Characterisation of glucose-induced serotonin secretion from primary cultured human enterochromaffin cells in health and disease

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The gastrointestinal tract hosts a variety of enteroendocrine cells, with important roles in metabolism and health. The most abundant enteroendocrine cell-type, enterochromaffin (EC) cells, produce the majority (~95%) of total body serotonin (5-hydroxytryptamine, or 5-HT), a bioamine now known to powerfully influence liver and adipocyte function. Importantly, genetic deficiency or pharmacological blockade of peripheral serotonin protects against metabolic features of obesity and type 2 diabetes (T2D) in mice fed a high-fat diet. Plasma 5-HT increases in T2D and high fat fed rodents and polymorphisms in the rate-limiting enzyme for gut 5-HT, Tph1, are linked to human obesity. However, information is limited on how peripheral serotonin is released in human health and disease.

Primary EC cells were isolated from human subjects to assess functional release mechanisms. Using density fractionation, an EC cell purity of >98% was achieved, as assessed by immunocytochemistry using antibodies against 5-HT and Tph1. EC cells from control, obese and T2D human subjects were directly activated by glucose in a dose-dependent, glucose-specific manner, with no significant difference in cellular response across subject groups. No response occurred at 30mM glucose, indicating that high plasma glucose does not activate gut 5-HT release. However concentrations of 100-300mM, equivalent to ingested glucose levels during a meal, did induce significant EC cell 5-HT secretion. Importantly this is not due to osmotic stress, as equivalent concentrations of the non-metabolisable sugar, α-methyl-d-glucoside, did not trigger secretion.

Ongoing investigation into the secretory mechanism has excluded glucose-dependent release *via* sodium/glucose transporters, cyclic AMP/PKA signalling and activation by sweet taste receptors, and confirmed a requirement for extracellular calcium and intracellular glucose metabolism.