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Oleic acid promotes adaptability against oxidative stress in 3T3-L1 cells through lipohormesis

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Abstract Although fatty acids are important components of biological membranes, energy sources, and signal transducers or precursors of lipid mediators, excess intake of fatty acids and their accumulation cause obesity and metabolic syndrome. Thus, fatty acid quantity is known to be an important factor for obesity-related diseases, but the effects of different types of fatty acids (i.e., fatty acid quality) on human health are not completely understood. We here focused on the relationship between fatty acid quality and oxidative stress by investigating whether resistibility to *tert*-butyl hydrperoxide (*t*-BuOOH)-induced oxidative stress in 3T3-L1 cells varied according to the fatty acid type. Among eight fatty acids (both saturated and unsaturated) tested, oleic acid (OA) exerted the most pronounced cytoprotective effects, with efficacy over a wide range of concentrations. OA treatment markedly enhanced the intracellular levels of lipid peroxidation markers, including N^{ϵ}-(hexanoyl)lysine, 4-hydroxy-2-nonenal, and acrolein. The levels of these markers in OA-treated cells were decreased after *t*-BuOOH exposure, whereas the levels in untreated control cells were notably increased after *t*-BuOOH exposure. Our results suggested that unsaturated fatty acids, particularly OA, could promote an adaptive response and enhance cell tolerance through increased cellular antioxidative capacity via OA-induced mild lipid peroxidation (lipohormesis), and thus protect cells against subsequent oxidative stress-related injury.

Keywords Oleic acid · Fatty acid quantity · Fatty acid quality · Lipid peroxidation · Cell injury · Lipohormesis

Introduction

Fatty acids have important functions as components of biological membranes, energy sources, and signal transducers or precursors of lipid mediators. However, excess intake of fatty acids and their accumulation in adipose tissues can induce inflammation, endoplasmic reticulum stress, and oxidative stress [1–3], whereas lipid accumulation in non-adipose tissues, including the pancreas, heart, liver, kidney, and blood vessel walls, can cause cell dysfunction and cell death, termed lipotoxicity [4, 5]. These fatty acid-overloaded states cause obesity, type 2 diabetes, and arteriosclerosis, which ultimately results in metabolic syndrome and serious medical complications [1, 2, 6]. Thus, it is apparent that the "fatty acid quantity" is closely related to the onset of various diseases. In addition, it is believed that the differences in the types and composition ratios of fatty acids, i.e., "fatty acid quality," play critical roles in regulating various cellular functions. For example, it is well known that n-3 polyunsaturated fatty acids (PUFAs) have anti-inflammatory properties, whereas saturated fatty acids or n-6 PUFAs have pro-inflammatory properties. Epidemiological studies have reported that n-3 supplementation had beneficial effects on cardiovascular disease [7] and that a reduced n-3/n-6 ratio was associated

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