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Mini-review

Linoleic acid: Between doubts and certainties

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ABSTRACT

Linoleic acid is the most abundant polyunsaturated fatty acid in human nutrition and represents about 14 g per day in the US diet. Following the discovery of its essential functions in animals and humans in the early 1920's, studies are currently questioning the real requirement of linoleic acid. It seems now overestimated and creates controversy: how much linoleic acid should be consumed in a healthy diet? Beyond the necessity to redefine the dietary requirement of linoleic acid, many questions concerning the consequences of its excessive consumption on human health arise. Linoleic acid is a direct precursor of the bioactive oxidized linoleic acid metabolites. It is also a precursor of arachidonic acid, which produces pro-inflammatory eicosanoids and endocannabinoids. A majority of the studies on linoleic acid and its derivatives show a direct/indirect link with inflammation and metabolic diseases. Many authors claim that a high linoleic acid intake may promote inflammation in humans. This review tries to (i) highlight the importance of reconsidering the actual requirement of linoleic acid (ii) point out the lack of knowledge between dietary levels of linoleic acid and the molecular mechanisms explaining its physiological roles (iii) demonstrate the relevance of carrying out further human studies on the single variable linoleic acid.

Because they are basic components involved in the architecture and function of cellular membranes, polyunsaturated fatty acids (PUFA) play key roles in several biological processes. PUFA are endogenous mediators for cell signaling and involved in the regulation of gene expression. They are also precursors of eicosanoids such as prostaglandins and leukotrienes [1–3], and docosanoids such as protectins or resolvins [4]. By contrast with the nutritional dietary recommendations of n-3 PUFA which are clearly defined and consensual (amounts and types), the recommendations of the n-6 PUFA are more controversial. Their precursor, linoleic acid, is essential for human development (growth) and plays an active role in good health in general. Due to changes in agricultural practices, the intake of linoleic acid has increased over the last century. For example in the US diet, the median intake of linoleic acid represents 6% of total energy (14 g for 2000 kcal) [5]. Because the physiological requirement of linoleic acid appears to have been overestimated due to methodological bias during early investigations performed in the 1920's, the hypothesis that the current intake of linoleic acid could contribute to the development and increase of inflammation and metabolic diseases has gained momentum [6].

The purpose of this review is to present the necessity to re-estimate the physiological requirement and the general recommendations concerning linoleic acid. After a brief history of the studies which have contributed to demonstrate the essentiality of dietary linoleic acid, we describe the putative consequences of an excess of dietary linoleic acid. Finally based on elucidated biochemical mechanisms and putative physiological roles, we try to summarize why linoleic acid is still controversial in terms of dietary recommendations and drives two points of view in the nutritional debate: one which considers its deleterious pro-inflammatory properties and one which estimates that the linoleic acid requirement should increase up to 10–15% of the energy intake [7].

1. Consequences of a deficiency in linoleic acid

The first reports dating back to the 1920's claimed that dietary fats contained two vitamin-like substances, soon identified as linoleic acid (18:2 n-6) and α linolenic acid (18:3 n-3), precursors respectively of the n-6 and n-3 fatty acid families (Fig. 1). The first demonstration of essential requirement for linoleic acid in animal diet was obtained by Burr and Burr in 1929–30 [8,9]. They showed in the rat that the single linoleic acid consumption was able to prevent or correct the physiological symptoms of dietary total fat deficiency. Indeed rats receiving 0.6% of total diet mass of linoleic acid were 30% higher in body weight compared to total fat deficient group and did not develop skin desquamation and tail necrosis. Linoleic acid was thereafter described as an essential fatty acid. Subsequently, many dose–response studies designed by Holman

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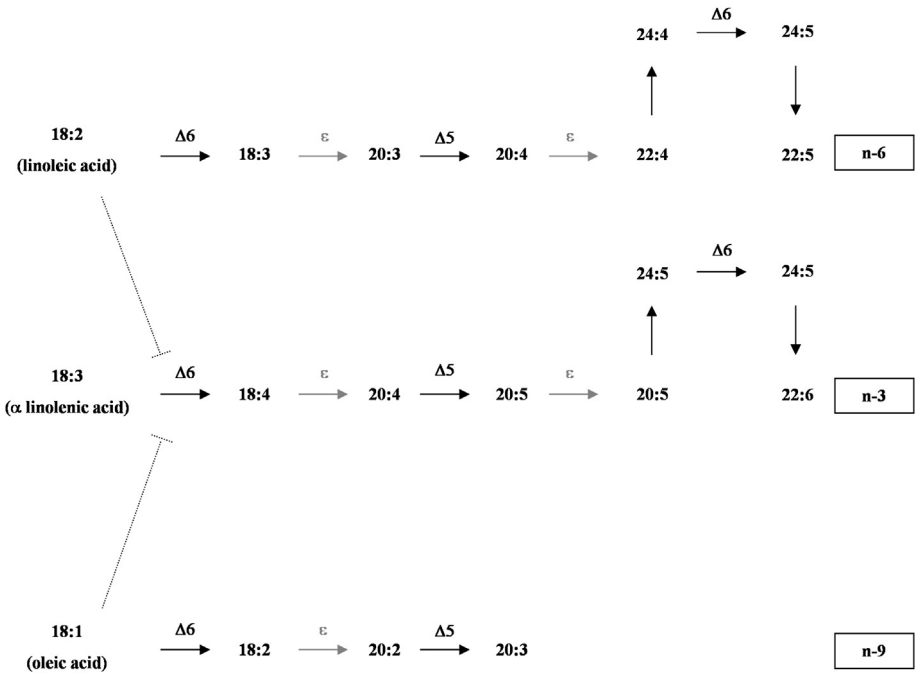

Fig. 1. The conversion of essential n-6, n-9 and n-3 polyunsaturated fatty acids to their longer chain more unsaturated derivatives.
Δ6: Δ6 desaturase; Δ5: Δ5 desaturase; ε: elongase ····· Inhibition.

during the 1950's tried to evaluate the optimal linoleic acid intake [10] based on health markers described in Burr and Burr studies. These works pointed out all physiological symptoms of linoleic acid deficiency (growth rate, fertility and skin symptoms) and histological changes in organs (liver, kidney and lung). These studies led to the widely admitted linoleic acid requirement in animals at about 1% of the dietary energy intake [11]. However, n-6 and n-3 PUFA have been acknowledged as nutritionally distinct since the 1960s and the first requirements of linoleic acid established in Burr and Holman studies did not take care of α linolenic acid dietary intake [12]. Nevertheless, the basis requirement of 1% was commonly accepted and extended to 2% of the dietary energy intake in humans to ensure the dietary requirement, as confirmed by two studies where the physiological symptoms of n-6 deficiency in human infants (scaling of the skin) were abolished [13,14]. It is however important to keep in mind that dietary requirements for linoleic acid were established using control diets deficient in both n-3 and n-6 polyunsaturated fatty acids and not exhibiting an exclusive n-6 PUFA deficiency. This double deficiency in the control diets seems to invalidate the majority of generated data for establishing n-6 requirement. Indeed, the concomitant absence of n-3 PUFA has corrupted the correct experimental plan and therefore the conclusion [15]. For example, Mohrhauer and Holman [16] have demonstrated that a 1.8% dietary energy intake of α linolenic acid made normal growth possible in rats consuming linoleic acid at 0.3% of energy intake. Moreover, several studies have shown that a minimal of 0.5% energy intake of α linolenic acid is required for normal reproduction and development [12,16–20]. Two recent studies have also shown that dietary α linolenic acid is able to diminish the symptoms of n-6 PUFA deficiency [21,22]. Thus the latter studies suggest that the absence of α linolenic acid in the former studies have probably heightened the significance of the physiological symptoms caused by a single linoleic acid deficiency. To conclude, it seems that at least for the rat model, the nutritional requirement in linoleic acid has probably been overestimated. Recently, Guesnet et al. recommended a more precise estimation of the linoleic acid requirement and evaluated that a more appropriate intake could be closer to 0.5% of the dietary energy rather than 2% [21]. Moreover, because the linoleic acid nutritional requirement has probably been overestimated, the same report [21] suggested that the actual intake (ratio linoleic acid/α linolenic acid >12) [23] could be considered as an excess and could therefore lead to negative side effects. Currently, linoleic acid is therefore still a hot topic for investigations.

2. Consequences of an excess of linoleic acid for several metabolic pathways

2.1. High levels of linoleic acid can reduce the conversion of α linolenic acid into highly unsaturated n-3 fatty acids

In the liver, long chain PUFA are synthetized from both dietary linoleic and α linolenic acids according to a similar multi step pathway including fatty acid desaturations and elongations (Fig. 1). The Δ6 desaturase (FADS2) catalyzes the first step of this common pathway and is described as the rate limiting enzyme [24]. Thus, linoleic acid shares the same enzymatic system and can compete with α linolenic acid conversion [25,26]. This competition also occurs with oleic acid, which is another known substrate for Δ6 desaturase. Indeed, when incubating α linolenic acid (0.01 μmol) *in vitro* in the presence of increasing amounts of linoleic or oleic acids (from 0 to 0.2 μmol), Brenner and Peluffo showed an inhibition of the conversion of α linolenic acid to longer n-3 fatty acids in rat liver microsomes (Fig. 2) [27]. In this study linoleic and oleic acids decreased by 25% and 15% the Δ6 desaturation of α linolenic acid toward 18:4 n-3, respectively.

More recently, physiological studies have shown a direct link between the nutritional status of linoleic acid and the activity of the Δ6 desaturase. Skrzypski et al., have reported that starch-based diets containing linoleic acid (4 g/100 g diet) as the single source of lipid led to a 40% increase of the Δ6 desaturation capacity in rat liver microsomes. In another study, the use of diets moderately enriched in linoleic acid (2.2 g/100 g), showed an increase in Δ6 desaturase activity but also a significant decrease in n-3 fatty acid