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\textsuperscript{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 \( \alpha \) 1-adrenergic, nonselective \( \alpha \) -adrenergic, and ganglionic
blockers at such doses that did not affect blood pressure in nontransgenic littermates.
Central administration of an \( \alpha \) -melanocyte stimulating hormone (\( \alpha \)-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\textsuperscript{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 \( A \)\textsuperscript{p} allele, in parallel with a reduction
in plasma leptin concentrations, but were sustained in transgenic mice
overexpressing leptin with the \( A \)\textsuperscript{p} allele, which remained to be hyperleptinemic. This
study demonstrates blood pressure elevation in transgenic skinny mice and obese
KKA\textsuperscript{y} mice, both of which are hyperleptinemic, thereby suggesting that leptin may
represent a missing link between obesity and hypertension.