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CARDIOVASCULAR DISEASE

Dissolving cholesterol to unclog arteries

> “cyclodextrin dissolves extracellular and intracellular cholesterol crystals and increases cholesterol efflux from macrophages”

Atherosclerosis is an inflammatory disease of the arterial wall that is caused by increased levels of cholesterol in the blood and an accumulation of cholesterol crystals in the subendothelial spaces. Reporting in *Science Translational Medicine*, Latz and colleagues describe the atheroprotective effect of the cyclic oligosaccharide 2-hydroxypropyl-β-cyclodextrin (referred to here as cyclodextrin), which dissolves cholesterol crystals, increases oxysterol production and promotes the anti-inflammatory reprogramming of macrophages in a liver X receptor (LXR)-dependent manner.

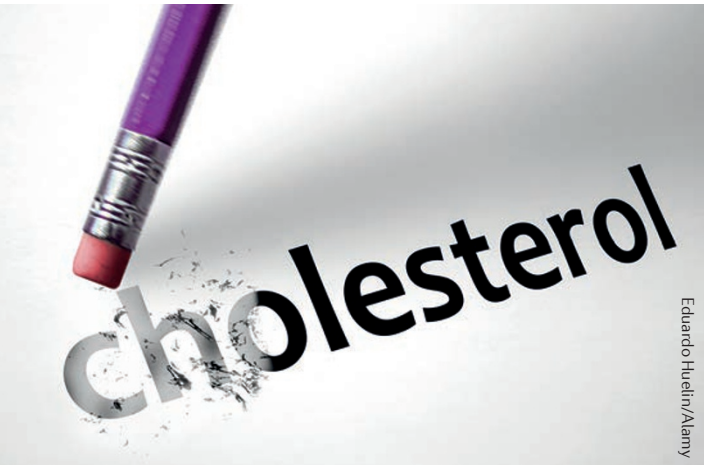
Cyclodextrin is known to solubilize cholesterol and is being used in a clinical trial for the treatment of patients with Niemann–Pick type C (NPC) disease, a rare genetic disorder in which cholesterol cannot be transported from lysosomes. Here, the authors showed that the size of atherosclerotic plaques, as well as the amount of cholesterol crystals within the plaques, were greatly reduced by the concomitant administration of cyclodextrin to apolipoprotein E (*Apoe*)$^{-/-}$ mice fed a cholesterol-rich diet for 8 weeks. The plasma concentrations of cholesterol were unaffected by cyclodextrin treatment, but the levels of pro-inflammatory cytokines were reduced. Furthermore, treatment of *Apoe*$^{-/-}$ mice with cyclodextrin after the onset of hypercholesterolaemia resulted in significantly decreased plaque size, even when the mice remained on a cholesterol-rich diet.

Macrophages take up and metabolize excess free cholesterol within the arterial wall, but excessive accumulation of cholesterol and deposition of cholesterol crystals trigger inflammatory responses. The authors showed that cyclodextrin dissolves extracellular and intracellular cholesterol crystals and increases cholesterol efflux from macrophages *in vitro*. Furthermore, cyclodextrin treatment resulted in a 15-fold increase in the levels of secreted oxysterols from crystal-loaded macrophages. Also, incubation of human atherosclerotic plaques with cyclodextrin resulted in cholesterol release into the supernatants and increased production of oxysterols. These data indicate that cyclodextrin increases oxysterol production by mouse macrophages and in human atherosclerotic plaques.

Oxysterols are known activators of the LXR pathway, which promotes reverse cholesterol transport (RCT) and anti-inflammatory processes. Gene expression analysis showed that cyclodextrin upregulated the expression of LXR target genes in mouse macrophages and in human plaques. Of note, cyclodextrin treatment downregulated expression of the inflammasome sensor *NLRP3* but upregulated expression of the inflammasome inhibitor *HSP90AA1*, both of which are LXR target genes. Furthermore, cyclodextrin treatment of mice that had received cholesterol crystal-loaded macrophages increased cholesterol excretion into the faeces, which indicates increased RCT, and also promoted urinary cholesterol excretion. Interestingly, patients with NPC on cyclodextrin treatment also excreted cholesterol into the urine. These data indicate that cyclodextrin promotes anti-inflammatory processes and RCT *in vivo*.

Finally, the authors showed that cyclodextrin treatment did not reduce the size of atherosclerotic plaques in mice with macrophages lacking LXR expression. Furthermore, the downregulation of *Nlrp3* and upregulation of *Hsp90aa1* in treated plaques was LXR dependent. These data indicate an important role for the LXR pathway in the atheroprotective and anti-inflammatory functions of cyclodextrin.

This study shows that cyclodextrin promotes atherosclerosis regression in mice and, because this drug is already approved for use in humans as a solubilizing agent for lipophilic drug delivery, cyclodextrin is a potential candidate for testing in humans to treat atherosclerosis.



Eduardo Huelin/Alamy

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FURTHER READING Tall, A. R. & Yvan-Charvet, L. Cholesterol, inflammation and innate immunity. *Nat. Rev. Immunol.* **15**, 104–116 (2015)