VI Seminario Nazionale per Dottorandi in Farmacologia e Scienze Affini
Siena, Certosa di Pontignano, 23 - 26 Settembre 2002

BENEFICIAL EFFECTS OF GW274150, A NOVEL, POTENT AND SELECTIVE INHIBITOR OF INOS ACTIVITY, IN A RODENT MODEL OF COLLAGEN-INDUCED ARTHRITIS

Di Paola R., 1° anno di corso del Dottorato in Medicina Sperimentale, XVII ciclo. Durata del dottorato in anni. 4. Sede di servizio: Dipartimento Clinico Sperimentale di Medicina e Farmacologia, Facoltà di Medicina, Università degli Studi di Messina.

The aim of this study was to investigate the role of inducible nitric oxide synthase (iNOS) on the modulation of the inflammatory response in mice subjected to collagen-induced arthritis (CIA). CIA was induced in wild-type mice (iNOS-WT) treated with GW274150, a novel, potent and selective inhibitor of iNOS activity, and in mice lacking the gene for iNOS (iNOS 'knock-out', iNOS-KO), by an intradermal injection of 100 ml of emulsion containing 100 mg of bovine type II collagen (CII) and complete Freund's adjuvant (CFA) at the base of the tail. After 21 days, a second injection of CII in CFA was administered. iNOS-WT mice developed erosive hind paw arthritis when immunised with CII in CFA. Over a 35-day period, macroscopic clinical evidence of CIA first appeared as peri-articular erythema and oedema in the hind paws. By day 28, the incidence of CIA was 100% in CII-challenged iNOS-WT mice and the severity of CIA progressed with radiographic evaluation revealing resorption of bone.
Histopathology of CIA mice demonstrated erosion of the cartilage at the joint margins. iNOS-WT mice treated with GW274150 (5 mg/kg i.p. daily) starting at the onset of arthritis (day 23), and iNOS-KO mice showed a delay of the development of the clinical signs at days 24-35 and an improvement of the histological status in the knee and paw. Immunohistochemical analysis for nitrotyrosine and for poly (ADP-ribose) polymerase revealed positive staining in inflamed joints from CII-treated iNOS-WT mice. The degree of staining for nitrotyrosine and poly (ADP-ribose) polymerase were markedly reduced in tissue sections obtained from CII-treated iNOS-WT mice, who had received GW274150 and from iNOS-KO mice. Furthermore, radiographic signs of protection against bone resorption were present in the joints of iNOS-WT mice treated with GW274150 as well as in the joint from iNOS-KO mice.
This study provides the first evidence that GW274150, a novel, potent and selective inhibitor of iNOS activity, attenuates the degree of chronic inflammation and tissue damage associated with CIA in mice. Furthermore, these results suggest that the induction of iNOS and NO production are essential for the up-regulation of the inflammatory response during experimental CIA.