Obstructive Coronary Artery Disease: A Review of the Medicinal Chemistry of Atherosclerosis and Gold-Standard Treatments with Metoprolol and Atorvastatin

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Abstract

This review focuses on the medicinal chemistry aspects of Coronary Artery Disease (CAD). As an exercise for the broad scope of medicinal chemistry, this review will highlight the design, synthesis, pharmacodynamics, and pharmacokinetics of two gold standard medications for Obstructive Coronary Artery Disease (OCAD). This review begins with an introduction that provides an overview of coronary artery disease, including its scope and history. Supplemented with statistics, the introduction will then lead into the pathology behind atherosclerosis, most notably the cell processes that lead to the disease. After that, the body of the paper extensively discusses two gold standard treatments for coronary artery disease, while also mentioning the rationale behind these two treatments. There will be accompanying figures in the body of the paragraph, or when statistics are relevant.

Introduction

Coronary artery disease (CAD) is the umbrella term for all the diseases that result from the buildup of plaque along the arterial tree. This process of buildup, termed atherogenesis, can lead to a wide variety of health struggles, the most common being atherosclerosis. The diagnosis for atherosclerosis has shifted from a cholesterol buildup issue to one of inflammation.[1] Atherosclerosis begins with intimal inflammation, necrosis, fibrosis, and eventually, calcification.[1,2] Complications that arise with atherosclerosis include ischemic stroke and peripheral vascular disease.[2] Individuals with CAD can display several symptoms, which include chest and back angina, shortness of breath, nausea, diaphoresis, and myocardial infarction resulting from various comorbidities.[3]

Today, OCAD is the leading cause of death in the United States, responsible for 610,000 deaths in the United States, and 17.8 million global deaths on an annual basis.[4] Unsurprisingly, the prevalence of stable ischemic heart disease (IHD) or myocardial infarction (MI) tends to increase with age. Data gathered by the Cardiovascular Health Study (CHS) (**Figure 1**) demonstrates that 30.2% of men between the ages of 75 and 79 have either of the two mentioned diseases, while only 21.7% of women in the same age range experience these illnesses. For ages 80 to 84, 36.6% of men and 24.6% of women will experience IHD or MI. This increases to 40.8% in men and 29.7% in women for ages 85 to 89.[5] This data suggests that men are more vulnerable to cardiovascular diseases than women as they grow older. It is accepted that the younger generation is less exposed to cardiovascular diseases. In a 5,869-participant study on the correlation between sudden cardiac death (SCD) and CAD in the young and middle-aged (under the age of 50), it was concluded that CAD was the most common cause of ischemic SCD.[6] The study's results concluded that men made up a significantly greater proportion (90%) of SCD than women, and 90.2% of participants who passed away from SCD were previously undiagnosed with CAD.[6] This brings attention to the

significance of early diagnosis of cardiovascular problems before the occurrence of a major adverse cardiovascular event (MACE).

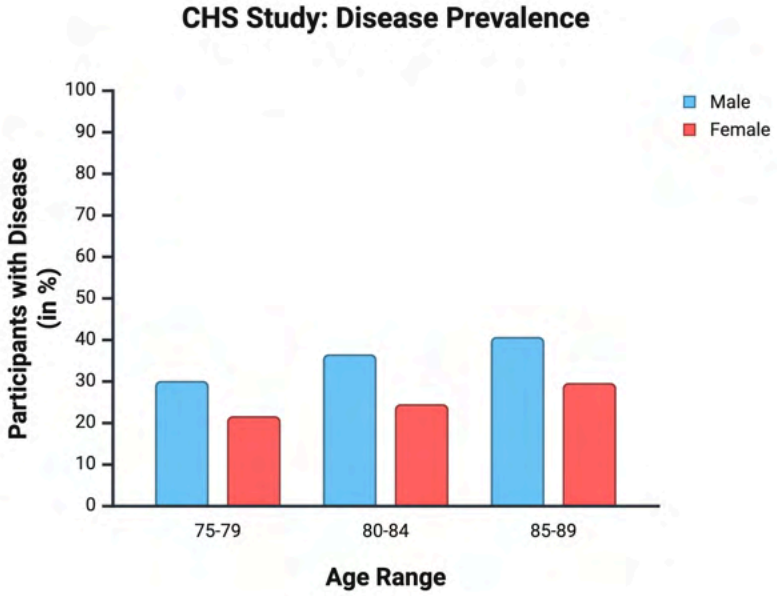


Figure 1 Percentage of patients with IHD or MI by gender across several age ranges.[5]

Although CAD is a result of dysfunction in the coronary arteries, the causes behind this disease can vary. The most common type of CAD is obstructive coronary artery disease (OCAD), in which plaque buildup leads to stenosis (narrowing of the blood vessels). More understood than its counterpart, OCAD is a disease that has several proven treatments and methods for diagnosis. However, non-obstructive coronary artery disease (NOCAD) is a vague variant with no established treatment. This issue arises from the cause of NOCAD: there is no presence of unusual plaque buildup, yet the arteries still experience dysfunction.[7]

The United States saw a sharp increase in CAD diagnoses from 1900 to the 1960s due to common societal and environmental exposures that predispose CAD risk. This includes smoking, unhealthy diets, and sedentary lifestyles.[8] Yet the number of diagnoses in the first decade of the century fails to account for a large population of those with CAD.[8] In the 1910s, John Herrick advocated for the electrocardiogram for more accurate diagnoses.[8] From 1950 onward to the present, the United States population experienced a 60% decline in cardiovascular disease-related mortalities.[9] However, presently, the treatment for CAD in the United States amounts to 200 billion dollars a year, demonstrating the large market and unmet need for therapies.[4]

Pathology

The causes behind plaque buildup in OCAD are attributed to the buildup of low-density lipoprotein (LDL), often referred to as “bad” cholesterol, in the vascular walls. Other factors that play a role in the formation of plaque are atherosclerosis, sex, diet, stress levels, and unhealthy daily habits.[2]

LDL originates from cholesterol esters and triglycerides from dietary fat. These esters and triglycerides are transported to the liver from the small intestines. The liver then assembles the triglycerides, cholesterols, and a lipoprotein called Apolipoprotein B-100 (Apo B-100) into a complex called Very Low Density Lipoprotein (VLDL). VLDL is then shuttled from the liver into the bloodstream for systemic endothelial and adipose cellular uptake. Enzymes on these cells, called lipoprotein lipase, remove the triglycerides from VLDL, thus forming LDL and free triglyceride (TG). LDL and TG are now absorbed into cells for energy and storage for other metabolic processes. The liver also has LDL receptors (LDLRs) that promote the liver uptake of excess LDL and subsequent conversion of LDL into cholesterol for secretion and excretion.[10]

However, in a high-fat diet, high levels of LDL in circulation and the resulting spike of cholesterol in the liver switch off the activity of liver LDLRs. This results in high amounts of circulating LDL from fatty foods as well as an increase in cholesterol production in the liver. This leads to fatty-liver disease, further reducing the ability of liver LDLRs to remove circulating LDL.[11]

When high amounts of circulating LDL accumulate in the tunica intima of blood vessels (**Figures 2 & 3**), these retained lipoproteins undergo oxidation, can initiate inflammation, and cause further lipoprotein aggregation. LDL binds to the proteoglycans in the intimal layer of the artery, making the artery's endothelium increasingly permeable. As greater amounts of LDL can pass through the artery, a constant cycle of LDL aggregation occurs, thus causing atherosclerosis.[2]

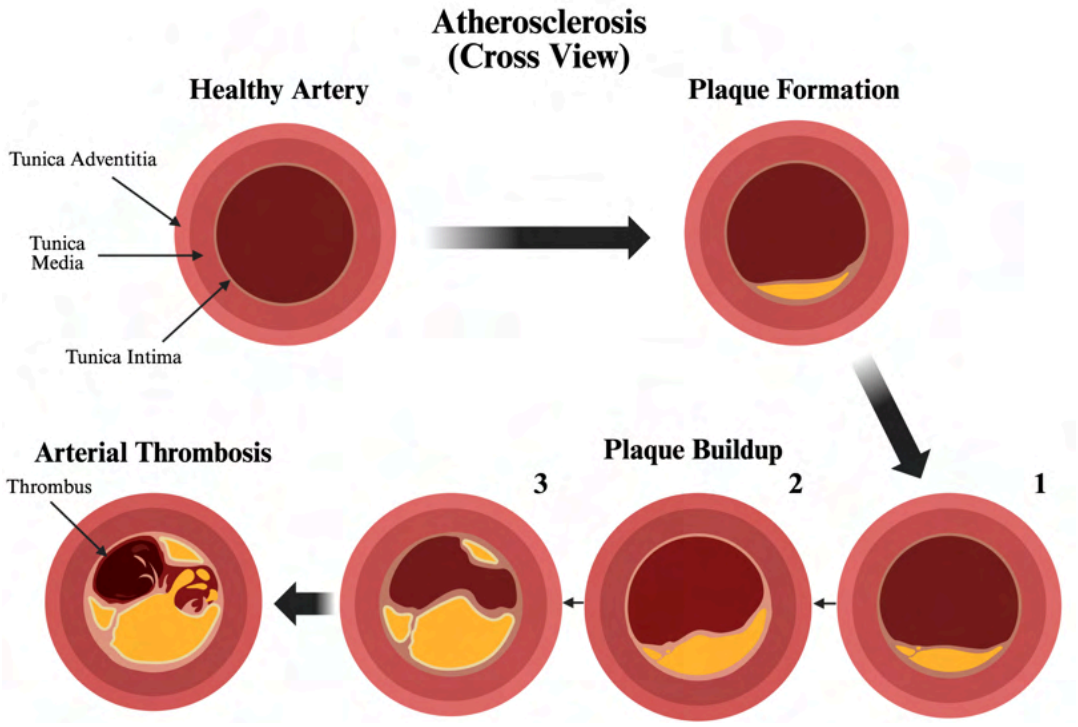


Figure 2 Cross-view of the process behind atherogenesis.[2,12]

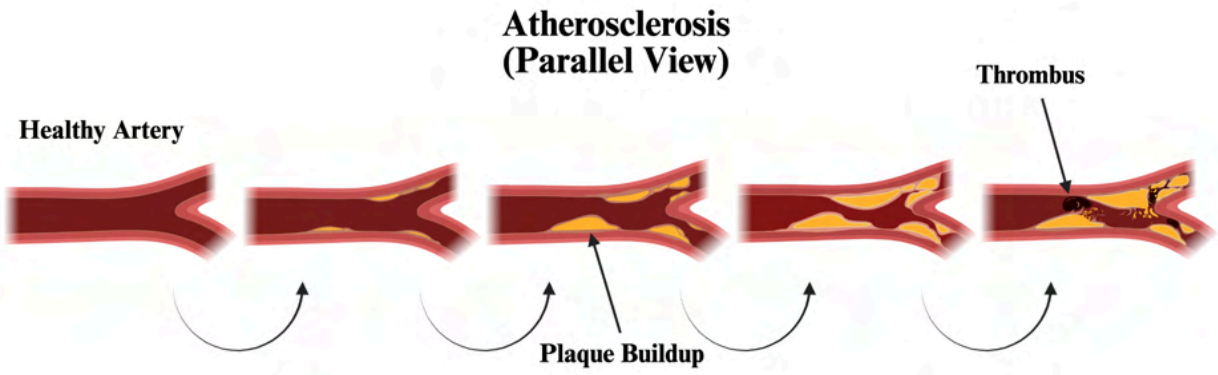


Figure 3 Parallel view of the processes behind atherogenesis.[2,12]

Inflammation is primarily involved in the mechanism of atherogenesis. As LDL accumulates in the bloodstream, they are absorbed through endothelial cells lining the tunica intima of blood vessels into the subendothelial space, where lies the smooth muscle cell layer of blood vessels. This excess and now-trapped LDL is oxidised to oxidised-LDL (oxLDL) by reactive oxygen species (ROS) produced by the smooth muscle cells. The resulting binding of oxLDL to lectin-like ox-LDL receptor-1 (LOX-1) on the neighboring vascular endothelial cells activates these endothelial cells via the NF-κB pathway. Cell adhesion molecules such as VCAM-1 and ICAM-1 begin to be expressed on these activated cells. VCAM-1 and ICAM-1 cause adhesion of immune cells in the area.

Another result of vascular endothelial cell activation is the secretion of monocyte chemoattractant protein-1 (MCP-1), which attracts monocytes, the precursors to macrophages (**Figure 4**). VCAM-1 and ICAM-1 now cause adhesion of the monocytes to these activated vascular endothelial cells in the subendothelial region. Monocyte-Colony Stimulating Factor (M-CSF), which is secreted by activated endothelial cells, transforms adhered monocyte immune cells into pro-inflammatory macrophages expressing LOX-1. The LOX-1 expressing macrophages do not have an off-switch for their LOX-1 receptors, resulting in engulfment of ox-LDL such that they transform into foam cells.[2] During the conversion of macrophages into foam cells, the high concentration of ox-LDL in the macrophages activates a powerful pro-inflammatory pathway called the NLRP3 pathway, ultimately secreting powerful cytokines such as IL-1□, and the cycle of pro-inflammation repeats itself - ultimately leading to a buildup of fibrous foam cells.

Foam cells join together to form xanthomas. Although the majority of these xanthomas are harmless due to processes like lipid efflux, a small percentage of the fat layers can develop into plaque. These regions contain what is called the necrotic core, marked by lipid pools. This core then develops into a location for calcium deposits to develop, forming a large portion of the atherosclerotic plaque.[2]

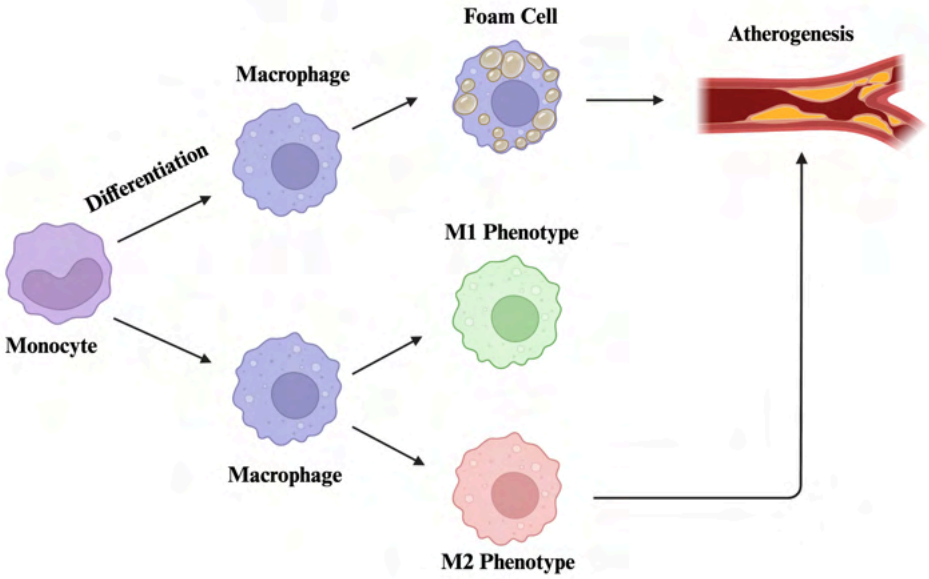


Figure 4 The role of monocyte differentiation in plaque buildup.[13]

Figure 5 Performance of atorvastatin compared to a placebo.[14]

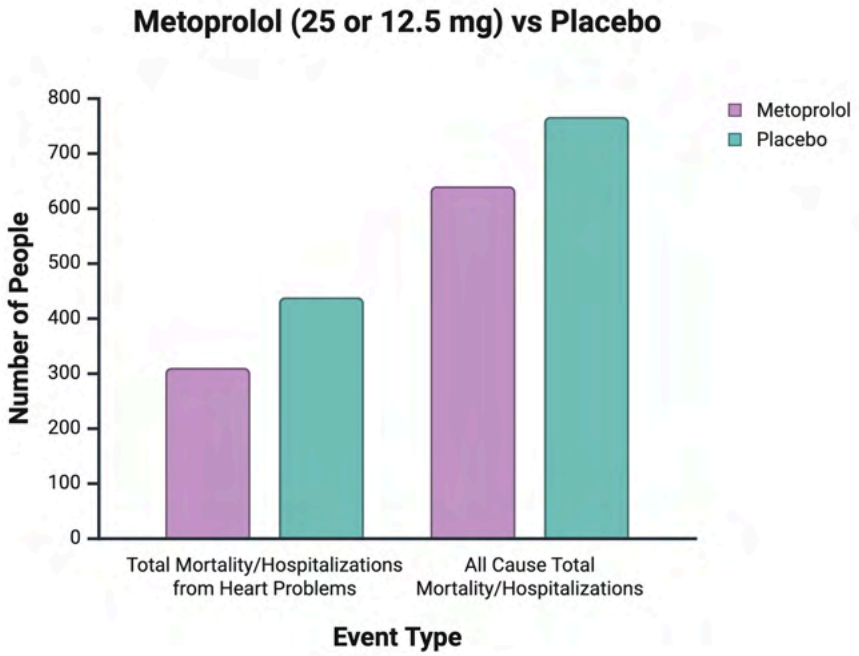


Figure 6 Performance of metoprolol compared to a placebo.[15]

Therapies

The generation of therapies for CAD has actively changed the gold standard medications in treating the disease. Notable therapies include the use of NSAIDs, statins, nitrates, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, thrombolytics, and percutaneous coronary intervention. Of these therapies, nitrate treatment dates back over a century, as seen in the use of nitroglycerin as a vasodilator.[16] Used to treat angina, notable adverse effects of nitrates include headaches, hypotension, syncope, and reflex tachycardia.[17] A fundamental pharmacokinetic limitation of this therapy is the building of nitrate tolerance, which can reduce its therapeutic effect.[18] Contraindications for using nitrates include administration in those who have experienced right ventricular infarction or hypertrophic cardiomyopathy.[17]

Towards the mid-1900s, Sir James Black synthesized beta-blockers, and their efficacy in treating a multitude of both cardiovascular and non-cardiovascular diseases led to a breakthrough in CAD therapy.[19] When administered in higher doses, beta-1 (B1) blockers can lose their selectivity and begin binding to beta-2 and beta-3 receptors.[20,21] Drawbacks to using this treatment method include a higher risk of stroke, bradycardia, hypotension, fatigue, nausea, and constipation.[21,22] Contraindications for this treatment include administration for those diagnosed with asthma (if not B1 selective), hypotension, or bradycardia.[21]

One of the most groundbreaking discoveries for CAD treatment, statins, was discovered by Akira Endo in 1976.[23] For its ability to treat high cholesterol levels directly, this drug targets atherosclerosis, the underlying cause of coronary artery disease.[24] However, as statins inhibit HMG-CoA reductase, coenzyme Q10 (CoQ10) levels are lowered.[24,25] This leads to the possible

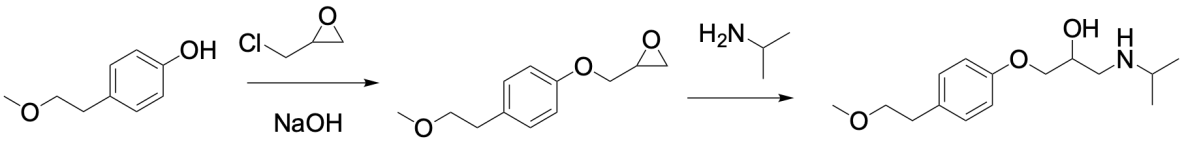
development of myopathy, as abnormal CoQ10 levels disrupt the function of calcium channels, which are crucial for proper muscle function.[24] A large portion of statins are prone to drug-drug interactions due to their hepatic metabolism by enzymes CYP3A4 or CYP2C9.[24] As these enzymes are easily inhibited or promoted by xenobiotics, plasma concentrations of statins can severely vary.[24] Contraindications include administration for those diagnosed with diseases of the liver with elevated aminotransferase levels.[25]

The following text explores the synthesis, pharmacokinetics, pharmacodynamics, mechanisms of action, and molecular docking of beta-blockers and statins. The selected drugs from each category are **metoprolol** and **atorvastatin**, respectively. These two drugs were chosen for their reputable and widely documented performance in their respective therapeutic categories.

Metoprolol succinate underwent a landmark trial of 3991 participants between 1997 and 1999, the MERIT-HF.[26] This study concluded that the drug lowered the risk of death in participants with chronic heart failure by 34%, and the risk of hospitalization from heart failure was reduced by 19%.[26] Other notable trials assessing metoprolol include the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial, which concluded that the risk of MACE was reduced when participants were administered metoprolol in comparison to thiazide diuretics.[26,27] A separate study of 50,000 participants deduced that metoprolol also lowered the risk of MI following a heart attack.[26] Atorvastatin's landmark Anglo-Scandinavian Cardiac Outcomes–Lipid Lowering Arm (ASCOT-LLA) of 10,305 participants concluded that atorvastatin treatment, even in those with lower-than-average cholesterol, reduced the likelihood of MACE (including stroke or mortality).[14] The PROVE IT-TIMI 22 study showed that atorvastatin, when given at high intensity, reduced the likelihood of MACE occurring in participants who have undergone percutaneous coronary intervention (PCI) more than another statin (paravastatin) given at medium intensity.[28]

Metoprolol

Synthesis



Scheme 1 Two-step reaction for the synthesis of metoprolol.[29]

Metoprolol is manufactured in just two steps, beginning with the alkylation of 4-(2-methoxyethyl)phenol with epoxy chloropropane in the presence of sodium hydroxide to afford the epoxide intermediate. This intermediate is then reacted with 2-isopropylamine to open the epoxide ring and form the synthetic product commercially known as metoprolol.[29]

Molecular Docking

Metoprolol can exert its therapeutic effect as a treatment for OCAD due to its chemical design and the resulting interaction of metoprolol as a ligand to its desired therapeutic target, the beta-1 adrenergic receptor. This is best understood by a visualization via molecular docking. The docking of metoprolol into the active site of the protein shows that the benzene ring participates in a critical hydrophobic pi-pi stacking interaction with Tryptophan 1134 in the active site of the protein. The polar ion-pi interactions of the ammonium ion and oxygen on metoprolol with Phenylalanine 1218, in conjunction with the Hydrogen bond between the hydroxyl group on metoprolol and residue Asparagine 1363, further imparts selectivity and affinity of the metoprolol for the beta-1 adrenergic receptor.

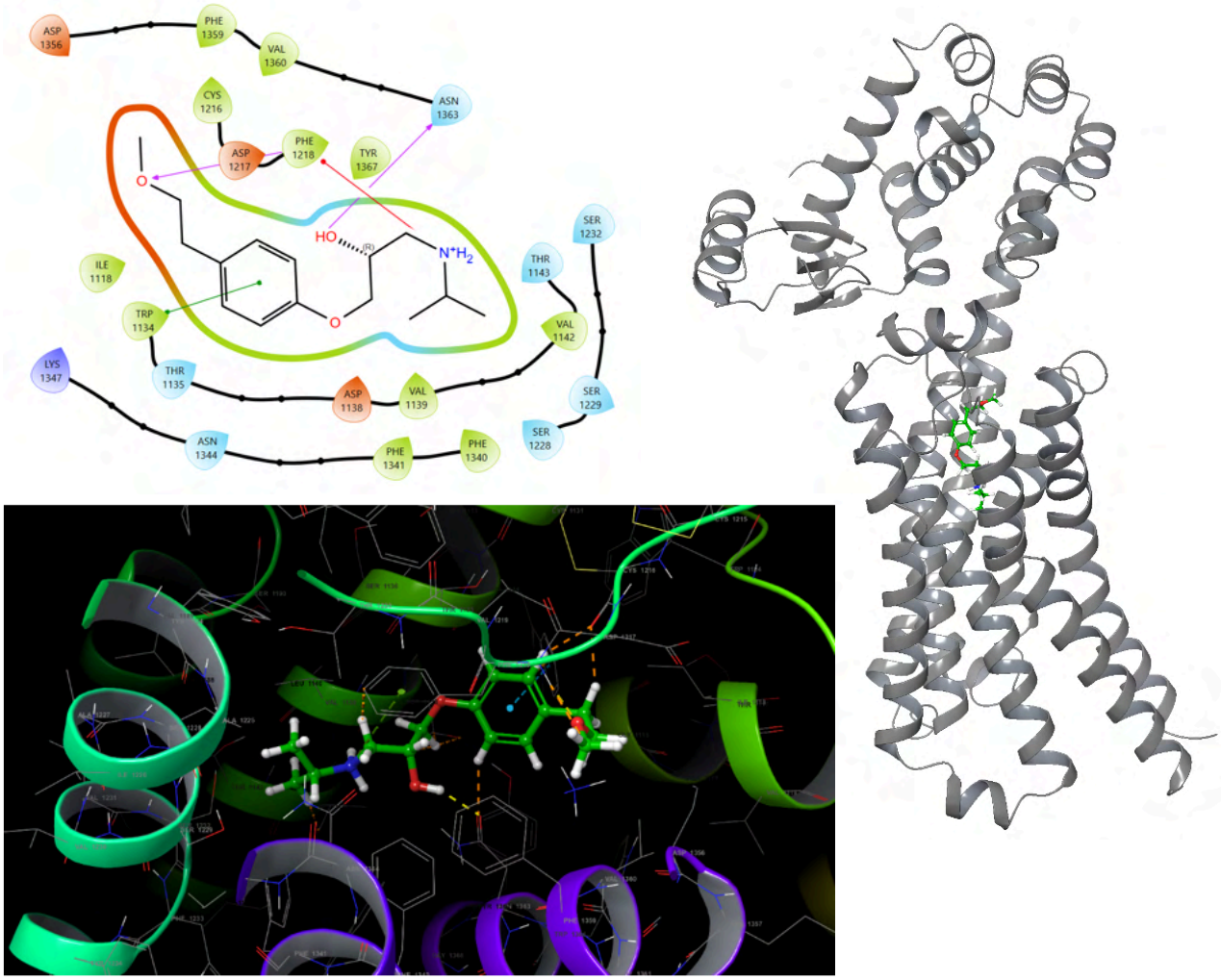


Figure 7 A. 2D Ligand-Interaction Diagram of Metoprolol and Active Site of the beta-1 adrenergic receptor. **B**. 3D Rendition of Metoprolol in the active site. **C.** Location of Metoprolol in the active site of the beta-1 adrenergic protein.

Mechanism of Action

Metoprolol is a selective beta-1 adrenergic receptor antagonist, meaning it inhibits the binding of catecholamines like noradrenaline and adrenaline to their respective receptors in cardiac cells of the sinoatrial node, the atrioventricular node, and the ventricular myocardium.[26]

Cyclic adenosine monophosphate and protein kinase A (PKA) are unable to initiate their intracellular cell pathways as a result of inhibition.[26] Other regions of beta-1 receptors include the kidney and fat cells.[30] Metoprolol avoids beta-2 receptors located in the lungs and blood vessels.[26]

The following is a broad overview of the cell pathway that metoprolol inhibits. Following the signaling of the Gs subunit by the beta-1 receptor, adenylyl cyclase continues the pathway by synthesizing cAMP from adenosine triphosphate (ATP). cAMP then mediates the phosphorylation of calcium channel blockers by protein kinase (PKA). This causes a positive inotropy in the heart, making it beat with a stronger force.[30]

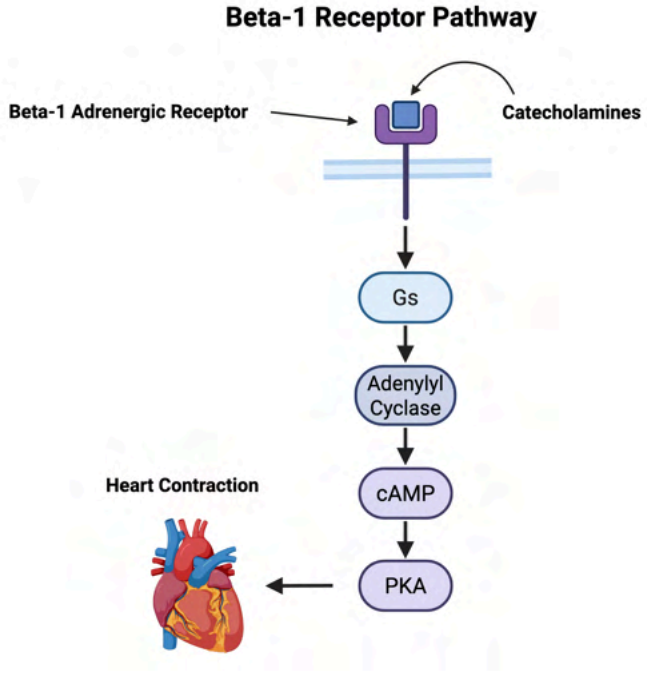


Figure 8 Beta-1 Receptor Pathway [30,31]

Following inhibition, the pacemaker cells in the sinoatrial node experience a decrease in the rate of spontaneous depolarization as the rate of sodium inflow is reduced, thus decreasing the action potentials of the pacemaker cells.[26] Metoprolol then hinders a quick repolarization of nodal action potential as cells become unable to release potassium ions at a standard rate, preventing the pacemaker cells from being able to contract rapidly.[26] Due to upstream inhibition, PKA is unable to phosphorylate L-type calcium channels to the same degree as in the uninhibited cellular pathway.[26,32] As less calcium can flow through the channels and into sarcomeres, there is a reduced amount of the ion that can bind to troponin.[26,32] Less of this interaction leads to lower amounts of free-floating tropomyosin that can bind to actin.[26,32] As a result, the cardiac cells of the ventricular myocardium exhibit a weaker contraction.[26] Also, metoprolol reduces the amount of renin released by the kidneys, which lowers blood pressure.[21,30]

Ultimately, metoprolol prevents ischemic problems by lowering the heart's required oxygen, reducing heart rate and blood pressure, and lessening angina pectoris.[26]

Pharmacokinetics

Broad information about metoprolol is that it is classified as a Biopharmaceutics Class System (BCS) 1 drug, meaning it is very permeable and soluble. Metoprolol has a pKa of 9.7 and a molar mass of 267.36 g/mol. Metoprolol's ability to pass the blood-brain barrier can be explained by its effective permeability value of 1.34 x 10^{-34} cm/s for the jejunum. The octanol-to-water coefficient is 1.88.[33]

Absorption

From clinical trials, it was shown that 95% of metoprolol is absorbed in the human intestine. The time it takes for metoprolol to reach its maximum concentration in the blood (T_{max}) is between 1 and 6.3 hours. As metoprolol undergoes first-pass metabolism, the bioavailability is a reduced value of 50% when taken orally. In oral studies, it was shown that when the dosage increased, so did the maximum drug concentration in the plasma (C_{max}), the T_{max}, and the area under the curve for the concentration-time graph. Other oral studies depicted how a controlled release administration led to a lower C_{max} and area under the curve. The S-enantiomer of metoprolol was more readily absorbed than its enantiomer; S-metoprolol had a C_{max} of 449.75 nmol/L and an area under the curve of 2324.62 (nmol x h)/L, while R-metoprolol had a C_{max} of 378.25 nmol/L and an area under the curve of 1955.27 (nmol x h)/L. One study showed that when taken with food, metoprolol had a higher C_{max} value than when in a fasting state, indicating a greater absorption. Metoprolol has displayed differing activity in women than in men, where a study documents that women had larger C_{max} and area under the curve values.[33]

Distribution

The volume of distribution at steady state (V_{ss}) of metoprolol is 3.2 L/kg. 88% of the drug is unbound to human serum albumin (HSA). This distribution value indicates a large portion of metoprolol remains in active form throughout the body, not strictly bound to blood plasma. The blood-to-plasma ratio is 1.3, meaning metoprolol tends to bind to the cellular makeup of blood instead of the plasma. Metoprolol belongs to Pregnancy Risk Class C, meaning that although metoprolol is safe for breastfeeding babies, animal studies have shown harmful effects on a developing fetus.[33]

Metabolism

A dose of metoprolol is given in a racemate mixture, meaning there are equal parts of the R- and S-enantiomers.[33] Metoprolol is metabolized by the CYP enzyme family in the liver into both alpha-hydroxymethoprolol and O-demethylmetoprolol.[33] The primary enzyme in this process is CYP2D6, and secondary enzymes include CYP3A4, CYP2B6, and CYP2C9.[33] Variations in the genotype of cytochrome P450, which contains the CYP enzymes, can

significantly influence the efficacy of metoprolol. A study has shown that on average, 65% of the metabolized metoprolol underwent O-demethylation (this process is R-stereoselective), 10% underwent alpha-hydroxylation (this process is S-stereoselective), and 10% underwent N-dealkylation.[34,35]

Excretion

Less than 5% of metoprolol is eliminated without any alteration. The drug is excreted renally, pertaining to a clearance (CL) value of 0.081 L/h/kg. The range of CL when administered intravenously is 48 to 72 L/h. Existing health concerns can impact the clearance of the drug from the body.[33]

Intravenous administration studies were conducted to develop metoprolol's ADME profile. In one study, 20 mg of metoprolol was intravenously administered to healthy patients and patients with renal impairment. Those with renal impairment had a greater rate of CL (60 L/h) than the healthy individuals (48 L/h). A study performed on participants with AMI demonstrated a higher C_{max} of 823 nmol/L compared to 248 nmol/L after 15 mg of metoprolol was administered by IV. A study performed on participants who were administered 20 mg of metoprolol by IV showed that participants with hepatic cirrhosis had a lower rate of clearance of the drug than healthy individuals (average of 36.6 L/h compared to average of 48 L/h).[33]

Regarding excretion, when administered orally at 50mg doses, diseased participants had a lower C_{max} value of 231 nmol/L than healthy participants (237 nmol/L), while C_{max} was greater at steady state. Diseased participants had a higher AUC value of 2251 (nmol x h)/L than healthy participants, 1951 (nmol x h)/L. In another oral study, participants with hepatic cirrhosis were administered 50 mg of metoprolol. Diseased participants had a greater C_{max} and AUC value than healthy study participants: averages of 429 nmol/L in comparison to 237 nmol/L and 5347 (nmol x h)/L in comparison to 1951 (nmol x h)/L, respectively. The rate of CL was lowered when metoprolol was administered with select antidepressants, namely escitalopram and sertraline, and other drugs that inhibit metabolic processes.[33]

Pharmacodynamics

Drug-drug interactions become a concern with metoprolol due to CYP enzyme metabolism. Any inhibition of the metabolizing enzymes can cause a significant increase in the C_{max} value. When cimetidine (a CYP enzyme inhibitor) was administered simultaneously with 100 mg of metoprolol, the C_{max} value was 610 nmol/L in comparison to 380 nmol/L. Similar results were seen with other inhibitors, such as diltiazem, dronedarone, amiodarone, and paroxetine. Other compounds with similar results include hydroxychloroquine and celecoxib. Interactions can be responsible for greater toxicity and stronger side effects.[33]

From seven different experiments on the CHO-K1 cell lines, the average log(K_d) values for beta-1 receptor binding affinity were determined to be -7.26 (standard error of the mean is 0.07).36 This translates to a K_d of 5.50 x 10^{-8} (standard error of the mean is 1.17).[36]

Atorvastatin

Synthesis

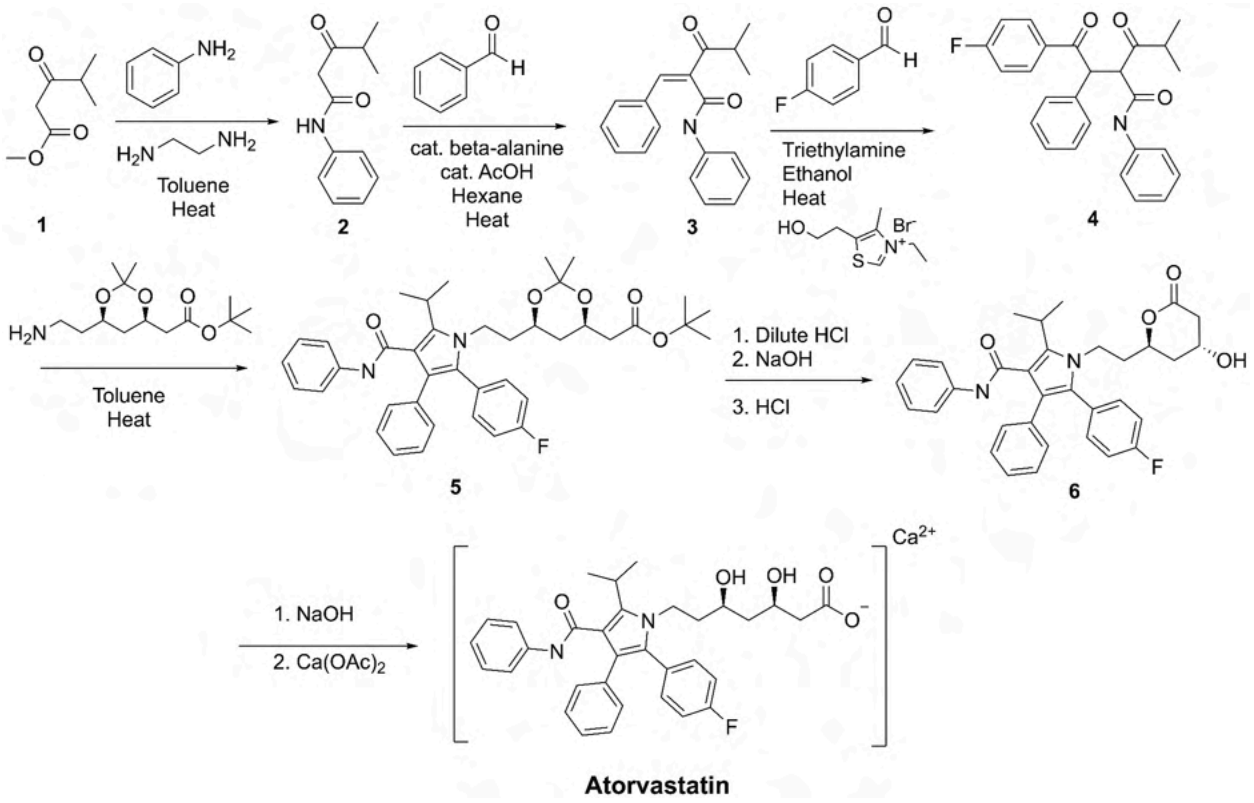


Figure 9 Synthesis of Atorvastatin[37]

The synthesis of atorvastatin begins with the reaction between 4-methyl-3-oxopentanoic acid methyl, aniline, and ethylene diamine in the presence of toluene to afford methyl-3-oxo-*N*-phenylamide. This intermediate then undergoes Knövenagel condensation with benzaldehyde in hexane, catalyzed by beta-alanine and glacial acetic acid to afford 4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)pentamide. This intermediate undergoes a Stetter reaction with 4-fluorobenzaldehyde in ethanol, catalyzed by 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and triethylamine, to synthesize a diketone compound. This intermediate then undergoes Paal-Knorr pyrrole synthesis with (4R-cis)-1,1-dimethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, forming the main structure of atorvastatin. Subsequent deprotection and ring-opening reactions finally afford Atorvastatin calcium.[37]

Molecular Docking

As discussed in the metoprolol, the chemical structure of atorvastatin defines its ability to act as a therapeutic agent. The presence of polar functional groups on atorvastatin enables it to interact via Hydrogen bond interactions with polar residues such as Asparagine, Lysine, Glutamine, and Arginine in the active site of HMG-CoA. The presence of the hydrophobic core

gives Atorvastatin a favorable lipophilic profile, enhancing its ability to permeate membranes to get to its target molecule of interaction.

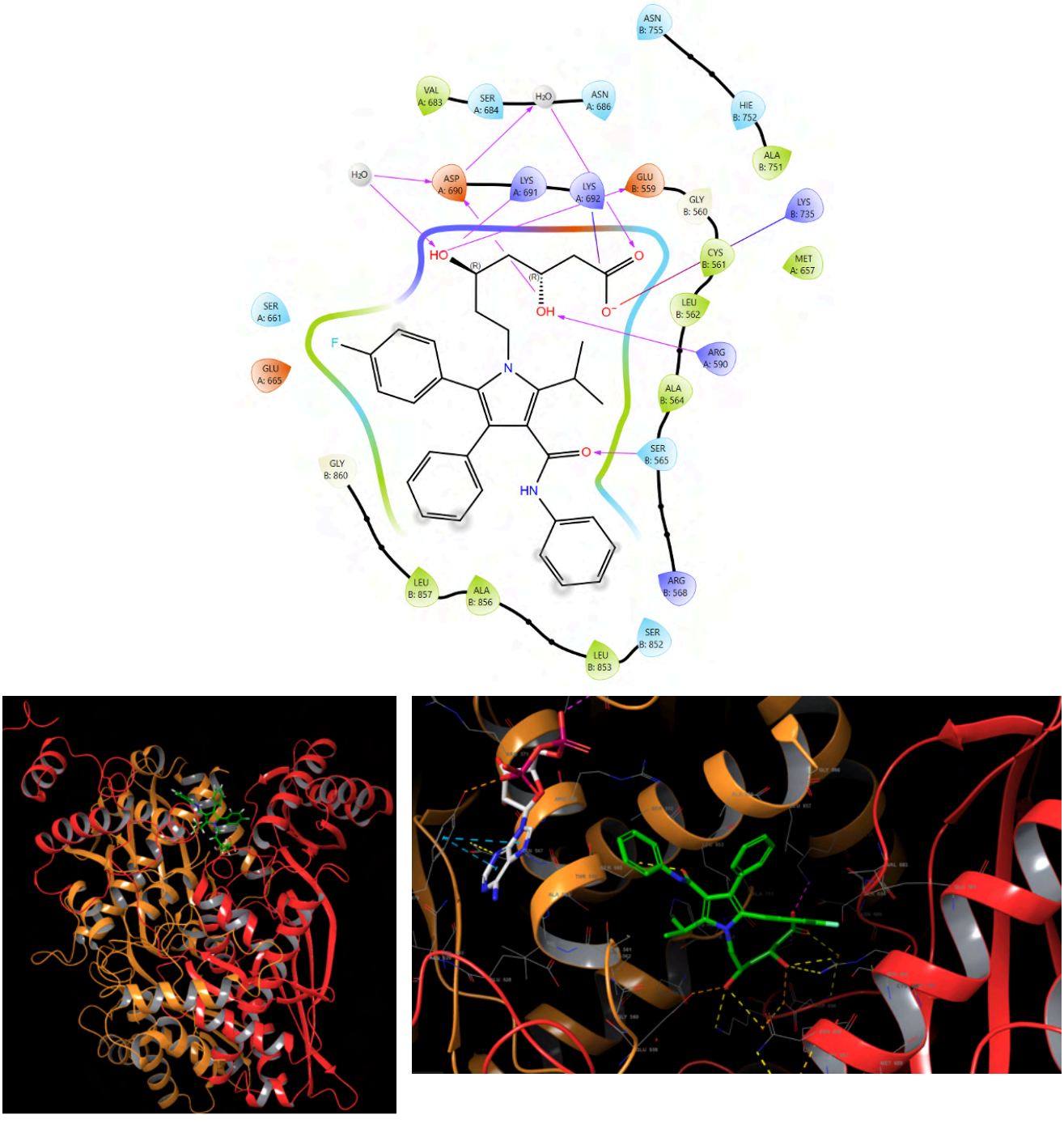


Figure 10 A. 2D ligand interaction diagram of Atorvastatin in the HMG-CoA active site. **B.** Supramolecular structure of the binding of Atorvastatin to HMG-CoA. **C.** 3D docking pose of Atorvastatin in the HMG-CoA active site

Pharmacodynamics

As determined by *in vitro* studies of the rat liver, atorvastatin had an IC_{50} value of 7.5 nmol/L in the inhibition of HMG-CoA.[38]

Mechanism of action

Atorvastatin reversibly inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), which is the rate-limiting enzyme in the mevalonate pathway;[39,40] the drug also increases the amount of LDL receptors in hepatic cell surfaces.[39,40]

Condensation reactions take place between acetyl-CoA to synthesize HMG-CoA.[41] Binding occurs between atorvastatin and HMG-CoA due to interactions between the lactone ring and side chains.[39] NADPH and HMG-CoA then undergo a reduction reaction to form mevalonic acid.[41] This acid is converted into mevalonate-5-phosphate after the addition of ATP.[41] Mevalonate-5-pyrophosphate is synthesized from the previous intermediate following the addition of ATP.[41] At any point during this time, if cholesterol is found to be at reduced levels, transcription increases take place, resulting in greater amounts of all these enzymes.[41] Finally, pyrophosphomevalonate decarboxylase is responsible for synthesizing isopentenyl-5-pyrophosphate from the previous intermediate.[41] From this point on, the biosynthesis of cholesterol can occur.[41] As a result of this inhibition, cholesterol production is reduced and upregulation of LDL takes place, where decreases in LDL-C, Apo B, VLDL-C, and increases in “good” cholesterol (HDL-C) were observed.[39,41] This effect is due to upstream inhibition, as this pathway is responsible for the biosynthesis of sterol isoprenoids (namely cholesterol) in the liver.[39,42]

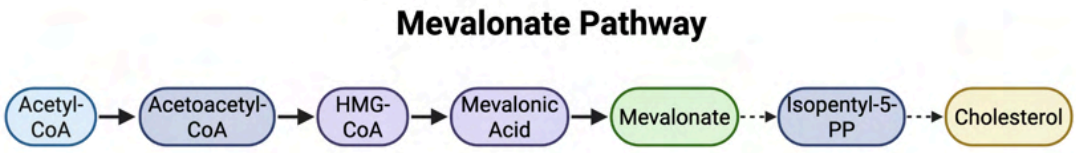


Figure 11 is a portrayal of the mevalonate pathway before inhibition.[41,43]

Atorvastatin attacks the fundamental inflammatory characteristic of CAD by reducing the amount of inflammatory cytokines, namely IL-1β and TNF-α. Even more so, the drug lowers the amount of NLRP3, an inflammatory protein. Furthermore, atorvastatin reduces macrophage signaling in plaque by lowering CD68 expression, addressing a key component of atherosclerotic progression and proving itself as a valuable CAD therapy.[44]

Pharmacokinetics

Absorption

Atorvastatin is typically administered orally as atorvastatin calcium, anywhere between 10 and 80 mg a day. Its solubility is determined to have a value of 1.23 mg/mL at pH 6.0, which replicates the acidity of the intestinal system, and the drug is very permeable. The drug

concentrations in the intestinal lumen can be around 70 μmol/L to 550 μmol/L following an oral dose. The Caco-2 colon cell line was dosed with atorvastatin to assess the drug's permeability, where the drug concentration was 1.3 μmol/L, which is unlike the normal 70 μmol/L to 550 μmol/L range. A pH of 7.4 was established to simulate the acidity at the apical side of the epithelial layer, which yielded a permeability of 4.9×10^{-6} cm/sec. When tested at a pH of 6.0, the permeability was 28.4×10^{-6}. These high permeability values at luminal pH indicate the drug in acid form is readily absorbed by the intestine. Although atorvastatin undergoes passive permeability, its role as a substrate introduces a rapid form of absorption through chemical transportation, as proven *in vitro*. The Caco-2 cell line study, along with other studies, showed how P-glycoprotein and the H^+-monocarboxylic carrier (MCT) enzyme play a crucial role in the speed of absorption.[45]

The absolute bioavailability following oral administration of 10 mg is 14%. This reduced bioavailability is likely due to first-pass metabolism both in the liver and the gut. The "gut wall extraction" (E_G) ratio approximately amounts to 0.76 when absorption and hepatic extraction ratios are accounted for. The resulting E_G value is likely due to the presence of the CYP3A4 enzyme in the gut, which is the primary metabolic enzyme for the drug. Other research indicates that uridinediphosphoglucuronyl transferase (UGT) could play a role in the extraction of atorvastatin from the gut. The C_{max} for atorvastatin is 3.61 μg/L, and the T_{max} is 1.5 hours. The rate of CL following intravenous administration of 10 mg of atorvastatin for 2 hours is 625 mL/min. The hepatic extraction ratio is 0.42.[45]

Distribution

During a study, 5 mg of atorvastatin was administered by IV, and the volume of distribution (V_d) was determined to be 381 L by GC-MS, which is a significantly large value. The plasma protein binding was determined to be in the 80 to upper 90 percent range when in the active form, depending on the study. The high V_d is a result of the drug's transport into tissue, as it is readily permeable from its nonpolar characteristic. Drug-drug displacement interactions in the plasma proteins are not likely, even though a large amount of the administered dose resides in a protein-bound state; this is most likely due to the oral administration rather than IV, and also a result of the slow mechanism of action.[45]

Metabolism

Atorvastatin is metabolized following administration, converting its hydroxy ring into a lactone and forming an equilibrium. The acid-to-lactone area under the curve values range from 1.1 to 1.3, as reported by clinical studies. The drug is metabolized by processes in the liver by enzymes of cytochrome P450, particularly by CYP3A4 oxidation. The active plasma metabolites are 2-hydroxy-atrovastatin acid (the most prominent metabolite) and 4-hydroxy-atorvastatin acid, which then establish equilibrium. Other metabolic processes observed from *in vitro* studies include beta-oxidation and glucuronidation by UGT1A1 and UGT1A3. Further *in vitro* studies show how the acid form was a substrate for P-glycoprotein and MCT, and was transported by OATP1B1. The metabolites play a larger role in the mechanism of action than the administered drug itself, pertaining to 70% of HMG-CoA reductase inhibition. The acid form's Michaelis-Menten constant (K_m) for CYP3A4 ranges from 70-80 μmol/L, while the lactone form

has a larger K_m, indicating that the active metabolites are formed from the lactone to acid conversion. Studies show that the lactone form is significantly more CYP3A4-dependent in metabolism than the acid form, drawing importance to this enzyme in the efficacy of the drug, as the metabolites play a larger role.[45]

Excretion

The primary route of excretion is by the liver through conversion into bile, and the secondary route of excretion is renal. This was proven after the administration of 20 mg of ^{14}C atorvastatin in a study's participants, where most of the radioactive drug was found in the bile. The renal route only accounted for 1% of the excreted drug in the same study. The plasma elimination half-life was determined to be 7 hours. The plasma half-life, including both atorvastatin and the active metabolites, ranged from 13 to 16 hours.[45]

Certain factors, like food intake accompanying administration, can make a difference. Although administration with medium to high-fat food does not impact how much the drug is absorbed, the rate at which absorption occurs is reduced. Studies indicate lower C_{max} values and larger T_{max} values when taken with food. Atorvastatin's performance varies in older individuals and in females. Study results show that Cmax was 42.5% greater in those aged 66 to 92 years compared to those aged 19 to 35 years. The same study results showed that C_{max} was 17.2% higher in females compared to males.[45]

Conclusion

This review highlights all aspects of the medicinal chemistry of two treatments, namely metoprolol and atorvastatin, for OCAD. This includes drug design, synthesis, mechanistic studies, absorption, distribution, metabolism, excretion, and the effect on the human body. The sciences behind drug discovery and development continue to progress and evolve, resulting in higher granularity in the main tenets of medicinal chemistry described above. This review provides a brief exploration of the world of medicinal chemistry in obstructive coronary artery disease (OCAD).

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