

Statin Therapy - Is Hypogonadism a Cause for Concern?

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The isoprenoids form one of the largest families of naturally occurring compounds [1]. In Figure 1 metabolic map of the isoprene metabolism is depicted [2]. The biosynthesis of these isoprenoids starts from two common precursors, Isopentenyl Diphosphate (IPP) and its isomer Dimethylallyl Diphosphate (DMAPP). After the synthesis of IPP and DMAPP, which in eukaryotes are synthesised via the mevalonate pathway, [3] the enzyme Geranyl Pyrophosphate Synthase (GPP synthase) catalyses the head-to-tail addition of IPP to DMAPP yielding Geranyl Pyrophosphate (GPP).

Condensation of GPP with IPP by farnesyl pyrophosphate synthase affords farnesyl pyrophosphate and subsequent condensation of FPP with IPP by GPP synthase affords geranylgeranyl pyrophosphate (GGPP) [4,5]. The isoprenoids FPP and GGPP are the key intermediates from which most isoprene metabolism products are derived.

Drug Development and the Mevalonate Pathway

Interference in the mevalonate pathway is an attractive and rewarding approach for the development of drugs toward several pathological disorders that are related to isoprenoid functioning. The most important is the development of cholesterol lowering agents.

Cholesterol Lowering Agents

An important approach toward the treatment of elevated cholesterol levels in the blood plasma involves inhibition of cholesterol biosynthesis. Well known examples are the statins 5ab compounds that act by inhibiting HMG-CoA reductase. As HMG-CoA reductase is situated early in the biochemical pathway, obstruction of this enzyme also influences the biosynthesis of other important products of the isoprene pathway.

The introduction of statin therapy had a major positive effect in lowering serum cholesterol levels and therefore a marked reduction in cases with hypercholesterolemia and Coronary Artery Disease (CAD)

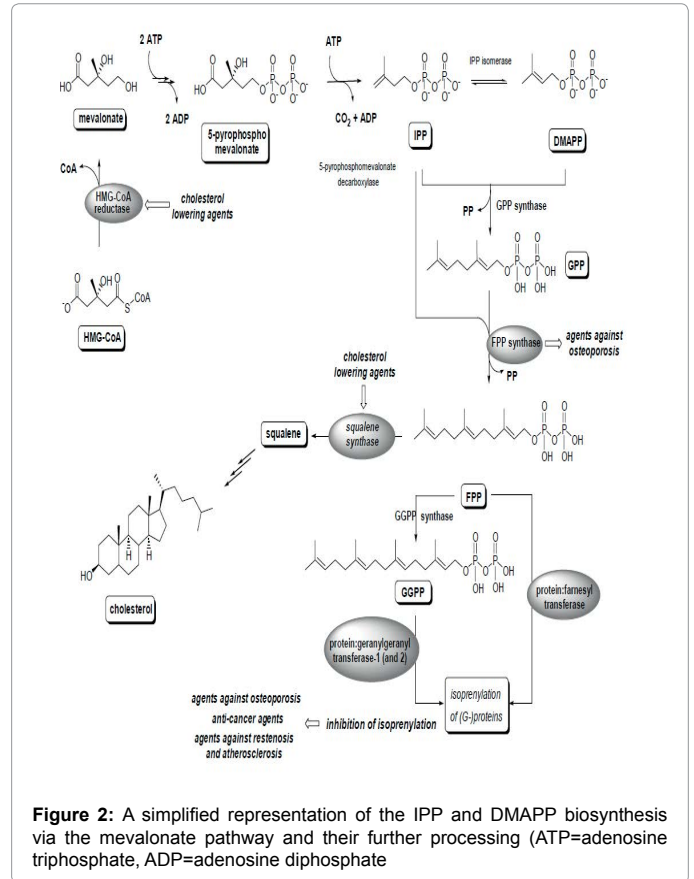


Figure 2: A simplified representation of the IPP and DMAPP biosynthesis via the mevalonate pathway and their further processing (ATP=adenosine triphosphate, ADP=adenosine diphosphate)

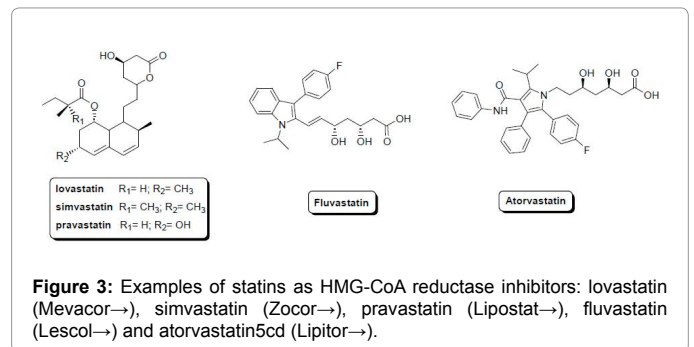


Figure 3: Examples of statins as HMG-CoA reductase inhibitors: lovastatin (Mevacor→), simvastatin (Zocor→), pravastatin (Lipostat→), fluvastatin (Lescol→) and atorvastatin5cd (Lipitor→).

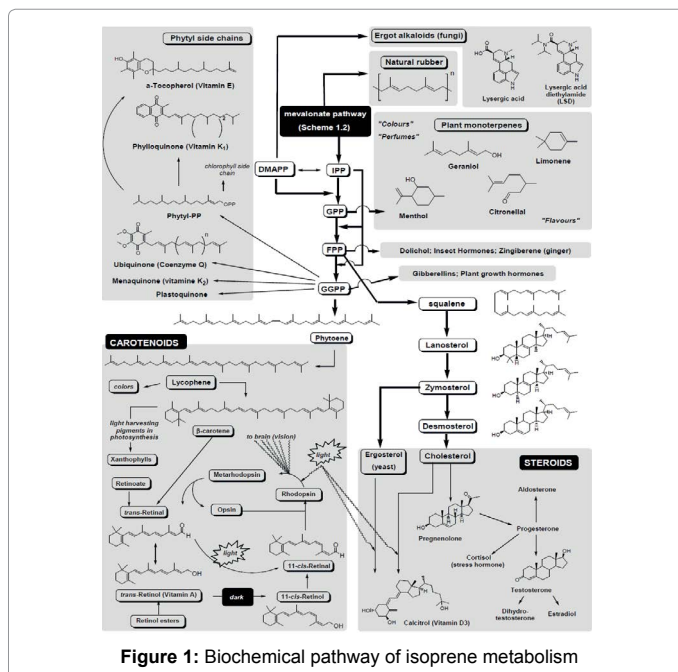


Figure 1: Biochemical pathway of isoprene metabolism

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[6]. Holistic approach to the treatment of well-being of the patient led to the observation that statin therapy is associated with hypogonadism [7]. The finding of hypogonadism has resulted in reviewing statin therapy and has cautioned the physician to use statins judiciously. Therefore, there is a need of introspecting the use of drugs we use for therapy and its possible adverse effects. It has necessitated the need to balance the beneficial as well as possible adverse effects of pharmacotherapy in question.

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