CRITICAL CARE

COMMENTARY

The gut-brain axis in the critically ill: Is glucagon-like peptide-1 protective in neurocritical care?

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Abstract

Enteral nutrient is a potent glucagon-like peptide-1 (GLP-1) secretagogue. *In vitro* and animal studies indicate that GLP-1 has immune-modulatory and neuroprotective effects. To determine whether these immune-modulatory and neuroprotective effects of GLP-1 are beneficial in the critically ill, studies achieving pharmacological GLP-1 concentrations are warranted.

In the previous issue of *Critical Care*, Bakiner and colleagues [1] reported the effects of so-called 'early' enteral nutrition (EN) on biomarkers of inflammation and early clinical recovery in patients admitted to a neurointensive care unit after thromboembolic stroke. The rationale underlying this study is that enteral nutrient is a potent stimulant of glucagon-like peptide-1 (GLP-1) secretion [2], and, in animal models, pharmacological GLP-1 administration has been reported to have immune-modulating and neuroprotective properties [3,4]. For these reasons, Bakiner and colleagues hypothesized that 'early' EN, when compared with 'delayed' EN, would stimulate endogenous GLP-1 secretion, thereby effecting cell-mediated immunity and improving neurological recovery.

GLP-1 is secreted from L cells that are located throughout the small and large intestine [2]. Physiologically, GLP-1 is a hormone that stimulates insulin and suppresses glucagon secretion and slows gastric emptying [5], and pharmacological administration of GLP-1 potently lowers blood glucose concentrations in healthy persons, patients with diabetes, and those who are critically ill [6-8]. Though originally identified in islet β-cells, the GLP-1 receptor is known to be widely expressed in extrapancreatic tissue; in particular, the receptor is found on neurons, and expression is increased in the ischemic penumbra [9]. Hence, in the central nervous system, GLP-1 functions as a neuropeptide [4]. In animals, pharmacological administration of a GLP-1 agonist or dipeptidylpeptidase-4 (DPP-4) inhibitor (which inhibits GLP-1 degradation) is reported to affect immune modulation [3]. Furthermore, preliminary animal data indicate that GLP-1 has neuroprotective effects, and pre-treatment with a GLP-1 agonist administered intraventricularly reduced infarct size by 50% in a rodent model of stroke [10]. Although the question of whether plasma GLP-1 can cross an intact blood-brain barrier is controversial [4], pre-treatment with supratherapeutic doses of linagliptin, a DPP-4 inhibitor, reduced neuronal loss in a mouse model of stroke [11], suggesting that GLP-1 may indeed have a central effect after injury. Accordingly, there is a strong rationale for evaluating the effects of GLP-1 on patients after an acute thromboembolic stroke.

Using a prospective, sequential-allocation, parallel open-label study design, Bakiner and colleagues compared the interventions of 'early' and 'late' EN to evaluate the effects of endogenous GLP-1 on this group of patients. Unfortunately, a potential confounder was that patients receiving 'late' EN also received parenteral nutrition (PN) while awaiting EN. The authors reported no difference in the primary outcome measure, plasma GLP-1 concentrations, between the two groups but did report significant increases in T-helper and regulatory T cell numbers and a reduction in cytotoxic T cells in the patients receiving 'early' EN.

Although the rationale for the study was robust, there were substantial limitations with the study design chosen to answer the question. GLP-1 concentrations were measured during EN, but because EN was delayed in the 'late' group, there may have been a period of 48 hours that went unmeasured when GLP-1 concentrations were greater in the 'early' group. Moreover, because intestinal nutrient is a potent GLP-1 secretagogue and gastric emptying is frequently delayed in critical illness, nutrient must be infused directly into the small intestine at a sufficient load (>2 kcal per minute) to guarantee GLP-1

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excursions [12,13]. Accordingly, measuring 'postprandial' GLP-1 concentrations after intragastric nutrient delivery represents an inadequate stimulus to achieve even physiological concentrations. As the beneficial effects in the animal models used pharmacological concentrations of GLP-1 agonists (administered either intraventricularly or with systemic doses many fold greater than administered in humans), studies evaluating the effects of GLP-1 at pharmacological concentrations are needed to adequately address this question posed by Bakiner and colleagues.

Perhaps of even more importance to the immune-modulatory effect was the period of PN. Administration of early PN when there is no contraindication for EN is associated with greater rates of infection [14]. The study by Casaer and colleagues [14] strongly supports the concept that early PN may actually be harmful if administered when not required. Hence, the inflammatory response observed by Bakiner and colleagues may be due to the 'toxicity' of PN rather than a beneficial effect secondary to 'early' EN. Although 'early' EN is intuitively appealing [15], we suggest that these data from Bakiner and colleagues be interpreted cautiously and that 'early' EN be compared with fasting to more effectively isolate the effects of 'early' EN on cell-mediated immunity.

This study, though preliminary, represents a novel foray into the potential therapeutic benefit of GLP-1 as an immune-modulator and neuroprotective agent in critical illness. Although the rationale for this approach is sound, we suggest that further studies targeting pharmacological GLP-1 concentrations are desirable to accurately evaluate the effect in neurocritical care.

Abbreviations

DPP-4, dipeptidylpeptidase-4; EN, enteral nutrition; GLP-1, glucagon-like peptide-1; PN, parenteral nutrition.

Competing interests

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