Aspirin – an Exceptional Supplement

Aspirin (acetylsalicylic acid) is included here not because it is a very old and familiar pain remedy that most people would find difficult to do without and not because it has become a daily requirement, much like a vitamin pill, by virtue of being prescribed in baby aspirin form to prevent cardiovascular disease. Rather, aspirin is included here because it has been shown to play a unique and vital in role eicosanoid metabolism.

This new role of aspirin in eicosanoid metabolism was unraveled only a decade ago by Serhan and co-investigators (93). They found that aspirin does not do what pharmaceutical science thought it did; it does *not* inhibit the COX-2 enzyme. This profound revelation has apparently not yet found its way into the data base of medical science.

What is the significance of COX-2 inhibition? As will be explained in Chapter Nine, COX-2 is the enzyme that causes pain by transforming arachidonic acid into proinflammatory eicosanoids. It was discovered several decades ago that aspirin exerted its analgesic effects by preventing the COX-2 enzyme from making proinflammatory eicosanoids from arachidonic acid (94). Pharmaceutical science assumed this meant that aspirin prevented pain by inhibiting (inactivating) the COX-2 enzyme and stopping its action.

Serhan's eicosanoid research has now revealed that aspirin does *not* inhibit COX-2 enzyme but rather changes it chemically and makes it operate in a contradictory manner; instead of metabolizing arachidonic acid to proinflammatory, pain-producing eicosanoids, the aspirin-modified COX-2 enzyme metabolizes arachidonic acid to *anti-inflammatory* eicosanoids. The beneficial effect of this unique biochemical mechanism is of immeasurable significance that is yet to be fully understood. From very unremarkable beginnings, aspirin is emerging a major participant in eicosanoid metabolism.

The story of aspirin starts with the methyl ester of salicylic acid, the principle ingredient of oil of wintergreen obtained from natural sources such as willow bark. Oil of wintergreen is a centuries-old liniment for the aches and pains of rheumatism. However, because of its considerable toxicity, it could not be taken internally. Throughout the decades, many derivatives of salicylic acid were synthesized in an effort to find a less toxic painkiller that would be acceptable for internal use. Some, including salicylic acid itself, were used internally and found to be very effective in relieving pain, but they were difficult to tolerate because of unpleasant side effects.

In the mid-nineteenth century, the acetic acid derivative of salicylic acid was synthesized by a chemist at the German chemical company now known as Bayer. Bayer patented the process for making acetylsalicylic acid and the name they gave it (Aspirin) in 1899. In the 100-plus years since aspirin was introduced to the public, it has become the most widely used medication in the world with a yearly production of 50,000 tons and a daily consumption by Americans of about 80 million tablets per day. It was acclaimed as the wonder drug of the twentieth century and is expected to be such for the twenty-first century (95). It is estimated that the 10,000 deaths that occur each year from cardiovascular disease could be prevented if the victims took aspirin on a regular basis (96, Introduction).

After 1982, when the Nobel Prize in Physiology and Medicine was awarded to Sune Bergstrom, Bengt Samuelsson, and Sir John Vane for "their discoveries concerning prostaglandins and related biologically active substances" (94), aspirin became the model for the class of pharmaceuticals known as NSAIDs (nonsteroidal anti-inflammatory drugs). The Nobel Laureates, in essence, explained that the beneficial effects of aspirin were due to its ability to prevent conversion of arachidonic acid to inflammatory prostaglandins by cyclooxygenase, the enzyme now known to the general public as COX enzyme. Thus began a massive program by the pharmaceutical industry to develop COX inhibitors (NSAIDs) as competitors for the nonpatentable aspirin.

During NSAID development, it was discovered that the COX enzyme has two forms: COX-1and COX-2. It was also discovered that COX-1 is the constitutive form that protects against stomach bleeding and that COX-2 is the inducible form that causes the pain of illness or injury. The ultimate goal of the pharmaceutical effort was to find drugs that would inhibit only COX-2 without interfering with the ability of COX-1 to protect against stomach bleeding.

Thus far, no NSAID acceptable for over-the-counter sale has been found that will inhibit only the COX-2 enzyme and not the COX-1. The effects of aspirin on COX-1 enzyme have not yet been fully elucidated but, thus far, they seem to be similar to the effects of other NSAIDs. As a result, stomach bleeding is a potential adverse effect of all current NSAIDs. However, despite the similarity, it has been demonstrated that the anticoagulant effect of aspirin in heart attack prevention, which is a COX-1 effect, are provided only by aspirin and not by any other over-the-counter NSAIDs.

A review of the literature by Heiby cites an interesting experiment on rats that perhaps sheds some light on the risk of stomach bleeding. Aspirin caused stomach bleeding in more rats fed a high carbohydrate diet than in rats fed a high protein diet. Gastric ulceration was very severe on the high carbohydrate diet (93). On the basis of these

animal studies, it is interesting to speculate that the apparent increase over the last half-century in the risk of stomach bleeding due to aspirin may be the result of the large increase in dietary carbohydrate intake during the same period.

In the last few decades many NSAIDs have been synthesized, most of which are available only by prescription. A small number of NSAIDs that have relatively few side effects, such as ibuprofen and naproxen, are available as over-the-counter painkillers. However, to date, none have been found to be more effective or safer than aspirin, and a few have been recalled because of unacceptable adverse effects. The reason for the difference between aspirin and aspirin copies is gradually being revealed by the research of Charles Serhan and colleagues.

A major difference between aspirin and NSAIDs is that they relieve pain by dissimilar biochemical mechanisms. NSAIDs prevent formation of proinflammatory eicosanoids from arachidonic acid by inhibiting COX-2 activity, but they do not prevent arachidonic acid from being diverted to other proinflammatory pathways. Aspirin, in contrast, modifies the structure of COX-2 by acetylating it, which, in turn, uses arachidonic acid to make anti-inflammatory eicosanoids; arachidonic acid is used rather than being diverted to other proinflammatory pathways (97; 98). This difference in mechanism removes aspirin from the NSAID category and helps explain why aspirin has beneficial effects, such as cardiovascular protection, not afforded by NSAIDs and why NSAIDs have adverse effects not seen with aspirin.

As important as aspirin is in its fundamental role in modifying inflammatory eicosanoid pathways, perhaps of even greater consequence for the health and well being of present and future generations are the more recent discoveries of the hitherto unsuspected role of aspirin in resolution (the healing process) and the unanticipated existence of whole new classes of aspirin-derived anti-inflammatory eicosanoids that have been revealed by the research into aspirin's mechanism of action (see Chapter Nine).

References

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