

Editorial

Aspirin-Inspired Analgesia: Old Drug, New Mechanism, Sans Cox?

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For many centuries it has been appreciated that willow bark possesses medicinal effects. Its active component, salicylate, has a number of potentially beneficial effects, but perhaps most notable are its anti-inflammatory and analgesic effects. Aspirin and salsalate are rapidly metabolized in the plasma (e.g., plasma esterases), erythrocyte, and liver, to salicylate in vivo (1).

Hippocrates, considered by some to be the father of modern medicine (~460 B.C.-377 B.C.), reportedly left historical records of pain relief treatments, including the use of powder from the bark and leaves of the willow tree to help heal headaches, pains, and fevers. In 1826, 2 Italians, Brugnatelli and Fontana, extracted a highly impure form of the active chemical substance of willow bark. Two years later, Johann Buchner isolated a very small amount of bitter tasting yellow crystals that he called salcin. A year later French chemist Henri Leroux extracted salcin in crystalline form with a much improved procedure, yielding about 30 grams from 1.5 kg of bark. In 1838, Raffaele Piria split salcin into a sugar and an aromatic compound, salicylaldehyde. He then converted salicylaldehyde by hydrolysis and oxidation to an acid (in its pure state) called salicylic acid. In 1853, in an effort to make this compound less irritating to the gastric mucosa, Charles Frederick Gerhardt neutralized salicylic acid by buffering it with sodium (sodium salicylate) and acetyl chloride, producing acetylsalicylic acid, but he later abandoned the compound.

Maclagan (2) utilized salcin, the bitter principal of the common white willow, in an effort to diminish the pain and inflammation of rheumatic fever. Arthur Eichengrün, the head of Bayer Research Laboratories, assigned Felix Hoffman to develop a compound which was safer and more effective than salicylic acid. Hoffman rediscovered Gerhardt's work and synthesized acetylsalicylic acid. Heinrich Dreser, Bayer's chief pharmacologist, tested the new compound and described its analgesic and antipyretic effects, giving it the name aspirin (3). Aspirin was patented on February 27, 1900. For 71 years aspirin's mechanism of action remained unknown, until John Vane revealed that it inhibited the synthesis of prostaglandins (4).

As for anti-inflammatory effects, it has likely been correctly postulated that aspirin and salicylate produce anti-inflammatory inhibition of cyclo-oxygenases and thus, prostanoid synthesis (5) and also protein kinase I κ B-kinase β (IKK β) in the NF- κ B pathway (6). However, these are not necessarily the most likely mechanisms for other effects from salicylate since some of these salicylate-induced effects are still observed in mice that are deficient in these pathways (7).

Aspirin may also contribute to antinociception via: activation of adenosine A(2) receptors (8), inhibiting the inhibitor of NF- κ B (I κ B) kinase β (thereby preventing translocation of NF- κ B) to the nucleus (9); inhibition of sphingosine-1-phosphate generation (10); inhibition of α , β -methylene ATP-induced nociception (11); inhibition of acid-sensing ion channels (with high doses of aspirin) (12); acetylation of COX-2 leading to aspirin-triggered lipoxins (e.g., 15-epi-LX A4) (13); promotion of aspirin-triggered DHA pathway (e.g., neuroprotectin D1/protectin D1 which is 10R, 17R-dihydrodocosa-4Z, 7Z, 11E,

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13E, 15Z, 19Z-hexaenoic acid) (14). Resolvins (and likely resolving-like compounds) derived from DHA appear to possess antinociceptive properties (15-18).

Smith (19) has postulated still another potential mechanism that could conceivably contribute to the antinociceptive actions of aspirin-induced analgesia. He proposes that aspirin may contribute to nociception via a salicylate-induced activation of AMP Kinase (19). AMP kinase (AMPK) is a serine/ threonine protein kinase that serves as a metabolic sensor and helps regulate a cell's energy balance, shifting cellular efforts toward generating more ATP when stores run low, suggesting that activation of the energy-sensing AMP kinase may underlie some of aspirin's health benefits (20). Salicylate has been found to activate AMP kinase when applied to human embryonic kidney (HEK) 293 cells with significant effects at 1mM and above (21), as well as activate AMP kinase in colorectal cancer cell lines (20). Hawley and colleagues (21) found results suggesting that salicylate can directly activate AMPK, likely primarily by inhibiting dephosphorylation of the activating phosphorylation site, threonine-172. In AMPK knockout mice,

the effects of salicylate to increase fat utilization and to lower plasma fatty acids in vivo were lost. These results suggest that AMPK activation could explain some beneficial effects of salicylate and aspirin in humans (21).

AMP kinase can also be activated by stress and exercise as well as metformin, thiazolidinediones resveratrol, (-)-epigallocatechin-3-gallate (EGCG), and A-769622 (22-24). Preclinical models have demonstrated that activation of AMP kinase appears to produce antinociception, in part likely via attenuation of ERK and mTOR signaling in sensory neurons (24,25). AMP kinase activation may lead to diminished inhibited translational regulation signaling, modulation of eukaryotic initiation factor (eIF)4F complex formation, and reduced nascent protein synthesis in injured nerves with resultant antinociceptive effects (25).

Even if there is any validity to this proposed mechanism for aspirin-induced analgesia (AIA), it is likely only a part of the AIA story. But if modulation of AMP kinase activity contributes at all, or plays any role in AIA, it may open up the potential for novel analgesic targets.

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