Introduction: Disuse of diarthrodial joints is accompanied not only by many musculoskeletal problems, but also as an adverse outcome of treatments for various disorders, such as immobilization. Stress deprivation has been regarded as the most essential causative factor in joint disuse [1]. In our previous studies [2,3], we have developed a stress-shielding model for the patellar tendon (PT) without joint immobilization and demonstrated that stress deprivation dramatically deteriorates the mechanical properties of the rabbit PT, depending on the degree of shielded stress. However, the mechanism of the tendon deterioration caused by stress deprivation has not been clarified as of yet. Recently, the authors have found that IL-1β is over-expressed in the fibroblasts of the stress-shielded PT using the stress-shielding model [4]. It is known that IL-1β induces MMPs-1, -3, and -13 in tendon fibroblasts [5] and that IL-1β inhibits collagen synthesis in tendon fibroblasts [6]. Therefore, there is a possibility that IL-1β plays a role in the tendon deterioration in response to stress deprivation. Then, we have conducted a study in which the IL-1 functions are inhibited with IL-1 receptor antagonist (IL-1ra) in the stress-shielding model. We have hypothesized that a local administration of IL-1ra may inhibit the deterioration of the stress-shielded PT. On the other hand, the tendon tissues have a hierarchical structure composed of bundles, fascicles (fas), fibrils and fibers [7]. Yamamoto et al. [8] found that the effect of stress shielding on the mechanical properties of PT fas is much smaller than that of bulk tendons. They suggested that the stress shielding predominantly affects mechanical interaction among collagen fas or among collagen fas and other minor matrix proteins in the PT rather than affects the mechanical properties of collagen fas themselves. Therefore, we have made the second hypothesis that the effect of the IL-1ra application on mechanical properties of the fas harvested from the stress-shielded PT may not be significant. The purpose of this study is to test these two hypotheses.

Materials and Methods: A total of 30 mature rabbits were used in this study. In all animals, the right PT was completely released from stress by stretching a flexible steel wire installed between the patella and the tibial tubercle [2]. After the stress shielding procedure, the animals were divided into the following two groups of 15 rabbits each. In Group I, 5-μg rhIL-1ra (Peprotech) with 0.2-ml phosphate buffered saline (PBS) solution was injected between the PT and the infra-patellar fat pad. In Group II, 0.2-ml PBS alone was injected in the same manner as Group I. All rabbits were sacrificed 3 weeks after the surgery [2,3]. We considered that the 3-week period was suitable for detecting the effect of a local application of IL-1ra on the mechanical properties of the stress-shielded PT. In each group, eight animals were used for biomechanical evaluation of the PT in the bundle level having a width of 2.5 mm and five were used for biomechanical evaluation of the PT in the fas level having a diameter of 300 μm. The remaining two were used for histological observation. Statistical analyses were performed using unpaired t-tests to compare the tissue dimension and the mechanical properties of the PTs between Groups I and II. A significance level was set at p= 0.05.

Results: The averaged stress-strain relation curves are shown in Fig.1. The tangent modulus of Group I was significantly greater (p=0.016) than that of Group II, while the tensile strength of Group I was significantly greater (p=0.006) than that of Group II. There were no significant differences in strain at failure between Groups I and II (Fig.1). All fas specimens failed between the two gauge-length markers drawn on a specimen. The averaged stress-strain relation curves are shown in Fig.2. We could not detect any significant differences in the tangent modulus (p=0.558), the tensile strength (p=0.764), and the strain at failure (p=0.235) between Groups I and II (Fig.2). Histologically, the number of fibroblasts in the PTs of Groups I and II was significantly higher than that of the normal PT. In the PTs of Group I, fibroblasts with spindle-shaped nuclei were predominantly observed, while cells with round or oval nuclei were scattered in the PTs of Group II. In addition, splitting tendon fibers in the PT appeared to be less remarkable in Group I than in Group II.

Discussion: This study demonstrated that a local administration of IL-1ra significantly inhibits the reduction of the mechanical properties of the PT caused by stress-shielding at 3 weeks. This result implied that the over-expressed IL-1β [4] plays an important role in the deterioration mechanism of the mechanical properties of the PT. This study also showed that the effect of the IL-1ra application on tendon fas in the stress-shielded PT was not significant at 3 weeks. Yamamoto et al. [8] reported that stress deprivation reduces mechanical interactions among the collagen fas or among other minor matrix proteins such as proteoglycan and fas in the PT. The results in the present study suggested a strong possibility that the IL-1β over-expressed in the stress-shielded PT [4] does not affect the fas themselves but the mechanical interactions among the collagen fas or among other minor matrix and fas of the PT. As to clinical relevance, an anti-IL-1 strategy has recently attracted notice as a clinical therapy for inflammatory diseases such as rheumatoid arthritis [9]. The present study highlights a possible application of anti-IL-1 strategies for reducing the mechanical deterioration of tendons and ligaments in response to stress deprivation.