Induction of Brain Edema Following Intracerebral Injection of Arachidonic Acid

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The effects of polyunsaturated fatty acids on brain edema formation have been studied in rats. Intracerebral injection of polyunsaturated fatty acids (PUFAs), including linolenic acid (18:3) and arachidonic acid (20:4), caused significant increases in cerebral water and sodium content concomitant with decreases in potassium content and Na^+- and K^+-dependent adenosine triphosphatase activity. There was gross and microscopic evidence of edema. Saturated fatty acids and monounsaturated fatty acid were not effective in inducing brain edema. The [^{125}I]-bovine serum albumin spaces increased twofold and threefold at 24 hours with 18:3 and 20:4, respectively, indicating vasogenic edema with increased permeability of brain endothelial cells. Staining of the brain was observed five minutes after injection of Evans blue dye followed by arachidonic acid perfusion. A major decrease in brain potassium content was evidence of concurrent cellular (cytotoxic) edema as well. The induction of brain edema by arachidonic acid was dose dependent and maximal between 24 and 48 hours after perfusion. Dexamethasone (10 mg/kg) was effective in ameliorating the brain edema, whereas a cyclooxygenase inhibitor, indomethacin (10 mg/kg), was not. These data indicate that arachidonic acid and other PUFAs have the ability to induce vasogenic and cellular brain edema and further support the hypothesis that the degradation of phospholipids and accumulation of PUFAs, particularly arachidonic acid, initiate the development of brain edema in various disease states.

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Brain edema develops with a characteristic delay following brain ischemia, infection, or trauma [20]. In an effort to understand the mechanisms responsible for this delay, our laboratory has focused attention on the biochemical changes that take place in the membranes of brain capillaries and brain cells in the pathogenesis of brain edema. Earlier work using in vitro cortical brain slices as a bioassay system has established that arachidonic acid and other polyunsaturated fatty acids (PUFAs) that are intrinsic constituents of the phospholipids of cellular membranes are potent inducers of cellular (cytotoxic) edema [3]. In these experiments the edematous brain slices were characterized by increased sodium and decreased potassium contents. Cellular metabolism was affected, because lactic acid levels were increased and high-energy nucleotides were reduced. Furthermore, arachidonic acid–induced edema was associated with the release of free radicals. Both corticosteroid and nonsteroidal antiinflammatory drugs, like indomethacin and aspirin, and the antioxidant vitamin E were ineffective in ameliorating swelling in brain slices [3]. These results prompted our studies of the local effects of arachidonic acid and other fatty acids on the induction of brain edema in vivo as well as the effects thereon of dexamethasone and indomethacin. Arachidonic acid is a major constituent of membranous products composing pus, as well as of normal brain and neoplasms. It is also the major precursor of the prostaglandins and leukotrienes [32]. Thus, this investigation of the local effects of arachidonic acid is considered pertinent to understanding the pathogenesis of brain edema of diverse origin.

Materials and Methods

Male Sprague-Dawley rats weighing 200 ± 20 g were anesthetized with intraperitoneal pentobarbital (50 mg per kilogram of body weight). In some experiments, animals were anesthetized with ketamine hydrochloride (175 mg/kg) and

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promazine hydrochloride (14 mg/kg). There were no differences in water content or other physiological measures when these two different anesthetics were used. Rectal temperature was maintained at 37°C with a regulated heating pad. Spontaneously breathing animals were placed in a stereotaxic head frame (Trent Wells, South Gate, CA), and 500 μl of either a control solution (Krebs Ringer buffer) or various fatty acids (5 mmol/L) in Krebs Ringer solution were infused at a rate of 10 μl per minute into the right thalamus using a 22-gauge spinal needle. Subcortical injections at a depth of 6 mm were chosen for these experiments to prevent the rapid escape of solution into the cerebrospinal fluid of the lateral ventricles or subarachnoid space. To test the volume effect, several animals were perfused with 100 μl of solution, and a similar result was obtained. Furthermore, separate experiments demonstrated that intracisternal or intraventricular infusions of 500 μl of control or fatty acid solution at a rate of 10 μl per minute for 50 minutes did not lead to increased intracranial pressure, as monitored by a cannula in the cisterna magna.

The animals were killled by decapitation. Tissues weighing about 50 mg around the injected area were quickly dissected and weighed. These steps usually took less than 1 minute. (The site injected, the thalamus, is composed chiefly of gray matter, as indicated by the water content of 79.5% in the normal control to be described.) The tissue water content was determined by drying the samples to a constant weight at 105°C in a vacuum oven for 16 hours [8]. Brain sodium and potassium were extracted with 2N nitric acid for 24 hours and analyzed with an Eppendorf flame photometer (Brinkman, Westbury, NY) or by atomic absorption spectrophotometry (Perkin-Elmer 560) [5, 8].

Sodium nonanoate (9:0), sodium arachidonate (20:4), and sodium docosahexaenoate (22:6) were dissolved directly in Krebs Ringer buffer. The micelles of sodium palmitate (16:0), sodium oleate (18:1), and sodium linolenate (18:3) in Krebs Ringer buffer were prepared according to the method of Milstein and Driscoll [24]. The fatty acid solutions were further sonicated for 10 minutes before use. The composition and pH (7.4) of Krebs Ringer buffer was reported previously [6].

[^{125}I]-bovine serum albumin (BSA) (0.828 mCi/mg, 99% purity, New England Nuclear, Boston, MA) was dialyzed against 50 mmol/L phosphate buffer (pH 7.4) overnight to eliminate the free iodine. Rats were injected with 1 μCi of [^{125}I]-BSA intravenously at the time of hemispheric injection 24 hours prior to decapitation. The percentage of [^{125}I]-BSA space was expressed as:

$$\frac{\text{dpm per gram of brain}}{\text{dpm per milliliter of plasma}}$$

where dpm = disintegrations per minute.

The 24-hour BSA space was used as a measure of the permeability of the blood-brain barrier; this space also reflects the brain's extracellular fluid volume [5].

Na^+- and K^+-dependent adenosine triphosphatase [(Na^+ + K^+)-ATPase] activity of brain tissue was assayed according to the method of Skou and Esmann [29]. A portion of brain tissue weighing about 50 mg immediately adjacent to the injection site was dissected out and homogenized in 1 ml of 0.32 M sucrose. The assay medium contained 80 mmol/L imidazole, 100 mmol/L NaCl, 20 mmol/L KCl, and 5 mmol/L $MgCl_2$, pH 7.5, and the assay was carried out at 37°C for 30 minutes. K^+ was omitted and 0.1 mmol/L ouabain was added to the incubation medium to obtain ouabain-sensitive ATPase activity. Mg^{++}-ATPase was derived from ATPase activity not inhibited by ouabain.

Histological Studies

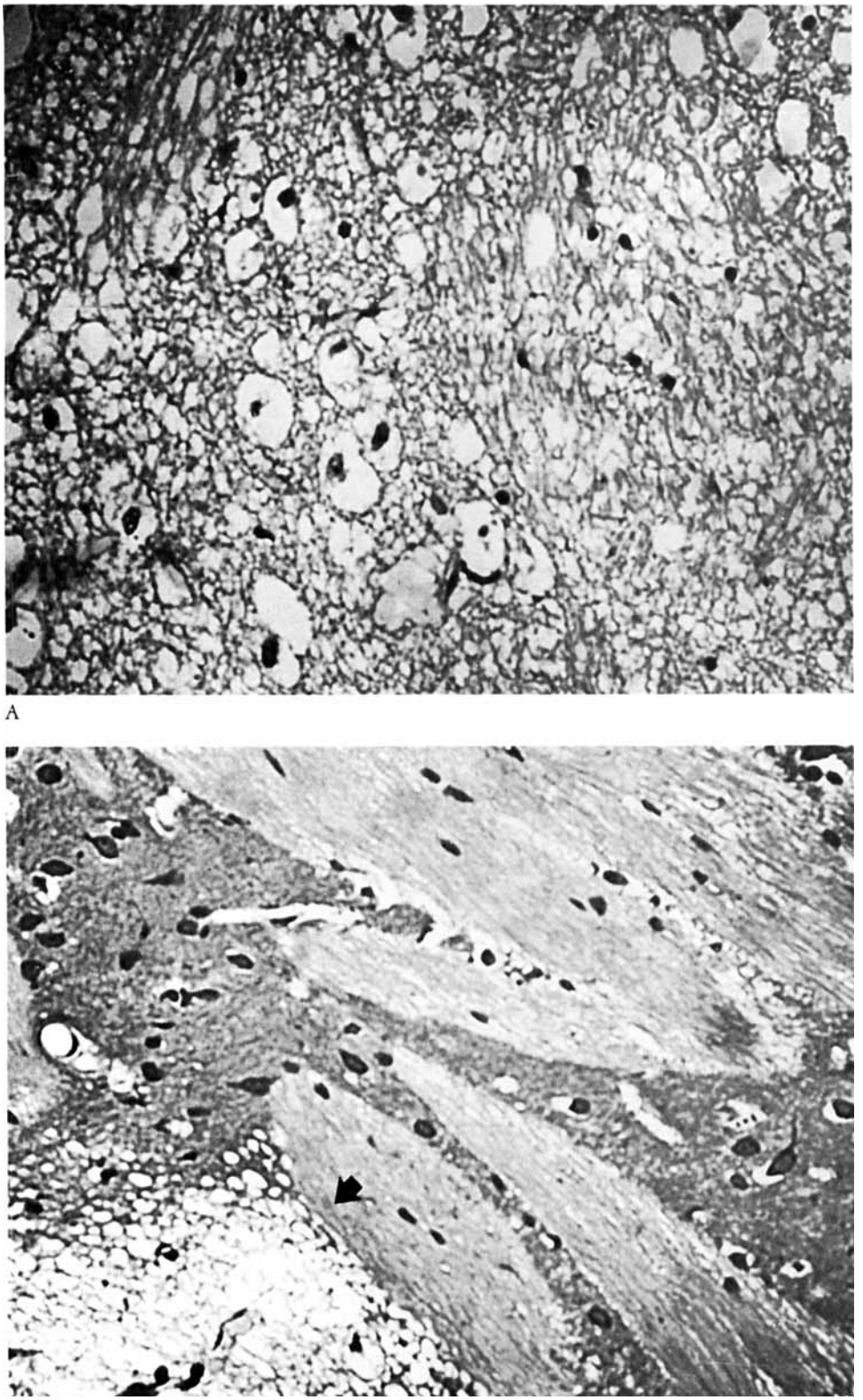
For histological studies, adult Sprague-Dawley rats were anesthetized with pentobarbital, 50 mg/kg, administered intraperitoneally, and placed in a Trent-Wells stereotaxic apparatus. A 22-gauge spinal needle was placed into the corpus striatum [27], and 500 μl of experimental solution (which contained 0.5 mmol/L 20:4 or 22:6 in Krebs Ringer buffer, or buffer alone) was infused over 37 minutes, using a Harvard pump. The animals were allowed to survive 1 to 6 hours, then reanesthetized if necessary and given 1 ml of 2% Evans blue in Krebs Ringer buffer intravenously. The Evans blue was allowed to circulate 5 to 30 minutes before the animals were killed by transcardiac perfusion of 2% glutaraldehyde, 4% paraformaldehyde in 40 mmol/L citrate-phosphate buffer, pH 3.5. After fixation the brains were removed, cut into 2 mm coronal blocks, dehydrated in ethanol, and embedded in glycol methacrylate. Sections for fluorescence microscopy were examined unstained, using a Zeiss fluorescence microscope with barrier filter 53, exciter filter BG12. Sections for light microscopy were stained with methylene blue–basic fuchsin.

Results

The animals used in the experimental model recovered from the anesthesia uneventfully. The behavior of the animals that had received infusions of PUFA solution was the same as that of animals given buffer alone. None of the animals developed focal neurological signs, seizures, or obtundation. Animals injected with Evans blue immediately became blue, but no adverse effects were noted.

On gross examination the hemispheres that had been injected with solutions of PUFA were swollen, and showed evidence of compression of the ipsilateral lateral ventricle. The edema dissected along the ipsilateral corpus callosum, expanding it to two to three times its normal width. An area of brain 3 to 4 mm in diameter, centered around the tip of the spinal needle, was stained blue, as was the ipsilateral corpus callosum. These changes were already evident 1 hour following the infusion of PUFA and were present to an equal extent in animals receiving 20:4 and 22:6. The pineal and median eminences were blue in both control and experimental animals. In control animals, very slight Evans blue staining was present only along the needle track; there was no compression of the ventricular system or expansion of the corpus callosum.

Microscopic examination of hemispheres injected with solutions of PUFA revealed a consistently abnormal area of neuropil 3 to 4 mm in diameter and centered at the tip of the needle (Fig 1A). The neuropil in



A

B

Fig 1. Effects of arachidonic acid on microscopic morphology of corpus striatum at 24 hours. (A) Animals injected with arachidonic acid. (B) Control animal. Arrow indicates the true area damaged by needle insertion. (Both ×160.)

Table 1. Effects of Free Fatty Acids on Cerebral Water, Sodium, and Potassium at 24 Hours[a]

Fatty Acid		Water Content (%)	Na^+ Content (mEq/kg dry wt)	K^+ Content (mEq/kg dry wt)
Krebs Ringer buffer (control) (n = 36)	RH	79.5 ± 0.2	241.1 ± 1.3	555.6 ± 2.0
	LH	79.2 ± 0.1	240.4 ± 2.0	550.3 ± 2.2
Nonanoate (9:0) (n = 9)	RH	79.1 ± 0.07	248.4 ± 0.7	553.8 ± 1.0
	LH	79.0 ± 0.07	244.3 ± 0.1	554.2 ± 2.0
Palmitate (16:0) (n = 17)	RH	79.3 ± 0.07	254.8 ± 0.5[b]	545.7 ± 0.7[b]
	LH	79.3 ± 0.07	253.8 ± 1.0	546.1 ± 1.0
Oleate (18:1) (n = 6)	RH	79.1 ± 0.08	264.5 ± 0.8[b]	536.3 ± 1.6[b]
	LH	78.8 ± 0.08	263.1 ± 1.2	536.5 ± 1.2
Linolenate (18:3) (n = 6)	RH	79.8 ± 0.04[b]	278.2 ± 1.2[b]	319.6 ± 0.8[b]
	LH	79.2 ± 0.08	275.7 ± 2.0	409.8 ± 0.4
Arachidonate (20:4) (n = 29)	RH	80.6 ± 0.2[b]	283.8 ± 1.1[b]	258.0 ± 1.7[b]
	LH	79.7 ± 0.1	272.3 ± 0.4	315.4 ± 1.9

[a]All values are expressed as means ± standard errors of the mean.
[b]$p < 0.01$, RH fatty acid–injected versus RH control group. Student's t test was used for statistical analysis. Significant differences also existed between RH versus LH and LH fatty acid–injected versus LH control groups in arachidonic acid–infused animals.

RH = right hemisphere; LH = left hemisphere.

this region stained poorly and contained cystic spaces. The demarcation between edematous and normal brain was quite sharp. Platelet aggregates were not seen in the blood vessels. The fibers of the corpus callosum above the area of injection were splayed by edema fluid, which dissected along this structure for a variable length.

In control animals (Fig 1B), changes similar to those described were limited to the areas immediately adjacent to the needle track (indicated by the arrow); the corpus callosum was normal, except in the area immediately adjacent to the needle track.

Fluorescence microscopy confirmed the gross observations on the distribution of Evans blue. Even in those animals killed 5 minutes after injection of Evans blue, the region of the PUFA injection was diffusely stained with the tracer.

The effects of intracerebral injection of various fatty acids on brain water, sodium, and potassium contents were studied. The fatty acids used included the saturated fatty acids nonanoic acid (9:0) and palmitic acid (16:0), the monounsaturated fatty acid oleic acid (18:1), and the PUFAs linolenic acid (18:3) and arachidonic acid (20:4) (Table 1). Among the fatty acids, arachidonic acid was the most potent in inducing cerebral edema. Arachidonic acid caused 0.9% and 1.1% increases in the water content of the injected right hemisphere when compared with the contralateral hemisphere ($p < 0.01$) and the Krebs Ringer buffer control group results in the injected right hemisphere ($p < 0.01$), respectively. The right hemispheric sodium content was increased 18% concomitant with a 54% decrease in potassium content, compared with the control group (dry weight). Furthermore, the changes in water, sodium, and potassium content were also reflected in the contralateral left hemisphere, which also differed from control animals. A lesser degree of change in hemispheric water, sodium, and potassium contents was seen after injection of linolenic acid. Oleic and palmitic acids did not induce changes in brain water and cation levels. Furthermore, nonanoic acid, the short-chain fatty acid, was also ineffective in inducing brain edema.

The permeability of the blood-brain barrier to [^{125}I]-BSA was studied following intracerebral injection of various free fatty acids. Arachidonic acid and linolenic acid caused threefold and twofold increases, respectively, in [^{125}I]-albumin space at 24 hours in the injected right hemisphere when compared with the right hemispheres injected with Krebs Ringer buffer (Table 2). Arachidonic acid and linolenic acid also caused twofold and 33% increases, respectively, in the albumin space in the contralateral left hemisphere. Oleic acid, palmitic acid, and nonanoic acid were not effective in altering the blood-brain barrier permeability. When compared with the contralateral left hemispheric albumin space, however, the right hemispheric albumin spaces of both Krebs Ringer– and nonanoic acid–injected animals were slightly elevated, indicating damage from the needle injection. This contralateral

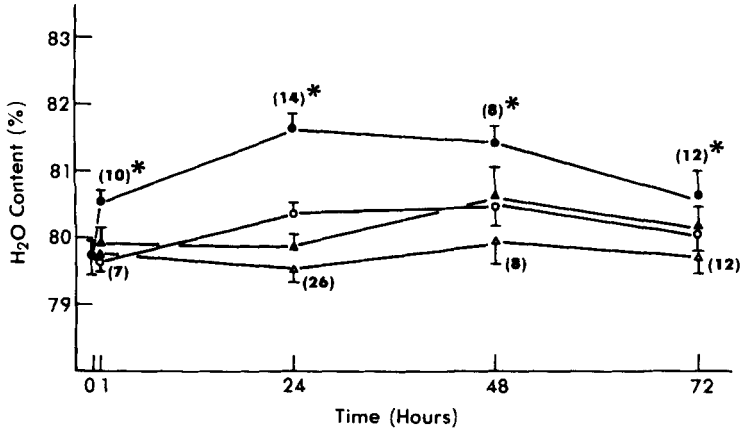
Table 2. Effects of Free Fatty Acids on Blood-Brain Barrier Permeability at 24 Hours[a]

Fatty Acid		[^{125}I]–Bovine Serum Albumin Space (%)
Krebs Ringer buffer (control) (n = 9)	RH	2.04 ± 0.1
	LH	1.60 ± 0.05
Nonanoate (n = 6)	RH	2.17 ± 0.02
	LH	1.90 ± 0.04
Palmitate (n = 6)	RH	2.30 ± 0.13
	LH	2.12 ± 0.05
Oleate (n = 6)	RH	2.40 ± 0.01[b]
	LH	2.20 ± 0.01
Linolenate (n = 6)	RH	4.25 ± 0.02[b]
	LH	3.20 ± 0.01
Arachidonate (n = 12)	RH	6.68 ± 0.29[b]
	LH	3.39 ± 0.18

[a]All values are expressed as means ± standard errors of the mean. [b]$p < 0.01$, RH fatty acid–injected versus RH control group. Student's t test was used for statistical analysis. Significant differences also existed between RH versus LH and LH fatty acid–injected versus LH control groups in arachidonic acid– and linolenic acid–treated animals.

RH = right hemisphere; LH = left hemisphere.

Fig 2. Time course of right and left hemispheric water content after right hemispheric injection of arachidonic acid. Mean ± standard error of the mean is given for right and left hemispheric water content. Number of animals used is given in parentheses. Filled circles, right hemisphere (RH) injected with arachidonic acid (20:4); open circles, left hemisphere (LH) of the experimental animal; filled triangles, RH control (Krebs Ringer) group; open triangles, LH control group. Asterisk indicates $p < 0.01$, *RH 20:4 versus RH control groups. Student's* t *test was used for statistical analysis. A significant difference also was evident between RH 20:4 and LH.*



increase in albumin space is assumed to represent diffusion of the albumin-containing edema fluid across the corpus callosum from the region of injury.

The intracerebral injection of arachidonic acid (5 mmol/L) in the right hemisphere caused a significant increase in brain water at 1 hour (Fig 2). The edema further progressed and appeared maximal at 24 hours, followed by a slight decline at 48 hours. At 72 hours after the injection, a profound decline in cerebral edema was seen. At this time there was no observable difference in water content in the ipsilateral right hemisphere when compared with the contralateral left hemisphere. The development of cerebral edema induced by arachidonic acid was dose dependent (Fig 3). After injection of a 1, 2, or 5 mmol/L concentration of arachidonic acid in the standard volume, right hemispheric water content was elevated 0.45, 1.55, or 1.9%, respectively.

Because both the nonsteroidal antiinflammatory drug indomethacin (an inhibitor of cyclooxygenase) and dexamethasone (an inhibitor of phospholipase A_2) influence the arachidonic acid cascade which forms prostaglandins, hydroxy fatty acids, and leukotrienes, the effects of these drugs on arachidonic acid–induced swelling were investigated. Indomethacin or dexamethasone was injected immediately prior to the infusion of fatty acid. Figure 4 indicates that neither indomethacin nor dexamethasone per se had an effect on brain water content in control animals. Intramuscular injection of dexamethasone, 10 mg/kg of body weight, however, reduced arachidonic acid–induced edema significantly. The brain water content decreased from 81.63 ± 0.21% [mean ($\bar{X}$) ± standard error of the mean (SEM)] (n = 14) to 79.89 ± 0.15% (n = 11; $p < 0.01$). The same concentration of dexamethasone also reduced docosahexaenoic acid (22:6)–induced edema. The brain water content decreased from 81.46 ± 0.17% ($\bar{X}$ ± SEM) (n = 7) to 80.48 ± 0.48% (n = 5, $p < 0.02$). Intramuscular injection of indomethacin at an identical dosage did not alter the edema induced by arachidonic acid, however.

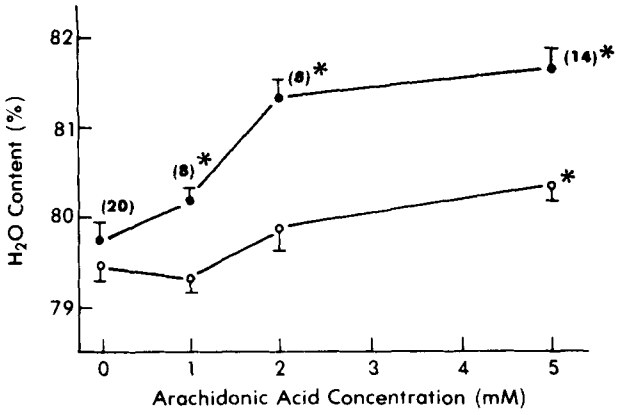


Fig 3. Dose-response curves of right and left hemispheric water content at 24 hours after right hemispheric injection of arachidonic acid. Mean ± standard error of the mean is given for right and left hemispheric water content. Number of animals used is given in parentheses. Filled circles, right hemisphere injected with 20:4; open circles, left hemisphere of the same animal. Asterisk indicates $p < 0.01$ *compared with control hemisphere (zero concentration); Student's* t *test.*

Because arachidonic acid caused changes in membrane integrity as well as inhibited the enzyme in brain slices, the effect of arachidonic acid on membrane-bound $(Na^+ + K^+)$-ATPase was investigated. Arachidonic acid significantly reduced $(Na^+ + K^+)$-ATPase activity of the injected hemisphere by 20% (Table 3), whereas the Mg^{++}-ATPase activity was unchanged. Nonanoic acid (9:0), the short-chain saturated fatty acid, was not effective.

Discussion

The present studies have demonstrated that intracerebral injection of PUFAs, especially arachidonic acid, induces vasogenic brain edema in rats. This process is PUFA-specific, because neither the saturated fatty acids nonanoic acid and palmitic acid nor the monounsaturated oleic acid in equal volumes and concentrations had such an effect. Both short-chain fatty acids [31] and long-chain PUFAs [25] in plasma have been suggested to play a role in the pathogenesis of brain edema in Reye's syndrome. The present data, however, do not support the direct involvement of short-chain fatty acids as edema-producing agents. They may have different effects when injected intravascularly. Furlow and Bass [14] have demonstrated platelet aggregation following intravascular administration of arachidonate. Although our studies did not show any platelet aggregation, it is still possible that some microvascular events contributed to the edema formation.

The [^{125}I]-BSA space was increased threefold by arachidonic acid at 24 hours, demonstrating that the edematous changes were vasogenic. Brain sodium was increased concomitant with a striking decrease in potassium content; the latter indicates cellular damage and the development of cellular (cytotoxic) edema as well [20]. Almost all brain potassium is intracellular, and these data confirm our previous in vitro studies indicating that arachidonic acid and other PUFAs induce cellular edema in brain slices [3, 6]. (In the in vitro model, there is no blood-brain barrier, and edema formation is cellular and associated with a decreased inulin space.) The morphological studies confirm that the PUFAs 20:4 and 22:6, when slowly infused into brain in nanomolar quantities, induce edema. This edema has pathological characteristics of vasogenic brain edema, namely, breakdown of the blood-brain

Fig 4. Effects of indomethacin and dexamethasone on hemispheric water content after right hemispheric injection of polyunsaturated fatty acid. Mean ± standard error of the mean is given for control and experimental cerebral water content. See text for drug dosages. Number of animals used is given in parentheses. Filled bars, *right hemisphere (RH);* open bars, *left hemisphere;* 20:4, *arachidonic acid,* 22:6, *docosahexaenoic acid;* K-R, *Krebs Ringer control. Significant differences were observed between the following groups:* [a]$p < 0.01$, *RH 20:4 versus RH K-R;* [b]$p < 0.01$, *RH 20:4 + indomethacin versus RH K-R;* [c]$p < 0.01$, *RH 20:4 + dexamethasone versus RH 20:4;* [d]$p < 0.01$, *RH 22:6 versus RH K-R;* [e]$p < 0.02$, *RH 22:6 + dexamethasone versus RH 22:6. Student's* t *test was used for analysis.*

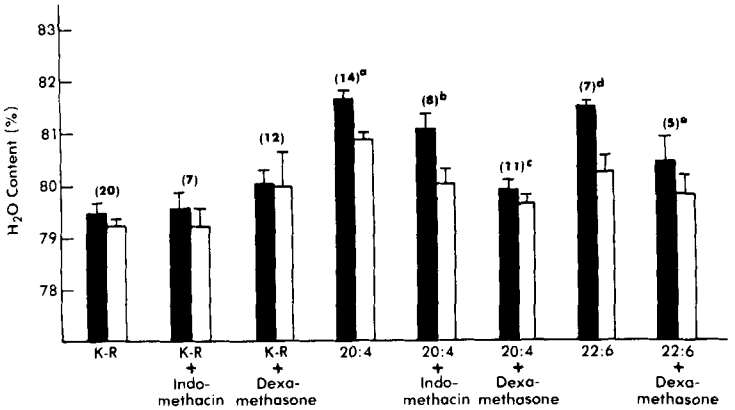


Table 3. Inhibition of (Na^+ + K^+)-ATPase by Polyunsaturated Fatty Acids in Rat Brain Cortex[a]

Fatty Acid	Total ATPase (μmol Pi mg protein^{-1} · hr^{-1})	Mg^{++}-ATPase (μmol Pi mg protein^{-1} · hr^{-1})	(Na^+ + K^+)-ATPase (μmol Pi mg protein^{-1} · hr^{-1})
Krebs Ringer buffer (control) (n = 11)	31.11 ± 1.43	11.53 ± 0.55	19.57 ± 1.02
Nonanoic acid (9:0) (n = 8)	31.82 ± 1.28	12.33 ± 0.56	19.49 ± 1.16
Arachidonic acid (20:4) (n = 11)	25.31 ± 1.25	9.61 ± 0.31	15.69 ± 0.97[b]

[a]All values are expressed as means ± standard errors of the mean. Fatty acid (0.25 mM) was injected intracerebrally in the right hemisphere. After 24 hours, hemisphere homogenates were assayed for enzyme activity.
[b]$p < 0.02$; Student's t test.

barrier to protein tracers and a tendency for edema fluid to spread along white matter. The route by which proteins cross the cerebral endothelium will have to be defined by ultrastructural studies.

The induction of brain edema by arachidonic acid was initiated within 5 minutes, as evidenced by the penetration of Evans blue. Brain edema was detected both biochemically and pathologically 1 hour after the intracerebral infusion, and the degree of edema was much greater at 24 hours and 48 hours. This time course of edema development is similar to the time course of the edema induced by cold injury [12]. We demonstrated earlier that the release of arachidonic acid and other PUFAs and the degradation of phospholipids are very early events in the development of vasogenic edema induced by cold injury [12]. The edema was not detected at 1 minute after the onset of cold injury but appeared at 30 minutes and continued to progress 24 hours later. Based on these observations, we hypothesize that the release and accumulation of arachidonic acid and its metabolites derived from cellular membranes are responsible for the progressive degradation of membrane phospholipids and sequential peroxidative damage to cellular membranes. This mechanism is suggested to underlie the extraordinary tendency for the brain to develop progressively severe edema with trauma, ischemia, infarction, and pus, as well as the edema associated with malignant brain tumors undergoing necrosis.

Other studies have also demonstrated that the release of free arachidonic acid from membrane phospholipids of brain cells is associated with various pathological insults, such as ischemia, hypoxia, and trauma [1, 2, 5, 12, 15, 23, 33]. Arachidonic acid, once released from cellular membrane phospholipids, is converted either by cyclooxygenase to prostaglandins and lipid peroxides, or by lipoxygenase to hydroxy fatty acids and leukotrienes [28, 32]. Although prostaglandins have been related to various aspects of inflammatory processes in biological systems [16, 22], our present studies indicate that indomethacin, the inhibitor of cyclooxygenase, was not effective in ameliorating brain edema caused by arachidonic acid. The data confirm our in vitro studies indicating that prostaglandins may not be involved in the membrane changes associated with the development of brain edema [3]. This likelihood does not exclude another role for the prostaglandins in edema formation, particularly one stemming from their effects on the microcirculation [18].

It has been suggested that arachidonic acid is an amphipathic molecule and is capable of forming micelles that bind either hydrophilic or hydrophobic substances [30]. It readily intercalates into membranes and produces changes in the packing of lipid molecules [21]. Thus, arachidonic acid has the physical ability to modify membrane integrity. We demonstrated earlier that free arachidonic acid, when incubated with rat brain cortical slices, can induce membrane perturbations with increased lipid peroxidation and superoxide radical formation [4, 9]. Recently we further demonstrated that arachidonic acid reduced (Na^+ + K^+)-ATPase activity associated with the alteration of membrane integrity in brain slices and in neuroblastoma and C-6 glioma cells [5, 7]. The present report supports and extends these findings; the modification of membrane stability and integrity by arachidonic acid is a fundamental change occurring in the development of both vasogenic and cellular brain edema. This hypothesis is also supported by our observations that treatment with dexamethasone, a proposed membrane stabilizer [10], has some beneficial ameliorative effects on brain edema in vivo. On the other hand, the antiinflammatory action of corticosteroids has been related to their inhibitory effects on phospholipase A_2 and the subsequent release of arachidonic acid [13, 19]. It was demonstrated that the corticosteroid dexamethasone may stimulate the synthesis of an inhibitory protein (lipomodulin) that inhibits phospholipase A_2 [17]. Although dexamethasone modifies the functional state of the brain in response to therapy, these effects appear independent of its effect on local cerebral glucose utilization [26]. Thus, the mechanism by which steroids exert a beneficial effect on various forms of brain edema requires further elucidation; such clarification would make possible more rational therapies [11].

The present studies suggest that alteration of en-

dothelial cell permeability and increased vesicular transport may be important effects of arachidonic acid. Changes in the integrity of the cellular membranes of neurons and glia are also initiated by this fatty acid [5, 7]. Further biochemical and morphological studies are warranted to clarify the mechanisms involved.

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