Old Drug, New Tricks
The Unexpected Effect of Doxazosin on High-Density Lipoprotein

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Ironically, even though there are currently only a few drugs to specifically treat low high-density lipoprotein (HDL), numerous drugs have been observed to inadvertently alter HDL levels. This has been particularly noted for some antihypertensive drugs. Because they are used long-term, any positive or negative effect of antihypertensive drugs on lipids and lipoproteins can significantly impact on their effectiveness in preventing cardiovascular disease. Recently, advances in our understanding of HDL metabolism have helped us to unravel the mechanism of action of these and other drugs that unexpectedly alter HDL levels. This work has largely been led by the laboratory of Shinji Yokoyama and colleagues, who have previously identified the mechanism of action of three drugs on HDL metabolism. Propranolol, which has been used to treat patients at risk for cardiovascular disease, is an antioxidant and lowers LDL, but it also lowers HDL. Probucol is now known to decrease HDL by inhibiting the activity of the ABCA1 transporter, a key protein involved in reverse cholesterol transport pathway and in HDL biogenesis. Verapamil, a calcium channel blocker, which can be used as antihypertensive and antiarrhythmic agent, and fenofibrate, a lipid-lowering drug, both raise HDL by increasing the gene expression of the ABCA1 transporter. In this issue of Circulation Research, Iwamoto et al describe the mechanism of action of a fourth agent that unexpectedly alters HDL, namely the antihypertensive agent doxazosin. The results of this study raise the possibility of a new strategy for developing drugs to increase HDL.

Doxazosin (Cardura) is a quinazoline based compound that is sold by Pfizer and is a long lasting selective inhibitor of the α-1a subtype of adrenergic receptors. It blocks the binding of norepinephrine to adrenergic receptors in the autonomic nervous system, which leads to decreased vascular tone from the relaxation of smooth muscle cells. It thus reduces peripheral vascular resistance and is an effective agent for lowering blood pressure. It can be used as single agent but is also often used in conjunction with other anti-hypertensive medications for those patients that need more than one antihypertensive drug. Doxazosin can also be used to treat urinary retention problems in patients with benign prostatic hyperplasia. By acting as an α-1a adrenergic antagonist, it reduces the tone of smooth muscles within the prostate and in the neck of the bladder, thus relieving the urinary outflow obstruction symptoms from an enlarged prostate. Interestingly, it appears to also have some other long-term beneficial effects on urinary retention symptoms, by possibly increasing apoptosis and reducing prostrate growth. Independent from its effect as an α-1a adrenergic antagonist, chronic treatment with doxazosin is known to alter the expression of many genes, some of which are related to apoptosis.

Doxazosin was first noted to alter lipid and lipoprotein levels in the 1980’s in studies examining its utility as an antihypertensive agent. Its effect on lipids is dose-dependent and variable, but many studies have shown that it has a beneficial effect on lipids by modestly lowering both total cholesterol and triglycerides. It has also been reported to lower LDL-C, prevent the oxidation of LDL, decrease small dense LDL, improve glucose tolerance, and decrease CRP. In addition, HDL has been reported to be elevated by approximately 5% by treatment with doxazosin, but this has not been observed in all studies. These changes in the lipoprotein profile, glucose tolerance, and inflammation suggest that doxazosin in some way may be altering biochemical pathways related to the metabolic syndrome. Treatment with doxazosin was estimated in one study to decrease the average 5-year risk for coronary heart disease by 15%, largely because of its beneficial effect of on lipoproteins. In various animal models, doxazosin has also been shown to reduce cholesterol accumulation in the vessel wall and the formation of atherosclerotic plaques.

A diagram, based on the article in this issue, on how doxazosin increases HDL is shown in the Figure. Doxazosin was first found to increase cholesterol and phospholipid efflux by approximately 50% from the macrophage cell line THP-1 to apoA-I, the main protein constituent of HDL. This effect was found to be specific for doxazosin and did not occur with other α-1a adrenergic antagonists. Furthermore, ABCA1 protein was found to be increased in THP1 cells treated with doxazosin. ABCA1 is a member of the ATP Binding Cassette transporter family, and when defective leads to low HDL and Tangier disease. ABCA1 is expressed in the liver and intestine, where it forms HDL by transferring cholesterol and phospholipid to apoA-I. ABCA1 is also expressed in peripheral cells, such as macrophages, and mediates the removal of excess cellular cholesterol to apoA-I and its eventual return to the liver to complete the reverse cholesterol transport pathway. Thus the ability of doxazosin to increase the level of ABCA1 protein likely explains its in
vivo effect on HDL and suggests that it increases HDL by increasing HDL biosynthesis and not by delaying catabolism.

ABCA1 is a relatively labile protein and is regulated by various transcriptional and post-transcriptional mechanisms. Doxazosin but not other α1a adrenergic antagonists was found to increase ABCA1 mRNA. Analysis of the promoter region of ABCA1 revealed the presence of a negative control element from region –368 to –147 bp, which was responsive to doxazosin treatment. This region of the promoter was found to contain an element for binding Adaptor Protein (AP) 2α, a member of the retinoic acid inducible AP2 transcription factor family. By a series of chromatin immunoprecipitation studies, gel shift assays, and transfection studies, it was convincingly demonstrated that AP2 α binds to the ABCA1 promoter and subsequently represses the transcription of the ABCA1 gene (Figure). Doxazosin did not alter the overall level of the AP2α, but it decreased the relative amount of the phosphorylated form of AP2α. Phosphorylation of AP2α is necessary for it to bind to its control element in promoters. How doxazosin decreases the phosphorylation of AP2α was not fully established, but it is known to decrease the phosphorylation and subsequent activation of several protein kinases, such as Akt/protein kinase B, which may then phosphorylate AP2α. 

ABCA1 is an attractive drug target for raising HDL in the prevention of coronary heart disease for several reasons. First, as already discussed, ABCA1 is a key protein for the biosynthesis of HDL. Once formed, HDL can then promote the efflux of excess cellular cholesterol from peripheral cells and can also mediate its other potential beneficial properties, such as its anti-inflammatory and antioxidant effects. From transgenic mouse studies of apoA-I and ABCA1, there is strong evidence that increasing biosynthesis of HDL is antiatherogenic, whereas it is still not clear if increasing HDL by delaying its catabolism, as with CETP inhibitors, is a good approach, and in some cases, such as the inhibition of hepatic SR-BI, may even be even counterproductive for preventing the development of atherosclerosis. Finally, the induction of ABCA1 in macrophages is especially beneficial for preventing atherosclerosis, because macrophages are heavily dependent on ABCA1 for the efflux of excess cholesterol. All these reasons account for the great interest that was generated when it was found that LXR family of transcription factors can up regulate the expression of the ABCA1 gene. LXR, however, affects the expression of many genes, some of which may also increase the reverse cholesterol transport pathway, but some gene changes induced by LXR are problematic. Chronic treatment of mice with LXR agonists, for example, leads to hypertriglyceridemia and a fatty liver. Based on the results of the current study, AP2α may be an alternative approach for increasing ABCA1 expression that may obviate some of the off-target problems encountered with LXR agonists. In contrast to the positive regulation of ABCA1 by LXR, AP2α binds to a negative control element on the ABCA1 promoter, which suppresses gene expression. Thus inhibiting the kinase that phosphorylates AP2α with doxazosin or a related compound or increasing the activity of the phosphatase for AP2α may be an effective means for increasing HDL. AP2α like LXR, however, affects the expression of many genes, but it is encouraging that doxazosin is already an FDA approved drug. It is relatively well tolerated and has little side effects, although in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a higher
incidence of cardiovascular events, particularly congestive heart failure, was found for treatment with doxazosin compared with the diuretic chlorthalidone. If AP2α does not prove to be a good target for drug development, the recent discovery of an alternative hepatic ABCA1 promoter, which helps explain the ability of statins to increase HDL, offers the possibility of the existence of other transcription factor targets for selectively modulating ABCA1 gene expression. Investigation of other drugs that unexpectedly alter HDL levels may also yield new ideas for developing drugs to raise HDL for the prevention of coronary heart disease.

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References

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