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Resialylation of sialic acid deficit vascular endothelium, circulating cells and macromolecules may counteract the development of atherosclerosis: A hypothesis.

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Abstract

Deficit sialylation of vascular endothelium, circulating cells and macromolecules has been associated with the development of atherosclerosis. On the other hand, an elevated serum level of sialic acid is a long-lasting marker of atherosclerosis and complications from atherosclerosis. One may speculate that the inverse associations with atherosclerosis risk are due to some common underlying cause. One mission for the elevated serum sialic acid level might be to act as a substrate for resialylation of sialic acid deficit structures and thereby counteract the atherosclerotic process.

Introduction

Human sialic acids (SA) are N-acetylated derivates of neuraminic acid that are abundant terminal monosaccharides of glycoconjugates. A significant quantity of serum SA constitutes parts of glycoproteins, e.g., orosomuroid, alpha 1-antitrypsin and haptoglobin and of lipoproteins and complement proteins [1].

SA are attributed a number of biological functions; they impart a net negative charge to cell surfaces and are important in cell-to-cell or cell-to-matrix interactions; they have ability to mask specific cellular recognition sites; they play an important role in the transfer of biological information, they are often parts of antigenic determinants of glycoproteins or glycolipids and they can affect the macromolecular structure of glycoconjugates [2].

Vascular endothelium most likely depends on sufficient sialylation to protect from atherosclerosis, i.e., atherosclerotic lesions are most frequent at low-sialylated areas of aortic endothelium and removal of SA from the intima of rabbit aorta by the action of neuroaminidas increases the adhesion of circulating platelets as well as the uptake of low

density lipoprotein (LDL) and fibrinogen [3-5]. Also, insufficient sialylation of circulating macromolecules may contribute to their atherosclerotic prosperities. In vitro desialylated LDL, as well as SA deficit LDL from atherogenic patients, are more rapidly accumulated in human aortic intimal smooth muscle cells as compared to non-desialylated LDL and LDL from healthy donors respectively [6]. According to Bastida and colleagues, asialo von Willebrand factor enhances platelet adhesion to vessel subendothelium [7]. Hadengue and colleagues found an inverse association between serum SA level and erythrocyte membrane SA content [8]. They concluded that decreased erythrocyte membrane SA content might participate in the development of atherotrombotic complications.

However, high serum level of SA is a determinant of atherosclerosis and complications from atherosclerosis. My colleges and I have reported positive associations, lasting for twenty years, between elevated serum SA level and of deaths from myocardial infarction and stroke [9,10]. We also have reported a significant positive association between asymptomatic carotid atherosclerosis measured by B-mode ultrasound and serum SA level [11].

Other investigators have attained similar results. During 17 years of follow-up of western Australians free from cardiovascular disease at baseline, the risk of coronary artery disease was positively associated with serum SA level [12]. Further, Watts and colleagues reported an association for serum SA level with change in coronary artery disease [13].

Thus, SA-deficit vascular endothelium, circulating cells and macromolecules as well as excess level of serum SA is associated with atherosclerosis risk. One may speculate that the inverse associations with atherosclerosis risk are due to some common underlying cause. One task for the elevated serum SA level might be to act as a substrate for resialylation of SA-deficit structures and thereby counteract the atherosclerotic process.

One major step in resialylation is the activity of sialyltransferase. Recently, Gracheva and co-workers reported that sialyltransferase activity of human plasma and aortic intima is enhanced in atherosclerosis [14]. Although they assumed that the increase in sialyltransferase activity might be related to the pathological processes in atherosclerosis, this does not leave out the possibility that the enzyme activity participate in resialylation.

Resnitzky and co-workers provides one more example of possibly resialylation. The SA content of erythrocyte membranes is essential for the electrophoretic mobility of erythrocytes. In the seventies, Resnitzky and colleagues reported low electrophoretic mobility of erythrocytes from patients with atherosclerotic complications. When incubated in plasma

from healthy donors, the electrophoretic mobility returned to normal [15]. Their results indicate the existence of a plasma factor affecting the electric charge of erythrocytes. It is possible that this plasma factor transfers SA from a plasma substrate to erythrocyte membranes and thereby restores the negative charge of the membrane. Later, Kelm and co-workers reported in vitro resialylation of erythrocytes [16].

The impact from pharmacological drugs on serum levels of SA and possibly resialylation is not investigated. However, many common drugs are anti-inflammatory and thereby may possess the ability to lower the serum concentration of SA-containing acute phase glycoproteins.

Thus, anti-inflammatory drugs have been associated with an elevated cardiovascular risk. A recent observational study reported a significantly increased risk of first myocardial infarction in users of most non-steroid anti-inflammatory drugs (NSAID) [17]. Further, in the APPROVE trial, the relative risk of myocardial infarction in users of rofecoxib was 2.8 compared with placebo [18]. An increased risk of serious cardiovascular events has also been reported for celecoxib when used in a clinical trial [19].

Influence on blood pressure and increased thrombotic risk by altering the COX-1 / COX-2 balance has been suggested as causes of the cardiovascular risk associate with NSAID [20]. The present hypothesis adds the possibility that NSAID, due to their anti-inflammatory property, reduce the availability of SA and possibly also other compounds necessary for resialylation.

However, low-dose aspirin (acetylsalicylic acid) is widely used to prevent thrombosis and myocardial infarction. The mechanism mediated by aspirin is believed to be via irreversible inhibition of COX-1-mediated platelet aggregation [21]. Apparently, the low dose of aspirin used to prevent cardiovascular events does not interrupt resialylation. Also, the anti-inflammatory effect of statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be too weak or not specific enough to seriously affect resialylation.

One may object that atherosclerosis is a process of advanced age and therefore counteracting atherosclerosis has low evolutionary priority. However, lipid accumulation in the vascular wall starts in early life and the development of advanced atherosclerotic lesions may be successfully inhibited by resialylation [22].

The hypothesis

Based on the observations given above, it may be hypothesised that a fraction of the elevated serum level of sialic acid observed in subjects with elevated risk of atherosclerosis and complications from atherosclerosis originate from a SA providing substrate for resialylation of SA deficient structures. The postulated substrate provider may be a glycoside or glycoprotein. Indeed, the serum levels of several glycoproteins are elevated in sera from atherosclerotic subjects. My colleagues and I have previously reported elevated levels of serum orosomucoid, haptoglobin and alpha-1-antitrypsin in asymptomatic carotid artery atherosclerosis [11].

The following mechanism for development and prevention of atherosclerosis and complications from atherosclerosis involving desialylation and resialylation is suggested:

i) Desialylation of vascular endothelium, circulating cells and macromolecules enhance the formation and rupture of atherosclerotic plaques due to disturbed endothelial function and enhanced migration, adherence and endothelial uptake of monocytes. Further, intima macrophage uptake of desialylated LDL as well as adherence of platelets and fibrinogen to dysfunctional endothelium may promote subendothelium lipid accumulation and formation of thrombus respectively. ii) Macrophage cytokines from the atherosclerotic lesions trigger liver synthesis and release of sialylated glycoproteins. iii) Liver released sialylated glycoproteins or glycolipids provide substrate for resialylation of desialylated vascular endothelium, circulating cells and macromolecules and thereby counteracting the atherosclerotic and thrombotic processes.

Hypothesis testing

The effect by desialylation on endothelial function and on the development of atherosclerosis may be tested in animal models. The possibly resialylation of sialic acid deficient compounds may be confirmed in vitro (in the presence of plasma) and in vivo by use of free radioactivity labelled SA and also by use of SA donors such as glycoproteins and glycolipids with radioactivity labelled SA.

The impact on atherosclerosis may be indirectly tested in animal models by blocking one or more steps in the proposed pathway of resialylation. Most straightforward would be to block the transfer of SA from circulating glycoproteins or glycolipids. Transfer of SA probably involves acting of a specific sialyltransferase. Blocking the transferase activity may result in a more rapid development of atherosclerotic lesions and thrombus formation. Another step to

block may be the action of macrophage cytokines on the liver synthesis of SA rich glycoproteins and thereby lower the output of SA compounds from the liver. Also, more unspecific actions to lower the concentration of sialylated glycoproteins and glycolipids may be utilised. The hypothesis of resialylation is supported if these interventions accelerate the development of atherosclerotic lesions. However, until the mechanism of possibly resialylation is further understood, it may be too early to identify interventions appropriate for enhancing the resialylation of SA deficit structures.

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