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Glucosamine infusion in rats mimics the beta-cell dysfunction of non-insulin-dependent diabetes mellitus.

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Abstract

Sustained hyperglycemia can cause peripheral insulin resistance and pancreatic beta-cell dysfunction and has been termed glucose toxicity or glucose-induced desensitization. Glucosamine, a product of glucose flux through the hexosamine biosynthetic pathway (HBP), causes insulin resistance in peripheral tissues and has been shown to cause abnormal glucose-insulin secretion coupling, and thus has been implicated in the pathogenesis of glucose toxicity. Here, we investigate whether glucosamine-induced insulin secretory dysfunction is specific to glucose or also extends to nonglucose secretagogues such as arginine. Two groups of 12 weight-matched Sprague-Dawley rats underwent hyperglycemic clamp studies (steady-state blood glucose, approximately 220 mg x dL(-1)) during infusion of normal saline or glucosamine 3.5 mg x kg(-1) x min(-1) over a 100-minute period. Insulin levels were measured at baseline and between 90 and 100 minutes. One hundred minutes into the hyperglycemic clamp, subgroups of seven rats each (saline- and glucosamine-infused rats) received a bolus of arginine (100 mg x kg(-1)) while the glucose infusion rate was unaltered. Glucose and insulin levels were measured at 1, 3, 5, 10, 15, and 30 minutes after the arginine bolus. Both groups had similar fasting glucose and insulin levels. At steady state (60 to 100 minutes), glucose levels were almost identical in both groups (223.58+/-3.94 v 224.58+/-4.34 mg x dL(-1)), but the glucose infusion rate (26.55+/-1.60 v 8.83+/-1.35 mg x kg(-1) x min(-1), P < .0001) and insulin level (41.36+/-6.47 v 18.04+/-2.95 mU x mL(-1), P < .0001) were markedly reduced in animals receiving glucosamine. Peak insulin levels 1 minute after the arginine bolus were lower in rats infused with glucosamine versus saline (274.00+/-30.38 v 176.25+/-20.12 microU x ml(-1), P=.0319). Total insulin secretion in response to arginine was significantly lower in the glucosamine group as determined by the area under the curve (1,268.09+/-142.27 v 706.77+/-84.79 microU x mL(-1) x min, P=.0054). In conclusion, glucosamine causes severe impairment in glucose-induced insulin secretion. Further, glucosamine-induced beta-cell secretory dysfunction extends to nonglycemic stimuli like arginine. This pattern of insulin secretory dysfunction is similar to that observed in patients with non-insulin-dependent diabetes mellitus (NIDDM).

These data suggest that glucosamine may participate in the pathogenesis of glucose toxicity at the level of the beta cell in NIDDM patients.

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