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COMMENTARY

Squalene synthase inhibitors

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Abbreviations: CHD, coronary heart disease; FXR, farnesoid X-activated receptor; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; LXR, liver X receptor; PP, pyrophosphate

The serum cholesterol concentration is one of the most important factors in predicting (Simons, 1986) and preventing (Grundy, 1986) coronary heart disease (CHD). Statin drugs are HMG-CoA reductase inhibitors and, because this is the primary rate-limiting enzyme in the hepatic biosynthesis of cholesterol, they are effective inhibitors of cholesterol synthesis. The statin-induced decrease in intrahepatic cholesterol concentration is associated with the upregulation of hepatic receptors for low-density lipoprotein (LDL) which increase the fractional catabolic rate of LDL. Despite the upregulation of HMG-CoA reductase, statins remain effective in lowering serum cholesterol. Statins have been consistently shown to reduce both CHD-related morbidity and mortality and, with the exception of cerivastatin, do so with a wide margin of safety (Gaw & Packard, 2000). The main problems with the use of statins relate to dose and response. There is considerable interindividual variation in the magnitude of the effect of statins on LDL cholesterol. There is evidence that people with low rates of cholesterol synthesis (Naoumova *et al*., 1996), perhaps due to increased absorption of dietary cholesterol (Miettinen & Gylling, 2002), may be most resistant. Accordingly, a poor responder to any one statin at a given dose may not benefit from an increased dose of that statin or from treatment with a different statin. Even in people whose initial response to statin therapy is good, the dose response remains relatively flat with further decreases of LDL cholesterol of the order of 6% resulting from doubling doses (Roberts, 1997).

In this issue of the *British Journal of Pharmacology* (pages.....), Nishimoto and co-workers present a well-designed study on the effects of a potent and selective inhibitor of squalene synthase (TAK-475), in a number of animal models. Squalene synthase is another enzyme in the cholesterol biosynthetic pathway (Figure 1). It appears that inhibition of this enzyme may also decrease circulating LDL levels by inducing LDL receptors. There may, however, be important differences between the other effects of squalene synthase inhibitors and those of HMG-CoA reductase, because squalene synthase, which acts downstream of mevalonate, is the first committed step of hepatic cholesterol biosynthesis at the final branch point of the cholesterol biosynthetic pathway (Figure 1) (Gibbons *et al*., 1982). Inhibition at this level might avoid effects associated with decreased formation of isoprenoids and other intermediates and metabolites in the pathway beyond HMG-CoA reductase (Flint *et al*., 1997a, b). Thus, prenylation (post-translational modification of proteins by farnesyl pyrophosphate or geranylgeranyl pyrophosphate)

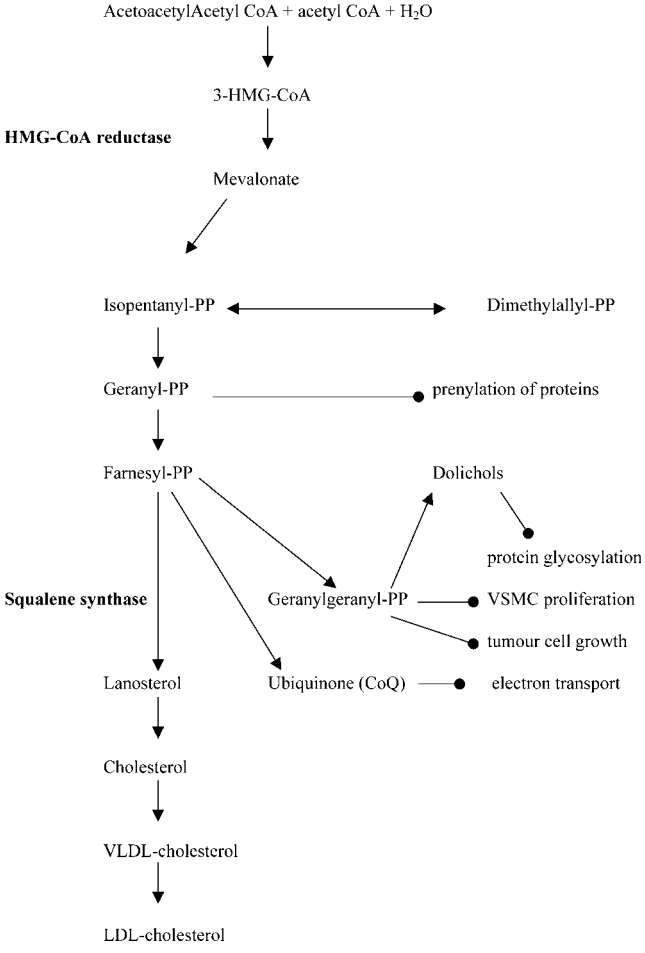

Figure 1 Sites of action of HMG-CoA reductase inhibitors and of squalene synthase inhibitors are shown. Putative functions of intermediates and derivatives of intermediates up to the first branch point in the biosynthetic pathway for cholesterol synthesis are shown (—●). PP; pyrophosphate.

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regulates the subcellular location of G-proteins influencing many signalling cascades within the cell (Edwards & Ericsson, 1999). Oxysterols and farnesyl pyrophosphate derived from the cholesterol biosynetic pathway after mevalonate, but before squalene synthase, affect also the activity of nuclear orphan receptors like liver X receptor (LXR) and farnesoid X-activated receptor (FXR), which are important in biliary cholesterol metabolism, lipoprotein metabolism and excretion and in macrophage foam cell formation (Edwards *et al*., 2002). It will thus be fascinating to see whether squalene synthase inhibitors have a greater effect compared to statins and the extent to which their roles might be complementary. Pharmacokinetic and more especially pharmocodynamic and toxicological studies will be required to determine whether squalene synthase inhibitors might offer advantages over statins. HMG-CoA reductase is the site of physiological regulation of cholesterol biosynthesis, making it unlikely that accumulation of metabolites before it would be toxic, but this is not necessarily true of squalene synthase inhibition. Triparanolol, another inhibitor of cholesterol biosynthesis, downstream of mevalonate, was found to cause cataract formation (Laughlin & Carey, 1962) and it would be of particular interest to determine if newer squalene synthase inhibitors such as TAK-475 cause lens opacities or other toxicity.

On a final note, another source of cholesterol is from the intestine. Ezetimibe is a selective inhibitor of intestinal cholesterol absorption and has recently been approved by the FDA for use in man. Ezetimibe alone has only a limited cholesterol-lowering effect because hepatic cholesterol synthesis is upregulated when intestinal sources are diminished. However, it is an effective add-in for use with HMG-CoA reductase inhibitors (Gupta & Ito, 2002) producing a 20% additional decrease over and above the statin dose. The LDL cholesterol-lowering goal might be achieved with lower doses of the latter, avoid potential side effects associated with high statin doses and overcome their disappointing dose response. Squalene synthase development will thus occur against this background.

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