Progress in Lipid Research 52 (2013) 446–464

Contents lists available at SciVerse ScienceDirect

Progress in Lipid Research

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

Review

Postprandial lipoproteins and the molecular regulation of vascular homeostasis

Kathleen M. Botham *, Caroline P.D. Wheeler-Jones

Department of Comparative Biomedical Sciences, The Royal Veterinary College, Royal College St., London NW1 0TU, UK

ARTICLE INFO

Article history:
Received 6 July 2012
Received in revised form 6 June 2013
Accepted 6 June 2013
Available online 15 June 2013

Keywords:
Triglyceride-rich lipoproteins
Postprandial lipemia
Inflammation
Endothelial cells
Monocytes
Macrophages

ABSTRACT

Blood levels of triglyceride-rich lipoproteins (TRL) increase postprandially, and a delay in their clearance results in postprandial hyperlipidemia, an important risk factor in atherosclerosis development. Atherosclerosis is a multifactorial inflammatory disease, and its initiation involves endothelial dysfunction, invasion of the artery wall by leukocytes and subsequent formation of foam cells. TRL are implicated in several of these inflammatory processes, including the formation of damaging free radicals, leukocyte activation, endothelial dysfunction and foam cell formation. Recent studies have provided insights into the mechanisms of uptake and the signal transduction pathways mediating the interactions of TRL with leukocytes and vascular cells, and how they are modified by dietary lipids. Multiple receptor and non-receptor mediated pathways function in macrophage uptake of TRL. TRL also induce expression of adhesion molecules, cyclooxygenase-2 and heme-oxygenase-1 in endothelial cells, and activate intracellular signaling pathways involving mitogen-activated protein kinases, NF-κB and Nrf2. Many of these effects are strongly influenced by dietary components carried in TRL. There is extensive evidence indicating that raised postprandial TRL levels are a risk factor for atherosclerosis, but the molecular mechanisms involved are only now becoming appreciated. Here, we review current understanding of the mechanisms by which TRL influence vascular cell function.

Contents

Abbreviations: ABC, ATP binding cassette transporter; AMPK, AMP kinase; AP, activator protein; Akt, protein kinase B; Apo, apolipoprotein; apoB48R, apolipoprotein B48 receptor; CD, cluster of differentiation; CM, chylomicrons; CMR, chylomicron remnants; COX, cyclooxygenase; CREB, cAMP response element binding; CRP, C reactive protein; DHA, docosahexaenoic acid; EC, endothelial cell; EGF, epidermal growth factor; Egr, early growth response protein; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; EPC, endothelial progenitor cell; ERK, extracellular-signal-regulated kinase; FAK, focal adhesion kinase; FFA, free fatty acid; GPIHBP1, glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1; HAEC, human aortic endothelial cell; HDL, high density lipoprotein; HSPG, heparan sulfate proteoglycans; HMDM, human monocyte-derived macrophages; HO, hemeoxygenase; HUVEC, human umbilical vein endothelial cells; ICAM, intercellular adhesion molecule; IFN, interferon; IκB, inhibitor of κB; IL, interleukin; JNK, c-Jun N-terminal kinase; LDL, low density lipoprotein; LDLR, low density lipoprotein receptor; LOX, lectin-like oxidized low density lipoprotein receptor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LR11, sortilin-related receptor; LRP, low density lipoprotein receptor-related protein; M1, classically activated macrophages; M2, alternatively activated macrophages; MAPK, mitogen-activated kinase; MCP, monocyte chemoattractant protein; MEK, mitogen activated protein kinase kinase; MIP, macrophage inflammatory protein; MMP, matrix-metalloproteinase; Mox, macrophage phenotype induced by oxidised phospholipids; MUFA, monousaturated fatty acids; NF-κB, nuclear factor-κB; NO, nitric oxide; Nox, NAD(P)H oxidase; Nrf, nuclear factor (erythroid-derived 2)-like 2; ox, oxidized; P, pomace olive oil test meal; PAI-1, plasminogen activator inhibitor type 1; PAPC, 1-palmitoyl-2-arachidonyl-*sn*-glycerol-3-phosphocholine; PGE_2, prostglandin E2; PKC, protein kinase C; PL, phospholipid; POA, pomace oil supplemented with oleanolic acid test meal; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; RLP, remnant-like particles; RAP, receptor associated protein; ROS, reactive oxygen species; RXR, retinoid X receptor; SFA, saturated fatty acids; SR, scavenger receptor; TG, triacylglycerol; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; TRL, triglyceride-rich lipoproteins; V, virgin olive oil test meal; VCAM, vascular cell adhesion molecule; VE cadherin, vascular endothelial cadherin; VEGF, vascular endothelial growth factor; VLDL, very low density lipoprotein; VLDLR, very low density lipoprotein receptor; VSMC, vascular smooth muscle cells.

* Corresponding author. Tel.: +44 20 7468 5274; fax: +44 20 7468 5204.
E-mail addresses: kbotham@rvc.ac.uk (K.M. Botham), cwheeler@rvc.ac.uk (C.P.D. Wheeler-Jones).

0163-7827/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.plipres.2013.06.001

1. Introduction

Atherosclerotic cardiovascular disease is a primary cause of death worldwide [1] and the single most common cause of death in developed countries [2,3]. The development of atherosclerotic lesions begins with dysfunction of the vascular endothelium, followed by activation and recruitment of monocytes to the artery wall, where they differentiate in macrophages and take up cholesterol and other lipids from the plasma lipoproteins to form foam cells. The accumulation of these lipid-engorged cells, together with the proliferation of vascular smooth muscle cells (VSMC), causes fatty streaks, the first visible arterial lesions, to appear [4,5]. It has been known for many years that low density lipoprotein (LDL), particularly when oxidatively modified, plays a major role in atherosclerosis initiation and development [6], and the molecular mechanisms involved in its effects have been studied extensively [7–9]. In recent years, however, it has become clear that postprandial lipemia, which is caused by the raised levels of triglyceride-rich lipoproteins (TRL) present in the blood after a meal containing fat, is also a risk factor for the disease [10–12]. Postprandial lipemia is induced by fat meals containing >30 g [13,14], and, given that on average in Western countries 3–4 meals containing of 20–40 g fat are consumed each day, it has been estimated that raised levels of TRL may persist for 18 h per day in these populations [15].

After absorption in the intestine, dietary lipids are packaged into large TRL called chylomicrons (CM), and secreted into lymph and ultimately into the blood via the thoracic duct. Lipolysis by lipoprotein lipase (LPL) in extrahepatic capillary beds then converts the CM to smaller, but still triglyceride (TG)-rich, chylomicron remnants (CMR) which are cleared from the circulation by the liver [16,17]. The fatty acids derived from the TG delivered in CMR may either be used by the liver or re-synthesized into new TG and returned to the blood (together with cholesterol and phospholipid) in very low density lipoprotein (VLDL) [18]. Thus, blood levels of CM, CMR and VLDL all contribute to postprandial lipemia [19] and these lipoproteins are collectively known as TRL. In humans, TRL derived from the intestine (CM and CMR) contain apolipoprotein (apo) B48, while those derived from the liver (VLDL) contain apoB100 [16,19].

It has become clear over the past two decades that atherosclerosis is a chronic inflammatory disease. Inflammatory processes have been shown to be important in both the initiation and progression of lesion development [20,21]. Evidence indicates that postprandial lipemia is pro-inflammatory, with each meal causing a transient change, known as postprandial metabolic inflammation [12,22], and TRL are thought to play a major role in a number of the inflammatory processes involved, including the excessive formation of damaging free radicals, leukocyte activation, endothelial dysfunction and foam cell formation [12,23,24].

Since experimental, epidemiological and clinical evidence for considering non fasting TRL as a risk factor for atherosclerosis is now very strong [10–12,14,22–27], a better understanding of the molecular events by which they influence lesion initiation and development is of great importance. In this article, we review recent studies which have begun to delineate the receptors and signal transduction pathways mediating the potentially atherogenic interactions of TRL with circulating leukocytes and cells of the vasculature, and how they are influenced by dietary components carried in the particles, including the type of fat (saturated, unsaturated or oxidized) and other micronutrients.

2. Postprandial lipoproteins and atherosclerosis

Zilversmit first suggested that postprandial lipemia may play a role in atherogenesis about thirty years ago [28]. Although this idea was slow to gain acceptance, in recent years a great deal of epidemiological, clinical and experimental evidence has accumulated to support the proposal, and there is now a consensus that non-fasting TRL levels are a clinically significant risk factor for atherosclerosis and the progression of cardiovascular disease [12,29–33]. Atherosclerosis progression has been linked with delayed clearance of TRL [12,34–36] and postprandial hyperlipidemia is implicated in the increased risk of premature atherosclerosis in patients with common metabolic conditions such as obesity, diabetes and the metabolic syndrome [26,37–39]. Furthermore, in two Japanese studies involving sudden death cases, the majority of cardiac deaths were found to be associated with postprandial hyperlipidemia and plasma remnant lipoprotein levels rather than with LDL cholesterol, leading the authors to propose that plasma remnant lipoprotein concentration is a major pathological factor in cardiovascular events [40,41]. Supporting evidence is also provided by three recent large scale prospective studies, which reported an association between non-fasting plasma TG levels and the incidence of cardiovascular events which was independent of other risk factors [10,42,43]. Postprandial hyperlipidemia or increased plasma TRL levels have also been shown to be related to increased thickness of the carotid artery intima in humans [44,45] and in experiments with a rabbit model of postprandial hypertriglyceridemia [46].

The role of TRL as a risk factor for atherosclerosis is also supported by the concept of 'residual risk' [39]. Statin therapy aimed at lowering LDL cholesterol reduces cardiovascular events by about one third, leaving a residual two thirds which do not appear to be related to LDL, and the 'residual risk' is greater for subjects undergoing treatment for diabetes or the metabolic syndrome than in healthy individuals [47,48]. Thus, it has been proposed that the 'residual risk' of atherosclerosis is dependent on plasma remnant lipoprotein concentrations in addition to LDL cholesterol [39].