Apolipoprotein C-III's role in cardiovascular diseases, a short review

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ABSTRACT

In this short review I show the important role played by ApoC-III in the lipid dysregulation present in the majority of cardiovascular diseases. With an emphasis on the mutations present in a minority of individuals that confer protection. With this in mind I state that ApoC-III should be considered a valid target for pharmaceutical intervention and cardiovascular disease control and progression.

INTRODUCTION

As the body of evidence grows for apolipoprotein C-III's (apoC-III) role in normal lipid homeostasis as well as its role in cardiovascular diseases, apoC-III is being put under the magnifying glass as a target for pharmacological [1], [2]. Studies first done on transgenic and knockout mice have given insights into the function of apoC-III. The overexpression of apoC-III in mice has resulted in severe hypertriglyceridemia [3], while endogenous apoC-III deficiency decreases plasma triglycerides [4]. The overall effects of apoC-III modulation in mice models are supported by genetic association studies in various human populations [5]. High levels of apoC-III play a direct role in hypertriglyceridemia [6], as hypertriglyceridemia is associated with metabolic syndrome, which in its self has a plethora of pathological consequences.

APOC-III SUMMARY

The gene encoding apoC-III is located on the chromosome 11q23.3 [7]. The apoC-III gene is highly expressed by hepatocytes and by enteric cells. The final version of the expressed protein is a 79 amino-acid glycoprotein that is part of VLDL, chylomicrons, and HDL [5].

Function

ApoC-III is synthesized chiefly in the liver and in small quantities by the intestines. ApoC-III appears to be the most abundant C apolipoprotein in human plasma at a concentration of ≈ 12 mg/dL, but this measurement was established by Nestel PJ [8], a more up-to-date measurement needs to be obtained. ApoC-III predominantly affects VLDL-triglyceride metabolism

which is a resultant of three variables: (1) increased intestinal triglyceride absorption, (2) increased VLDL-triglyceride production, and (3) disturbed lipolytic conversion of hepatic clearance of VLDL.

The two main properties of apoC-III are inhibition of lipolysis and displacement of apolipoproteins from lipoprotein particles. The displacement of ApoC-II by ApoC-III from lipoproteins would generate a reduce ApoC-II mediated activation of lipoprotein lipase (LPL). Thus resulting in decreased catabolic rate of VLDL and chylomicrons and progression to hypertriglyceridemia. Also, raised levels of apoC-III on the particle would displace apoE, a vital ligand for remnant removal, which would result in decreased remnant clearance and thus lipid overload.

Another role of apoC-III seems to be as a noncompetitive inhibitor of LPL [4]. An interesting discovery was made by Lins et al. [9] that showed the 6–20 fragment of apoC-III is in a tilted peptide conformation, which is normally found only in viral fusogenic peptides (i.e. penetrating lipid bilayers); the structure of such a peptide seems to offer the potential flexibility to respond to its environment. From this, van Dijk et al. [5] offer the hypothesis that the apoC-III protein can adapt or perhaps sense its lipid or apolipoprotein context, and that this mechanism presents apoC-III with the ability to dynamically regulate its function (i.e. the inhibition of LPL or hepatic remnant clearance) by changing its allosteric conformation.

A study done by Hernandez et al. [2] concluded that peroxisome proliferator activated receptor γ coactivator 1- β (PPAR γ C1 β) regulates plasma triglyceride metabolism through stimulating apoC-III expression, thus elevating apoC-III circulating levels. The liver-specific knockdown of apoC-III (in mice) significantly ameliorates PGC-1 β -induced hypertriglyceridemia. The study also showed that PGC-1 β or apoC-III knockdown in the liver recapitulates the hypolipidemic effect of nicotinic acid, thus denoting the importance of PGC-1 β as an important regulator of the apoC-III gene, and it also reveals a mechanism via which nicotinic acid achieves its therapeutic effects.

ApoC-III-beneficial and detrimental mutations

The involvement apoC-III in cardiovascular pathology has been established using a genome-wide association study on Lancaster Amish Pollin et al. [10]. The study pinpointed that 5% of the population are heterozygous carriers of a null mutation (RX19) in the gene encoding apoC-III; as a result of this mutation, they only express half of the circulating apoC-III present in noncarriers. Furthermore, the mutation carriers had lower fasting and postprandial serum triglycerides, higher levels of HDL-cholesterol and lower levels of LDL-cholesterol; the coronary artery calcification was less common in carriers than in noncarriers, and overall this would suggest that lifelong deficiency of apoC-III has a pronounced cardioprotective effect.

Among the mutations that produce a protective status for the carrier of the mutation, scientific inquiry has revealed harmful mutations. Increased restriction fragment length polymorphism (RFLPs) was shown to be associated with diverse hyperlipidemic phenotypes. The rare allele of Sst-1 RFLP was correlated to some degree with primary hypercholesterolaemia, type III hyperlipoproteinaemia, as well as with hypertriglyceridaemia [11].

Dammerman et al. [12] detected in the promoter region a 5 DNA polymorphisms in the apoC-III gene in a subject with type III hyperlipidemia and severe hypertriglyceridemia. Experiments done on transgenic mice that overexpress plasma apoC-III have shown profiles of hypertriglyceridemia. The study also correlated loss of insulin regulation and mapped to polymorphic sites at -482 and -455 (shown to be an insulin response element), with overexpression of apoC-III gene and development of hypertriglyceridemia [16]. From this, a hypothesis can be derived in which the overall insulin dysregulation in type I and complicated type II diabetes can promote a hypertriglyceridemic status and consequent cardiovascular complications. Variants of the insulin response element in the apoC-III gene promoter were shown to modulate insulin secretion and lipids load [13]. The study employed the administration of oral glucose tolerance test. Two variants of the insulin response element were evaluated (455T>C and 482C>T); the study's datum showed that the carriers of the specified variant alleles of the insulin response element had a disturbed glucose homeostasis and a unfavorable lipid load.

Another very interesting correlation was found by Oliviero Olivieri [14] between the level of circulating apoC-III and the coagulation pathway, in subject with or without coronary artery disease (CAD). The study employed 933 subjects among which 687 were diagnosed angiographically with CAD while 246 were CAD free; also the 687 were not taking anticoagulant drugs. The plasma activities of factor II (FII:c), factor V (FV:c), factor VIII (FVIII:c), and activated factor VII (FVIIa) were analyzed. Subjects with >12.6 mg/dL of circulating apoC-III had high levels of FII:c statistically similar of

carriers of 20210A allele. The presence of high apoC-III combined with high thrombin activity could be accounted for high levels of cardiovascular incidents caused by thrombi formation in cardiovascular diseased subjects with hyperlipidemia. The newest study done on apoC-III showed [15] that an aggregate of rare mutations in the gene encoding apoC-III was associated with lower plasma triglyceride levels. Among the four mutations that drove this result, three were loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2+1GA and IVS3+1GT). The fourth was a missense mutation (A43T). The triglycerides levels in the carriers of one mutation at least were 39% lower than levels in noncarriers. The risk of coronary heart disease among 498 carriers of any rare apoC-III mutation was 46% lower than the risk among 110,472 noncarriers.

CONCLUSIONS

As the majority of scientific articles concluded, the importance that apoC-III plays in cardiovascular pathologies, coupled with metabolic dyshomeostasis, makes the apolipoprotein an important target to consider in future pharmaceutical development. The success of mimicking a beneficial mutation, thus lowering the apoC-III levels or producing an inactive form of the protein, can bring tremendous burden release from cardiovascular diseases in a western society that is increasingly weighted down by this type of pathology.

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COMPETING INTERESTS

The authors declare no competing interests.

PUBLISHING NOTES

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