Hypoglycemia Increases Serum Interleukin-6 Levels in Healthy Men and Women

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OBJECTIVE — Inflammation may have a major role in the pathogenesis and prognosis of critical illness. Hyperglycemia increases levels of the inflammatory cytokine interleukin-6 (IL-6) and is associated with increased risks of morbidity and mortality. Because hypoglycemia is also associated with adverse outcomes, we tested the hypothesis that hypoglycemia increases IL-6.

RESEARCH DESIGN AND METHODS — Seventeen healthy men and women participated in hypoglycemic and euglycemic-hyperinsulinemic clamp studies (target blood glucose levels 2.7 and 5.0 mmol/l, respectively), separated by 1–3 months. IL-6, ACTH, and cortisol were measured at baseline and at 45, 75, 105, and 135 min after initiation of the insulin infusion.

RESULTS — IL-6, ACTH, and cortisol levels increased significantly ($P < 0.0001$) during hypoglycemia but not euglycemia. IL-6 increased from mean ± SEM 1.0 ± 0.2 pg/ml at baseline to 2.6 ± 0.2 pg/ml after 135 min of hypoglycemia, whereas IL-6 levels were unchanged during euglycemia.

CONCLUSIONS — Hypoglycemia increases IL-6 levels in healthy individuals.

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Hyperglycemia and hypoglycemia are associated with increased risks of morbidity and mortality in critically ill patients (1,2). In intensive care unit (ICU) patients, hyperglycemia is associated with elevated levels of interleukin-6 (IL-6), an inflammatory cytokine that may have a role in the pathogenesis and prognosis of critical illness (1). Acute hyperglycemia increases IL-6 levels in healthy individuals (3). The goal of this study was to determine whether hypoglycemia stimulates IL-6 levels.

RESEARCH DESIGN AND METHODS — Euglycemic and hypoglycemic hyperinsulinemic clamp studies, separated by 1–3 months, were performed in random order in healthy volunteers not taking any medications. The institutional review boards at Brigham and Women's Hospital and Beth Israel Deaconess Medical Center approved study protocols. Informed consent was obtained. For 5 days before each study, subjects consumed an isocaloric diet including 125 ± 10 mEq/day sodium, 100 ± 10 mEq/day potassium, and 800 ± 50 mg/day calcium. Subjects were admitted to the General Clinical Research Center at Brigham and Women's Hospital and were asked to fast and remain supine after midnight. Clamp studies were performed in the morning with insulin (80 mU/m^{2} body surface area/min, Novolin R; Novo Nordisk, Princeton, NJ) infused for 135 min. Dextrose (20%) was infused to maintain glucose levels at 5.0 and 2.7 mmol/l for euglycemic and hypoglycemic clamps, respectively. In one subject, the insulin infusion rate was increased by 50% at 77 min to achieve target hypoglycemia. Serum glucose levels were measured every 5 min using a Beckman Glucose Analyzer II (Brea, CA). At −15, 0, 45, 75, 105, and 135 min of the insulin infusion, blood was drawn for measurement of IL-6, cortisol, ACTH, and insulin. Baseline values are reported as the average of the values measured at −15 and 0 min.

Serum was analyzed for IL-6 (R&D Systems, Minneapolis, MN), cortisol (Access Cortisol Immunoassay; Beckman Coulter, Chaska, MN), and insulin (Access High Sensitive Insulin Immunoassay; Beckman Coulter). Plasma was assayed for ACTH (DiaSorin ACTH IRMA; DiaSorin, Stillwater, MN). Data were analyzed using repeated-measures ANOVA with main effects of treatment (hypoglycemia and euglycemia) and time (baseline and 45, 75, 105, and 135 min). Nonrepeated measures were analyzed using Student's two-tailed *t* test. Data are expressed as means ± SEM.

RESULTS — We studied nine women and eight men (mean ± SEM age 28.9 ± 2.0 years, BMI 23.5 ± 0.7 kg/m^{2}, systolic blood pressure 106.6 ± 2.4 mmHg, and diastolic blood pressure 68.5 ± 2.1 mmHg). Baseline glucose, insulin, and homeostasis model assessment (HOMA) index values did not differ between euglycemic and hypoglycemic studies, averaging 5.08 ± 0.06 mmol/l (glucose), 24.0 ± 2.4 pmol/l (insulin), and 1.32 ± 0.38 (HOMA index). Serum insulin levels during the insulin infusions were similar for hypoglycemic and euglycemic studies: 723.4 ± 16.7 and 729.2 ± 42.4 pmol/l, respectively. Serum glucose levels decreased to 2.79 ± 0.05 mmol/l by 30 min and averaged 2.79 ± 0.02 mmol/l for the remainder of the hypoglycemic clamp (Fig. 1A). Glucose levels were 4.91 ± 0.03 mmol/l during the euglycemic clamp. During hypoglycemic and euglycemic studies, baseline measurements were similar for IL-6 (1.0 ± 0.2 vs. 1.5 ± 0.3 pg/ml, respectively), ACTH (7.4 ± 0.6 vs. 7.6 ± 0.6 pmol/l), and cortisol (291 ± 25 vs. 268 ± 13 nmol/l). There were significant ($P < 0.001$) increases in IL-6 and, as anticipated, in ACTH and cortisol levels during hypoglycemia compared with euglycemia (Fig. 1). IL-6 levels increased from 1.0 ± 0.2 pg/ml at base-
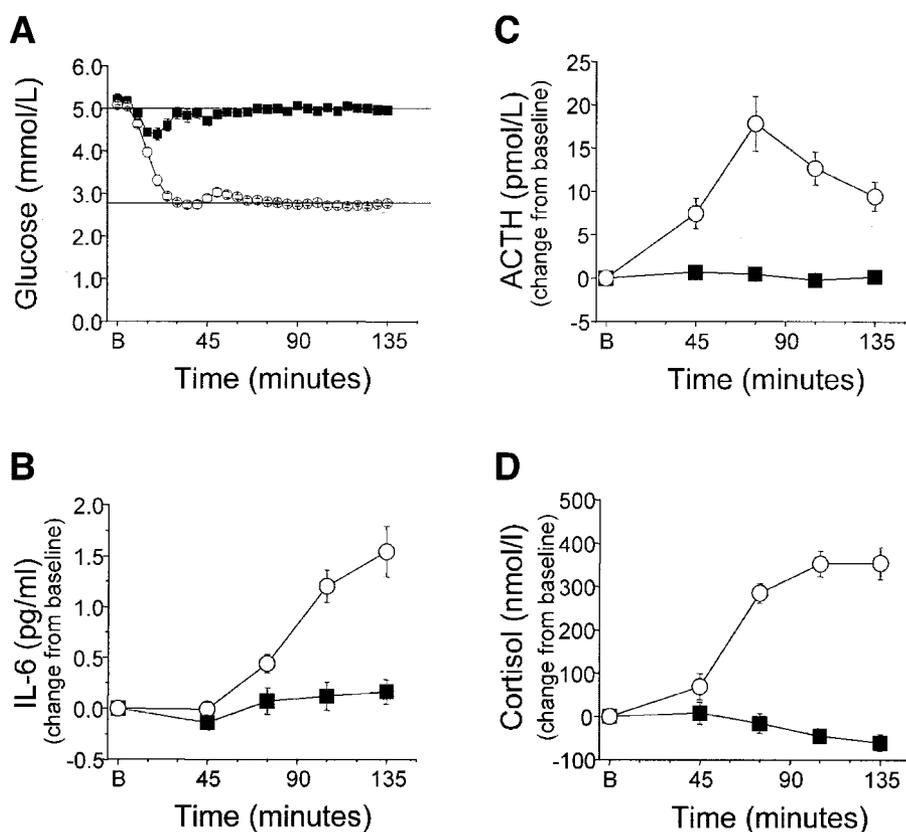
Figure 1—*Serum glucose levels (A) and change in serum IL-6 (B), plasma ACTH (C), and serum cortisol (D) from baseline levels during euglycemic-hyperinsulinemic clamps (dark squares) and hypoglycemic-hyperinsulinemic clamps (open circles). Horizontal lines in panel A indicate the target glucose levels of 5.0 mmol/l for euglycemia and 2.7 mmol/l for hypoglycemia. Data are means ± SEM.*

line to 2.6 ± 0.2 pg/ml at the end of the hypoglycemic study. There was no significant change in IL-6 during the euglycemic clamp: 1.5 ± 0.3 pg/ml at baseline vs. 1.6 ± 0.3 pg/ml at end of the study. The increase in IL-6 with hypoglycemia did not correlate with BMI, HOMA index, or increases in ACTH or cortisol levels.

CONCLUSIONS — Serum IL-6 levels increase in response to prolonged (>60 min) insulin-induced hypoglycemia. This increase is similar in magnitude to the IL-6 increase induced by hyperglycemia and endotoxin in healthy individuals (3,4). Although our results differ from those of a small study, showing no effect of hypoglycemia on IL-6 (5), this difference is likely due to the longer duration of hypoglycemia in the current study.

IL-6 has multiple physiological actions that affect glucose metabolism and may underlie the association of IL-6 with the development of insulin resistance and type 1 and type 2 diabetes (6). Although the current study design does not allow us to determine cause-and-effect relationships between IL-6 and ACTH or cortisol during hypoglycemia, IL-6 is known to stimulate all levels of the hypothalamic-pituitary-adrenal axis. In humans, IL-6 administration increases cortisol, glucagon, and blood glucose levels (7). Thus, IL-6 may aid in the counterregulatory response to hypoglycemia, especially during prolonged hypoglycemia.

IL-6 influences inflammation and immune function (6). IL-6 levels are also elevated in hyperglycemic ICU patients, and acute hyperglycemia increases IL-6 in healthy subjects (1,3,4). Our finding that IL-6 levels increase with hypoglycemia in healthy subjects raises the possibility that IL-6 levels will be elevated in hypoglycemic ICU patients. This possibility is relevant given the recent emphasis on achieving euglycemia in ICU patients

through intensive intravenous insulin administration, which increases the risk of severe hypoglycemia (2). Interestingly, recent insulin infusion trials in medical ICU patients fail to show clear benefits with tight glycemic control (2).

Our finding, coupled with those in the literature, led us to conclude that both hypoglycemia and hyperglycemia increase IL-6 levels. Additional studies are needed to determine whether hypoglycemia-induced increases in IL-6 affect health outcomes in acutely ill patients.

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