Drug ADME

D'Eustachio, P., Huddart, R., Jassal, B., Stephan, R., Thorn, CF.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 83

This document contains 9 pathways (see Table of Contents)
Pharmacokinetics (PK) is a branch of pharmacology dedicated to determining the chemical fate of substances in living organisms, from administration to elimination from the body. PK can be described as how an organism affects a drug, whereas pharmacodynamics (PD) is the study of how a drug affects the organism. Both PK and PD are described for each drug annotated in the Drug Absorption, Distribution, Metabolism and Excretion (ADME) pathways. For example, although paracetamol ADME (PK) is described in this section, the pharmacological inhibition (PD) of its targets (PTGS1 and PTGS2) is described in the relevant pathway where these enzymes perform their physiological duties. A connection is made between the two pathways to link PK and PD annotations.

The disposition of a pharmaceutical compound within an organism can be described by four main stages; absorption, distribution, metabolism, and excretion, abbreviated to ADME (Pallasch 1988, Ruiz-Garcia et al. 2008, Currie 2018). Sometimes, separate steps can be tacked on to ADME depending on what is being described. For example, where a drug is released from a pharmaceutical formulation, liberation (L) is added to ADME (LADME) or where the toxicity of a compound is described, T is added (ADMET).

ADME of various drugs is annotated in this section.

**Literature references**


**Editions**

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https://reactome.org
Azathioprine ADME

Location: Drug ADME

Stable identifier: R-HSA-9748787

Thiopurines were originally developed for cancer treatment in the early 1950s, with 6-mercaptopurine (6MP) being the first thiopurine approved by the FDA for the treatment of leukaemia, just two years after its discovery. Azathioprine (AZA), a prodrug of 6MP, was developed by the addition of a nitroimidazol group a few years later to bypass the high first-pass metabolism of 6MP due to oxidation in intestinal cells by xanthine oxidase (XDH). AZA is a thiopurine prodrug, and its pharmacological action is based on the release of the active metabolite 6-mercaptopurine (6MP) which is further metabolised to pharmacologically active 6-thioguanine nucleotides (6-TGNs). These 6-TGNs achieve their cytotoxic effects in one of four ways:

1. Incorporation of 6-thioguanosine triphosphate (6TGTP) into RNA
2. Incorporation of 6-thiodeoxyguanosine triphosphate (6TdGTP) into DNA
3. Inhibition of de novo purine synthesis by methylmercaptopurine nucleotides such as methylthiinosine monophosphate (meTIMP)
4. Inhibition of RAC1 by 6TGTP which induces apoptosis in activated T-cells.

While AZA has been supplanted as an antitumour drug, it remains useful as an immunosuppressant antimetabolite drug indicated to treat rheumatoid arthritis, Crohn’s disease, ulcerative colitis, cancer and to prevent rejection in kidney transplant patients (Axelrad et al. 2016, Tominaga et al. 2021).

The molecular steps of AZA metabolism are described in this pathway (Cuffari et al. 1996, Dubinsky 2004). Briefly, oral AZA is rapidly converted to 6MP. Initial 6MP metabolism occurs along competing catabolic (XDH, TPMT) and anabolic (HPRT) enzymatic pathways. Once formed, 6-thiosine 5'-monophosphate (6TIMP) is further metabolized by inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS) to 6-thioguanosine 5’monophosphate (6TGMP). 6TGMP is then converted to the pharmacologically-active di- and tri- derivatives by their respective kinases.

**Literature references**


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In water aspirin (acetylsalicylic acid, ASA) dissolves, dissociating into the acetylsalicylate ion (ASA-). ASA- is an anti-clotting agent and nonsteroidal anti-inflammatory drug (NSAID); the therapeutic effects are mediated through its interaction with PTGS enzymes. On a molar basis ASA- (a) is more potent as an analgesic/anti-inflammatory agent, (b) has greater gastric ulcerogenic activity, and (c) is much more effective as an inhibitor of prostaglandin biosynthesis and platelet aggregation than salicylate (ST) (Flower 1974; Mills et al, 1974; Rainsford 1975; Rainsford 1977).

Acetylsalicylic acid is only slightly soluble in conditions being found in the stomach mucosa, mostly because of unavailability of sufficient amount of solvent. The absorption, as well as the absorbing area, increases in the small intestine. Further increased absorption is achieved by dissolving tablets before ingestion or usage of ASA salts (Dressman et al, 2012). Practically 100% of therapeutic aspirin doses are taken up, mostly by intestinal mucosal cells (Artursson & Karlsson, 1991; Yee 1997).

Only a few percent of ASA- remain unchanged, the rest is hydrolyzed to salicylate (ST). The major route of ST catabolism is conjugation with glycine to form salicyluric acid. This accounts for 20–65% of the products. Conjugation to glucuronides (ester and ether) removes up to 42% of ST. Finally, a minor part also gets hydroxylated by cytochromes (Hutt et al, 1986).

**Literature references**


https://reactome.org
**Paracetamol ADME**

**Location:** Drug ADME

**Stable identifier:** R-HSA-9753281

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Paracetamol (APAP, aka acetaminophen or N-acetyl-p-aminophenol) is an analgesic drug used for to treat mild to moderate pain and as an antipyretic agent. It is one of the most widely used drugs in the world and is available alone or in combination with other drugs for pain relief, fever and allergy. It is thought to act through the inhibition of cyclooxygenases 1 and 2 (Graham et al. 2013, Esh et al. 2021). Paracetamol is generally safe at therapeutic doses but in overdose cases, it causes mitochondrial dysfunction and centrilobular necrosis in the liver which can lead to death.

APAP has a high oral bioavailability (~88%), is well absorbed and reaches peak blood concentrations after 90 minutes after ingestion. APAP binds plasma proteins to a small extent and has a plasma half-life of 1.5-3 hours. Most of the drug is eliminated by glucuronidate and sulfate conjugation (~55% and ~30% respectively) in the liver or as unchanged drug (~5%) (Forrest et al. 1982). A small amount (5-15%) is oxidised to the reactive metabolite N-acetyl-para-benzoquinone imine (NAPQI). NAPQI is usually detoxified by binding to liver glutathione but in overdose cases, glutathione is depleted and NAPQI instead, binds to sulfhydryl groups on proteins, leading to liver damage. ABCC2, ABCC3, ABCC4 and ABCG2 transporters mediate the efflux of APAP metabolites out of cells (McGill & Jaeschke 2013).

**Literature references**


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Abacavir ADME

Location: Drug ADME

Stable identifier: R-HSA-2161522

Abacavir is a nucleoside analogue reverse transcriptase inhibitor with antiretroviral activity, widely used in combination with other drugs to treat HIV-1 infection (Yuen et al. 2008). Its uptake across the plasma membrane is mediated by organic cation transporters SLC22A1, 2, and 3; the transport proteins ABCB1 and ABCG2 mediate its efflux. Abacavir itself is a prodrug. Activation requires phosphorylation by a cytosolic adenosine phosphotransferase and deamination by ADAL deaminase to yield carbovir monophosphate. Cytosolic nucleotide kinases convert carbovir monophosphate to carbovir triphosphate, the active HIV reverse transcriptase inhibitor. Abacavir can be glucuronidated or oxidized to a 5'-carboxylate; these are the major forms in which it is excreted from the body.

Literature references


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Atorvastatin (ATV, brand name Lipitor), is a lipid-lowering drug of the statin class of medications. It inhibits the endogenous production of cholesterol in the liver, thereby lowering abnormally high cholesterol and lipid levels, and ultimately reducing the risk of cardiovascular disease. Statins inhibit the enzyme hydroxymethylglutaryl-coenzyme A reductase (HMGCR), which catalyzes the critical step in cholesterol biosynthesis of HMG-CoA conversion to mevalonic acid. Statins are the most commonly prescribed medication for treating abnormal lipid levels (Malhotra & Goa 2001). ATV and its hydroxy-metabolites collectively inhibit HMGCR to reduce circulating low-density lipoprotein cholesterol.

ATV is transported in the blood almost exclusively bound to plasma proteins (>98%) (Lennernas 2003), and is subject to pre-systemic clearance at the gastrointestinal tract and to first-pass hepatic clearance, which explains its low systemic bioavailability (~12%) (Garcia et al. 2003). Organic anion transporters OATP1B1, OATP1B3 and OATP2B1, encoded by SLCO1B1, SLCO1B3, and SLCO2B1, respectively are expressed on the sinusoidal membrane of hepatocytes and can facilitate the liver uptake of drugs such as ATV (Kalliokoski & Niemi 2009).

In hepatocytes (and to a lesser extent, the GI tract), ATV can be hydroxylated by cytochrome P450 3A4 (CYP3A4) to hydroxy-metabolites, or undergo lactonization via an unstable acyl glucuronide intermediate to ATV lactone (ATVL) mediated by UGT1A3 and 1A1. ATVL may also be hydroxylated by CYP3A4 to hydroxylactone-metabolites. The lactone metabolites are inactive against HMGCR, but can be hydrolyzed via paraoxonases (PONs) to their corresponding hydroxy acids, which are active against HMGCR. Elimination of ATV and its metabolites is principally biliary with apparently no significant enterohepatic recirculation. Half-life (t1/2) is approximately 14 h for atorvastatin and 20–30 h for its metabolites (Schachter 2005).
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Ribavirin (RBV) is a synthetic nucleoside analog structurally related to guanine. It is given orally as part of the treatment of HCV infection, and by inhalation for the treatment of RSV infection. According to the WHO, ribavirin can also be used for the treatment of viral hemorrhagic fevers (WHO 2015).

RBV is administered orally in doses of 400 to 600 mg. It is highly soluble in water and a typical dose is dissolved completely over a wide range of acidities. RBV is rapidly absorbed into the circulation. After the oral administration of 600 mg radiolabeled ribavirin, approximately 61% of the drug was detected in the urine and 12% was detected in the feces. 17% of an administered dose was in unchanged form. RBV accumulates in human erythrocytes and remains in the body for weeks, with a half-life of >100 hours (Goodarzi et al, 2016). A consequence of the accumulation in erythrocytes is the well-known side effect of hemolytic anemia, which is reversible by cessation of administration (FDA label Rebetol, 2013).

Ribavirin is a prodrug. It is metabolized through two different paths: phosphorylation, yielding the active triphosphate (RBV-TP), and degradation via de-ribosylation and hydrolysis of the amide group. The GI tract, and not the liver, appears to be the major site of first-pass elimination (Dixit and Perelson, 2006).

**Literature references**

Food and Drug Administration, FDA. (n.d.). HIGHLIGHTS OF PRESCRIBING INFORMATION. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020903s052,021546s008lbl.pdf


Prednisone (PREDN) is a prodrug of prednisolone (PREDL), and is rapidly absorbed. To achieve high uptake of the near water-insoluble molecule the highest dose 50 mg has to be dissolved in 250 ml water. Its conversion to the highly active prednisolone (PREDL) in liver cells is reversible but represents the favored reaction direction (Pickup, 1979).

Prednisone and prednisolone are considered to be fully therapeutically equivalent. The theoretical advantage of avoiding high GI concentrations of prednisone by administering prednisolone directly has never been shown to be clinically relevant (Vogt et al, 2007).

Only 2–5% of a given dose of prednisone is excreted unchanged in urine. After hydrogenation to prednisolone at least 20 metabolites and their conjugates are formed and excreted. The main metabolites both after systemic and topical use are 20alpha- and 20beta-dihydro-prednisone, as well as 20alpha- and 20beta-dihydro-prednisolone (20AH-PREDN, 20BH-PREDN, 20AH-PREDL, 20BH-PREDL), in addition to the 6beta-hydroxy compounds 6B-OH-PREDN and 6B-OH-PREDL (Matabosch et al, 2015; Mazzarino et al, 2019).

Hydrogenation of PREDN and dehydrogenation of PREDL are complementary reactions that are dominant in different cell types. While liver and fat cells convert PREDN to PREDL, colon and kidney cells partly convert PREDL back to PREDN (Jamieson et al, 1995; Ricketts et al, 1998; Diederichs et al, 2002). We have depicted this equilibrium by showing example reactions in hepatocytes and kidney cells in the diagram.

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Ciprofloxacin (Cipro) is a widely used broad spectrum bacterial antibiotic. Due to its association with disabling and potentially persistent adverse reactions and current high levels of resistance its use is now recommended in patients who have no alternative treatment option for respiratory and urinary tract infections, skin and soft tissue infections, bone and joint infections, infectious diarrhea, typhoid fever and gonorrhea with susceptible strains. Adverse reactions include tendinitis, tendon rupture, peripheral neuropathy, and CNS effects. The usual dosages are 250 mg and 500 mg (FDA, 2016; Bayer Inc, 2020). Cipro is highly soluble in aqueous media below pH 5 and above pH 10. About 60 to 80 percent are taken up by the body. The main absorption site of ciprofloxacin is the upper GI tract, up to the jejunum (Harder et al, 1990; summarized in Olivera et al, 2011). In the context of the Biopharmaceutics Classification System (BCS) Cipro is "not highly soluble", and "not highly permeable". It is classified as BCS class 2, 3, and 4, and uptake and efflux transporters have a big effect on its absorption and excretion. BCS class 4 drugs are primarily excreted unchanged via the biliary or renal routes (Wu and Benet, 2005). Very high concentrations of Cipro with respect to plasma concentrations are seen in kidney and gall bladder; high concentrations are also found in liver, prostatic tissue, and lung. The main excretion routes for unchanged Cipro are renal (about 65% of plasma amount) and intestinal (about 10%) (Rohwedder et al, 1990; Viell et al, 1992; reviewed by Sörgel, 1989). The intestinal figure includes excretion through epithelial GI cells, and through hepatic cells and the bile duct. The rest of plasma Cipro (10 to 20%) is metabolised, with the major species recovered from urine being oxociprofloxacin and, in faeces, sulfociprofloxacin. Both account for about five per cent each of total excretion (reviewed by Campoli-Richards et al, 1988).
Literature references


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