Title
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Permalink
https://escholarship.org/uc/item/10r522th

Journal
NPJ science of food, 4(1)

ISSN
2396-8370

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Publication Date
2020-01-02

DOI
10.1038/s41538-019-0061-9

Peer reviewed
Linoleic acid—good or bad for the brain?

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Increased intake of omega-6 rich plant oils such as soybean and corn oil over the past few decades has inadvertently tripled the amount of n-6 linoleic acid (LA, 18:2n-6) in the diet. Although LA is nutritionally “essential,” very little is known about how it affects the brain when present in excess. This review provides an overview on the metabolism of LA by the brain and the effects of excess dietary LA intake on brain function. Pre-clinical evidence suggests that excess dietary LA increases the brain’s vulnerability to inflammation and likely acts via its oxidized metabolites. In humans, excess maternal LA intake has been linked to a typical neurodevelopmental delay, but underlying mechanisms are unknown. It is concluded that excess dietary LA may adversely affect the brain. The potential neuroprotective role of reducing dietary LA merits clinical evaluation in future studies.

INTRODUCTION

Linoleic acid (LA, 18:2n-6) is an essential n-6 polyunsaturated fatty acid (PUFA) required for normal growth and development at 1 to 2% of daily energy. LA has become ubiquitous in Western diets over the past few decades due to agricultural shifts towards high-LA soybean and corn oils during the late 1930s, resulting in a greater than 3-fold increase in intake. Historic levels of LA intake ranged between 1 to 2% of daily calories pre-1930s, but currently average more than 7% of daily calories. Based on economic disappearance data, the majority of LA in the US diet comes from soybean oil.

Amongst other dietary PUFAs important for optimal health, LA is the only one that has markedly changed in the diet over the past few decades. Contrary to common misconception, the intake of LA’s elongation-desaturation product, arachidonic acid (AA, 20:4n-6), and the essential n-3 fatty acid, alpha-linolenic acid (ALA, 18:3n-3), and its elongation-desaturation products eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has remained relatively constant at <1% energy since the early 1900s. Excess LA in the food supply has shifted the n-6 to n-3 ratio from 4:1 to 20:1:4.5

Surprisingly, little is known about how this increase in dietary LA affects the brain. It is mainly viewed as an essential precursor to AA, which is important for neurodevelopment and other physiological processes. Despite being a major part of the diet, LA has been considered non-functional in the brain because of its low concentration (<2% of total fatty acids) compared to palmitic acid (16:0), stearic acid (18:0), oleic acid (18:1n-9), DHA, and AA which make up over 84% of brain fatty acids in rats and humans.6.7

LA is known to enter the brain at a rate of ~4 pmol/g/s, which is comparable to the rate of entry of AA, DHA, and other fatty acids into the brain. However, unlike AA and DHA which mostly incorporate into brain membrane phospholipids, the majority (~59%) of LA entering the brain is rapidly β-oxidized into aqueous products, likely composed of carbon dioxide, acetate, and other polar metabolites of β-oxidation. Some of the 2-carbon acetate molecules produced by β-oxidation are recycled into cholesterol via de novo lipid synthesis pathways within the brain.10 LA is also a precursor to oxidized products known as ‘oxidized linoleic acid metabolites’ (OXLAMs) that are produced by auto-oxidation or enzymatically via lipooxygenase (LOX), cyclooxygenase (COX), cytochrome P450 (CYP450), and soluble epoxide hydrolase (sEH). OXLAMs are lipid mediators known to regulate pain and inflammatory signaling in peripheral tissue, where they are abundant. In the brain, they are presumed to be formed by LOX, COX, CYP450, and sEH enzymes, but their role there is not fully understood.

This review highlights the current state of knowledge on the role and metabolism of LA and OXLAMs in the brain. Studies linking LA and OXLAMs to reported biochemical, neuropathological, or behavioral endpoints in chickens, rodents, and humans are discussed, and directions for future research are proposed.

EFFECTS OF LA OR OXLAMS ON CHICKENS

Studies in the late 1950s and 1970s showed that chicks fed a vitamin (V)-E deficient diet containing LA developed encephalomalacia, a neurodegenerative condition characterized by necrosis, edema, and microvascular abnormalities that can lead to ataxia and death. Studies in the late 1950s and 1970s showed that chicks fed a vitamin (V)-E deficient diet containing 1.5% ethyl-AA induced encephalomalacia faster than a V-E deficient diet containing 1.5% ethyl-AA or lard (mixed source of LA and AA). These studies demonstrated that when V-E is absent from the diet, AA and to a lesser extent LA, damage the brain of young chicks. ALA caused no damage. Follow-up studies in chickens demonstrated that oxidized LA metabolites (i.e., OXLAMs) were the likely cause of encephalomalacia, and that this effect was linked by maternal dietary LA content. Bartov and Bornstein reported that maternal intake of a 4% soybean oil (relatively high in LA) or 4% tallow (low in LA) diet containing 5 or 25 mg/kg α-tocopherol acetate each, from 6 to 11 months of age, reduced egg-yolk LA concentration in the tallow group (independent of V-E dietary content), and decreased V-E concentration in yolk of both groups fed the tallow and...
### Table 1. Effect of LA or OXLAMs on neurological outcomes in chickens.

| Reference | Animal model | Age/sex (male, female) | Diet | Duration | Outcome |
|-----------|--------------|------------------------|------|----------|---------|
| Dam et al., 21 | Chicks | 2-day/unknown | V-E-free diet | 28 days | 11/12 chicks died from encephalomalacia in the Vitamin E free + 1.5% ethyl-LA group, versus 0/12 in the other 2 groups |
| Dam et al., 24 | Chicks | ~6-days/unknown | V-E free diet + 30% lard (source of AA) | 35 days\(^a\) | All chicks in lard group developed encephalomalacia by 29 days. All chicks in ethyl AA group developed encephalomalacia with 13 days. Only 70% in ethyl-LA group developed encephalomalacia by 35 days |
| Bartov and Bornstein, 23 | White rock hens | 30 months/female | Maternal diet had 4% soybean oil or tallow with 5 or 25 mg α-tocopherol acetate. Chick diet contained 4 or 10% oxidized safflower oil. | Up to 31 days of age | Increased incidence of ataxia and mortality in chicks born to mothers on a 4% soybean oil diet with low (5 mg) vitamin E content |
| Budowski et al., 25 | Chicks | 1-day/male | Exp 1 (20 chicks per group): V-E free diet + 4% oxidized safflower oil methyl esters | 3 weeks | 35% ataxia; 25% mortality |
| | | | V-E free diet + 10% oxidized safflower oil methyl esters | 2 weeks | 60% ataxia; 45% mortality |
| | | | V-E free diet + 10% safflower oil methyl esters | 19 days | 70% ataxia; 30% mortality |
| | | | V-E free diet + 10% oxidized safflower oil methyl esters | 21 days, from day 8 | 100% ataxia, 75% mortality |
| | | | Exp 2 (20 chicks per group): V-E free diet + 10% oxidized safflower oil methyl esters | 10% ataxia | 50% ataxia |
| | | | V-E free diet + 4% safflower oil methyl esters \(^d\) + 0.3% polar lipid fraction | 21 days, from day 8 | 40% ataxia, 5% mortality |
| | | | V-E free diet + 4% safflower oil methyl esters \(^d\) + 0.2% keto-oleate esters \(^e\) | 21 days, from day 8 | 50% ataxia |
| | | | V-E free diet + 4% safflower oil methyl esters \(^d\) + 0.12% keto-LA esters \(^f\) | 21 days, from day 8 | 80% ataxia |
| | | | V-E free diet + 4% safflower oil methyl esters \(^d\) + 200 µg/g dicumarol | 21 days, from day 8 | 60% ataxia, 40% mortality |
| | | | V-E free diet + 4% safflower oil methyl esters \(^d\) + 400 µg/g dicumarol | 21 days, from day 8 | 40% ataxia, 35% mortality |
| | | | V-E free diet + 4% safflower oil methyl esters \(^d\) + 200 µg/g dicumarol | 7 days | Encephalomalacia seen in: 17% |
| Fischer et al., 22 | Chickens | Unknown | Control diet (“Startena”): V-E basal diet + 150 mg V-E on alternate days | 5, 10 or 15 days | Development of autoflorescent granules, Acid phosphatase reaction products and electron-dense bodies in brain capillaries by day 10 of V-E def + 8% LA group |
| Kokatnur et al., 27 | Chickens | 1 week/male | Exp 1 (12 chicks per group, except last group, n = 11): V-E free diet + 10% corn oil diet | 7 days | Encephalomalacia seen in: 17% |
| | | | V-E free + 10% corn oil diet | | 100% |
| | | | V-E free + 10% corn oil + 0.25% 12-oxo-cis-9-octadecenoic acid | | 42% |
| | | | V-E free + 10% corn oil + 0.25% 12-oxo-octadecenoic acid | | 42% |
| | | | V-E free + 10% corn oil + 0.25% 12-oxo-trans-10-octadecenoic acid | | 91% |
Diet Duration Outcome

| Reference | Animal model | Age/sex (male, female) | Diet | Positive symptoms of Encephalomalacia seen most frequently when oil was achieved by heating it at 145 °C for 24 h.
|-----------|--------------|-----------------------|------|----------------------------------------------------------------------------------|
| Budowski et al. | Newborn male chicks | Non-heated or heated 10% (w/w) saf oil | 0.25% 12-oxo-cis-9-octadecenoic acid methyl ester at 4% or 10% (w/w) | Oxidation of the oil was achieved by heating it at 145 °C for 3 h.
| Kokatnur et al. | Newborn male chicks | Non-heated or heated 10% (w/w) saf oil | 0.25% 12-oxo-cis-9-octadecenoic acid methyl ester at 4% or 10% (w/w) | Oxidation of the oil was achieved by heating it at 145 °C for 3 h.

Note: This table is not fully visible in the provided image. It appears to be part of a larger document, possibly a research paper or report, that discusses the effects of different diets on chick development and health. The table likely includes information on the diets, age, sex, and outcomes related to the study. The text references several studies conducted by Budowski et al. and Kokatnur et al., which have explored the effects of maternal diets on chick development, particularly in the context of vitamin E deficiency and the induction of ataxia and mortality. The studies suggest that maternal diets low in vitamin E or containing oxidized safflower oil can lead to increased ataxia and mortality in offspring. The table might be used to summarize these findings or to organize data from related experiments.
and to a lesser extent oxidized oleic acid metabolites, induce ataxia and mortality due to encephalomalacia in chickens.

In the Budowski et al. study, the administration of the anticoagulant dicumarol to a V-E free diet containing 4% safflower oil reduced the incidence of ataxia and mortality, suggesting that the neurotoxic effects of OXLAMs may be caused by blood coagulation and disturbances in the brain’s microvasculature. This is in agreement with a study by Fischer et al. who showed morphologic changes in cerebral vasculature, characteristic of pre-ceroid formation in adult chickens fed an 8% LA diet lacking V-E, compared to chickens on a similar diet containing V-E. Fully developed ceroids have been linked to neurodegeneration.

EFFECTS OF LA OR OXLAMS ON RODENTS

The few studies that explored the direct role of LA and its metabolites in rodents have shown that LA is involved in regulating brain immunity, seizure threshold, and neuronal signaling, and that some of these effects are mediated by its oxidized metabolites (i.e., OXLAMs).

In rats, LA lowering was found to attenuate LPS-induced neuroinflammation, reduce brain concentration of pro-inflammatory lipid autacoids and increase brain levels of anti-inflammatory lipid mediators. Taha et al. reported that compared to a “high” 5.2% energy LA diet, chronic consumption of a “low” 0.4% energy LA diet for 15–18 weeks, reduced the incorporation rate of radiolabeled AA into the brain and prevented the increase in brain AA-derived prostaglandin E2 concentration and COX-2 activity induced by 2-day lipopolysaccharide (LPS) administration into the 4th ventricle. Two independent studies reported that dietary LA lowering (from 5.2% to 0.4% energy) reduced brain concentrations of pro-inflammatory AA-derived eicosanoids (e.g., 5-Hydroxyeicosatetraenoic acid) and increased concentrations of anti-inflammatory EPA or DHA derived metabolites. This may partially explain why LA lowering increased resilience to LPS-induced neuroinflammation in the Taha et al. study.

Acute administration of LA was reported to confer seizure protection in rats. When infused intravenously at a dose of 0.028 mg/kg, it decreased the incidence of tonic-clonic convulsions by 3-fold, but increased the incidence of cortical spike-wave discharges by 1.5 to 2 folds. Voskuyu et al. showed that intravenous administration of 56–64 mg/kg LA raised cortical focal and generalized seizure thresholds by 3-fold and 1.3–9.0-fold, respectively, in a cortical stimulation seizure model compared to saline and oleic acid controls. The effect of chronic LA administration on seizure thresholds has not been tested.

Recent studies suggest that the effects of LA in the brain are likely mediated by OXLAMs. Hennebelle et al. showed that OXLAMs are increased in various rat brain regions following acute ischemic injury, possibly due to their involvement in the response to ischemic brain injury. Direct application of LA itself to rat hippocampal slices did not alter paired-pulse facilitation within soma or dendrites, whereas LA-derived 13-hydroxyoctadecadecenoic acid (13-HOODE) increased somatic paired pulse facilitation. Although the Hennebelle et al. study raises the possibility that LA’s effects on the brain might be mediated by OXLAMs, it only tested one OXLAM (13-HOODE). Future studies should address the isolated and collective effects of other hydroxy, epoxy, dihydroxy, trihydroxy, and ketone metabolites of LA on neurotransmission and other brain processes.

Although OXLAMs are known to be abundant in rodent brain, it is not known whether they are preferentially formed in the brain from LA, or incorporated directly from circulating OXLAMs provided in the diet. This issue was recently addressed by two studies. Taha et al. fed rats a graded LA diet (0.4%, 5.2%, and 10.4% energy) for 15–18 weeks, and showed that increasing dietary LA increased cerebral cortex and cerebellum OXLAM concentrations in a dose-dependent manner (Fig. 1). In a follow up study, Ramsden et al. fed mice a high LA diet (17% energy), or a low LA diet (4% energy) with or without oxidized corn oil as a source of OXLAMs. The authors found no evidence of dietary OXLAM incorporation into the brain, but consistent with a previous report, the high LA diet increased brain OXLAM concentrations compared to the low LA diet with or without OXLAMs. These studies suggest that dietary OXLAMs are not readily incorporated into rodent (mouse) brain, and that LA is the main source of OXLAMs in the brain. Behavioral studies on dietary OXLAMs in rodents are yet to be performed, as has been done previously in chickens. Notably, although the chicken studies outlined in Table 1 showed an effect of OXLAMs on behavior, none assessed their bioavailability. In rodents, dietary LA hydroperoxides were reported to degrade into aldehydes in the stomach, raising the possibility that the reported effects of OXLAMs on the brain might be mediated by their degradation products.

EFFECTS OF LA OR OXLAMS ON HUMANS

Most of the clinical evidence on the effects of LA on the brain stem from epidemiological studies. One prospective cohort study reported an inverse association between high PUFA intake and mortality linked to neurodegenerative disease. Although it is difficult to establish causation with such studies, the same study, found no association between LA on neurodegenerative disorders after adjusting for confounders using multi-variate analysis, but reported a significant 4–15% risk reduction in neurodegeneration with increased AA, ALA, or EPA and DHA intake. Randomized controlled trials are needed to confirm these findings.

Ramsden et al. reported that dietary LA lowering from 7% to 2% energy combined with a high EPA and DHA diet (~1.5 g per day) for 12 weeks, reduced migraine frequency and improved quality of life in patients with drug-resistant migraine. Lowering dietary LA without changing EPA and DHA did not significantly alter migraine frequency or improve quality of life. Although this study did not have a parallel group that received EPA and DHA alone, it provides evidence of a potential synergistic benefit to lowering LA and increasing EPA and DHA simultaneously. It is possible that longer-term LA lowering regimens might reduce migraine frequency as well, although this remains to be tested.

Several epidemiological studies explored the role of LA on neurodevelopment. Like other dietary fatty acids, LA accumulates...
in breast milk, which is the primary source of infant nutrition for the first few months of life.41 Thus, consistent with the increase in dietary LA in the food supply, breastmilk LA composition has increased from 7% to 12% of total fatty acids between 1970 and 2000.41,42 The 12% composition value corresponds to 8% energy, which exceeds the minimum 1–2% energy required for developing infants by 4–8-fold.7

Overall, studies have shown an adverse effect of maternal breast milk or dietary LA on neurodevelopment. One study reported that a high maternal breast milk LA percent composition (>9.7% of fatty acids) was associated with reduced motor and cognitive scores in 2- to 3-year-old infants.43 In the same cohort, maternal breastmilk LA percent composition was associated with reduced verbal IQ at 5 to 6 years of age.44 In fact, children breastfed with the highest levels of LA had cognitive scores comparable to children who were never breastfed.43 These effects were independent of AA or DHA breast milk composition, suggesting a direct impact of excess breast milk LA (and hence maternal intake) on brain development. Consistent with these findings, Lasser and Gaulin found an inverse correlation between breast milk LA percent composition and cognitive scores in 15-year-old children, suggesting a long-lasting impact of maternal LA on offspring cognitive skills.45 Steenweg-de Graaff et al. also reported a significant positive association between maternal plasma LA composition measured at mid-pregnancy and the risk of autistic traits in children at the age of 6 years.46 A more recent study found that prenatal intake of diets high in the ratio of LA to ALA, was associated with a 2-fold increase in the risk of delayed psychomotor and mental developmental in 6 months infants.47

CONCLUSION

Pre-clinical and clinical studies dispel previous assumptions that LA is a benign fatty acid in the brain. On the contrary, when present in excess and chronically, it induces ataxia in chickens, promotes neuroinflammation in rats and is linked to abnormal neurodevelopment in humans. LA administered acutely to rats confers seizure protection, although its chronic effects on seizures has not been tested.

Recent animal studies suggest that the effects of LA might be mediated by OXLAMs generated from LA entering the brain. Although OXLAMs are present in the diet,48 the extent of their bioavailability and accumulation in the brain from dietary sources appears to be minimal.5,39 However, further assessment of their degradation products on brain neurophysiology and other organs is warranted.

Chronic consumption of low LA diets might protect the brain against inflammation, as evidenced by rat studies showing an anti-inflammatory lipidome in the brains of rats fed a low LA diet,29–31 and human studies showing that LA lowering combined with EPA and DHA reduced headache frequency in patients with drug-resistant migraines.38,39

In conclusion, this review presents evidence that excess LA in the food supply might adversely affect the brain. The potential benefit of LA lowering merits detailed evaluation in well-designed and adequately-powered clinical studies, to test whether this translates into tangible reductions in the risk of neurodegenerative disorders and neurodevelopmental abnormalities at a population level.

Received: 3 September 2018; Accepted: 29 October 2019; Published online: 02 January 2020

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ACKNOWLEDGEMENTS

The author acknowledges Dr. Chris Ramsden for drawing his attention to some of the chicken studies cited herein. Dr. Marie Hennebelle is thanked for creating Fig. 1.

AUTHOR CONTRIBUTIONS

The author wrote the paper.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Supplementary information is available for this paper at https://doi.org/10.1038/s41538-019-0061-9.

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