Dysregulation of intestinal glucose sensing and transport in critical illness

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Background: Provision of adequate nutrition is a major determinant of clinical outcome for critically ill patients. Effective delivery of enteral feeds, however, is often compromised by glucose malabsorption (Deane *et al.*, 2007). While no human data exist, levels of the major intestinal glucose transporter, SGLT1, are reduced in animal models of acute critical illness (Amador *et al.*, 2007). It is also established that the sweet taste receptors T1R2 and T1R3 are expressed in the proximal intestine of rodents and humans, and in rodents, act to increase SGLT1 levels in the presence of glucose or a sweetener (Margolskee *et al.*, 2007; Young *et al.*, 2009). Here we determined if (i) the expression of intestinal SGLT1 and T1R2 and (ii) SGLT1 function was impaired in critically ill patients and in a mouse model of the disease.

Methods: Endoscopic biopsies were collected from fasted and ventilated critically ill patients and matched healthy subjects (n = 12) prior to, and after, 30 min duodenal infusion of glucose (4 kcal/min) plus the absorption marker 3-O-methylglucose (3OMG). Intestinal tissues were also collected from mice 4 days after cecal ligation and puncture (CLP) and after 30 min of duodenal infusion with glucose + 3OMG. Expression of SGLT1 and T1R2 in intestinal tissues was quantified by RT PCR; plasma 3OMG levels were determined by spectrometry.

Results: SGLT1 and T1R2 expression was lower in critically ill patients at baseline (50, 54% respectively, $P < 0.05$) and after glucose infusion (53, 61% $P < 0.01$), in association with reduced plasma 3OMG levels (55%, $P < 0.05$). Similar findings were apparent in CLP mice for SGLT1 and T1R2 transcript, and 3OMG levels (50 and 78, 91% reduced respectively $P < 0.01$).

Conclusions: Intestinal expression of T1R2 is markedly lower in human and modelled critical illness, in association with reduced expression and impaired absorptive function of SGLT1. Reduced T1R2 signalling may uncouple control of SGLT1 from luminal glucose, and represent the molecular basis of carbohydrate malabsorption in critical illness. Therapies targeting these molecules may have potential to improve clinical management in this setting.

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