# PHARMACEUTICAL CHEMISTRY OF MOLECULAR THERAPEUTICS



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eCampus Onterio

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# Pharmaceutical Chemistry of Molecular Therapeutics (de Araujo, Saqib, Keillor, and Gunning)

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# TABLE OF CONTENTS


Licensing

1: Acknowledgements

Authors

## 1: Medicinal Chemistry of Drugs

- 1.1: Different Avenues of Drug Discovery

## 2: Drugs for Treatment of Venous Thromboembolism

- 2.1: Pathology
- 2.2: Anti-Coagulant Treatments
- 2.3: Summary

## 3: Drugs for Treatment of Hyperlipidemia

- 3.1: Pathology
- 3.2: Treatments
- 3.3: Summary

## 4: Drugs for Treatment of Diabetes Mellitus

- 4.1: Pathology
- 4.2: Insulin
- 4.3: Treatments for Type I Diabetes
- 4.4: Treatments for Type II Diabetes
- 4.5: Summary

## 5: Drug Treatments for Pain and Inflammation

- 5.1: Pathology
- 5.2: Treatments for Pain and Inflammation
- 5.3: Summary

## 6: Summary

- 6.1: Identifying drugs from functional groups

Index

Glossary

Detailed Licensing

Accessibility Statement

Appendix

Detailed Licensing

# Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

# 1: Acknowledgements

2

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4

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# CHAPTER OVERVIEW

## 1: Medicinal Chemistry of Drugs

1.1: Different Avenues of Drug Discovery

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# 1.1: Different Avenues of Drug Discovery

Medicinal chemistry synergizes applications in cellular and molecular biology with pharmaceutical and organic chemistry to intercept natural processes in the human body. Modern drugs have emerged from different facets of discovery including astute observation from repeated use of natural products, serendipity, as well as hypothesis-driven rational- or targeted- chemical design.

For example, the discovery of the widely used analgesic drug, acetaminophen (also referred to as **Tylenol** or paracetamol) occurred through what was published as 'a fortunate accident'. In 1884, Prof. Adolf Kussmaul (University of Strasbourg) had two assistants who were evaluating different agents against intestinal worms in parallel to their effects on patients. One of their compounds, 'naphthalene' was shown to have unexpected antipyretic effects. However, as is the often the response when obtaining unanticipated results, the dataset and experimental protocols were examined with a deeper level of scrutiny, and it was revealed that the dispensing pharmacy supplied the patient with acetanilide (in error) as opposed to naphthalene. Acetanilide and other derivatives such as phenacetin were further investigated over several years. Each analog had different benefits and toxicities associated with it (some toxicities were associated with metabolites of the compounds, while others were found to be contaminants in the synthesis and/or purification steps). Eventually, the molecule, paracetamol, was identified. In 1955, it was marketed as Tylenol Elixir and was heavily promoted through unique branding campaigns as an over-the-counter medication for bed-ridden sick children.

Other drugs have been identified through more rational and target-based design approaches such as the 'miracle drug', **Gleevec** (imatinib), which is the prototype kinase inhibitor. In the 1950s, two researchers, Peter Nowell and David Hungerford, were analyzing cells from different blood cancer patients. In a specific sub-type of blood cancers, called chronic myeloid leukemia (CML), they identified an unusually small chromosome present in these patients (named the 'Philadelphia chromosome'). Following more than a decade from this discovery, cytogeneticist, Janet Rowely, was able to recognize that the Philadelphia chromosome results from a translocation event between chromosome 9 and 22. Across the span of another decade, researchers were able to identify this translocation specifically results in the fusion of two genes (ABL and BCR from chromosome 9 and 22 respectively), leading to a new gene-product called BCR-ABL. Under normal conditions, ABL is an important kinase protein that is responsible for accelerating cellular growth, especially in white blood cells. The new fusion protein, BCR-ABL decouples ABL kinase from its conventional regulatory controls, leading to highly proliferative cell growth. Oncologist Brian Druker was focussed on developing a molecule that could bind the active site (ATP-binding site) of BCR-ABL and effectively shut-down the protein. His team used computational models to predict chemical structures that could engage in appropriate interactions, and these compounds were synthesized and screened against CML cancer cell lines, *in vitro*. After ~2 years, the top compound, ST1571 (renamed Gleevec) was evaluated in a Phase I clinical trial with all 31 patients demonstrating complete remission. Gleevec was approved by the US FDA in 2001 and shown to have a >95% complete response rate over 60 months. The approval of Gleevec represents a convergence of multiple learnings across distinct disciplines including cancer biology, structural biophysics, organic chemistry, and clinical sciences. Since the discovery of Gleevec, there have been many drugs developed through the iterative pipeline of building on biology-enabled pharmaceutical chemistry.

Regardless of the path towards innovative drug design, the goal for any drug is to maximize therapeutic benefits and while minimizing off-target interactions, which can help maintain the safety window of the drug. There are >13,000 drugs available in Canada for many different indications. Here, we aim to provide an overview of some of the more commonly prescribed drugs and their relationship within the chemical and biological origin, as well as some of the common themes in medicinal chemistry between different drugs.

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# CHAPTER OVERVIEW

## 2: Drugs for Treatment of Venous Thromboembolism


2.1: Pathology

2.2: Anti-Coagulant Treatments

2.3: Summary


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# 2.1: Pathology

The circulatory system distributes blood throughout the body, carrying oxygen, nutrients, and hormones to different organs, while removing carbon dioxide and other waste products. Blood contains multiple components including blood cells and an array of different proteins, lipids, and carbohydrates. Maintaining a constant flow of blood is essential for viability of all organs and tissues. **Venous thromboembolism** (**VTE**) refers to a blockage that occurs from a blood clot in the veins and impedes blood flow. There are generally two types of VTE, which refer to the location the blockage – deep vein thrombosis (DVT) or superficial vein thrombosis (SVT). Superficial veins are closer to the surface of the skin and are often translucently visible. Blood clots that occur in these regions usually resolve naturally (on the timescale of hours to days) and are less medically serious unless they travel to the deep veins (such as within the legs). Conversely, DVT can lead to life-threatening conditions including pulmonary embolisms and must be treated as soon as possible.

## Blood Flow Blockages

Blockages that occur in the blood have different names. If blood cells aggregate and form a semi-solid mass that is attached to a blood vessel, this is referred to as a **thrombus**. If this thrombus detaches from the blood vessel, it is referred to as a **blood clot**. This is a minor but significant difference. For example, if blood is left in a test tube and coagulates into a semi-solid mass, it would be called a blood clot (and not a thrombus) because it is not attached to any blood vessels. A blood clot is also a specific example of an **embolus**, which is a substance that travels through the blood stream and can create a blockage. Blood clots, gas bubbles, cholesterol aggregates, or foreign bodies can all be identified as emboli within the blood stream.

There are situations in which blockage of blood flow is required, especially when there is damage to the circulatory system and bleeding occurs. In this case, the body has a system of responses to limit bleeding and repair the damage. This occurs in two stages called **primary hemostasis**, where platelets assemble in the area of damage and start to stick to each other, and **secondary hemostasis** (or **coagulation**), where a mesh of proteins (mostly a protein called fibrin) forms to hold the platelets together. During coagulation, the strands of fibrin protein wrap around the platelet plug that forms during primary hemostasis and become insoluble (via the action of FXIIIa), helping block the loss of blood.

## Coagulation Cascade

Coagulation or the clotting of blood is controlled by “clotting factors” or “coagulation factors” in the biochemical pathway known as the coagulation cascade. In total, there are 12 clotting factors labelled with Roman numerals (I, II, III, IV, V, VII, VIII, IX, X, XI, XII, and XIII). Note that there is no clotting factor VI, since these proteins were numbered in the order of their discovery, and the protein species identified as clotting factor VI was later recognized as a different version of clotting factor V. Importantly, the clotting factors exist in two forms, an active form and an inactive form. The active form is labelled with a lower case ‘a’ following the Roman numeral. In addition to this naming convention, specific active and inactive factors have common names, which are identified in Figure 2.1.

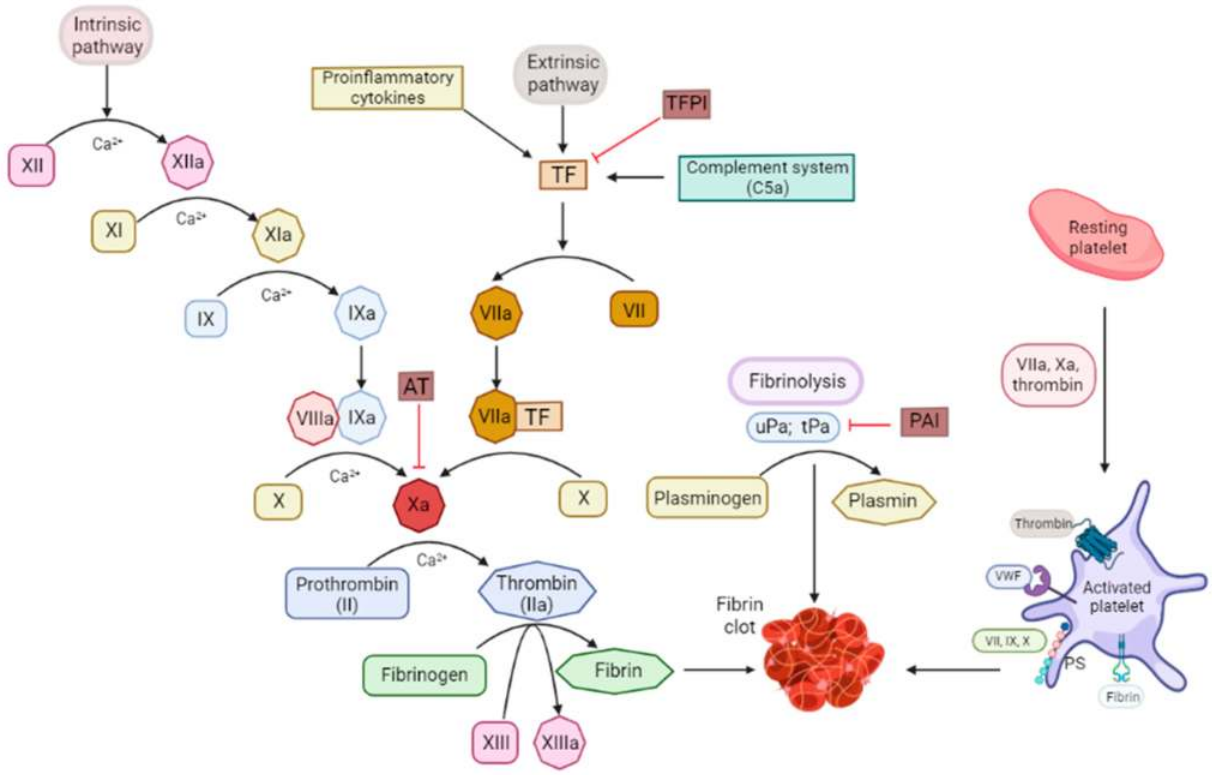



*Figure 2.1 The coagulation cascade. Note that both the intrinsic and extrinsic pathways converge on activation of factor Xa. (Adapted from Guillamat-Prats, IJMS, 2022) Image source: (Figure 1) by Raquel Guillamat-Prats is used under a CC-BY 4.0 license.*

These factors all participate in the coagulation cascade, which has an end-goal of creating fibrin protein (factor Ia) for the insoluble mesh formation. Several of these factors are enzymes with serine protease activity that will cleave and activate the downstream factor. The biochemical underpinnings of the full cascade are complex and can be initiated when there is internal vascular endothelium damage (intrinsic pathway) or external trauma (extrinsic pathway). Regardless, both pathways converge of activation of factor X to Xa, which leads to activation of thrombin (IIa) and fibrin (Ia). This pathway is also naturally regulated by the protein **anti-thrombin**, which can bind thrombin (IIa), but also has activity for blocking factor Xa.

The goal for anti-coagulation treatments is to interfere with any of these processes in the coagulation cascade, which will effectively enable shutting down the fibrin formation process and forms the mechanism for all anti-coagulants that are currently on the market.

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# 2.2: Anti-Coagulant Treatments

## Warfarin

Warfarin is an anti-coagulant that was approved in 1954, and there is a substantial amount of clinical information available on its use across many patients. As such, warfarin is the most clinically comfortable anti-coagulant to prescribe. Warfarin targets factor X and II (Pro-thrombin) but also blocks factor IX and VII, leading to very potent anti-coagulation effects. These broad inhibition effects arise from the $Ca^{2+}$-binding requirement of these enzymes. Warfarin blocks the proper synthesis of these factors and prevents them from binding $Ca^{2+}$ in an intricate pathway.

### Warfarin Blocks VKORC Leading to Downstream Effects on the Clotting Factors

Calcium ion binding within blood clotting factors occurs in a unique binding mode. The blood clotting factors X, II, IX, and VII all possess a specific glutamic acid where the side chain is converted to a di-carboxylic acid. Unlike normal glutamic acid side chains where there is a single acid functionality, this modified amino acid now possesses two carboxylic acids that enables it to chelate a $Ca^{2+}$ ion. The di-carboxylation is performed by the enzyme **gamma glutamyl carboxylase** in a vitamin K dependent process. In this process, Vitamin K is converted from a hydroquinone to an epoxide resulting in an inactive Vitamin K species. In order to generate an additional di-carboxylated glutamic acid, Vitamin K must also be re-generated. The re-generation is carried out an enzyme called **vitamin K epoxide reductase complex 1** (VKORC1). Warfarin can competitively bind at the active site of VKORC1 and block this reaction, thereby blocking the regeneration of vitamin K. (Figure 2.2)

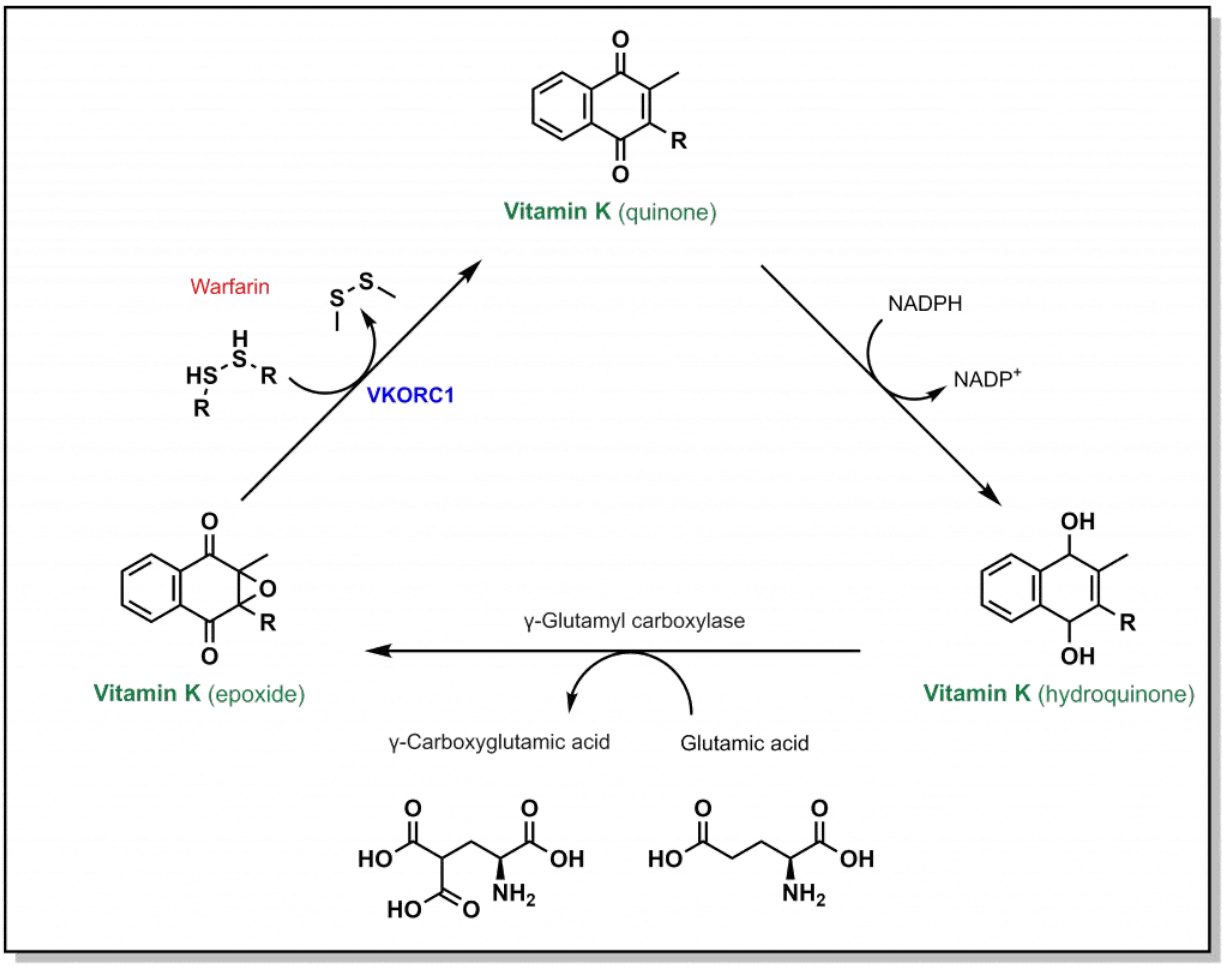



Figure 2.2 Vitamin K is used to generate di-carboxylated glutamic acid residues. Vitamin K is regenerated by the reaction of VKORC1 and this process is inhibited by warfarin.

### Properties of Warfarin

Vitamin K is a **quinone** (6-membered unsaturated ring that is conjugated with two carbonyls). There are two versions of vitamin K found in humans, which depend on the saturation level of the hydrophobic tail. Warfarin will competitively displace vitamin K from the active site of VKORC1. Unlike vitamin K, warfarin has a coumarin structure. (Figure 2.3). Importantly, warfarin possesses a stereogenic centre leading to two different chiral molecules (*R*-warfarin and *S*-warfarin). The *S*– enantiomer is ~5-fold more active, although the pharmaceutical drug is delivered as a racemic mixture (equal concentrations of both enantiomers).

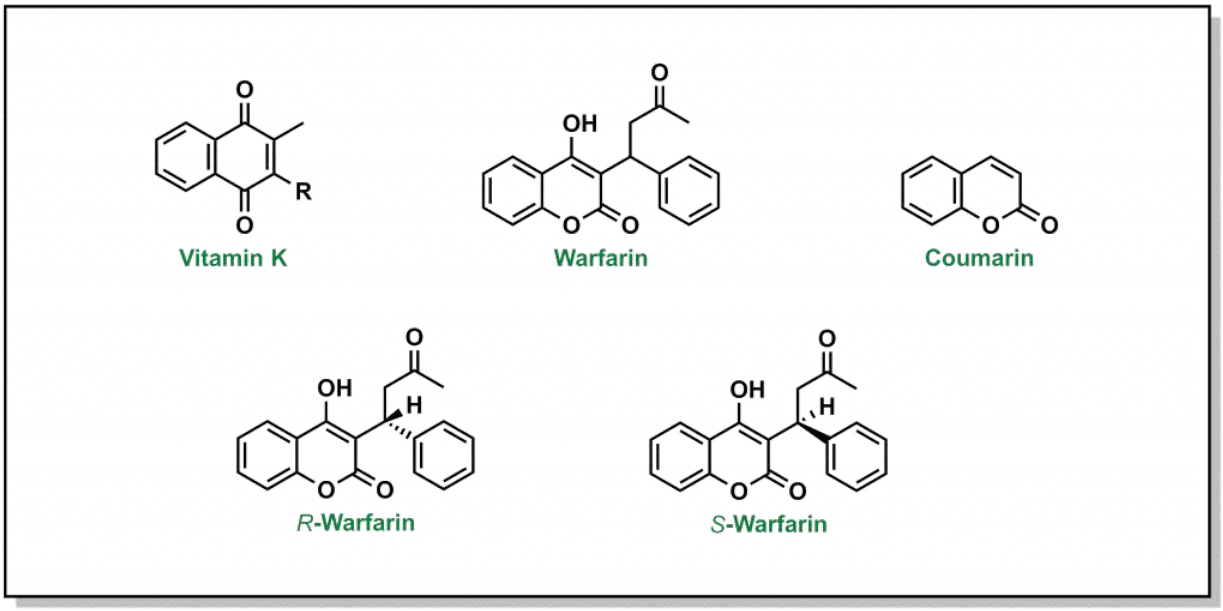



Figure 2.3 Structures of vitamin K and vitamin K competitive inhibitors.

Warfarin can be administered orally and displays a bioavailability of >99%, which indicates that nearly all the drug ingested will be absorbed and enter the blood stream without degradation/metabolism (which is unusual for an oral drug). As such, warfarin also has a relatively long half-life in the body (>40 h). However, it is also a slow-acting drug in that it will take ~3-4 days to observe any effects. This is because the mechanism of action of warfarin involves blocking synthesis of new blood clotting factors, and it will not have an effect on the current proteins. Therefore, the "older" blood clotting factors need to complete their normal lifecycle in the body and be degraded before the effects of warfarin are observed (blood clotting factor turnover usually occurs within 3-4 days). Warfarin is also teratogenic and crosses the placenta and should not be used if the patient is pregnant.

Warfarin dosing can also be a complicated process, since there can be a high degree of variability between different individuals – by 20-fold in extreme cases. From a dietary perspective, since warfarin is a competitive vitamin K inhibitor, if patients consume foods with significant quantities of vitamin K (i.e. leafy green vegetables) this can reduce the effects of warfarin. For these reasons, patients are often recommended to maintain a consistent level of leafy greens in their diet to avoid continuous variations in dosing. Another point of variability is that warfarin is metabolized by the CYP2CP enzyme, and specific genetic populations have different isoforms that metabolize warfarin at different rates. For example, CYP2C9*2 (R144C variant) and CYP2C9*3 (I359L variant) lead to significant reduction in metabolic activity. Based on all of these factors, warfarin dosing needs to be monitored closely and adjusted (via an INR [international normalized ratio] test, which provides a quantitative measure of how fast blood clots from a patient).

## Heparins

After warfarin, **heparins** emerged as the second most common anti-coagulant. While warfarin is a small molecule inhibitor that does not occur naturally in the body, heparin is a naturally occurring sugar derivative. The structure of heparin involves a specific sequence of five carbohydrate monomers (**pentasaccharide sequence**) followed by additional carbohydrate monomers of variable length. Naturally occurring heparin is a collection of these sugars with different sizes/lengths of sugar tails.

The main target for heparin is the protein anti-thrombin. Recall that anti-thrombin regulates the activity of both thrombin (factor IIa) and also factor Xa. (Figure 2.1) This is carried out by the conserved pentasaccharide sequence found on all heparin molecules

that binds to anti-thrombin. This binding triggers a conformational change at the active site of anti-thrombin which enables it to engage with either factor Xa or factor IIa (since the binding sites are similar on both proteins). (Figure 2.4) When anti-thrombin binds to thrombin (factor IIa), the heparin can wrap around anti-thrombin (in a process called 'bridging') and engage the bound thrombin protein. This bridging function blocks the protein more effectively (provided it is long enough – i.e. heparin has at least 13 sugar molecules). This second bridging interaction is generally required for heparin to fully block the activity of thrombin. However, this interaction site does not occur between heparin and factor Xa (regardless of the length of the heparin molecule). Since heparin exists as a polymer with variable sizes (sugars), there are different forms that are utilized clinically and lead to different therapeutics effects.

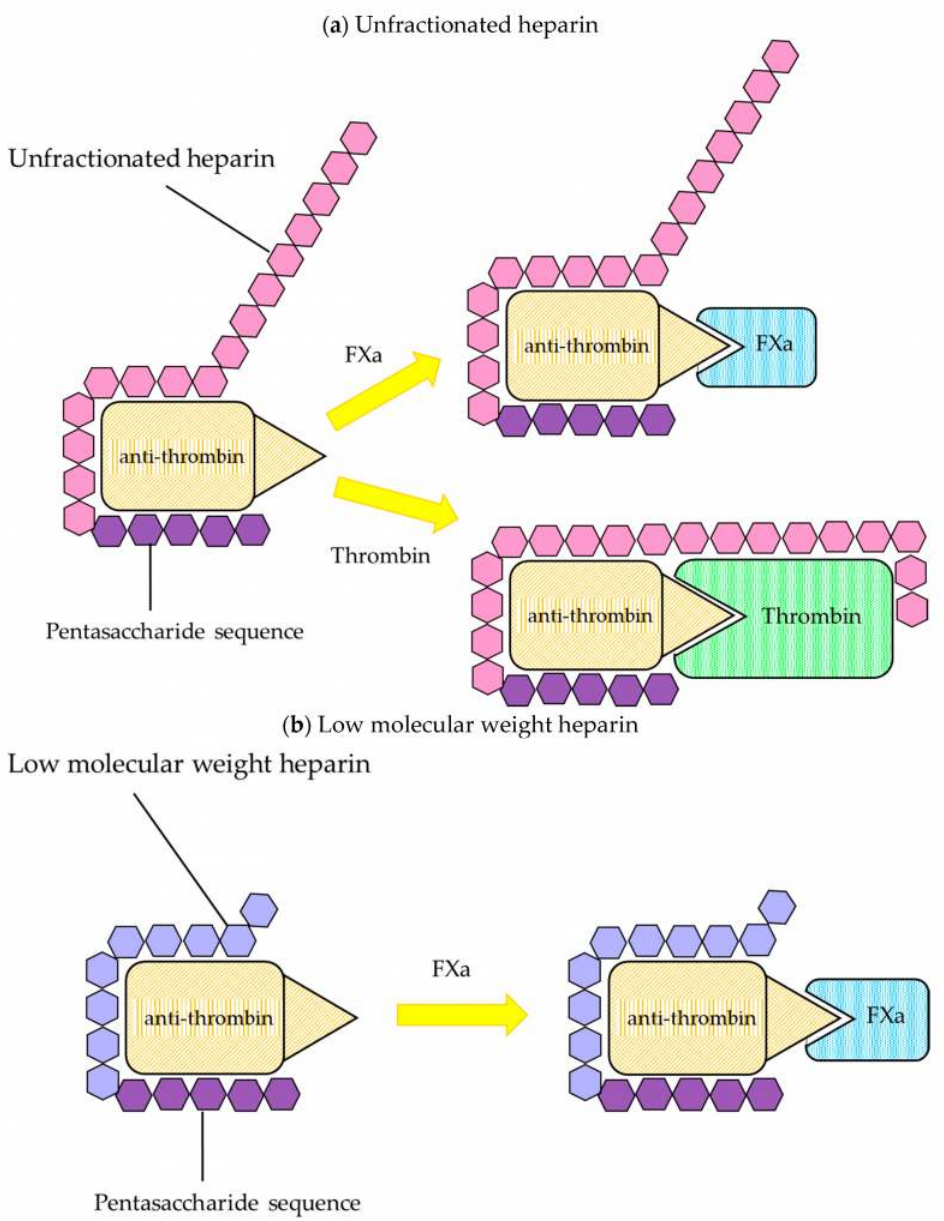



Figure 2.4 Schematic of inhibition profiles of heparin and low molecular weight heparin. Image Source: (Fig 1) by Osamu Kumano, Kohei Akatsuchi, Jean Amiral is used under a CC-BY 4.0 license.

## Unfractionated Heparins

**Unfractionated heparin** (**UFH**) is heparin that is isolated from porcine blood, and contains a complete mixture of sugars (the molecular weight of each heparin molecule ranges from 5000 – 15000 Da). This heparin is easier to generate since there are fewer purification steps. Furthermore, since this mixture contains both large and short heparin molecules, both thrombin and factor Xa are

inhibited effectively. However, the variability in size of the molecules translates into variability in pharmacokinetic profiles following administration.

### Low Molecular Weight Heparins

To compensate for the variability in pharmacokinetic profiles, the heparin can be further purified into a more homogeneous mixture. **Low molecular weight heparin** (**LMWH**) is generated such that the molecules have molecular weights lower than 8000 Da, which greatly improves the pharmacokinetic profile reproducibility/predictability. However, the larger portion of shorter heparin molecules also results in a reduced binding/inhibition of factor thrombin (since a smaller subset of the heparin molecules can carry out the bridging function). As such, LMWH is generally less efficacious than UFH.

### Fondaparinux

Continuing with the theme of truncating the heparin molecule for more reproducible pharmacokinetic profiles, heparin can be further abridged to the pentasaccharide sequence. This version does not exist naturally and is only generated synthetically and is marketed as **Fondaparinux**. This is an extremely potent inhibitor, although it can only block the activity of factor Xa (and not thrombin).

### Heparin Induced Thrombocytopenia

The purpose of heparin is to “thin” the blood and act as an anti-coagulant. However, there are scenarios (~5% of patients) when administration of heparin leads to the opposite effect. This is referred to as **heparin induced thrombocytopenia (HIT)** and there are two sub-types. Type I HIT is generally milder and occurs when heparin engages with a positively charged protein called platelet factor 4 (PF4) to create an IgG-antigenic complex. Type II HIT is usually an immune-mediated response as a result of the patient generating antibodies due to a component of the heparin injection (especially relevant since UFH or LMWH originate from another species). This can be life-threatening since the patient can enter a hypercoagulable state. In this case, usually the patient is treated with a substance that can neutralize the effects of heparin (which is a negatively charged species). In this case, protamine sulfate (a cationic peptide) is administered. It is important to note, that there are no cases of HIT observed with administration of Fondaparinux, but there are also no counteragents in case there is an overdose.

Challenges with the common anti-coagulants such as warfarin (which requires a high degree of personalization, monitoring, and has a slow onset) and heparin (which requires injections and has the potential of HIT) led to development of new inhibitors that could engage with thrombin or factor Xa. The goal for these drugs was to find a balance between efficacy, ease of administration, and onset of action. These drugs were developed as novel oral anti-coagulants (NOACs), although this term has fallen out of favour in place of **DOACs** (**direct oral anti-coagulants**).

## DOACs: Direct Thrombin Inhibitors

Thrombin is the next upstream target in the coagulation cascade, and the protein structure was known to have key distinct sites including an active site, exosite site 1 (fibrin binding site), and exosite 2 (heparin binding site). The first inhibitors were identified as derivatives of hirudin analogues (compounds isolated from the salivary glands of the leech *Hirudo medicinalis*) which correspond to ~20 residue synthetic peptides. These molecules directly bind to thrombin in an L-shape such that they blocked both the active site and exosite 1. Although these inhibitors were potent, as large peptides these molecules had to be administered subcutaneously. Newer generations of molecules are active as oral agents, such as dabigatran, which engages only at the active site of thrombin and contains a critical **benzamidine** group.

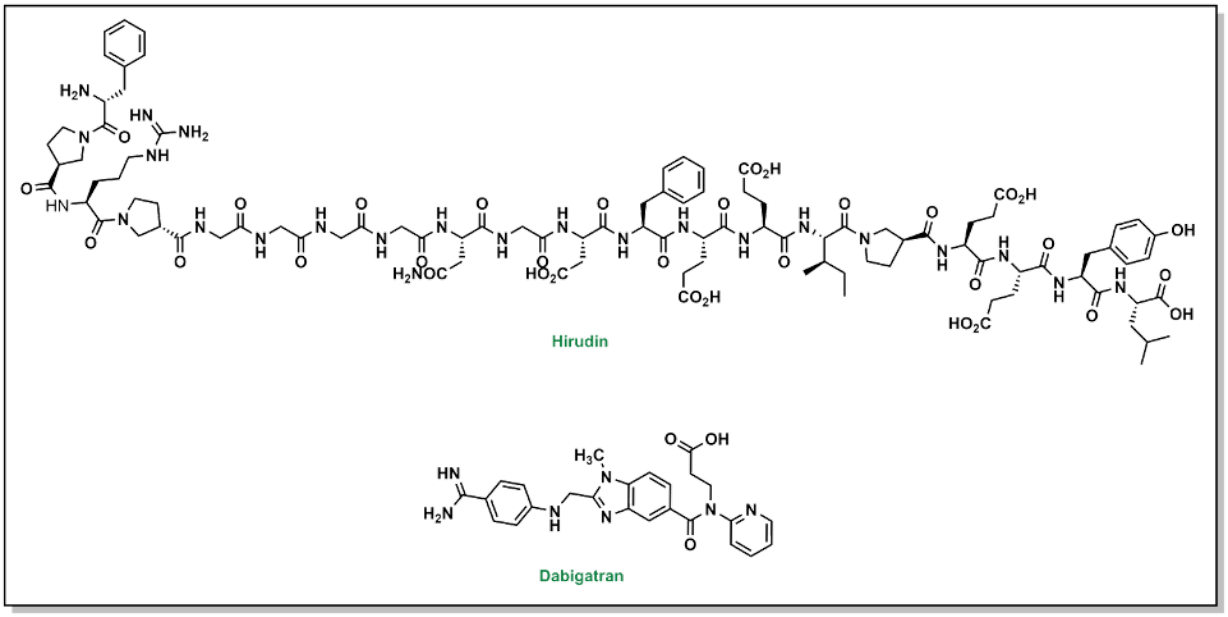



Figure 2.5 Structures of direct thrombin inhibitors hirudin and dabigatran.

## DOACs: Direct Xa Inhibitors

There are also DOACs that target factor Xa, and can be employed as substitutes for warfarin that have a reduced emphasis on blood clot testing, more predictable PK profiles, and a rapid onset of action. Similar to direct thrombin inhibitors, these molecules also bind in an L-shape across 4 sub-pockets of factor Xa (named S1, S2, S3, and S4). From a nomenclature viewpoint, these drugs are usually easily recognisable since they all contain 'Xa' in their name, such as rivaroxaban, aprixaban, edoxaban, and betrixaban. (Figure 2.6) The pharmacophore for these inhibitors is less readily identifiable, and is based on facilitating pi-pi stacking interactions between a phenyl ring of the inhibitors and the indole of Trp214 on factor Xa, as well as additional hydrogen bonding interactions throughout the molecule.

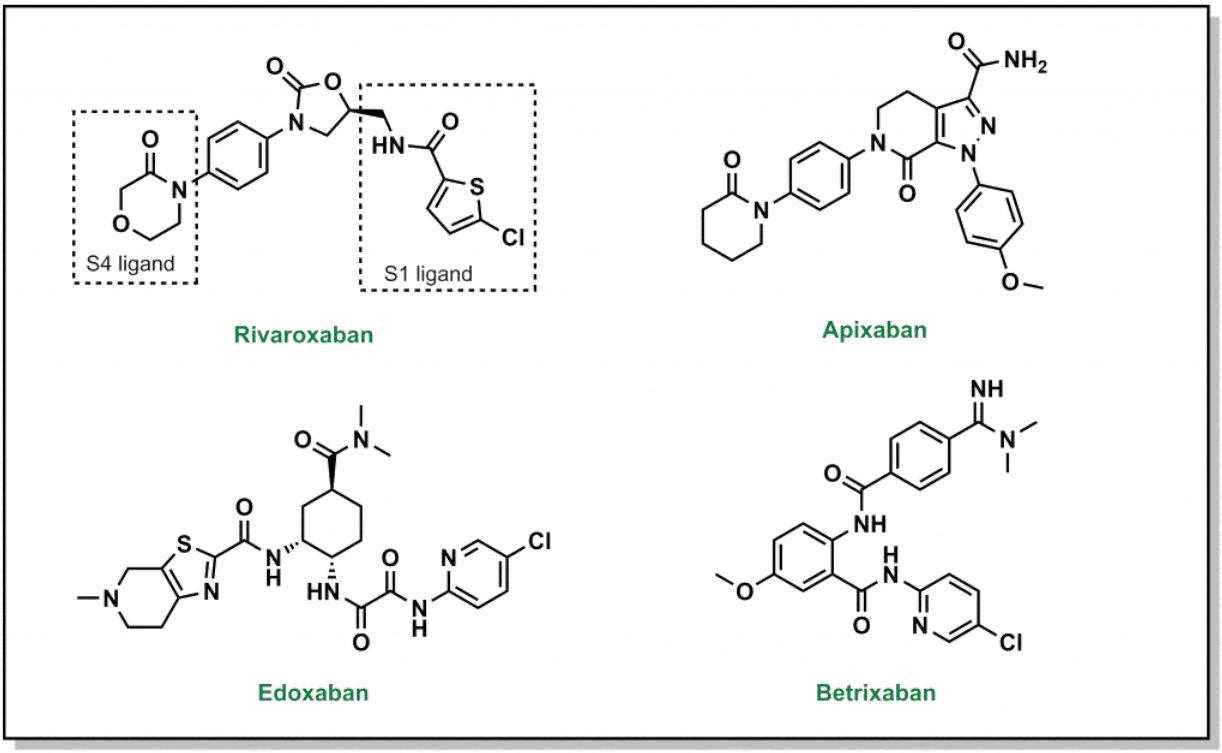



Figure 2.6 Direct Xa inhibitors

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## 2.3: Summary

The following table summarizes important properties for blood anti-coagulant drugs.

Table 2.1: Summary of anti-coagulation agents.

| | Warfarin | Heparins | | | DOACS | | |
|---|---|---|---|---|---|---|---|
| | | UFH | LWMH | Fondaparinux | Dabigatran | Rivaroxaban | Apixaban |
| **Target** | VKORC1 / Indirectly II, X, VI, XI | Anti-thrombin / Indirectly IIa, Xa | Anti-thrombin / Indirectly Xa, IIa (lesser extent) | Anti-thrombin / Indirectly Xa | IIa | Xa | Xa |
| **Type of Molecule** | Vitamin K Agonist (coumarin) | Glycosaminoglycan | Glycosaminoglycan | Glycosaminoglycan | Benzamidine | Oxazolidinone | Pyrazolopyridine |
| **Route of Administration** | Oral (>99% bioavailability) | IV | IV | IV | Oral | Oral | Oral |
| **Onset** | Slow | Fast | Fast | Fast | Fast (1-3 h) | Fast (1-3 h) | Fast (1-3 h) |
| **Duration** | Long | Short | Short | Short | Modest | Modest | Modest |
| **Countermeasure** | Vitamin K | Protamine Sulfate | Protamine Sulfate | None | Idarucizumab | Andexanet alfa | Andexanet alfa |
| **Other Concerns** | Teratogenic | HIT | HIT | No countermeasure | Requires 5-10 days of LMWH priming | Taken with food | |

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# CHAPTER OVERVIEW

## 3: Drugs for Treatment of Hyperlipidemia


3.1: Pathology

3.2: Treatments

3.3: Summary


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# 3.1: Pathology

The previous section examined the importance of clotting factors in maintaining the necessary integrity of the circulatory system and fluidity of blood. However, there can be instances where there are disequilibria of other components such has macronutrients. There are three main macromolecules which include proteins, carbohydrates, and lipids. This section is largely focussed on altered blood lipid concentrations.

Lipids have multiple essential functions in the body:

- **Compartmentalization**: Every cell in the human body is separated from the external environment by a phospholipid bilayer structure. Additionally, lipids are also used in sub-cellular compartmentalization.
- **Energy storage**: Lipids contain the highest energy per gram (compared to other macronutrients) and are used as efficient energy storage molecules. Generally, the more reduced a carbon atom is in a biological molecule, the more energy is stored.
- **Cellular signalling**: Different biochemical pathways rely on the presence or absence of specific lipids, such as the inflammatory response or hormones signalling.
- **Dietary absorption**: The body uses different lipids (often stored as bile) to aid the digestion and absorption of hydrophobic or fatty substances.

Although lipids are critical for normal physiological functioning, excess cholesterol or fatty acids in the blood can lead to a condition referred to as **hyperlipidemia**.

## Types of Biological Lipids

It is recommended to consume ~20-35% of the total daily caloric intake from dietary lipids. There are three main types of lipids that are also shown in Figure 3.1:

- Triglycerides: These lipids have an invariant glycerol backbone (3-carbon chain with 3-hydroxyl groups) where each hydroxyl group is esterified to a fatty acid. The type of fatty acid that is bound to the glycerol can vary. These molecules are highly non-polar and comprise ~95% of dietary lipid uptake (fats and oils).
- Phospholipids: These are similar to triglycerides in that they have a glycerol backbone. However, phospholipids only have two fatty acid groups and the third group is a phosphate head group. The phosphate headgroup drastically alters the properties of the lipid, in that there is now a highly hydrophilic moiety on one end of the molecule and two lipophilic tails on the other. Phospholipids comprise ~2% of the dietary lipids.
- Sterols: These are compounds based on a cyclopentaphenathrene ring (3 six membered rings and 1 five membered ring) and comprise approximately 3% of dietary lipids. In mammals, the most commonly known sterol lipid is cholesterol and all steroid-based hormones and bile acids are synthesized from cholesterol.

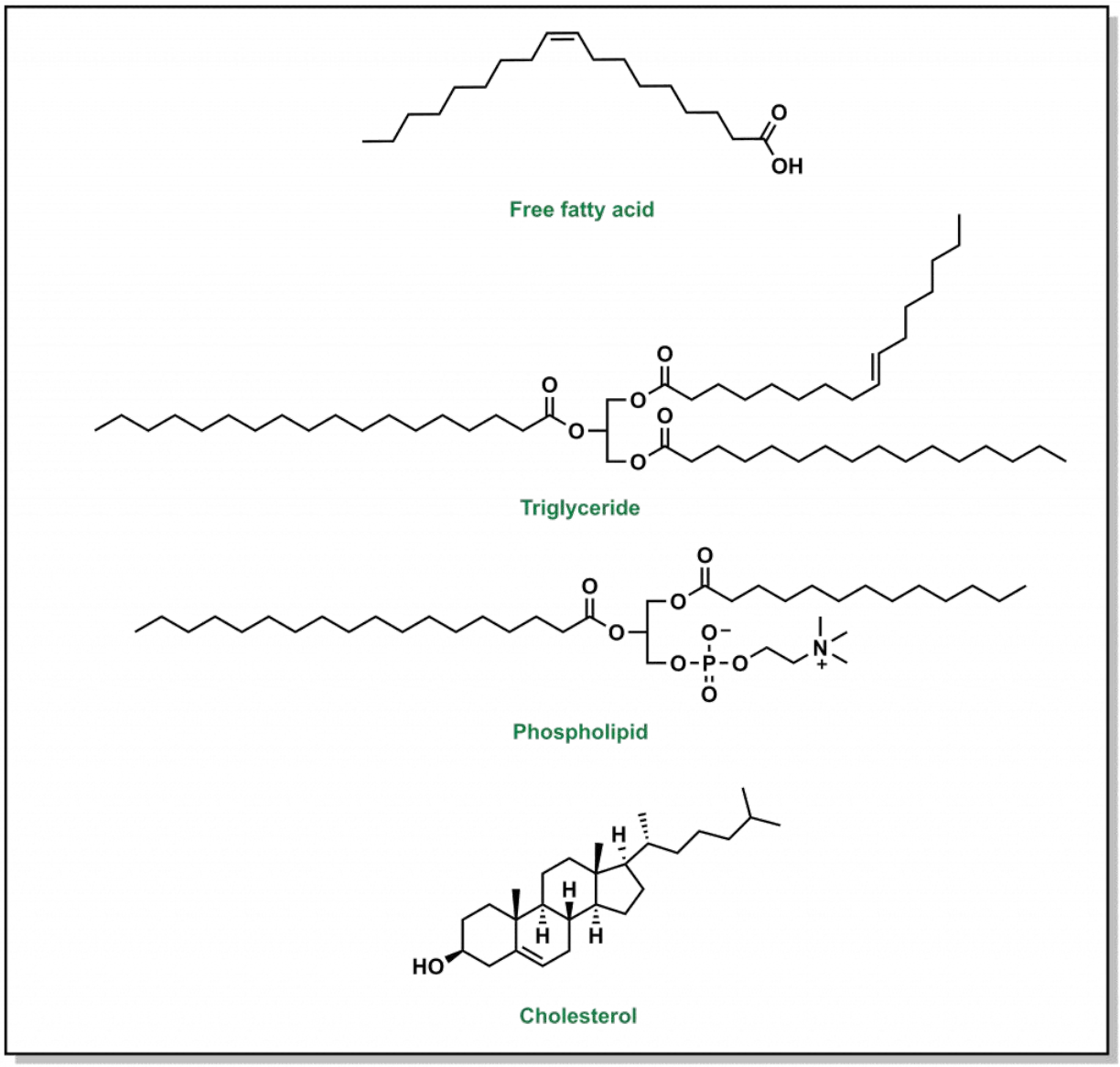



Figure 3.1 Representative structures of a generic fatty acid and the three main types of lipid macromolecules.

Lipids are very different from the other macromolecules in that they are largely hydrophobic and do not associate with water. Considering that the human body is ~70% water and that lipids are essential for every single cell in the body, transporting them across the body in the aqueous environment of blood is challenging because of the hydrophobicity. Therefore, lipids are transported in a complex particle comprised of both proteins and lipids, which are referred to as **lipoproteins**. The structure of a lipoprotein is shown in Figure 3.2. Lipoproteins have an outer shell of phospholipids intercalated with different proteins (referred to as apolipoprotein), and the inside is occupied with triglycerides and cholesterol. These lipoproteins travel through the blood stream and facilitate the transport of lipids.

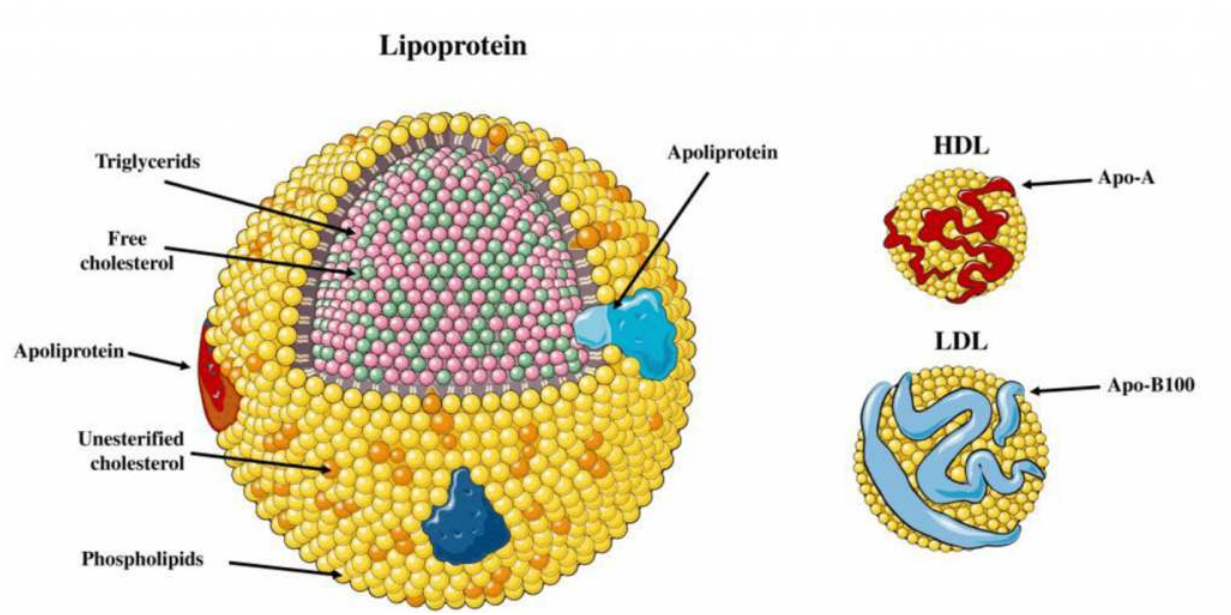



Figure 3.2 Representative structure of a lipoprotein. Image Source: (Fig 2) by Stamatios Lampsas, Maria Xenou, Evangelos Oikonomou, Panteleimon Pantelidis, Antonios Lysandrou, Savvas Sarantos, Athina Goliopoulou, Konstantinos Kalogera, Vasiliki Tsigkou, Athanasios Kalpis, Stavroula A. Paschou, Panagiotis Theofilis, Manolis Vavuranakis, Dimitris Tousoulis, Gerasimos Siasos is used under a CC-BY 4.0 license.

Lipoproteins have different names based on their composition and density. (Figure 3.3) Lipids that are high in protein content are referred to as high density lipoproteins (**HDLs**) and if they have intermediate, low, or very low densities of lipoproteins they care called **IDL**, **LDL**, and **VLDL**, respectively. HDLs are also relatively small in diameter (5-10 nm) compared to LDL and VLDL which are 20 – 50 nm. There are also larger classes of lipoproteins called **chylomicrons** which are important for digestion and absorption of fats. Colloquially, the HDLs are often thought of as “heathy cholesterol” and the LDLs and VLDLs are referred to as the “unhealthy fats”. From a general sense, larger particles have higher lipid content and lower stability.

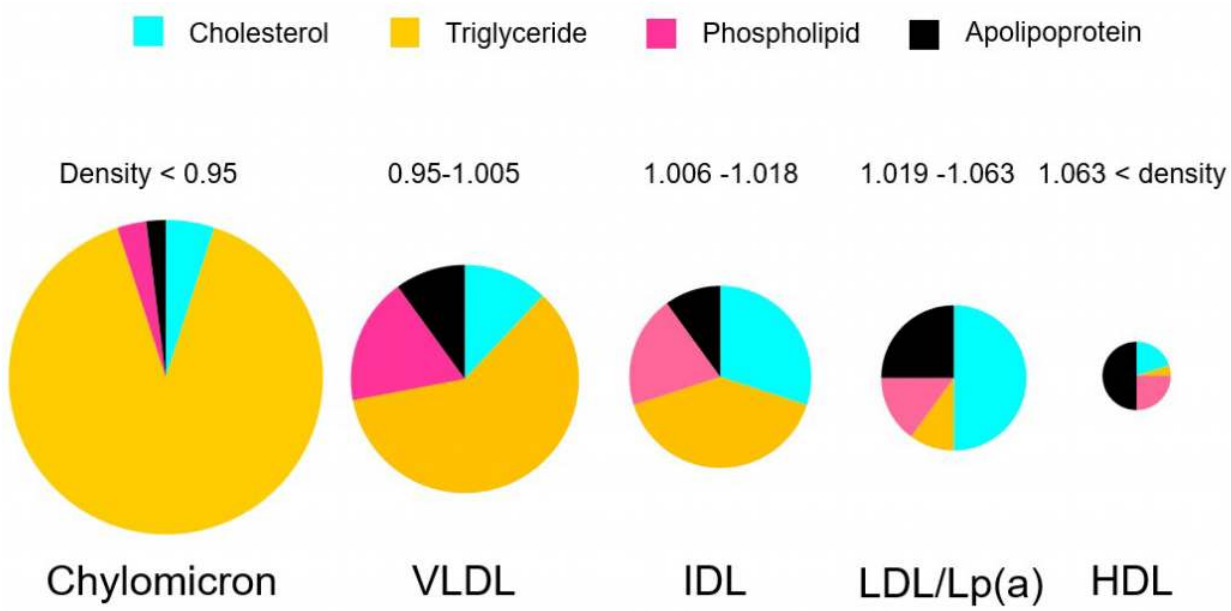



Figure 3.3 Approximate proportion of lipids and proteins in different types of lipoproteins. Image Source: (Fig 1) by Hayato Tada, Atsushi Nohara and Masa-aki Kawashiri is used under a CC-BY 4.0 license.

Hyperlipidemia occurs when there is an excess of lipids leading to a high concentration of LDL and VLDL. These fats can precipitate out of the blood stream and start to nucleate on the arterial walls and form a blockage of blood flow. (Figure 3.4) These

blockages are referred to as plaques and reduce the arterial lumen, leading to a reduction in blood vessel elasticity, and create a nucleation site for additional thrombi. The primary goal of treating hyperlipidemia is to reduce concentrations of LDL and VLDL.

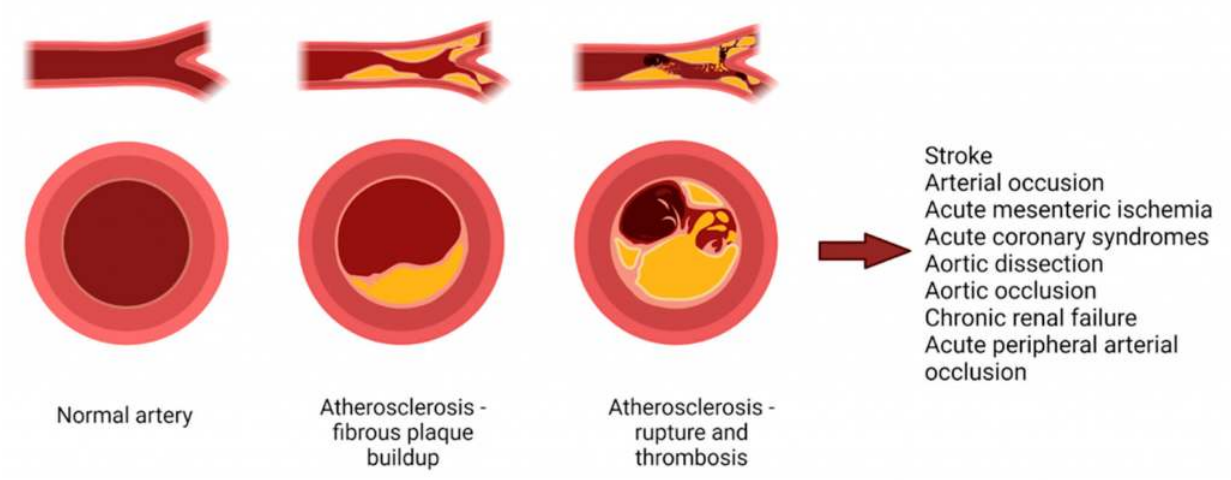



Figure 3.4 Effects of hyperlipidemia on the arterial lumen. Image Source: (Fig 1) by Dragos Cretoiu, Ruxandra Florentina Ionescu, Robert Mihai Enache, Sanda Maria Cretoiu and Silviu Cristian Voinea is used under a CC-BY 4.0 license.

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## 3.2: Treatments

One approach to treating hyperlipidemia is to initially reduce dietary intake of fats and cholesterol and increase cardiac exercise. Although this is important, ~80% of cholesterol is synthesized by the liver and only ~20% is obtained from dietary sources. Therefore, altering diet and exercise may be insufficient and reduction of cholesterol may require pharmacological intervention. There are three main strategies to reducing blood lipid concentrations: inhibit lipid synthesis, inhibit lipid absorption/uptake, or accelerate lipid degradation/clearance. Each of the therapeutic approaches below fit into one of these three themes.

### Inhibiting Lipid Synthesis: Statins

The **statins** are a class of cholesterol-reducing agents that are the most prescribed drugs, and therefore it is important to have a thorough understanding of their mechanism of action. The statins are designed to block cholesterol synthesis. Cholesterol synthesis occurs in the liver through the mevalonate pathway, which is ~25 step biochemical pathway that begins with acetyl-CoA. One of the key features of the pathway is the rate limiting step which is the reaction that converts HMG-CoA to mevalonate. This reaction is carried out by the enzyme **HMG-CoA reductase**. Therefore, if this enzyme is pharmaceutically intercepted, the mevalonate pathway and cholesterol synthesis can be effectively shut down.

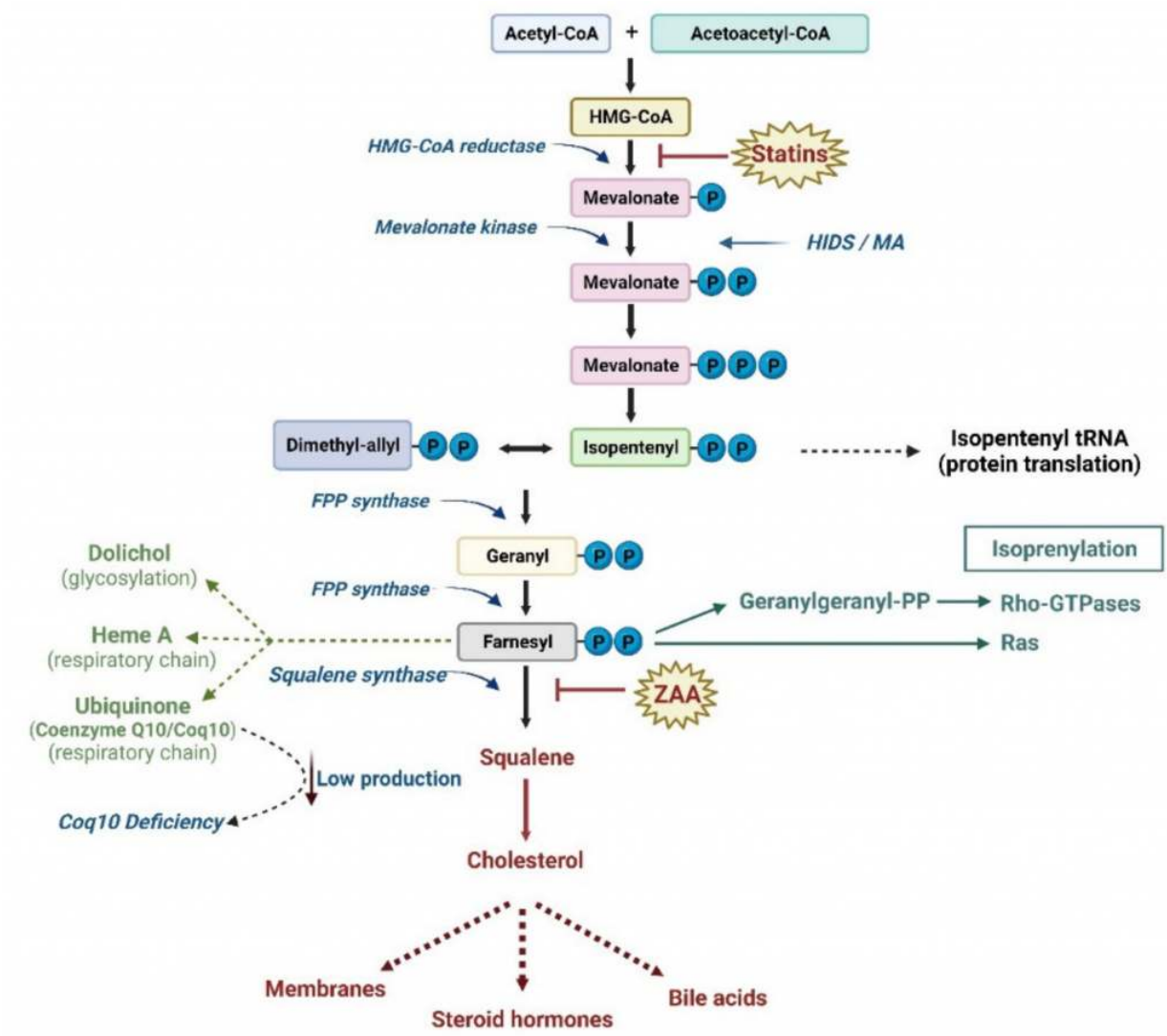



Figure 3.5 The mevalonate pathway leads to the synthesis of cholesterol among other biomolecules. Image Source: (Fig 1) by Simona Pisanti, Erika Rimondi, Elena Pozza, Elisabetta Melloni, Enrico Zauli, Maurizio Bifulco, Rosanna Martinelli and Annalisa Marcuzzi is used under a CC-BY 4.0 license.

HMG-CoA reductase catalyzes the reduction of HMG-CoA with 2 equivalents of NADPH to generate mevalonic acid. Initial approaches in identifying molecules that engage this enzyme involved large natural product screens in the 1970s. The first molecule that was identified to inhibit the enzyme was compactin, produced by the fungi Penicillium. (Figure 3.6) Compactin has several important chemical features:

- Lactone ring: This ring functions as a pro-drug that opens up to form a carboxylate, whose anionic charge is necessary to engage a critical Lys735 of HMG-CoA Reductase. The hydrolyzed lactone mimics the 3,5-dihydroxylheptaonic acid of the natural enzyme substrate. Importantly, stereochemical configurations of the 3- and 5- position are important to engage with the enzyme.
- Didehydrodecalin ring: This hydrophobic ring engages with a pocket that forms upon the acid binding to the enzyme.

Compactin was ultimately not approved as a drug, due to safety concerns, but similar compounds were advanced, such as lovastatin and simvastatin. These drugs maintain the same lactone-spacer-didehydrodecalin chemotemplate. An interesting compound is pravastatin which does not contain the lactone, but closely resembles the 3*R*,5*R*-dihydroxyheptaonic acid moiety of the substrate, mevalonic acid. Note that all of these molecules have relatively short half-lives. Since cholesterol synthesis mainly occurs at night, it is recommended to take these medications in the evening so that they can be most effective in blocking cholesterol synthesis.

Although blocking HMG-CoA reductase inhibits cholesterol synthesis in the liver, the liver still requires cholesterol for proper functioning. The lower concentrations of cholesterol in the liver stimulate the uptake of cholesterol from LDL and VLDL in the blood. Therefore, extracting the LDL/VLDL from the blood will reduce the total cholesterol levels.

Second-generation statins retain some of the key structural properties that were identified above, including the dihydroxyhepatonic acid, which is critical for enzyme binding to Lys735, as well as the stereochemical configuration of the alcohol groups. However, the moiety that engages with the hydrophobic pocket was altered to contain heteroatoms, leading to atorvastatin (Lipitor) and rosuvastatin (Crestor). Both molecules contain *p*-fluorophenyl and isopropyl substituents which contribute to receptor affinity. The key distinguishing feature between these molecules is that atorvastatin contains an amide where as rosuvastatin contains a sulfonamide, which leads to differential properties. Atorvastatin is the most lipophilic statin and can cross through several cellular membranes including different muscles and tissues. Contrastingly, rosuvastatin is the most hydrophilic statin and the most potent. Both drugs have different CYP metabolic profiles, where atorvastatin is largely metabolized by CYP3A4 and rosuvastatin is metabolized by CYP2C9.

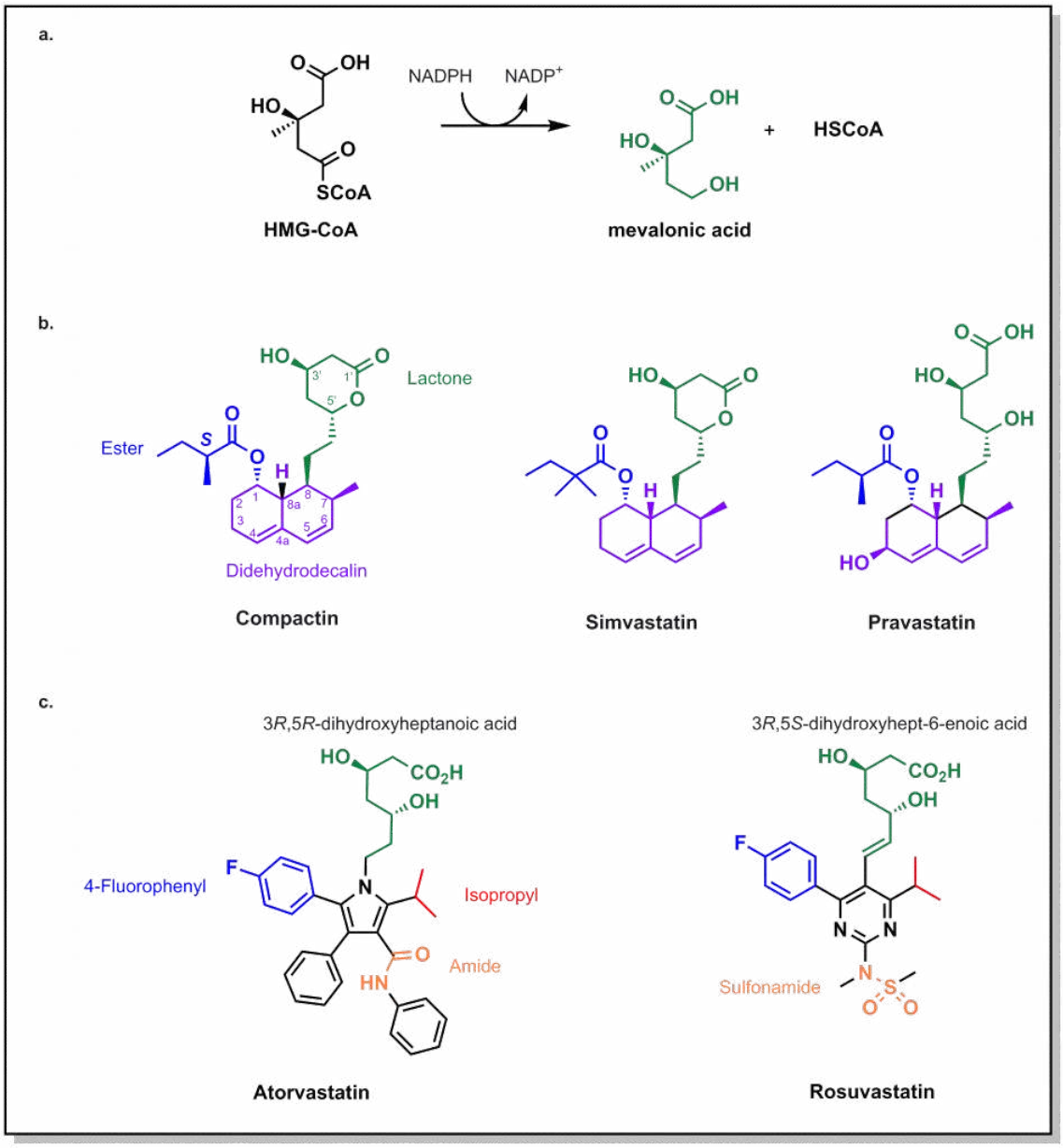



Figure 3.6 Inhibitors of HMG-CoA reductase (statins).

There is also controversy over the types of side effects observed with these statins, with the most common (1-25%) observed as muscle weakness and rhabdomyosis (where the muscle breaks down and releases substances in the blood which can lead to renal or cardiac damage). Although the mechanism is not fully understood, blocking HMG-CoA reductase and reducing mevalonic acid formation reduces the substrates for other biochemical pathways, such as synthesis of Coenzyme Q10 (which is a molecule that is important for muscles and energy usage, Figure 3.5). Although some patients can take supplements, the available data are inconclusive. Additionally, the more lipophilic statins can pass through the CNS which can lead to effects in the brain, including memory loss.

## Inhibiting Lipid Synthesis: Niacin

Niacin (or vitamin B3) is a small molecule that has been used to block triglyceride synthesis from adipose tissue. (Fig 3.7) Although it has been in use in the clinics for >50 years, the mechanism of action is still not fully understood.

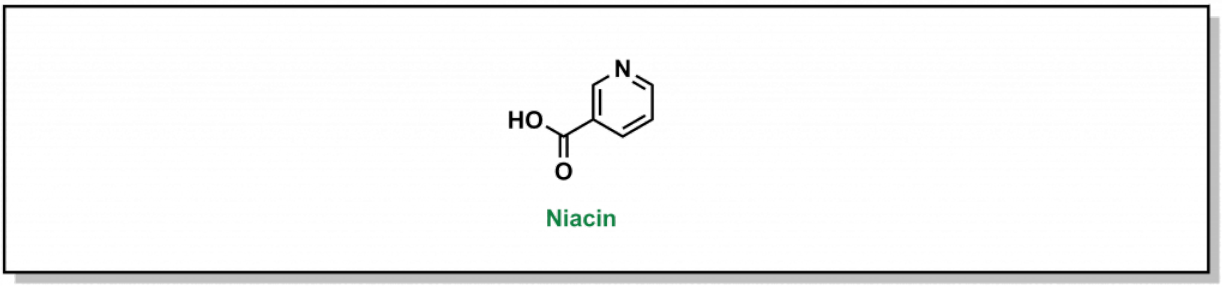



Figure 3.7 The structure of niacin.

Niacin binding occurs at GPR109A (a GPCR receptor) that ultimately inhibits adenyl cyclase activity (reducing the conversion of ATP to the secondary messenger cAMP). This blocks PKA activation, and subsequent Hormone Sensitive Lipase (HSL) activity. HSL is responsible for degrading triglycerides into free fatty acids that would be released into the blood stream. The reduced concentrations of free fatty acids in the blood, leads to lower VLDL formation and triglyceride synthesis in the liver. (Figure 3.8)

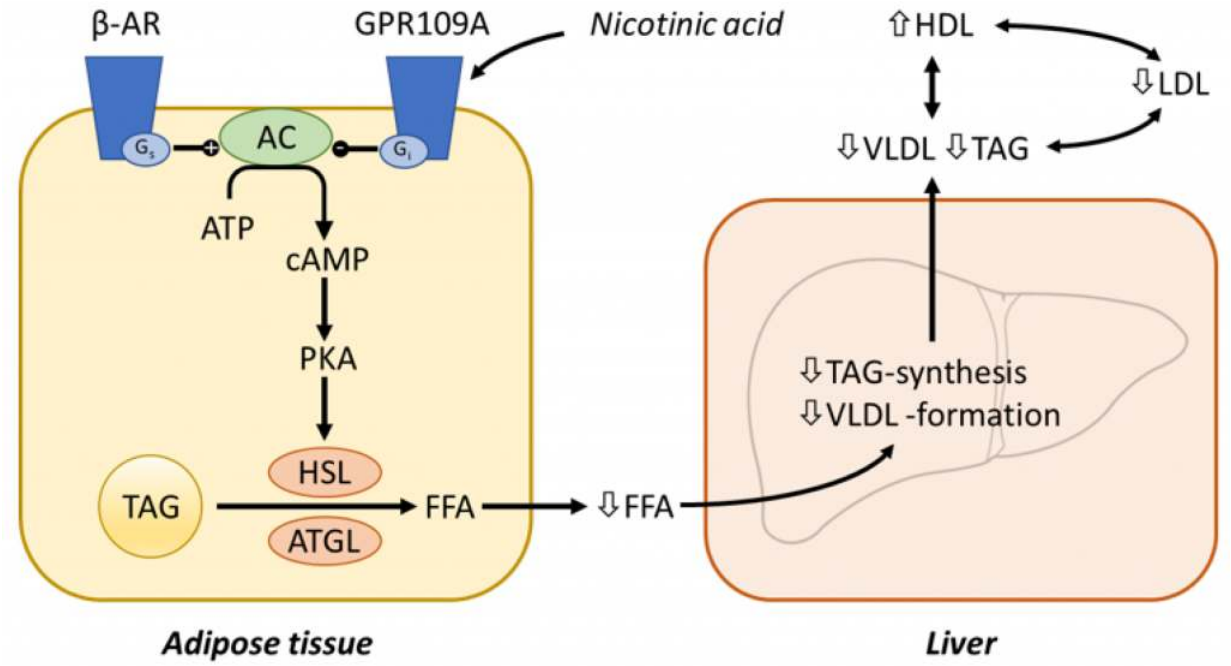



Figure 3.8 Biochemical inhibition of fatty acid synthesis by the action of niacin on GPR109A. Image Source: (Fig 12) by Marcel Hrubša, Tomáš Siatka, Iveta Nejmanová, Marie Vopršalová, Lenka Kujovská Krčmová, Kateřina Matoušová, Lenka Javorská, Kateřina Macáková, Laura Mercolini, Fernando Remião, Marek Máťuš, Přemysl Mladěnka has been modified (cropped) and is used under a CC-BY 4.0 license.

## Inhibiting Lipid Uptake: Ezetimibe

Another mechanism for reducing cholesterol levels is to prospectively prevent cholesterol from being absorbed during food intake. Dietary cholesterol is absorbed in the small intestine via the action of a receptors called NPC1L1. (Figure 3.9) Cholesterol will bind these receptors, and the cholesterol-receptor complex will be internalized via the AP2-clathrin mediated processes.

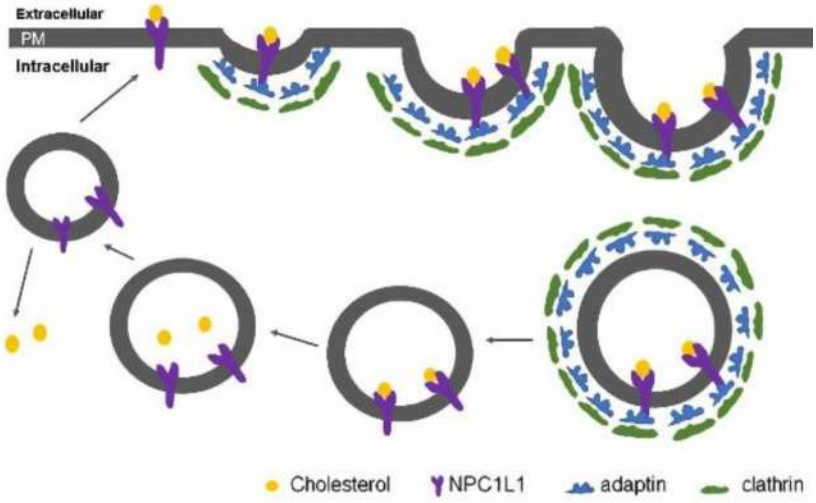



Figure 3.9 Clathrin mediated update of cholesterol. Image Source: (Fig 1) by Jun Zeng, Wenjing Liu, Bing Liang, Lingyu Shi, Shanbo Yang, Jingsen Meng, Jing Chang, Xiaokun Hu, Renshuai Zhang, and Dongming Xing has been modified (cropped) and is used under a CC-BY 4.0 license.

Ezetimibe is a drug that blocks the interaction between the NPC1L1 receptor and the clathrin molecules, which prevents the cell from absorbing cholesterol. The 1,4-diaryl-β-lactam structure is critical for activity. These drugs can be combined with statins to effectively reduce the amount of cholesterol that is absorbed as well as synthesized. (Figure 3.10)

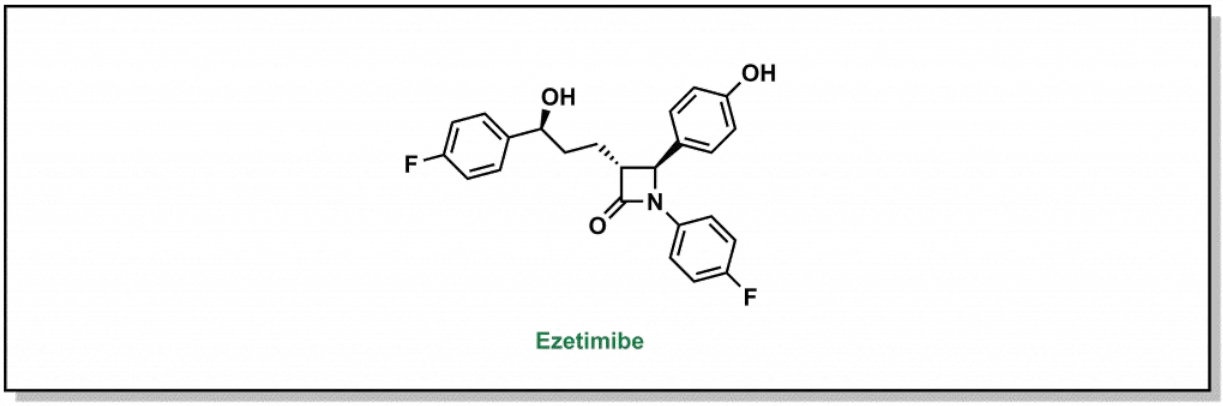



Figure 3.10 Structure of ezetimibe.

## Accelerating Lipid Degradation/Clearance: Fibrates

**Fibrates** are a class of compounds that can reduce effects of hypertriglyceridemia. Fibrates activate **peroxisome proliferator-activated receptor alpha** (PPARα) which heterodimerizes with another protein called retinoid X receptor (RXR) and subsequently binds the PPARα response elements to regulate the expression of a cluster of genes involved in lipid metabolism. This increases HDL and reduces TG synthesis. (Figure 3.11)

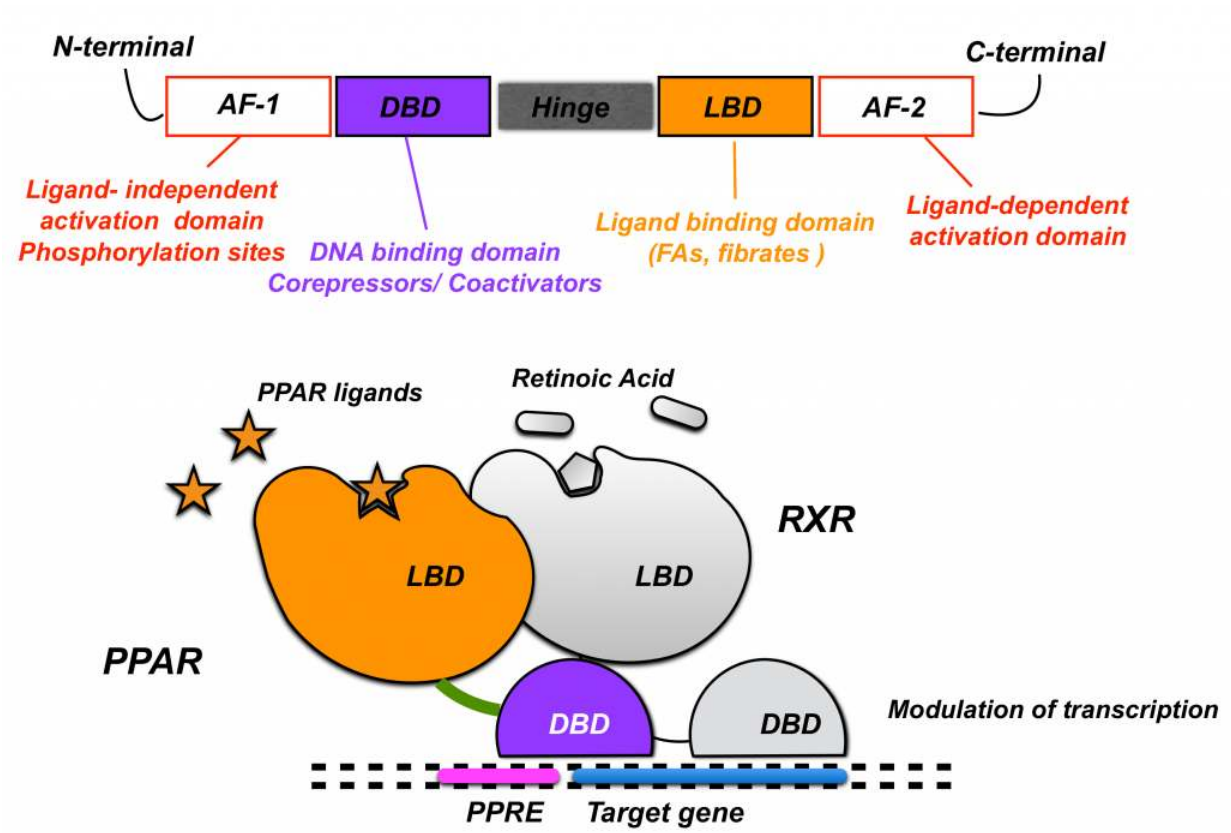



Figure 3.11 Mechanism of PPARα activation of genes involved in lipid metabolism. Image Source: (Fig 1) by Simona Scheggi, Graziano Pinna, Giulia Braccagni, Maria Graziella De Montis and Carla Gambarana is used under a CC-BY 4.0 license.

The main pharmacophore for fibrates binding and activating PPARα includes a phenoxyisbutyric acid, which forms an ionic-dipole interaction with a specific tyrosine residue (Tyr464) on PPARα. There are two main fibrates referred to as fenofibrate and gemfibrozil. (Figure 3.12)

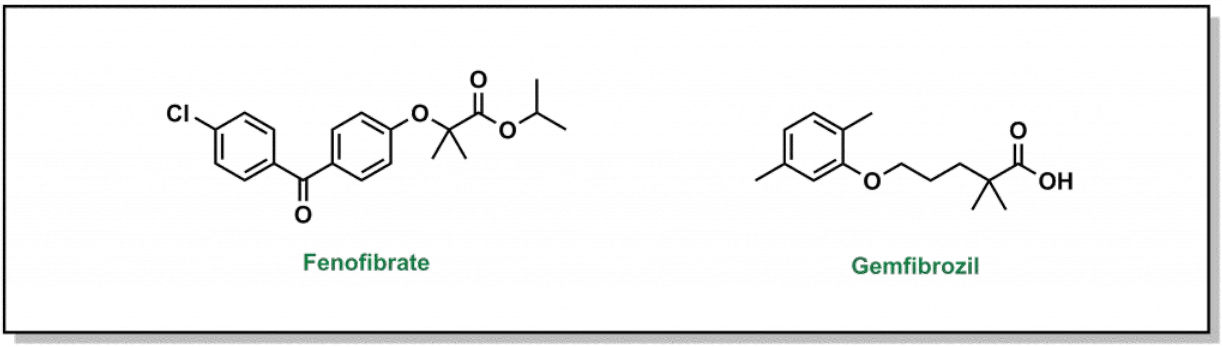



Figure 3.12 Structures of common fibrates.

## Accelerating Lipid Degradation/Clearance: Bile Acid Sequestrants

As mentioned above, the hydrophobic nature of lipids can create challenges during digestion and absorption, considering the aqueous environment of the stomach and small intestine. Dietary lipids are digested with the help of bile (which is a complex fluid largely consisting of bile acids and cholesterol derivatives). Bile is produced by the liver and stored in the gall bladder. Following digestion, ~97% of the bile is re-absorbed in the ileum and stored in the gall bladder. However, the introduction of bile acid sequestrants will bind to the bile, which prevents it from being re-absorbed and causes it to be excreted. In response to this loss of bile, the liver synthesizes additional bile acids, which requires uptake of cholesterol and LDL from the blood, ultimately lowering the lipid concentration.

**Bile acid sequestrants** (**BAS**) are positively charged cations that will bind to negatively charged bile acids, and this interaction creates a complex that is incapable of being absorbed. BAS are normally powders that are taken orally. They are not absorbed by the small intestine, which limits any systemic adverse effects, but they can be challenging to consume and can cause different forms of GI distress.

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## 3.3: Summary

A summary of the different pharmacological properties of lipid lowering agents is shown in Table 3.1.

Table 3.1: Summary of lipid lowering agents.

| | Statins | Niacin | Ezetimibe | Fibrates | BAS |
|---|---|---|---|---|---|
| **Pathway** | *De novo* cholesterol synthesis | *De novo* lipid synthesis | Cholesterol absorption | Triglyceride clearance | Cholesterol clearance |
| **Target** | Inhibit HMG-CoA Reductase | Inhibits GPR109A | Inhibits NPC1L1-AP2 Cathrin interaction | Activates PPARα | Binds bile acids |
| **Functional Group** | Di-hydroxy heptanoic acid | Carboxylic acid and pyridine | 1,4-Diaryl-β-lactam | Isobutyrate | Anion exchange resin |
| **Effect** | Blocks cholesterol synthesis | Blocks TG breakdown | Blocks cholesterol absorption in the gut | Activates lipoprotein lipase | Prevents bile absorption |
| **[Lipid] Effect** | LDL decreases | LDL decreases<br>HDL increases | LDL decreases | TG decreases<br>HDL increases | LDL decreases |

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# CHAPTER OVERVIEW

## 4: Drugs for Treatment of Diabetes Mellitus


4.1: Pathology

4.2: Insulin

4.3: Treatments for Type I Diabetes

4.4: Treatments for Type II Diabetes

4.5: Summary


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# 4.1: Pathology

Diabetes mellitus is a condition that occurs when there is an elevated concentration of glucose in the blood. Glucose is the principal type of carbohydrate that the body uses for energy, and carbohydrates are one of the three macronutrients (along with proteins and lipids). In contrast to hyperlipidemia where there is a high concentration of hydrophobic lipids in the blood, in diabetes mellitus the situation is somewhat reversed. There is a high concentration of sugars in the blood, which are highly polar due to the multiple hydroxyl groups on each sugar molecule. This can lead to the blood becoming very 'sticky' and viscous. This can become more serious in organs with tiny blood vessels such as the eyes, kidneys and other extremities as it becomes challenging for the blood to reach these locations and deliver necessary components or immune cells. Therefore, it is very important to maintain appropriate concentrations of blood sugar.

Diabetes mellitus is a chronic condition and there are three different types: Type 1, 2, and gestational diabetes. Type 1 diabetes is generally thought of as a genetic condition, with early onset and lower frequency (~10% of diabetes cases). Type 2 diabetes may also have a genetic component but is largely driven by lifestyle and has a late onset. Gestational diabetes can occur when the patient is pregnant, and usually resolves naturally following the pregnancy term.

The incidence of diabetes in Canada has been increasing over the past two decades (4.7% of the population in 2001, compared to 8.1% in 2017), which may be attributed to changes in diet and lifestyle. Carbohydrates represent the most accessible form of energy for body, and form a large part of the natural human diet. They are digested and absorbed by different organs of the body, which provides a foundation for medicinal chemistry efforts to treat diabetes.

## Carbohydrate Digestion – Mouth and Stomach

Carbohydrate digestion begins in the mouth. Although the mechanical action of chewing helps to physically separate carbohydrates, the enzyme salivary amylase starts hydrolyzing some of the complex sugars. Approximately 5% of carbohydrate digestion occurs in the mouth. These enzymes are inactivated by the gastric acid of the stomach. The mechanical action of the stomach coupled to the acidic conditions may help to further separate carbohydrates, but these are not the predominant sites of carbohydrate digestion.

## Carbohydrate Digestion – Small Intestine

The stomach empties the mixture of food (now called chyme) into the small intestine, where several enzymes become involved. There is a different type of amylase (**pancreatic amylase**) that continues breaking down larger sugars. Another enzyme, **α-glucosidase**, breaks down polymer sugar molecules into monomers, such as glucose or fructose. These monomers can now be absorbed by different transporters. Proteins in cells of the small intestine are expressed asymmetrically on the cell membrane. (Figure 4.1) For example, **SGLT1** (sodium glucose transporter) enables glucose transport into the cells from the small intestine lumen. **GLUT2** (glucose transporter) faces the blood vessel lumen and deposits glucose in the blood stream. Both of these transporters are important and part of larger families of carbohydrate transporters and have different tissue expression throughout the body. SGLT1 is one of twelve members of the SLC5A (solute carrier family member 1) proteins. GLUT transporters represent a family of fourteen transporters with different affinities for glucose or other carbohydrate monomers (for example GLUT5 absorbs fructose).

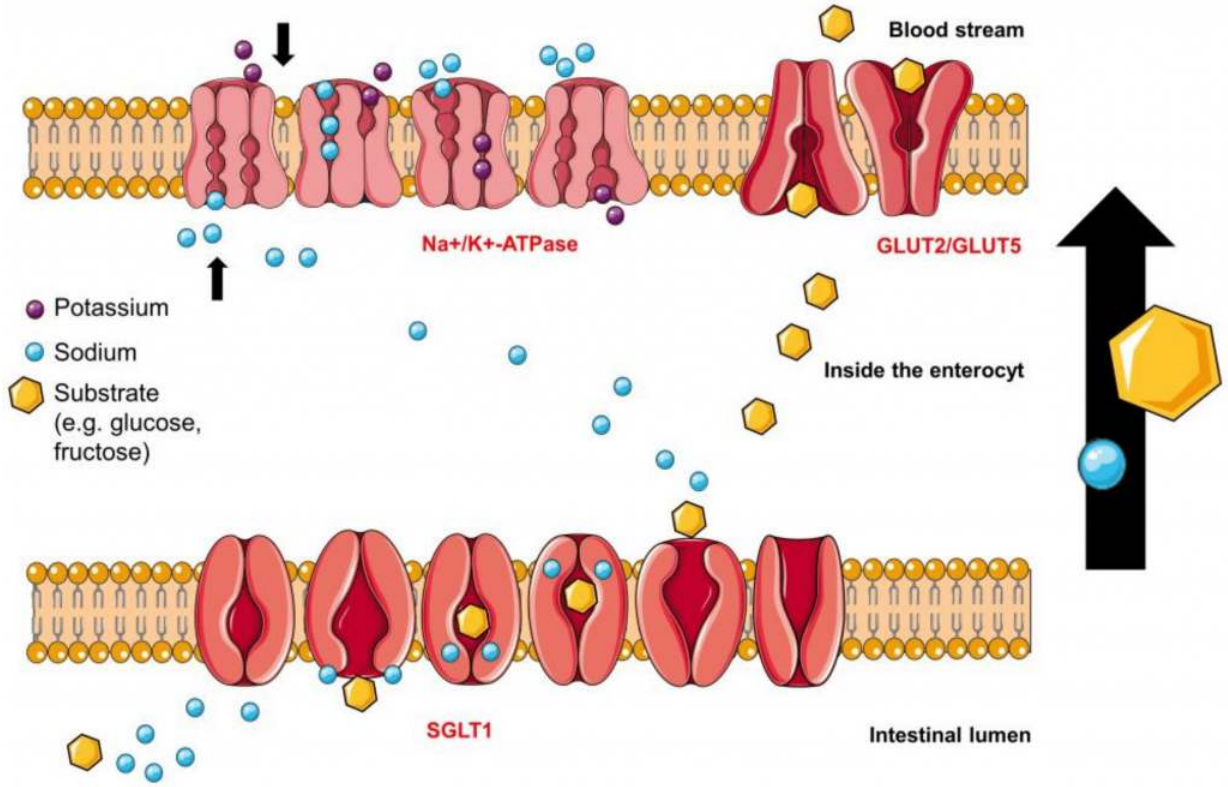



Figure 4.1 Glucose uptake in the small intestine occurs via different protein transporters. Image Source: (Fig 5) by Katharina Schreck and Matthias F. Melzig is used under a CC-BY 4.0 license.

As soon as chyme is released into the small intestine, it also triggers the release of hormones called **incretins**. (Figure 4.2) There are two incretins that are very important called glucagon-like peptide 1 (**GLP1**) and glucose-dependent insulinotropic peptide (**GIP1**). These are polypeptides that are secreted by specific cells of the upper and lower intestine that travel to the pancreas and help prepare it for the incoming spike in blood sugar. In this way, the action of incretins occurs even before any glucose enters the blood stream.

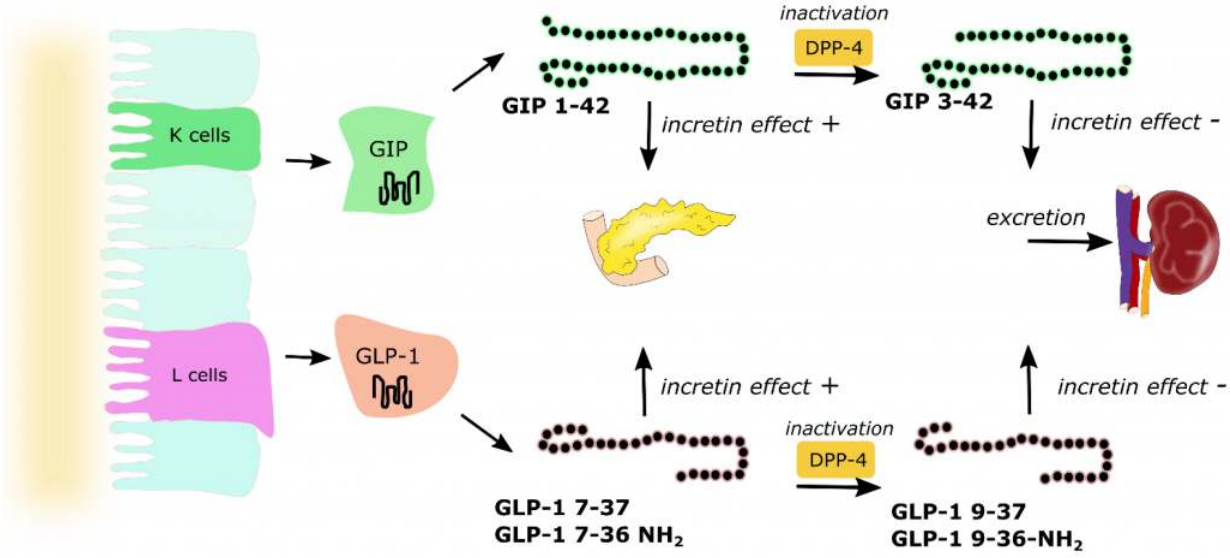



Figure 4.2 Incretin signalling in the small intestine. Image Source: (Fig 3) by Joanna Michałowska, Ewa Miller-Kasprzak and Paweł Bogdański is used under a CC-BY 4.0 license.

GIP has multiple roles including promoting insulin secretion, suppressing glucagon release, and retarding gastric emptying to provide additional time for digestion thereby softening large peaks in glucose levels. Incretins also provide a feeling of satiety,

which reduces food consumption. Incretins are rapidly deactivated by a set of enzymes called DDP-4 (dipeptidyl peptidase) in the blood stream and incretins are only active for a few minutes.

## Carbohydrate Digestion – Pancreas

The pancreas is one of the most important organs for regulating blood glucose levels. (Figure 4.3) Once glucose enters the blood stream via the small intestine, multiple organs within the body start to respond. The pancreatic cells harbour GLUT2 transporters (similar to the small intestine) and these transporters uptake the glucose from the blood (specifically the pancreatic β-cells). The increased of intracellular glucose concentrations triggers ATP generation (via glycolysis, Krebs/TCA cycle, etc.) which leads to a high [ATP] state. ATP binds to $K_{ATP}$ channels (ATP sensitive potassium channels) which causes the potassium channels to close, leading to a change in membrane polarization. This change triggers opening of voltage gated $Ca^{2+}$ channels. The increase in $Ca^{2+}$ ion content triggers secretion of **insulin** from the β-cells into the blood stream. Insulin is a critical hormone in carbohydrate digestion, and is responsible for making cells more permeable to glucose, which ultimately reduces glucose concentrations in the blood.

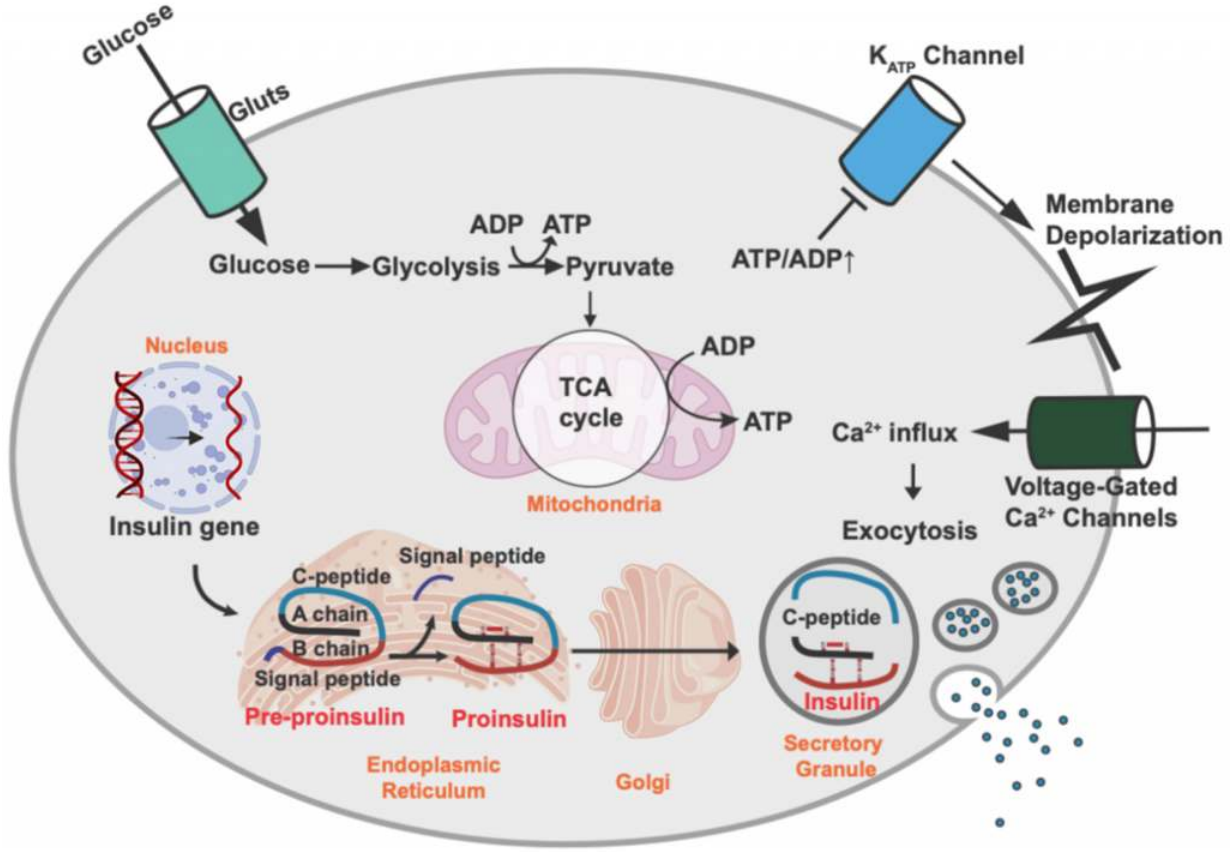



Figure 4.3 Release of insulin from pancreatic β-cells following glucose stimulation. Image Source: (Fig 1) by Ji-Hye Lee and Jaemin Lee is used under a CC-BY 4.0 license.

Insulin will travel through the blood stream and bind to insulin receptors on different types of cells. The binding event initiates a signal cascade inside the cell with a net result of glucose transporters translocating to the cell surface. The glucose transporters on skeletal and cardiac muscle are insulin expression dependent GLUT4 (whereas the transporters in the pancreas and small intestine are insulin independent GLUT2 proteins). The presence of these transporters enables the uptake of glucose from the blood providing an energy source to the cells and restoring normal glucose levels.

In cases where energy is required but food intake is not occurring, blood sugar levels can start to fall. The α-cells of the pancreas sense lowering of blood sugar levels and release the polypeptide, glucagon. **Glucagon** is the complementary hormone to insulin, and it signals the liver to release glucose (which is stored in the liver in a polymer called glycogen). The release of glucose will correspondingly raise blood sugar levels, and in this way, the interplay between the pancreas and liver by way of the hormones, insulin and glucagon, regulates homeostasis in the body. (Figure 4.4)

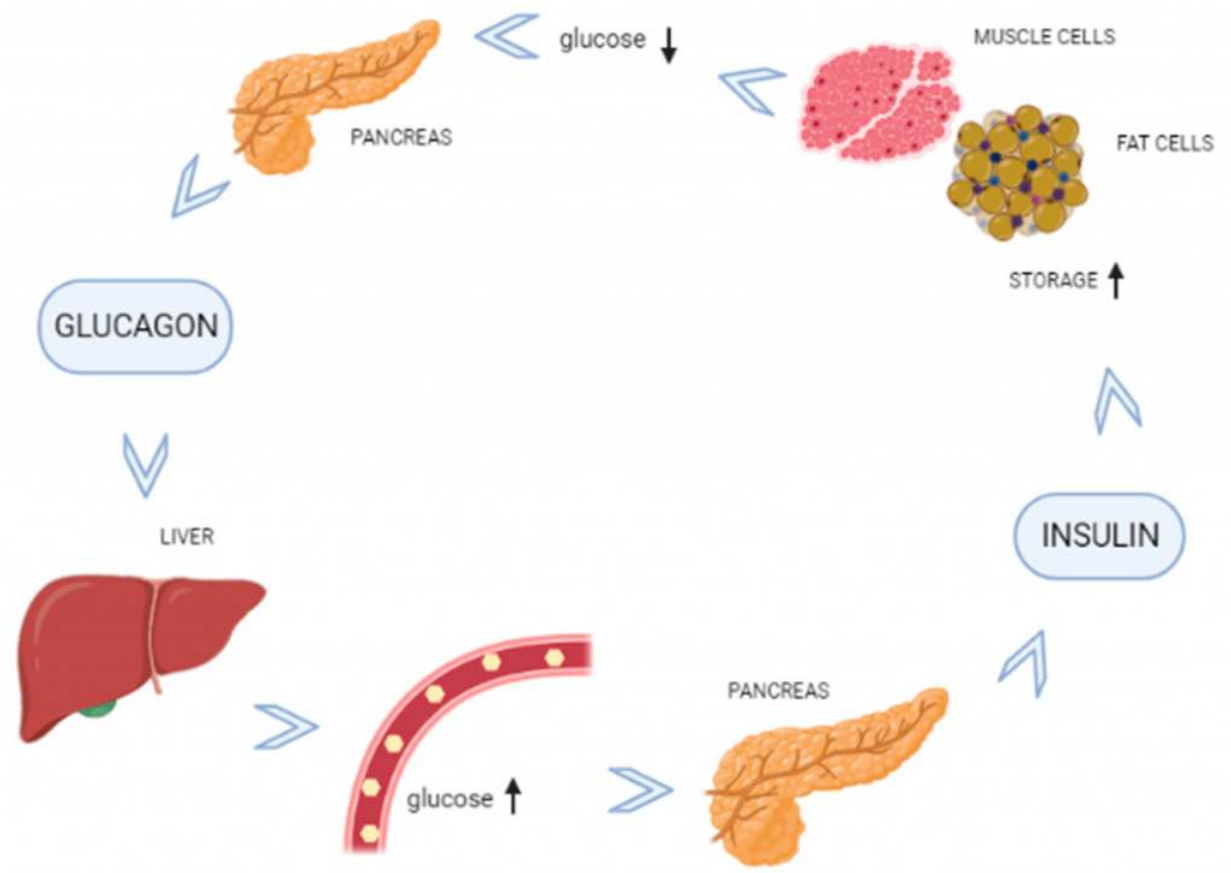



Figure 4.4 Regulation of blood glucose homeostasis by hormone signaling between the pancreas and liver. Image Source: (Fig 1) by Selvaraj Jayaraman, Anitha Roy, Srinivasan Vengadassalapathy, Ramya Sekar, Vishnu Priya Veeraraghavan, Ponnulakshmi Rajagopal, Gayathri Rengasamy, Raktim Mukherjee, Durairaj Sekar and Reji Manjunathan is used under a CC-BY 4.0 license.

## Carbohydrate Digestion – Liver

The liver is critical in maintaining blood sugar levels. The liver stores excess glucose in the form of **glycogen** (a massive polymer of glucose). The pancreas and liver work in lockstep to ensure blood glucose levels remain constant throughout the daily demands and resources available to the body. Therefore, when the body has extra glucose, the pancreas releases insulin which causes the liver to starting storing glucose, and during periods where blood glucose levels fall, the pancreas releases glucagon which causes the liver to start breaking down glycogen to release glucose in the blood stream.

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## 4.2: Insulin

Insulin is a polypeptide that is naturally synthesized by the pancreas. Insulin is comprised of two polypeptide chains called Chain A (21 amino acids) and Chain B (30 amino acids) with a combined molecular weight of ~6 kDa. Additionally, there are three critical di-sulfide linkages within insulin:

- Intramolecular: Cys6 (Chain A) and Cys11 (Chain A)
- Intermolecular: Cys7 (Chain A) with Cys7 (Chain B)
- Intermolecular: Cys20 (Chain A) and Cys19 (Chain B)

Insulin is biosynthesized as a single polypeptide chain in the β-cells of the pancreas. The ribosomes generate the polypeptide with four continuous segments which is called **preproinsulin**. (Figure 4.5) The N-terminal segment contains the signal sequence for the excretory pathway, and it is cleaved from the main protein segment in the rough endoplasmic reticulum (the polypeptide is now called **proinsulin**). This enables the protein to fold over on itself and form the three characteristic di-sulfide bridges. In the trans-Golgi network, the proinsulin peptide is cleaved at two sites to give the final insulin molecule. This is the version of the protein that is excreted by the pancreas beta cells and travels through the blood stream.

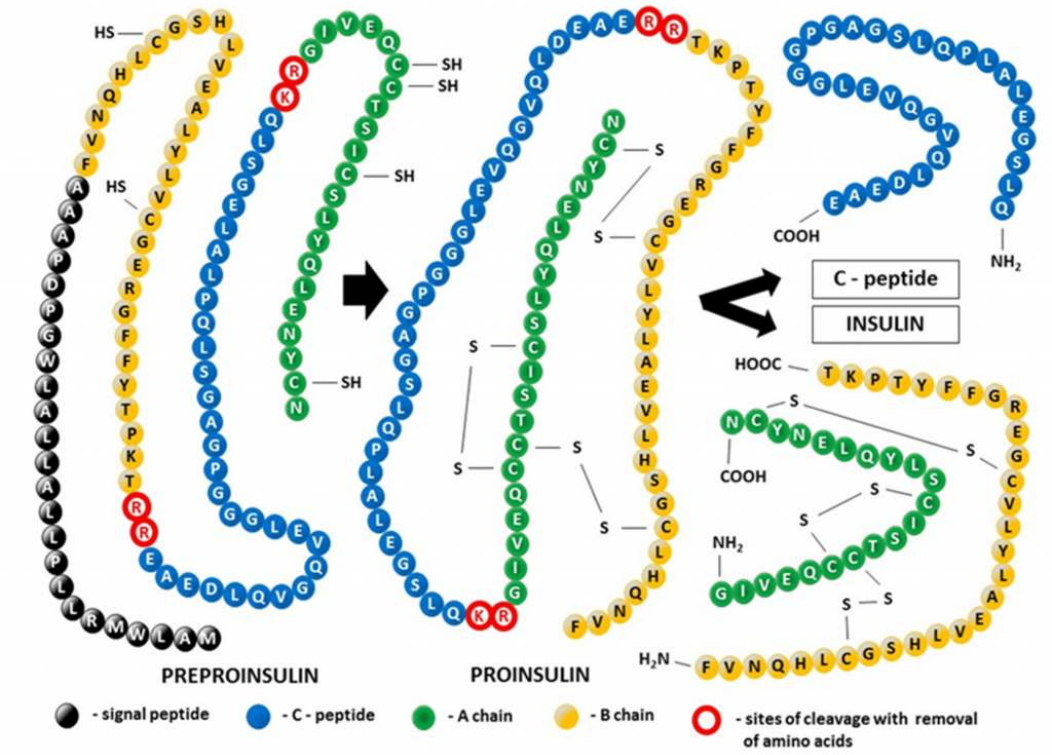



Figure 4.5 Multiple cleavage steps of preproinsulin lead to the active insulin signalling protein. Image source: (Fig 1) by Dariusz Szukiewicz is used under a CC-BY 4.0 license.

Insulin biosynthesis occurs in the pancreas, and results in very high intracellular concentrations. β-Cells also maintain a relatively high concentration of $Zn^{2+}$ ions and, coupled to the high concentration of insulin, this causes the insulin peptides to crystallize around the $Zn^{2+}$ ions. The crystals exhibit a 3-fold symmetry. There are two $Zn^{2+}$ ions at the centre of the polymer along with 6 insulin molecules surrounding these ions (i.e. a trimer of dimers). Specific histidine residues from chain B on insulin coordinate the $Zn^{2+}$ ions. (Figure 4.6)

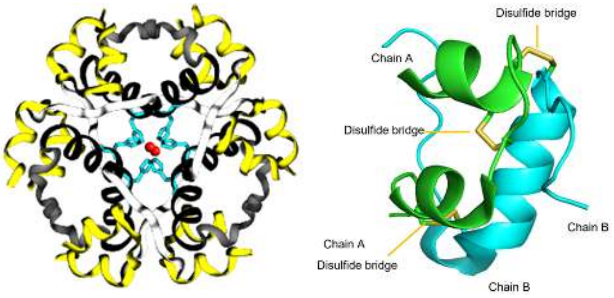



Figure 4.6 Insulin monomers combine to form insulin hexamers that coordinate a central zinc ion. Image Source: (Fig 1) by Beatrice Rosetti and Silvia Marchesan is used under a CC-BY 4.0 license & (Fig 2) by Harish Vashisth has been modified (cropped) and is used under a CC-BY 4.0 license.

These hexamers become extremely important pharmacologically. In particular, the insulin hexamers are inactive and cannot perform their natural biological function in this state. However, when the pancreas releases insulin into the blood stream, the concentration of $Zn^{2+}$ is substantially diluted, and the hexamers rapidly dissociate into monomers and become active. Therefore, the equilibrium and transition from insulin hexamers to monomers is critical. The cellular vessels that store insulin are also quite acidic which further reduces the solubility and increases the crystalline packing of insulin. Insulin has a very short half-life in the blood (~3-10 min) and is rapidly degraded. Therefore, the effects of insulin are short-lived but extremely potent.

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# 4.3: Treatments for Type I Diabetes

Type I diabetes patients may have genetic limitations in producing sufficient quantities of insulin, which means that they will not be able to respond to changes in blood glucose concentrations. One treatment strategy that has emerged is to supply exogenous insulin to the body (which can be prepared synthetically or obtained from biological sources). In this way, the insulin producing functions of β-cells are replaced. (Figure 4.7)

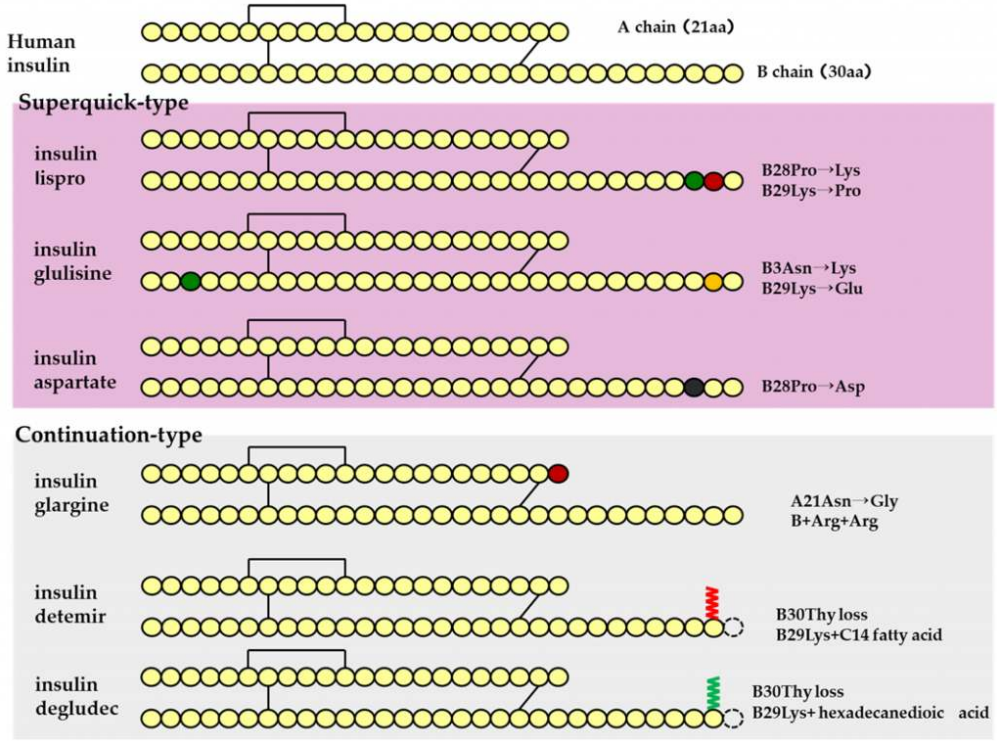



Figure 4.7 Schematic diagram of the different types of insulin-based pharmacological agents. Image Source: (Fig 4) by Takuo Ogihara, Kenta Mizoi and Akiko Ishii-Watabe is used under a CC-BY 4.0 license.

## Short Acting Agents

The first strategy involves supplying insulin directly (in the form that it naturally exists in the body). This agent is called **Regular Insulin**. Regular Insulin has the exact same protein sequence as human insulin, and therefore also forms the same hexameric structure in the presence of $Zn^{2+}$. The main difference is that Regular Insulin is injected subcutaneously (unlike natural insulin which enters the blood stream directly from pancreatic β-cells). The direct release of natural insulin into the blood stream leads to near instantaneous dissociation of the hexamers. However, in subcutaneous injections, the hexamers need to dissociate into smaller monomers before they can find their way into the blood stream. This means that there is a delayed onset of action, as the insulin needs to dissociate into monomers before it can be effectively absorbed, which can take approximately 30 – 60 min. This can be inconvenient, because if a patient is consuming food, they would need to administer an injection and wait for ~30 min before eating.

## Rapid Acting Agents

To help compensate for the delayed onset of action, different modifications were generated and evaluated in the peptide sequence of insulin. One modification that demonstrated improved efficacy involved switching Pro and Lys at positions B28 and B29 respectively. (Figure 4.7) This amino acid switch destabilized the hexadimerization interaction and resulted in rapid dissociation, which led to rapid absorption following injection. This resulting absorption profile is less than 15 min, and this version of insulin is called **Insulin Lispro**.

Another version that was generated is called **Insulin Aspart** where the Pro at position B28 was replaced with Asp. The newly introduced negative charge destabilizes the hexadimerizaiton interface, leading to a rapid absorption profile as seen with Insulin

Lispro. Comparatively, Insulin Lispro has a slightly faster absorption rate and faster plasma peak time as well as rate of decline, although Insulin Aspart demonstrates slightly better stability. However, these differences are minor, and the real-world use of these products is relatively indistinguishable.

**Insulin Glulisine** is another version of insulin where Gly at B3 and Pro at B28 are replaced with Lys and Glu respectively. In addition to these modifications, the formulation contains polysorbate 20 instead of $Zn^{2+}$. This becomes important because $Zn^{2+}$ is required to maintain the insulin as hexamers. Without the hexamer formation, there is a significantly faster rate of absorption than Insulin Lispro or Insulin Aspart.

## Intermediate Acting Agents

There are also relatively slower acting agents as well, with the most common version as **Neutral Protamine Hagedorn (NHP) Insulin**. In this case, the insulin molecule has the exact same sequence as naturally occurring insulin, but protamine is also included in the formulation. Protamine is a highly positively peptide and the introduction of this cation species creates a large, aggregated network of insulin hexamers. Once injected, insulin monomers need to be released from the hexameric structure, but also need to snake their way out of the mesh-like formulation. This leads a slow release of insulin over a period of hours, and NHP Insulin has a more delayed onset of action. NHP Insulin helps provides a steady low supply of insulin to the bloodstream, without repeated or continuous injections.

## Long-Acting Agents

There are also agents that lead to significantly longer periods for onset of action, where the release of insulin is further delayed. These long-acting agents have similar pharmacokinetic profiles that lead to insulin release over 12-24 h. **Insulin Glargine** is the most prescribed long-acting agent (where A21 has Gly that replaces an Asn, and two Arg residues are added to the C-terminus of the B-chain). These changes lower the pI of the protein to 6.7, which results in precipitation at neutral pH as well as at the site of injection. Over time, Insulin Glargine will slowly re-enter solution and dissociate into monomers that can enter the blood stream.

There are other versions as well such as **Insulin Determir** (where a Thr at B30 is removed and a 14-C myristoyl fatty acid group is added) which creates additional binding to albumin proteins, and **Insulin Degludec** (where a Thr at B30 is removed and a 16-C fatty acid with Glu-spacer is added) which forms multi-hexamers and also binds albumin. In all cases, these versions add additional interactions that extend the timeframe required for insulin to dissociate into active monomers.

The different dissociation patterns of each type of insulin agent are shown in Figure 4.8.

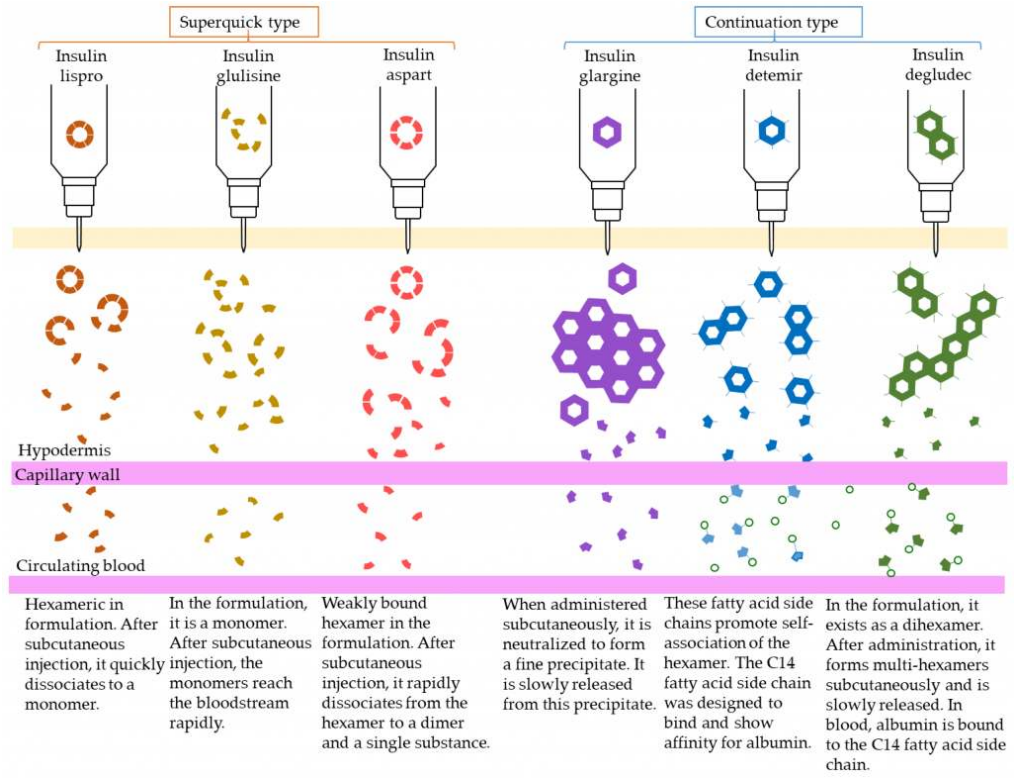



Figure 4.8 Dissociation processes for different types of insulin molecules for the treatment of Type I diabetes. Image Source: (Fig 5) by Takuo Ogihara, Kenta Mizoi and Akiko Ishii-Watabe is used under a CC-BY 4.0 license.

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# 4.4: Treatments for Type II Diabetes

Importantly, the treatments for Type I diabetes all involve injections as they are large peptides that would not be suitable as oral agents since they would not survive in the stomach or be absorbed by small intestine without cleavage/modification. Type II diabetes usually emerges as a loss of sensitivity to insulin, and introduction of more insulin may not be the most efficient method to reduce blood sugar concentrations. In these cases, there have been a number of small molecules or oral agents developed.

## Multiple Blood Glucose Lowering Effects: Biguanides

Biguanides were originally identified in the 1840s from herbs such as the French lilac, which is rich in guanidine derivatives. However, from an array of these guanidine compounds, several had significant adverse effects, and were not advanced. However, they were revisited again in the 1950s for treatment of diabetes, and the compound metformin was explored further. Chemically, a biguanide involves the linkage of two guanidine molecules, and metformin is capped with two methyl- groups on one end. Other compounds such as butformin (capped with a butyl group) or phenformin (capped with a phenyl group) presented with several side effects and were found to be less useful in treating diabetes. (Figure 4.9) Metformin is a relatively planar molecule, and is monoprotonated at neutral pH. It has approximately 50% oral bioavailability and a $t_{max}$ of ~2.5 h. The mechanism of action for metformin is still heavily debated and it has been described to have at least three key effects:

- Reduced hepatic glucose formation (blocking gluconeogenesis)
- Reduced intestinal absorption of glucose
- Increased insulin sensitivity

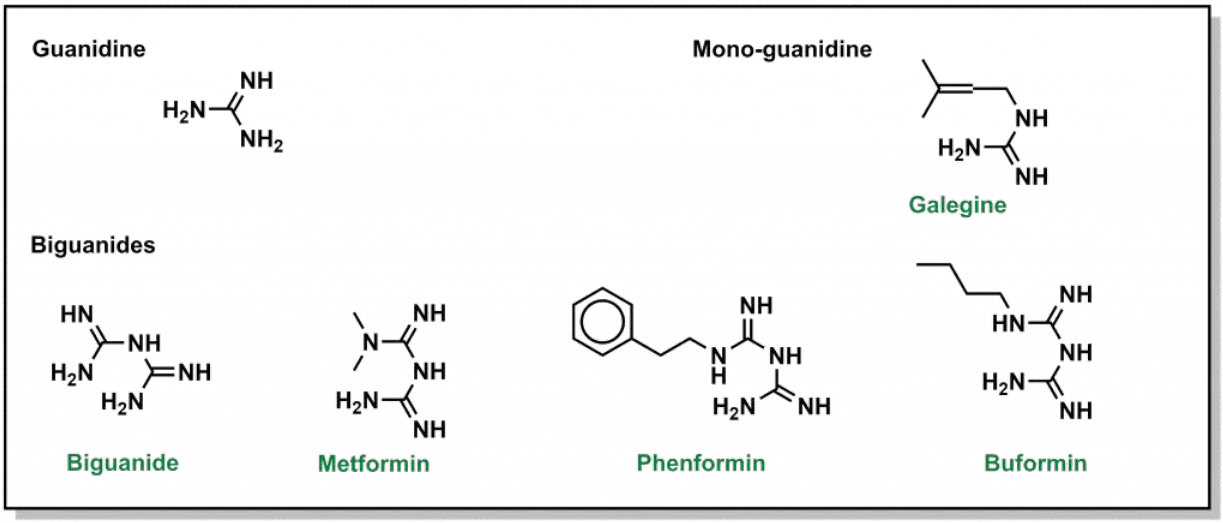



Figure 4.9 Structures of guanidine derivatives.

Physiological and biochemical studies have revealed that metformin enters the liver via action of OCT1 (organic cation transporter) and ultimately blocks the electron transport chain which is required for oxidative phosphorylation and energy generation. (Figure 4.10) Since the key molecule in electron shuttling and energy generation (NADPH) deposits electrons in the ETC to re-generate $NADP^+$, shutting down the ETC leads to build up of NADPH in the cell. Excess NADPH causes multiple biochemical effects and signals the cells to stop converting glycogen to glucose. Additionally, the build up of NADPH can lead to NADPH reducing pyruvate to form lactic acid. As such, one of the potential adverse effects of metformin is lactic acidosis.

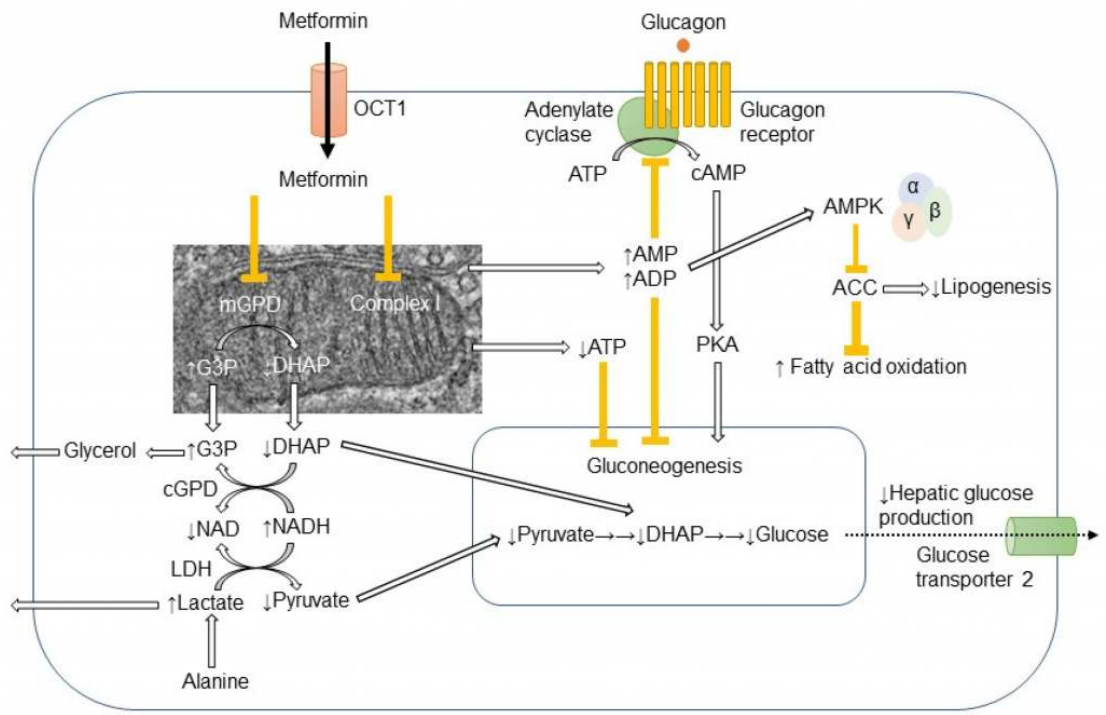



Figure 4.10 Different effects of metformin in the cell. Image Source: (Fig 1) by Ichiro Nojima and Jun Wada is used under a CC-BY 4.0 license.

Metformin is ultimately excreted by the kidneys and because of these effects, it is usually discontinued if a patient is admitted to the hospital for a condition where a CT scan may be likely. This is because the contrast agent is also processed by the kidneys. If both metformin and contrast agent are administered, since they are competing for renal clearance, metformin may remain in the body longer, and lead to excess concentrations and lactic acidosis.

## Increasing Insulin Release: Sulfonylureas

Sulfonylureas are drugs that contain a sulfonylurea functional group (usually neighbouring an aryl ring) and bind the aptly named, **sulfonylurea receptors(SURs)** in the pancreas. (Fig 4.11) SUR proteins are ABC transporters that are part of a larger complex of ATP-sensitive potassium channels (called $K_{ATP}$ channels) and act as gatekeepers of releasing insulin. These drugs have been utilized for several decades and are relatively inexpensive. Under normal function, the presence of glucose in the pancreas cells also leads to high concentration of intracellular ATP. High levels of ATP block the KATP channel, which leads to membrane depolarization triggering voltage gated $Ca^{2+}$ channels and $Ca^{2+}$ ion influx. As shown previously (Figure 4.3), the introduction of $Ca^{2+}$ leads to insulin release.

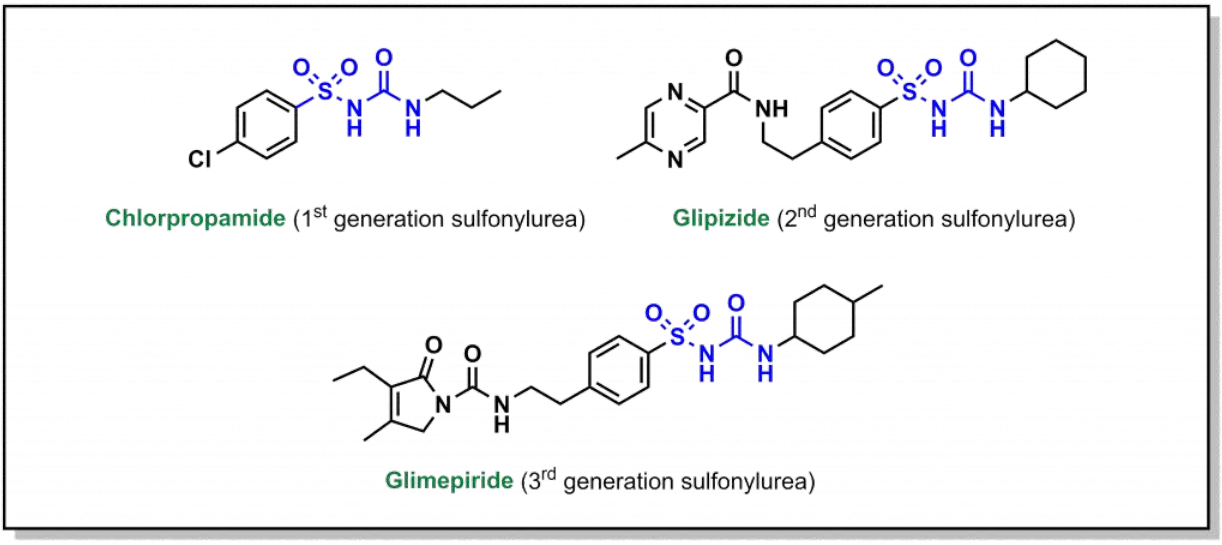



Figure 4.11 Structures of sulfonylurea inhibitors.

Administering sulfonylurea drugs produces the same response as high levels of intracellular ATP. Specifically, the sulfonylurea will bind the $K_{ATP}$ channel, leading to membrane depolarization and $Ca^{2+}$ influx. This essentially decouples the release of insulin from blood glucose concentrations. However, it should be noted that if excess sulfonylureas are administered, this can cause blood glucose concentrations to drop dramatically.

Some additional side effects of sulfonylureas are that they can cause the patient to gain weight (as sulfonylureas lead to additional insulin release, which triggers cells throughout the body to uptake more glucose). Furthermore, $K_{ATP}$ channels are also located in other tissues in the body including the heart, and non-specific binding of sulfonylureas can lead to an increased risk of cardiac events.

## Increasing Insulin Release: Meglitinides

Meglitinides have a similar mechanism of action as sulfonylureas – they bind to the $K_{ATP}$ channel (at a different site on the SUR protein compared to sulfonylurea drugs). (Figure 4.12) However, the interaction between meglitinides and the SUR protein is not as strong as the sulfonylurea-SUR binding. This results in a relatively weaker effect that has a shorter duration of action. This reduced activity can be very useful, since it can lead to more flexibility in treatment options and meglitinides are not associated with adverse cardiovascular events. Meglitinides also present as a suitable option in case the patient is allergic to sulfonylureas.

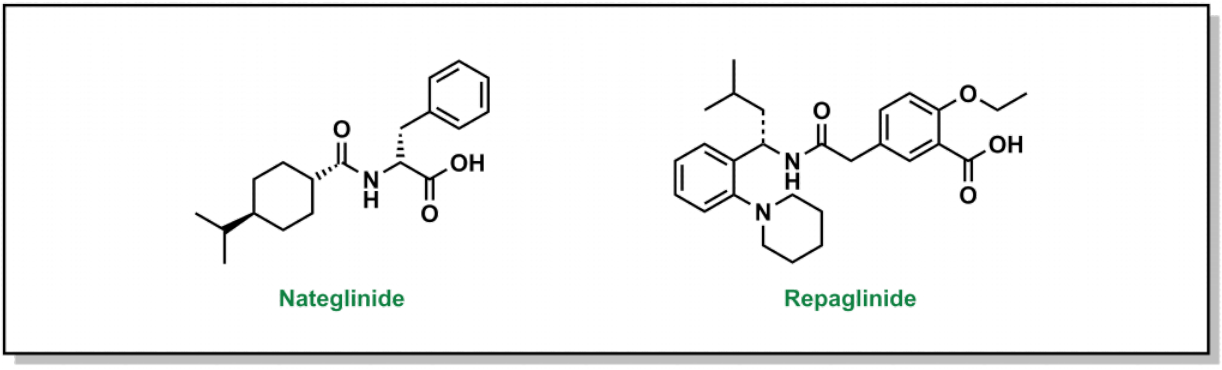



Figure 4.12 Structures of representative meglitinides.

## Increasing Insulin Production: Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

In addition to the hormones produced by the pancreas, there are also hormones produced by the small intestine called incretins (including GIP and GLP1). These incretins stimulate the body to prepare for food intake as well as insulin production/release. These incretins are very rapidly degraded by dipeptidyl peptidase 4 (DDP-4). Prolonging the effects of GIP/GLP1 (by inhibiting DDP-4 with small molecules) can increase insulin levels in the body as well as other digestion and absorption effects. DDP-4

inhibitors engage with DPP-4 at the GLP1 interaction site, and they are considered protein-protein interaction inhibitors. Several drugs contain azolopyrimidines which are important for hydrogen bonding interactions within the binding site. (Figure 4.13)

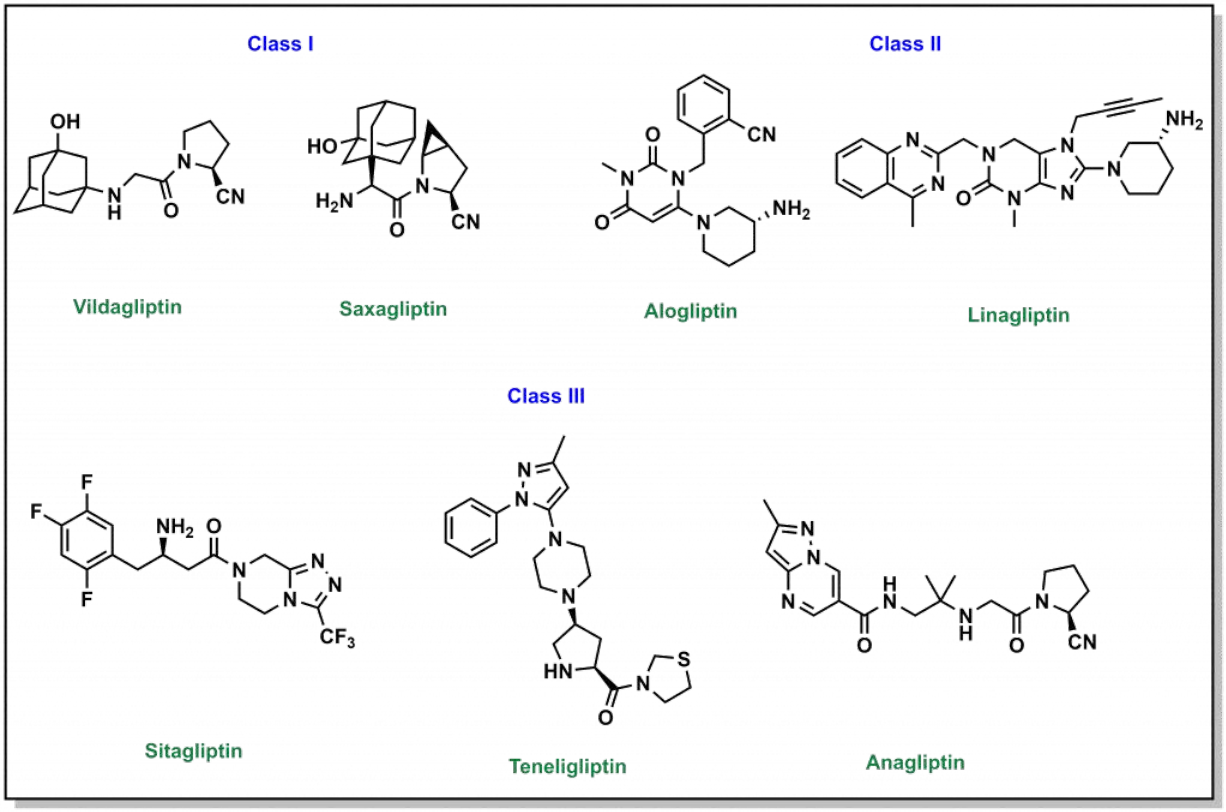



Figure 4.13 Structures of DDP-4 inhibitors.

One side effect of these drugs is that they are usually associated with weight loss (although they lead to increased insulin release as with sulfonylureas ore meglitinides). This is because the prolonged incretin lifetime also increases feelings of satiety that usually suppresses diet and therefore reduce caloric intake.

## Increasing Insulin Production: GLP1 Agonists

Similar to the mechanism with DDP-4 inhibitors, GLP1 agonists involve directly injecting the incretin GLP1 (comparable to injecting the hormone insulin in Type 1 Diabetes). GLP1 is preferred over GIP since it has more potent effects. There are two peptide backbones for these drugs, which are based on GLP1 and exendin-4 (originally isolated from the venom of the Gila monster reptile). (Figure 4.14) Since it is not a mammalian incretin, exendin-4 is not a substrate for DDP-4 and has longer life-time. As with DDP-4 inhibitors, these drugs slow the digestion of food, increase insulin output, and increase the feelings of satiety.




Figure 4.14 Peptide sequence of GLP1 agonists. Image Source: (Fig 2) by Wenwei Wan, Qikai Qin, Linshan Xie, Hanqing Zhang, Fan Wu, Raymond C. Stevens and Yan Liu has been modified (cropped) and is used under a CC-BY 4.0 license.

## Blocking Glucose Absorption: α-Glucosidase Inhibitors

Absorption of carbohydrates occurs in the small intestine. However, blocking carbohydrate absorption can act as a preventative measure to reduce blood glucose concentrations. Large oligosaccharides cannot be directly absorbed and need to be cleaved into monosaccharides. This occurs by the action of **α-glucosidases** which are present at the small intestinal brush border. The drug, acarbose, is structurally very similar to oligosaccharides, but has a substantially higher affinity for α-glucosidase and is also non-

cleavable. This leads to competitively blocking the active site of α-glucosidase, which prevents cleavage of oligosaccharides into monosaccharides, which subsequently blocks their absorption. These inhibitors can be more effective than traditional sulfonylureas, because they aim to prevent the spike in blood glucose levels proactively, as opposed to dealing with high concentrations after consumption.

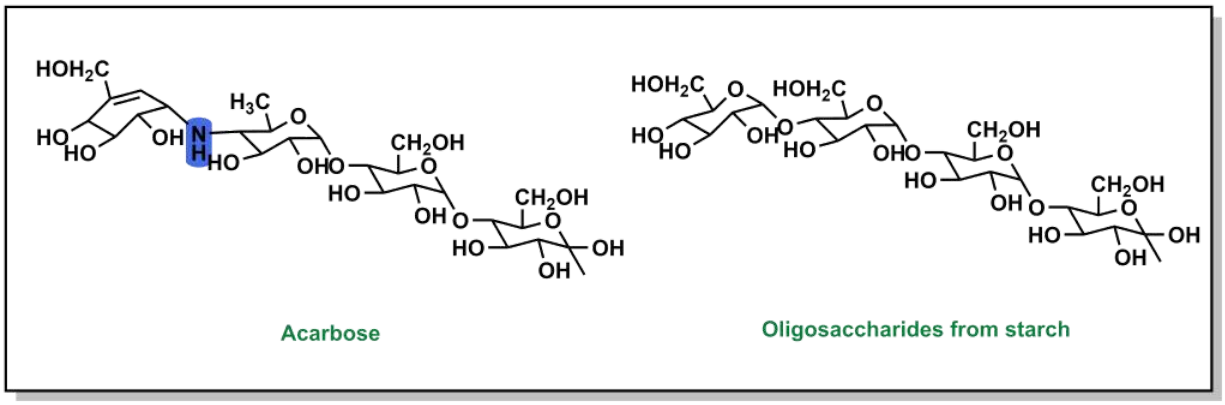



Figure 4.15 Structure of acarbose in relation to an oligosaccharide from starch.

## Blocking Glucose Re-absorption: SGLT-2 Inhibitors

Since Type 2 diabetic patients have a higher concentration of glucose in the blood, this will result in higher concentrations of glucose in the kidneys. The nephrons of the kidneys are designed to reabsorb glucose via sodium glucose L-transporters (largely performed by SGLT-2 transporters). (Figure 4.16) This function is physiologically beneficial since it helps retain nutrients. However, blocking these transporters in Type II diabetic patients can reduce blood glucose levels.

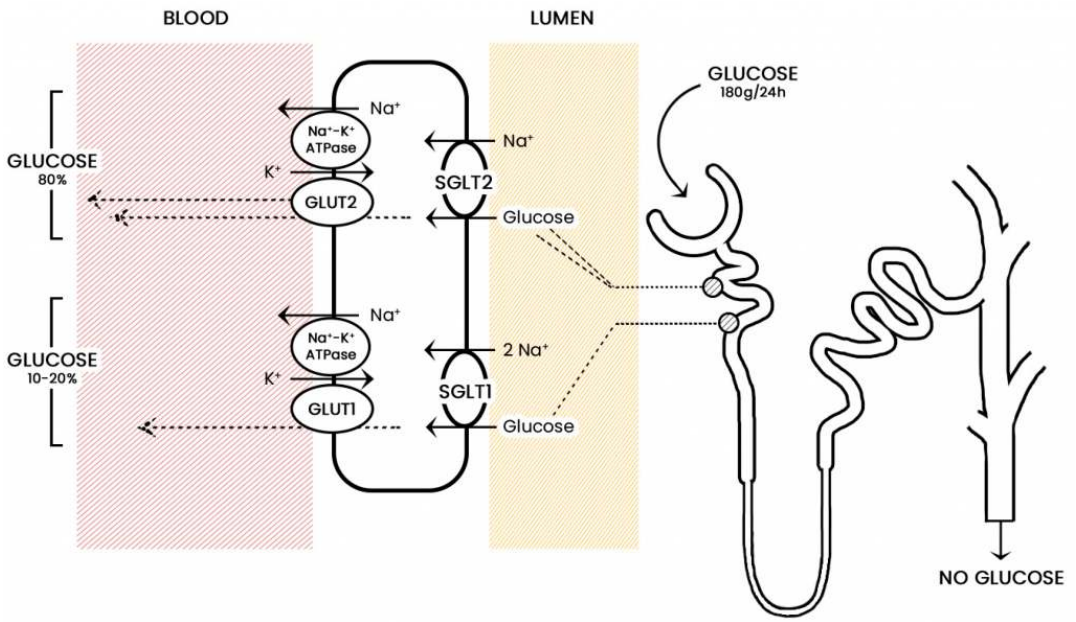



Figure 4.16 Reabsorption of glucose from the nephron of the kidney. Image Source: (Fig 1) by Daria M. Keller, Natasha Ahmed, Hamza Tariq, Malsha Walgamage, Thilini Walgamage,Azad Mohammed, Jadzia Tin-Tsen Chou, Marta Kałużna-Oleksy, Maciej Lesiak and Ewa Straburzyńska-Migaj is used under a CC-BY 4.0 license.

Phlorizin is the first drug for this purpose and consists of a glucose moiety linked to a system of two phenyl rings (the “aglycone” moiety) that is connected by an ethylene bridge. (Figure 4.17)

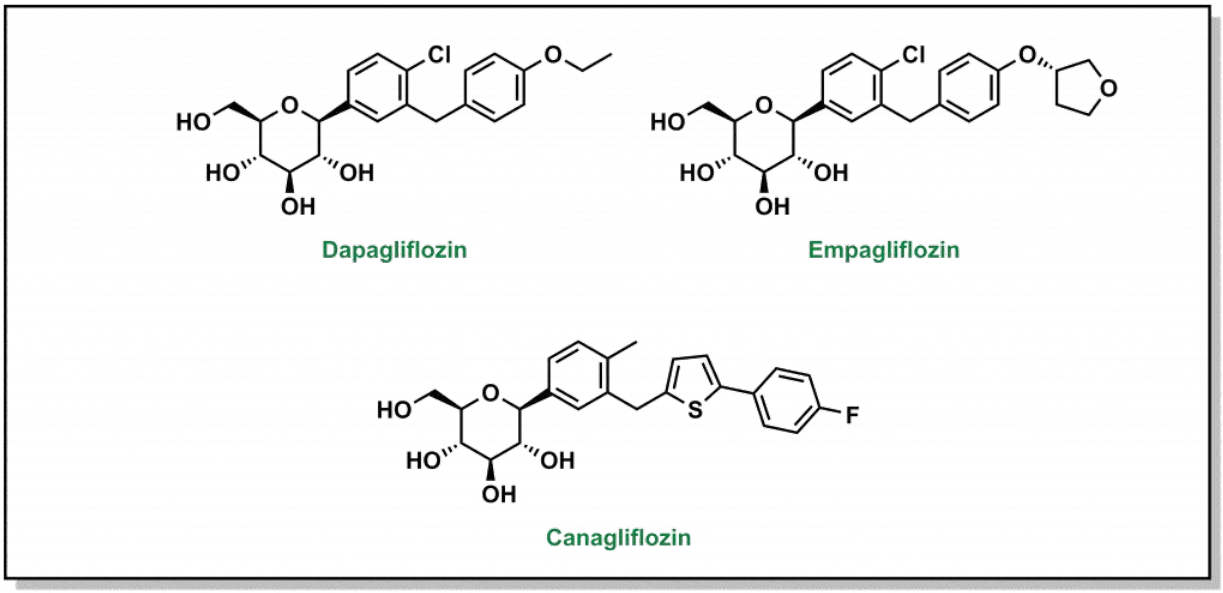



Figure 4.17 Structures of SGLT-2 inhibitors which are all linked to a glucose moiety.

## Indirect Blood Glucose Reduction: Blocking Triglycerides with Thiazolidinediones / Glitazones

Thiazolidinediones, also called glitazones, encourage cells to switch to carbohydrates / glucose as the principal energy source, which ultimately lowers blood glucose levels. (Figure 4.18)

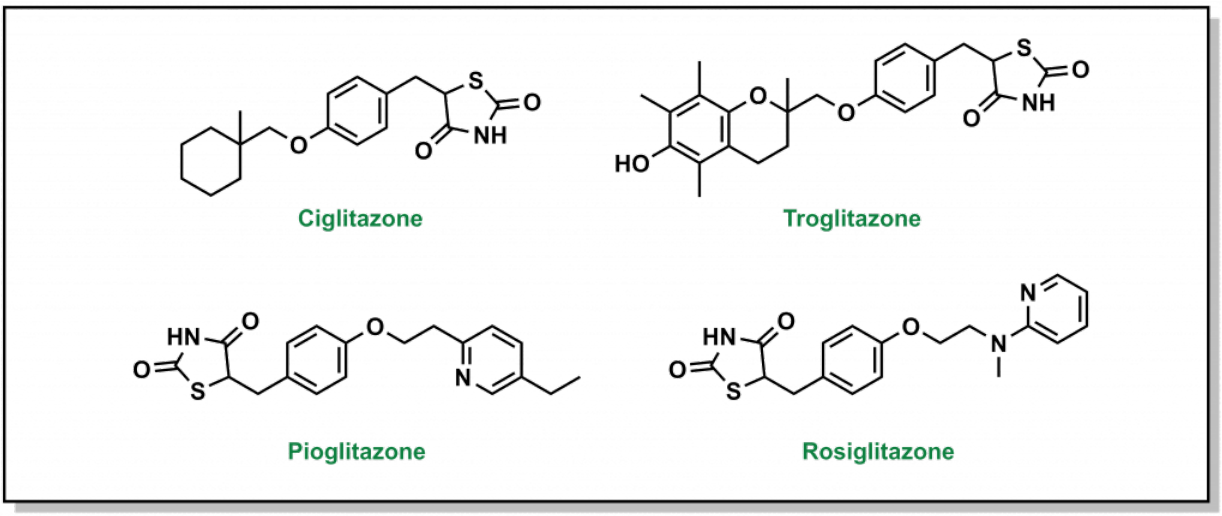



Figure 4.18 Structures of thiazolidinediones.

These drugs are agonists for PPARγ (peroxisome proliferator-activated receptor gamma), which is a transcription factor that complexes with retinoid X receptor (RXR). The end result is increased gene expression that will store fatty acids (reducing free fatty acids in blood circulation) and causing an increased cellular dependence on glucose. GLUT4 is an additional gene target for PPARγ, leading to increased glucose into cells. (Figure 4.19) However, it should be noted that the increased fatty acid storage is also correlated with reduced osteoblast formation, and there is a decrease in bone mineral density and increase risk of fractures with prolonged use of thiazolidinediones.

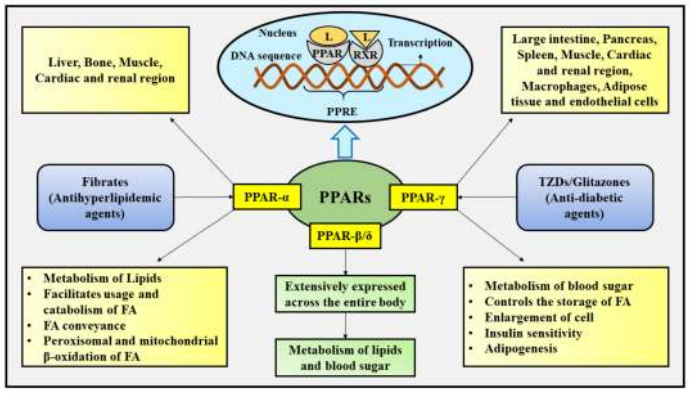



Figure 4.19 Agents targeting the PPAR family of proteins. Image Source: (Fig 1) by Tapan Behl, Piyush Madaan, Aayush Sehgal, Sukhbir Singh, Neelam Sharma, Saurabh Bhatia, Ahmed Al-Harrasi, Sridevi Chigurupati, Ibrahim Alrashdi and Simona Gabriela Bungau is used under a CC-BY 4.0 license.

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# 4.5: Summary

The following table provides a summary of treatments for Type II diabetes. The different types of insulins used for Type I diabetes are summarized in Figure 4.8.

Table 4.1 Pharmacological properties of Type II diabetes treatments.

| | TARGET | FUNCTIONAL GROUP | EFFECT | SUFFIX | WEIGHT CHANGE | Side Effects |
|---|---|---|---|---|---|---|
| **Biguanides** | Electron Transport Chain | Biguanide | 1) Reduce glucogenesis 2) Increase insulin sensitivity 3) Reduces absorption | -formin | Neutral / Decrease | Lactic Acidosis |
| **Sulfonylureas** | $K_{ATP}$ channel | Sulfonylurea | Directly stimulate insulin release | -ide | Increase | Weight gain / hypoglycemia / cardiac issues |
| **Meglitinides** | $K_{ATP}$ channel | Benzamide* | Directly stimulate insulin release | -inide | Increase | Weight gain / hypoglycemia / cardiac issues |
| **DPPR-4 Inhibitors** | DPP-4 | Azolopyrimidines* | Increase GLP1 function (indirectly stimulate insulin) | -liptin | Neutral / Decrease | Pancreatitis |
| **GLP1 Agonists** | GLP1 receptor | GLP1 / Exadin-4 peptide template | Increase GLP1 function (indirectly stimulate insulin) | N/A | Neutral / Decrease | Nausea / GI issues |
| **SGLT2 Inhibitors** | SGLT-2 | C-Linked glycosides | Prevent Glucose reabsorption | -flozin | Decrease | Urinary infections / dehydration |
| **α-Glucosidases** | α-glucosidase | N-linked glucose | Prevent glucose absorption | N/A | Decrease | Nausea / GI issues |
| **Thiazolidinediones** | PPARγ | Thiazolidinediones | Increase glucose utilization | -azone | Increase | Increase bone fractures |

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# CHAPTER OVERVIEW

## 5: Drug Treatments for Pain and Inflammation


5.1: Pathology

5.2: Treatments for Pain and Inflammation

5.3: Summary


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# 5.1: Pathology

Responding to tissue damage is usually accompanied by a physiological and psychological response via inflammation and pain. Although these are associated with negative responses, acute pain and inflammation are important in helping remove the negative stimuli, fighting off foreign invaders, and healing injuries. However, prolonged inflammation and pain can lead to additional damage and discomfort. The regimen of drugs developed for pain and inflammation are designed to deal with physiological and/or psychological responses.

In the simplest example, damage to a cell can occur through a puncture or rupture of the membrane which can lead to a cascade of different responses. For example, one initial aspect can involve the influx of $Ca^{2+}$ into the cell. $Ca^{2+}$ is a potent biochemical messenger and multiple proteins and transcription factors are sensitive to $Ca^{2+}$ binding which can trigger different responses depending on the type of cell. One of the key responses is the activation of a protein called phospholipase A2 (PLA2). PLA2 interacts with phospholipids of the cell bilayer and will cleave fatty acids from the phospholipid.

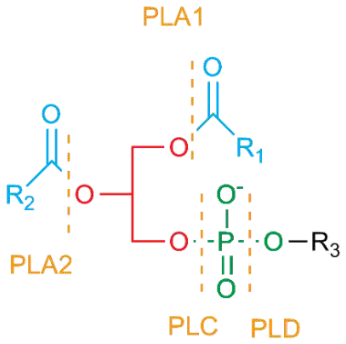



Figure 5.1 Sites of cleavage by the phospholipase family depicted on the phospholipid backbone. Image Source: Phospholipases2) by Roadnottaken is used under a CC BY-SA 3.0 license.

Recall that the structure of a phospholipid has a glycerol backbone with a phospholipid head group esterified to one oxygen of glycerol (called stereospecific numbering 1 or SN1) and fatty acid chains esterified to the other two oxygen atoms (called SN2 and SN3). (Figure 5.1) Phospholipase enzymes cleave at specific SN positions (PLA1 cleaves at the SN1 position, PLA-2 cleaves at SN2, PLAB cleaves at either SN1 or SN2, and PLAC and PLCD cleave on specific sides of the phosphate at the SN3 position). During the inflammatory responses, one of the most important phospholipases is PLA2 which cleaves the fatty acid in the middle (SN2) position. The fatty acid released is often an arachidonic acid. (Figure 5.2)

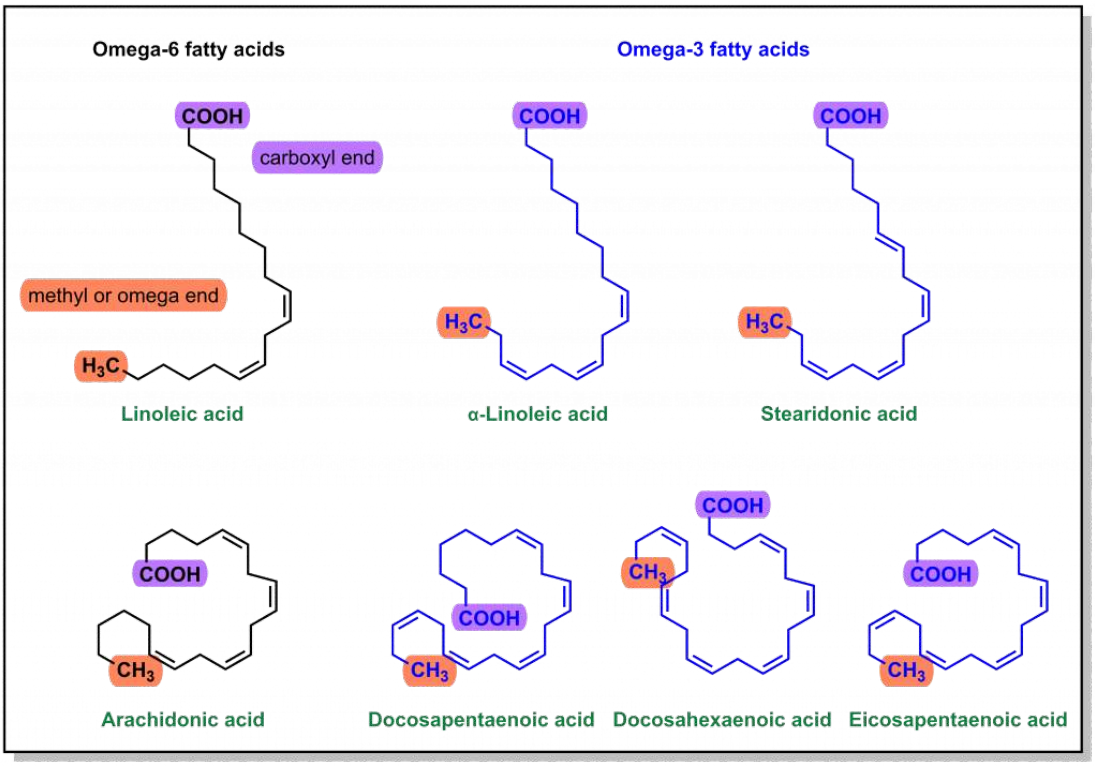



Figure 5.2 Structures of fatty acids.

## Arachidonic acid and inflammation

There are multiple types of fatty acids that are incorporated into phospholipids. Since physiological fatty acids can have variable lengths and degrees of saturation, historically it has been more convenient to name fatty acids from the omega end (final carbon) rather than the alpha end. Omega-3 fatty acids have a double bond at the 3-C from the omega position and omega-6 fatty acids have a double bond at the 6-C from the omega position. (Figure 5.2) Arachidonic acid is an omega-6 fatty acid and it contains 4 double bonds, which are in the '*cis*' configuration, leading to a more closed geometry that contributes to cell membrane fluidity. The double bonds are also highly susceptible to oxidation, which makes arachidonic acid a good target for downstream signalling pathways. (Figure 5.3)

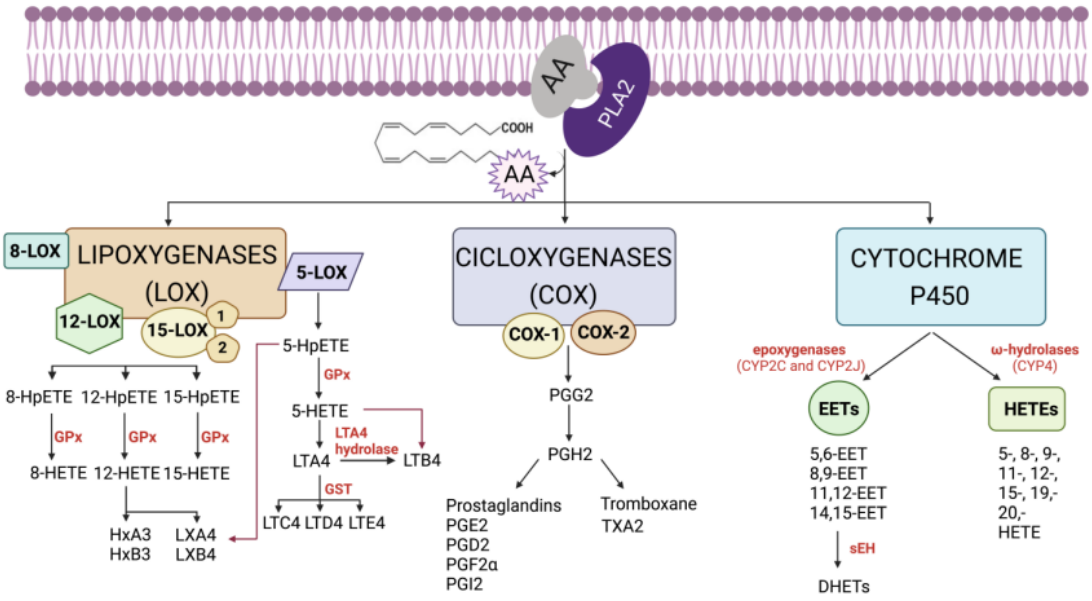



Figure 5.3 Arachidonic acid metabolism in response to cell damage. Image Source: (Fig 1) by Cándido Ortiz-Placín, Alba Castillejo-Rufo, Matías Estarás and Antonio González is used under a CC-BY 4.0 license.

Arachidonic acid signalling pathways begin following the influx of $Ca^{2+}$ and activation of PLA2 which cleaves specific phospholipids and releases arachidonic acid from the SN2 position. Free arachidonic acid acts a substrate for many different proteins, which are mainly stratified into three classes, cyclooxygenases (**COX enzymes**), cytochrome P450 (CYP) enzymes, and lipoxygenases (LO enzymes). Arachidonic acid is oxidized into different molecules that are called eicosanoids and includes molecules such as prostaglandins and thromboxanes. Each of these molecules can have different effects, such as increased inflammation or platelet aggregation.

Inhibition of this pathway can occur at different points. At the top of the pathway is PLA2, and this enzyme is potently inhibited by steroids, which shuts down the inflammatory response. However, steroids are hormones, and they can have multiple effects throughout the body. Therefore, targeting enzymes lower in the biochemical response pathway such as arachidonic acid metabolizers represents a more selective strategy. The most common approach is inhibition of the COX enzymes which generate the prostacyclins, prostaglandins, and/or thromboxanes.

There are two key isoforms of the COX enzymes, referred to as COX1 and COX2. COX1 is shown to be constitutively active, albeit at low levels in multiple tissues, and helps maintain homeostasis. COX1 has important roles in maintaining the stomach lining, normal functioning of the kidneys, and platelet aggregation. COX2 is upregulated in response to inflammatory signals. Upon activation, both COX1 and COX2 are found at the cell membrane surface and are positioned in such a way that a long channel within the enzyme is oriented towards the membrane to accommodate any free arachidonic acid molecules. (Figure 5.4)

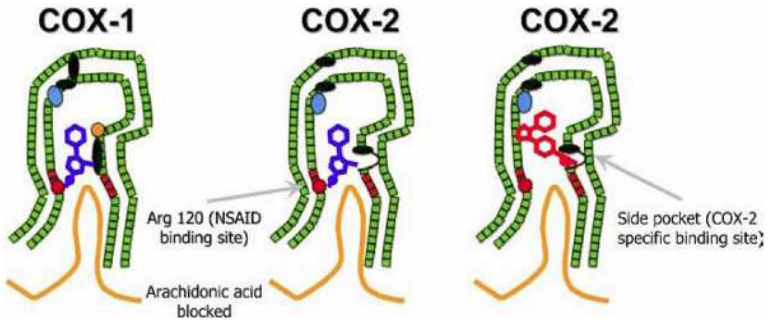



Figure 5.4 Schematics of COX1 and COX2 binding sites. Image Source: (Fig 1) by Inger L. Meek, Mart A.F.J. Van de Laar and Harald E. Vonkeman is used under a CC-BY 3.0 license.

When arachidonic acid is bound inside the COX enzymes, it is oxidized to form prostaglandin G2, which is converted into prostaglandin H2 and serves as a substrate for other enzymes. (Figure 5.5)

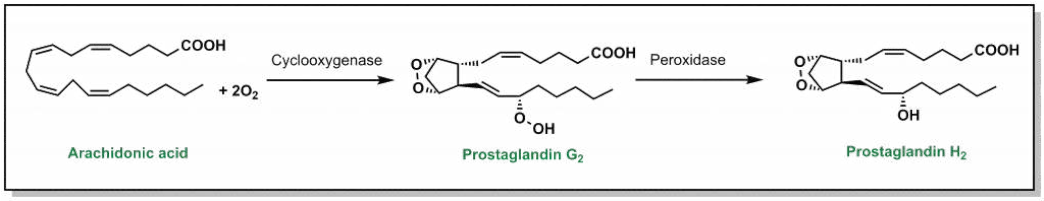



Figure 5.5 Oxidation of arachidonic acid by COX enzymes. The COX enzymes have allosteric side pockets that are sterically blocked by isoleucine residues in COX1, but available for binding in COX2.

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# 5.2: Treatments for Pain and Inflammation

Since the molecules involved in targeting the COX enzymes are not steroids but still reduce inflammation, they are referred to as **Non-Steroidal Anti-Inflammatory Drugs** or **NSAIDs**. Although the COX enzyme was first isolated and purified in 1976, it has been inhibited by the action of natural products used by multiple civilizations (such as the bark of white willow or meadowsweet trees). The active ingredient from these plants (salicylic acid) was eventually identified, and some of the more adverse reactions (such as GI discomfort) were ablated with the use of the esterified acetylsalicylic acid (aspirin). Aspirin was the first drug to be developed, patented, and marketed in 1899 and represents a large milestone in the history of pharmaceutical agents.

## Aspirin

The anti-inflammatory effects of aspirin arise through inhibition of the COX enzyme. Acetylsalicylic acid binds the positively charged side chain of Arg120 on the COX enzyme and blocks arachidonic acid from entering the protein channel and being oxidized to inflammatory metabolites. (Figure 5.4) Aspirin also has a unique mechanism of action in which it covalently (or irreversibly) engages with the COX enzyme by reacting with Ser29. (Figure 5.6) The acetyl-group acts a leaving group, and the COX enzyme is permanently modified with the salicylic acid. Cells (such as those in the gastric lining) need to biosynthesize new COX1/COX2 enzymes to restore proper function. However, unnucleated cells (such as platelets) cannot re-synthesize these proteins and aspirin is a potent inhibitor of platelet aggregation.

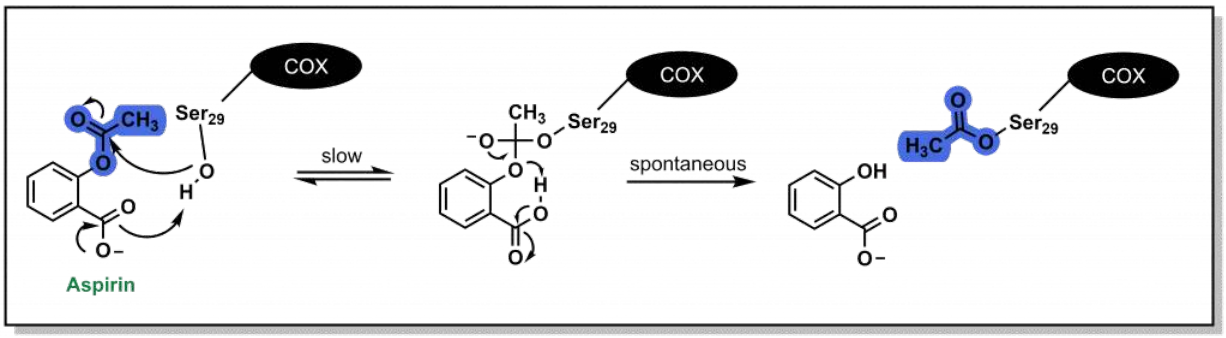



Figure 5.6 Aspirin is a covalent modifier of COX enzymes.

## Other Non-steroidal Anti inflammatory Drugs

There are multiple NSAIDs that are employed (other than aspirin), although they differ in that they do not operate via a covalent mechanism of action. They can generally be classified into salicylic acids, arylalkanoic acids, and oxicams. (Figure 5.7) In all cases, they have an acidic functionality that is critical to engage with Arg120 of the COX enzyme and sterically block access to the pocket.

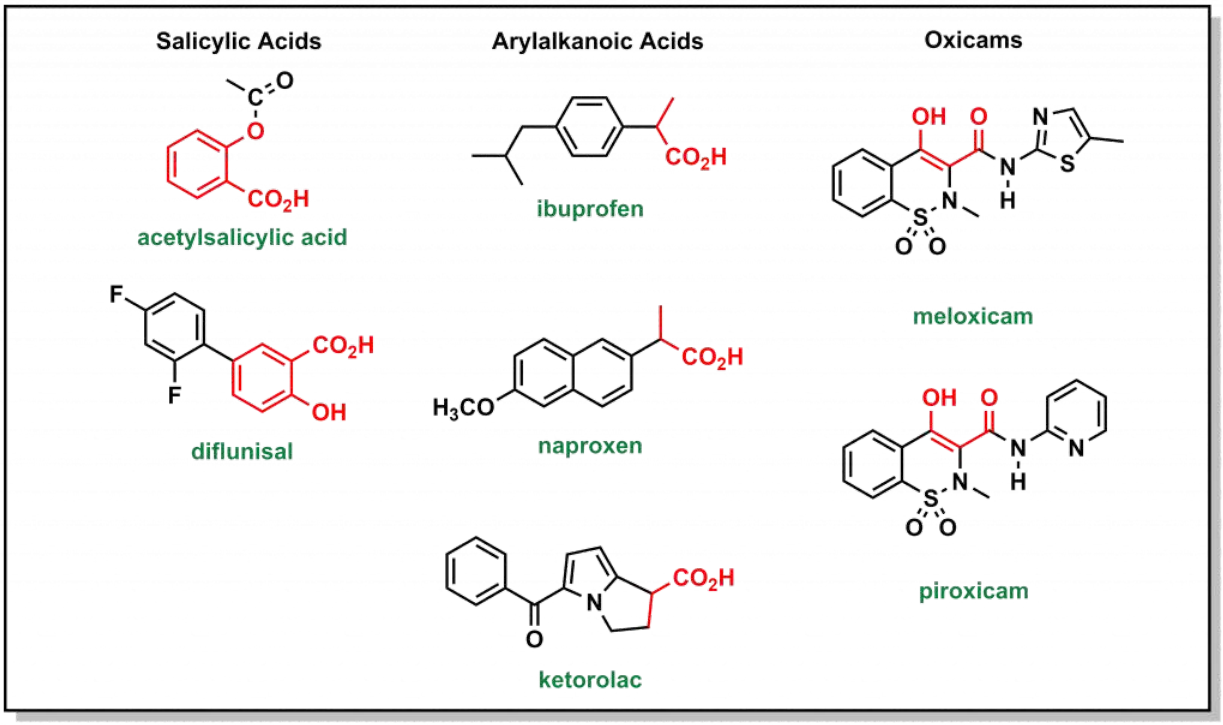



Figure 5.7 Structures of different classes of NSAIDs.

## Tylenol

Tylenol or **acetaminophen** is a common analgesic that was previously thought to inhibit COX enzymes. However, it was shown to only weakly bind to the COX enzymes *in vitro* and as such is not an NSAID, likely due to low acidity of the hydroxyl group. Acetaminophen is thought to act centrally in the brain to block pain signals and directly engage with arachidonic acid. (Figure 5.8a) However, it is also capable of inducing anti-inflammatory responses. One of the largest concerns with Tylenol is the potential for toxicity with excessive doses. Nearly all (~95%) Tylenol is metabolized by glucuronidation and sulfonylation. (Figure 5.8b) However, a small amount will be metabolized by CYP2E1 which leads to generation of the superoxide and NAPQI (*N*-acetyl-*p*-benzoquinone imine). This intermediate is toxic because it is highly reactive and can covalently modify different residues or nucleotides. In the presence of glutathione, NAPQI is rapidly de-toxified. However, if there are substantial amounts of Tylenol, this will deplete the reservoir of liver glutathione leaving free NAPQI available to react with other biomolecules.

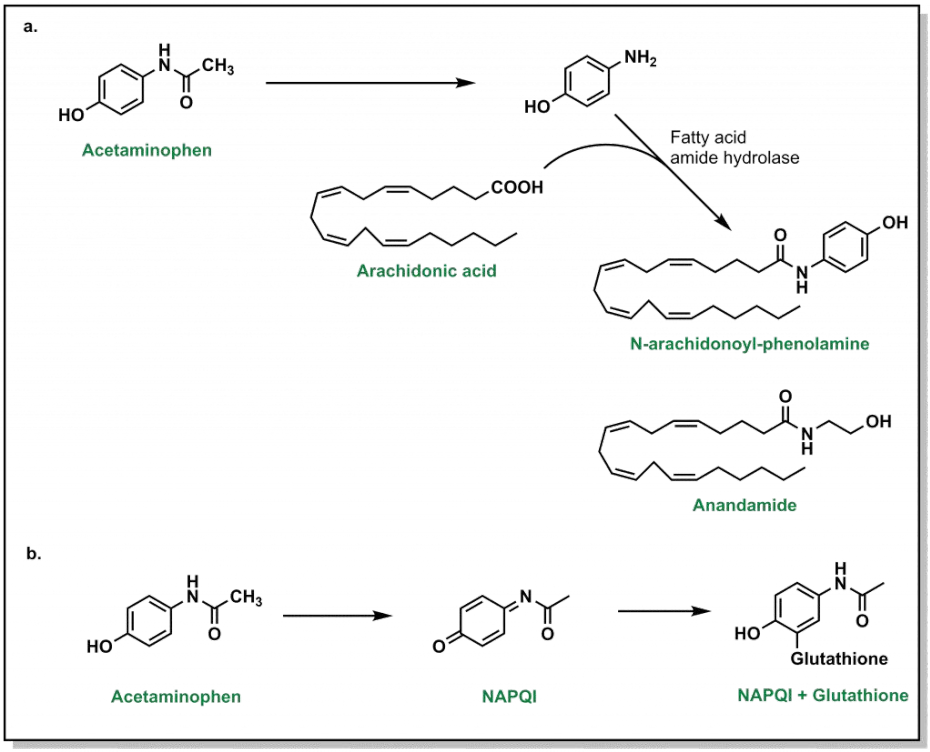



Figure 5.8 Mechanism of Tylenol metabolism and potential toxicity.

## Opioids

Pain generally begins at the nociceptors, and the signal is transmitted to secondary neurons in the dorsal root ganglion and subsequently to the brain via the spinal cord nerves. The signal transmission occurs via action potentials that fire with increased frequency depending on the severity of the pain. Neurons release multiple neurotransmitters that help facilitate different responses:

- Glutamate: This activates different receptors on the post-synaptic neuron (such as NMDA, AMPA) and causes $Ca^{2+}$ and $Na^{+}$ to enter the cell (increasing the positive charge of the cell)
- Substance P: This leads to the release of substances of such as arachidonic acid, and reinforces the pain signal.
- CGRP: This alters GPCR expression which reinforces response to pain.

At the same time, the body also releases endogenous molecules to help alleviate some of the effects of pain such as dynorphins and endorphins. These molecules can bind to mu, delta, or kappa receptors. Euphoric effects arise upon binding and activation of the mu receptors in the brain. These receptors reduce the response of GABA receptors, and the net result is the removal of limiters on dopamine release. These natural ligands produce analgesic effects. However, opioids are substantially more potent binders and lead to more powerful analgesic effects.

Opioids have been used for thousands of years and they originate from the milky fluid (called latex) of the poppy plant. Morphine is the primary alkaloid of the opium family. (Figure 5.9) It contains multiple functional groups that are critical for analgesic activity. This includes:

- A tertiary nitrogen that is positively charged to engage with the side chain of an aspartic acid on the mu receptor.
- The tertiary nitrogen attached to a quaternary carbon by a 2-C bridge.
- The quaternary carbon has a phenyl group attached for pi-pi stacking interactions with the mu receptor.
- Functional groups on $C_3$ and $C_6$ are important for H-bonding interactions.

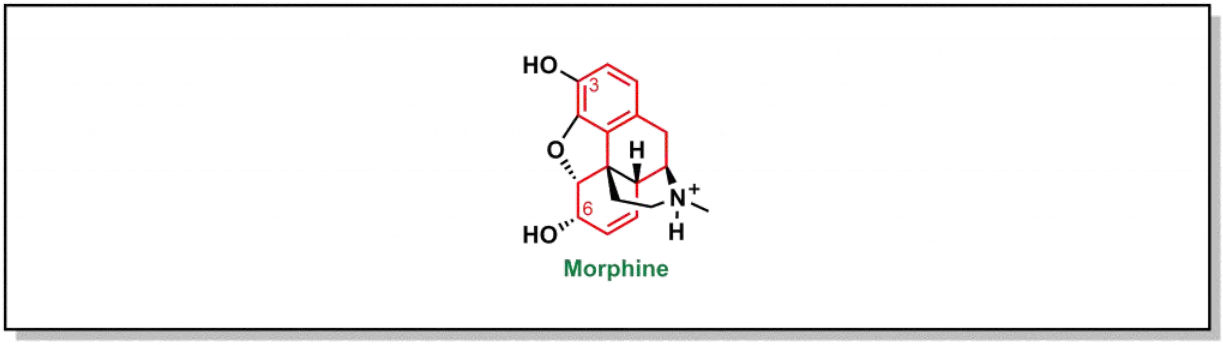



Figure 5.9 Structure of morphine.

Natural, synthetic, and semi-synthetic opioids have been explored which offer alternative properties in bioavailability. (Figure 5.10) For example, codeine is a naturally occurring opiate, and the only difference between morphine, is in the $C_3$ position (with a methoxy instead of the hydroxyl). This increases the lipophilicity of the molecule substantially. However, the $C_3$ methoxy can no longer participate in H-bonding and also has substantially lower binding to the mu receptor. Although codeine would be extremely potent if it was metabolized to morphine, this does not occur efficiently. In fact, even though the lipophilicity of codeine is higher than morphine, because of the slow rate of metabolism, an oral dose of 100 mg is required to achieve the same response as 10 mg of morphine.

Heroin is a version of morphine where the hydroxyl groups on $C_3$ and $C_6$ are both acetylated. This increases the lipid/membrane solubility leading to rapid CNS penetration. The acetyl groups are also readily metabolized to hydroxyls (unlike codeine) and heroin is approximately two-fold more potent than morphine.

To compensate for the low binding affinity of codeine, different derivatives were examined such as hydrocodone. In hydrocodone, the hydroxyl at $C_6$ is converted to a ketone which increases the lipophilicity while preserving the double bond. However, the carbonyl alters the positions of the oxygen relative to the hydrogen bond donor and removing the double bond at $C_3$-$C_4$ helps re-align the atoms. These changes result in similar potencies between hydrocodone and morphine. Hydrocodone can be metabolized to more potent hydromorphone which is similar with the exception of the hydroxyl instead of methoxy at $C_6$.

Another SAR modification was the introduction of a hydroxy at $C_{14}$ to hydrocodone. Oxycodone has further improved bioavailability and is about two-fold more potent than morphine.

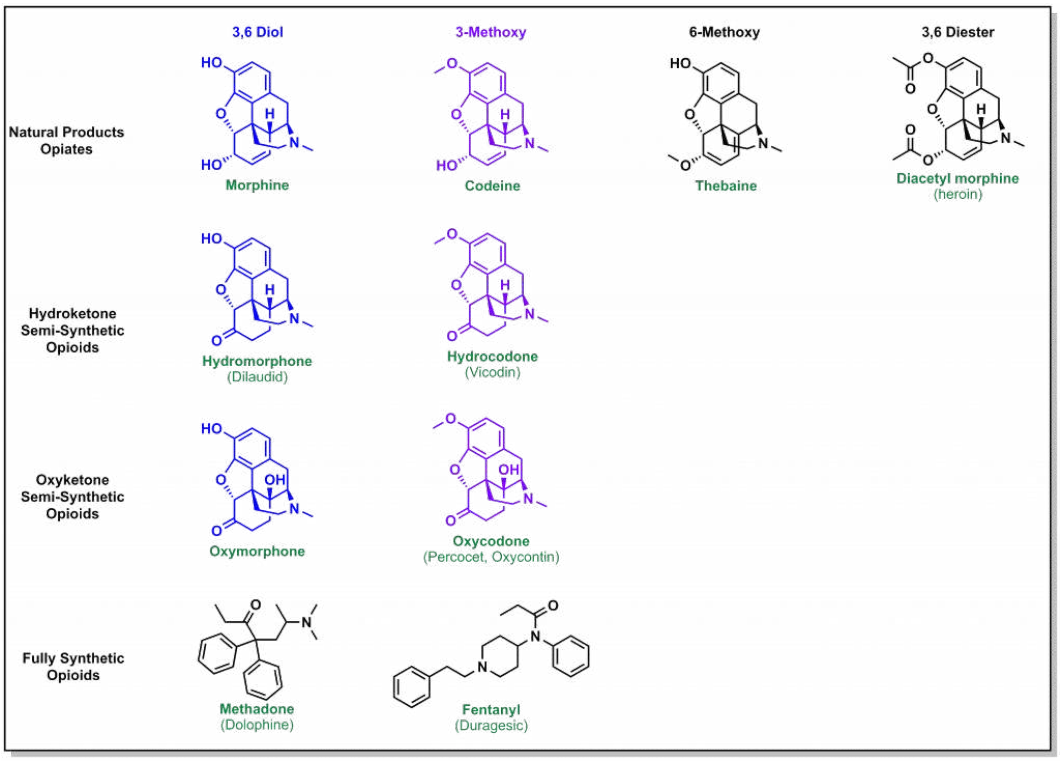



Figure 5.10 Natural, semi-synthetic, and synthetic opioids.

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## 5.3: Summary

Table 5.1: Summary of over-the-counter analgesic drugs.

| | Aspirin | Ibuprofen | Tylenol |
|---|---|---|---|
| **Other Names** | Acetylsalicylic Acid | Advil, Bufen | Acetaminophen, Paracetamol |
| **Sub-class** | NSAID | NSAID | non-NSAID |
| **Target** | COX | COX | TRPV1 |
| **Anti-Inflammatory** | Yes | Yes | No |
| **Blood Thinner** | Yes | No | No |
| **Blood Pressure** | Uncommon | Increase | Uncommon |
| **Gastric Issues** | Potential | Potential | Uncommon |
| **Liver Damage** | Uncommon | Uncommon | High Doses |

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# CHAPTER OVERVIEW

## 6: Summary

6.1: Identifying drugs from functional groups

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# 6.1: Identifying drugs from functional groups

There are thousands of different types of drugs that have been investigated and clinically approved for an array of indications. The capacity to recognize a drug and its potential target is important in pharmaceutical sciences. Often, there are key functional groups that are associated with specific drug targets. This is largely because the drug will target exclusive pockets on a protein. These pockets will have specific van der Waals volumes as well as electrostatic and hydrophobic surfaces that will ideally accommodate certain functional groups. A large aspect of drug discovery is identifying the critical functional groups that will engage with the binding pocket, and building out the molecule to create or optimize additional interactions.

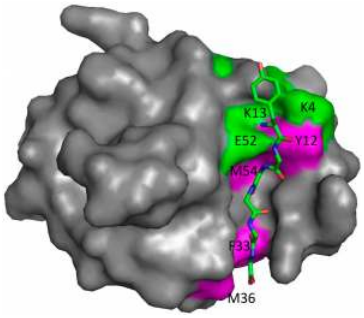
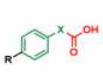
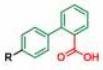
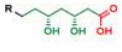
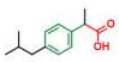
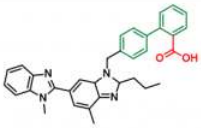
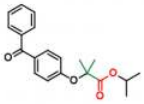
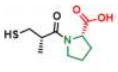
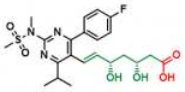



Figure 6.1 Surface structure of SH3b shown with a stick peptide model to indicate interaction grooves and surfaces. Image Source: (Fig 1) by Mike P. Williamson is used under a CC-BY 4.0 license.

Throughout these topics, we have explored specific types of functional groups and associated them to different targets (such as sulfonylurea moieties for $K_{ATP}$ channel sensitivity and coumarins for VKORC1 binding). Some functional groups can be further classified. For example, carboxylic acids are key functional groups found across multiple drugs. They introduce an acidic functionality into a molecule and alter the electrostatic and hydrogen bonding potential. A functionalized carboxylic acid can also be a key indicator for the type for drug target. (Table 6.1) Identifying trends in different types of functional groups is critical in recognizing drugs and their targets.

Table 6.1 Functionalized carboxylic acids are chemotemplates of multiple drug classes.

| Drug Class | NSAIDs | ARB Inhibitors | Fibrates | ACE inhibitors | Statins |
|---|---|---|---|---|---|
| Chemotemplate |  |  |  |  |  |
| Example |  Ibuprofen |  Telmisartan |  Fenofibrates |  Captopril |  Rosuvastatin |

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# Index


## I

insulin

4.2: Insulin

## P

preproinsulin

4.2: Insulin

## T

Type I diabetes

4.3: Treatments for Type I Diabetes

## W

warfarin

2.2: Anti-Coagulant Treatments

# Glossary

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    - 2.2: Anti-Coagulant Treatments - *Undeclared*
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    - 4.4: Treatments for Type II Diabetes - *Undeclared*
    - 4.5: Summary - *Undeclared*
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    - 5.2: Treatments for Pain and Inflammation - *Undeclared*
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    - 4.3: Treatments for Type I Diabetes - *Undeclared*
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