

Anti-inflammatory Effects of a Novel Class of 5-HT₂ Receptor Binding Compounds

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Objective/Purpose

Serotonin (5-HT) has been shown to play an important role in the inflammatory process and its receptors are potential targets for the treatment of rheumatoid arthritis. We have developed a novel proprietary class of substances with high affinity for the 5-HT₂ receptors (exemplified by AMAP332; K_i=15 nM for 5-HT_{2C}). The objective of this study was to investigate the anti-inflammatory effects of these compounds both *in vitro*, in rat synovial cells, and *in vivo*, in antigen-induced arthritis (AIA) in rat.

Methods

In the *in vivo* experiments, inflammation and pannus formation was induced by immunization of Dark Agouti rats with methylated BSA followed by an intra-articular challenge with the antigen. The animals were treated with peroral or intra-articular administration of the substances, starting on the day of challenge and continuing for 4 days. The anti-inflammatory effect was assessed by measuring the decrease in knee-joint swelling. At the end of the experiment, knee joints were removed for histological examination. Tissue sections were stained with haematoxylin/eosin or toluidine blue and tissue damage was estimated. Synovial cells were isolated from pannus tissue originating from arthritic rats. The tissue was digested enzymatically, and the isolated cells were allowed to proliferate for 7-10 days before stimulation with LPS and simultaneous exposure to the compounds. After three days of stimulation and compound exposure, the supernatants were collected and the IL-6 content was measured using ELISA.

Results

Peroral treatment with two of the substances, AMAP312 and AMAP332, significantly ($p < 0.05$) reduced the knee-joint swelling at the doses 3 and 10 mg/kg. Furthermore, AMAP332 showed significant anti-inflammatory effects upon intra-articular administration of 50 μ l of a 10 μ M solution of substance ($p < 0.01$). Histological examination showed that there was reduced joint inflammation and reduced cartilage and bone destruction. *In vitro*, AMAP312 and AMAP332, in the dose-range 0.1-10 μ M, suppressed synovial cell production of IL-6.

Conclusion

Peroral treatment with AMAP312 and AMAP332 significantly decreases the severity of antigen-induced arthritis. These effects are probably due to local modulation of the 5-HT₂ signaling, since intra-articular administration of AMAP332 also reduced inflammation. Histological evaluation of joint sections confirmed the anti-inflammatory properties of our compounds, and furthermore indicated cartilage- and bone-protecting effects. The anti-inflammatory and tissue-protecting properties of our compounds could be associated with a suppressed production of IL-6 by synovial cells, as indicated by our *in vitro* results.