Invited commentary

Glucagon-like peptide-1, satiety and appetite control

After eating a meal several subjective and behavioural changes occur. Normally hunger is reduced, the feeling of fullness increases and eating is inhibited. This state is called post-ingestive satiety: the inhibition of appetite resulting from food consumption. What mechanisms control this phenomenon? During and after eating there occurs a series of overlapping physiological responses, most of which organize the gastrointestinal response to food. The profile of physiological responses can reflect the amount and type of food consumed and, in detecting these variables, the responses have the capacity to act as physiological satiety signals. For more than 20 years it has been supposed that certain gastrointestinal hormones could have the status of physiological satiety signals, mediating between food consumption and the reduction of the drive to eat. Most evidence has been accumulated for cholecystokinin (Kissileff *et al.* 1981). Because the mediation of satiety is never the exclusive function of such hormones and because these hormones often have multiple functions, there will always be some debate about the mechanisms responsible for any suppression of food intake (Greenough *et al*. 1998), or about the validity of any suppression as a true reflection of satiety.

In the last few years glucagon-like peptide-1 (GLP-1) has been proposed to play a role in the mediation of satiety. GLP-1 (7-36)amide is a peptide of thirty amino acids produced in, and released from, the L-cells of the intestinal mucosa into the circulation after a mixed meal. Plasma concentrations of GLP-1 rise 10–20 min after a meal and reach 'peak' levels after approximately 60 min, reflecting the time it takes for nutrients to reach the ileum where the L-cells are most abundant. As such it is unlikely that GLP-1 would affect the termination of the meal (satiation) since most meals are terminated within 20 min, but it may contribute to inter-meal satiety (and therefore influence eating at a later meal and hunger in the inter-meal period).

GLP-1 is considered to be an incretin; it also inhibits gastric emptying and acid secretion and, as such, has been considered to be a candidate mediator of the 'ileal brake'. In previous reports GLP-1 has been shown to inhibit food intake and result in reduced feelings of hunger in the postprandial state (Flint *et al*. 1998; Naslund *et al*. 1998; Gutzwiller *et al.* 1999). We showed that after a fixed energy breakfast, intravenous infusion of GLP-1 (0·75 pmol/kg per min) in obese subjects for 8 h resulted in reduced food intake at *ad libitum* lunch and dinner meals, as well as lower feelings of hunger in-between meals, compared with infusion with saline (Naslund *et al*. 1999).

In this issue of the *British Journal of Nutrition*, Long *et al*. (1999) have investigated the effect of intravenous GLP-1 on food intake in lean male subjects. GLP-1 was infused at 1·2 pmol/kg per min for 20 min after which 400 ml water was given and gastric emptying was measured. After an additional 20 min of GLP-1 infusion an *ad libitum* dinner was served. Ratings of hunger were assessed before the meal and 20 min after the meal. The authors found no effect of GLP-1 on hunger before the meal and no difference in energy intake at dinner between GLP-1 and saline infusion. There was a trend towards decreased hunger ratings 20 min after the meal during GLP-1 infusion. As a result of this the authors conclude that it is unlikely the GLP-1 is a major satiety factor in human subjects.

The question is whether or not the study by Long *et al*. (1999) allows for this conclusion. As GLP-1 is released well into the postprandial period its likely physiological role in satiety would relate to late acting (rather than instantaneous) postingestive and postabsorptive regulators of satiety and food intake. One such factor may be gastric emptying. It is well established that GLP-1 delays gastric emptying. In the study by Naslund *et al*. (1998) less than 50 % of the meal had emptied at 180 min after meal intake during GLP-1 infusion compared with infusion with saline. This would presumably result in a prolonged period of gastric distension, release of other gastrointestinal hormones and prolonged stimulation of gastrointestinal vagal receptors involved with the control of food intake. This may therefore be one mechanism by which GLP-1 can regulate postingestive satiety resulting in decreased energy intake at the next meal.

In the study by Long *et al*. (1999), approximately 10 % of the water remained in the stomach at the time of the test meal and this may have been an insufficient stimulus to be augmented by the raised plasma levels of GLP-1. More importantly, the use of a water load would not generate a realistic post-meal state which would include the presence of nutrients in the stomach and gastrointestinal tract and the profile of peptides, gut activities and other physiological agents, all of which contribute to a profile of events which influence the intensity and duration of post-meal satiety.

Another feature which may influence any observed effect of GLP-1 infusion is the actual achieved plasma levels. Due to different radioimmunoassay systems it is unrealistic to compare plasma concentrations in different studies (assays usually target the C-terminal of the peptide but one group has managed to develop an assay for the biologically active N-terminal). However, it can be noted that in the study by Long *et al*. (1999) plasma concentrations were approximately 120 pmol/l during GLP-1 infusion and approximately 50 pmol/l 20 min after the meal during saline infusion (Fig. 1 from Long *et al*. 1999). As the plasma concentrations usually 'peak' after about 60 min it is likely

that the plasma concentrations of GLP-1 would continue to increase after the meal during saline infusion. Therefore, it is not clear whether the plasma concentrations achieved by the GLP-1 infusion at the time of assessment by Long *et al.* (1999) actually were twice those achieved in the postprandial period. It is important in these studies to map the time course of the plasma levels of GLP-1 following infusion and this might be one technical reason why no effect was seen on food intake in the study (in contrast to the study of Gutzwiller *et al.* (1999) where food intake was reduced at doses of 0·75 pmol/kg per min and 1·5 pmol/kg per min). Of course, if GLP-1 were infused in a pharmacological dose (e.g. 1·50 pmol/kg per min; see Gutzwiller *et al.* 1999) then this could be a sufficiently strong stimulus to suppress appetite even in the absence of the profile of accompanying physiological signals.

It is worth noting that GLP-1 levels are very low in the fasting (hungry) state, and that simply raising plasma levels to postprandial values or above may not be sufficient to mimic a meal-induced satiety effect. This is because satiety is not based on any single physiological event but reflects a cascade of physiological responses. Within this cascade different physiological events act at different moments, with differing intensities and varying durations. For example, it seems that cholecystokinin acts very rapidly to induce early termination of the meal which has induced its release and, when infused intravenously to fasted subjects, effects may be seen even in the pre-meal hungry state (Greenough *et al.* 1998). In contrast the effects of GLP-1 would be expected to be seen in the fed state (not in the fasting state) when it would act at some mid-point in the physiological satiety cascade to prolong the satiety effects of the previous meal and to inhibit eating at a subsequent meal. Accordingly, in assessing the contribution of any gastrointestinal peptide to the control of eating, the timing and duration of its appearance in the physiological satiety cascade is probably critical to understanding its action, and to being able to design experiments to effectively capture the effect. GLP-1 is certainly not 'the' satiety hormone, but there are good reasons to believe that it contributes to the intensity and the duration of meal-induced satiety. It remains to be demonstrated whether the action is central or peripheral (or both), and where GLP-1 plays a role in the time course of satiety following a meal.

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