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Regulation of TNF-α and NF-κB activation through the JAK / STAT signaling pathway downstream of histamine 4 receptor in a rat model of LPS-induced joint inflammation (Article)

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Abstract

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Histamine 4 receptor (H4R) is a novel target for the pharmacological modulation of histamine-mediated immune signals during inflammatory diseases. The purpose of this study was to assess the effects of the H4R agonist 4-methylhistamine dihydrochloride (4-MeH) and antagonist JNJ7777120 (JNJ) in the inflamed rat knee. Animals were fasted for 18. h before a single dose of 4-MeH or JNJ (30. mg/kg) was administered intraperitoneally (i.p.), both followed by intra-articular (i.a.) injection of LPS 2. h later. Blood and synovial fluid were collected after a short incubation period and TNF-α, NF-κB, and IkB-α levels were measured via flow cytometry. Additionally, we assessed the effects of H4R engagement on the expression of IL-1β, TNF-α, and NF-κB mRNAs and the protein levels of TNF-α, NF-κB, JAK-1, and STAT-3 in the inflamed knee tissue. These results revealed increased TNF-α and NF-κB expression and decreased IkB-α levels in both the LPS alone and 4-MeH treated groups in whole blood and synovial fluid. Further, IL-1β, TNF-α, and NF-κB mRNA levels were significantly increased and western blot analysis confirmed increased expression of TNF-α, NF-κB, JAK-1, and STAT-3 in both LPS and 4-MeH treatment groups. Furthermore, these increases were completely inhibited in the inflamed knee tissue of the JNJ-treated group. Thus, the inhibition of inflammatory mediators and signaling pathways by the H4R antagonist JNJ suggests the anti-arthritic importance of this molecule. © 2015 Elsevier GmbH.

SciVal Topic Prominence

Topic: Receptors, Histamine | Histamine | receptor H4R

Prominence percentile: 87.380

Reaxys Database Information

View Compounds

Author keywords

4-Methylhistamine dihydrochloride | Histamine 4 receptor | Inflamed rat knee | JAK-STAT signaling pathway | JNJ77777120 | Lipopolysaccharide | Tumor necrosis factor-alpha

Indexed keywords

EMTREE drug terms:

histamine H4 receptor | immunoglobulin enhancer binding protein | interleukin 1beta | Janus kinase | Janus kinase 1 | lipopolysaccharide | messenger RNA | STAT protein | STAT3 protein | tumor necrosis factor alpha | 1-((5-chloro-1H-indol-2-yl)carbonyl)-4-methylpiperazine | 4-methylhistamine | antihistaminic agent | antiinflammatory agent | G protein coupled receptor | histamine agonist | histamine derivative | histamine receptor | Hrh4 protein, rat | I kappa B | IL1B protein, rat | immunoglobulin enhancer binding protein | indole derivative | interleukin 1beta | Jak1 protein, rat | Janus kinase 1 | messenger RNA | NF-kappaB inhibitor alpha | piperazine derivative | STAT3 protein | Stat3 protein, rat | tumor necrosis factor alpha

EMTREE medical terms:

adult | animal experiment | animal model | animal tissue | arthritis | Article | blood analysis | blood level | controlled study | disease activity | enzyme activity | enzyme assay | female | flow cytometry | immune response | molecular dynamics | molecular pathology | nonhuman | priority journal | protein determination | protein expression | protein function | rat | signal transduction | synovial fluid | Western blotting | animal | biosynthesis | blood | enzyme activation | gene expression regulation | genetics | immunology | inflammation | knee | metabolism | pathology | Wistar rat

MeSH:

Animals | Anti-Inflammatory Agents | Enzyme Activation | Female | Gene Expression Regulation | Histamine Agonists | Histamine Antagonists | I-kappa B Proteins | Indoles | Inflammation | Interleukin-1beta | Janus Kinase 1 | Knee Joint | Lipopolysaccharides | Methylhistamines | NF-kappa B | Piperazines | Rats | Rats, Wistar | Receptors, G-Protein-Coupled | Receptors, Histamine | RNA, Messenger | STAT3 Transcription Factor | Tumor Necrosis Factor-alpha

Chemicals and CAS Registry Numbers:

histamine H4 receptor, 272100-58-0; Janus kinase, 161384-16-3;

1-((5-chloro-1H-indol-2-yl)carbonyl)-4-methylpiperazine; 4-methylhistamine; Anti-Inflammatory Agents; Histamine Agonists; Histamine Antagonists; Hrh4 protein, rat; I-kappa B Proteins; IL1B protein, rat; Indoles; Interleukin-1beta; Jak1 protein, rat; Janus Kinase 1; Lipopolysaccharides; Methylhistamines; NF-kappa B; NF-kappaB inhibitor alpha; Piperazines; Receptors, G-Protein-Coupled; Receptors, Histamine; RNA, Messenger; Stat3 protein, rat; STAT3 Transcription Factor; Tumor Necrosis Factor-alpha

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