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HYPOTHESIS
Are Fatty Acid Patterns Characteristic of Essential Fatty Acid Deficiency Indicative of Oxidative Stress?

JOHN M. C. GUTTERIDGE[a,*], GREGORY J. QUINLAN[b] and YORIHIRO YAMAMOTO[c]

[a]*Oxygen Chemistry Laboratory, Directorate of Anaesthesia and Critical Care, Royal Brompton Hospital, Sydney Street, London, SW3 6NP,* [b]*National Heart and Lung Institute, Imperial College of Science Technology and Medicine, and* [c]*Research Centre for Advanced Science and Technology, University of Tokyo, Komaba, Tokyo 153, Japan*

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Several unrelated diseases show plasma and tissue fatty acid patterns characteristic of those seen in Essential Fatty Acid Deficiency Disease (EFADD). A common feature occurring in all these diseases is oxidative stress. We hypothesize that reactive oxygen species or products of oxidative damage, particularly those derived from lipids, act as signal molecules to alter desaturase enzymes and induce the fatty acid patterns characteristic of EFADD.

Keywords: Essential fatty acid deficiency, desaturases, oxidative stress, lipid peroxidation, antioxidants, signal molecules

OXIDATIVE STRESS AND PATTERNS OF ESSENTIAL FATTY ACID DEFICIENCY

Free radicals have been implicated in almost every disease state (reviewed in 1). A major question, therefore, is whether they play causative or consequential roles. In the latter context it should be remembered that almost any form of tissue damage is accompanied by increased free radical activity.[2]

Oxidative stress occurs when an imbalance is brought about between the generation of molecules involved in oxidative reactions and the body's ability to remove them.[3] Their formation may exceed normal protection, or protection may fail to cope with normal levels of them. Oxidative stress often triggers an adaptive gene response whereby new proteins are upregulated to cope with the additional stress. These proteins are collectively known as oxidative stress and heat shock proteins. If oxidative stress persists, oxidative molecular damage is inevitable with every biological molecule at risk. Lipids, proteins, and DNA are modified in a way usually characteristic of the oxidising species. The most intensively

* Corresponding author. Tel.: (618)82224320. Fax: (618)82233870.

studied of these oxidations is the peroxidation of polyunsaturated fatty acids (PUFAs). The more double bonds the PUFA has the more susceptible to peroxidation it becomes, fragmenting to a plethora of primary peroxidic and secondary aldehydic products. The extreme susceptibility of PUFAs to oxidation might in itself be protective by sacrificially removing the free radicals with which they react. It is interesting to note that PUFA-containing molecules such as phosphatidylcholine (lecithin) have long been used as antioxidants by the food industry (see Waters 1971).[4]

Many years ago[5] we suggested that the products of lipid peroxidation, resulting from tissue damage, may serve as signal molecules for regeneration or repair. It is interesting to extend this speculation to the desaturase enzymes. Depending on the level of oxidative stress, desaturase enzymes might be 'activated' or 'inactivated' by products of PUFA peroxidation. Could the loss of ω3 and ω6 PUFAs by oxidative stress-induced peroxidation provide the signal for Δ9—desaturase activity? To understand the background to this proposal we give a brief introduction to fatty acids and essential fatty acid deficiency.

FATTY ACIDS AND ESSENTIAL FATTY ACID DEFICIENCY

There are two main types of fatty acids, namely saturated and unsaturated; the former containing no double bonds. Fatty acids are named after their parent hydrocarbons with the addition of the suffix "oic". For unsaturated fatty acids the position of the double bond is indicated by either: (A) designate the terminal COOH group as C1 and count back to the methyl end of the fatty acid. Using this system oleic acid can be defined as Δ9, 10 octadecenoic acid. (B) In the second system the terminal methyl group is designated as ω (omega) and the first carbon having a double bond is counted. Using this system oleic acid is 18: 1 ω 9. The naturally occurring fatty acids we shall be describing here are either ω3, ω6, ω7 or ω9. In 1929 George and Mildred Burr,[6] at the University of Minnesota, published their studies which showed that dietary fat was essential for the survival of mammals. In the absence of fat, rodents developed a deficiency disease which could be prevented, or cured, when certain polyunsaturated fatty acids, particularly linoleic acid, were present. They, therefore, coined the term "essential fatty acids" and observed and described essential fatty acid deficiency (for a review see Holman, 1966).[7] Symptoms of essential fatty acid deficiency (EFAD) in rats were most noticeable from diminished growth rates and lower body weights (although the weight of certain individual organs actually increased) and from the development of dermatitis (reviewed in 7). Animals fed fat-free diets generally showed a loss in plasma and tissue, particularly in liver, of hexaenoic and pentaenoic acids and extremely low levels of linoleic acid, whereas 20:3 (ω-9), often called mead acid, oleic, and palmitoleic (ω7) acids usually increased. Human studies of low-fat intakes show similar changes in fatty acids with often a high incidence of respiratory tract complications.

From the pioneering work of Burr and Burr it is clear that saturated fatty acids and fatty acids of the ω9 and ω7 families are unable to maintain the health of mammals, and diets, therefore, require the addition of ω3 and, or, ω6 fatty acids. Because mammals lack Δ_{12}- and Δ_{15}-desaturases they have to obtain their ω3 or ω6 fatty acids from dietary origin. For this reason, as previously discussed, they are called "essential fatty acids".

FATTY ACID DESATURASES

The body can synthesize fatty acids such as palmitic acid (16:0) from acetyl-S-CoA derived from carbohydrate, or some aminoacids, and the chain length can be increased by an elongase enzyme system to form stearic acid (18:0) and longer-chain saturated fatty acids. Long-chain polyunsaturated fatty acids (PUFAs) can be made from stearic acid by a group of enzymes

TABLE I Some conditions in which changes in fatty acid patterns are characteristic of essential fatty acid deficiency

Condition	*Oxidative Stress*	*Comments*	References
Alloxan and Streptozotocin treated diabetic rats	Redox cycling drugs	Δ9—desaturation of stearic acid decreased and impaired Δ5—desaturase activity	11, 12
Diabetes	Abnormal glycation reactions	Decreased desaturase activities particularly Δ6—desaturation—18:2 ω 6 normal but 18:3 ω6 low	13, 14
Vitamin E and Selenium deficiencies	Antioxidants	Proposed that vitamin E and selenium play a role in desaturation of ω3 and ω6 *PUFAs*	15
Cystic fibrosis	Impaired fat absorption including vitamin E	Low serum levels of EFA with pulmonary infections	16, 17
Copper deficiency	depleted CuZnSOD activity and increased lipid peroxidation	Decreased 18:2 ω6 and 20:4 ω6 and increased 16:1 ω 7	18
Kwashiorkor	Low nutritional antioxidants and increased mobilization of reactive forms of iron	Fatty acid patterns characteristic of EFAD often found	19
Adult respiratory distress syndrome	High FIO_2 therapy, and activated neutrophils in the lungs	Decreased plasma 18:2 ω6 with increased 18:1 ω9 and 16:1 ω7	20
Chronic carbon tetrachloride (CCl_4) poisoning	CCl_4 activated to a radical species which damages the liver	Rapid decrease in plasma levels of PUFA and rapid increase in level of 16:1 ω7 and 18:1 ω9	21
Acute carbon tetrachloride poisoning	CCl_4 activated to a radical species which damages the liver	Decrease in PUFA and increase in 16:1 ω7 and 18:1 Δ9 in plasma and liver. Increase in Δ9 desaturase activity in liver	22
Multiple sclerosis (MS) Neurological diseases Acute diseases (non-neurological)	Sick patients under oxidative stress	Treatment of MS patients with 18:2 ω6 suggested that relapses were less frequent and less severe	23
		In all groups serum lipid patterns were characteristic of EFAD (low 18:2 ω6, increased 18:1 ω9, 16:0, and 16:1 ω7)	24

TABLE I *(Continued)*

Condition	Oxidative Stress	Comments	References
Long Evans Cinnamon (LEC) rat model of fulminant hepatitis, hepatic cancer, and Wilson's disease	Iron and Copper overload	Increase in plasma level of 16:1 ω7 after the onset of hepatitis. Prevention of hepatitis and increase in plasma 16:1 ω7 by treatment with a copper chelator	25
Sudden cardiac death	Epidemiological links between low antioxidant status and intake, and risk of death from heart disease	The percentage content of linoleic acid in adipose tissue was inversely related to risk of sudden cardiac death	26
	Increased LDL peroxidation leads to macrophage scavenger receptor recognition and unregulated uptake of LDL to form foam cells and ather osclerotic lesions	'Sinclair hypothesis' (1956) coronary thrombosis due to a deficiency of linoleic acid	27
β-Thalassaemia major	Low molecular mass iron often present (LMrFe). Decreased levels of vitamin E and vitamin C	Red blood cells show low 18:2 ω6 and increased 18:1 ω9	28
Umbilical cord blood cells	LMrFe often present. Decreased vitamin E, thiols and caeruloplasmin present in the plasma at birth	Red blood cells show low 18:2 ω6 and increased 18:1 ω9	28

known as desaturases which allow double bonds to be introduced. Thus, Δ9-desaturase introduces a double bond between the 9th and 10th carbon from the COOH end, and other desaturases are named in a similar way. Restrictions to the introduction of double bonds above C-9, by the desaturases, means that only members of the ω9 and ω7 PUFA families can be endogenously formed biosynthetically (reviewed in 8).

DISEASES WITH FATTY ACID PATTERNS CHARACTERISTIC OF ESSENTIAL FATTY ACID DEFICIENCY

To support our hypothesis we have listed in Table I several conditions in which some form of oxidative stress can lead to changes in fatty acid patterns characteristic of EFAD. Δ9-desaturase can convert palmitic and stearic acids respectively into 16:1 ω7 and 18:1 ω9 fatty acids, and so it seems likely that this enzyme is in some way sensitive to oxidative stress. The increased synthesis of oleic acid during situations of oxidative stress is often significant and probably represents an adaptive response to loss of PUFAs. Large increases in oleic acid, however, may not necessarily be beneficial to the host since this fatty acid is frequently used to induce experimental acute lung injury.[9,10] It is interesting to note that respiratory problems are a common feature of induced EFAD. Finally, is it possible that 'essential fatty acid deficiency disease is itself a classical example of an oxidative stress disease?

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