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MEDICINE

Interactions with Iron Can Explain Anti-Cancer Effects of Aspirin

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Long-term use of low-dose aspirin at 75 mg daily or more is associated with remarkable decreases in the incidence of a number of different cancers.[1] Meta-analyses have found reductions in cancer death overall of 21%, and benefit increased with duration of use, with cancer deaths decreasing by 31% with greater than 7.5 years of aspirin use. Gastrointestinal cancer deaths were 59% lower with aspirin use of greater than 7.5 years.

What accounts for this remarkable decrease in cancer deaths? Most explanations have focused on the ability of aspirin to inhibit cyclooxygenase-1 and -2. (COX-1 and -2).[2]

However, little attention has been paid to the ability of aspirin to both lower body iron stores and to chelate free iron.

Iron is a demonstrated carcinogen in numerous animal studies, and can be a considered a ferrotoxic disease.[3] In humans, excess iron is a risk factor for cancer, and lowering iron levels can reduce the risk of cancer.[4]

Long-term aspirin use lowers body iron stores.[5] Serum ferritin values in regular aspirin users have been found to be from 20 to 50% lower than in non-users.

The mechanism suggested for lower iron stores with aspirin use is mucosal blood loss. Since aspirin also inhibits platelet function, small blood losses, unnoticed by the person, may occur that lead to lower iron stores over the long term. Even a daily loss of 1 ml of blood might substantially alter iron stores over time.

However, aspirin may lower iron stores in another, more direct way, and this possibility does not seem to have been considered. That way is by direct iron chelation.

A standard laboratory method for the analysis of aspirin in fluids is to acidify it and add excess ferric chloride. Acidification causes the deacetylation of aspirin to salicylate, which then forms a colored complex with iron, and which can then be measured spectrophotometrically.[6]

In vivo, aspirin is rapidly deacetylated to salicylate.[7] Therefore it would be capable of reacting with free iron.

Are the conditions *in vivo* suitable for reaction with iron? It appears so.

Bacterial iron requirements are often met by the secretion of siderophores, small molecules that bind iron which can then be used by the bacteria for growth. Several species of *Pseudomonas* produce a siderophore which turned out to be none other than salicylate.[8] So physiological conditions are appropriate for the binding of aspirin-derived salicylate with iron.

Mycobacterium tuberculosis also uses salicylate to sequester iron *in vivo*, and in fact an older anti-tuberculosis drug, para aminosalicylate, works by withholding iron from mycobacteria.[9]

Additionally, the salicylate-iron complex has superoxide dismutase activity, and its ability to remove superoxide radicals could account for much of its anti-inflammatory as well as anti-cancer effects.[10]

The molar mass of aspirin is 180 g/mol, while that of iron is 55. One molecule of aspirin produces one of salicylate, which then reacts on a one to one basis with an atom of iron. It can be seen that the ingestion of 75 mg of aspirin daily has the theoretical potential to eliminate ~25 mg of iron, a large amount exceeding the estimated daily intake of approximately 20 mg a day for both men and women in the U.S. Therefore long-term aspirin use could result in a large decrease in body iron stores.

Much of aspirin's benefit in decreasing cancer incidence may be due to its ability to lower body iron stores, and much of this in turn may be due to the chelation of iron.

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