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Intracerebroventricular interleukin-6 treatment decreases body fat in rats

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Abstract

Recently we found that interleukin-6 (IL-6) knockout mice develop mature-onset obesity and that a single intracerebroventricular (ICV) injection of IL-6 increases energy expenditure. In the present study we investigated if chronic ICV treatment with IL-6 can suppress body fat mass. IL-6 was injected ICV daily for two weeks to rats fed a high-fat diet. IL-6 treatment but not saline treatment decreased body weight by 8.4% and decreased the relative weights of mesenteric and retroperitoneal fat pads. Consistent with this, circulating leptin levels were decreased by 40% after IL-6 treatment but not after saline treatment. Average food intake per day was decreased in the IL-6 treated group compared to the saline treated rats. IL-6 treatment did not change hepatic expression of the acute-phase protein haptoglobin, serum levels of insulin or insulin-like growth factor-I, or the weights of the heart, liver, kidneys, adrenals, and spleen. We conclude that centrally administered IL-6 can decrease body fat in rats without causing acute-phase reaction.

Keywords: IL-6; Adipose tissue; Leptin; Intracerebroventricular

Obesity and obesity-related disorders are among the leading causes of illness and mortality in the developed world [1]. Obesity is caused by an imbalance between food intake and energy expenditure, two factors that are to a large extent regulated by the hypothalamus [2]. The regulation of energy homeostasis by the hypothalamus is influenced for example by the adipose tissue derived hormone leptin. Leptin levels in blood reflect adipose tissue mass and leptin treatment can reverse obesity in leptin-deficient mice [3,4]. Central treatment with leptin is more potent than systemic treatment showing that leptin acts at the hypothalamic level to decrease food intake and body weight [5].

Recently we demonstrated that interleukin-6 (IL-6)-deficient mice developed obesity and obesity-related metabolic disorders and that these effects could partly be reversed by IL-6 replacement [6]. IL-6 is well known for its effects on immune functions and is released from immune cells during inflammation [7]. However, IL-6 also has important anti-inflammatory properties, such as down regulation of the inflammatory cytokines tumor necrosis factor α (TNFα) and interferon γ during acute-phase reaction [8]. In the absence of inflammation, circulating IL-6 is to a large part derived from adipose tissue [9] and IL-6 levels in blood correlate with adipose tissue mass [9,10], in a way similar to leptin. Both short-term and long-term changes in food intake increase serum levels of IL-6 [11,12]. Circulating IL-6 levels, but not TNFα and interleukin 1β (IL-1β), increase during exercise due to increased expression of IL-6 in skeletal muscle [13,14]. Further, IL-6 and its receptor are expressed in discrete hypothalamic nuclei that have an established role in the regulation of metabolism and body composition [15,16]. Therefore, several non-immune organs that have an established role in the regulation of metabolism and body composition also produce IL-6.

We and others have reported that intracerebroventricular (ICV) injection of a low dose of IL-6 but not

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peripheral treatment with the same dose, acutely increases energy expenditure [6,17]. Moreover, it has been reported that ICV treatment with IL-6 can suppress 2-h food intake [18], but not 24-h food intake [19]. However, to our knowledge, it has not been investigated whether long-term treatment with centrally acting IL-6 can decrease body fat. The aim of the present study was to investigate whether central treatment with IL-6 can decrease adipose tissue mass and body weight in non-IL-6-deficient animals.

Materials and methods

Animals. Male Wistar rats (Charles River, Margate, UK) were maintained under standardised environmental conditions, i.e., 24–26 °C, 50–60% relative humidity, artificial lighting at 06.00–19.00 h, with water and pelleted food ad libitum. The rats were placed on high fat diet (Dairy Butter Diet, 40-energy % fat, ICN Biomedicals, Costa Mesa, CA, USA) two weeks before ICV cannulation and were kept on the diet throughout the study. All animal procedures were conducted in accordance with the UK Animals (Scientific Procedures) Act 1986.

Intracerebroventricular (ICV) cannulation. The rats were anaesthetised by intraperitoneal injection of tribromoethanol/amylhydrate (avertin, 10 ml/kg) and placed in a stereotactic frame with the nose bar set at 3 mm below the interaural line. Permanent 28 gauge stainless steel guide cannulae (Plastics-One, Roanoke, VA, USA) were positioned in the lateral ventricle using stereotactic co-ordinates (0.6 mm posterior to the bregma, 1.6 mm lateral to midline and 4.0 mm below the outer surface of the skull). Guide cannulae were held in position by dental cement attached to three stainless steel screws driven into the skull. A stainless steel obdurator (Plastics One, Roanoke, VA, USA), which protruded 0.5 mm beyond the guide cannula, was inserted to maintain cannula patency. After one-week recovery from the surgery, the rats were handled on a daily basis and injected with saline. Prior to the study, human angiotensin II (Sigma, Poole, Dorset, UK) was injected ICV (150 ng per rat; volume = 10 μl) to confirm the correct position of the cannula. Rats, which showed a sustained drinking response within two minutes following injection of angiotensin II, were included in the study [20].

Study. Two weeks after ICV cannulation, the rats were given a daily ICV injection of either rat recombinant IL-6 (0.4 μg/day, lot # 10786 J207, endotoxin content <0.1 ng/μl, PeproTech EC, London, UK), or an equal volume (10 μl) of saline (Animal Care limited, York, UK) for two weeks. Measurement of specific activity of this lot of IL-6 by the in vitro bioassay (SBH Sciences, Natick, MA, USA) showed an $ED_{50} \leqslant 0.01$ ng/ml. A third group was injected with an irrelevant peptide, Apelin-13, (3 nmol/day, Phoenix Pharmaceuticals, Belmont, USA) in a dose that had been shown to have acute effects on food-intake (Sunter et al., manuscript in preparation). Food intake and body weight were monitored every day. At the end of the study the rats were terminally anaesthetised (barbiturate 70 mg/kg; Rhone Merieux, Harlow, Essex, UK). Three intra-abdominal fat pads (gonadal, retroperitoneal, and mesenteric) and one subcutaneous fat pad (inguinal) as well as several other organs were dissected and weighed. The rats were not treated with IL-6 or saline the day the study ended.

Serum analyses. A blood sample was collected from the tail vein of conscious rats on the day before the study started. At the end of the study, blood was collected by cardiac puncture from anaesthetised rats. The blood samples were immediately placed on ice and later centrifuged to obtain serum. Serum samples were kept at −80 °C until analysed. Serum leptin and insulin were assayed using enzyme linked immunosorbent assays (Crystal Chem, Chicago, IL, USA). Glucose was measured using reagents from Sigma Diagnostics (Infinity glucose reagent; Sigma diagnostics, St Louis, MO, USA). Insulin-like growth factor I (IGF-I) was analysed by radioimmunoassay (Mediagnost GmbH, Tubingen, Germany). Corticosterone was analysed by radioimmunoassay (ImmunoChem ICN Biomedicals, CA, USA).

Western blot. Liver protein for Western blotting was prepared from fresh frozen liver samples by sonication in a buffer containing 10 mM K_2HPO_4, 10 mM KH_2PO_4, 10 mM EDTA, 6.0 mg/mL CHAPS (3-[(3-Cholamidopropyl) dimethyl ammonio]-1-propanesulfonate), and one tablet of Complete (protease inhibitor cocktail tablets, Roche, Mannheim, Germany) per 25 mL of buffer. Fifty mM DTT (Dithiothreitol) and Novex NuPage sample buffer was added to the samples (Novex, San Diego, CA). Fifty μg protein per sample was run on NuPage 4–12% gradient gels in MOPS buffer using a Novex Xcell II system (Novex), and then transferred to PVDF (Polyvinylidene difluoride) membranes by electroblotting. The membranes were blocked overnight in 5% dry milk in a TBS–Tween buffer (50 mM Tris–HCl, 137 mM NaCl, 0.1% Tween 20), and then incubated with a primary rabbit-antihuman haptoglobin antibody (cross-reactive with rat haptoglobin; Dako, Denmark) and a secondary swine anti-rabbit HRP-conjugated antibody (Dako). Membranes were developed using ECL+ (Amersham, Uppsala, Sweden). Quantification of protein bands was performed by scanning of films and analysis of band volume using ImageQuant software (Amersham).

Statistical analysis. Values are given as means ± standard error of the mean (SEM). Comparisons between two groups of rats were made by unpaired Students *t* test. Comparisons within each group before and after treatment were made by paired Students *t* test.

Results

Body weight

Rats were given daily ICV injections of IL-6 or saline from day 1 to day 14 and body weight was monitored every day. At day 5 of treatment the body weights of the IL-6 treated group started to decrease and deviate from the saline treated group (Fig. 1A). On day 10, the body weights were significantly decreased in the IL-6 treated group compared to the saline treated group and this difference remained throughout the study (Fig. 1A). At the end of the study, the body weights of the IL-6 treated rats had decreased 35.6 g (8.4%) ($P < 0.003$) while there was no effect on body weight in the saline treated group (Fig. 1B). Injection of the irrelevant peptide apelin, did not affect body weight, suggesting that the effect of IL-6 was not due to a non-specific protein effect (before: 414.5 ± 11.8 g, after: 416.5 ± 12.2 g, ns).

Food intake

Daily food intake per body weight was not significantly lower in the IL-6 treated group compared to the saline treated group (Fig. 2A). However, the average daily food intake measured over the whole study was decreased in the IL-6 treated group compared to the

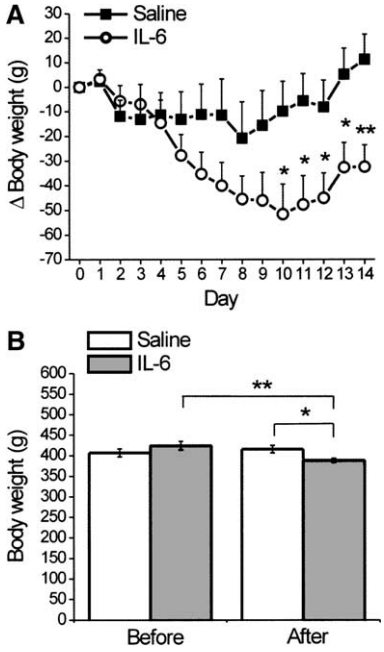

Fig. 1. Changes in body weight during two weeks of ICV treatment with IL-6 (0.4 μg/day) or saline to male rats on a high fat diet (A). Body weights before (day 0) and after (day 14) two weeks of ICV treatment with saline or IL-6 (B). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. corresponding control. $n = 7$–9.

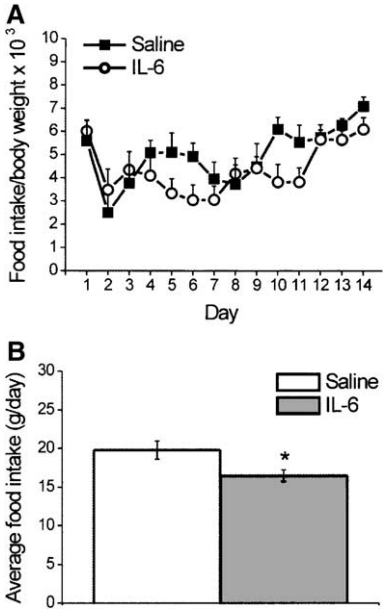

Fig. 2. Variations in daily food intake/body weight over a two-week ICV treatment period with IL-6 (0.4 μg/day) or saline (A). Average daily food intake during the whole study (g/day) in saline and IL-6 treated rats (B). $^{*}P < 0.05$, vs. corresponding control. $n = 7$–9.

saline treated group (Fig. 2B). Apelin treatment did not change food intake compared to the saline treated group (saline: 19.8 ± 1.2 g vs. apelin 19.0 ± 1.3 g, ns).

Dissected fat pads and serum leptin

Fat pads were dissected and weighed at the end of the study. The total weight of all dissected fat pads was significantly lower in the IL-6 treated compared to the saline treated group (Fig. 3A). The relative weights of the mesenteric and retroperitoneal fat pads were decreased by 20 and 30%, respectively, in the IL-6 treated compared to the saline treated group (Fig. 3B). In line with the decreased weight of dissected fat pads, circulating leptin levels were decreased by 40% in the IL-6 treated group at the end of the study compared to before treatment (Fig. 3C). The leptin levels of the IL-6 treated group also tended to be lower than in the saline treated group at the end of the study ($P = 0.054$) (Fig. 3C). Leptin levels in the saline treated rats were not signifi-

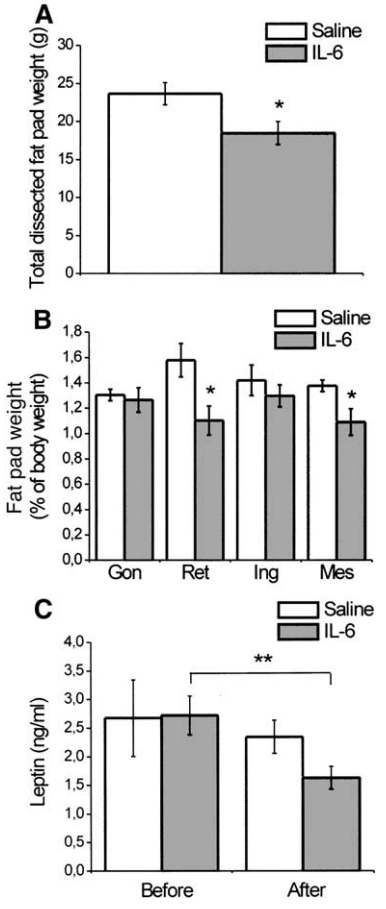

Fig. 3. Dissected fat pads and serum leptin. Three intra-abdominal fat pads (gonadal (Gon), retroperitoneal (Ret), and mesenteric (Mes)) and the inguinal (Ing) fat pad (a subcutaneous fat pad in the groin) were dissected. The total weight of the dissected fat pads after two weeks of ICV treatment with saline or IL-6 (0.4 μg/day) (A). Comparison between the relative weight of the different dissected fat pads (% of body weight) after saline and IL-6 treatment (B). Leptin levels before and after two weeks of ICV treatment with saline or IL-6 treatment (C). (A, B) $^{*}P < 0.05$, vs. corresponding control, (C) $^{**}P < 0.01$ vs. before IL-6 treatment $n = 7$–9.

cantly decreased during the study (Fig. 3C). There was no difference in the total weight of the dissected fat pads (23.7 ± 1.5 vs 22.8 ± 2.1 g, ns) or the relative weights of any of the dissected fat pads (not shown) between the saline treated animals and the apelin treated animals.

Serum chemistry

The levels of insulin-like growth factor-I (IGF-I) in serum did not change from the start to the end of the study and did not differ between the groups (saline: 975.3 ± 31.1 vs. 923.6 ± 42.9 ng/ml and IL-6: 1012.2 ± 35.5 vs. 949.2 ± 51.1 ng/ml). Insulin levels were not changed during the study in either group and were not different between the groups (saline: 3.06 ± 0.39 vs. 4.71 ± 1.88 ng/ml and IL-6: 3.76 ± 0.67 vs. 3.43 ± 0.42 ng/ml). Glucose levels were not significantly different between the IL-6 and saline treated groups at the end of the study (saline vs. IL-6: 274.8 ± 9.6 vs. 248.0 ± 13.4 ng/ml). Corticosterone levels were significantly increased by about 60% after IL-6 treatment (123.3 ± 22.2 ng/ml vs. 204.8 ± 19.4 ng/ml, $P < 0.01$) but not by saline treatment (214.1 ± 38.4 vs. 159.4 ± 33.2 ng/ml). Neither the saline nor the IL-6 treated rats showed any signs of illness such as staring coat, reduced grooming, or discharge from eyes, or reluctance to move.

Liver haptoglobin

Haptoglobin was measured in livers from saline and IL-6 treated rats, to assess acute-phase reaction. The liver of a rat in the animal colony that was killed because of signs of illness was used as a positive control for acute-phase reaction. Quantification of the Western blots showed that haptoglobin expression did not differ between saline and IL-6 treated rats, while it was increased in the ill animal (Figs. 4A and B).

Organ weights

The relative weights of the heart, liver, kidneys, adrenals, and spleen were not affected by IL-6 treatment compared to saline treatment (Table 1). Despite the increase in serum corticosterone levels, there was no increase in adrenal weight in IL-6 treated rats arguing against a pronounced long-term activation of the adrenals. Apelin treatment did not affect the weights of any of the dissected organs compared to saline treatment (not shown).

Discussion

This study provides the first demonstration that chronic central treatment with IL-6 reduces adipose tissue mass. The decrease in adipose tissue mass after

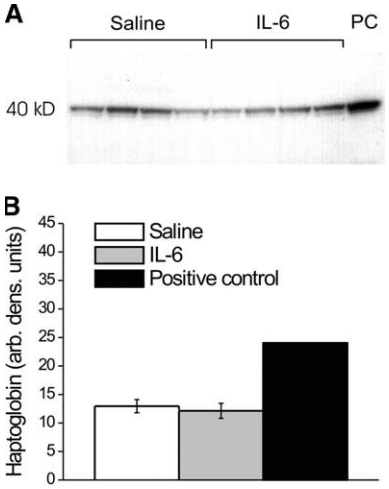

Fig. 4. Hepatic expression of haptoglobin was measured by Western blotting after two weeks of ICV treatment with saline or IL-6 (0.4 μg/day). The liver from a rat with behavioural signs of illness was included as a positive control (PC) (A). Quantification of haptoglobin expression by densitometry of Western blots (B). $n = 7$–9 ($n = 1$ for positive control).

Table 1
Organ weights

	Saline	IL-6
Adrenal glands (% of body weight)	0.031 ± 0.00	0.031 ± 0.00
Heart (% of body weight)	0.29 ± 0.01	0.29 ± 0.01
Liver (% of body weight)	7.12 ± 0.27	7.31 ± 0.24
Spleen (% of body weight)	0.41 ± 0.02	0.49 ± 0.04
Kidneys (% of body weight)	0.69 ± 0.02	

Organs were dissected and weighed after ICV treatment with saline or IL-6 (0.4 μg/day) for two weeks ($n = 7$–9).

IL-6 treatment in rats fed a high fat diet was accompanied by a decrease in leptin levels, while the weight of several non-fat organs was unchanged. The average food intake per day measured over the whole two-week study was decreased in the IL-6 treated group. Central administration of IL-6 did not affect levels of IGF-I, insulin, or the acute-phase reactant haptoglobin, while corticosterone levels were increased, as reported previously [21].

Energy homeostasis is regulated by a balance between energy expenditure and food intake and the neural pathways that control these two factors are tightly interrelated [22]. The mechanism resulting in decreased adipose tissue mass in the present study may therefore be a combination of increased energy expenditure, as we and others have reported previously [6,17], and the slight reduction of food intake that we saw in the present study. Previous studies have reported suppression of 2-h food intake after a single ICV injection, but not of 24-h food intake following chronic ICV IL-6 infusion with osmotic minipumps [18,19].

IL-6 in high doses over a long time may affect lean body mass. Chronic and extreme elevation of IL-6 levels throughout the whole developmental period causes muscle atrophy in some IL-6-transgenic mouse models [23]. This muscle atrophy has been assumed to mimic the muscle wasting during severe infections and cancer cachexia [23,24]. However, mice carrying an IL-6 secreting tumour for 18 days with IL-6 levels of up to 40 ng/ml in blood displayed a specific reduction of body fat, but no change in lean body mass, compared to pair-fed mice bearing a non-IL-6-secreting tumour [25]. At the end of this study serum IL-6 levels were 40 ng/ml, which is higher than the levels seen during bacterial infection and sepsis [26]. The latter reports support our data that IL-6 has a specific effect on adipose tissue mass in adult animals. In the present study we have eliminated the possibility that effects of tumour burden and secretion of other factors from the tumour are permissive for the effect of IL-6 on adipose tissue mass.

Stunted growth is observed in some IL-6 transgenic mouse lines and this effect is thought to be due to decreased serum IGF-I levels [27]. In the present study, serum IGF-I levels and the weights of several non-adipose organs were not affected by the ICV IL-6 treatment. Moreover, IL-6 treated rats did not have acute-phase reaction, and did not show behavioural alterations associated with illness, which is also in line with earlier studies [21].

Ciliary neurotrophic factor (CNTF) is a cytokine that is structurally related to IL-6. The ligand binding parts of the CNTF receptor and the IL-6 receptor are closely related and both bind to the same signal transducing subunit (gp130) [28,29]. Low doses of CNTF, which do not cause acute-phase reaction or fever, have been shown to reduce body fat in mice with diet induced obesity [30,31] and clinical trials with a CNTF analogue have shown that CNTF can reduce body weight also in humans [32]. Comparisons between the effects of chronic treatment with high doses of CNTF or IL-6, that both caused similar degrees of acute-phase reaction, showed that CNTF caused protein degradation and anorexia, while neither of these effects were observed after IL-6 treatment [33]. This suggests that IL-6 is even less catabolic than CNTF.

It remains unclear whether the endogenous IL-6 that participates in the regulation of body composition at the CNS level originates from the CNS or the periphery. A large part of circulating IL-6 is derived from adipose tissue during normal, non-inflammatory conditions in humans, and IL-6 levels correlate well with BMI [9,10,34]. IL-6 could be a mediator in the feedback regulation from adipose tissue to the hypothalamus, in a similar manner to the adipostat hormone leptin [3]. IL-6 is also produced and released in high amounts to the circulation from muscle tissue during exercise [13,14] but it is not known to which extent this IL-6 reaches the CNS. Another possibility is that IL-6 produced locally in the CNS may be of importance for the regulation of energy homeostasis. IL-6 is produced by neurons in the hypothalamus in areas involved in the regulation of body composition [15,16]. IL-6, like CNTF, is also produced by non-neuronal cells within the CNS, e.g., microglia [35]. Thus the origin of the centrally acting endogenous IL-6 is not clear and it also remains to be determined whether IL-6 given peripherally, at higher doses than those given centrally in the present study has a therapeutic potential in the treatment of obesity in humans.

In summary, the results from the present study show that ICV administration of IL-6 decreases adipose tissue mass in rats. Taken together, our present and previous data [6] show that IL-6 has a physiological and possibly pharmacological role in regulation of body fat at the CNS level by increasing energy expenditure and to a certain degree by reducing food intake.

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