

The Neuropharmacology of Aspirin

(You are permitted, nay encouraged, to come up with a more creative title)

by

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Background (10% of grade): Acetylsalicylic acid (a.k.a. ASA or Aspirin) is a derivative of another drug called salicylic acid. Around 400 B.C. Hippocrates described relief of pain using the bark and leaves of willow trees. In 1829, John Buchner isolated a compound in willow bark that provided pain relief which he called salicin. Later this product was further purified and called Salicylic acid. Unfortunately, this was very upsetting to the stomach so it was later buffered with other compounds to become acetylsalicylic acid. In 1899 Felix Hoffmann who worked for the Bayer pharmaceutical company rediscovered it and patented it as Aspirin. After the Germans lost World War I, Bayer, a German company, was forced to abandon its trademark as part of the treaty of Versailles [1]. Interestingly, Canada allowed Bayer to keep its patent and here generic forms of Aspirin are labeled ASA. Today, Aspirin is the most extensively used therapeutic chemical in the world.

Drug Effects (10% of grade): Aspirin is a member of a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin is the drug of choice for rheumatoid arthritis (as an anti-inflammatory) and is widely used for its analgesic (pain relief) and antipyretic (fever reducing) properties. More recently it has been used at lower doses as an anti-platelet agent (blood thinner) to prevent arterial thrombosis leading to stroke or heart attack. Aspirin is contraindicated (medically inadvisable) in infants as it has been shown to complicate the symptoms of and worsen Reyes syndrome. This is a lethal syndrome in children that can occur after viral infection such as the flu or chicken pox.

Pharmacokinetics (40% of grade): Aspirin is taken orally. It is a weak acid with a pKa of 3.5 [2]. The stomach has a pH of 1, thus driving the drug more into its un-ionized form. This reduced charge increases its lipid solubility and most of it is absorbed through the stomach. The intestine has a pH of 5-6, making the drug relatively more ionized, so less of it is absorbed through the intestine compared to stomach. The rate of absorption of aspirin is about 2-3 hrs [3]. Once into the bloodstream, which has a more neutral pH of 7.4, aspirin is again ionized, making it water soluble, so it stays in the bloodstream until it leaks out at target tissues. Aspirin does enter the brain although it has no known blood-brain barrier transporter and it is not lipid soluble when in the blood. It probably crosses the blood-brain barrier because of its small size. It has a molecular weight of 180.15 [2] and any molecule with a molecular weight less than 500 should be able to pass through the blood-brain barrier.

During first pass metabolism in the liver, Aspirin is converted to salicylic acid via hydrolysis, a phase 1 non-synthetic reaction [3]. Only 68% of intact Aspirin makes it into the bloodstream after passing through the liver [4]. Yet, its phase 1 metabolite, salicylic acid, is

biologically active (bioactivation) and continues to have an effect. Phase 2 of aspirin metabolism is a synthetic reaction involving conjugation of glucuronic acid forming two metabolites that are highly water soluble, no longer bioactive and are readily excreted by the kidneys [3]. The half-life of Aspirin is about 5.8 hours [4]. I was unable to find the therapeutic index (TI) of this drug. However, a rough estimate was calculated from what information was available. For pain relief in humans, a dose of 1 to 2 tablets is recommended. Not to exceed 12 tablets in a day. If we assume that the lower dose of the former is the ED_{50} and the latter is the TD_{50} , then for 325 mg tablets, the TI would be $(12 \times 325) / 325$ or 12. The LD_{50} of Aspirin in rats is 1.5 g/kg. By either measure, this gives Aspirin a very large TI and accounts for its relative safety.

Drug Actions (40% of grade): *Note: Aspirin does not act on a receptor per se. If it did, here I would discuss its affinity for all the receptors it binds to along with its K_d for each receptor. I would also talk about whether it acts as an agonist, antagonist etc. I would also mention its molecular actions at the receptors.*

The primary action of Aspirin is inhibition of prostaglandins. Prostaglandins are part of a group of so-called lipid mediators called eicosanoids because they are derived from eicosatetraenoic acid, more commonly known as arachidonic acid [5]. Prostaglandins are produced in almost every tissue of the body. They are capable of directly causing vasodilation to induce swelling and acting synergistically with other chemicals to sensitize pain receptors to mechanical and chemical stimulation, thus increasing pain sensitivity. They have also been implicated in fever mediation when infused into the hypothalamus. The hypothalamus is the thermoregulatory control centre of the body, although the exact mechanism of how the prostaglandins induce fever via the hypothalamus is unknown. Finally, when produced in blood platelets, prostaglandins are a powerful inducer of blood platelet aggregation to aid in clotting.

Aspirin irreversibly binds, via covalent bond, to cyclooxygenase enzymes called COX-1 and COX-2 which are involved in the synthesis of prostaglandins from arachidonic acid. By binding to the enzyme, Aspirin blocks the channel in the enzyme and prevents arachidonic acid from entering the active site of COX-1 or COX-2. By inhibiting the synthesis of prostaglandins, Aspirin relieves the effects of pain, inflammation and fever. The irreversible bond that Aspirin makes with the enzyme allows for lower effective doses when used to prevent heart attack and stroke. Because blood platelets cannot produce new cyclooxygenase enzymes (they do not contain DNA), Aspirin's irreversible binding permanently inactivates the platelet itself. [5]

References:

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2. *The Merck Index*. Eleventh ed, ed. S. Budavari. 1989, Rahway, NJ: Merck and Co.
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4. Trnavsky, K. and M. Zachar, *Correlation of serum aspirin esterase activity and half-life of salicylic acid*. *Agents and Actions*, 1975. **5**(5): p. 549-552.
5. Koester, M.C., *An Overview Of The Physiology And Pharmacology Of Aspirin And Nonsteroidal Anti-inflammatory Drugs*. *J Athl Train*, 1993. **28**(3): p. 252-259.

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