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Anti-inflammatory effect of quetiapine on collagen-induced arthritis of mouse

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ABSTRACT

Quetiapine is an atypical antipsychotic and has also been used in the treatment of depression. Since anti-inflammatory effects of antidepressants are well established, we hypothesized that quetiapine may also exert anti-inflammatory effects. Thus this study was designed to examine the anti-inflammatory effect of quetiapine in murine collagen-induced arthritis. Mice were immunized with collagen type II for the induction of arthritis and treated with quetiapine (10 mg/kg) daily for 2 weeks. Mice were divided into 3 groups: control, CIA, and CIA + quetiapine treatment. Arthritic index and paw thickness were used to compare severity of arthritis. In additions, radiological and histological assessments were employed. Anti-type II collagen-specific antibody, interleukin-6 (IL-6), interleukin-17 (IL-17), and prostaglandin E_2 (PGE_2) were evaluated at the end of the treatment period. Both arthritic index and paw thickness were markedly improved in CIA + quetiapine treatment group compared with those in CIA groups (arthritic index; $P<0.01$, paw thickness; $P<0.05$). Radiologic assessment revealed decreased cartilage damage and bone erosion in CIA + quetiapine treatment group compared with those in CIA groups. Articular cartilage destruction observed in CIA group was not found in CIA + quetiapine group. The concentrations of anti-type II collagen-specific antibody, IL-6, IL-17, and PGE_2 in CIA + quetiapine group were significantly lower than those in CIA groups ($P<0.05$). Weight gain which is commonly observed with the treatment of antipsychotics was not observed. Taken together, these results suggest that quetiapine shows anti-inflammatory effects in murine collagen-induced arthritis.

1. Introduction

Rheumatoid arthritis is an autoimmune disease which is characterized by persistent synovitis, systemic inflammation, and autoantibodies. The synovial membrane is infiltrated by immune cells like macrophages and T-cells, resulting in the chronic production of pro-inflammatory cytokines and matrix metalloproteinases (MMPs), leading to cartilage and bone degradation (Feldmann et al., 1996). Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α (Chu et al., 1991), interleukin (IL)-1 (Buchan et al., 1988), interleukin (IL)-6 (Hirano et al., 1988) and interleukin (IL)-17 were produced from synovial tissue and maintain the inflammatory environment. Increased serum and synovial fluid levels of IL-6 are correlated with rheumatoid arthritis disease activity (Patel and Moreland, 2010). IL-17 is a potent inducer of other pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8 from synovial fibroblasts (Hwang et al., 2004).

Rheumatoid arthritis can be studied experimentally using a wide variety of animal models one of which is collagen-induced arthritis (Williams, 1998). Collagen-induced arthritis is widely recognized as an animal model to accurately simulate the clinical, symptomatic, and pathological manifestations of rheumatoid arthritis (Holmdahl et al., 1989; Trentham, 1982). Collagen-induced arthritis model is also known to present histologic similarities to human rheumatoid arthritis, with comparable synovitis, bone erosion, and pannus formation, and to respond similarly to anti-TNF therapy (Holmdahl et al., 2002).

Numerous studies in relation to the anti-inflammatory effects of antidepressant have been reported (Bianchi and Panerai, 1996;

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Taler et al., 2008). Evidence indicate that antidepressant may suppress the productions of monocytic cytokines, such as IL-1β and TNF-α. Tricyclic antidepressants and selective serotonin reuptake inhibitor significantly suppress IL-1β, IL-6 and TNF-α productions (Kubera et al., 2011). Citalopram and fluoxetine, selective serotonin reuptake inhibitors, also suppress inflammatory cytokine production in human rheumatoid arthritis tissue (Sacre et al., 2010).

Quetiapine is a new atypical antipsychotic drug that is widely used to treat the symptoms of schizophrenia and other psychotic disorders (Arvanitis and Miller, 1997). Moreover quetiapine is the first atypical antipsychotic drug that has proven antidepressant efficacy (Thase et al., 2006). Very recently, a case report which suggests anti-inflammatory effects of quetiapine in arthritis and comorbid major depression was published (Baune and Eyre, 2010). Since no studies as to the effect of quetiapine on arthritis has been reported, we designed the current study to investigate the potential anti-inflammatory effect of quetiapine in murine models of rheumatoid arthritis.

2. Materials and methods

2.1. Animals

DBA/1J mice (SLC, Inc., Japan), 6–8 weeks old, were housed in polycarbonate cages and fed with standard mouse chow (Ralston Purina, MO, USA) and water *ad libitum*. All experimental procedures were examined and approved by the Animal Research Ethics Committee of the Keimyung University.

2.2. Experimental arthritis

Sixty male DBA/1J mice were randomly divided into three groups ($n=15$ in each group): control, CIA, and CIA + quetiapine groups. CIA was induced according to previous report with some modifications (Trentham, 1982). Briefly, male DBA/1J mice were given an intradermal injection of 100 μg of bovine type II collagen emulsified in complete Freund's adjuvant (1:1, w/v; Chondrex, WA, USA) into the base of the tail. Two weeks later, mice were given a booster intradermal injection of 100 μg of bovine type II collagen emulsified in incomplete Freund's adjuvant (1:1, v/v; Chondrex, WA, USA) into the hind paw. Quetiapine (10 mg/kg) was given intraperitoneally after the secondary immunization five times per week for 2 weeks. The control mice were injected with saline. Blood samples and articular tissues were collected from all treated and control mice 8 weeks after the primary immunization and stored at −70 °C until use.

Mice were examined 3 times/week and arthritic score was assigned based on the following criteria: 0 = normal: no inflammation; 1 = mild: definite redness and swelling of the ankle or wrist or apparent redness and swelling limited to individual digits, regardless of the number of affected digits; 2 = moderate: redness and swelling of ankle and wrist; 3 = severe redness and swelling of the entire paw including digits; and 4 = maximally inflamed limb involving multiple joints. The sum of hind limbs was calculated and reported as the arthritic score.

2.3. Radiological assessment

After the hind limbs were removed, the legs were fixed in formalin for radiographic imaging. The plain radiographs of the knee joints were obtained using a mammographic imager based on a direct detection flat panel array design (Mammomat NovationDR, Siemens Medical Solutions, Germany). A full field flat panel digital detector measuring 24 cm × 29 cm (maximum matrix size, 3328 × 4096; pixel size, 70 μm) was used. All images were obtained using exposure settings of 30 kVp and 90 mAs and taken with a 1.5× magnification. The extents of cartilage damage and bone erosion in interphalangeal and metatarsophalangeal joint were determined and separately scored according to the following criteria: 0 = no destruction, 1 = minimal erosion, limited to single spots, 2 = slight to moderate erosion in a limited area, 3 = more extensive erosion and 4 = severe erosions. Radiological arthritic score was determined by combining interphalangeal and metatarsophalangeal joint scores. All X-ray assessments were made by a radiologist.

2.4. Immunohistochemistry

A hind limb of each mouse was fixed with 10% formalin, decalcified in hydrochloric acid, and embedded in paraffin, and sectioned. The sections were stained with H&E or Safranin O for light microscopic examinations. The stained sections were examined under microscopy and all histological assessments were made by a pathologist.

2.5. Enzyme-linked immunosorbent assay (ELISA)

The serum levels of type-II-collagen-specific antibodies, TNF-α and IL-6, prostaglandin E_2 (PGE_2) were measured by ELISA. Briefly, plates were coated with appropriate proteins at 4 °C overnight, followed by a blocking step for 1 h at room temperature. Serum samples were then diluted 1:20,000 in Tris-buffered saline (pH 8.0) containing 1% bovine serum albumin and 0.5% Tween-20, and incubated in the plates for 4 °C overnight, after which the plates were washed five times. The concentrations were measured using mouse ELISA Kits (Chondrex, WA, USA). Standard serum from arthritic mice was added to each plate in serial dilutions, and a standard curve was constructed to assign arbitrary units. The absorbance values were determined with an ELISA microplate reader operating at 450 nm.

2.6. Reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA of synovial tissue in each experimental group was pooled with Trizol (Gibco, Grand Island, NY) according to the manufacturer's protocol and divided into two samples. For RT-PCR, 2 μg of total RNA was reverse transcribed for 1 h at 37 °C in a reaction mixture containing RNA, 40 units RNase inhibitor (Amersham, Piscataway, NJ), 0.5 mM deoxynucleotide triphosphate (Boehringer Mannheim, Indianapolis, IN), 2 μM random hexamer primers (Stratagene, La Jolla, CA), 5× AMV reverse transcriptase reaction buffer and 30 units AMV reverse transcriptase (Promega, Madison, WI). PCR was performed three times in duplicate using the above-prepared cDNA as a template. The levels of microsomal prostaglandin E synthase-1 (mPGES-1) expression were determined by normalizing to GAPDH expression. The forward and reverse primers used for mPGES-1 were as follows: forward, 5′-CTT GCC AAG TTT CCT CTT GC-3′; reverse, 5′-CAC CCT CAA CAC ACG TCA TC-3′.

2.7. Statistical analysis

Statistical analysis was performed using Mann–Whitney *U* test, unpaired Student's *t*-test and one way analysis of variance (one way-ANOVA). The Mann–Whitney *U* test was used to analyze the arthritic severity, radiographic findings. The unpaired Student's *t*-test and one way-ANOVA were employed to analyze the other results. The accepted level of significance was preset as P value <0.05. Each experiment was executed at least three times in duplicate. Data are presented as means ± S.D. The SPSS Statistical for windows, version 12.0, was used.

3. Results

3.1. Quetiapine alleviated mouse anti-type II collagen antibody-induced arthritis

We first assessed whether quetiapine suppresses disease development and progression. DBA/1 mice were intraperitoneally injected

with quetiapine five times per week for 2 weeks after the induction of arthritis. The severity of arthritis was measured by an arthritic score and the hind paw thickness. The quetiapine treated mouse group showed decreased joint swelling compared with the CIA group (Fig. 1A). Both the arthritic score and the hind paw thickness

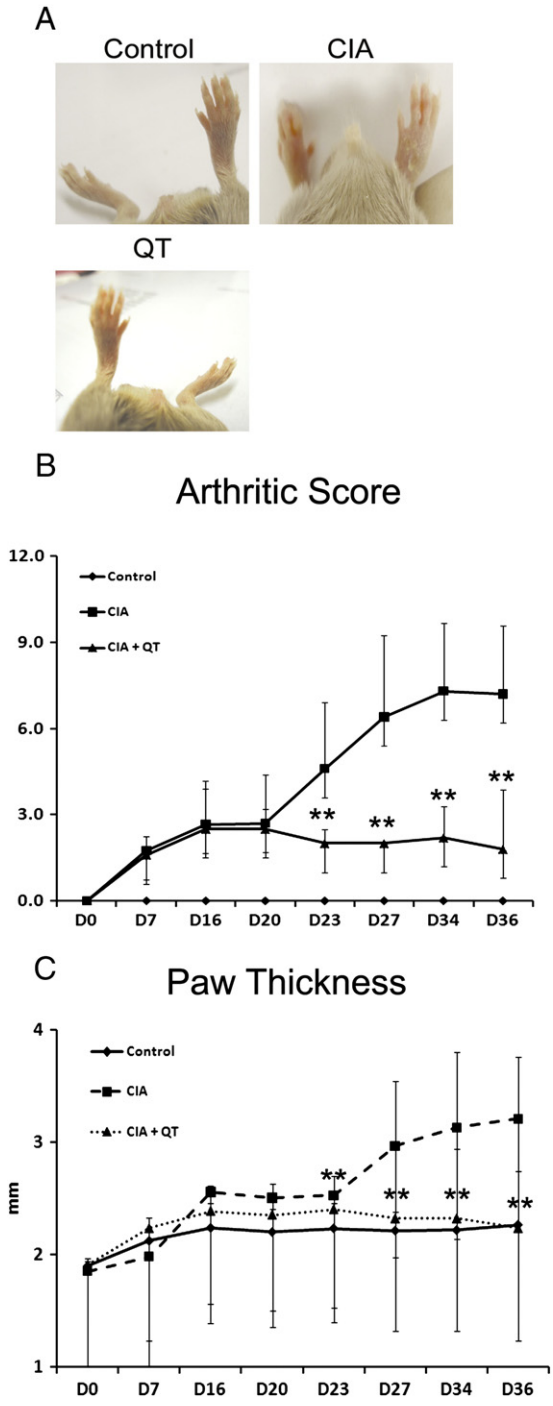

Fig. 1. The effects of quetiapine (QT) on collagen-induced arthritis (CIA). Male DBA/1J mice were given an intradermal injection of 100 μg of bovine type II collagen and were again given a booster intradermal injection of 100 μg of bovine type II collagen 2 weeks after. QT was given intraperitoneally (10 mg/kg) after the secondary immunization five times per week for 2 weeks. (A) Representative images of paws. (B) Arthritic score was measured and calculated as described in the "Materials and methods" section. (C) Paw thickness. The hind paw swelling was measured with an electric caliper. The value is represented as the average change in the paw thickness obtained from each mouse. $^{**}P<0.01$ *versus* corresponding CIA.

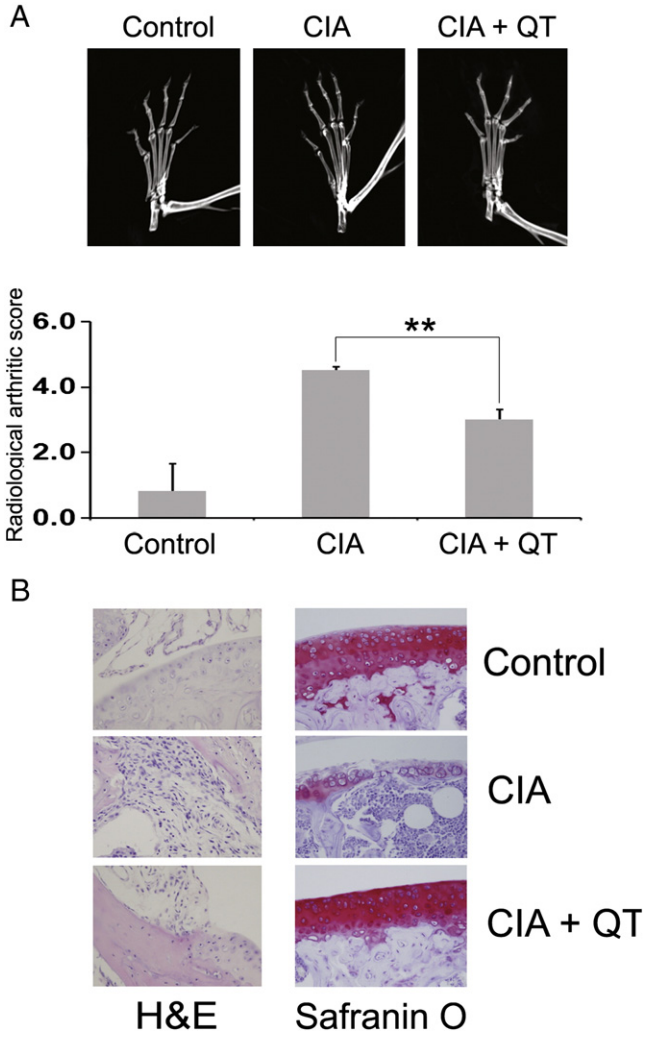

Fig. 2. The effects of quetiapine (QT) on bone destruction in collagen-induced arthritis (CIA). (A) The legs were fixed in formalin for radiographic imaging. The plain radiographs of the knee joints were obtained using a mammographic imager based on a direct detection flat panel array design. Upper panel; representative mammographic images of paws, lower panel; the degree of joint destruction and bone erosions were scored. (B) A hind limb of each mouse was fixed with 10% formalin, decalcified in hydrochloric acid, and embedded in paraffin. The sections were then stained with H&E (left panel) and Safranin O (right panel). $^{**}P<0.01$.

demonstrated that arthritis was significantly suppressed by quetiapine (Fig. 1B and C).

3.2. Quetiapine attenuated disease progression in the murine collagen-induced arthritis model

On plain radiograph, no definitive erosive change in both interphalangeal and metatarsophalangeal joints in control was observed while multiple erosions in 2nd, 3rd and 4th interphalangeal joints and 2nd, 5th metatarsophalangeal joints in CIA group were found. In CIA + quetiapine group, there were mild erosive changes in 3rd interphalangeal joints and 2nd metatarsophalangeal joints (Fig. 2A, upper panel). The radiographic arthritic scores also indicated that the bone erosions and destruction of the joints were significantly suppressed in the CIA + quetiapine group (Fig. 2A, lower panel).

Histological sections of hind paw joints of mice were shown in Fig. 2B. Severe destruction and synovial proliferation were found in the articular joints of CIA group. Microscopically, the articular joints of CIA + quetiapine group revealed mild proliferation without inflammation (Fig. 2B, left panel, H&E staining). In Safranin O staining of articular joint, severe destruction of joint cartilage with decreased

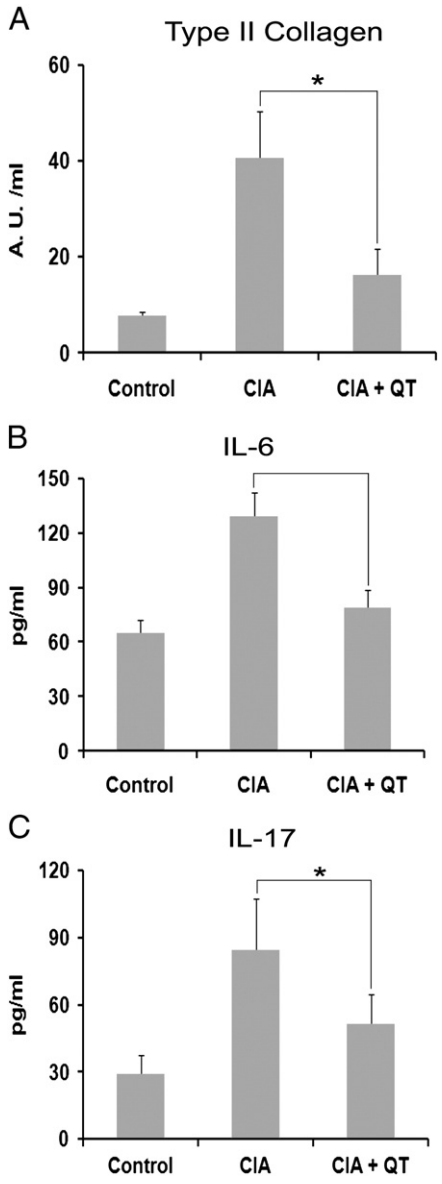

Fig. 3. The effects of quetiapine (QT) on the production of pro-inflammatory cytokines. The serum levels of type-II-collagen-specific antibodies (A), IL-6 (B), and IL-17 (C) were measured by ELISA according to the manufacturer's manual. $^{*}P<0.05$.

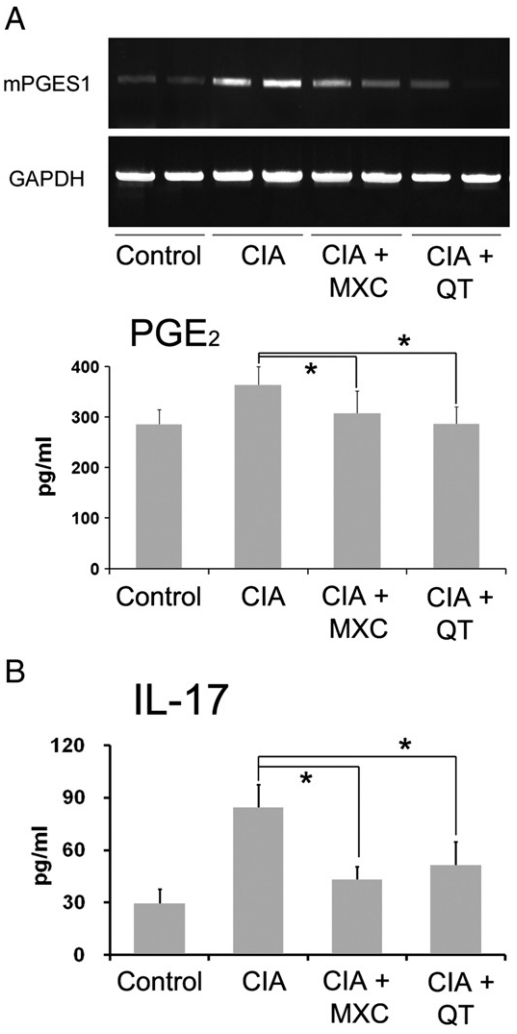

Fig. 4. The effects of quetiapine (QT) on the mRNA level of microsomal prostaglandin E synthase-1 (mPGES1) and the production of prostaglandin E_2 (PGE_2) in collagen-induced arthritis (CIA). QT (60 mg/kg) and meloxicam (MXC, 10 mg/kg) were given intraperitoneally after the secondary immunization with bovine type II collagen five times per week for 2 weeks. (A) mRNA expression levels of mPGES1 were observed by RT-PCR. The productions of PGE_2 were measured by ELISA according to the manufacturer's protocol. (B) The serum levels of IL-17 were measured by ELISA according to the manufacturer's protocol. $^{*}P<0.05$.

number of chondroblast was found in CIA group. The extents of joint destruction and decrease in the number of chondroblast were markedly attenuated in CIA + quetiapine group (Fig. 2B, right panel).

3.3. Quetiapine inhibited cytokine production in anti-type II collagen antibody-induced arthritis

To investigate whether quetiapine affects the immune response, the levels of anti-type II collagen antibody, IL-6 and IL-17 were measured by ELISA. As shown in Fig. 3A, the concentrations of anti-type II collagen-specific antibody in CIA group (40.5 ± 9.8 pg/ml) were significantly higher than those in control group (7.6 ± 1.0 pg/ml). The concentrations of anti-type II collagen-specific antibody in CIA + quetiapine group (16.0 ± 5.6 pg/ml) were significantly reduced compared with those in CIA group ($P<0.05$). The concentrations of IL-6 in CIA + quetiapine group (78.1 ± 10.5 pg/ml) were lower than those in CIA group (128.3 ± 14.1 pg/ml). Although it's not statistically significant, there is a tendency that IL-6 is lower in quetiapine treated mice than those in control group (Fig. 3B). As shown in Fig. 3C, the concentrations of IL-17 in CIA + quetiapine group (51.2 ± 13.5 pg/ml) were significantly lower than those in CIA group (84.3 ± 23.2 pg/ml, $P<0.05$).

To further investigate the anti-inflammatory effect of quetiapine, the effect of quetiapine on PGE_2 productions was evaluated in CIA + quetiapine group (60 mg/kg) and compared to those in CIA + meloxicam group (Fig. 4A). As shown in Fig. 4A upper panel, mRNA levels of mPGES1 in CIA + quetiapine group were markedly decreased, which were comparable to those in CIA + meloxicam group. Consistent with the results in Fig. 4A, PGE_2 productions in CIA + quetiapine group (285.0 ± 35.2 pg/ml) were significantly lower than those in CIA group (362.0 ± 37.9 pg/ml, $P<0.05$). PGE_2 productions in CIA + meloxicam group were 305.5 ± 46.2 pg/ml (Fig. 4A, lower panel). We also found that the decreased level of IL-17 in CIA + quetiapine group (51.2 ± 13.5 pg/ml) was comparable to that in CIA + meloxicam group (42.8 ± 8.8 pg/ml, Fig. 4B).

3.4. Quetiapine didn't induce weight gain in mice

Although quetiapine is known to show low incidence of extrapyramidal side effects such as dystonia, akathisia, and Parkinsonism, it commonly induces significant weight gain. Thus we investigated the changes in

the body weight of quetiapine treated mice. Surprisingly, in the current study, we found no significant weight changes in CIA + quetiapine group compared to those in CIA group (Fig. 5).

4. Discussion

Based on the analogies between depressive symptoms and signs and cytokine mediated physiological and behavioral responses to infection, a notion that depression is a psychoneuroimmunological disorder has been increasingly recognized (Castanon et al., 2002). Accordingly, evidence that antidepressants show immunoregulatory effects have been accumulated. Antidepressants have been shown to lower the levels of systemic inflammation markers (Bianchi and Panerai, 1996; Martelli et al., 1967). Studies indicate that patients with depression have elevated blood levels of cytokines, as compared with healthy controls, and that these levels are reduced upon treatment with selective serotonin reuptake inhibitor (Basterzi et al., 2005; Tsao et al., 2006). A recent study also reported that fluoxetine and citalopram exhibit anti-inflammatory activity in murine models of rheumatoid arthritis, in which fluoxetine and citalopram significantly inhibited the productions of TNF and IL-6 (Sacre et al., 2010). Rheumatoid arthritis is associated with pain, sleep disturbance, and fatigue that can overlap or mimic symptoms of depression. Depressive symptoms are also highly frequent in patients with rheumatoid arthritis. Thus inflammatory pathways may hold the key to a link between depression and rheumatoid arthritis (Bruce, 2008).

An intriguing case report that suggests anti-inflammatory effects in arthritis and comorbid major depression in a 49-year-old patient prompted us to commence this study (Baune and Eyre, 2010). Although anti-inflammatory effects of antidepressant are well established, very little is known as to the effect of quetiapine on inflammatory disease. In the current study, we demonstrated that quetiapine, an antidepressant as well as an atypical antipsychotic, decreased arthritic inflammation and bone destruction in the murine collagen-induced arthritis model. Quetiapine reduced the severity of arthritis and joint destruction, the underlying mechanism of which may be associated with the inhibitory effect of quetiapine on pro-inflammatory cytokine productions.

Evidence indicate that antipsychotics modulate the productions of cytokines (Yamaguchi et al., 2009). In the present study, quetiapine treatment significantly suppressed IL-17 in CIA group. IL-17 is known to induce proinflammatory cytokines such as TNF-α, IL-1β and IL-6 (Korn et al., 2007) and promote bone and joint damage through induction of matrix metalloproteinases and osteoclasts (Li et al., 2010). IL-17 also enhances both the joint inflammatory and destructive capacity of TNF-α (Buckland, 2011). Given the abovementioned information, the inhibitory effect of quetiapine on IL-17 production may suggest the possibility of quetiapine as an anti-inflammatory drug in arthritic disease.

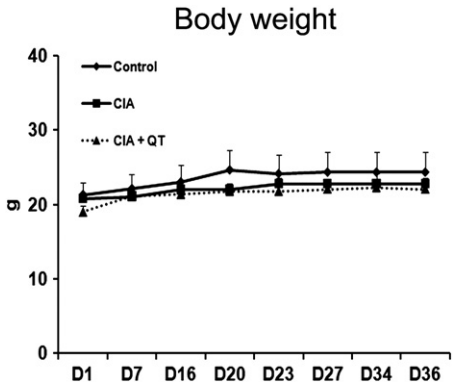

Fig. 5. The effects of quetiapine (QT) on the body weight in collagen-induced arthritis (CIA). Body weight of mice in each group was measured during the experimental period.

Quetiapine usually produces weight gain (Komossa et al., 2010). In the current study, however, significant weight gain with quetiapine treatment was not observed. This is not in line with the previous study in which treatment with 60 mg/kg quetiapine for 4 weeks showed significant weight gain compared to placebo and 30 mg/kg quetiapine treatment (Cope et al., 2005). The reason that weight gain was not observed in our study might be that the treatment period was 2 weeks, which may not be enough to produce weight gain effect.

In conclusion, our study demonstrates anti-inflammatory effect of quetiapine on murine collagen-induced arthritis and provides the possibility that quetiapine might be of great benefit in the treatment of arthritic disease.

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