Linoleic acid, antioxidants and coronary heart disease

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Questions

1. Why do populations with a high incidence of coronary heart disease (CHD) and coronary patients have a low dietary intake and low tissue concentrations of linoleic acid?

2. What is the status of naturally occurring antioxidants in relation to CHD?

3. What is the pathogenic significance and the therapeutic implication of low dietary and tissue linoleic acid and low anti-oxidant levels?

Adipose linoleic acid and CHD

More than 30 years ago, Sinclair postulated that a deficiency of arachidonic acid might lead to atherosclerosis [1]. He asked whether 'diets high in saturated unnatural fats and low in essential fatty acids occur'. Many populations have been shown to contribute to a better understanding of the role of these fatty acids in cell function. It may thus open the development of new approaches to the therapy and prevention of disorders in which cellular responses to injury, such as inflammation and exaggerated cell proliferation, are a hallmark of the disease process [25–27].

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Adipose linoleic acid and CHD

More than 30 years ago, Sinclair postulated that a deficiency of arachidonic acid might lead to atherosclerosis [1]. He asked whether 'diets high in saturated unnatural fats and fairly low in essential fatty acids occur'. Many populations with low dietary and tissue linoleic acid and low density lipoprotein.

n-6 unsaturated fatty acids in our food chain, i.e. in vegetable oils and in livestock fattened with grain rich in C18:2, n-6, which is slowly desaturated and elongated to AA in the mammalian organism. The further evaluation of the relationship between n-6 versus n-3 fatty acids and their eicosanoids and membrane receptor function, the modulation of transmembrane signalling mechanisms, phospholipase activation, formation of 1,2-DAG and PAF, Ca2+ release, modified phosphate turnover and gene expression should contribute to a better understanding of the role of these fatty acids in cell function. It may thus open the development of new approaches to the therapy and prevention of disorders in which cellular responses to injury, such as inflammation and exaggerated cell proliferation, are a hallmark of the disease process [25–27].

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compared with Stockholm men and, on multivariate analysis, that this was an independent risk factor for CHD. This inter-
population difference in adipose linoleic acid was confirmed by us with the demonstration of lower adipose linoleic acid in North Karelia, where CHD mortality is highest, and high levels in Calabria where CHD mortality is low [4]. Adipose linoleate levels in Edinburgh were similar to those in North Karelia. Subsequently, we have demonstrated that apparently healthy individuals who were found to have clinically occult CHD had lower adipose linoleic acid concentrations than comparably healthy men without CHD [5]. These data were obtained from a cross-sectional survey of a random sample of 448 middle-aged men living in Edinburgh. North Karelia, South-West Finland and Calabria in Italy showed no consistent relationship between plasma carotene, vitamins A, C and E and CHD mortality. These studies have been extended and an inverse relation between plasma vitamin E plus C with CHD mortality rates has now been reported [12].

A recent unpublished study (Edinburgh data) of case-
control design has shown that is high levels of vitamin E and C and carotene in plasma are related to an increased risk of angina pectoris in men. For plasma vitamin E (standardized for plasma lipid concentration), this relation remained highly significant (P < 0.02) after adjustment for conventional risk factors such as total and high-density lipoprotein cholesterol, non-fasting triacylglycerol, blood pressure, weight and smoking. A similar inverse relationship existed for plasma vitamin C levels and angina but this was confounded by cigarette smoking, although it still remained significant. The inverse relationship between vitamin C and smoking habit has been widely reported elsewhere.

Relation to cardiovascular risk factors

There are a number of mechanisms through which low tissue levels of linoleic acid might favour the development of atheroma and coronary heart disease. Low ω-6 fatty acid intake means in general, a relatively high intake of saturated fats and therefore the possibility of higher plasma cholesterol and low density lipoprotein concentrations in such populations and people. There will probably be an increased tendency to thrombosis among smokers. Within the lowest quartile for plasma vitamin E plus C, smokers were more likely to have cardiovascular disease and angina pectoris in men. For plasma vitamin E, this relation remained significant after adjustment for conventional risk factors.

Low tissue concentrations of naturally-occurring anti-
oxidants might lead to impaired free radical scavenging activity and long chain polyunsaturated fatty acid peroxidation. These results might favour atheroma formation, thrombus formation and influence free radical scavenging in the ischaemic myocardium. The evidence is increasing that formation of foam cells from macrophages is favoured when LDL is in the oxidized or modified form [13]. It has been demonstrated that a decrease in the uptake of oxidized LDL by macrophages occurs when a drug with antioxidant properties, Probucol, is used [14].

Conclusion

There is strong evidence that the incidence of coronary heart disease is higher in some populations with low concentra-
tions of linoleic acid in adipose tissue and also when the plasma concentrations of vitamin E and vitamin C are low.

Two formal case-control studies have demonstrated a significantly increased odds-ratio for CHD when tissue and
platelet concentrations of linoleate are low and also when plasma concentrations of vitamin E and C are low. Cigarette smoking has a powerful effect in decreasing the dietary intake of linoleic acid and vitamin C, but not of vitamin E.

The evidence in these studies is sufficiently strong to include regular monitoring of tissue and plasma linoleate concentrations and plasma concentrations of vitamin E and C in epidemiological surveys and dietary studies related to CHD. A public health measure which follows from these findings is to recommend an increase in the consumption of ω-6 fatty acids and at the same time an increase in vitamins E and C.


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Smoking, antioxidants, essential fatty acids and coronary heart disease

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Introduction

More than 246 risk factors have been associated with coronary heart disease (CHD) [1]. Even assuming that CHD has a complex multifactorial aetiology, many of these risk factors are presumably non-causal and thus spurious. However, in northern latitudes strong correlations exist between low intakes of essential fatty acids (EFA) and antioxidants, the number of cigarettes smoked and the incidence of CHD [2, 3] suggesting that the increased consumption of tobacco and decreased consumption of vitamin E and EFA may exacerbate the development of the atherosclerosis.

Recent experimental evidence indicates that free radical-mediated modification of low-density lipoproteins (LDL) and their subsequent preferential uptake by monocytes/macrophages plays an important role in the formation of foam cells [reviewed in 3]. As the gas and tar phases of tobacco smoke contain many reactive oxidizing species, smokers incur a high and sustained free radical load which may be injurious to cells and accentuate the peroxidative events involved in the pathogenesis of CHD.

Free radicals in cigarette smoke

The free radical chemistry of cigarette smoke has been recently reviewed [4]. In brief, each puff of a cigarette is estimated to contain 10^{14} free radicals in the tar phase and 10^{15} in the gas phase. These radicals can be divided into distinct groups:

(a) The first group consists of long-lived quinone–semiquinone radicals that are associated with the particular phase matrix and appear to be generated by oxidation of polycyclic aromatic hydrocarbons during the combustion process. When extracted into water the tar radical 

\[ \text{H}_{2}\text{O}_{2} \] 

can reduced oxygen to superoxide (O_{2}^{-}) and hydroperoxide (H_{2}O_{2}) and can also catalyse the conversion of H_{2}O_{2} to the highly reactive hydroxyl radical (OH') as follows:

\[ \text{O}_{2}^{-} + \text{Q}^{-} \rightarrow \text{O}_{2} + \text{Q} \]

\[ \text{O}_{2}^{-} + \text{Q}^{-} + 2\text{H}^{+} \rightarrow \text{H}_{2}\text{O}_{2} + \text{Q} \]

\[ \text{H}_{2}\text{O}_{2} + \text{Fe}^{2+} \rightarrow \text{OH}^{-} + \text{OH}^{+} + \text{Fe}^{3+} \]

OH' can abstract a hydrogen from a wide range of biomolecules and is potentially a very damaging free radical.

(b) The second group are short-lived, reactive carbon- and oxygen-centred peroxo (ROO') radicals often detected by spin trapping methods. Although the lifetime of these radicals is less than 1 s, they have an apparent lifetime of over 5 min because a steady state between production and destruction is attained as the smoke ages. This steady state of short-lived radicals may result from the slow oxidation of nitric oxide (NO) in cigarette smoke to the radical, nitrogen dioxide (NO_{2}) which reacts with smoke components such as aldehydes and olefins to continually produce ROO'. Moreover, NO and NO_{2} may react with hydrogen peroxide to produce OH'

\[ \text{NO} + \text{H}_{2}\text{O}_{2} \rightarrow \text{HNO}_{2} + \text{OH}^{-} \]

\[ \text{NO}_{2} + \text{H}_{2}\text{O}_{2} \rightarrow \text{HNO}_{2} + \text{OH}^{-} \]

Potential sources of the hydroperoxide in the above reactions include activated pulmonary macrophages and neutrophils; oxidant production by phagocytes may be stimulated by nicotine. Cigarette smoke also contains Cu and Fe which can promote OH' formation by Fenton-type reactions.

Cellular antioxidant defence mechanisms

Living organisms can protect themselves from the injurious effects of free radicals in many ways [reviewed in 3...