IGF-1 bioavailability in tissues determines body size

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IGF−1 Bioavailability in Tissues Determines Body Size

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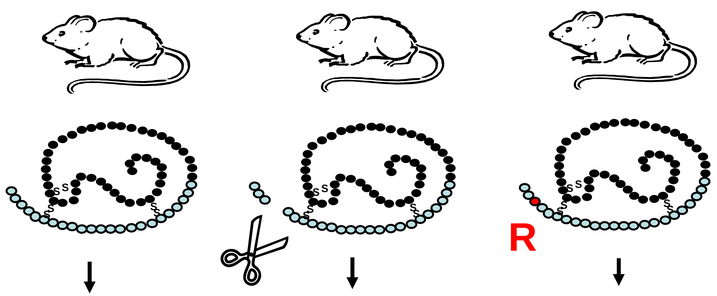
BACKGROUND

IGF-1 is an important regulator of somatic growth and body size. IGF-1 forms complexes with a family of high affinity IGF-binding proteins (IGFBPs) that protect it from proteolytic degradation in serum and regulate its bioavailability. The IGF-1 analog des-IGF-1 has a three amino acid truncation at its N-terminus, which significantly decreases its binding affinity to the IGFBPs, but does not affect its affinity for the IGF-1 receptor. The Long R IGF-1 analog (LR3) has one amino acid substitution at position 3 (glu>arg), which significantly reduces its affinity to IGFBPs.

AIM

Determine whether IGF-1 binding to IGFBPs is both necessary and sufficient for regulation of somatic growth

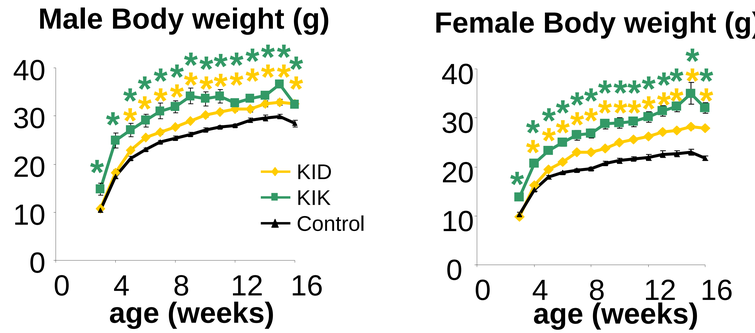
Knock-In Mouse Models



Knock-in mice generated on B6 background

RESULTS

Free IGF-1 in tissues leads to increased body weight



Organ Weight to Body Weight Ratios for Mouse Models

Female

Model	Gonadal fat	Pancreas	Uterus and Ovaries
KID	0.73	0.95	1.17
KIK	0.66	0.82	1.14
Control	1.31	0.61	0.78

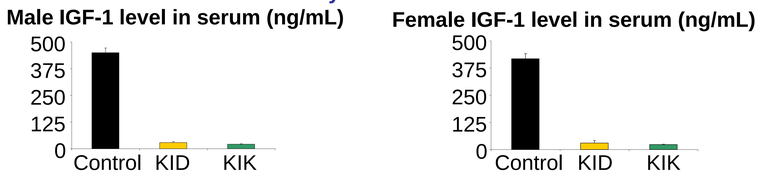
Male

Model	Gonadal fat	Pancreas
KID	0.78	0.89
KIK	0.89	0.77
Control	1.41	0.59

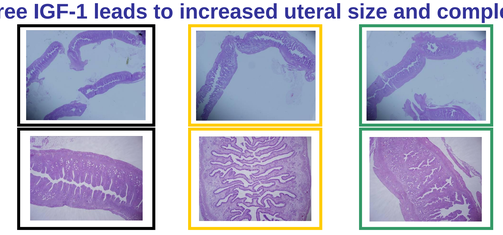
16w organs

Male reproductive tract

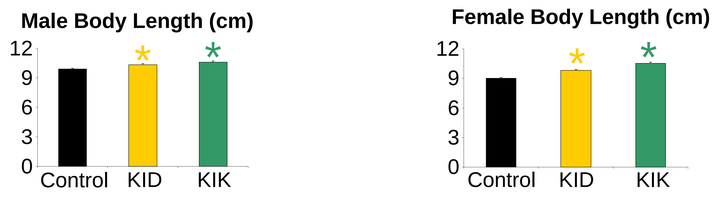
Knock-in mice show nearly undetectable levels of IGF-1 in serum



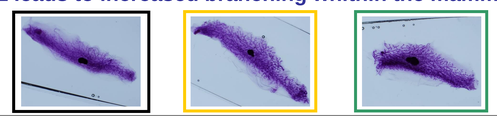
Free IGF-1 leads to increased uteral size and complexity



Free IGF-1 increases body length

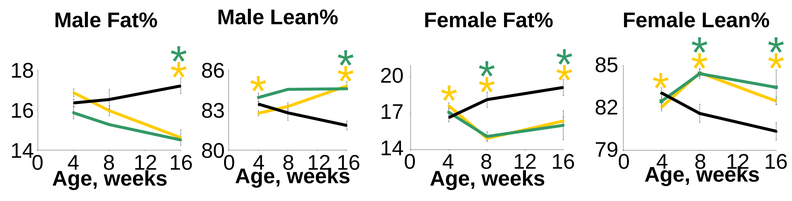


Free IGF-1 leads to increased branching whithin the mammary gland



Mammary gland

Free IGF-1 increases lean mass and decreases fat mass



CONCLUSIONS

Loss of IGFBP binding increases body size and organ size in both males and females, likely through increased IGF-1 bioavailability. Further studies are needed to determine how changes in IGF-1 bioavailability affect skeletal growth, carbohydrate metabolism and tumor susceptibility.

GRANTS

National Institute of Health : R01AR055141- R01AR054919