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Abstract
This article contains information from a talk given by the author at the RMS on 14/01/03, entitled: Statins and Immuno-modulation: A New Frontier. Statins represent one of the major successes of cardiology in the secondary prevention of coronary artery disease. This article attempts to understand the very molecule which makes many quake in their boots, cholesterol, and how basic science research continues to find novel methods in which statin therapy can participate.

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Statins: More than Cholesterol Reduction

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Introduction.

This article contains information from a talk given by the author at the RMS on 14/01/03, entitled: Statins and Immuno-modulation: A New Frontier. Statins represent one of the major successes of cardiology in the secondary prevention of coronary artery disease. This article attempts to understand the very molecule which makes many quake in their boots, cholesterol, and how basic science research continues to find novel methods in which statin therapy can participate.

> "Currently the most potent treatment for hyperlipidaemia are the HMG-CoA reductase inhibitors or statins."

Large scale epidemiological studies in the general population, especially through the Framingham Heart study, the largest and most comprehensive medical study in the history of cardiology and some would say in modern day epidemiology, has identified several risk factors pertinent to the development of cardiovascular disease. The study based in the small town of Framingham on the outskirts of Boston, Massachusetts in the USA, has provided the means for risk assessment and public health targets in the prevention of coronary artery disease. Some of these risk factors for coronary artery disease include age, hypertension, hypercholesterolaemia, diabetes, and cigarette smoking [1]. However, one factor that has proved to be, and continues to be, one of the great successes of 21st century medicine has been the introduction of the HMG-CoA reductase inhibitors. Yet, to better comprehend this "magic drug" one has to appreciate the drug's target, that of cholesterol.

Cholesterol.

Cholesterol is a ubiquitous alicyclic compound, a member of the lipid family, which is distributed in both free and esterified forms throughout the body. Cholesterol can exist in a number of different structural isomers, from having a single hydroxyl group at C-3 to having an unsaturated centre between the C5 and C-6 atoms (see figure 1). Physically, cholesterol like other lipids is hydrophobic except for a single hydrophilic OH group, attached to which are several hydrophobic rings.

Given the hydrophobic nature of cholesterol, it is therefore surprising that the concentration of cholesterol in the plasma of healthy people is usually 150-200mg dL^{-1}. The high level of solubility of cholesterol in blood is attributed to the formation of protein-lipid complexes, called lipoproteins (ie. LDL and VLDL) which through the aid of apo-lipoproteins are able to bind and hence dissolve large amounts of cholesterol within blood. Physiologically, approximately 30% of the total circulating cholesterol in the human body occurs as free cholesterol, whilst the remainder exists as cholesterol esters attached to plasma lipoproteins.

Cholesterol is a vital biological molecule, playing an essential role in the architecture of the cell membrane, by providing rigidity but also fluidity for the flipping of lipids on the cell membrane. Cholesterol is also the precursor for the steroid hormones such as the sex hormones Oestrogen and Testosterone, and the cortico- and mineralocorticosteroids such as cortisol and aldosterone respectively. Cholesterol is also

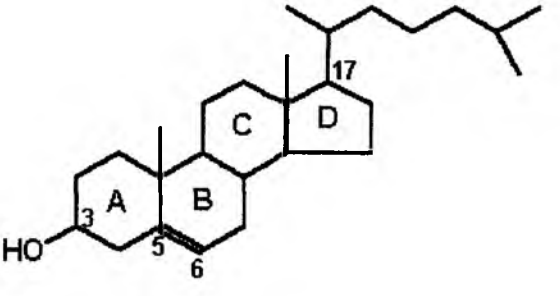

Figure 1 . The chemical structure of Cholesterol.

abundant in bile salts, allowing the process of emulsification for fat metabolism.

Cholesterol Synthesis - The Mevalonate Pathway.

The derivation of cholesterol can either be through diet or through de *novo* biosynthesis, which accounts for 45% of the cholesterol in the body. Whilst biosynthesis in the liver and the small intestines accounts for 10% and 15% respectively; other major synthetic sites include the adrenal cortex and reproductive tissues. The synthesis of cholesterol occurs in the cytoplasm and results from the reduction of the high energy bonds of ATP and Acetyl-CoA (ACT-CoA). As the pre-cursor in the cholesterol pathway ACT-CoA is converted to mevalonate via the formation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). This critical early step is rate-limiting in cholesterol synthesis and is regulated by the enzyme HMG-CoA reductase.

Upon successive phosphorylations of mevalonate and its intermediates an activated isoprenoid molecule, Isopentenyl Pyrophosphate, (IPP) is produced. Through the subsequent condensations of IPP to farnesyl pyrophosphate (FPP), and through the catalysis of the NADPH-requiring enzyme, squalene synthase, squalene is produced. It is the cyclisation of squalene to Lanosterol that produces the end product of cholesterol.

Cholesterol regulation.

The level of cholesterol synthesis can in part be regulated through the dietary intake of cholesterol and so the cellular level of cholesterol is maintained through the following independent but interacting mechanisms:

1) Cholesterol levels act as a negative feedback inhibitor for HMG-CoA reductase. Additionally, during times of excess, there is decreased expression of the HMG-CoA reductase gene resulting in low levels of mRNA for translation of HMG-CoA reductase.

2) The activity of HMG-CoA reductase is varied through covalent modification. This is achieved through either phosphorylating or dephosphorylating the enzyme, whereby phosphorylation of the enzyme reduces its activity. Phosphorylation is stimulated in context to the levels of cAMP in the body, under the hormonal control of insulin and glucagon. Increases in cAMP lead to the activation of the cAMP-dependent protein kinase, PKA, which in turn results in the phosphorylation and an increase in the activity of the phosphoprotein phosphatase inhibitor-1 (PPI-1). PPI-1 inhibits the activity of numerous phosphatases of which HMG-CoA reductase is one. It is through this method that hormones such as insulin, which causes a decrease in cAMP levels, leads to the activation of cholesterol synthesis.

3) Finally, both LDL and HDL receptor-mediated transport can also regulate plasma cholesterol levels. This process is based on the active uptake of excess hepatic cholesterol from the liver into the serum through LDL . Cholesterol in plasma membranes can be later extracted and esterified by HDL in the peripheral tissues. Cholesterol is finally excreted in the bile either in the form of bile salts or as free cholesterol.

HMG-CoA reductase inhibitors - Statins.

Currently the most potent treatment for hyperlipidemia are the HMG-CoA reductase inhibitors or statins. In 2000, statins were the second most popular drug in terms of sales , with sales of $15.9 billion - up 21% from 1999.[2]

Statins are HMG-CoA reducatase inhibitors, inhibiting the rate limiting enzyme HMG-CoA reducatase which conducts the breakdown of HMG-CoA to mevalonate, vital for the synthesis of cholesterol and isoprenoids further downstream in the pathway.

Statins are used extensively in current medical practice as a proven method of lowering blood lipid levels. Through numerous clinical trials this class of drugs have demonstrated their benefit in greatly reducing cardiovascular morbidity and mortality, as well as in the primary and secondary prevention of coronary disease in patients with and without coronary artery disease [3-9].

In addition to these clinical trials further *in vitro* and *in vivo* findings suggest that statins, through their highly effective lipid lowering abilities have other pleiotropic effects, in particular anti-inflammatory properties.[3]

Statins: Anti-inflammatory Properties.

An association between statin treatment and an anti-inflammatory response can be defined from markers of acute inflammation, including cytokines, C reactive protein (CRP) and white cell count. Needless to say, all the above factors are also indicative of being in a higher coronary risk factor group[10].

Further analysis into the schematic scenario of the atherosclerotic process allowed a definite conclusion that the evolution of atherosclerotic lesions involves an interaction between four major cell types: endothelial cells (ECs), smooth muscle cells (SMCs), macrophages, and lymphocytes. It has since been suggested that statins may interfere directly with several key mechanisms necessary for the involvement of different cellular elements in all the steps of atherogenesis.

The effect of Statins on endothelial function.

Since the observation that endothelial dysfunction arises early in the presence of elevated cholesterol levels [11] several experimental studies began to explore the effects of statins on preserving endothelial function. As a result it has shown that statins can alter the bioavailability of nitric oxide (NO) through the posttranslational up regulation of endothelial NO synthase (eNOS) mRNA and the decrease of superoxide anion production within vascular endothelial cells.[1] production within vascular endothelial cells[12].

Atherosclerosis over vascular endothelium having activated the endothelium has also been shown to increase the expression of adhesion molecules such as ICAM-1, VCAM-1 and E-selectin, vital for the extravasation of leuokocytes. Using a rat model Katoh *et al.* [13] showed how a particular statin (Fluvastatin) can reduce the expression of soluble ICAM-1. This result was also seen in hypercholesterolaemic patients, where there was also a reduction in the level of soluble P-selectin[14]. In addition statins have also been shown to inhibit the monocyte-endothelial interaction stimulated by oxidised LDL[15]. It is thought that oxidised LDL is able to be chemotactic for monocytes and human T lymphocytes[16], through inducing the expression of factors such as MCP-1 by both human endothelial cells and smooth muscle cells [17].

The effect of Statins on T-cell function.

It has been demonstrated that statins inhibited the Interferon-g (IFN-g)-mediated induction of class II major histocompatibility complexes (MHC II) on antigen presenting cells, including human monocytes/macrophages [18]. More recently, evidence by Weitz-Schmidt has also indicated that the statins Lovastatin and mevastatin selectively block the lymphocyte function associated antigen-1 (LFA-1). LFA-1 is involved in the adhesion of leukocytes to the

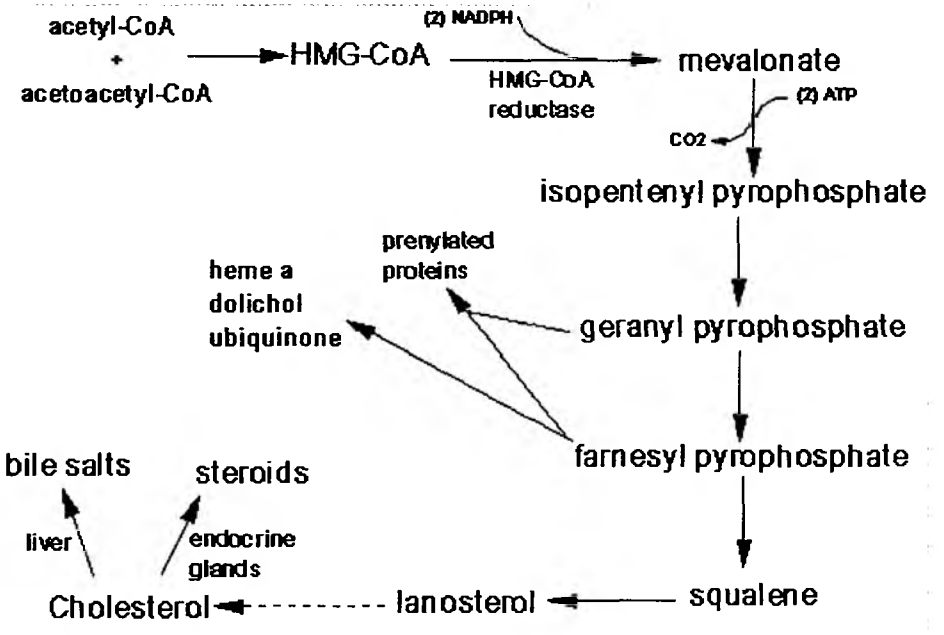

Figure 2. The Cholesterol synthesis pathway.

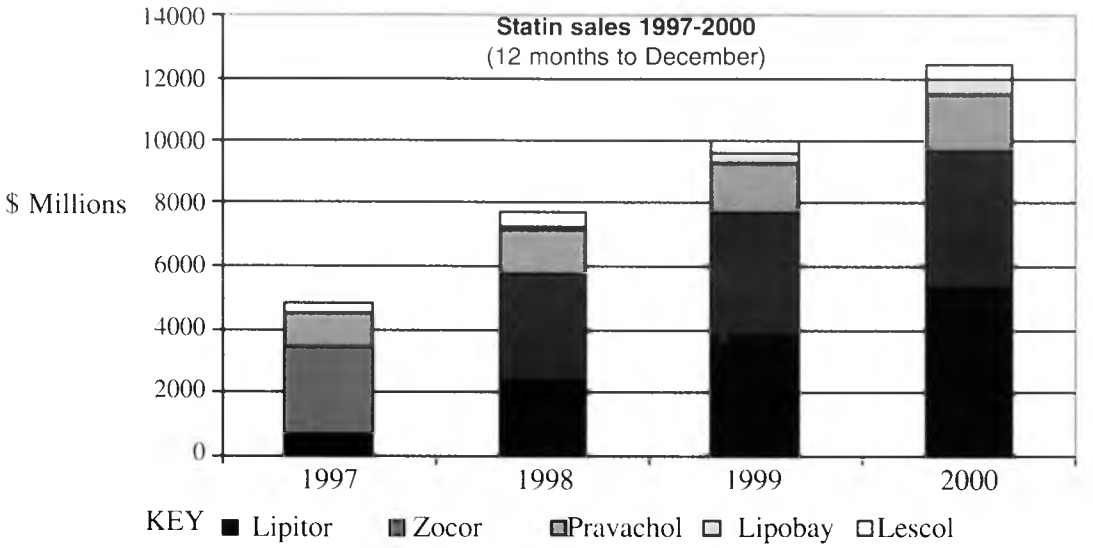

Figure 3. Statin sales 1997-2000.

binding molecules ICAM-1 and also in the process of lymphocyte re-circulation and effective T cell activation by antigen presenting cells. Statin-induced LFA-1 inhibition resulted in a decrease in lymphocyte adhesion to ICAM-1 and impaired T-cell co-stimulation [19].

As research continues into these and the other pleiotropic effects of statins, we can expect a new generation of cholesterol reduction drugs which are able to target a number of the secondary downstream products in the mevalonate pathway, which play an integral part in the inflammatory process.

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