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Gastrointestinal satiety in animals other than man

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The present paper reviews the development of some of our ideas of how physiological stimuli on the gastrointestinal tract contribute to the onset of satiety. The various signals originating from the gut caused by stretch, osmo-concentration or specific chemical stimuli must be relayed to the brain, either neurally or hormonally, to be integrated with post-absorptive signals from other sites including the brain itself, to produce a response, which will also take into account the animal's previous experience, the importance of the different signals varying with the feeding regimen. In free-feeding animals, individual meal size varies and relates to the succeeding inter-meal interval (Le Magnen, 1983), so that long-term intake can be adjusted by the number of meals. In animals that are meal-fed once or twice daily, long-term intake relates to meal size, which must involve a learned anticipation of metabolic requirements. As the meal terminates long before absorption is complete, meal size will be largely signalled from the gastrointestinal tract.

PREGASTRIC FOOD STIMULI ALONE CANNOT CONTROL MEAL SIZE

In free-feeding sham-fed rats, in which stomach contents are allowed to drain out continuously, feeding was prolonged in the first meal after opening the cannula (Davis & Campbell, 1973), showing that feedback signals from the stomach and small intestine must normally initiate satiety. The gastrointestinal signalling of meal size is not, therefore, an unconditioned stimulus for the learned oral control of intake from the texture and taste of food.

STOMACH CONTROL OF INTAKE

Gastric distension (e.g. placing inert gum or a balloon in the stomach of the dog through a gastric fistula; see Janowitz & Grossman, 1949) has long been known to decrease food intake. In the rat, the stomach can sense both the amount and composition of the food when onward passage of digesta is prevented by a pyloric noose, even after vagotomy (Kraly & Gibbs, 1980). The existence of a stomach satiety factor has been suggested as food placed in extra transplanted (and hence decentralized) stomachs in inbred Lewis rats reduced intake by mouth in a dose-related manner (Koopmans, 1983).

INTESTINAL CONTROL

Parenteral infusions of glucose either do not alter food intake (e.g. dog, Janowitz *et al.* 1949; pig, Stephens & Baldwin, 1974) or reduce intake by less in energy terms than the energy infused (e.g. 0·6–0·8-fold in the baboon; Woods *et al.* 1984) and are less effective than the equivalent gastrointestinal infusions (e.g. pig; Stephens, 1980). Using sham-fed rats, glucose infusions into the small intestine have now been shown to inhibit intake physiologically by eliminating intestinal signals from the digesta, the threshold rate of infusion for intestinal inhibition of satiety (0·46 kJ (0·11 kcal)/min) being less than the normal rate of emptying (1·34 kJ (0·32 kcal)/min; Reidelberger *et al.* 1983).

The effects of intestinal infusions might be post-absorptive via liver glucoreceptors in the rat, as portal glucose infusion effectively reduced intake (Campbell & Davis, 1974). However, the intestinal response to glucose seems to originate in the intestine and to be mainly neural in the pig, as the response to glucose infused into the duodenum was reduced by intraduodenal local anaesthetic and truncal vagotomy (Houpt *et al.* 1979; Stephens, 1980). Free-feeding rabbits decrease intake in response to duodenal, but not portal, glucose infusion and the effect is again blocked by vagotomy (Vanderweele *et al.* 1974). In contrast, responses to intraduodenal glucose were only found in fasted and not in fed chickens (Shurlock & Forbes, 1981).

Another approach is to use parabiotic rats with crossed small intestines, but results have been variable. When only a small segment was crossed, there was no evidence for intestinal signalling of intake (Koopmans, 1975). However, only one of a pair of parabiotic rats (each with crossed intestines so that chyme passed from each rat to the other) fed while the other gave the appearance of satiety (Lepkovsky *et al.* 1974); long-term intake in parabiotic rats with intestines crossed from the donor to the recipient rat was 3·6-fold greater in the donor than in the recipient rats (Koopmans, 1985).

MECHANISM OF INTESTINAL CONTROL OF EMPTYING AND INTAKE

Recording from afferent fibres of the vagus has shown the presence of specific receptors responding to glucose, amino acids, acid and alkali and of superficial multi-modal receptors which respond to osmotic stimuli (Mei, 1985). Although osmotic stimuli affect receptors distinct from the specific chemoreceptors, emptying and intake are equally reduced by glucose and the equivalent osmotic load of sodium chloride (Houpt *et al.* 1979; McHugh & Moran, 1979), although in some cases isotonic glucose, but not saline, is able to reduce intake (e.g. in the rabbit; Vanderweele *et al.* 1974).

These intestinal receptors can regulate gastric emptying to allow a constant rate of energy flow into the small intestine in the monkey on different liquid diets (McHugh & Moran, 1979), suggesting that stomach fill (Wirth & McHugh, 1983), sensed by gastric stretch receptors, then gives a measure of the energy eaten. Thus, glucose infusion into the pig duodenum inhibits both intake and emptying of a normal pig ration in the feeding period (Rayner & Gregory, 1989) according to the amount of energy infused, so that satiety occurs at a constant stomach volume. However, pigs may be able to quantify the total amount of energy reaching the small intestine in the feeding period independent of stomach stretch; dry matter (DM) intake and DM emptied in the feeding period were identical when the same ration was wet fed (1 part ration + 2 parts water) or dry (with access to water), but the rate of DM emptying was doubled on the wet meal, which was

eaten twice as fast as the dry meal (Rayner & Miller, 1990). In contrast, gastric emptying occurred isoenergetically in the feeding period on liquid meals over a range of dilutions in the rat; the total amount emptied in the feeding period and the stomach volume at satiety were the same, but the intake in energy terms decreased with dilution, being limited by stomach fill (Kalogeris *et al.* 1983). Isoenergetic emptying is one factor in the complex relationships between stomach volume and satiety, but cannot provide a unifying hypothesis to explain the interaction between stomach and intestine to measure the energy density and amount eaten under all conditions.

FATS, EMPTYING AND INTAKE

Gastrointestinal signals are important in the control of fat intake: long-term intravenous infusions of emulsified lipid in rats only inhibited intake equivalent to 40% of the energy infused (Walls & Koopmans, 1989), while emulsified fat infused into the pig duodenum is more effective than non-emulsified fat and has a greater effect on intake and gastric emptying than expected from the energy infused, probably because of its rapid digestion to monoacylglycerol; emulsified fat inhibits intake according to the energy infused only when infused into the stomach, indicating the involvement of gastric emptying in these responses (Rayner & Gregory, 1989). The route of absorption may be unimportant: emulsified fats of different chain lengths infused into the stomach inhibit intake according to the energy infused (Maggio & Koopmans, 1987).

GASTROINTESTINAL HORMONES AND THE CONTROL OF INTAKE

Cholecystokinin (CCK). The role of CCK as a peripheral and central satiety hormone has recently been reviewed (Silver & Morley, 1991). It is thought to interact with afferent vagal pathways in the stomach, as responses are abolished by selective section of vagal branches to the stomach (Smith *et al.* 1981), although these effects of gastric vagotomy have been disputed (Le Sauter *et al.* 1988). CCK receptors are found both on the muscle of the pylorus (McHugh & Moran, 1986) and on the vagus nerves (Zarbin *et al.* 1981). CCK is thought either to constrict the pylorus, slowing emptying and increasing stomach stretch (McHugh & Moran, 1986), causing firing of vagal afferents and an inhibition of intake, or increase the sensitivity of vagal afferent receptors (Davison & Clarke, 1988).

The effects of endogenous CCK on intake in the pig are not dependent on the slowing of gastric emptying as MK-329, an inhibitor of peripheral CCK-A receptors, completely reverses the effect of Intralipid on intake, but not on emptying (Rayner *et al.* 1991). Exogenous CCK infusions do not significantly slow the rate of gastric emptying during the feeding period in the pig at rates of infusion which decrease food intake (Rayner & Miller, 1990). Endogenous CCK released by Intralipid is also reduced by intraduodenal local anaesthetic (Rayner & Gregory, 1985), suggesting that the CCK effect on intake might be a paracrine effect in the upper small intestine and might not be mediated by circulating CCK on stomach receptors. This is supported by findings that CCK infusions in the pig were most effective in decreasing intake when directed to the post-gastric mesenteric circulation (Houpt, 1983). There is some doubt too whether endogenous circulating CCK levels are high enough to alter intake via afferent receptors in the stomach. For instance, circulating post-prandial venous CCK levels reach 5 pM in the dog, whereas infusion rates of 200 pmol/kg per h, giving far higher circulating plasma CCK concentrations, are required to produce satiety (Reidelberger *et al.* 1989).

Endogenous CCK does, however, seem to modulate intake physiologically. MK-329 increases intake when administered alone in satiated but not in fasted rats (Hewson *et al.* 1988) and mice (Silver *et al.* 1989) and in both operant-fed pigs (Ebenezer *et al.* 1990) and, more surprisingly, those given a single meal after an overnight fast (Rayner *et al.* 1991). Recently it has been shown that pigs immunized against CCK increased their food intake by 8·2% and their rate of growth by 10·6% (Pekas, 1991).

Other gastrointestinal hormones. Gastrointestinal hormones such as secretin, gastrin and gastric inhibitory polypeptide, which may be expected to be released synergistically with CCK, are ineffective in reducing sham-feeding in the rat (Lorenz *et al.* 1979). Gastrin, which has the same terminal pentapeptide sequence as CCK, slows stomach emptying (Dozois & Kelly, 1971) but has no effect on voluntary food intake (Garlicki *et al.* 1990). Bombesin, which shares its terminal sequence with gastrin-releasing peptide, decreases intake in the rat, but does not affect gastric emptying (Hostetler *et al.* 1989). Somatostatin inhibits food intake in rats and baboons (Lotter *et al.* 1981).

THE RUMINANT ANIMAL

Short-chain volatile fatty acids (VFA), the major energy source for ruminants, are largely absorbed in the rumen and omasum. The reticulo-rumen contains both tension receptors and chemoreceptors (Leek, 1986), the acid-sensitive chemoreceptors being sensitive to VFA (Baile & McLaughlin, 1970). Pentagastrin, CCK and secretin all reduce intake in the sheep, albeit at quite high doses, which also have direct effects on motility (Grovum, 1981). In contrast to the response of single-stomach animals to energy dilution, ruminants on low-digestibility roughages decrease their voluntary food intake. Rumen outflow rates of both solid and liquid phases decreased, even when the rations were ground and pelleted to eliminate the effects of particle size on flow; this may be associated with decreases in rumination and salivary flow (Hovell *et al.* 1989).

CONCLUSIONS

No unifying scheme for the gastrointestinal control of intake can be produced. Any factor found important in one experiment sometimes seems unnecessary in another species or using a different design. Perhaps this indicates that animals receive more information from the gastrointestinal tract than they need, and are able to select and integrate information as required in relation to past experience. One strategy for advance is to study changes in physiological variables both during and after adaptation to changes in diets or methods of feeding.

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