Dietary salicylates

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Another benefit of fruit and vegetable consumption?

There is overwhelming epidemiological evidence that a high consumption of fruit and vegetables is associated with reduced mortality from cardiovascular disease, cancer, and other causes.¹⁻⁵ In part, this may simply indicate that high fruit and vegetable consumption is a marker of a healthy lifestyle, but there is also strong evidence from *in vitro* studies and clinical trials that micronutrients and other components of fruit and vegetables have beneficial biological effects.⁶⁻⁸ Most attention has focused on antioxidants, B group vitamins, minerals, and fibre, but several strands of evidence now indicate that increased intake of salicylates may be another benefit of fruit and vegetable consumption.

In this issue of the journal, Lawrence and colleagues show that urinary excretion of salicylic acid (SA) and salicylic acid (SA) is significantly increased in vegetarians compared with non-vegetarians.⁹ They previously reported that serum SA was also significantly increased in vegetarians compared with non-vegetarians.¹⁰ Interestingly, urinary excretion of SA was similar in vegetarians and patients consuming 75 or 150 mg of aspirin/day, although SU excretion was substantially greater in the aspirin groups.

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After oral administration, aspirin (acetylsalicylic acid) is rapidly absorbed in the upper gastrointestinal tract.¹¹ This drug follows first order kinetics and has an absorption half life of five to 16 minutes.¹² Aspirin is mainly absorbed unchanged from the lumen of the gastrointestinal tract, but is rapidly hydrolysed to salicylate by carboxylesterases in the gut wall and liver, so that only 68% of the dose reaches the systemic circulation as acetylsalicylic acid.¹²⁻¹⁵ Salicylate and acetylsalicylate are extensively bound to serum albumin (~50–80%) and are distributed in the synovial cavity, central nervous system, and saliva. The serum half life of acetylsalicylate is 20 minutes, and the decrease

in concentration after this time is paralleled by a concurrent rise in salicylate concentrations,¹² the half life of which is between two and 30 hours, depending on concentration. SA is metabolised through glucuronide formation, conjugation with glycine, and oxidation to produce SU, salicyl phenolic glucuronide, salicyl acyl glucuronide, gentisic acid, and gentisuric acid.¹²⁻¹⁵ The kidney eliminates salicylates. The major urinary metabolites are SU (80%) and salicyl phenolic glucuronide (10%), but SA is also partially excreted unchanged (5%).¹⁴

Despite the fact that aspirin has been in routine use for almost a century, there is still no common agreement about its mechanisms of action. Aspirin acts by preventing the conversion of arachidonic acid to the cyclic prostenoids via inhibition of the enzyme cyclooxygenase (COX) through acetylation of an essential serine at its active site.¹¹⁻¹⁵ There are two main COX isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in most cells (including platelets) and, among other functions, is essential for the production of thromboxane A₂, which causes platelet aggregation.¹⁴ COX-2 is not routinely expressed in cells, but is induced rapidly by inflammatory stimuli and growth factors,¹¹ and is the major isoform responsible for prostaglandin biosynthesis in inflamed tissue. Aspirin acts on both forms but is a less potent inhibitor of COX-2.¹⁶ Inhibition of COX-1 is achieved by acetylation of serine 530, which is located close to the active site (tyrosine 385 of COX-1). Acetylation of this serine residue hinders the access of arachidonic acid to the active site. Aspirin inhibits COX-2 by a similar mechanism, but is less potent because the substrate channel of COX-2 is larger and more flexible than that of COX-1.¹⁶ Mitchell *et al.*, using a variety of *in vitro* models, suggested that aspirin inhibition of COX-1 was between 25 and 166 times greater than inhibition of COX-2.¹⁷

In contrast to aspirin, salicylic acid has virtually no effect on purified COX-1 and COX-2 at pharmacological concentrations, but inhibits prostaglandin synthesis in intact cells.¹⁸ The mechanism by which salicylic acid inhibits COX-2 is the subject of much current debate.¹¹⁻²³ One possibility for which there is experimental evidence is that salicylic acid at

therapeutic concentrations may suppress COX-2 gene transcription by inhibiting COX-2 mRNA synthesis and COX-2 promoter activity.¹⁶⁻¹⁸ As such, with respect to its role as an anti-inflammatory agent, aspirin could be acting as a prodrug for salicylic acid, which has a much longer half life than aspirin.²⁴

The presence of naturally occurring salicylates in fruits, vegetables, spices, confectionaries, and beverages (both alcoholic and non-alcoholic) has been confirmed by several research groups,²⁵⁻²⁹ although concentrations determined do not always agree. Swain *et al.* suggested that a normal mixed diet contains total salicylates in the range of 10 to 200 mg/day,²⁶ although other groups have suggested that this may be an overestimate owing to a lack of analytical specificity.²⁷⁻²⁸ Janssen *et al.* suggested that intake of dietary salicylates in subjects taking a mixed diet was only in the order of 2 to 4 mg/day, an amount probably too low to affect disease risk.²⁸ However, the work reported here⁹ and previously¹⁰ indicates that dietary salicylate intake may be significant in vegetarians and can produce concentrations of SA that overlap with those seen in subjects taking 75 mg of aspirin/day. Because the anti-inflammatory action of aspirin is probably the result of SA,²⁴ and the concentrations of SA seen in vegetarians have been shown to inhibit COX-2 *in vitro*,¹⁸ it is plausible that dietary salicylates may contribute to the beneficial effects of a vegetarian diet, although it seems unlikely that most people who consume a mixed diet will achieve sufficient dietary intake of salicylates to have a therapeutic effect.

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