Drug ADME

D'Eustachio, P., Huddart, R., Jassal, B., Stephan, R.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

23/03/2022
**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: 79

This document contains 5 pathways (see Table of Contents)
Drug ADME

Stable identifier: R-HSA-9748784

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**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021-07-27</td>
<td>Authored, Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2021-09-23</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
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 methylthioinosine 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 5â€²-mono- phosphate (6TIMP) is further metabolized by inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS) to 6-thioguanosine 5â€²-monophosphate (6TGMP). 6TGMP is then converted to the pharmacologically-active di- and tri- derivatives by their respective kinases.

**Literature references**


https://reactome.org


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021-07-27</td>
<td>Authored, Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2021-10-19</td>
<td>Reviewed</td>
<td>Huddart, R.</td>
</tr>
</tbody>
</table>
Aspirin ADME

Location: Drug ADME

Stable identifier: R-HSA-9749641

Compartments: cytosol, mitochondrial matrix, endoplasmic reticulum lumen, extracellular region

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 20â€“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


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021-08-03</td>
<td>Authored</td>
<td>Stephan, R.</td>
</tr>
<tr>
<td>2021-10-13</td>
<td>Reviewed</td>
<td>Huddart, R.</td>
</tr>
<tr>
<td>2021-11-12</td>
<td>Edited</td>
<td>Stephan, R.</td>
</tr>
</tbody>
</table>
Paracetamol ADME

Location: Drug ADME

Stable identifier: R-HSA-9753281

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 sulphydryl 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


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021-09-06</td>
<td>Authored, Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2021-10-13</td>
<td>Reviewed</td>
<td>Huddart, R.</td>
</tr>
</tbody>
</table>
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


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-03-14</td>
<td>Authored</td>
<td>D'Eustachio, P.</td>
</tr>
<tr>
<td>2012-03-16</td>
<td>Edited</td>
<td>D'Eustachio, P.</td>
</tr>
<tr>
<td>2012-03-16</td>
<td>Reviewed</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>