Augmented capacity for intestinal serotonin release in obese subjects

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Introduction: Peripheral serotonin (5-HT) derived from intestinal enterochromaffin cells (EC) is an important regulator of gastrointestinal function but has recently been shown to also regulate function in metabolic tissues as a free bioamine signal. These signals sculpt hepatic gluconeogenesis, adipose lipolysis and thermogenesis to control energy balance during periods of fasting, but are also disordered in modelled obesity (Sumara *et al.*, 2012, Crane *et al.*, 2015, Young *et al.*, 2015). While much of this evidence is in animal models, increased plasma 5-HT levels have also been linked to poorer glycaemic control in subjects with type 2 diabetes (T2D), while polymorphisms in tryptophan hydroxylase expression (Tph1, which synthesises gut 5 HT) link strongly with the incidence of human obesity. Together these findings demand a better understanding of this metabolic potential.

Methods: We assessed 5-HT in plasma prior to, and during, intraduodenal infusion of glucose (4 kcal/min, 30 min) in non-diabetic control (BMI 24 ± 1 kg/m^2, N=10) and obese subjects (BMI 44 ± 4 kg/m^2, N=14), and expression of Tph1 in their duodenal and colonic tissues. Glucose-stimulated 5-HT release was also assessed in primary EC cells from the duodenum and colon of control and obese subjects. Finally, EC cell density and their functional activation (immunodetection of phospho-extracellular related kinase, pERK) was assessed in duodenum. All subjects provided informed consent and protocols were approved by the Human Research Ethics Committees of the Royal Adelaide Hospital and Flinders Medical Centre.

Results: Fasting plasma 5-HT levels were positively related to BMI in control and obese subjects ($P < 0.05$) and higher in obese subjects prior to (1.7-fold, $P < 0.05$ *vs* control) and after intraduodenal glucose infusion (2.7-fold AUC, $P < 0.01$ *vs* control). Tph1 was expressed at similar levels throughout the duodenum, left and right colon in control subjects (N=6) and 40% higher in the duodenum of obese subjects ($P < 0.05$), where expression related positively to BMI ($P < 0.001$). 5-HT content in primary duodenal and colonic EC cells and their dose-dependent responses to glucose were similar across study groups, however, the density of duodenal EC cells in obese subjects ($P < 0.05$) and their functional activation after glucose infusion (pERK colocalisation, $P < 0.001$) was double that in control subjects.

Conclusion: Glucose triggers gut-5-HT release *in vivo* and *ex vivo* in humans, with evidence for augmented biosynthesis and release from a larger EC cell population in the duodenum of obese subjects (rather than increased sensitivity of individual EC cells). These findings support further research into the metabolic role(s) of gut-5 HT in human obesity.

Crane JD, Palanivel R, Mottillo EP, Bujak AL, Wang H, Ford RJ, Collins A, Blümer RM, Fullerton MD, Yabut JM, Kim JJ, Ghia JE, Hamza SM, Morrison KM, Schertzer JD, Dyck JR, Khan WI, Steinberg GR. (2015) *Nat Med* **21**, 166-72.

Sumara G1, Sumara O, Kim JK, Karsenty G. (2012) *Cell Metab* **16**, 588-600.

Young RL, Lumsden AL, Keating DJ. (2015) *Gastroenterology* **149**, 253-5.