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Endogenous formation of *trans* fatty acids: Health implications and potential dietary intervention

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ABSTRACT

Unsaturated fatty acids naturally occur as *cis* configuration and most dietary *trans* fatty acids (TFAs) originate from partially hydrogenated oils. High consumption of *trans* fats may cause several adverse effects on human health. However, the dietary source is not the only path by which TFAs are produced, but *in vivo*, they can also be formed endogenously via oxidative stress and by free radicals. Recent studies have demonstrated that thiyl radicals and nitrogen dioxide serve as the effective catalysts responsible for endogenous TFA formation through *cis–trans* isomerisation. Several *in vivo* studies have indicated that the occurrence of endogenous TFAs is closely linked with the development of some chronic diseases. Additionally, some vitamins and polyphenols exhibit inhibitory effects against the free radical-catalysed TFA formation in different *in vitro* experiments. Therefore, we postulate that dietary supplementation of antioxidants may serve as an effective strategy against endogenous TFA formation during pathogenesis of chronic diseases.

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Abbreviations: AAPH, 2,2′-azobis(2-amidinopropane) dihydrochloride; AD, Alzheimer's disease; BHT, 2,6-di-tert-butyl-4-methylphenol; DOPC, 1,2-dioleoylphosphatidylcholine; GC, gas chromatography; hAPP, human amyloid precursor protein; iNOS, inducible nitric oxide synthase; 2-ME, 2-mercaptoethanol; LPS, lipopolysaccharides; LUVET, large unilamellar vesicles; MUFA, monounsaturated fatty acids; NF-κB, nuclear factor kappa B; OIR, oxygen-induced retinopathy; POPC, 1-palmitoyl-2-oleoylphosphatidylcholine; PUFA, polyunsaturated fatty acids; RNase A, ribonuclease A; SAPC, 1-stearoyl-2-arachidonoylphosphatidylcholine; STZ, Streptozotocin; TFAs, *trans* fatty acids; THP-1, monocytic leukemia cells; TNF-α, tumour necrosis factor alpha

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Contents

1. Introduction

Fatty acids are considered one of the most important constituents in living organisms due to their structural role in cell membranes and as sources of metabolic energy. Most natural unsaturated fatty acids in eukaryotes typically occur as *cis* configuration, which is strictly controlled by the stereoselectivity of desaturase enzymes (Fox, Lyle, & Rogge, 2004). The *trans* double bonds of unsaturated fatty acids only exist naturally in some bacteria or ruminants (Cronan, 2002; Kelley, Hubbard, & Erickson, 2007; Park, Albright, Storkson, Liu, & Pariza, 2007). Most *trans* fats come from partially hydrogenated vegetable oils, a process of hardening liquid vegetable oils and fats. Hence, the major dietary sources of *trans* fats include shortening, margarines, deep-fried fast foods, bakery products and crackers (Mozaffarian, Katan, Ascherio, Stampfer, & Willett, 2006).

Many nutritional and epidemiological studies indicate that the high consumption of *trans* fats may cause several adverse effects on human health including cardiovascular disease, diabetes mellitus and cancers (Mozaffarian et al., 2006; Smith, Robinson, Nam, & Ma, 2009; Thompson, Minihane, & Williams, 2011). Much epidemiological evidence has demonstrated that the high consumption of *trans* fats is a significant risk factor of cardiovascular disease. For example, in a community-based case-control study, the levels of *trans* isomers of linoleic acid were directly correlated with a 3-fold increase in risk of sudden cardiac death after adjustment for other risk factors (Lemaitre et al., 2002). The consumption of a diet containing large amounts of hydrogenated oil promoted inflammatory responses, such as increasing the production of prostaglandin E2, tumour necrosis factor alpha (TNF-α) and interleukins in a double blind cross-over study (Han et al., 2002). It is estimated that replacing 2% of energy obtained from TFA with unhydrogenated fats could reduce the risk of coronary heart disease (CHD) by 53% (Hu, Manson, & Willett, 2001). Emerging evidence also suggested that consumption of *trans* fats is correlated with diabetes (Salmeron et al., 2001). During a 14 year of follow-up, a prospective study indicated that the intake of *trans* fats was associated with risk of type 2 diabetes (Salmeron et al., 2001). In addition, *trans* fats may also have a positive link to cancers (Kohlmeier et al., 1997).

Due to several adverse health effects caused by high human intake of *trans* fats, many countries are regulating the removal of *trans* fats from foods. The amount of *trans* fats in products such as baked foods, meals and desserts has been dramatically reduced since the execution of these TFA-banned rules (Brownell & Pomeranz, 2014). However, the elimination of *trans* fats from diet may not guarantee prevention of the adverse effects caused by TFAs. In the past few years, it has been shown that the occurrence of TFAs *in vivo* is not only exogenously obtained from dietary sources but also endogenously generated by oxidative/radical stress (Zambonin et al., 2006, 2008). Thiyl radicals and nitrogen dioxide have emerged as the major free radicals that can catalyse the *cis–trans* isomerisation process to form *trans* double bonds in fatty acids (Chatgilialoglu, Ferreri, Melchiorre, Sansone, & Torreggiani, 2014). Conjugated linoleic acids (CLAs), which have been studied extensively for their health benefits, also contain *trans* double bonds (Yang et al., 2015). However, CLAs cannot be formed through thiyl radicals and nitrogen dioxide. In this review, the mechanism of the *cis–trans* isomerisation reaction by free radicals and the occurrence of endogenously formed TFAs in certain pathophysiological conditions or chronic diseases are presented. A discussion of using antioxidants for inhibiting the formation of endogenous TFAs will also be included.