

# Abstract

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## **L-glutamine supplementation induces insulin resistance in adipose tissue and improves insulin signalling in liver and muscle of rats with diet-induced obesity.**

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**AIMS/HYPOTHESIS:** Diet-induced obesity (DIO) is associated with insulin resistance in liver and muscle, but not in adipose tissue. Mice with fat-specific disruption of the gene encoding the insulin receptor are protected against DIO and glucose intolerance. **In cell culture, glutamine induces insulin resistance in adipocytes, but has no effect in muscle cells.** We investigated whether supplementation of a high-fat diet with glutamine induces insulin resistance in adipose tissue in the rat, improving insulin sensitivity in the whole animal.

**MATERIALS AND METHODS:** Male Wistar rats received standard rodent chow or a high-fat diet (HF) or an HF supplemented with alanine or glutamine (HFGln) for 2 months. Light microscopy and morphometry, oxygen consumption, hyperinsulinaemic-euglycaemic clamp and immunoprecipitation/immunoblotting were performed.

**RESULTS:** HFGln rats showed reductions in adipose mass and adipocyte size, a decrease in the activity of the insulin-induced IRS-phosphatidylinositol 3-kinase (PI3-K)-protein kinase B-forkhead transcription factor box 01 pathway in adipose tissue, and an increase in adiponectin levels. **These results were associated with increases in insulin-stimulated glucose uptake in skeletal muscle and insulin-induced suppression of hepatic glucose output,** and were accompanied by an increase in the activity of the insulin-induced IRS-PI3-K-Akt pathway in these tissues. In parallel, there were decreases in TNFalpha and IL-6 levels and reductions in c-jun N-terminal kinase (JNK), IkkappaB kinase subunit beta (IKKbeta) and mammalian target of rapamycin (mTOR) activity in the liver, muscle and adipose tissue. There was also an increase in oxygen consumption and a decrease in the respiratory exchange rate in HFGln rats.

**CONCLUSIONS/INTERPRETATION:** **Glutamine supplementation induces insulin resistance in adipose tissue, and this is accompanied by an increase in the activity of the hexosamine pathway. It also reduces adipose mass, consequently attenuating insulin resistance and activation of JNK and IKKbeta, while improving insulin signalling in liver and muscle.**

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