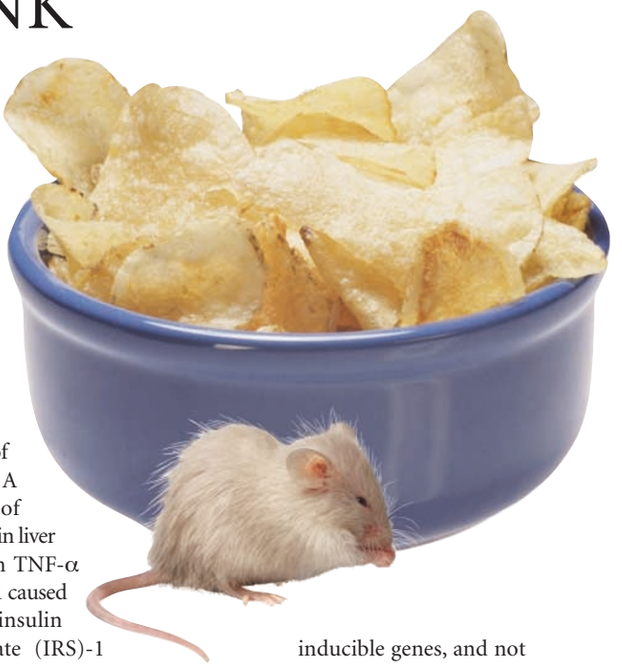
OBESITY

# A high dose of JuNK for fat mice



Mice fed on a high-fat diet, and mice genetically prone to obesity, have extremely high activity of the protein Jun N-terminal kinase (JNK)-1 in their livers, muscle and fat, according to research from Hotamisligil and colleagues, published in the 21 November issue of *Nature*. Mice lacking JNK1 suffer less obesity and insulin-resistance than wild-type mice, showing that the elevated expression of JNK1 is a cause of the disease, and not an effect.

It is well-known that obesity and type 2 diabetes are prevalent and serious metabolic diseases in the developed world. These conditions are associated with a chronic inflammatory response characterized by abnormal cytokine production. Elevated production by adipose tissue of one such inflammatory cytokine, tumour-necrosis factor (TNF) α, has been detected in several experimental obesity models and obese humans. Free fatty acids (FFAs) are also implicated in the aetiology of obesity-induced insulin resistance, although the molecular pathways involved remain unclear. Because both TNF-α and FFAs are potent JNK activators, the authors speculated that obesity could be causally linked to aberrant metabolic control of JNK signalling.

There are multiple subtypes of the JNK regulatory enzyme, each of which induces the expression of genes in a cell- and stimulus-specific manner. Having established that JNK1 causes obesity and insulin resistance, the next step was to examine the molecular mechanisms that lay downstream of JNK1 activation. A cellular model of insulin resistance in liver cells treated with TNF-α showed that JNK1 caused an increase in insulin receptor substrate (IRS)-1 phosphorylation of serine 307, which has an inhibitory effect on insulin signalling. Importantly, no such increase in serine 307 phosphorylation was seen in JNK1-deficient mice. In addition, insulin-induced tyrosine phosphorylation, a positive signal, was strongly enhanced in the absence of JNK1. This study shows that JNK1 is a crucial mediator of obesity and insulin resistance and adds to growing evidence that the JNK signalling cascade could be a potential therapeutic target for metabolic diseases.

The JNK pathway is also a focus in the search for drugs to treat rheumatoid arthritis, epilepsy, neurodegenerative diseases and cancer. Drugs that inhibit JNK activation should selectively block the over-activation of inducible genes, and not affect normal cellular functions, since JNKs do not regulate normal gene expression. Mice engineered to be deficient in the brain-specific JNK subtype JNK3 are resistant to experimental epilepsy and the neuronal cell death. JNK3 inhibitors may therefore have therapeutic value for treating neurodegeneration associated with Alzheimer's disease, Parkinson's disease, stroke and head trauma.

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## References and links

**ORIGINAL RESEARCH PAPER** Hirosumi, J. *et al*. A central role for JNK in obesity and insulin resistance. *Nature* **420**, 333–336 (2002)
**FURTHER READING** Crowley, V. E. *et al*. Obesity therapy: altering the energy intake-and-expenditure balance sheet. *Nature Rev. Drug Disc.* **1**, 276–286 (2002)
**WEB SITES** Hotamisligil's lab: http://www.hsph.harvard.edu/GSH-LAB/