

Convincing pharmacological effects on inflammation and pain by targeting the 5-HT₂ receptors

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Background

At inflammatory sites thrombocytes, the major source of peripheral serotonin (5-HT), accumulate and become activated. Thus, in the arthritic joints 5-HT is released into the synovial fluid where it boosts the inflammatory response by binding to 5-HT receptors on synovial cells. We have developed several compounds targeting the 5-HT₂ receptors. The compounds are structurally diverse, have different binding characteristics and pharmacological profiles. They have previously been shown to reduce IL-6 and TNF-production *in vitro* and to diminish arthritis activity in two different animal models. The objective of the present study was to (1) further give evidence to that the effects of our compounds are mediated by antagonizing the 5-HT₂ receptors, (2) show effects of our compounds during ongoing inflammation in glucose-6-phosphate isomerase (GPI)-induced arthritis in the mouse, a third animal model of RA, (3) evaluate our compounds in an inflammatory pain model. Recently, one of our compounds entered the first tolerability and kinetic evaluation in a phase I clinical trial.

Methods

The 5-HT₂ receptor expression pattern on our target cells was evaluated by RT-PCR. *In vitro* our compounds were added to rat synoviocytes together with commercial 5-HT₂ agonists to investigate their effects on IL-6 release. In GPI-induced arthritis, DBA/1 mice were immunized with rabbit GPI. The mice were orally treated with our compound AMAP102 (10 and 30 mg/kg) once daily and scored for arthritis. To investigate the effect of the compounds on inflammatory pain, AMAP102 and AMAP312 (1, 10 and 30 mg/kg) were orally administered to rats before injection of formalin into one of the paws. Nociceptive responses to the formalin injection that occurs in two phases were measured. The first phase is caused by the direct stimulation of nerve ends by formalin and the second represents the pain response to the inflammatory reaction.

Summary of the results

In vitro target validation experiments showed that the 5-HT₂ receptors are expressed on our target cells and that our compounds reverse the effects induced by selective 5-HT₂ agonists and thus likely act through the 5-HT₂ receptors. AMAP102, was shown to reduce severity in the GPI-induced arthritis model, even when treatment was initiated after the first manifestations of disease. Finally, compounds from two different chemical classes, significantly reduced the inflammatory pain response at 1-30 mg/kg, without significantly influencing the first part of the nociceptive response.

Conclusion

The present study shows that impressive anti-arthritic effects are established by antagonizing the 5-HT₂ receptors with our proprietary compounds. In addition, the sensitivity to inflammatory pain is diminished. In conclusion, the study supports the clinical development of our compounds targeting the 5-HT₂ receptors.