culating progesterone. The concentrations of progesterone and 17β-estradiol in the serum after Kepone administration were measured by radioimmunoassay (*16*) and compared to the concentration achieved by injecting doses of progesterone or 17β-estradiol that give intermediate to full induction of ovalbumin and conalbumin. The serum concentration of 17β-estradiol was unaffected by Kepone, but the concentration of progesterone increased from 0.7 n*M* to about 2 n*M* with 12.5 mg of Kepone and to about 3.5 n*M* with 50 mg of Kepone (injected intraperitoneally). A 3.5 n*M* concentration of total serum progesterone is sufficient to achieve about 70 percent of maximum conalbumin induction and 25 percent of maximum ovalbumin induction. This effect of Kepone on serum progesterone is similar to that of ethionine which also induces egg white protein synthesis in the chicken oviduct (*17*). These drugs may raise serum progesterone either by stimulating the synthesis and secretion of progesterone from the adrenals or ovaries or by inhibiting the breakdown and excretion of progesterone. The end result is that Kepone behaves in vivo like a combination of estrogen plus progesterone. Consistent with this interpretation is our observation that tamoxifen only partially inhibits Kepone induction of egg white protein synthesis in vivo, whereas it is completely effective in vitro. Doses of tamoxifen (30 mg) were used that completely prevented the induction of ovalbumin by 1 mg of estradiol-benzoate but had no effect on the induction of ovalbumin by 1 mg of progesterone. The effect of Kepone on oviduct growth is entirely consistent with this dual effect of Kepone in vivo (*5*, *6*).

The fact that Kepone has estrogenic activity is surprising to us, considering its structure. Although it may be modified in vivo, this is less likely in vitro and only a remote possibility in the competition assay with nuclear estrogen receptors. The neurological symptoms appear in chicks at doses slightly lower than those required to induce egg white protein synthesis. These symptoms are not ameliorated by tamoxifen, suggesting that they are unrelated to the estrogenic activity of Kepone. It is likely that exposure of humans and other vertebrates to high levels of Kepone would have deleterious effects on normal reproductive physiology as well as the more obvious neurological manifestations.

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Brain Edema: Induction in Cortical Slices by Polyunsaturated Fatty Acids

Abstract. *The presence of polyunsaturated and saturated fatty acids in leukocytic membranes prompted study of their possible role in the induction of brain edema. Polyunsaturated fatty acids including sodium arachidonate, sodium linoleate, sodium linolenate, and docosahexaenoic acids induced edema in slices of rat brain cortex. This cellular edema was specific, since neither saturated fatty acids nor a fatty acid containing a single double bond had such effect.*

Granulocytes and their products (pus) are associated with the massive brain edema found in fatal cases of purulent meningitis and brain abscess. Experimental models of such cases of "granulocytic brain edema" have the features of vasogenic, cytotoxic, and interstitial (hydrocephalic) edema (*1*). Using single cortical slices of the rat brain as a bioassay system in vitro, we have demonstrated that metabolism was altered by incubation of the slices with crude preparations of membranes from granulocytic leukocytes (WBC) obtained from glycogen-induced rat peritoneal exudates. Such leukocytic preparations induced brain edema characterized by increases in water content, cellular swelling (decreases in inulin space), increased intracellular sodium, and decreased intra-

Table 1. Effects of leukocyte membrane fractions on brain swelling and lactate production in vitro. Single, first cortical brain slices 40 to 50 mg in weight and 0.35 mm in thickness, and leukocyte membranes from glycogen-induced rat peritoneal exudates were prepared as described (*1*, *17*). Each slice was incubated in 5 ml of Krebs-Ringer medium or medium with lipid for 90 minutes at 37°C. The membranes obtained from 3.0×10^7 leukocytes were extracted with chloroform-methanol (2:1, by volume) and centrifuged at 12,000 rev/min for 10 minutes at 4°C. The pellet was dialyzed for 24 hours with at least one change of Krebs-Ringer buffer. The chloroform-methanol soluble fraction was dried under a stream of N_2 in the dark. A mixture of 0.5 ml of methanol and water (1:1, by volume) was added and mixed, and the two phases were then separated. The water-soluble fraction was dried in vacuo and then washed again with water and dried several times. The final water-soluble fraction was dissolved in Krebs-Ringer buffer. The methanol-soluble fraction was dried under N_2 in the dark, and the solvent was changed to methanol-ethanol (1:1, by volume) followed by ethanol-water (1:1, by volume) and finally to Krebs-Ringer buffer to obtain the experimental medium. Cortical slices were dried at 105°C for 16 hours to determine tissue water. The percentage of swelling was determined by subtracting the percentage of initial from the final water content and dividing by the initial water content. Lactate was determined enzymatically as described (*1*, *17*). Values are means ± standard error of slices given in parentheses.

Experiment	Swelling (%)	Lactate production [mmole (kg dry wt)$^{-1}$ 90 min^{-1}]
Medium alone (control)	1.85 ± 0.09 (13)	213.8 ± 7.2 (13)
Medium plus lipid fraction	3.40 ± 0.27 (8)*	305.2 ± 35.2 (6)†
Medium plus water-soluble fraction	1.99 ± 0.17 (6)	276.5 ± 9.6 (6)*
Medium plus insoluble fraction	1.70 ± 0.35 (9)	220.2 ± 19.2 (6)

*$P < .001$. †$P < .05$, Student's t-test.

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cellular potassium. Glucose oxidation and lactate production were also stimulated, and the energy charge was reduced in the edematous brain tissue.

To better define the factors in WBC responsible for edema formation, we prepared a crude membrane fraction of peritoneal exudate cells as described (*1*) and partitioned the preparation with chloroform-methanol extraction into three major fractions (*2*): (i) a chloroform-methanol soluble lipid fraction (containing free fatty acids, phospholipids, and glycolipids); (ii) a water-soluble fraction (containing free amino acids, glucose, salts, and other small water-soluble molecules); and (iii) an insoluble fraction (containing protein, glycoprotein, and other insoluble particulates). Table 1 shows that cortical brain slices swell 1.85 percent in Krebs-Ringer medium. The addition of chloroform-methanol soluble lipid fraction increased brain swelling to 3.4 percent, but water-soluble and insoluble fractions had no effect. The lipid fraction also increased brain lactate production, the water-soluble fraction had a lesser effect, and the insoluble fraction had none.

The chloroform-methanol soluble lipid fraction of rabbit peritoneal exudate granulocytes, as well as human leukocytes, have predominantly these fatty acids (*3*): linoleic (C18:2), palmitic (C16:0), oleic (C18:1), stearic (C18:0), and arachidonic (C20:4) acids. The local injection of arachidonic acid induces rat paw edema (*4*), and inhibition of arachidonic acid release from membrane phospholipids has been suggested as a mechanism for the anti-inflammatory action of corticosteroids (*5*). These observations have led us to compare the effects of individual saturated and unsaturated fatty acids on brain swelling in vitro, inulin (extracellular fluid) space, and on sodium and potassium content. The data are shown in Table 2. Cortical slices incubated for 90 minutes in Krebs-Ringer medium swelled 1.81 percent, and the inulin space was 46.11 percent. The saturated fatty acids nonanoic (C9:0), lauric (C12:0), and palmitic (C16:0) affected neither brain swelling nor the inulin space. The polyunsaturated fatty acids (PUFA's) including linoleic (C18:2), linolenic (C18:3), arachidonic (C20:4), as well as docosahexaenoic acid (C22:6) increased brain swelling two- to threefold. Sodium arachidonate was much more effective than the other PUFA's. Although lactate production was increased by both unsaturated and saturated fatty acids, PUFA's induced lactate production twofold, whereas the saturated fatty acids had much smaller effects. Brain sodium was dramatically increased and potassium decreased in association with the edema induced by PUFA's. (A lesser increase in sodium induced by palmitic acid is not explained.) These opposing changes in tissue sodium and potassium induced by PUFA's are characteristic of both vasogenic and cytotoxic brain edema (*6*).

The mechanism of the induction of brain edema by PUFA's requires elucidation. The PUFA's might induce cellular swelling by a nonspecific detergent effect on cellular membranes or by a more specific effect on membrane permeability to cations. Thus, arachidonic acid has been identified as the precursor for the biosynthesis of prostaglandins which are involved in the induction of various aspects of inflammation (*7*). The transformation of arachidonate to prostaglandins by cyclooxygenase (E.C. 1.14.99.1) is inhibited by aspirin or indomethacin. Our data indicate that prostaglandins are not involved in the cellular swelling induced by PUFA's, because incubation of aspirin or indomethacin with cortical slices did not inhibit arachidonate-induced brain swelling (*8*). Furthermore, incubation of prostaglandin PGE_2 or $PGF_{2\alpha}$, the prostaglandin products of arachidonate, at a concentration of 0.5 m*M*, did not induce brain swelling (*9*). These data suggest that neither the prostaglandins nor their intermediate precursors were responsible for the induction of edema. The various PUFA's may also undergo oxygenation by means of lipoxygenase (E.C. 1.13.11.12) to form hydroxyl or hydroperoxyl fatty acids (*10*), a reaction not inhibited by aspirin or indomethacin.

The addition of arachidonic acid or homo-γ-linolenic acid to a suspension of rabbit peritoneal neutrophils led to the synthesis of 5-L-hydroxy-9,11,14-eicosatetraenoic acid and 8-L-hydroxy-9,11,14-eicosatrienoic acid by way of lipoxygenase (*10*). Our data indicate that when cortical slices were incubated with linoleate in the presence of lipoxygenase (0.1

Table 2. Effects of saturated and unsaturated fatty acids on brain swelling, inulin space, lactate production, and Na^+ and K^+ content in vitro. Single, first cortical brain slices weighing 40 to 50 mg were incubated with individual fatty acids (0.5 m*M*) in 5 ml of Krebs-Ringer buffer in the presence of 1 μCi of [^{3}H]inulin for 90 minutes at 37°C. Inulin was repurified by column chromatography (*1*, *17*). After the incubation, the lactate content of the incubation media was measured. Dried slices were extracted with 2.0*N* nitric acid for 16 hours, and the portions were used to determine inulin space and Na^+ and K^+ content as described (*1*, *17*). All the fatty acids were in sodium form, except docosahexaenoic acid which was in oil form. Fatty acids (Sigma) had a purity of 99+ percent. Fatty acids were free of peroxides determined by the method of Kellogg and Fridovich (*18*). Sodium laurate was dissolved in Krebs-Ringer buffer containing 0.1 percent ethanol. Sodium oleate was dissolved in fatty acid-free bovine serum albumin (BSA) with a molar ratio of 5 (oleate/albumin) according to the method of Spector *et al.* (*19*). Sodium palmitate was dissolved in hot ethanol and finally prepared in Krebs-Ringer buffer containing 0.1 percent ethanol, or was dissolved in BSA as described above. (The effect of palmitate solubilized with these two methods on brain swelling was very similar.) The control values of swelling with 0.1 percent ethanol and BSA (0.1 m*M*) were 1.58 ± 0.15 percent (N = 7) and 1.65 ± 0.12 percent (N = 5) (mean ± standard error), respectively. The control values of lactate production with 0.1 percent ethanol and BSA (0.1 m*M*) were 231.5 ± 2.6 (N = 4) and 241.3 ± 25.7 (N = 4) mmole/kg dry weight (mean ± standard error), respectively. The values are means ± standard error; the number of slices is given in parentheses.

Fatty acid	Swelling (%)	Inulin space (%)	Lactate (mmol/kg dry wt)	Na^+ (meq/kg dry wt)	K^+ (meq/kg dry wt)
Control	1.81 ± 0.13 (15)	46.11 ± 0.87 (14)	235.6 ± 8.8 (14)	599.2 ± 15.4 (14)	392.7 ± 15.4 (14)
		Saturated fatty acids			
Nonanoic (C9:0)	2.02 ± 0.19 (8)	49.42 ± 2.16 (5)	268.7 ± 6.2 (6)*	518.8 ± 29.1 (4)	311.7 ± 31.4 (4)
Lauric (C12:0)	1.86 ± 0.37 (5)	49.22 ± 0.8 (5)	319.9 ± 16.9 (5)*	651.0 ± 54.1 (5)	315.4 ± 5.8 (5)
Palmitic (C16:0)	1.51 ± 0.14 (12)	46.12 ± 2.7 (4)	257.9 ± 28.9 (4)	838.0 ± 10.8 (4)*	386.7 ± 17.8 (4)
		Unsaturated fatty acids			
Oleic (C18:1)	1.69 ± 0.14 (6)	41.07 ± 1.68 (6)†	277.9 ± 11.4 (6)†	694.2 ± 19.8 (6)†	418.5 ± 17.8 (6)
Linoleic (C18:2)	5.21 ± 0.16 (16)*	33.43 ± 1.92 (6)*	519.3 ± 21.2 (13)*	1339.8 ± 32.8 (4)*	91.56 ± 2.2 (4)*
Homo-γ-linolenic (C18:3)	4.16 ± 0.34 (5)*	42.88 ± 2.16 (5)	390.9 ± 4.0 (5)*	948.7 ± 9.5 (5)*	188.4 ± 16.3 (5)*
Arachidonic (C20:4)	5.64 ± 0.10 (17)*	32.6 ± 1.7 (4)*	527.1 ± 13.9 (12)*	1239.1 ± 32.8 (9)*	140.1 ± 22.4 (8)*
Docosahexaenoic (C22:6)	5.36 ± 0.24 (5)*	41.47 ± 1.5 (5)*	542.7 ± 19.2 (5)*	1215.0 ± 21.9 (5)*	76.7 ± 3.4 (5)*

*P < .001. †P < .02; Student's t-test.

mg per 5-ml bath), brain edema formation was not affected. Autooxidation of PUFA's occurs readily in the presence of light and oxygen; such effects were eliminated by performing our experiments in the dark, and by the addition of free radical scavengers and antioxidants (*11*). These data suggest that the hydroxyl and hydroperoxyl fatty acids produced enzymatically or chemically by autooxidation are not the primary factors affecting brain swelling in vitro.

With regard to the possible nonspecific detergent effect of PUFA's on cellular membranes, it has been suggested that PUFA's are capable of forming micelles which can bind either hydrophilic or hydrophobic substances, rendering them soluble in otherwise incompatible media (*12*). The PUFA's could then be inserted into membranous structures and act in a manner similar to detergents by denaturing membrane proteins (*13*).

In order to differentiate the specific effects between PUFA's and detergents on the induction of brain edema, we studied the dose-response kinetics of sodium arachidonate and sodium dodecyl sulfate (SDS), an ionic detergent, on brain swelling, inulin space, lactate production, and Na^+ and K^+ content. Figure 1, A and B, shows the similarities between arachidonate and SDS on cortical slice swelling, lactate production, and Na^+ and K^+ content, although the Na^+ concentration in the SDS dose-response curve at the 0.5 m*M* concentration did not achieve saturation. However, the extracellular space, expressed as percentage of inulin space and shown in the SDS curve, was quite different. Extracellular space increases with the increases in SDS concentration. These data suggest that the ionic detergent effect on brain edema is similar, but not identical to, the effect of sodium arachidonate. We have also shown that when oil forms of oleic acid and PUFA's were used in place of the respective sodium salt forms, a similar effect on brain edema resulted (*14*). These data suggest that the increased aqueous solubility of the sodium salts of PUFA's probably was not the primary factor inducing brain swelling in vitro. Furthermore, the dose-response curves for brain swelling, induced with a nonionic detergent, were not similar to the curves of either arachidonate or SDS (*15*). Whether the detergent-like action of the ionic or nonionic forms of PUFA's has a role in inducing brain edema in vivo requires further study. Nevertheless, our present data indicate that PUFA's with multiple double bonds specifically induce brain edema in vitro. The

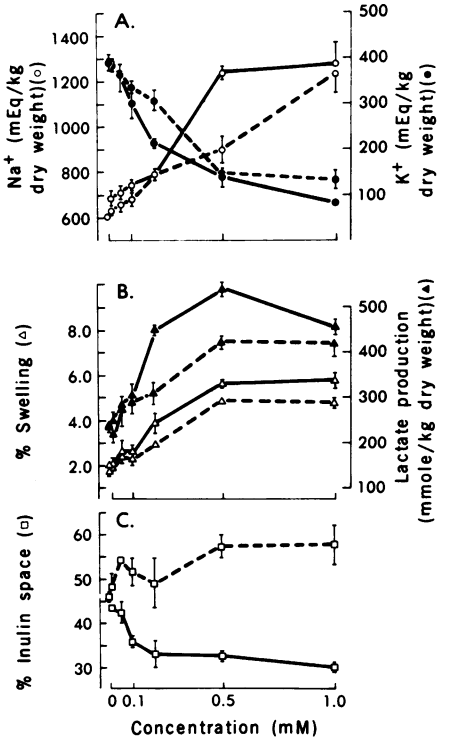

Fig. 1. Dose-response curves of sodium arachidonate and sodium dodecyl sulfate on brain swelling, inulin space, lactate production, and Na^+ and K^+ content. Sodium dodecyl sulfate (SDS; Sigma) was dissolved in 5 ml of Krebs-Ringer buffer. Experimental procedures are described in the legends to Tables 1 and 2. Dashed lines, sodium dodecyl sulfate; solid lines, sodium arachidonate. Each point represents the mean from at least four rat brain cortical slices (mean ± standard error).

presence of arachidonic acid and other PUFA's in leukocytic membranes suggests their importance in the genesis of granulocytic brain edema. Similarly, the major PUFA in the phospholipids of normal brain and brain tumors (*16*) is arachidonic acid, and its release might have a role in inducing the edema characteristic of brain injury and tumors.

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8. In these experiments, cortical swelling with aspirin (0.5 m*M*) and aspirin (0.5 m*M*) plus arachidonate (0.5 m*M*) was 1.66 ± 0.34 percent (N = 4) and 5.25 ± 0.24 percent (N = 4), respectively (mean ± standard error). Cortical swelling with indomethacin (0.1 m*M*) and indomethacin (0.1 m*M*) plus arachidonic acid (0.5 m*M*) was 2.04 ± 0.27 percent (N = 3) and 5.83 ± 0.56 percent (N = 3), respectively (mean ± standard error).
9. In these experiments, PGE_2 (0.5 m*M*) and $PGF_{2\alpha}$ (0.5 m*M*) (Sigma) were used. Swelling with PGE_2 and $PGF_{2\alpha}$ was 1.90 ± 0.26 percent and 1.92 ± 0.18 percent, respectively; lactate (millimoles per kilogram of dry weight per 90 minutes) was 460.6 ± 46.3 and 318.7 ± 10.0, respectively; Na^+ (milliequivalents per kilogram of dry weight) was 707.4 ± 42.5 and 679.6 ± 32.1, respectively; K^+ was 313.9 ± 32.2 and 330.3 ± 21.3, respectively. The [^{3}H]inulin space was 43.79 ± 0.41 percent and 46.45 ± 4.17 percent for PGE_2 and $PGF_{2\alpha}$, respectively. Each value is a mean of three determinations (cortical slices) ± standard error.
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15. In these experiments, Triton X-100 (Sigma; 99 percent solution; density, 1.0595) was dissolved in Krebs-Ringer buffer to obtain various concentrations for the dose-response curve studies. Although the dose-response curves of Na^+ and K^+ were similar to sodium arachidonate, the percentage of swelling, lactate production, and inulin space were different from both the sodium arachidonate and SDS dose-response curves.
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