Acquired leptin resistance by high-fat feeding reduces inflammation induced by collagen antibody induced arthritis (CAIA) in mice.

INTRODUCTION:
Leptin is a peptide hormone secreted by adipocytes which regulates body weight and food intake. Serum leptin concentration is increased in obesity and is strongly correlated with total body fat mass. Also leptin was reported to be necessary in T-helper 1 (Th1) dependent inflammatory processes [1]. Severity of antigen-induced arthritis in leptin-deficient ob/ob mice was reduced [2] Clinically, rheumatoid arthritis (RA) patients with high body mass index (BMI) have lower disease activity compared to thinner patients [3]. These results are paradoxical findings in leptin efficacy in immune systems. In the previous studies, it has been suggested that most obesity have resistance to the anorectic and weight-reducing effects of leptin. It is uncertain whether any role that leptin may play in leptin resistance obesity is linked to changes in the immune system. Consequently, we have adopted high fat diet-induced obese mice which acquired leptin resistance as a means of examining the underlying causes of human obesity. And then we examined the effects of leptin resistance on collagen antibody induced arthritis (CAIA) in these model mice.

METHODS:
Diet therapies were induced in C57BL/6J mice (4 weeks old, female) by exposure to 50% fat to obesity and 11.5% fat to normal for 6 weeks. We examined serum leptin concentration and peripheral or central leptin response to confirm the development of leptin resistance. A cocktail of arthritogenic monoclonal antibodies to type II collagen (CAIA Chondrex, Redmond, CA) (day1 and 1) combined with a boost of LPS (day3) is used to induced CAIA. Leptin injections were started day 2 continued for 6 days by intraperitoneally (ip) or intracerebroventricular (ICV). The animals were sacrificed at day 11. Daily assessment of four paws swelling was used to monitor the development of arthritis according to Terato criteria [4]. The histopathologic features were also analyzed by Toluidine blue.

RESULTS:
Mice fed a high-fat diet (obese) had a significantly higher body weight in comparison to mice fed the control diet (control) from week 2 onwards until 6 weeks (Fig 1). After feeding period, serum leptin concentrations were about four times higher in obese mice (mean 430ng/ml) than control mice (111ng/ml). The simple linear regression analyses of obese group indicated that serum leptin levels correlated positively with body weight (Fig2).

Leptin administered by ip did not inhibit food intake in obese mice, but ICV injection of leptin inhibited feeding and significantly decreased body weight. Normal mice responded both ip and ICV leptin injections (Fig3a,b). These results indicate that obese mice with high fat diet for 6 weeks developed resistance to peripherally administered leptin, but these mice remained responsive to leptin delivered directly to the Central nervous systems.

Clinical symptoms of active arthritis reached a peak on day 8 with marked swelling or redness of the joints of the limbs (Fig4 c photgraf). Arthritis in the control mice progressed on day 8 with a score of 11.0±1.2 (mean ± SD). In contrast, arthritis score on day 8 in the obese mice with ip injection of PBS was 8.0 ± 1.0. Obese mice treated with i.p. injection of leptin did not exacerbation in the score compared with the mice treated with PBS (7.75 ± 0.96 vs 8.0 ± 1.0, respectively). ICV leptin injection mice showed a 26% exacerbation in the peak score compared with the mice treated with PBS (p < 0.05). The peak score had reached a similar level of that of controls (Fig4a). We then examined the histological features of arthritis knee joints on days 11. The effect of CAIA on articular cartilage degradations were evaluated according to the proteoglycan content, as demonstrated by Toluidine blue staining. As shown in Fig.4b, damage score of cartilage after arthritis were significantly lower in obese mice receiving PBS by any route or leptin by ip (p<0.01). The score of obese mice with ICV leptin injection was high equal to that of normal mice group (Fig4c).

DISCUSSION:
We demonstrated that acquired leptin resistance by high-fat feeding reduced inflammation induced by CAIA in mice. This fact could explain the discrepancy in the degree of arthritis between leptin-rich obese RA patients and leptin-deficient ob/ob mice. One reason of leptin resistance may be due to a defective transport of serum leptin across the blood-brain barrier (BBB) and an inability of leptin reaching target sites within the brain [5]. Therefore, in obese mice, systemic administration of leptin did not increase severity of arthritis, but central administration of leptin exacerbated arthritis and cartilage damage. The data presented in leptin sensitivity might be related with progression of arthritis as same as susceptibility of food appetite. There is some possibility that RA patients with high BMI who decrease sensitivity or resistant to leptin inhibit progression of arthritis.

REFERENCE: