Relationships Between Motor and Sensory Function in the Proximal Gut, Appetite, & Nutrients In Healthy Human Subjects

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SUMMARY

The motor and sensory interactions between nutrients and the proximal gut in humans are not well understood, despite the pivotal importance of these interactions on appetite, absorption and thus, nutrition. In part, this lack of knowledge results from technical difficulties in studying motor function in the human gut. In particular, the inability to continuously measure intraluminal flow with any degree of temporal resolution, has impeded progress in this field. The studies described in this thesis focus on nutrient-gut interactions; and the development of novel methodologies aimed at advancing our understanding and interpretation of the relationships between intraluminal pressures and flows.

Nutrient-Gut Interactions

To examine the roles of insulin and other gastrointestinal hormones in mediating appetite suppression in response to intraduodenal (ID) infusion of glucose, subjects received either ID glucose, ID saline or ID glucose with intravenous octreotide (somatostatin analogue) during euglycaemic hyperinsulinaemia. It was confirmed that ID glucose suppressed appetite and decreased intake compared to ID saline. Moreover, the suppression of appetite did not appear to be due to elevation of plasma insulin, and was abolished by octreotide implying a role for other gastrointestinal hormones in the production of satiety.

Different macronutrients may vary in their effects on gastrointestinal motor and sensory function. The relative potencies of ID lipid and glucose in suppressing appetite and stimulating pyloric motility was therefore compared. In young healthy subjects (18-40 yrs), lipid was found to be more potent at both suppressing appetite and stimulating pyloric motility.

As there is substantial evidence to suggest that regulation of appetite is impaired with ageing, this comparison was repeated in healthy older subjects (65-80 yrs). In the elderly, the two nutrients did not differ in their effects on appetite or intake. The older subjects were less hungry at baseline and had an enhanced phasic pyloric response to lipid, compared to the young. In addition, the elderly had both a higher fasting level of cholecystokinin (CCK) and a greater incremental CCK response to ID lipid. All of which is consistent with dysregulation of appetite with ageing.

Usual diet, and modification of intake are known to influence the gut's subsequent handling of meals containing the nutrient whose intake was altered. The motor mechanisms by which dietary changes influence proximal gut function are unknown. Whether regulation of appetite is likewise affected by changes in diet is also unknown. To determine whether motor modifications occur by "nutrient specific" mechanisms, and to determine whether appetite changes occur at all, pyloric motility and appetite (in response to separate ID infusions of glucose and lipid) were evaluated before and after dietary supplementation with glucose. The motor adaptation which occurred was nutrient specific; in that pyloric tone in response to glucose decreased after supplementation, whilst the motor response to lipid was not substantially altered. Dietary modification did influence appetite, but this change occurred across macronutrient class, with attenuation of the appetite suppressant effects of ID lipid seen after dietary glucose supplementation, whilst perception of appetite in response to ID glucose did not change.

Given the changes found in motor responses to nutrients after dietary manipulation, the effect of diet on fasting motility was then examined. Fasting small intestinal motility was evaluated in longstanding lacto-ovo vegetarian and omnivorous subjects, and also in omnivores who consumed a lacto-ovo vegetarian diet for a 14 day period. No differences in fasting motility were found between long-term vegetarian and control subjects; although when control subjects acutely adopted a vegetarian diet, their interdigestive motor cycle length decreased by approximately one third, due a shortening of phase II. This change was unrelated to total dietary fibre intake. Dietary change may therefore be capable of also modifying fasting motility.

Plasma glucose concentrations in the pathological range (such as seen in diabetes mellitus) are well documented to affect both motor and sensory function in the proximal gut. It is less clear whether plasma glucose within the physiological postprandial range has any effect, and whether physiological levels of hyperglycaemia interact with the presence of small intestinal nutrients. Gastric motor and sensory function were therefore studied at ~4-5 mmol/L (fasting level) and at ~8-9 mmol/L (physiological hyperglycaemia). Physiological hyperglycaemia increased the perception of fullness during fasting and decreased hunger during ID lipid infusion. It also suppressed antral pressure waves, and altered the temporal patterning of phasic pyloric pressures, but had no effect on proximal gastric compliance, or perception of distension. Thus, although physiological hyperglycaemia does affect some proximal gastrointestinal functions, others are spared.

Novel Methodology

To better define the spatiotemporal patterning of duodenal pressures, high resolution manometry along the length of the human duodenum was performed during fasting and 3 different rates of ID lipid infusion. The overwhelming majority of pressure wave (PW) sequences were short (1.5-4.5 cm). ID lipid was associated with a dose-related suppression of the number of PW sequences and regional variation along the duodenum in the patterning of PW sequences compared to fasting. Under all conditions, a greater proportion of sequences were antegrade than retrograde. Further interpretation of the mechanical significance of the temporospatial patterning of duodenal pressures, will require concurrent measurement of intraluminal flows. To date this has not been achievable in human subjects.

In order to concurrently measure intraluminal pressures and flows, a novel laser-Doppler velocimeter was developed. Fibre-optic technology was used to quantify particle speed within the gut lumen and this was implanted in a manometric assembly to enable concurrent pressure measurements. The initial human validation study of this instrument was performed in the oesophagus with concurrent assessment of flow by barium fluoroscopy. The onset of the flow signal from the velocimeter correlated well, particularly in the distal oesophagus, with the occurrence of flow documented fluoroscopically. In analysing data from this study, technical and timing problems with the instrument were discovered. Consideration of these matters has lead to further refinements of the instrument being proposed.