Surfing the Heart

Martindale's—The Reference Desk – National Library of Medicine Gateway metaRegister of Controlled Trials – National Guideline Clearinghouse

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Martindale's—The Reference Desk

http://www-sci.lib.uci.edu/HSG/Ref.html

This extraordinary reference resource site has been maintained by James Martindale, a consultant to the University of California at Irvine College of Medicine since 1994. It covers a wide range of topics, including international business, astronomy, entertainment, and the arts. The topics are divided into different "Information Centers." The "Cardiology and Pulmonary Center" **(http://www-sci.lib.uci.edu/HSG/MedicalCardio.html)** is a comprehensive, but not always easy to use, resource about the most disparate areas of cardiopulmonary medicine: if you are searching for something unusual that is not indexed in the usual search engines, then this can be a good starting point. Are you looking for videos on physical examination or for an atlas of perfusion SPECT? Try here. Yahoo! rated this among its "50 most incredibly useful sites."

National Library of Medicine Gateway

http://gateway.nml.nih.gov

The "gateway" of the National Library of Medicine Gateway offers an interesting new possibility, which extends searching power far beyond the well-known MEDLINE/PubMed. The new databases accessed through this gateway are OldMEDLINE, MEDLINEPlus, Locator Plus, Dirline, AIDS Meetings, Health Services Research Meetings, Space Life Research Meetings and HSRProj. This tool is particularly useful for wide and unrestricted searches. For instance, entering the multiword search term "Congestive Heart Failure" results in 51 737 journal citations, 539 items for book or audiovisual materials, 117 consumer health records, 82 meeting abstracts, etc. Good work!

*meta*Register of Controlled Trials

http://www.controlled-trials.com/mrct/

Several sites provide databases of clinical trials, but the "metaRegister of Controlled Trials" (mRCT) is likely to be the richest one, with 10 875 records listed in February 2002! This is a free resource, but registration is required.

National Guideline Clearinghouse

http://www.guideline.gov/index.asp

The National Guideline Clearinghouse (NGC) is a comprehensive database of evidence-based clinical practice guidelines produced by the Agency for Healthcare Research and Quality (AHRQ) in partnership with the American Medical Association and the American Association of Health Plans. The aim of NGC site is to provide physicians, nurses, and other health professionals with accessible and objective information on clinical practice guidelines. Key components of the NGC site include summaries, a comparison tool, links to full-text guidelines, annotated bibliographies, and even an electronic discussion list. In February 2002, the guidelines relevant to cardiovascular diseases numbered 106.

All sites accessed 15 February 2002

Dialogues Cardiovasc Med. 2002;7:43

Plants and the heart

Aspirin and salicylates

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Despite its very simple structure (a hydroxyl group placed next to a carboxylic group on a 6-carbon benzene ring), salicylic acid and its derivatives are arguably one of the most popular drugs worldwide. The synthesis of its acetyl derivative (Aspirin) at Bayer, is credited with virtually launching the pharmaceutical industry and, more importantly, introducing humans to counter-top inflammation science via antipyretics, analgesia, and antiprostanoids. Salicylic acid is very corrosive, but its acetyl (and other ester derivatives) are agreeably nontoxic. Both salicylate and its various esters are found throughout in higher plants, in particularly high concentrations in willows *(Salix)*, spireas (where the "spirin" comes from), and poplars, to name a few.

While the first decoctions from willow bark may have been inspired by the Doctrine of Signatures (wherein the Good Lord provides plants growing in bogs and swamps with therapies against associated agues and fevers),[1] legendary medical greats such as Hippocrates, Galen, but also tribes worldwide, may have been inspired by careful ethnobotanical observations.

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Dialogues Cardiovasc Med. 2002;7:44-47

"Old Man Willow"

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"Great Willow (. . .) was a master of the winds, and his song ran through the woods on both sides of the river. His gray thirsty spirit drew power out of the earth and spread like fine root-threads in the ground, and invisible twig-fingers in the air, till it had under its dominion nearly all the trees of the Forest from the Hedge to the Downs."

J. R. R. Tolkien - *The Lord of the Rings*
I. The Fellowship of the Ring
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Beginning first with its use in rheumatic inflammation, salicylates proved to be beneficial against infarction and then "cardiovascular disease,"[1,2] with aspirin showing least adverse side effects. Interestingly, the favorable effects are subtle and either require huge populations, or demand that overall survival be factored into the statistics.[2-5] In our own mechanistically obsessed times, we only grow more confused as to why it works!

Cardiovascular pharmacologists initially related salicylates to a propensity for bleeding. This led to a spectacular theory of anticoagulation, discovery of platelet actions in thrombosis, and, thereafter, the individual cyclooxygenase (COX) isoforms that produce eicosanoids responsible for many inflammatory and pyretic actions were identified.[1,6]

COX-1 is the constitutively expressed enzyme and produces eicosanoids—including thromboxane A_2 (TXA_2), which is essential for platelet-induced coagulation. This isoform is irreversibly acetylated (aspirin donates its acetyl group very readily) when we take a few pills (325 to 650 mg, low dose) to produce a physiological concentration of around 100 μM.[6] COX-2, on the other hand, is induced by transcriptional promoters such as nuclear factor kappa B (NF-κB) and produces a variety of proinflammatory prostanoids, prolifically.[7,8] COX-2 is weakly inhibited by aspirin at physiological concentrations around 1 mM (intake several grams of aspirin).[1,9] Though newer and better COX-2–directed inhibitors are in vogue, aspirin remains the only inhibitor that modifies both COX enzymes covalently (by acetylation).[8] In contrast, the unacetylated salicylate can appear inactive against both isoforms when tested in broken cells or in purified forms.[1,10]

However, the synthesis of more selective drugs showed that simple acety-

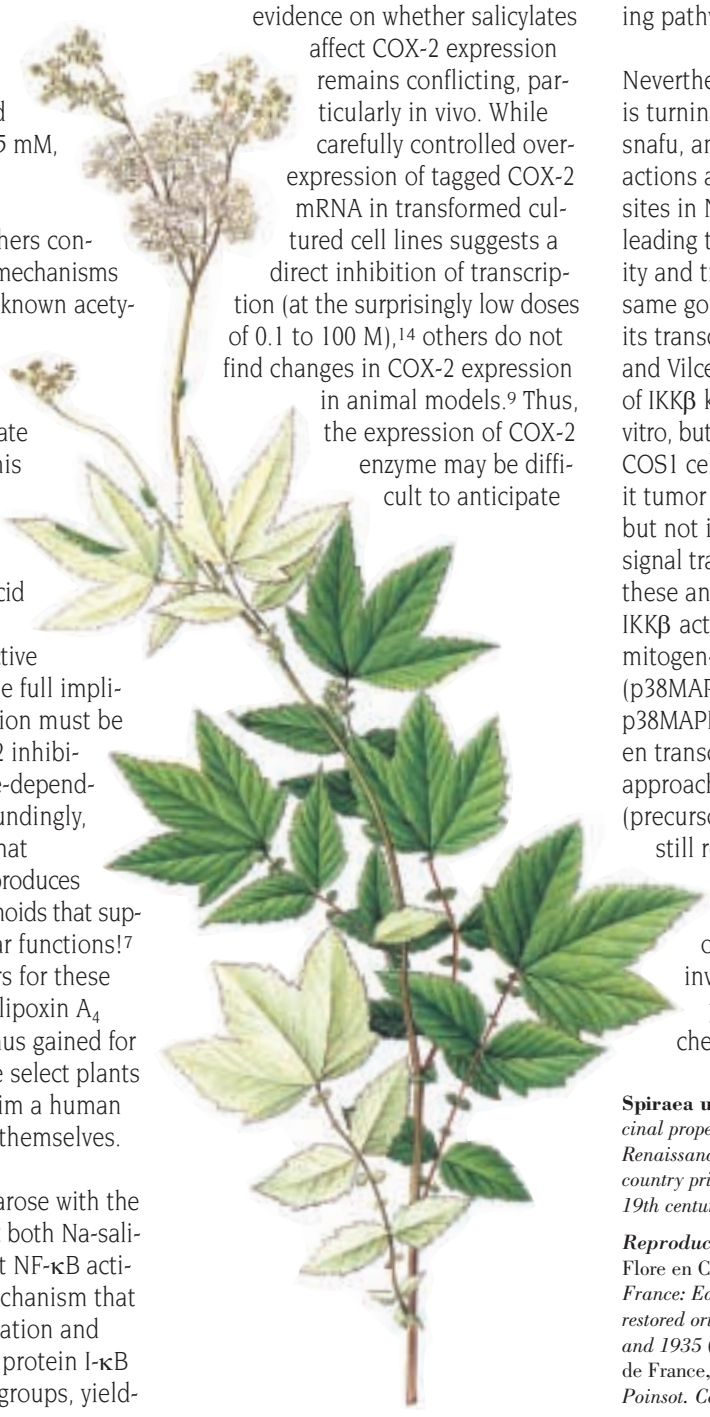
lation of COX-1 and other enzymes did not quite explain all the observations. Indeed, salicylate itself has antipyretic and analgesic effects. Many salicylate-derived drugs that are in clinical use as nonsteroidal anti-inflammatory drugs (NSAIDs) lack any acetyl group to transfer! (eg, diflunisal, salazine).[6] We may conclude that salicylate itself must be a credible anti-inflammatory agent in vivo, which, in whole cells, inhibits COX-1 and -2 at about 2 μM and <0.5 mM, respectively.[9]

Vane's coworkers and others continue to find interesting mechanisms that go beyond the well-known acetylation mechanism.[2] Mitchell showed that the presence of arachidonic acid causes salicylate to inhibit very weakly. This interpretation fits well with the crystal structure of COX-2, which shows that arachidonic acid can bind in a channel at the base of the COX-2 active site.[9] Mechanistically, the full implications of COX-2 inhibition must be incomplete, since COX-2 inhibition involves subtle time-dependent kinetics.[8] Most astoundingly, Serhan and Oliw show that aspirin-modified COX-2 produces anti-inflammatory eicosanoids that suppress polymorphonuclear functions![7] Indeed, specific receptors for these aspirin-triggered lipids (lipoxin A_4 receptor [ALXR]) have thus gained for aspirin a rank among the select plants that can legitimately claim a human protein christened after themselves.

A radical line of inquiry arose with the seminal observation that both Na-salicylate and aspirin inhibit NF-κB activation in vitro.[11] The mechanism that prevents the phosphorylation and degradation of inhibitor protein I-κB was attacked by several groups, yielding a selective blockade of an upstream I-KK kinase (IKKβ, at its ATP-binding site),[12] that was reported amidst great ferment. And justifiably so, since influencing NF-κB transcription would have a big impact on not only an extremely wide variety of inflammatory mechanisms in vivo, but, pertinently, on COX-2 expression as well.[13] However, evidence on whether salicylates affect COX-2 expression remains conflicting, particularly in vivo. While carefully controlled overexpression of tagged COX-2 mRNA in transformed cultured cell lines suggests a direct inhibition of transcription (at the surprisingly low doses of 0.1 to 100 M),[14] others do not find changes in COX-2 expression in animal models.[9] Thus, the expression of COX-2 enzyme may be difficult to anticipate from a single transcription factor such as NF-κB, and, in fact, Xu et al[14] did decipher an upstream site (192-2) that is different from the two NF-κB consensus sites upstream of COX-2. Indeed, some workers have shown that salicylates may inhibit activation of activator protein–1 (AP-1), and affect several other COX-independent signaling pathways as well.[13]

Nevertheless, the activation of NF-κB is turning into major mechanistic snafu, and not only because of interactions among promoter sites. Novel sites in NF-κB are phosphorylated, leading to subtle changes in its stability and transcriptional efficacy.[15] The same goes for upstream elements of its transduction cascade.[12,15] Alpert and Vilcek[16] reproduced the inhibition of IKKβ kinase activity by salicylate in vitro, but found, at least in transformed COS1 cells, that salicylates only inhibit tumor necrosis factor alpha (TNFα), but not interleukin–1 (Il-1)-stimulated signal transduction to IKKβ. Curiously, these and other authors[16,17] find that IKKβ activation is inhibited by p38 mitogen-activated protein kinase (p38MAPK), but others suggest that p38MAPK is necessary for NF-κB driven transcription.[15] Or is the whole approach moot, since p105 knockouts (precursor for a NF-κB subunit) are still repressed by salicylates?[18]

Shaking the bushes harder, other mechanistically inclined investigators recognized the potent antioxidant and metal chelation properties of the adja-



Spiraea ulmaria *(meadowsweet):* *its medicinal properties were already known during the Renaissance, but were forgotten until a French country priest rediscovered them in the early 19th century.* Spiraea *gave its name to aspirin.*

Reproduced from: *Gaston Bonnier.* La Grande Flore en Couleurs, *plate 169, No. 905. Paris, France: Editions Belin; 1990. Reprint of the restored original edition published between 1911 and 1935* (Flore Complète Illustrée en Couleurs de France, Suisse et Belgique), *colored by Julie Poinsot. Copyright © 1990, Editions Belin.*

cent phenol and benzoic acid groups and have sporadically championed therapeutic mechanisms based on these.[19]

And why not? At concentrations close to millimolar in the plasma (and probably intracellularly), and given that a significant fraction of the cell volume is occupied by large proteins and organelles, local concentrations of salicylate might be orders of magnitude higher. The consequence of this powerful binding group sandwiching itself between with dozens of residues interacting at protein-protein binding surfaces or at catalytic sites could be mechanistically diverse.

In short, significant concentrations of salicylate probably affect large numbers of pathways, albeit to a small degree. It is the cumulative impact on several vulnerable pathways that, say: (i) somewhat inhibits transcription for an enzyme; (ii) that enzyme is weakly inhibited; but (iii) then proceeds to manufacture anti-inflammatory agents! Interestingly, these large studies continue to confound individual (mechanistic) outcome measures, but instead prove overall survival.[2-5]

After midwifing the pharmacological industry, the arenas of prostaglandins, coagulation, COX IKK, and more recently Q-waves, angiotensin II (AT-II) signaling, and breast and colon cancer,[2,6] salicylates have more to teach us, I should think. Perhaps we need to look again to the plant. Plants lack a beating heart and circulatory system. Each cell must fend for itself as best as it can against infection. The best they can do for the organism is to convey "under attack signals" throughout the plant. This is why plants produce diffusible salicylates: to boost resistance gene expression in concert with reactive oxygen species (ROS) and

Branch of* Salix alba *(common willow): *its bark was used for its febricide properties as early as the 17th century.* Salix *gave its name to salicylic acid.*

Reproduced from: *Gaston Bonnier.* La Grande Flore en Couleurs, *plate 561, No. 2526. Paris, France: Editions Belin; 1990. Reprint of the restored original edition published between 1911 and 1935* (Flore Complète Illustrée en Couleurs de France, Suisse et Belgique), *colored by Julie Poinsot. Copyright © 1990, Editions Belin.*

nitric oxide (NO)-related amplificatory loops.[20] Indeed, plants utilize versions of the NF-κB[21] and COX[22] genes to mount their systemic defense mechanisms.[20]

Perhaps Old Man Willow will next make us wonder if the Doctrine of Mechanism is getting up there with the Doctrine of Signatures or the Quantification of Angels Dancing on a Pinhead?

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