Stimulation of the endogenous incretin glucose-dependent insulinotropic peptide by enteral dextrose improves glucose homeostasis and inflammation in murine endotoxemia

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Loss of glucose homeostasis during sepsis is associated with increased organ dysfunction and higher mortality. Novel therapeutic strategies to promote euglycemia in sepsis are needed. We have previously shown that early low-level intravenous (IV) dextrose suppresses pancreatic insulin secretion and induces insulin resistance in septic mice, resulting in profound hyperglycemia and worsened systemic inflammation. In this study, we hypothesized that administration of low-level dextrose via the enteral route would stimulate intestinal incretin hormone production, potentiate insulin secretion in a glucose-dependent manner, and thereby improve glycemic control in the acute phase of sepsis. We administered IV or enteral dextrose to 10-week-old male C57BL/6J mice exposed to bacterial endotoxin and measured incretin hormone release, glucose disposal, and proinflammatory cytokine production. Compared with IV administration, enteral dextrose increased circulating levels of the incretin hormone glucose-dependent insulinotropic peptide (GIP) associated with increased insulin release and insulin sensitivity, improved mean arterial pressure, and decreased proinflammatory cytokines in endotoxemic mice. Exogenous GIP rescued glucose metabolism, improved blood pressure, and increased insulin release in endotoxemic mice receiving IV dextrose, whereas pharmacologic inhibition of GIP signaling abrogated the beneficial effects of enteral dextrose. Thus, stimulation of endogenous GIP secretion by early enteral dextrose maintains glucose homeostasis and attenuates the systemic inflammatory response in endotoxemic mice and may provide a therapeutic target for improving glycemic control and clinical outcomes in patients with sepsis. (Translational Research 2017;■■:■■–■■)

Abbreviations: AUCg = area under the glucose curve; DPP IV = dipeptidyl-peptidase IV; FSIVGTT = frequently sampled intravenous glucose tolerance test; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; IV = intravenous; LPS = lipopolysaccharide (also referred to as endotoxin); Si = insulin sensitivity

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AT A GLANCE COMMENTARY

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Background

Dysregulation of glucose control during sepsis is associated with increased morbidity and mortality. Therapies targeting tight glycemic control in septic patients have been limited in part by the development of hypoglycemia. Novel treatment strategies that promote glucose homeostasis in sepsis are needed.

Translational Significance

In this study, we demonstrate that early enteral dextrose improves glucose disposal, increases insulin secretion, and attenuates systemic inflammatory responses in endotoxemic mice by increasing the incretin hormone glucose-dependent insulinotropic peptide. Our results suggest that targeting the endogenous incretin hormone axis may provide a novel therapeutic strategy for improving outcomes in patients with sepsis.

INTRODUCTION

Dysregulation of glucose control complicates approximately 12% of sepsis cases and increases both morbidity and mortality.[1-3] Glucose homeostasis in critical illness is impacted by inflammation, insulin resistance, stress hormone release, calorie provision (intentional or unintentional), and insulin administration.[4-7] Although initial clinical trials supported tight glycemic control using exogenous insulin to improve patient outcomes,[8,9] subsequent trials highlighted a risk of hypoglycemia with this strategy.[10-13] Thus, a treatment approach that maintains euglycemia in septic patients without increased hypoglycemic risk is needed. To date, such a strategy has presented a therapeutic challenge but is potentially achievable by activation of endogenous metabolic regulatory pathways.

Hyperglycemia in sepsis shares many characteristics with an accelerated form of type 2 diabetes mellitus: insulin resistance, pancreatic insufficiency, and impaired glucose disposal in the setting of systemic inflammation.[4,14-16] Treatment of diabetes with exogenous insulin carries a risk of hypoglycemia,[17] similar to insulin therapy in sepsis. New diabetic treatment strategies target incretin hormones, which stimulate endogenous insulin secretion in a glucose-dependent manner thereby minimizing the risk of hypoglycemia. The gut-derived incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) are released in response to enteral nutrients and signal to increase pancreatic insulin secretion.[18] Additionally, from a therapeutic perspective, incretin hormones have pleiotropic effects with the potential to reduce inflammation and to increase insulin sensitivity (Si) of peripheral metabolic organs.[19-23] We were interested in potential therapeutic benefits of manipulating enteral nutrients to stimulate endogenous incretin hormone production in sepsis, facilitating both calorie provision and appropriate insulin secretion to control hyperglycemia while preventing hypoglycemia. Thus, in this study, we tested the effects of acute low-level enteral dextrose provision on glucose disposal, incretin hormone release, and systemic inflammation in endotoxemic mice.

METHODS

Animal care. All experiments were performed in 10-week-old male C57BL/6J mice (Jackson Laboratory) and were carried out in strict accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. Animal protocols were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Mice were sacrificed via cervical neck dislocation in accordance with guidelines established by the American Veterinary Medical Association.

Vascular catheterization and gastric cannula placement. Detailed descriptions of catheterization techniques have been published previously.[24] Briefly, femoral arterial catheters (MRE-025; Braintree Scientific, Braintree, MA) were implanted in all mice for the purposes of hemodynamic monitoring, arterial blood sampling, and metabolic testing. Catheters were tunneled subcutaneously through the left upper back and connected to a dual channel swivel (Instech Laboratories Inc., Plymouth Meeting, PA) to allow the mice to move freely throughout the experimental period. Catheter patency was maintained with a continuous infusion (7 μL/h) of sterile heparinized normal saline (20 U/mL; Sagent Pharmaceuticals Inc., Schaumburg, IL).

Mice then received femoral venous catheters or gastric cannulas depending on experimental group. Femoral intravenous (IV) catheters were implanted in a similar fashion to the arterial catheters. Gastric cannulas were fashioned from 60-cm Portex polythene tubing (Smiths-Medical, Dublin, OH) and were implanted via laparotomy: the abdominal cavity was opened with a 0.5–1.0-cm ventral midline incision on the right side followed by puncture of the greater curvature of the stomach with a 16-gauge sterile needle. Cannulas were inserted into the gastrostomy site, secured with 6.0 silk sutures, tunneled subcutaneously to the base of the neck, and