Biochimie xxx (2015) 1–16

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Oxidative theory of atherosclerosis and antioxidants

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ARTICLE INFO

Article history:
Received 3 September 2015
Accepted 18 December 2015
Available online xxx
Dedicated to the memory of L. Douste-Blazy (MD, DrSc, Professor of Biochemistry, Faculty of Medicine, University of Toulouse, France).

Keywords:
Free radicals
Reactive oxygen species
Oxidized LDL
Atherosclerosis
Antioxidant
Mediterranean diet

ABSTRACT

Atherosclerosis is a multifactorial process that begins early in infancy and affects all the humans. Early steps of atherogenesis and the evolution towards complex atherosclerotic plaques are briefly described. After a brief history of the 'Lipid theory of atherosclerosis', we report the most prominent discoveries on lipoproteins, their receptors and metabolism, and their role in atherogenesis. The main focus is the 'oxidative theory of atherosclerosis', with emphasis on free radicals and reactive oxygen species, lipid peroxidation and LDL oxidation, biological properties of oxidized LDL and their potential role in atherogenesis. Then, we report the properties of antioxidants and antioxidant systems and their effects *in vitro*, on cultured cells, in animal models and in humans. The surprising discrepancy between the efficacy of antioxidants *in vitro* and in animal models of atherosclerosis and the lack of protective effect against cardiovascular events and death in epidemiological study and clinical trials are discussed. In contrast, epidemiological studies seem to indicate that the Mediterranean diet may protect (in part) against atherosclerosis complications (myocardial infarction and cardiovascular death).

1. Introduction

"Ils ne mouraient pas tous, mais tous étaient frappés" ("All did not die, but all were affected" – Les animaux malades de la peste (The Animals Sick of The Plague), J. de La Fontaine VII-1). This is also true for atherosclerosis. All humans develop atherosclerotic lesions, but only some of them experience cardiovascular (CV) events. This discrepancy may suggest that two linked, but partly different, pathophysiological processes, are involved in the genesis of CV events. Atherosclerotic lesion formation (atherogenesis) is a general process that expands with age in all humans, whereas clinical events subsequent to athero-thrombotic complications affect 20–40% of elderly in Western countries.

The aim of this review is to summarize the evolution of ideas on atherosclerosis with particular emphasis on the 'lipid theory of atherosclerosis', the 'oxidative theory of atherosclerosis', and the attempt to use dietary and pharmacologic antioxidants to delay the progression of atherosclerosis and to prevent CV events.

2. Brief picture of the natural history of atherosclerosis and atherogenesis

2.1. Atherosclerosis is a universal process in humans

The universality of atherosclerosis lesions in adult humans has been demonstrated by systematic geographic studies and by investigations on ancient mummies. While the prevalence of atherosclerosis in adult humans is universal, the rate of progression and the severity of lesions depends on genetic and environmental factors, which are variable geographically [1,2]. The evolution of early (fatty streaks) towards advanced lesions may be different in aorta and coronary arteries. In aorta, fatty streaks occur in all persons, regardless of race or environment, whereas the progression towards advanced lesions seems to be different between individuals and geographic groups [2]. In contrast, in coronary arteries, advanced lesions are apparently more proportional to fatty streaks, thus suggesting that early prevention of hypercholesterolemia could be of interest to prevent late events of CAD [2]. In a large cooperative study on coronary atherosclerosis from different geographic and ethnic populations, pathologists established a rank

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http://dx.doi.org/10.1016/j.biochi.2015.12.014
0300-9084/

Abbreviations

ApoE	apolipoprotein E (protein)
Apoe	(animal gene coding for apoE)
APOE	(human gene coding for apoE)
Apoe−/−	mice (homozygous *apoe* ko mice)
AAPH	2,2′-azobis(2-amidinopropane) dihydrochloride
ALEs	advanced lipid end-products
BHA	butylhydroxyanisole
BHT	butylhydroxytoluene
CAD	coronary artery disease
CHD	coronary heart disease
CRP	C reactive protein
CoQ/$CoQH_2$	Coenzyme Q (reduced/oxidized)
CT imaging	computer tomography imaging
CV	cardiovascular
CVD	CV disease
ECM	extracellular matrix
FA	fatty acid
MUFA	monounsaturated FA
PUFA	polyunsaturated FA
FH	familial hypercholesterolemia
GPx	glutathione peroxidase
GR	glutathione reductase
GSH	(reduced) glutathione
GSSG	(oxidized) glutathione
GSS	glutathione synthetase
4-HNE	4-hydroxynonenal
HHE	hydroxyhexenal
ICAM	intercellular adhesion molecule
VCAM	vascular cell adhesion molecule
9-HODE	9-Hydroxy-10,12-octadecadienoic acid
13-HODE	13-hydroxy-9,11-octadecadienoic acid
LPPs	lipid peroxidation products
LDLs	low density lipoproteins
LDLR	LDL-receptor (protein)
LDLR	(human gene of LDLR)
Ldlr	(animal gene)
LOX-1	lectin-like oxidized LDL receptor
MCP1	monocyte chemotactic protein 1 (MCP1)
MI	myocardial infarction
MMPs	metalloproteinases
MPO	myeloperoxidase
oxLDLs	oxidized LDLs
eNOS	endothelial NO synthase
NO	nitric oxide
PAI-1	plasminogen activator inhibitor-1
PPAR	peroxisome proliferator-activated receptor
Prx	peroxiredoxin
RCCs	reactive carbonyl compounds
ROS	reactive oxygen species
S1P	sphingosine-1-phosphate
SMC	smooth muscle cell
SOD	superoxide dismutase
TF	tissue factor
Trx	thioredoxin
TrxR	thioredoxin reductase
UCP-2	uncoupling protein-2
VEGF	vascular endothelial growth factor

order by advanced lesions, which are generally correlated with mortality from CAD.

Interestingly, in ancient times long before modern civilization, atherosclerotic lesions were present in ancien Egyptians mummies, as shown by autopsies and CT imaging [3–5].

2.2. Brief picture of atherogenesis

Atherogenesis is a long and complex (multifactorial) complex process characterized by intimal lipid deposition and abnormal remodeling of the arterial wall that starts early in infancy and then progresses silently and surreptitiously for decades to form advanced atherosclerotic plaques [6–8].

Napoli et al. (1997) [9] report that fatty streaks are present in fetal arteries and are enhanced by maternal hypercholesterolemia. These lesions may partially regress in early infancy, but fatty streaks are often detected in childhood, and atherosclerosis progress faster when cardiovascular risk factors are present in young people [6,10]. Early atherosclerotic lesions are formed in areas of turbulent blood flow (e.g. arterial bifurcation) that triggers endothelial activation characterized by a local endothelial inflammatory response, with increased permeability and expression of adhesion molecules such as ICAM and VCAM. This leads to increased adhesion of leukocytes that pass into subendothelial intima where they are converted into macrophages. In the same time, the increased endothelial permeability favors the entry of lipoproteins into the intima, where the inflammatory cells generate reactive oxygen species (ROS) that may induce a progressive oxidation of LDLs. In case of hypercholesterolemia, the influx of LDLs is increased in the intima, their clearance is delayed, and they are progressively oxidized by free radicals and ROS generated by activated vascular cells. OxLDLs exhibit various proinflammatory and toxic properties that disturb local cellular physiology, aggravate the endothelial injury and increase the accumulation of cholesterol in macrophagic cells, which form foam cells and fatty streaks. These lesions may regress in part, in case of decrease of risk factors (e.g. lowering of LDL-cholesterol). In contrast, if the risk factors persist, the lesions progress slowly, during decades, through a local inflammatory process resulting from leukocytes activation and persistent endothelial injury, and through a complex mechanism involving a mix of destructive and repair/healing processes [7,11,12]. The destructive processes (e.g. cell death, proteolysis) lead to the accumulation of lipids and cell debris constituting the lipid-rich necrotic core. In the same time healing processes are activated, involving migration of smooth muscle cells (SMC) and myofibroblasts in the intima where they secrete a collagen-rich extracellular matrix (ECM) leading to the formation of the fibrous cap surrounding the plaque. Then atherosclerotic plaques are complicated by intraplaque angiogenesis, calcification and hemorrhages leading to more complex plaques, prone to athero-thrombotic complications [13]. Stable plaques may remain clinically silent, whereas unstable plaques are clinically symptomatic and lead to ischemic cardiovascular events. Finally, the occurrence of CAD events result from the structure of plaques, since in patients with CAD, more than half of the coronary intimal surface is covered by advanced atherosclerotic lesions, including vulnerable plaques [10].

Please cite this article in press as: R. Salvayre, et al., Oxidative theory of atherosclerosis and antioxidants, Biochimie (2015), http://dx.doi.org/10.1016/j.biochi.2015.12.014