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COMMENTARY

Allopurinol for pain relief: more than just crystal clearance?

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Gout and pain are synonymous, and a study in this issue of the *BJP* reports a novel anti-nociceptive effect of allopurinol, the drug most commonly used to treat gout. Allopurinol works by inhibiting xanthine oxidase (XO), the enzyme responsible for converting hypoxanthine to uric acid which is deposited as crystals in the joints of gout sufferers. Hypoxanthine is a metabolite of, and a possible precursor to, adenosine. Schmidt *et al.*, find that acute inhibition of XO with allopurinol produces a modest adenosine A_1 receptor-mediated anti-nociceptive effect in common tests of chemical and thermal nociception in mice. A concomitant increase in cerebrospinal fluid levels of adenosine supports their hypothesis that inhibiting XO increases adenosine levels via salvage from hypoxanthine. Elevating endogenous adenosine levels by inhibiting metabolism is a well-established strategy for producing anti-nociception in many preclinical models, but inhibiting XO is likely to be particularly beneficial in some chronic pain states because of the pro-nociceptive reactive oxygen species that are produced by XO activity. Thus, allopurinol may have unexpected benefits in pain associated with chronic inflammation, diabetes and vascular dysfunction.
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Abbreviations: ROS, reactive oxygen species; XO, xanthine oxidase

Allopurinol is the first-line treatment for gout, a painful condition caused by the deposition of crystals of uric acid in joint cartilage. Allopurinol and its major metabolite oxypurinol inhibit xanthine oxidase (XO), the enzyme responsible for the formation of uric acid from hypoxanthine and xanthine (Pacher *et al.*, 2006). XO is a ubiquitously expressed enzyme that metabolises an array of endogenous and xenobiotic compounds, and it is notable for its capacity to generate reactive oxygen species (ROS) – superoxides and peroxides. ROS generated by XO have been implicated in a wide variety of pathophysiological processes including diabetes, ischaemia-reperfusion injury and chronic heart failure (Pacher *et al.*, 2006). Recently, chronic allopurinol inhibition of XO-generated ROS has been suggested to inhibit symptoms of painful diabetic neuropathy in rats (Inkster *et al.*, 2007) and in the present issue of the *BJP*, Schmidt *et al.* (2008) report that allopurinol shows acute anti-nociceptive activity against a variety of noxious stimuli in mice. Most interestingly, the effects of allopurinol in this study are not ascribed to inhibition of ROS generation, but to activation of adenosine A_1 receptors following elevation of adenosine levels by allopurinol.

The data are quite straightforward, administration of allopurinol rapidly and dose-dependently inhibits nociceptive responses produced by injection of capsaicin or glutamate into the mouse paw, as well as increasing the time it takes for the mouse to react to heating its tail or being placed on a hot surface. The effects of allopurinol are in each case reversed by the specific adenosine A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) and unaffected by the adenosine A_{2a} receptor antagonist 5-amino-2-(2-furyl)-7-phenylethyl-pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5*c*]pyrimidine (SCH58261). Parallel experiments measured significantly increased concentrations of adenosine (and other purines) and decreased levels of uric acid in the cerebrospinal fluid of the mice following allopurinol dosing. The maximal anti-nociception produced by allopurinol was less than that produced by a moderate dose of morphine in each assay other than the tail flick test of thermal nociception, but this lack of profound acute activity dose not detract from the potential of XO inhibitors contributing to analgesic regimens in chronic disease.

The study of Schmidt *et al.* (2008) seems to be the first to demonstrate acute anti-nociception with allopurinol and

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many questions remain about how this may be happening. First, a direct interaction of allopurinol or oxypurinol with adenosine A_1 receptors has not been ruled out. Although there is no published evidence to support the possibility, allopurinol is a simple purine analogue and such interactions cannot be discounted. Second, the precise mechanism by which allopurinol elevates adenosine levels remains unclear. The authors suggest that the increases in adenosine produced by allopurinol may result from metabolic salvage pathways utilizing the elevated amounts of hypoxanthine resulting from XO inhibition but they provide no direct evidence to support this contention. Allopurinol, oxypurinol and their metabolites inhibit other enzymes involved in purine metabolism (Takano *et al.*, 2005), and these interactions cannot be excluded from the possible mechanisms involved in elevating adenosine levels. Third, the authors do not provide any evidence that adenosine levels are changing in regions important for adenosine-mediated anti-nociception, whether they be the periphery, spinal cord or brain. Finally, it remains possible that some of the effects of allopurinol are mediated by inhibiting the generation of ROS by XO, as a reduction in the levels of these pro-nociceptive mediators may potentiate adenosine A_1 receptor-mediated anti-nociception, independently of a change in adenosine levels. None of these questions are unanswerable and the availability of non-purine-based XO inhibitors such as febuxostat (Bruce 2006; Pacher *et al.*, 2006) will be very helpful in addressing these issues.

The idea of using drugs that modulate the levels of endogenous neurotransmitters by inhibiting degradation or transport out of the extracellular space is a venerable one. Adenosine levels rise in spinal cord following a noxious stimulus and are also elevated at sites of inflammation, and agents inhibiting another major adenosine metabolizing enzyme, adenosine kinase (AK), are very effective antinociceptive agents in a wide range of pain models (Jarvis *et al.*, 2002; Sawynok and Liu, 2003). Inhibitors of adenosine transport or an alternative enzyme for adenosine metabolism, adenosine deaminase, are less effective (Sawynok and Liu, 2003). XO lies downstream of adenosine deaminase and it is perhaps not surprising that adenosine-mediated analgesia following allopurinol administration is not as profound as that produced by AK inhibitors, although it would be useful to compare them directly, and also in combination. It would also be interesting to determine the effects of allopurinol in other types of preclinical pain models, particularly chronic inflammation or neuropathic pain, situations where ROS may play a more prominent role in the pathology and where AK inhibitors have proven efficacy (Jarvis *et al.*, 2002).

Could these results have any implications for treatment of human pain? There does not seem to be any evidence that allopurinol provides acute pain relief in gout, although it is not clear that analgesic effects *per se* have been considered alongside the uric acid lowering, disease modifying, effects of the drug, probably because allopurinol therapy is not started until after an acute attack subsides. The analgesic effects of allopurinol have been examined in pancreatitis, but these small trials provide little useful information (Salim, 1991; Banks *et al.*, 1997). Allopurinol is a generally safe drug, with well-recognized unwanted effects, and it is often taken safely for many years. It is tempting to speculate that it or other XO inhibitors may provide useful adjunct therapies in chronic diseases such as sickle cell anaemia and diabetic neuropathy, where its possible dual actions on ROS and adenosine levels may be particularly helpful in improving vascular endothelial function and limiting pain (Inkster *et al.*, 2007, Wood and Granger, 2007). Allopurinol may also be a useful agent to combine with other analgesics which act predominantly on non-adenosine systems. A caveat on this speculation is that both XO function (Pacher *et al.*, 2006) and the constituents of the purine salvage pathways are likely to differ between humans and experimental animals. Of course, the major unresolved question regarding the use of allopurinol to modify adenosine receptor function in the human nervous system is whether therapeutic doses of allopurinol change adenosine concentrations in brain at all, let alone sufficiently to produce analgesia.

Allopurinol was synthesized as part of the Burroughs Wellcome programme to develop purine analogs as antibacterial and chemotherapeutic agents and it was originally utilized for its capacity to inhibit 6-mercaptopurine degradation by XO (Elion *et al.*, 1963). The present study of Schmidt *et al.* (2008) is at very least a pharmacological curiosity, where an old drug is revealed to have an unexpected but not implausible effect. Whether the observed anti-nociceptive effects of allopurinol extend to other murine pain models or to other species is well worth exploring, and it will be interesting to see the degree to which potentiation of adenosine signalling and/or inhibition of ROS generation contributes to any anti-nociceptive effects. The more selective inhibitors of XO now available will help in teasing out these mechanisms, and they too may turn out to have clinical uses not foreseen by their developers. Regardless of the eventual outcome, this study illustrates the potential benefits of a little lateral thinking and it may provide an unexpected footnote to one of the most famous and fruitful programmes of drug discovery.

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Conflict of interest

None.

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