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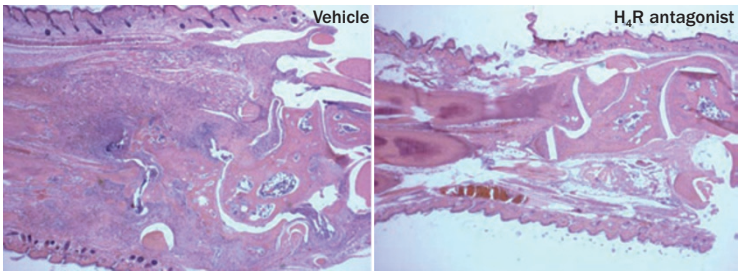
EXPERIMENTAL ARTHRITIS

Antihistamines as treatments for autoimmune disease?



H&E staining of paws from mice with CIA. Reduced inflammation and damage is evident in the H_4R-antagonist-treated mouse versus the vehicle-treated mouse. Image courtesy of Robin L. Thurmond.

Research from San Diego, published in the *Annals of the Rheumatic Diseases*, shows that histamine is not only involved in allergies but that it also has a role in potentiating inflammation in experimental inflammatory arthritis. As Robin Thurmond, the lead author on this paper explains: "There has been literature showing that histamine appears to be increased in arthritic joints, but I think this was dismissed as being unimportant. Our work shows that histamine, acting via the H_4 receptor, amplifies both the innate and adaptive immune responses that underlie the disease."

The researchers investigated the role of histamine$_4$ receptor (H_4R) in the development of autoimmune arthritis (CAIA; collagen antibody-induced arthritis) and inflammatory arthritis (CIA, collagen-induced arthritis) in studies involving H_4R-deficient mice or an H_4R antagonist (JNJ 28307474).

In the CAIA model, H_4R-deficient and H_4R-antagonist-treated mice developed less severe disease than the wild-type or vehicle-treated mice; disease scores were lower, and levels of inflammation, pannus formation, and bone and cartilage damage were reduced. Similar results were seen in the CIA model. Treatment with the H_4R antagonist resulted in a dose-dependent reduction in disease severity compared with vehicle-treated mice, as confirmed by histological examination (see figure). Of 12 H_4R-deficient mice, only seven developed inflammatory arthritis (score >2) in comparison with the wild-type mice who all developed disease. After 14 days, two of the H_4R-deficient mice had fully recovered (score <2), whereas the disease scores remained unchanged in the wild-type mice. Disease severity in wild-type mice with established disease was reduced after treatment with an H_4R-receptor antagonist.

These findings indicate a role for histamine, via the H_4R, in the pathogenesis of experimental inflammatory arthritis, but how might H_4R mediate its effects? The authors discovered that, in the CIA model, animals with disease had more lymph nodal IL-17$^+$ CD4$^+$ T cells than healthy mice and that treatment with an H_4R antagonist reduced the number of these cells and the level of IL-17 produced. Therefore, H_4R might, in part, act by influencing type 17 T helper cells.

"If the preclinical data translates into clinical efficacy, targeting H_4R may provide novel oral treatment options for patients with RA," states Thurmond. He concludes: "H_4 R antagonists may become the antihistamines for autoimmune diseases."

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Origianl article Cowden, J. M. *et al.* The histamine H_4 receptor mediates inflammation and Th17 responses in preclinical models of arthritis. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2013-203832