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Review

Linoleic acid and the pathogenesis of obesity

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ABSTRACT

The modern Western diet has been consumed in developed English speaking countries for the last 50 years, and is now gradually being adopted in Eastern and developing countries. These nutrition transitions are typified by an increased intake of high linoleic acid (LA) plant oils, due to their abundance and low price, resulting in an increase in the PUFA n-6:n-3 ratio. This increase in LA above what is estimated to be required is hypothesised to be implicated in the increased rates of obesity and other associated non-communicable diseases which occur following a transition to a modern Westernised diet. LA can be converted to the metabolically active arachidonic acid, which has roles in inducing inflammation and adipogenesis, and endocannabinoid system regulation. This review aims to address the possible implications of excessive LA and its metabolites in the pathogenesis of obesity.

Contents

Abbreviations: 2-AG, 2-arachidonyl glycerol; 20-HETE, 20-hydroxy-5,8,11,14-eicosatetraenoic acid; 9-HODE, 9-hydroxy-octadecadienoic; 13-HODE, 13-hydroxy-octadecadienoic; AA, arachidonic acid; AEA, anandamide; ALA, α-linolenic acid; BMI, body mass index (kg/m^2); cAMP, cyclic adenosine monophosphate; CD 68, cluster of differentiation 68; COX2, cyclooxygenase-2; CRP, C-reactive protein; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EI, energy intake; EPA, eicosapentaenoic acid; FA, fatty acid; FADS1, fatty acid desaturase 1; FADS2, fatty acid desaturase 2; FAS, fatty acid synthase; FAT/CD36, fatty acid translocase cluster of differentiation 36; HO-1, heme oxygenase 1; IL-1β, interleukin 1β; IL-6, interleukin 6; LA, linoleic acid; MCP-1, monocyte chemoattractant protein-1; MUFA, monounsaturated fatty acid; NF-κβ, nuclear factor kappa-light-chain-enhancer of activated B cells; OA, oleic acid; OXLAMs, oxidised linoleic acid metabolites; PKA, protein kinase A; PPARβ, peroxisome proliferator-activated receptor beta; PPARδ, peroxisome proliferator-activated receptor delta; PPARγ, peroxisome proliferator-activated receptor gamma; PUFA, polyunsaturated fatty acid; RANTES, regulated on activation, normal T cell expressed and secreted; SCD-1, stearoyl-coenzyme A desaturase 1; SFA, saturated fatty acid; SREBP1c, sterol regulatory element-binding protein 1c; T2DM, type 2 diabetes mellitus; TNF-α, tumour necrosis factor α; WHO, World Health Organisation.

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For the last half century, worldwide dietary guidelines and recommendations by peak public health bodies have emphasised the intake of plant based polyunsaturated fats (PUFA), the most abundant of which is the 18 carbon n-6 linoleic acid (LA). Despite this, recent research, and reanalysis of existing data, has questioned the purported beneficial effects of LA and its protective health properties [1]. Importantly, recent research has questioned LA requirements to meet physiological needs, with the current estimated requirements of 0.2-0.4% of total energy intake (EI) being approximately 5–10 times less than what has previously been accepted [2,3]. This is due to the unintentional exclusion of α-linolenic acid (ALA) from the diets used in the original research assessing LA adequacy, the addition of which prevents deficiency symptoms at lower LA intakes [3]. Similarly, a major flaw in the early research investigating replacing saturated fatty acids (SFA) with PUFA to decrease cardiovascular disease (CVD) risk is the absence of consideration of the n-3 PUFA family (including ALA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) [1,4,5]. It has recently been determined that the increase in LA in the original research assessing CVD prevention resulted in a concomitant increase in n-3 PUFA, due to changes to dietary composition, conferring the observed cardiovascular benefits [5]. Due to these factors, some have gone as far as beginning to question LA essentiality, though it is agreed that far more research is required [2]. In addition there is still a lack of consensus on whether the ratio of fatty acids (FA), the proportions of particular FA (e.g. n-6 PUFA: n-3 PUFA ratio) in the diet, or the specific load of FA is more important in its impact on health and disease, making definitive conclusions difficult to draw.

Current Australian dietary recommendations state that 10% of energy from LA is an acceptable level, based off levels of intake which appear not to have negative effects on health [6]. US recommendations only state that an intake level of LA is required to prevent deficiency [7], with evidence that long term/large scale human research is lacking [8]. The current intake of 6.0% of total energy in Australia [9], and 7.2% [10] in the United States, are however between 14 and 18 times what is required to prevent deficiency.

Worldwide, many studies have shown an increase in dietary LA, regardless of the methodologies used to collect the food intake data (e.g. self-reporting recall, food disappearance data/balance sheets, adipose and erythrocyte FA composition) [9–12]. This increase in LA is believed to have resulted from a series of country or region-specific nutrition transitions [13]. Nutrition transitions involve changes to agricultural practice, strengthened transport and trade networks, increased urbanisation of populations and globalisation of food systems [14]. These nutrition transitions have resulted in a shift towards a more homogenous diet worldwide, with many traditional foods (e.g. wild yams and cowpea in East Africa [15]) all but disappearing from diets, replaced by a higher proportion of processed and ultra-processed snack foods [16–18]. During almost all of the nutrition transitions worldwide (with South Korea being an exception [19]) an increase in energy from plant based fats has occurred, resulting in an increase in dietary LA [13]. Furthermore, due to changes in animal feed practices resulting in an increase in grain feeding, animal products now also have an increased LA content than their traditional counterparts [20,21]. A key follow-on from these nutrition transitions has been an increase in obesity rates and the prevalence of non-communicable diseases such as CVD and type 2 diabetes mellitus (T2DM) [22].

Due to changes in dietary patterns in developing, African or Eastern countries occurring over a relatively short time span, it is possible to hypothesise that there is a link between the elevated consumption of LA in these populations and an increased risk of developing obesity. Currently African countries including Botswana, Lesotho, Namibia, Swaziland and South Africa are undergoing nutrition transitions, with the higher socio-economic countries beginning to notice the negative effects associated with dietary change, in the form of increased obesity and non-communicable disease rates [23]. In southern African countries the World Health Organisation (WHO) estimates that 40–60% of adults aged 25–64 are overweight, with urban southern Africans having a higher fat intake than their rural counterparts (due to an increase of all fat classes) [24,25]. This increased fat intake is possibly influenced by the increase in vegetable oil consumption due to its lower purchase price, with an intake of 11.5% of energy from LA being found in a Zambian population subset [26]. Additionally, Inuit populations of the Canadian Arctic are also currently undergoing a nutrition transition, demonstrated by a decrease in the intake of traditional foods (including marine products) and an increase in dietary and erythrocyte LA levels, with a concomitant decrease in all major n-3 FA [27].

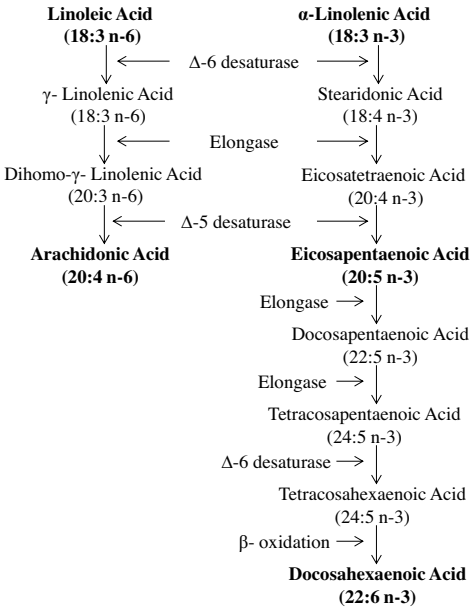

Fig. 1. Metabolism of the essential fatty acids linoleic and α-linolenic acid to longer chain fatty acids. This figure shows the common enzymes required for these conversions [28,29], the fatty acids of importance to this review are shown in bold.

This increase in LA intake is an important factor in health and disease development due to its ability to decrease the incorporation of n-3 PUFA into phospholipid membranes [28]. In addition LA and ALA compete for the same enzyme (Δ-6 desaturase) for their conversion to arachidonic acid (AA) and DHA and EPA, respectively [29] (Fig. 1 summarises the two conversion pathways). Importantly, high LA levels decrease the conversion of ALA to DHA and EPA [29]. Though both n-6 and n-3 FA are capable of being converted into inflammatory mediators the n-3 products have lower inflammatory properties and in some instances (e.g. the series 3 prostaglandins and thromboxanes) are anti-inflammatory [30].

1. Linoleic acid induced inflammation: is adiposity a factor?

The role of LA in inflammation has been extensively debated, due in part to the majority of dietary guidelines worldwide recommending people replace saturated FA (generally from animal products) with plant oils to decrease CVD risk [31]. AA, generated from LA or from dietary AA intake is capable of being converted into numerous inflammatory metabolites by cytochrome P450, cyclooxygenase and lipoxygenase pathways [32]. The AA metabolite 20-Hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) is capable of inducing oxidative stress and is