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## **Abstract**

Circulating factors implicated in insulin resistance (e.g. saturated fats, inflammatory cytokines, and glucocorticoids) stimulate production of the sphingolipid ceramide, which is a ubiquitous regulator of cellular stress. Genetic or pharmacological inhibition of ceramide biosynthesis in rodents ameliorates insulin resistance caused by dexamethasone, saturated fats, or obesity, while preventing the onset of frank diabetes. Moreover, they ameliorated hypertension resulting from high fat feeding. These data identify enzymes controlling ceramide accumulation as therapeutic targets for combating insulin resistance associated with nutrient excess or glucocorticoid therapy.