effect of arachidonic acid and PUFA on glutamate transport at the membrane level. Past work has indicated a parallel reduction in amino acid uptake and Na^+-K^+-ATPase activity (Chan et al., 1983). Therefore, the possibility exists that unsaturated fatty acids exert a general depressor effect on Na^+-dependent high-affinity uptake systems secondary to altered Na^+ co-transport. We have investigated this possibility by comparing the effect of the Na^+-K^+-ATPase inhibitor, ouabain, with that of arachidonic acid on glutamate uptake. Ouabain was tested at a concentration reported to completely inhibit Na^+/K^+ATPase. As shown in Figure 5, ouabain produced a reduction in glutamate

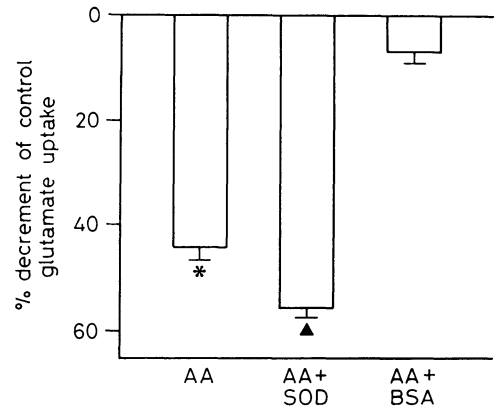

Figure 3. Arachidonic acid-induced inhibition of glutamate uptake in synaptosomes in absence or presence of superoxide dismutase (SOD, 90 U/ml) or bovine serum albumin (BSA, 0.1% w/v). Uptake assay: 10 μM glutamate, 5 min, 25°C. Data are the mean ± SD of two experiments in triplicate. Statistical analysis: AA vs BASAL and AA+SOD vs SOD ($P<0.001$); AA+BSA vs BSA (n.s., F-test).

uptake. However, at least three different observations militate against the hypothesis that the effect of arachidonic acid is secondary to Na^+-K^+-ATPase blockade: i) arachidonic acid is significantly more potent than ouabain; ii) the time-course of arachidonic acid inhibition is more rapid than that of ouabain; and iii) the two effects are not mutually exclusive and are partially additive, indicating that they involve different mechanisms.

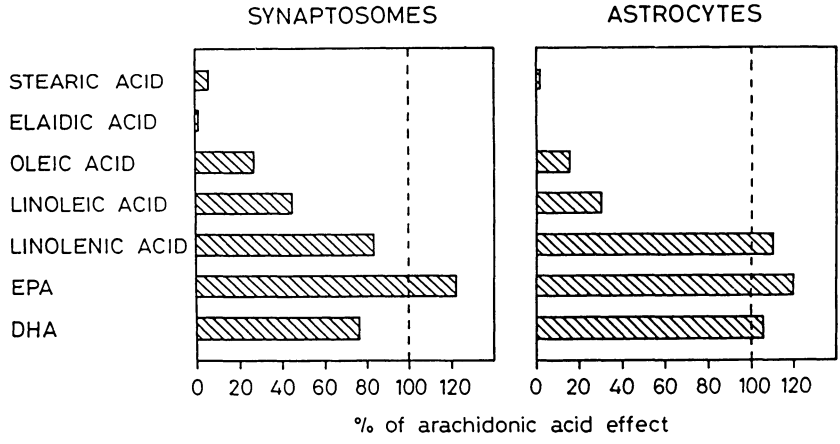

Figure 4. Glutamate uptake inhibition in cortical synaptosomes and astrocytes by different fatty acids: comparison with the arachidonic acid effect. All fatty acids, 100 μM. Synaptosome uptake assay: glutamate 10 μM, 1 min, 25°C; AA inhibition: 36.9%. Astrocyte uptake assay: glutamate 40 μM, 5 min, 25°C; AA inhibition: 51.8%. EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

As noted above, arachidonic acid and PUFA need not be incorporated into membrane phospholipids to act on glutamate transport. Therefore, general changes in membrane fluidity following phospholipid remodeling are not required for their fast action. As reported for ion channels, PUFA could act "directly" on their membrane target proteins. Several proteins have been shown to possess fatty acid-binding domains. Serum albumin and lipoproteins are two established examples. Particularly attractive is the case of protein kinase C, which exists in several isoforms, some of which seem to have a recognition site for single unsaturated fatty acids together with the diacylglycerol binding site (Shearman et al., 1989). Since cloning and sequencing of the glutamate transporter is in progress, it will be of interest to see if the protein displays sequence homology with protein kinase C at those sites.

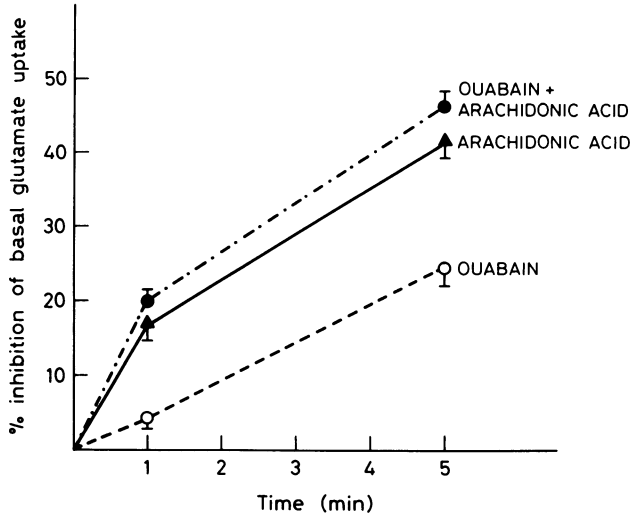

Figure 5. Time-course of glutamate uptake inhibition by ouabain (200 μM), arachidonic acid (100 μM), and ouabain + arachidonic acid in cortical synaptosomes. Uptake assay: 10 μM glutamate, 1 or 5 min, 25°C. Data are the mean ± SD of two experiments in triplicate. AA vs ouabain, $P<0.01$ at 1 and 5 min; ouabain+AA vs AA, $P<0.05$ at 5 min (F-test).

Another possible mode of action for arachidonic acid and related unsaturated fatty acids is to alter integral membrane protein function by interfering with the specific lipidic microenvironment. Cell membranes possess lipid domains with different fluidity. Free fatty acids can readily intercalate in these domains and induce changes in the packing of the lipid molecules. According to their structural and chemico-physical properties, different fatty acids target different domains. In particular, *cis*-unsaturated fatty acids, which have a rigid folded structure, target more fluid domains, whereas linear trans-unsaturated and unsaturated fatty acids prefer gel-like domains (Klausner et al., 1980). On the other hand, membrane-spanning proteins such as ion channels, pumps, transmitter receptors, and carriers have specific hydrophobic motifs in the trans-membrane regions allowing them to interact with the surrounding lipid moieties. It is therefore possible that, according to the amino acid organization of the protein in the trans-membrane region, a specific and appropriate lipidic microenvironment is selected. Free fatty acids, by intercalation in this microenvironment, may cause a structural reorganization of the lipid-protein interaction that can, in turn, lead to modifications in the functional properties of the protein.

Relevance of Arachidonic Acid and PUFA-Induced Inhibition of Glutamate Uptake Systems in Synaptic Potentiation and Excitotoxicity

Central glutamatergic synapses may undergo short- and long-term plasticity phenomena. Of particular interest and widely studied as a cellular model of memory storage is long-term potentiation (LTP; see Kennedy, 1989, for a review). LTP is induced by short high-frequency stimulation of the presynaptic neuron which results in enhanced excitatory responsiveness of the postsynaptic cell to normal stimulation lasting for hours or days. Both pre- and postsynaptic adaptive phenomena that could explain this change in synaptic efficiency have been reported, including enhanced glutamate release and increased responsiveness of postsynaptic glutamate receptors. At least in the case of LTP in area CA1 and the dentate gyrus of the hippocampus, it is known that the molecular event triggering LTP is Ca^{2+} entry into the postsynaptic neuron through the NMDA receptor-channel. How can this event be related to adaptive changes in the releasing system located in the presynapse? The existence of a retrograde trans-synaptic messenger has been postulated, which could be released by the postsynaptic site to bring adaptive information to the presynaptic pole. Early efforts to identify this messenger were concentrated on small peptides. More recently, following the discovery that amphiphilic 12-lipoxygenase derivatives of arachidonic acid are involved in synaptic modulation, the arachidonic acid cascade has become an attractive candidate. Indeed, a series of findings confirms the possible involvement of the arachidonic acid system in LTP: i) NMDA receptors release arachidonic acid and 12-lipoxygenase metabolites; ii) arachidonic acid levels are enhanced following LTP generation *in vivo*; iii) arachidonic acid cascade inhibitors prevent LTP induction; iv) exogenous arachidonate induces slow and persistent enhancement of synaptic efficacy; and v) arachidonic acid *in vitro* enhances glutamate release. However, there is conflicting evidence showing both increased and decreased glutamate release following the administration of 12-lipoxygenase products.

Our data suggest that another very simple mechanism for enhancing glutamate synaptic availability would be uptake inhibition. Thus, arachidonic acid released extracellularly from neurons carrying NMDA receptors can act directly on the outer side of the presynaptic terminal to reduce the rate of glutamate uptake. Following uptake inhibition, more glutamate would accumulate in the synaptic space. Still, it could be removed by diffusion. However, at the same time, arachidonic acid may also reduce perisynaptic astrocytic uptake, thus leading to a significant impairment of total glutamate clearance. Therefore, an increased amount of glutamate would remain in the synaptic area and be available to activate glutamate receptors. Function studies show that glutamate-induced postsynaptic depolarization is enhanced in hippocampal neurons in the presence of glutamate uptake inhibitors such as dihydrokainate and 3-hydroxy-DL-aspartate (Sawada et al., 1985). Moreover, the NMDA-dependent excitatory postsynaptic current elicited by afferent fiber stimulation in CA1 pyramidal cells is increased in the presence of dihydrokainate (Hestrin et al., 1990).

As mentioned above, free arachidonic acid levels are slightly increased following LTP generation (Lynch et al., 1989). In contrast, large amounts of arachidonic acid and PUFA are liberated in pathological conditions such as seizures and ischemia (Bazan, 1970). At the same time, a massive build-up of extracellular glutamate is also seen (Benveniste et al., 1984). This latter phenomenon leads to glutamate receptor overstimulation accompanied by the influx of excessive amounts of Ca^{2+} into neuronal cells which, supposedly, is responsible for the neurotoxic damage accompanying these pathologies. Our data suggest that the extracellular accumulation of arachidonic acid, PUFA, and glutamate may be interconnected, in that glutamate can release arachidonic acid which, in turn, both stimulates the release and inhibits the uptake of glutamate. In this way, a vicious cycle could be set up, ending in neuronal cell death.

In conclusion, it is possible that arachidonic acid and PUFA, by targeting a single mechanism (i.e., glutamate transport) and exerting the effect to different degrees, may either contribute to enhancement of synaptic efficacy or induce cell damage by excitotoxicity.

CONCLUSIONS

The information presented here leads to some general conclusions. The arachidonic acid cascade and polyunsaturated fatty acids may act as fast messengers in the CNS. Upon specific neurotransmitter receptor activation, neuronal cells release these compounds not only into their own internal medium, but also into the extracellular milieu which, *in vivo*, is the synaptic space and the perisynaptic area. Membrane-spanning proteins seem to possess sites—either in their own amino acid structure or in their lipid microenvironment—that directly bind these amphiphilic molecules. Our studies show examples of an ion channel and a neurotransmitter transporter protein which may be "directly" modulated in this way. These findings suggest the intriguing possibility that, in the CNS, these small amphiphilic molecules also serve to send information rapidly from a cell to its neighbors and, thereby, to integrate groups of cells to act in a concerted fashion. For example, amino acid neurotransmitters such as glutamate and GABA are taken up by both neuronal terminals and astrocytes and it would seem that coordinated action by these cells is necessary in order to control the extracellular levels of the two transmitters.

Modulation of ion channels and neurotransmitter transporters by arachidonic acid and related molecules has important functional implications, such as a role for these compounds in the regulation of both electrical and chemical neurotransmission. It is now an important goal to better understand this role and, in particular, to discover differences and similarities of action among different fatty acid molecules, as well as arachidonic acid and its many bioactive products.

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