Journal of Clinical Lipidology (2015) 9, 384–389

Journal of Clinical Lipidology

Review Article

Adenosine triphosphate citrate lyase: Emerging target in the treatment of dyslipidemia

Hernán N. Lemus, Carlos O. Mendivil, MD, PhD*

Universidad de los Andes Medical School, Bogotá, Colombia (Mr Lemus and Dr Mendivil); and Section of Endocrinology, Department of Internal Medicine, Fundación Santa Fe de Bogotá, Bogotá, Colombia (Dr Mendivil)

KEYWORDS:
LDL;
Lipid metabolism;
Cholesterol;
Hypercholesterolemia;
Dyslipidemia;
ATP citrate lyase;
AMPK;
ETC-1002;
Statin intolerance

Abstract: Despite major advances in pharmacologic therapy over the last few decades, dyslipidemia remains a prevalent, insufficiently recognized, and undercontrolled risk factor for cardiovascular disease. Statins are the mainstay of hypercholesterolemia treatment, but because of adherence and tolerability issues that limit dose titration, there is a need for additional therapies with good efficacy and better tolerability. Adenosine triphosphate (ATP) citrate lyase, a cytoplasmic enzyme responsible for the generation of acetyl coenzyme A for the de novo synthesis of fatty acids and cholesterol, is a very interesting molecular target for the reduction of plasma lipids. Furthermore, ATP citrate lyase inhibition may be accompanied by activation of 5′-adenosine monophosphate–activated protein kinase, a key signaling molecule that acts a central hub in cellular metabolic regulation. ETC-1002 is a small molecule inhibitor of ATP citrate lyase that also activates 5′-adenosine monophosphate–activated protein kinase, effectively reducing low-density lipoprotein cholesterol and inducing some other positive metabolic changes. Recent evidence from phase I and II clinical trials in humans has shown a positive efficacy and safety profile of ETC-1002, with low-density lipoprotein cholesterol reductions similar to those attainable by usual doses of many statins and with no major apparent side effects. These results potentially introduce a new family of medications that may expand our therapeutic arsenal against hypercholesterolemia.
© 2015 National Lipid Association. All rights reserved.

Alterations of lipoprotein metabolism are highly prevalent risk factors for cardiovascular disease, and their appropriate treatment has the potential to generate a major public health impact. There is now abundant evidence to support the concept that among the different lipoprotein fractions, tight control of plasma low-density lipoprotein (LDL) cholesterol (LDL-C) has the most impact on hard outcomes in both primary and secondary cardiovascular (CV) prevention.[1,2]

Statins, a family of medications that work as inhibitors of 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase (the rate-limiting enzyme in the cholesterol biosynthesis pathway), are currently the mainstay of hypercholesterolemia treatment, and their use has consistently shown to reduce CV morbidity and mortality.[1–3] Despite the overall safety and efficacy of these medications, statin intolerance remains a major clinical issue. The most important unwanted effects of statins can be grouped into 3 categories: (1) overt myopathy and/or myalgia, even without significant elevations of plasma creatine phosphokinase[4,5];

Conflict of Interest: The authors have no conflict of interest to declare.

* Corresponding author. Universidad de los Andes Medical School, Carrera 7 # 116-05, Of. 413, Bogotá, Colombia.
E-mail address: carlosolimpo@gmail.com

Submitted October 21, 2014. Accepted for publication January 9, 2015.

1933-2874/© 2015 National Lipid Association. All rights reserved.
http://dx.doi.org/10.1016/j.jacl.2015.01.002

(2) asymptomatic increases in liver transaminases[4,6]; and (3) an increase in the risk of developing type 2 diabetes mellitus, or a slight impairment in glycated hemoglobin A1c among patients already diagnosed with type 2 diabetes mellitus.[7,8] Although these adverse effects are only seldom severe or life threatening, they do compromise patient adherence or treatment continuation and therefore the expected CV benefit of therapy.

Furthermore, despite the wide availability and clinical use of statins, the percentage of patients who reach LDL-C goals remains worryingly low.[9,10] This may be related to the dose-dependent nature of statin-related adverse effects, which prevents strict dose escalation when necessary.[4] To overcome the limitations inherent to statin intolerance, and to provide patients with the full benefit that can be derived from LDL-C reduction, new families of cholesterol-lowering medications are being developed, exploiting molecular targets different from HMG-CoA reductase. One such pharmacologic family is proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, but concerns still remain about subcutaneous administration, cost, and the potential for neurocognitive side effects.[11] Recently, an entirely new approach to cholesterol lowering has been developed.

Adenosine triphosphate citrate lyase and its role in lipid synthesis

Adenosine triphosphate (ATP) citrate lyase (ACL) is a cytosolic enzyme most highly expressed in lipogenic tissues such as liver and white adipose tissue.[12] ACL catalyzes a reaction in which 2 carbons from citrate are transferred to CoA, with consumption of 1 ATP molecule and generation of acetyl CoA and oxaloacetate. ACL is thus a major contributor to the cytosolic pool of acetyl CoA, the fundamental building block for the biosynthesis of both fatty acids and cholesterol. X-ray diffraction analyses of ACL have revealed that it is conformed by 4 polypeptide chains of similar size.[13] Recent studies have identified the binding site of both citrate and ATP to ACL, as well as two thirds of the enzyme's complete 3-dimensional structure.[14] The ACL gene is under transcriptional regulation by sterol regulatory element binding protein 1 (SREBP-1).[15] The mature protein seems to be stabilized by posttranslational phosphorylation of specific serine and threonine residues,[16] although the relevance of these modifications has not been tested in vivo.

In liver, the essential organ of lipoprotein synthesis, ACL plays a fundamental role in lipogenesis and steroidogenesis by supplying cytosolic acetyl CoA to both pathways. By using a tricarboxylic acid cycle intermediate (citrate) to produce acetyl CoA, ACL can be seen as an important bridge between carbohydrate and lipid metabolism. Intramitochondrial citrate is transported via the so-called citrate shuttle to the cytosol, where it encounters ACL (Fig. 1). Acetyl-CoA carboxylase (ACC—the rate-limiting enzyme in de novo fatty acid biosynthesis) carboxylates acetyl CoA to produce malonyl CoA. Then, through repetitions of the 4-reaction cycle of de novo lipogenesis, palmitic acid is synthesized. Modifications of this primary product lead to other (shorter, longer, or unsaturated) fatty acids.[17] Depending on the set of biosynthetic enzymes that is predominantly expressed, acetyl CoA from ACL can also be used for cholesterol synthesis: HMG-CoA is formed by condensation of acetyl CoA and acetoacetyl CoA (catalyzed by HMG-CoA synthase) and later reduced by HMG-CoA reductase to mevalonate.[18] Mevalonate is then converted into 3-isopentenyl pyrophosphate by 3 consecutive reactions requiring ATP. Multiple extension steps involving iterative addition of extra 5-carbon modules leads to squalene, which is cyclized to form lanosterol. The removal of 3 methyl groups plus reduction of one double bond and migration of another double bond in lanosterol finally yields cholesterol (Fig. 1).

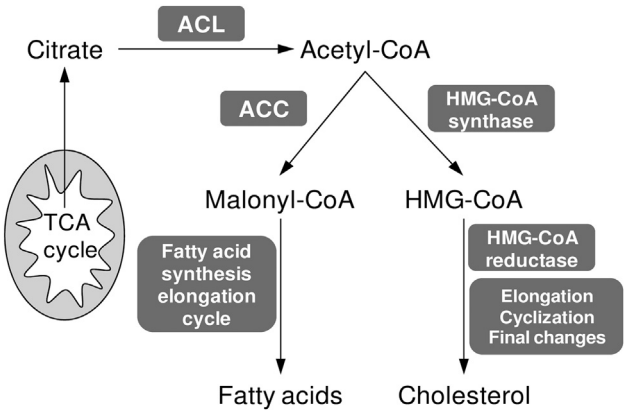

Figure 1 Crucial role of ACL as a precursor supplier for both fatty acid and cholesterol synthesis. ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; ATP, adenosine triphosphate; CoA, coenzyme A; HMG, hydroxymethylglutaryl; TCA, tricarboxylic acid.

ACL and AMPK have opposite effects on lipid biosynthesis

The enzyme 5′-adenosine monophosphate–activated protein kinase (AMPK) is a serine/threonine kinase that works as a sensor for cellular depletion of ATP, whose activation results in the simultaneous shutting down of several energy-consuming pathways and in the activation of energy-generating pathways. Activation of the AMPK pathway also influences a plethora of cellular functions through phosphorylation of other enzymes and transcription factors, which ultimate leads to changes in expression of multiple genes.[19] Among these target genes are the rate-limiting enzymes for steroidogenesis and fatty acid synthesis (HMG-CoA reductase and ACC), but also enzymes with a crucial role in gluconeogenesis and liver glucose production, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. The role of AMPK in lipid metabolism also

Download English Version:

https://daneshyari.com/en/article/5985560

Download Persian Version:

https://daneshyari.com/article/5985560

Daneshyari.com