Leptin and nerve growth factor regulate adipose tissue

To the editor — In a recent *in situ* study of white adipose tissue (WAT) from lean and obese subjects[1], Lönnqvist *et al.* observed that the *ob* gene is overexpressed in obese people. Similarly, Maffei *et al.*[2] reported that plasma leptin, the gene product of the *ob* gene, is highly correlated with body mass index in rodents and in lean and obese humans. They propose that this protein is "an afferent signal in a feedback loop that regulates body fat mass," and that "in some cases, resistance . . . to its physiologic effects leads to obesity."

Moinat *et al.*[3] have reported that the *ob* gene mRNA level is increased also in brown adipose tissue (BAT) of obese rats as compared with that of their lean controls. The significance of the synthesis of leptin and its increased production in BAT of obese subjects is not known. BAT is a highly specialized tissue, which grows and produces heat in response to norepinephrine secreted from the sympathetic nerves, particularly during cold exposure (nonshivering thermogenesis) or after eating (diet-induced thermogenesis)[4]. Interestingly, in obese animals sympathetic stimulation is reduced, and BAT is consequently in a relatively atrophied and thermogenically quiescent state[4].

We have recently demonstrated that nerve growth factor (NGF) is expressed in rodent and human dispersed brown fat cells[5], and we speculated that it can modulate the sympathetic innervation of BAT. The levels of NGF protein are higher in *fa/fa* Zucker rats and *ob/ob* mice than in their lean controls (Fig. 1). WAT, obtained from subcutaneous and epididymal depots of *fa/fa* rats or *ob/ob* mice, expresses very low amounts of NGF (data not shown).

Because animal and human studies reported a significant decrease in turnover of noradrenaline and in sympathetic nervous system activity in those fed energy-restricted diets, and blunted adaptive responses of the sympathetic nervous system to changing energy states in the obese subjects[6], we studied the NGF expression in brown fat cells obtained from lean or obese *fa/fa* rats after 50% food restriction, and compared it with the *ob* gene expression. Either 48 hours food deprivation or 1 week of a restricted diet induced a significant increase in NGF production in lean rats as with obese rats (Fig. 1). This could indicate that in lean subjects BAT tries to compensate for the decreased sympathetic stimulation by synthesizing NGF, whereas in obese subjects BAT actually maximally produces NGF. Under acute (36 hours) and chronic (10 days) food restriction, *ob* gene mRNA levels significantly decreased not only in WAT but also in BAT compared with respective controls[3] in lean and obese animals (unpublished results).

Altogether, these findings seem to suggest that both NGF and leptin may be markers for a given state of differentiation in BAT, according to the genetic background and the environmental stimuli. When the differentiation state shifts in response to the effects of carrying *fa/fa* or *ob/ob* genes or to a restricted diet, NGF and leptin may change differently in accordance with these factors.

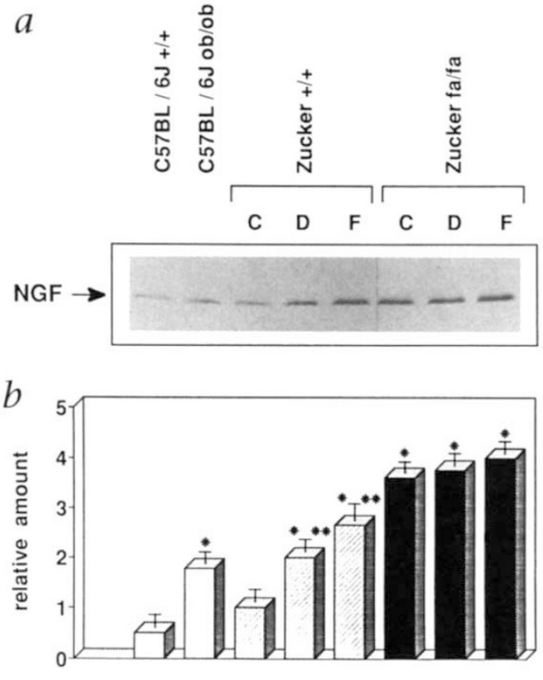

Fig. 1 Nerve growth factor (NGF) expression in 8-week-old mutant mice and rats. *a*, Western blot of brown adipocyte proteins obtained from *obese* and lean animals. The immunoblot was obtained by separating 100 µg of protein on 15% SDS-polyacrylamide gel. Electrophoresis was conducted under reducing conditions, after boiling the samples in 5% β-mercaptoethanol-containing electrophoresis sample buffer for 5 min. C, control fed *ad libitum*; D, 50% food restriction for 1 week; F, fasting (48 hours). C57BL/6J +/+ and *ob/ob* mice and Zucker +/+ and fa/fa rats were purchased from Harlan-Nossan (Correzzana, Milan, Italy). *b*, Densitometric analysis ($n = 6$ for each group); bars represent means ± s.e.m., plotted relative to the area under the curve, with NGF in brown adipocytes of lean rats at room temperature taken as one. The measurements were performed with the LKB UltroScan XL laser densitometer. The normalized data were statistically analyzed by analysis of variance together with Newman-Keuls' multiple comparisons *post hoc* test for effects of metabolic condition (normal weight or obese), and for experimental procedure (dieting or fasting). $^{*}P \leq 0.01$ vs. lean rats; $^{**}P \leq 0.01$ vs. *ad libitum* fed rats.

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