[*Pharmacology*, **54**, 144-152 (1997)] [Lab. of Pharmacology]

Inhibition of Tumor Necrosis Factor-alpha and Interleukin-1-beta Production by Beta-adrenoceptor Agonists from Lipopolysaccharide-stimulated Human Peripheral Blood Mononuclear Cells.

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The effects of β-adrenoceptor agonists (β-agonists) on the production of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-8 by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs) were investigated. The β-agonists inhibited the production of TNF-α and IL-1β, but not IL-8. Dibutyryl cyclic AMP also inhibited the production of TNF-α and IL-1β, but not IL-8. Moreover, β-agonists elevated cAMP levels in LPS-stimulated PBMCs. These results indicate that β-agonists inhibit the production of TNF-α and IL-1β by elevating intracellular cAMP levels.

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Participation of Leukotriene D4 and Tumor Necrosis Factor on Lipopolysaccharide-induced Airway Hyperresponsiveness in Guinea Pigs.

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In guinea pigs, a marked increase in airway responsiveness to acetylcholine (Ach) was observed at 2 h after lipopolysaccharide (LPS) inhalation. To examine the mediators responsible for the airway hyperresponsiveness (AHR), the changes of peptide-leukotrienes (LTs), tumor necrosis factor (TNF), interleukin-1 (IL-1), histamine and 5-hydroxytryptamine (5-HT) levels in bronchoalveolar lavage fluid (BALF) were measured. Airway responsiveness to Ach reached a peak 2 h after LPS inhalation. The influx of neutorphil into BALF increased gradually and reached a peak 24 h after LPS inhalation. After the inhalation of LPS, Leukotriene D4 (LTD4) and TNF contents in BALF increased within the first 2 h after LPS inhalation, however, other mediators, including IL-1, histamine and 5-HT, were not detected or increased. Aeroinhalation of LTD4 and murine recombinant TNF-α caused AHR. These results suggest that LTs and/or TNF play an important role in the onset of AHR in guinea pigs.

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The Effect of Anti-IL-4 Monoclonal Antibody, Rapamycin and Interferon-γ on Airway Hyperreactivity to Acetylcholine in Mice.

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In order to clarify the role of IgE in airway hyperreactivity (AHR), we investigated the effect of anti-IL-4 monoclonal antibody (mAb), rapamycin and interferon-γ (IFN-γ) on the antigen-induced IgE response, airway eosinophilia and AHR in mice. Three inhalations of antigen caused airway eosinophilia and AHR with a significant elevation of serum IgE levels. Anti-IL-4 mAb at a dose of 1000 μg/animal and rapamycin at doses between 0.1 and 1 mg/kg inhibited the IgE production, but not affect the airway eosinophilia or AHR. In contrast, IFN-γ inhibited the antigen-induced AHR and eosinophilia, but did not affect the IgE antibody production. These results suggest that the inhibition of IgE production does not suppress the onset of AHR and airway eosinophilia in mice, and that IFN-γ inhibits the antigen-induced AHR, probably due to the inhibition of airway eosinophilia.

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Immunopharmacological Studies on Collagen-induced Arthritis in DA Rats.

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DA and Lewis strains of rats were tested for susceptibility to collagen-induced arthritis (CIA). All of the DA rats developed arthritis following a single intradermal injection of more than 20μg of type II collagen (CII) and showed a swelling rate. This swelling rate showed little deviation among the animals. There was a strong correlation between the severity of the arthritis and the strength of the immune response to CII in DA rats with CIA. Following immunization with even 800 μg of CII, Lewis rats showed a maximum rats of a hind paw swelling of only 45%. In the pharmacological studies, prednisolone, indomethacin, FK-506 and mizoribine suppressed arthritis in DA rats as well as in Lewis rats is serviceable as an experimental animal model of rheumatoid arthritis.