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COMMENTARY

Ezetimibe – new anti-atherogenic properties?

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Ezetimibe, a Niemann Pick C1-like1 inhibitor, inhibits cholesterol absorption. The drug has been shown to affect lipid raft function in monocytes and therefore may inhibit lipid accumulation in the atheromatous plaque with a mechanism that is unrelated to its effect in reducing cholesterol absorption. In this issue of the *British journal of pharmacology*, Gómez-Garre *et al.* demonstrate that ezetimibe and simvastatin both have a beneficial effect on the atheromatous plaque, which may be due to their effect on both monocyte/macrophage function and reduction in nuclear factor-κB activity. Whether these results in a rabbit model of atherosclerosis can be translated into human atherosclerosis awaits further studies.
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Abbreviations: NPC1L1, Niemann Pick C1-like 1

Unlike cancer, atherosclerosisis is, at least to a large extent, a preventable disease. Yet, the prediction is that the incidence and prevalence will rise dramatically due to changes in our lifestyle with increasing childhood obesity and decreasing physical activity. Already the disease causes an enormous burden on healthcare budgets and all the indications are that this burden will rise. Against this background, there has been a dramatic increase in our understanding of the disease process. The cholesterol hypothesis, developed some 50 or more years ago, gained wide acceptance with the discovery of the statins (a group of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and are so effective in lowering cholesterol) by Akira Endo *et al.* in 1976 and the large clinical trials that followed 10 or more years later (see Steinberg, 2008).

Not all patients respond to statins and it now appears that patients who are high absorbers of cholesterol and have low synthesis rates provide at least one explanation for a lack of response. The regulation of cholesterol absorption remained a mystery until recently. It was known that the regulation between cholesterol absorption and synthesis was tight and the case history reported many years ago of the 80-year-old man who ate 25 eggs per day yet maintained a virtually normal cholesterol demonstrates the magnificent cholesterol regulatory ability of the body. Studies have demonstrated that high-dose statin therapy that results in greater cholesterol lowering is more efficacious than low-dose statin therapy and it has been suggested that there is no lower limit of cholesterol which statins can attain, that is, not beneficial. Thus, there is considerable impetus for new drugs to be found that would complement statin therapy and cause further cholesterol reduction. One such drug, ezetimibe, was discovered and the discovery of this compound disclosed a major regulatory mechanism for cholesterol absorption. Niemann Pick C1-like 1 (NPC1L1) protein regulated by the NPC1L1 gene is part of a family of transporters and is found particularly in the brush borders and subcellular compartments including lysosomes and mitochondria of the intestine and also in the liver. Knockout animal experiments demonstrated beyond doubt that the NPC1L1 gene product regulated cholesterol absorption (Altmann *et al.*, 2004). Genetic variation of NPC1L1 contributes to the variability of cholesterol uptake and plasma levels of low density lipoprotein (LDL) (Cohen *et al.*, 2006). The drug ezetimibe, which was found to inhibit NPC1L1, is now in clinical use and, whereas on its own it is only a weak cholesterol-lowering drug, in combination with a statin it has proved very effective in reducing cholesterol by 50% or more.

Questions, however, have been asked about the efficacy of the drug in reducing cardiovascular events. This is particularly so since the discovery that the first of the cholesteryl ester transfer protein inhibitors, which raised high-density lipoprotein considerably, did not reduce cardiovascular disease and was in fact associated with an increase in cardiovascular mortality! A recent study (Kastelein *et al.*, 2008) demonstrated no beneficial effect of ezetimibe on carotid intimal thickness and a further study of aortic valve stenosis found not only no benefit, but an increase in cancer, although there was a reduction in risk of ischaemic cardiovascular events, mainly through fewer coronary bypass graft procedures (Rossebø *et al.*, 2008). It is for this reason that questions are being asked

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as to the benefit of using ezetimibe in the treatment of atherosclerosis, even though cholesterol lowering is still accepted as the major reason why statin therapy is so effective in reducing myocardial infarction.

This is the background that makes the paper by Gómez-Garre *et al*. (2009) so exciting. The authors set out to examine whether ezetimibe, either alone or in combination with simvastatin, could modify two characteristics of the atherosclerotic plaque, that is, monocyte/macrophage infiltration and fibrosis, the two hallmarks of the pathological lesion of atherosclerosis. The authors induced femoral atherosclerosis in New Zealand rabbits using a combination of a hyperlipidaemic diet and vascular injury. The animals were randomized to receive ezetimibe, simvastatin or a combination of ezetimibe and simvastatin or no treatment. Vascular injury was also induced in a group of rabbits fed a normolipidaemic diet during the study. Following the hyperlipidaemic diet, total cholesterol increased more than 10-fold with a 40-fold increase in low-density lipoprotein. Ezetimibe had no statistically significant effect on plasma lipid profiles whereas the addition of simvastatin did show slightly, but not significantly, lower levels of cholesterol. This is an important feature in the study because the results obtained cannot be related to a decrease in serum cholesterol by ezetimibe. Treatment with ezetimibe, simvastatin or the combination reduced the intima : media ratio in the femoral artery and increased lumen area. Quantitative analysis of lipid-rich areas and fibrosis demonstrated that treatment with ezetimibe or simvastatin alone significantly reduced the lipid-rich areas within the femoral lesions compared with untreated rabbits. Further reduction in plaque lipid content was observed after combined treatment. The authors then went on to look at the effect of ezetimibe on vascular inflammation. The authors show that all treatments significantly reduced the amount of monocyte/macrophages in the atherosclerotic lesions. The combination of ezetimibe and simvastatin reduced the monocyte/macrophage content more markedly than each drug alone. Monocyte chemoattractant protein 1 was measured and was found to be significantly lower in the animals treated with ezetimibe, simvastatin or the combination. Examination of systemic inflammation demonstrated that ezetimibe, simvastatin or the combination reduced NF-κB activation and lowered C-reactive protein levels. Finally, the authors examined the effect of ezetimibe on monocyte migration and demonstrated that both ezetimibe and simvastatin could inhibit a migratory response in a dose-dependent manner using THP-1 monocytes.

Prior to this study, it was known that ezetimibe interacted with the transmembrane proteins implicated in adhesion and cell interactions (Bauvois and Dauzonne, 2006) and, in monocyte/macrophages, decreased the surface expression of proteins involved in macrophage differentiation and lipid uptake (Orsó *et al*., 2006). Now, this exciting paper (Gómez-Garre *et al*., 2009) suggests that ezetimibe may have anti-atheroma properties over and above its effect of lowering cholesterol in much the same way as the statins, and a combination of drugs, therefore, would have benefit beyond lowering cholesterol. Of course, the animal model with the huge increase in diet induced serum lipids and the artificial injury technique to make atheroma may not translate to human atherosclerosis, and it should be remembered that clinical studies have shown an excellent correlation between the amount of cholesterol reduction by many different techniques (diet, bile salt binding, ileal resection, fibrates, etc) and reduction in coronary artery disease risk, suggesting that the extra anti-atherogenic properties of the statins may not be relevant to their major action of lowering cholesterol.

This study makes it even more important that we obtain outcome studies as soon as possible and in the meantime presents evidence to suggest that clinicians are right to continue using the drug enthusiastically when statins alone have not been successful in reducing cholesterol to target levels.

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