Role of leptin in body fluid homeostasis and blood pressure control: Studies with transgenic skinny mice overexpressing leptin

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Summary

Leptin is an adipocyte-derived hormone that plays an important role in energy homeostasis. To explore the pathophysiological role of leptin in obesity-related hypertension, we examined cardiovascular phenotypes of transgenic skinny mice with elevated plasma leptin concentrations comparable to those in obese subjects. We also studied genetically obese KKA^y mice with hyperleptinemia, in which hypothalamic melanocortin system is antagonized by ectopic expression of the agouti protein. The tail-cuff systolic blood pressure was significantly elevated, accompanied by an increase in urinary catecholamine excretion in transgenic skinny mice relative to nontransgenic littermates. The blood pressure elevation was abolished by an α 1-adrenergic, nonselective α -adrenergic, and ganglionic blockers at such doses that did not affect blood pressure in nontransgenic littermates. Central administration of an α -melanocyte stimulating hormone (α -MSH) antagonist caused a marked increase in cumulative food intake in both genotypes, whereas no significant changes in blood pressure were noted. The obese KKA^y mice developed blood pressure elevation with increased urinary catecholamine excretion relative to control KK mice. After a 2-week caloric restriction, blood pressure was reversed in nontransgenic littermates with the A^y allele, in parallel with a reduction in plasma leptin concentrations, but were sustained in transgenic mice overexpressing leptin with the A^y allele, which remained to be hyperleptinemic. This study demonstrates blood pressure elevation in transgenic skinny mice and obese KKA^y mice, both of which are hyperleptinemic, thereby suggesting that leptin may represent a missing link between obesity and hypertension.