Collagen-induced arthritis (CIA) is an experimental model of inflammatory arthritis induced by immunization of rats (1), mice (2) or primates (3) with type II collagen (CII), a major protein of articular cartilage. It is characterized by a chronic, polyarticular, proliferative, and erosive arthritis. CIA shares certain clinical, histopathological and immunological features with rheumatoid arthritis (RA) in humans (4). Common histologic and immunologic features include the erosion of cartilage and subchondral bone at joint margins by pannus and the presence of immunity to native CII. Both cellular and humoral immune responses to native CII can be detected in these animals, and there appears to be some correlation between higher levels of sensitivity to CII and the presence of arthritis (5–7).

CIA was developed explosively 10–16 days after immunization in 40–100% of several strains of rats (1, 8–11). Susceptibility to CIA and immune responsiveness to CII are controlled in part by genes within or closely linked to the major histocompatibility complex (2, 10, 12). Griffiths et al. (10) reported that dark Agouti (DA) rats were among the most susceptible strains and CII-injected DA rats showed strong positive skin test responses to CII. However, the rats were immunized with comparatively high doses of CII (2–2.5 mg/kg). We conducted the present study to find the minimum dose of CII which would cause CIA in DA rats, thereby giving us a more detailed understanding of the rats’ susceptibility to CIA. We also sought to determine the usefulness of this model for the evaluation of anti-rheumatic drugs.

MATERIALS AND METHODS

Animals
Female DA rats (weighing 130–150 g) were kindly donated by Japan SLC, Inc., Shizuoka. Female Lewis rats (weighing 190–210 g) were purchased from Seiwa Experimental Animals, Fukuoka. Animals were housed in an air-conditioned room at 22±1°C and were 11-weeks-old at the beginning of the experiment. Standard diet and water were available ad libitum.

Induction of arthritis
CIA was induced according to the previously reported method (13). The rats were divided into various groups, each containing 5–6 rats. Bovine CII solution (Collagen Research Center, Tokyo), diluted with 0.1 M acetic acid at various concentrations, was mixed with an equal
volume of incomplete Freund adjuvant (IFA; Nacalai Tesque, Inc., Kyoto) and emulsified thoroughly. A total volume of 0.4 ml of the emulsion was injected intradermally (i.d.) at four sites in the back of the animals.

Treatment with drugs

The drugs used in this experiment were prednisolone acetate (Takeda Chemical Industries Ltd., Osaka), indomethacin (Sigma Chemical Co., St. Louis, MO, USA), FK-506 (tacrolimus; Fujisawa Pharmaceutical, Osaka), mizoribine (Asahi Chemical Industry, Osaka), bucillamine (Santen Pharmaceutical, Osaka), and D-penicillamine (Aldrich Japan, Inc., Tokyo). The drugs were dissolved or suspended in 0.5% sodium carboxymethylcellulose (CMC-Na; Nacalai Tesque, Inc.) and were administered orally 6 days a week (Monday-Saturday) for 5 weeks beginning on the day following immunization.

Evaluation of arthritis

The severity of CIA was assessed by quantitation of hind paw swelling. The paw volume was measured with a plethysmometer (TK-101; Unicorn, Chiba) twice a week throughout the test period.

Anti-CII antibody titer

Sera were routinely collected by retroorbital bleeding, using a capillary tube, at 2, 3, 4, 5 and 6 weeks after immunization. Serum anti-CII antibody levels were measured by an enzyme-linked immunosorbent assay (ELISA) technique. Immunoplates (Nunc, Roskilde, Denmark) were coated with 50 μl of bovine CII at a concentration of 4 μg/ml and incubated overnight at 4°C. After washing with phosphate-buffered saline containing 0.05% Tween 20, the plates were blocked with Block Ace (Dainippon Pharmaceutical, Tokyo) for 1 hr at room temperature. After being washed again, 50 μl of sample sera diluted 1600-fold were added to the wells and incubated for 1 hr at room temperature. After washing again, 50 μl of peroxidase-conjugated goat anti-rat IgG(H + L) (Kirkegaard & Perry Laboratories Inc., Gaithersburg, MD, USA), diluted 6400-fold, was added and incubated for 1 hr at room temperature and for another 30 min with 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS; Wako Pure Chemical Industries, Osaka) solution as the substrate. The reaction was stopped by adding 50 μl of 5% oxalic acid. The reaction product was measured by determining the absorbance at a 414-nm test wavelength and a 492-nm reference wavelength using a microplate photometer (Multiskan MCC/340; Titertek, Helsinki, Finland).

Delayed-type hypersensitivity (DTH) response

The DTH response to CII was determined at 5 or 6 weeks after immunization. Fifty microliters of 0.4 mg/ml CII solution (containing 0.2 M NaCl and 0.05 M Tris-HCl, pH 7.5) was injected i.d. into the skin of the left ear, and an equal volume of the buffer solution was injected into the skin of the right ear. After 48 hr, the thickness of both ears was measured with an Upright Dial Thickness Gauge (Ozaki Seisakusho, Tokyo). The difference in

Fig. 1. The severity of arthritis produced by various dosages of bovine type II collagen (CII) in DA rats. The rats were immunized with 5 μg (△), 20 μg (▲), 50 μg (□) or 100 μg (■) of collagen in incomplete Freund adjuvant (IFA) emulsion. The negative control groups included untreated rats (○) and rats that were immunized with IFA (●). The hind footpad volume was measured by a plethysmometer. The values represent the mean ± S.E. of 5-6 rats per group.

Fig. 2. The severity of arthritis produced by various dosages of bovine CII in Lewis rats. The rats were immunized with 50 μg (○), 200 μg (△) or 800 μg (▲) of collagen in IFA emulsion. The rats in the normal group were untreated (●). The hind footpad volume was measured by a plethysmometer. The values represent the mean ± S.E. of 5 rats per group.
thickness between the CII- and buffer-injected ears was regarded as the index of DTH response.

Statistical analyses
The data were analyzed by Student's t-test or Welch's t-test. These results were considered to be significantly different when P values were less than 0.05.

RESULTS

Induction of arthritis and immune responses to CII
Arthritis was induced in both DA and Lewis rats by a single injection of heterologous (bovine) CII in the skin of the back, and the intensity of the arthritis in the two strains was compared. The increase in hind paw volume was regarded as the index of the intensity of the arthritis. In DA rats, the hind paws became extremely red and edematous 2 weeks after immunization. Peak severity occurred within about 7 days after the onset and then hind paw swelling gradually decreased (Fig. 1). Swelling was mild, reaching a maximum of about 30%, following immunization with 5 μg of CII, but the maximum swelling rate rose to about 90% when the rats were all injected with 20 μg of CII. The swelling rate increased to a maximum of about 120% when the rats received 50 μg of CII, but doses of more than 50 μg caused no further increase in swelling. Deviation of the swelling rate among animals was comparatively small. DA rats receiving more than 20 μg of CII showed marked redness and edema, not only in the hind limbs, but also in the fore limbs (data not

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Fig. 3. Cell-mediated response (A) and humoral response (B) to CII in collagen-induced arthritic DA rats. A: The rats were injected with 20 μg of collagen into the left ear at 5 weeks after the immunization, and ear thickness was measured at 48 hr after the challenge. B: Serum anti-CII antibody titer was measured by an ELISA technique as described in Materials and Methods. The rats were immunized with 5 μg (△), 20 μg (▲), 50 μg (■) or 100 μg (●) of collagen in IFA emulsion. The rats in the negative control group were immunized with IFA (○). The anti-CII antibody titer in the untreated control rats and that in the negative control group were both very low. The values represent the mean ± S.E. of 5–6 rats per group.

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Fig. 4. Cell-mediated response (A) and humoral response (B) to CII in collagen-induced arthritic Lewis rats. A: The rats were injected with 20 μg of collagen into the left ear at 6 weeks after the immunization, and ear thickness was measured at 48 hr after the challenge. B: Serum anti-CII antibody titer was measured by an ELISA technique as described in Materials and Methods. The rats were immunized with 50 μg (●), 200 μg (▲) or 800 μg (△) of collagen in IFA emulsion. The rats in the normal group were untreated (○). The values represent the mean ± S.E. of 5 rats per group.
shown). Moreover, intradermal injection of IFA (200 μl) without further additives also induced mild, short-term swelling in the hind paws.

In contrast, Lewis rats showed a maximum rate of hind paw swelling of only 45% following immunization with even 800 μg of CII, although the swelling increased as the dose of CII increased (Fig. 2). The onset of arthritis in Lewis rats occurred 3 weeks postimmunization; i.e., redness and edema appeared one week later in Lewis rats than in DA rats and then the swelling gradually increased.

The DTH response to CII and serum anti-CII antibody levels in DA rats and Lewis rats are shown in Figs. 3 and 4, respectively. DA rats that received 5 μg of CII showed both a low DTH response and a low anti-CII antibody titer, but immunization with more than 20 μg of CII induced a clear DTH response and a high anti-CII antibody titer in these animals. DA rats immunized with IFA alone showed no immune responses to CII. Lewis rats showed a clear DTH response and the intensity of the response showed almost no variation with the dose of CII (50, 200 or 800 μg). Anti-CII antibody titer in Lewis rats with CIA was gradually increased and depended on the dose of CII.

Effect of various drugs on CIA in DA rats

The suppressive effects of various drugs on CIA in DA rats were examined. DA rats receiving 50 μg of CII were orally treated with drugs 6 days a week for 5 weeks beginning on the day after the immunization.

Prednisolone, a steroidal anti-inflammatory drug, significantly reduced hind paw swelling in a dose-dependent fashion at 1, 3 and 5 mg/kg (Fig. 5). Prednisolone at doses of more than 3 mg/kg significantly suppressed the DTH response to CII and decreased anti-CII antibody levels, although the drug had no effect on either of these responses at a dose of 1 mg/kg.

Figure 6 shows the effect of indomethacin, a non-steroidal anti-inflammatory drug, at doses of more than 1 mg/kg on CIA in DA rats. Administration of indomethacin at a dose of 5 mg/kg induced marked weight loss (data not shown), indicating a possible overdose. Indomethacin reduced hind paw swelling in a dose-dependent fashion at doses of 1 and 3 mg/kg and significantly reduced the swelling at a dose of 3 mg/kg. These doses of this drug did not affect body weight gain. DTH response was suppressed by 3 mg/kg of indomethacin, but antibody levels were not affected.

FK-506, an immunosuppressant, at a dose of 1 mg/kg scarcely affected hind paw swelling, but at doses of 3 and 5 mg/kg, FK-506 almost completely suppressed arthritis (Fig. 7). Anti-CII antibody levels decreased markedly following administration of more than 3 mg/kg of FK-506, and the DTH response to CII was significantly suppressed by 5 mg/kg of this drug.

Figure 8 shows the effect of mizoribine, another immunosuppressant, at doses of 5, 10 and 20 mg/kg. Mizoribine significantly reduced hind paw swelling in a dose-dependent fashion until 4 weeks after immunization when the swelling was at its maximum. However, mizoribine scarcely affected DTH response and anti-CII antibody levels.

Figures 9 and 10 show the effects of disease modifying anti-rheumatic drugs (DMARDs), bucillamine and D-penicillamine, respectively. Bucillamine did not affect hind paw swelling at any of the three doses (10, 30 and 100 mg/kg), although at a dose of 100 mg/kg, the drug suppressed the DTH response and slightly suppressed anti-CII antibody levels. D-Penicillamine slightly suppressed anti-CII antibody levels at a dose of 100 mg/kg. A dose of 100 mg/kg of D-penicillamine caused swelling to worsen significantly, but doses of 10 and 30 mg/kg had no effect on swelling.

DISCUSSION

CIA seems to be the experimental model that is most similar to human RA. Several strains of rats, e.g., Lewis, Wistar and Sprague-Dawley (SD), have generally been used for the study of pathogenesis and the assessment of drugs for anti-rheumatic activity in rats with CIA. Although DA rats have been reported to be among the most susceptible strains (10), there are few reports studying CIA using DA rats. In this study, we have examined whether the CIA model in DA rats is useful as an experimental animal model of RA, in comparison with CIA using Lewis rats, which are commonly used for the study of CIA.

Immunization with 20 μg of CII (130–150 μg/kg rat weight) caused arthritis in all DA rats, and the maximum rate of hind paw swelling reached about 90%. The maximum rate of the swelling was 100–120% in DA rats that received 50–500 μg of CII, and the onset of the swelling in DA rats receiving more than 300 μg of CII was slightly earlier than in the rats receiving less than 100 μg of CII (data not shown). On the other hand, the maximum rate of hind paw swelling was only 45% in Lewis rats following immunization with CII, even at doses as high as 800 μg. Thus more (obvious) severe swelling of hind paws was found in DA rats receiving only 20 μg of CII than in Lewis rats receiving 800 μg (3.8–4.2 mg/kg rat weight), a 40-fold higher dose, of CII. Moreover, there was less deviation in the swelling rate in the DA rats than in the Lewis rats. In DA rats, the swelling of the hind paws began 2 weeks postimmunization, reached a peak one week later and then gradually decreased. In Lewis rats, however, the onset of arthritis occurred 3 weeks postimmunization and the swelling gradually increased. There-
Fig. 5. Clinical (A) and immunologic (B and C) effects of prednisolone on collagen-induced arthritis in DA rats. The rats were immunized with 50 μg of collagen in IFA. The rats were treated orally with 0.5% CMC-Na (○), 1 mg/kg (●), 3 mg/kg (△) or 5 mg/kg (▲) of prednisolone 6 days a week for 5 weeks. The values represent the mean ± S.E. of 6 rats per group. *P<0.05, **P<0.01, significantly different from the 0.5% CMC-Na-treated control.

Fig. 6. Clinical (A) and immunologic (B and C) effects of indomethacin on collagen-induced arthritis in DA rats. The rats were immunized with 50 μg of collagen in IFA. The rats were treated orally with 0.5% CMC-Na (○), 1 mg/kg (●), 3 mg/kg (△) or 5 mg/kg (▲) of indomethacin 6 days a week for 5 weeks. The values represent the mean ± S.E. of 6 rats per group. *P<0.05, **P<0.01, significantly different from the 0.5% CMC-Na-treated control.
Fig. 7. Clinical (A) and immunologic (B and C) effects of FK-506 on collagen-induced arthritis in DA rats. The rats were immunized with 50 µg of collagen in IFA. The rats were treated orally with 0.5% CMC-Na (○), 1 mg/kg (●), 3 mg/kg (▲), 5 mg/kg (▲) of FK-506 or 3 mg/kg of prednisolone (□) 6 days a week for 5 weeks. The values represent the mean±S.E. of 5 rats per group. *P<0.05, **P<0.01, significantly different from the 0.5% CMC-Na-treated control.

Fig. 8. Clinical (A) and immunologic (B and C) effects of mizoribine on collagen-induced arthritis in DA rats. The rats were immunized with 50 µg of collagen in IFA. The rats were treated orally with 0.5% CMC-Na (○), 5 mg/kg (●), 10 mg/kg (▲), 20 mg/kg (▲) of mizoribine or 2 mg/kg of prednisolone (□) 6 days a week for 5 weeks. The values represent the mean±S.E. of 5 rats per group. *P<0.05, **P<0.01, significantly different from the 0.5% CMC-Na-treated control.
Fig. 9. Clinical (A) and immunologic (B and C) effects of bucillamine on collagen-induced arthritis in DA rats. The rats were immunized with 50 µg of collagen in IFA. The rats were treated orally with 0.5% CMC-Na (○), 10 mg/kg (●), 30 mg/kg (△), 100 mg/kg (▲) of bucillamine or 3 mg/kg of prednisolone (□) 6 days a week for 5 weeks. The values represent the mean ± S.E. of 5 rats per group. *P < 0.05, **P < 0.01, significantly different from the 0.5% CMC-Na-treated control.

Fig. 10. Clinical (A) and immunologic (B and C) effects of D-penicillamine on collagen-induced arthritis in DA rats. The rats were immunized with 50 µg of collagen in IFA. The rats were treated orally with 0.5% CMC-Na (○), 10 mg/kg (●), 30 mg/kg (△), 100 mg/kg (▲) of D-penicillamine or 3 mg/kg of prednisolone (□) 6 days a week for 5 weeks. The values represent the mean ± S.E. of 5 rats per group. *P < 0.05, **P < 0.01, significantly different from the 0.5% CMC-Na-treated control.
fore, the onset of arthritis in DA rats was one week earlier than in Lewis rats. In general, hind paw swelling in Lewis rats, as well as Wistar and SD rats, appears 2 weeks after immunization. It is not clear why the onset of arthritis in Lewis rats occurred about one week later in this study.

We next examined the immune responses to CII, i.e., DTH response to CII and anti-CII antibody titer, in the arthritic rats. DA rats receiving 5 μg of CII showed a weak immune response to CII, but immunization with more than 20 μg of CII induced severe swelling of the hind paws and intensive immune responses to CII. Therefore, the severity of the arthritis correlated with the degree of the immune responses to CII in DA rats with CIA. The intensity of the DTH responses to CII in Lewis rats was almost the same, regardless of the dose of CII and the severity of the arthritis, but the anti-CII antibody titer was raised in a dose-dependent fashion.

Some reports describe oil-induced arthritis (OIA) in DA rats, which is induced by IFA alone, without the addition of antigen (14–18). An intradermal injection of IFA induces erosive polyarthritis in DA rats but not in Lewis rats. The initial signs of arthritis appear 2 weeks after injection and the arthritis declines and disappears by about 45 days postimmunization. Re-administration of IFA to rats that have recovered from OIA failed to induce arthritis a second time. OIA is successfully transferred to naive recipients after intravenous injection of T cells from OIA rats but not after intravenous injection of sera. Lymph node cells from DA rats with OIA do not respond to native or denatured CII, 65-kDa heat shock protein or proteoglycan. Histological examination reveals joint inflammation, first with polymorphonuclear cells and synovial hyperplasia, and subsequently, with both bone and cartilage destruction by pannus overlying. In the present experiments, immunization with IFA (200 μl) was also shown to induce hind paw swelling in DA rats. The maximum rate of swelling reached about 20% 3 weeks after immunization and then the swelling disappeared. Therefore, DA rats simultaneously suffer CIA induced by CII and OIA induced by IFA when they are immunized with CII in IFA emulsion. But the swelling of the hind paws in OIA rats was much smaller than that of CIA rats. Footpad swelling was limited in the hind paws of OIA rats.

To demonstrate the usefulness of CIA in DA rats as a model for the assessment of drugs, we investigated the effect of various drugs on this arthritis model. Prednisolone, indomethacin, FK-506 and mizoribine significantly suppressed hind paw swelling; i.e., these drugs reduced the severity of arthritis in a dose-dependent fashion. Prednisolone suppressed arthritis in a dose-dependent fashion, showing significantly suppression even at a dose of 1 mg/kg. The DTH response and anti-CII antibody production were suppressed by more than 3 mg/kg of this drug. Prednisolone is known to affect the inflammatory and immune responses of RA patients directly or indirectly via several possible mechanisms, including inhibition of the cellular secretion of agent such as interleukin (IL)-1, IL-2, tumor necrosis factor (TNF), phospholipases, etc. These suggest that prednisolone suppressed arthritis because of its ability to restore normal immune function via its immunosuppressive action, in addition to its anti-inflammatory effect. Indomethacin, a classical inhibitor of prostaglandin synthesis, was more effective at a dose of 3 mg/kg than at a dose of 1 mg/kg (we regarded 5 mg/kg of this drug as overdose). Indomethacin at a dose of 3 mg/kg suppressed the DTH response but did not decrease the anti-CII antibody titer. Since indomethacin had no effect on anti-CII antibody production, the anti-arthritis effect of the drug is probably related to its anti-inflammatory effect. FK-506, at doses of more than 3 mg/kg, almost completely prevented the development of CIA. FK-506 significantly suppressed the DTH response at a dose of 5 mg/kg and decreased the anti-CII antibody titer at doses more than 3 mg/kg. In the mouse CIA model, FK-506 significantly suppressed both the DTH response and anti-CII antibody production at a dose of 3 mg/kg, but, at a dose of 2 mg/kg, this drug significantly suppressed anti-CII antibody production but not the DTH response when given prophylactically (19). In in vitro studies in mice, FK-506 suppressed mixed lymphocyte reactions, cytotoxic T cell generation, the production of T cell-derived soluble mediators such as IL-2, IL-3 and interferon (IFN)-γ, and the expression of IL-2 receptor at low concentrations (20, 21). Based on these results, the suppressive effect of FK-506 on the arthritis and the immunological responses to CII is based on its suppression of T cell activation. Treatment with mizoribine significantly suppressed arthritis but did not affect the immunological responses to CII. We previously reported that in the mouse CIA model, mizoribine suppressed the DTH response and restored the increased L3T4+/Lyt-2+ ratio to the level seen in normal mice; therefore, we suggest that the inhibitory effect of mizoribine is based on its suppression of cellular immunity (22). Therefore, the suppressive mechanism of mizoribine on rat CIA, as well as mouse CIA, is probably related to its suppression of cellular immunity. These drugs have been reported to have suppressive and/or therapeutic effects on mice and on other rat strains with CIA (9, 13, 19, 22–27).

On the other hand, neither bucillamine nor D-penicillamine (both DMARDs) showed a suppressive effect on CIA in DA rats. Therefore, the arthritis in DA rats induced by injection of CII was suppressed by steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs and immunosuppressants, but not by DMARDs.
The above results show that anti-rheumatic drugs act on CIA in DA rats in a fashion similar to that seen in other rat strains including Lewis rats. Actarit, a recently developed DMARD, significantly lowered the arthritis score in murine CIA (28). However, other DMARDs, not only bucillamine and d-penicillamine (9, 13, 29, 30) but also gold salts (9, 13, 19, 30–32) and levamisol (9, 13, 19, 33), generally had little or no effect on CIA in other rat strains.

The above results clearly show that CIA induced in DA rats is quite useful as an experimental model of RA. DA rats are more susceptible to CIA because DA rats developed arthritis following a single injection of CII in all animals, showing more than a 100% swelling rate of the hind paws, and deviation of the swelling rate among animals, showing more than a 100% swelling rate of the paws, and deviation of the swelling rate among animals was comparatively small. In pharmacological studies, this arthritis was suppressed by treatment with steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs and immunosuppressants. However, CIA in DA rats as well as in other rat strains was scarcely suppressed by treatment with DMARDs. RA can not be controlled by indomethacin at all. Bucillamine and d-penicillamine are effective drugs for the treatment of RA. Moreover, RA is a disease of chronic nature in which disease activity lasts as long as tens years, although this arthritis model is a subacute disease. CIA is the experimental model most similar to human RA among numerous animal models. However, it should be pointed out that there is a difference between RA and animal arthritis models including CIA. Therefore, the CIA model is a serviceable model but the usefulness of it is limited.

We have not yet discovered why DA rats are so much more prone to develop CIA than Lewis rats are. Larsson et al. (34) reported that a spontaneous T cell reactivity to CII, as measured by rat CII-induced ear swelling, was observed in nonimmunized DA rats, but not in nonimmunized Lewis rats. The DTH response of nonimmunized DA rats was restricted to homologous rat CII; no response could be elicited by heterologous CII. We also confirmed that DA rats were susceptible to experimental allergic encephalomyelitis (EAE), which was induced by a lower dose of myelin basic protein (MBP) than that which induced EAE in Lewis rats (35). The DTH responses to autologous (rat) and heterologous (bovine) MBP appeared in nonimmunized DA rats, but not in Lewis rats (35). These results indicate that DA rats have spontaneous autoreactive T cells to CII or MBP. This spontaneous T cell reactivity may be an important reason for the high susceptibility of DA rats to CIA.

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