Female Sprague-Dawley rats were sympathectomized by neonatal guanethidine treatment or treated with saline. As adults, half of the rats in each group were injected daily with leptin (20 mg/kg/day, sc twice daily) and half with saline. Five days of leptin treatment reduced food intake more than 60%, interscapular brown adipose tissue (BAT) more than 39%, and metabolic white adipose tissue (WAT) collectively more than 80%. Leptin reduced body weight significantly in both sympathectomized rats (-15.4 ± 2.7 g) and controls (-19.5 ± 2.4 g), but the amount of weight loss did not differ between groups. Similarly, leptin-induced weight lost from individual metabolic WAT pads (retroperitoneal, mesenteric, parametrial, inguinal and interscapular) was significant, but did not differ between sympathectomized and control groups. Weight lost by these WAT pads often approached 100%. Interscapular brown adipose tissue weight was also significantly reduced by leptin (p < .03) without a significant interaction effect (p = .35). Loss of body weight appeared to be due to a highly selective targeting of metabolic adipose tissue by leptin. The weights of non-metabolic WAT (orbital fat) and organs sensitive to protein loss during food restriction and starvation (kidney and spleen) were not affected by either sympathectomy or leptin. Sympathectomy was confirmed in all guanethidine treated rats by the loss of nicotine-stimulated elevation of plasma norepinephrine and by immunohistochemical evidence revealing loss of sympathetic postganglionic neurons. We conclude that loss of body weight induced by systemic leptin treatment does not require sympathetic neurons. Leptin was a gift of Amgen. Supported by PHS No. DK 40498 to S.R.