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Editorial

Statin in Prevention of Cardiac Diseases

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Background and Significance

Statins are the competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (3-HMG-CoA) reductase, the enzyme which is responsible for the conversion of 3-HMG-CoA into mevalonate. Statins are capable of decreasing the level of the endogenous cholesterol in the humans and thus are used against hypercholesterolemia. Coronary artery disease represents the most important causes of death which is caused by fatty depositions called plaque build-up on the inner walls of arteries and progression of atherosclerotic lesions, related to the primary risk factor of hypercholesterolemia. Statins which are produced directly from the fermentations are called as natural statins (Lovastatin, compactin and Pravastatin). Natural statins can be obtained from different genera and species of filamentous fungi. Generally, statins are synthesized mainly by strains of Aspergillus terreus (Manzoni and Rollini, 2002). Statins interfere with events involved in bone formation and impede tumor cell growth. Recently, there are emerging interests in their use as anti-cancer agents based on preclinic evidence of their anti proliferative, pro-apoptotic, anti-invasive and radio sensitizing properties.

Structure and Properties of Statin

Natural statins have very similar chemical structure. They possess a common main polyketide portion, a hydroxy-hexahydro naphthalene ring system, to which different side chains are linked at C8 (R_1) and C6 (R_2). Lovastatin (or mevinolin, monacolin K, and Mevacor, Merck) contains a methylbutyric side chain (R_1) and a 6-α methyl group (R_2), which is lacking in mevastatin (or compactin, ML-236B, and CS-500). Pravastatin (or eptastatin and Pravachol, Bristol-Myers Squibb/Sankyo) has the β-hydroxylactone in the 6-hydroxy sodium salt form

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and is the C6-hydroxy analogue of mevastatin. Simvastatin (or Synvinolin and Zocor, Merck) contains an additional methyl group in the 2' position of the side chain.

The structures of the synthetic statins atorvastatin (Lipitor, Parke-Davis), fluvastatin (Lescol, Novartis) and cerivastatin (Baycol and Lipobay, Bayer) are dissimilar, and quite different from the natural statins. Unlike lovastatin and simvastatin, synthetic statins are obtained in hydroxy acid form. Fluvastatin derived from mevalolactone, was the first entirely synthetic statin available, while atorvastatin and cerivastatin, pyridine derivatives, are a new generation of highly purified statins.

The major form of lovastatin in fermentation is the open hydroxyl acid form (Mevinolinic acid) (Manzoni and Rollini 2002). However, it is generally in lactone form (Mevinolin) when administered to the patients as drug. In vivo, the lactone form of the compound is converted to open hydroxy acid, which is biologically active form of the statin. Besides, it has recently been indicated as a potential therapeutic agent for the treatment of various types of tumors because of its capability to suppress tumor growth in vivo through inhibition of the synthesis of non-sterol isoprenoid compounds (Jones *et al.*, 1994). Lovastatin is [1S-[1α(R*),3α,7β,8β(2S*,4S*), 8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl) ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its structural formula was shown in Fig 2.1. Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol and acetonitrile.

They possess a common main polyketide portion, a hydroxy-hexahydro naphthalene ring system Compactin, {7-[1,2,6,7,8,8α-hexahydro-2-methyl-8-(2-methylbutyryloxy) naphthyl]-3-hyroxyheptan-5-olide}, is an optically active compound. The molecular formula of compactin is C_{23} H_{34} O_5 and the molecular mass 390. The IR spectrum shows hydroxyl and lactone absorption, consistent with the formation of a benzoate (Brown *et al.*, 1976). The structure of compactin can be divided into two key fragments: a hexa hydro-naphthalene unit, the bottom portion and the lactone unit, the upper portion. Compactin produced as water soluble acid form which is converted to the water insoluble lactone form by acidification or drying. The molecule exists in two forms, lactone or acid, and the acidic form is responsible for its biological activity its structure is shown in Fig 2.1.

Pravastatin has the β-hydroxylactone in the 6-hydroxy sodium salt form and is the C6-hydroxy analogue of mevastatin. Pravastatin acts as HMG-CoA like moiety, responsible for HMG-CoA reductase inhibition, is common to both natural and synthetic statins. Pravastatin sodium chemical name was "sodium (3R,5R)-7-[(1S,2S,6S,8S,8αR)-1,26,7,8,8α-hexahydro-6-hydroxy-2-methyl-8-[(S)-2-methylbutyryloxy-1-naphthyl]]-3,5dihydroxyheptanoic acid)" is one of a class of lipid lowering compounds, Pravastatin sodium has empirical formula of $C_{23}H_{35}NaO_7$ and molecular weight 446.52. Pravastatin sodium is an odourless, white to yellowish-white powder or crystalline powder. It is a relatively polar hydrophilic compound with a partition co-efficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg mL^{-1}), slightly soluble in isopropanol and practically insoluble in acetone, chloroform and ether. The schematic diagram shows in shows the bioconversion of compactin to pravastatin through hydroxylation. The bioconversion takes place at C-6 position in the compactin molecule.

Mechanism of Action of Statin

Statins specifically and competitively inhibits HMG-CoA reductase, a regulatory enzyme of cholesterol biosynthesis. The K_i value of enzymes from rat liver and insects were 1 nM for compactin (Endo *et al.,* 1976b) while the K_m value for HMG-CoA is 10 μM, therefore the affinity of the enzyme for the inhibitor is about 10,000-folds higher than for its natural substrate. The structural similarity between the HMG-CoA and the δ-lactone ring of the acid form of statins plays an important role in the binding of compactin to the catalytic site of HMG-CoA reductase. This is supported by data showing that the inhibitory activity of compactin is reduced to 1/100 or less by acetylation of the hydroxy group at either C3′ or C5, and 5′-phosphocompactin is ten times less active as an inhibitor than compactin itself (Endo, 1985). The α-methylbutyrate portion of the compactin also adds to the effective inhibition of the enzyme and absence of the methyl group from thisportion, as in ML-236A, makes it less inhibitory. The decalin ring is also essential for the inhibitory activity of statins. HMG-CoA reductase is a regulatory enzyme with a half-life of 4 h; its biosynthesis is strongly regulated by various steroids and metabolites.

The structural homology between the β-hydroxyacid form of the statins and the HMG-CoA intermediate formed as shown in Fig 2.2. The affinity of the inhibitor (statins) is several times higher with respect to the intermediate. The K_m (Michaelis constant) for the substrate of the HMG-CoA reaction is 4×10^{-6} M, while a K_i (inhibition constant) of 6.4×10^{-10} M has been

determined for lovastatin (Alberts, 1988). Comparative kinetic analysis of HMG-CoA reductase has shown that the methyl group in lovastatin in the 6α-position confers a two-to three-fold enhancement of the intrinsic inhibitory activity with respect to mevastatin (Alberts *et al.,* 1980). The structures of the catalytic portion of HMG-CoA reductase complexed with six different statins [mevastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, (withdrawn in August 2001), and rosuvastatin (in the late stage of clinical development)] were recently described. The statins occupy a portion of the HMG-CoA binding site, thus blocking substrate access to the active site of the enzyme. The tight binding of statins is probably due to the large number of Van der Waals interactions between inhibitors and HMG-CoA reductase. 40 mg lovastatin dose reduce 30% in total plasma cholesterol, 40% in LDL-(low-density lipoprotein), 35% in VLDL-(very low-density lipoprotein) cholesterol, and 25% in triglycerides, and an increase of 10% high density lipoprotein (HDL) cholesterol was observed. In patients treated with simvastatin, a reduction of 25%–35% total cholesterol and LDL-cholesterol levels were observed.

The stereochemistry of the side chain ester moiety is not important for inhibitory binding to HMG-CoA reductase, as the spatial requirements of the acyl moiety are compatible with compact, branched chain aliphatic acylgroups, and additional branching at the α carbon of the acyl moiety increases potency. The differences in metabolism among the various statins lead to different distributions of the drugs in the liver (via enterohepatic circulation) or peripheral tissues (via systemic circulation) at equivalent doses. For example, pravastatin was found in lower concentrations in the liver (50%) but in higher concentrations (300–600%) in the peripheral tissues, including kidney, spleen, testis, adrenal gland, and nonglandular stomach as compared with lovastatin or simvastatin. It was thought that the lipophilic properties of the pro-drugs confer their selectivity to liver. Similarly, lovastatin and simvastatin were shown to cross the blood-brain and placental barriers but pravastatin and fluvastatin do not. In addition to reducing LDL cholesterol, the clinical data showed that lovastatin, simvastatin, and pravastatin increase HDL, with a subsequent decrease, by almost 50%, of the LDL to HDL cholesterol ratio, considered the best predictor of atherogenic risk (Alberts, 1988; Buckland *et al.,* 1989).

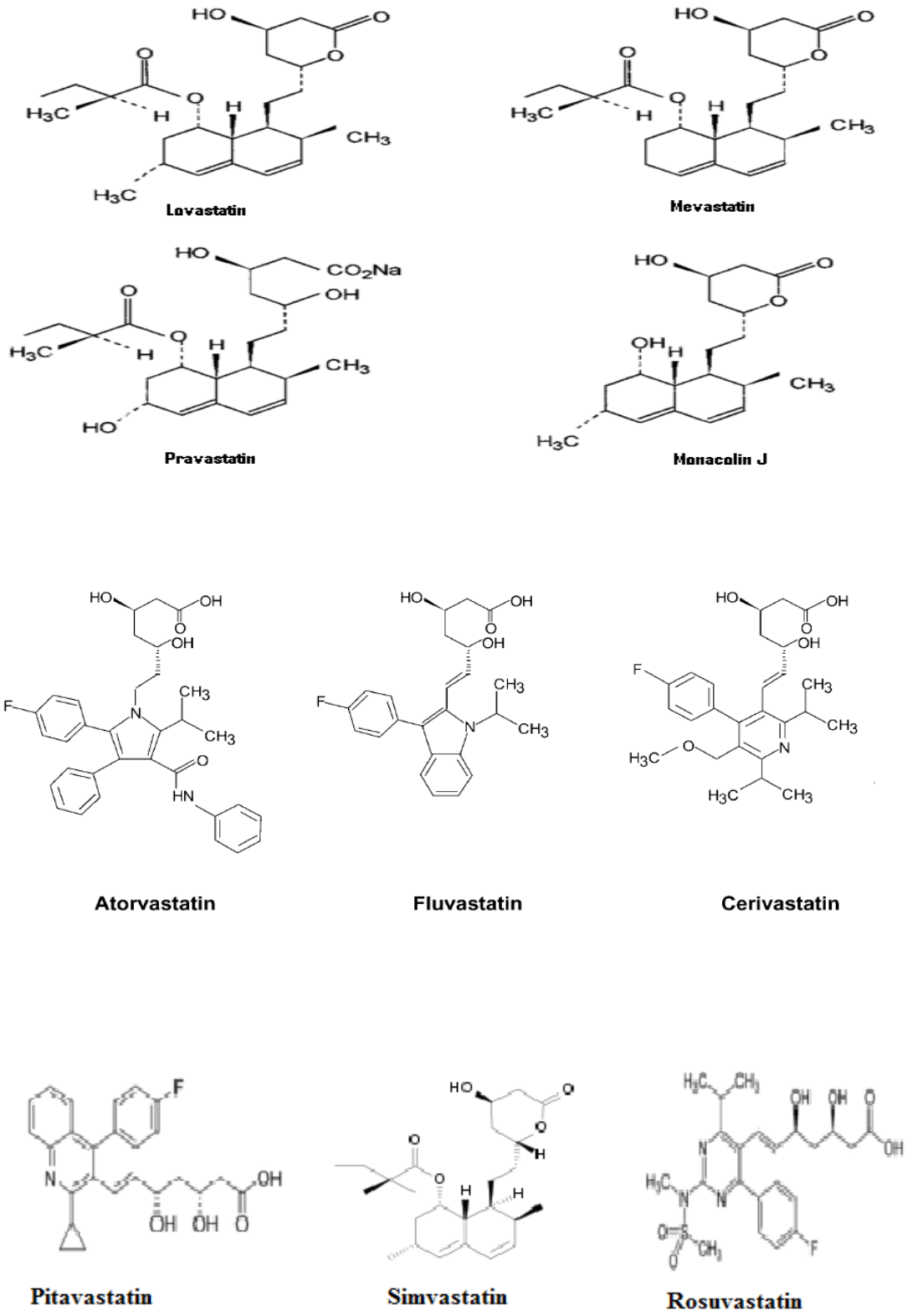

Fig 2.1. Different types of statin

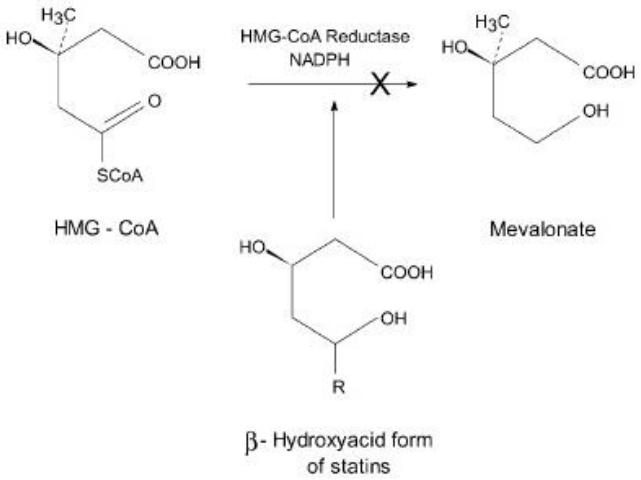

Fig 2.2. Statins inhibition into the active site of the enzyme there by blocking HMG-CoA to mevalonate

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