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Oral Presentation 3.4

EFFECTS OF THE *fa* MUTATION ON THE LEPTIN RECEPTOR

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Leptin, a hormone released by adipocytes and involved in the regulation of energy, binds to the leptin receptor (OB-R).¹ The activated OB-R induces the phosphorylation of the receptor itself and Janus kinases (JAKs). The JAKs then activate Signal Transducer and Activator of Transcription (STAT) proteins which translocate to the nucleus to regulate genes. A result of a single amino acid substitution, the *fatty* mutation of OB-R (OB-R(*fa*)) is found in the extracellular domain of the receptor. This mutation leads to an obese phenotype in homozygous *falfa* rats.² Preliminary experiments suggest that the *fatty* mutation may cause deficiencies in the signal transducing capabilities of the receptor.³ The goal of this study was to identify the precise signaling function of the OB-R(*fa*).

Human kidney 293 cells were generated that stably express either the wild type OB-R (OB-R(wt)) or OB-R(*fa*). These stable cells exhibited significantly increased ligand binding relative to the parental cell line. When treated with leptin, both OB-R(wt) and OB-R(*fa*) cells indicate an increase in STAT1 and STAT3 activity. The OB-R(*fa*) cells exhibit an increase in the basal level of DNA binding activity in the absence of leptin. The constitutive activity of OB-R(*fa*) was verified with gene induction experiments. In addition, leptin treatment also activates the SHP-2 protein tyrosine phosphatase, which is predicted to down-regulate OB-R signaling. This finding is in contrast to the previous report that suggested SHP-2 is not part of OB-R signaling.⁴ These results demonstrate that OB-R(*fa*) alters the function of the receptor by introducing a ligand-independent signal transduction, suggesting that the *fatty* phenotype is mechanistically distinct from the *diabetes* mutation of OB-R which causes a signal incompetent receptor.^{1,7}

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