ANTI-INFLAMMATORIES

No bones about it

Ones bones get more brittle with increasing age, and to add insult to injury, the most effective therapy for another problem that is associated with getting older, rheumatoid arthritis, often adds to the problem by causing bone resorption. The glucocorticoid steroids, such as hydrocortisone, are the best available anti-inflammatories, and are used widely in the treatment of arthritis, as well as in other inflammatory conditions such as dermatitis and autoimmune disease. But up to half those on chronic steroid therapy suffer bone fractures as a result of decreasing bone mass. Glucocorticoid drugs with less dire side effects are sorely needed.

Mauro Perretti and colleagues now report that a nitric oxide (NO)-releasing derivative of the commonly used steroid prednisolone can reduce inflammation in a rat model of arthritis without promoting the bone resorption that is characteristic of treatment with normal prednisolone. The new compound, nitro-prednisolone or NCX-1015, releases free NO on contact with biological fluids, and the authors have previously shown NCX-1015 to be more effective than prednisolone at reducing acute inflammation in animal models. Although the mechanism that underlies the increased anti-inflammatory potency of NCX-1015 remains unclear, they suggest that glucocorticoids and NO reinforce each others actions, inhibiting the expression of inducible genes under the regulation of the transcription factor nuclear factor-κB (NF-κB).

In the present study, the authors compared the effects of equimolar doses of prednisolone and NCX-1015 on collagen-II-induced arthritis (CIA) in rats. Although prednisolone significantly reduced the signs of induced inflammation, NCX-1015 produced an almost complete ablation of the inflammatory response. The degree of loss of bone mass after the two treatments was assessed both by histological analysis and by measuring the circulating levels of pyridinoline, a metabolite that is indicative of bone resorption. Although signs of bone resorption were apparent in both control-treated CIA and prednisolone-treated CIA rats, NCX-1015 treatment resulted in normal histology and normal levels of pyridinoline. NCX-1015 therefore seems to have bone-sparing properties, at least in inflammatory situations.

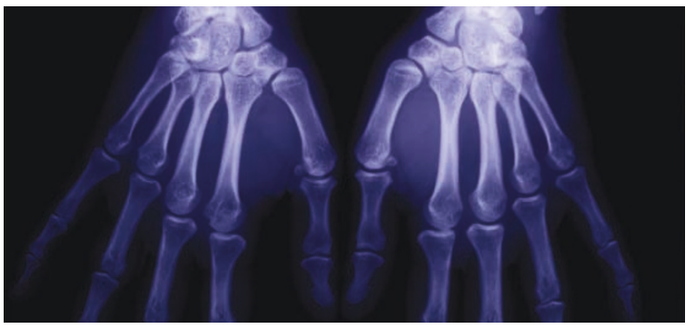
NO is known to regulate the activity of osteoclasts — cells that actively reabsorb bone — which might explain the normal histology and reduction in serum pyridinoline levels that were observed after NCX-1015 treatment in the CIA model. On the basis of this study, NO-donor glucocorticoids seem to offer the possibility of effective anti-inflammatory therapy without at least some of the serious side effects that are associated with prednisolone.

Adam Smith

References and links

ORIGINAL RESEARCH PAPER Paul-Clark, M. J. *et al.* Potent antiarthritic properties of a glucocorticoid derivative, NCX-1015, in an experimental model of arthritis. *Proc. Natl Acad. Sci. USA* **99**, 1677–1682 (2002)

WEBSITES **NicOx:** http://www.nicox.com/
William Harvey Research Limited: http://www.williamharvey.co.uk/



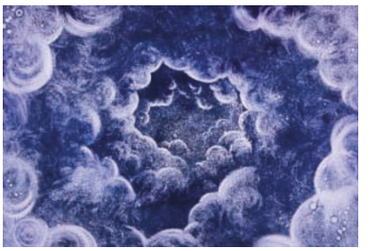
IN BRIEF

ANALGESIA

DREAM is a critical transcriptional repressor for pain modulation

Cheng, H.-Y. M. *et al*. *Cell* **108**, 31–43 (2002)

Effective management of chronic pain remains a major clinical challenge. Building on previous research, which indicated that DREAM (downstream-regulatory-element antagonistic modulator) is a transcriptional repressor that modulates the levels of the endogenous opioid dynorphin, Cheng *et al.* show that mice that lack DREAM have markedly reduced pain in various models owing to elevated levels of dynorphin, but seem otherwise normal. So, drugs that block the ability of DREAM to bind to DNA, or prevent the production of DREAM, could potentially be useful in pain management.



KIDNEY DISEASE

A chemokine receptor CCR-1 antagonist reduces renal fibrosis after unilateral ureter ligation

Anders, H.-J. *et al. J. Clin. Invest.* **109**, 251–259 (2002)

In the kidney, tubulointerstitial fibrosis is the main predictor for the progression to end-stage renal failure. Expression of chemokines and their receptors is thought to contribute to leukocyte infiltration and fibrosis after unilateral ureter obstruction (UUO). In a mouse model, nonpeptide antagonists of the chemokine receptor CCR1 could reduce leukocyte infiltration and fibrosis after UUO. Markers of renal fibrosis were all significantly reduced by CCR1-antagonist treatment compared with controls. CCR1 blockade could represent a new therapeutic strategy for reducing cellular infiltration and fibrosis as principal factors in the progression to renal failure.

NEURODEGENERATIVE DISEASE

Prolonged survival and decreased abnormal movements in transgenic model of Huntington disease, with administration of the transglutaminase inhibitor cystamine

Karpuj, M. V. *et al. Nature Med.* **8**, 143–149 (2002)

Huntington's disease (HD) is caused by an expanded polyglutamine domain in the protein huntingtin. The enzyme transglutaminase (TGase) has been proposed to have a crucial role in the pathogenesis of the trinucleotide-repeat diseases, by cross-linking huntingtin. In a mouse model of HD, administration of the TGase competitive inhibitor cystamine improved the course of the disease. The treatment increased transcription of a neuroprotective gene for polyglutamine toxicity. Inhibition of a TGase could provide a new treatment strategy for HD and other polyglutamine diseases.