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INHIBITION OF FOOD INTAKE IN THE RAT FOLLOWING COMPLETE ABSORPTION OF GLUCOSE DELIVERED INTO THE STOMACH, INTESTINE OR LIVER

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SUMMARY

1. Solutions of glucose or other carbohydrates were administered during the dark or light period of the circadian cycle to rats which had been only briefly deprived of food.

2. Food was restored to the animals at various times after administration of a glucose load by stomach tube. With delays between loading and access to food of up to 3 hr by night and 2 hr by day, subsequent food intake was less than intake after non-nutritive loads.

3. Measurement of the glucose content of the gastrointestinal tract at various times after glucose loading showed that this depression of intake was still apparent even when the rat was offered food some time after complete absorption of the stomach load.

4. Infusion of a glucose solution into the duodenum or the hepatic portal vein also inhibited subsequent food intake.

5. In all cases, the inhibition of food intake was expressed as a decrease in the size of the first meal after restoring access to food.

6. These results provide the first demonstration that the entry of normal amounts of carbohydrate into the body by the physiological route is followed by a depression of food intake which lasts until after absorption is complete.

INTRODUCTION

Theories of the physiological control of food intake generally presuppose that ingested foodstuffs have some effect on hunger after they have been absorbed. The present study was carried out in the rat to demonstrate such an effect for carbohydrate.

Rats eat less after stomach loads of glucose than after non-nutritive loads. This inhibition of food intake cannot be attributed to osmotic

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factors, except for a short period after loading. For example, the inhibition of eating which follows a glucose load is not matched by that after an equimolar load of the unmetabolized analogue 3-*O*-methylglucose (Booth, 1972*a*). It is also found that the total decrease in food intake is proportional to the amount of glucose administered, and approximately equivalent in content of utilizable energy, suggesting a satiating effect arising from the metabolism of the absorbed glucose (Booth, 1972*a*, *b*).

We report here the effects of complete food or starch loads or of gastric, intestinal or I.V. administration of glucose, in rats which had been deprived of food but only long enough to remove most food from the stomach at the time of loading. Complete absorption of the glucose load was usually allowed before effects on food intake were tested. This was to exclude the possibility that the carbohydrate administered, by slowing the emptying of residual or currently ingested food from the stomach, might inhibit eating by pre-absorptive mechanisms such as stomach distension or intestinal osmoreception. Equimolar doses of urea or 3-*O*-methylglucose were used as control substances to exclude any effects attributable to recent filling of the gut.

These results were reported at the International Physiological Congress Satellite Conference on the Regulation of Food and Water Intake in Cambridge, 1971, and parts were summarized by Booth (1972*b*) and Booth & Toates (1974).

METHODS

Sprague–Dawley male albino rats weighing 350–450 g were housed in individual cages on one of two lighting cycles, with the dark period between either 10.00 hr and 22.00 hr (reverse) or 20.00 hr and 08.00 hr (normal). They were maintained on powdered Small Animals Diet, autoclaved version (Spillers, London), with free access to water. The food was presented in large heavy glass jars with a 5 cm hole in the lid.

Solutions were prepared in distilled water at least a day before gastric or intestinal administration, being kept refrigerated and brought to room temperature just before use. Anhydrous D-glucose, D(−)fructose (glucose free), dextrin (starch), sodium chloride and urea came from B.D.H. Chemicals, Poole. 3-*O*-Methyl-D-glucopyranose, chromatographically pure, was supplied by Koch–Light, Colnbrook. A soluble, partially hydrolysed starch preparation, which contained about 5% free glucose and 5% maltose, was supplied by Manbré Sugars, Hammersmith (Maltodextrin MD 05).

Intragastric loads were delivered via a 0·2 cm outer diameter infant-feeding tube of polyethlyene (Portex, Hythe). The water-wetted tube was inserted without mandibular restraint in unanaesthetized rats which had previously been adapted to the procedure.

For duodenal loading, a permanent cannula was used. A rat kept under reverse lighting was anaesthetized with Nembutal (50 mg/kg). Then through an upper abdominal entry, a small incision was made in the pyloric antrum and the cannula passed into the stomach, through the pylorus and into the duodenum. The cannula was made of a 14 cm length of silicone rubber tubing (Dow Corning silastic 602 131, 0·05 cm i.d., 0·09 cm o.d.), sleeved with a 1·5 cm length of polyethylene tubing

(Portex, 0·10 cm i.d., 0·2 cm o.d.), 1·0 cm from one end. This sleeving was formed into a Z bend by immersing it in hot water while holding it bent. The sleeved part of the cannula lay in the stomach wall; while the 1 cm tip of silastic tubing went through the pylorus and lay in the duodenal lumen. This technique was developed by Dr C. S. Campbell in this laboratory and was found to be superior to direct cannulation of the more delicate duodenum (Campbell & Davis, 1974*a*). The silastic tube appeared not to disrupt the normal function of the pylorus. The gastric incision was closed with purse string sutures and the polythene sleeving stitched firmly to the stomach wall to prevent it being drawn into the intestine by peristalsis. The other end of the silastic tube was passed under the skin to an incision at the back of the neck and attached to a pedestal of silastic-sleeved 25-gauge steel needle bent to an L shape and attached with silastic glue to a small piece of Teflon-coated fibreglass netting sutured under the skin. Rikerspray antibiotic (Riker, Loughborough) was applied and the animals allowed 1 week to recover.

Permanent I.V. cannulae were implanted in other rats, also under barbiturate anaesthesia. For implantation into the hepatic portal vein, an oblique abdominal incision was made, slanting down to the right hind leg of the animal. Some intestines were lifted out and the duodenum exposed. The portal vein could then be seen going into the liver when the duodenum was moved to one side. A small hole was made in the mesenteric tissue under the vein by blunt dissection using small forceps. A stainless-steel rod was passed through this hole and lifted up so that the vein could be exposed more clearly. This hole was situated between the entry of the superior mesenteric vein and the splenic vein. The portal vein was clamped with a small needle holder whose ends were sleeved with silicone tubing to prevent damage to the vein. The vein could be left clamped for a maximum of about 3 min; it was found that circulation would not return after this time on unclamping the vein. Portal blood flow is maintained by the superior mesenteric vein which is downstream to the clamp. A small hole was made in the vein with an intestinal needle. A small length (3 cm) of PVC or Teflon tubing, with one end blocked and cut at an angle, was inserted into this hole to make it wider and to ensure that the wall was properly punctured on one side only. The permanent cannula was made of fine silicone tubing (Dow Corning silastic 602-101), the end being cut at a slant to facilitate insertion. At 1 cm from this end, a loop of fine silk was attached with silastic cement, leaving two loose ends of silk each about 5 cm long. Another similar loop was glued about 5 cm from this one. The total length of the cannula was 15 cm. The PVC tube was slowly pulled out of the vein and the silicone cannula inserted along the same track, thus ensuring that the silicone tube lay in the vein and not between two layers of connective tissue. Blood could then be drawn up the cannula. The vein was unclamped. Slight bleeding often occurred but soon stopped. Blood flowed up the cannula under the slight portal pressure, indicating that the cannula lay in the vein. One end of the first silk loop was then threaded under the vein and a loose knot tied round the vein. This prevented the cannula coming out of the vein, with no need for further suturing. The area was sprayed with Rikerspray and the intestines put back into place. The abdominal wall was sutured, starting from the costal end and using the two ends of the second silk loop to make the last stitch, leading the cannula out of the abdominal cavity ready to be passed under the skin. The skin was then sutured leaving a small space near the cannula, which was passed under the skin and attached either to a neck pedestal (as used for duodenal cannulae) or to a head pedestal. In this case, the dorsal aspect of the skull was exposed and three screws and a bolt fixed to the cranium. The cannula was connected to an L piece of stainless-steel tubing which was stuck to the skull and screws with dental cement.

For intrajugular cannulation, a small incision was made in the neck and the right jugular vein exposed by blunt dissection and a stainless-steel rod passed beneath it.

A small incision was made in the vein with a scalpel and the cannula (Dow–Corning 602-101) passed into the lumen. The tubing had a loop glued to it as for the portal cannula, exactly 5·2 cm from the tip. The cannula was pushed down the vein until the glued loop was at the entry point. It was confirmed after the experiment that the tip lay exactly in the heart. The cannula was sutured round the vein using the ends of the glued loop and tied firmly to the surrounding muscle. The incision was sutured and the other end passed under the skin to one of the two types of pedestal described above.

Except as noted in Results, all rats were deprived of food at 08.30 hr on experimental days, and 2·5 ml. fluid was inserted by tube into the stomach at noon or else fluid was infused into the duodenum at a rate of 10 ml./hr from 11.30 to 12.30 hr. A 4-channel motor-driven syringe apparatus was used, generally with two channels used for control infusions and two for experimental infusions on each occasion.

The food jars were replaced in the cages at various times after stomach intubation or 15 min after the duodenal or I.V. infusion apparatus had been disconnected. Food intake was measured by weighing the jars on a triple-beam balance to the nearest 0·1 g, usually at 1 hr intervals. In the case of duodenally infused animals, durations and spacings of feeding bouts were recorded by having the powdered food slightly moistened (0·1 ml. water/g) and connecting the floor of the cage and the food to a high impedance touch detector circuit. This activated a paper kymograph whenever the rat made contact with food.

To measure gastrointestinal contents at various times after removal of maintenance food or after glucose loading, the rats were killed by neck fracture. Then the abdomen was immediately opened and the gut ligated at the base of the oesophagus, at the pyloric constriction and sometimes at various positions along the intestine while the vasculature was rapidly being dissected away. The stomach contents were washed out into a graduated cylinder and made up to 50 ml. with distilled water. The small intestine was cut into 15 cm lengths and each piece washed through with distilled water to 5 ml volume. Glucose was assayed using a glucose oxidase-peroxidase-*o*-dianisidine method (kit no. 510, Sigma, London). The enzyme powder was dissolved in 0·5 M Tris pH 7·0 to inhibit any disaccharidases present in the enzyme reagent (Dahlquist, 1964). After adding the aliquot of the samples and standards to the reaction mixture the tubes were left for between 30 and 60 min at room temperature and absorption was then measured at 450 nm in an SP 500 spectrophotometer.

Blood glucose concentrations were measured in portal infusion experiments, using rats with a jugual cannula in addition. Heparin (100 u.) was injected through the jugular cannula which was then connected to the pump of a Technicon autoanalyser running at 0·9 ml./hr. Another 100 units of heparin were mixed with the portal infusion solution. The withdrawn blood was dialysed against 0·9 % saline containing Triton 0·5 ml./l. The glucose content of the dialysate was measured using Boehringer glucose oxidase reagents specially prepared for the Technicon autoanalyser. Glucose standards were passed through the machine before and after the experiment. The chart records of glucose concentration were directly reproduced for superposition in Fig. 5.

RESULTS

Inhibition of feeding following administration of starch

When freely fed rats in the light phase of the circadian cycle were stomach-tubed with 5 ml. of a solution containing 0·95 g of partly hydrolysed starch, they ate less maintenance diet in the subsequent hour than in

the first hour following intubation with the same volume of water (Fig. 1; $P < 0{\cdot}05$). When 1 g of glucose was intubated in 5 ml., feeding in the first hour was almost completely suppressed ($P < 0{\cdot}001$). The difference in initial effects between free glucose and carbohydrate requiring digestion ($P < 0{\cdot}05$) was consistent with an earlier finding that at least part of the immediate appetite-depressant effect of a concentrated gastric load of

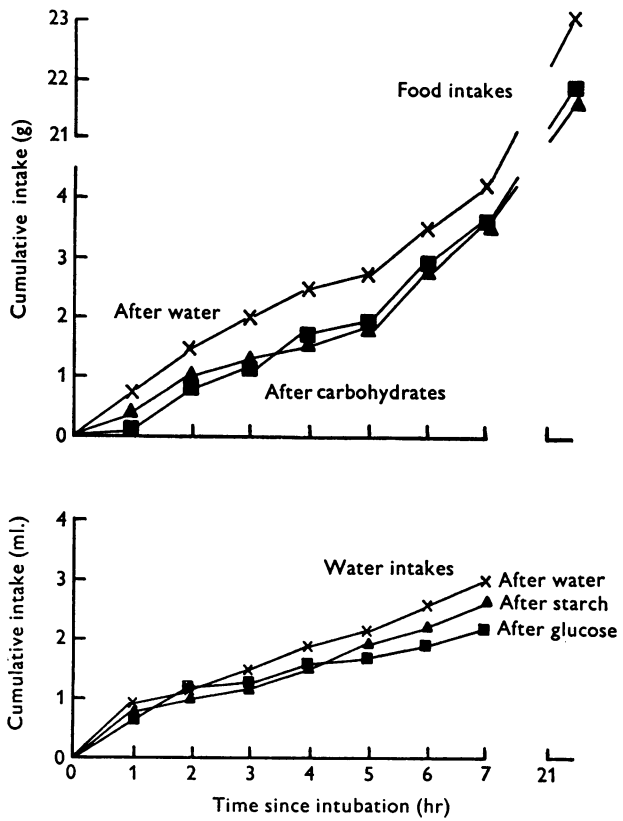

Fig. 1. Cumulative food intake (continuous lines) and water intake (interrupted lines) following gastric loading of eighteen freely fed rats with 5 ml. water ×, 20 % (w/v) glucose solution ■, or 19 % starch solution ▲.

glucose was attributable to the solution's colligative properties (Booth, 1972*a*). The difference in effect between glucose and starch was not apparent a few hours later (Fig. 1).

Booth (1972*a*) found that the removal of food for 1 hr following intubation of freely fed rats often prevented colligative factors influencing the suppression of food intake by intragastric glucose loads. In another comparison between glucose and starch, food was withheld for 2 hr after

intubation in the light phase. To reduce the interaction of a gastric load with food already in the stomach, food was also withheld for 2·5 hr before intubation. Administration of 5 ml. loads of glucose (1·0 g), dissolved starch (0·95 g) and dextrinized starch in suspension (0·9 g) were followed in the first hour of restored access by similar intakes of food which were markedly less than intake after a urea load (Fig. 2; $P < 0{\cdot}01$). There was no subsequent increase in the difference between the cumulative intake curves following carbohydrate loads and the cumulative intake curve following the urea load.

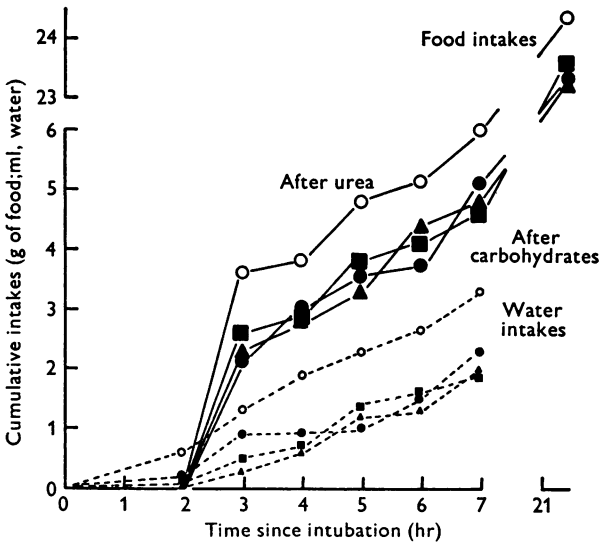

Fig. 2. Cumulative food intake (continuous lines) and water intake (interrupted lines) following intubation with 5 ml. gastric loads and 2 hr delay in 2·5 hr food deprived rats ($n = 15$). 6·7 % urea ○, 18 % dextrin suspension ●, 19 % starch solution ▲, 20 % glucose solution ■.

In both experiments, the asymptotic difference of about 1 g between cumulative intakes following carbohydrate and control loads approximately corresponded in digestible energy content (3·43 kcal/g of maintenance diet according to the manufacturer) to the oxidation energy of the carbohydrate loads (3·74 kcal). Thus it seemed possible that, even if the rat is left without access to food for sufficient time to permit considerable amounts of a starch or glucose load to be absorbed, effects of the administered carbohydrates could promptly suppress the intake of food by amounts sufficient to compensate for the energy made available. Differences in water intake in these experiments tended to develop later than differences in food intake (Figs. 1 and 2) and were not statistically reliable before or during the first hour of access to feed.

Delayed effects of ingested maintenance diet were also examined under the deprivation conditions of Fig. 2. Instead of a stomach load, 2 g of diet mixed with 2 ml. water was presented to the rat. This was rapidly eaten, providing a load consisting of 0·96 g digestible carbohydrate, 0·22 g crude protein and 0·05 g crude fat (manufacturer's analyses). In the control condition, a mixture of 1 g cellulose, 1 g kaolin and 2 ml 0·1 % sodium saccharin solution was consumed. Food intakes in the first hour of restored access were (mean ± S.E. of mean) 2·38 ± 0·40 g and 3·96 ± 0·26 g, respectively, an intake depression of 1·58 ± 0·35 g ($P < 0·02$). This value is close to that expected if the energy flow from starch and perhaps other nutrients in the diet quantitatively inhibits food intake under these conditions. Feeding was generally confined to the first 20–30 min of restored access to food and did not recur within the first hour of access. Thus a suppressant effect in the first hour is in fact a decrease in size of the first meal the rat took.

Absorption of glucose in the dark and light periods

To permit a closer examination of the relation between absorption of a load and its appetite-suppressant effects in both phases of the lighting

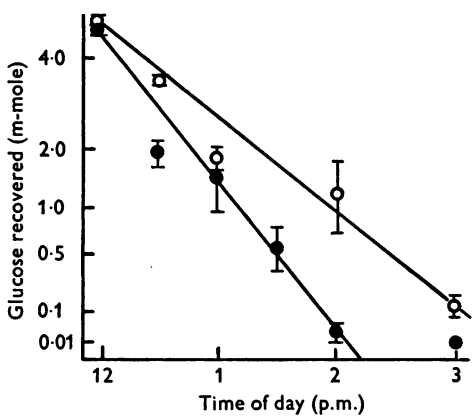

Fig. 3. Glucose content on the stomach and small intestine after gastric loading with 1 g glucose, in rats on a reverse cycle (●) and in rats under normal lighting (○). Vertical bars: S.E. of mean. To accord with previously observed characteristics of the evacuation of carbohydrate from an otherwise empty stomach (Hunt & Knox, 1968), the ordinate is a square root scale, and the least-squares regression lines exclude the data at 30 min after gavage in the dark and at 30 and 60 min in the light. The regression slopes differed reliably ($P < 0·02$ by t test) and the difference in stomach contents between dark and light at 2 p.m. was reliable ($P < 0·05$ by Mann–Whitney U test). The recovery 30 min after gavage in the dark deviated reliably from the square-root regression line ($P < 0·05$ by one-tailed t test).

cycle, rats were deprived of food for 3 hr from the beginning of the light or dark periods and were then tube fed with 1 g glucose in 2·5 ml water. There were generally no remains of food in the stomach after 3 hr deprivation in the dark. The glucose load was absorbed from the gastrointestinal tract considerably faster in the dark period than in the light period (Fig. 3). In the dark, the glucose was completely cleared within 2 hr, but absorption of the same dose took over 3 hr in the light. Thus the phase of the circadian cycle in which the rat sleeps more and feeds less frequently (Le Magnen & Tallon, 1966) is also the time when the stomach empties more slowly.

Food intake after an intragastric glucose load at night

Intake following gastric intubation of the 1 g dose of glucose was compared with intake following a water load of the same volume (2·5 ml.). The effects on feeding are presented as differences between the cumulative intakes at hourly intervals in the two conditions (Table 1). Under the same deprivation conditions as the experiment of Fig. 2 in the light phase, glucose in the dark phase produced a reliable and increasing inhibition of eating in the second and third hours of access (line *a*). No inhibition appeared when the deprivation of food prior to intubation was extended to 4·5 hr.

Under the conditions of the absorption measurements of Fig. 3, with a constant 3 hr of food deprivation before intubation, administration of

TABLE 1. Depression of cumulative food intake (g) after gastric loading with 1 g glucose in the dark period. Each datum is the mean difference between food intakes after glucose and water loads, totalled up to the time indicated by the column heading. Groups of twelve rats were used in the first 4 rows, and groups of sixteen in the lower 4 rows. Cumulative depression of intake after glucose was reliably greater than zero by one-tailed correlated *t* tests, with *P* values of less than 0·05*, 0·025** and 0·01***. When the intake depression for an individual 1 hr interval was reliably greater than zero, the cumulative intake value is printed in italics for $P < 0·05$, and bold for $P < 0·01$ by correlated *t* tests. In lines *a*–*c*, the first intake datum covers an initial 1·5 hr of access

	Deprivation-loading interval (hr)	Loading-re-feeding interval (hr)	Time since start of food deprivation (hr)						
			5	6	7	8	9	10	27
a	2·5	2		0·14	**0·88**	1·72*	—	—	—
b	4·5	2				−0·27	−0·04	—	—
c	3	0·5	*1·38***	1·28*	—	—	—	—	1·94***
d	3	1	0·66	0·80	1·35**	—	—	—	0·94
e	3	2		*1·17**	0·89	1·20*	—	—	1·12
f	3	3			*1·17**	1·49***	1·02	—	0·77
g	3	4				0·39	0·32	0·40	0·67*
h	3	5					−0·24	0·12	−0·37

glucose was generally followed by a marked inhibition of eating during the first hour of restored access to maintenance diet. This occurred when access to food was delayed for 2 hr (line *e*) during which time the load had been completely absorbed (Fig. 3). An equally large and reliable effect was seen when food was restored more than 1 hr after all the intubated glucose had been absorbed (line *f*). This difference between cumulative intakes following loads of glucose solution and water persisted during subsequent hours of feeding, through to the next day. With a delay of 4 hr between intubation and refeeding, the effect appeared to be reduced and was reliable only as a cumulative intake difference at 27 hr (line *g*). With 5 hr delay, intake was not depressed at all (line *h*).

The oxidation energy of the glucose load was equivalent to the utilizable energy of 1·09 g of maintenance diet. None of the statistically reliable depressions of intake differed reliably from 1·09. Furthermore, the mean of the cumulative intake depressions at 27 hr (Table 1, lines *c–g*) was 1·09 g, a value reliably greater than zero ($P < 0·01$).

Food intake after an intragastric glucose load by day

The pattern of results in the light phase was distinctly different (Table 2). Inhibition of eating during the first hour of restored access to food occurred only while there was rapid absorption of glucose (lines *a–c*). Even though there was still some glucose in the gut at 3 hr after stomach loading with glucose (Fig. 3), there was no depression of intake in the first or second hour of refeeding (line *d*). This contrasted with the result in the dark period after this same delay between loading and re-feeding.

Intake apparently compensated for the glucose load within a few hours

TABLE 2. Depression of cumulative food intake (g) after gastric loading with 1 g glucose in the light period. Groups of sixteen rats per condition. *$P < 0·05$, **$P < 0·025$, ***$P < 0·01$ for differences between cumulated intakes after glucose and water loads. Italics: $P < 0·05$ for intake difference in an individual 1 hr period, or 1·5 hr period in line *a*. The rats in lines *f–h* were intubated at the start of the light period, instead of at the start of its third hour as in the conditions of other lines in the Table

	Deprivation-loading interval	Loading-re-feeding interval	Time since start of food deprivation (hr)						
			5	6	7	8	9	10	27
a	3	0·5	*0·65**	0·74*	—	—	—	—	0·48
b	3	1	1·18***	1·14***	1·26***	—	—	—	1·43*
c	3	2		1·37***	0·90***	0·71**	—	—	1·58***
d	3	3			−0·12	−0·02	*0·51**	—	1·06
e	3	4				0·46	0·73**	0·41	1·50*
f	0	1	0·88**	1·02**	1·03***	—	—	—	1·04*
g	0	4				0·39	0·21	0·40	0·95
h	3	4				0·34	0·33	0·37	1·18**

of restored access to food, even when an inhibitory effect did not appear initially (lines *d* and *e*). The delay in the depression of intake until the ninth hour after deprivation appeared to depend on the approach or onset of the dark period; when intubated at light onset and fed 4 hr later, rats did not develop compensation of intake at 9 or 10 hr after deprivation, although it did appear overnight (lines *f* and *g*). The mean of all the cumulative intake difference values at 27 hr was 1·15 g, reliably greater than zero ($P < 0{\cdot}001$) but not greater than 1·09 ($P > 0{\cdot}1$).

Evidence that compensation for energy input during the light period could be rapid as well as precise was provided by a transient disinhibition of feeding at hour 7 ($P < 0{\cdot}01$) when there had been a 2 hr delay between loading and re-feeding (line *c*) and an initial strong depression of feeding in the immediately preceding hour.

Intragastric dose–response relationship

The stomach was found to be empty of food in rats from which maintenance diet had been withheld for 3 hr in the dark period. Doses of 0·5 and 1 g of glucose given intragastrically after 3 hr of deprivation were completely absorbed within the subsequent 2 hr. A dose of 1·5 g was mostly cleared in that time. Other rats were given access to food 2 hr after gastric intubation. They ate less after intubation with glucose than after intuba-

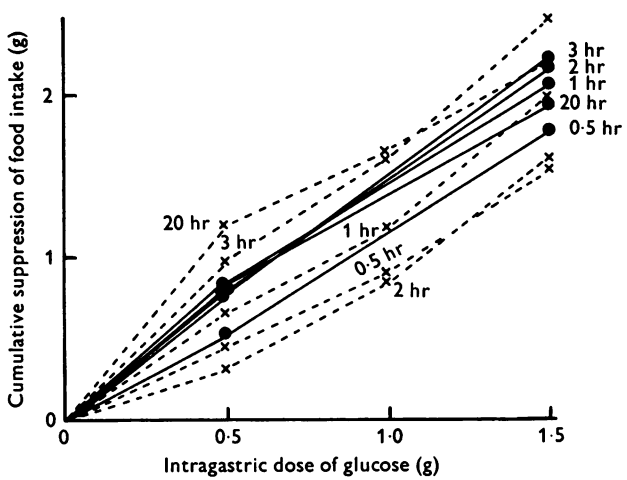

Fig. 4. Dose–response relationships between suppression of cumulative food intake and amount of glucose stomach-tubed. ● is suppression relative to intake after an equimolar dose of urea. × is suppression relative to intake after a water load of equal volume. Access to food was restored 2 hr after loading. Each dose–response line refers to a time period over which cumulative food intake was measured.

tion with water or with a dose of urea equimolar to the glucose dose. The differences between intake after glucose administration and intake in the control conditions were proportional to the dose of glucose, at all intervals over which cumulative intake was measured, from 0·5 to 20 hr after re-feeding (Fig. 4). Most of the depression in intake following stomach loading with glucose was realized within the first half hour of restored access to food, indicating that, under these conditions, intake compensated for effects of the load by adjustment of the first meal taken.

On other days in this experiment, the rats were intubated earlier within the same 5 hr deprivation period. With 2·75 hr delay between intubation and restored access to food, depression of intake still followed administration of glucose, although a dose–response relationship appeared only in the intake differences for the first 0·5 hr of feeding. When 3·5 hr was interposed between intubation and re-feeding, no reliable intake differences appeared. These results supported the indications in the experiment of Table 1 that compensation of intake for the load did not occur when re-feeding was delayed by substantially more than 1 hr after the end of absorption in the dark period.

Duodenal infusions

Effects on food intake following the absorption of gastrically intubated glucose could conceivably depend on after-effects of the presence of glucose in the stomach or of the taste of glucose as the injection tube is withdrawn. Such factors can be excluded by delivering the glucose directly into the duodenum through a permanently implanted cannula. Implanted rats were deprived of food for 3 hr in the dark phase, so that their stomachs would be empty at the start of infusion. A dose of 1 g (5·56 m-mole) of glucose was infused in 10 ml. aqueous solution over a period of 1 hr. The infusion tube was then disconnected from each rat and food jars were replaced 15 min later. This delay was to allow the last remaining amounts of infused glucose to be completely absorbed by the time the animals started to eat. In autopsies at the end of experiments, 0·04–0·06 m-mole of glucose was recovered from the stomach and small intestine 15 min after the end of infusion. Glucose recovery from uninfused rats at the same time was 0·01–0·05 m-mole.

Rats ate immediately access to food was restored. Six rats, which were found at autopsy to have cannulae with their tips in the duodenum, ate less in their first meal after infusion of glucose than after an equimolar urea infusion (Table 3). There was a tendency for the second meal to be taken sooner, which may represent a compensatory response to the large initial depression in intake (mean value 1·74 g).

The differences between effects following urea and glucose infusions were

not a result of stimulation of feeding by urea. For example, in rat 1 (Table 3), the first meal on a day without infusion was $6{\cdot}8 \pm 0{\cdot}3$ g and intake in the first 4 hr of access to food was $10{\cdot}9 \pm 0{\cdot}4$ g (means $\pm$ S.E. of mean for 25 days). Three other rats, in which many days without infusion were also recorded, proved on autopsy to have cannulae whose tips had moved into the stomach. Their food intake after urea infusion did not differ from that on days without infusion. Their first meals after urea infusion and after glucose infusion respectively were 100–110 % and 74–97 % of the weight of the first meals on days without infusion (27–36 observations in each condition).

Conditioned hypophagia has been observed after administration of glucose in large amounts or in greatly hypertonic solutions, orally (Booth, Lovett & McSherry, 1972), intragastrically (Le Magnen, 1959, 1969) or parenterally (Russek, 1970; Russek, Rodriguez-Zendejas & Pina, 1968). In the present experiment, urea and glucose were given in pseudo-random sequence on successive days, 4–5 days a week. No depression of food intake on days following a glucose infusion was detected under these conditions.

The inhibition of feeding after glucose infusion and absorption was also observed in another group of four rats with duodenal cannulae (Table 4). Kruskal–Wallis analyses of variance by ranks (Siegel, 1956) showed that intakes varied reliably among infusion conditions in rats 7, 8 and 9 ($P < 0{\cdot}01$). Infusion of fructose was followed by a suppression similar to and possibly greater than that after glucose, but 3-*O*-methyl-glucose or galactose infusions did not inhibit subsequent food intake.

Intravenous infusions

Effects following the absorption of gastrically or duodenally administered carbohydrate may be a result of action of the absorbed sugars or of a hormone released during absorption. The latter possibility, or any other effect specific to the process of intestinal absorption, can be excluded if an infusion directly into the vasculature draining the intestine is no less effective than a duodenal infusion.

Rats with permanent cannulae in the hepatic portal vein were deprived of food for 3 hr at the start of the dark phase, infused with 1 g glucose in 10 ml. over a period of 1 hr, and then given access to food 10 min after the end of infusion. Feeding was inhibited during the first meal, relative to feeding after infusion of 0·9 % NaCl (Table 5). The mean depression in meal size was not significantly different from the mean depression after duodenal infusion (1·46 g, Tables 3 and 4, $P > 0{\cdot}1$ by uncorrelated t test). As with duodenal infusions, the inhibitory effect of fructose appeared to be greater than that of glucose, whereas galactose and 3-*O*-methylglucose

TABLE 3. Food intake pattern following duodenal infusion of glucose or urea. *n* is the number of observations recorded for that rat under that condition. *P* is the probability of the null hypothesis according to a two-tailed *t* test (on mean intakes) or a two-tailed Mann–Whitney U test (on median intermeal intervals). n.s. = not significant ($P > 0.05$). No urea/glucose difference in 4 hr intakes was significant for an individual rat, but the group mean difference of 0·50 was significantly above zero ($P < 0.05$ by one-tailed *t* test)

	Size of first meal					Time interval between first and second meals					Food intake in first 4 hr			
	After urea		After glucose		Urea/glucose difference	After urea		After glucose		Urea/glucose difference	After urea		After glucose	
Rat	Mean (g)	*n*	Mean (g)	*n*	(*P*)	Median (min)	*n*	Median (min)	*n*	(*P*)	Mean (g)	*n*	Mean (g)	*n*
1	7·0	25	4·6	6	< 0·05	154	27	114	6	< 0·01	11·2	25	10·2	6
2	6·2	4	4·8	2	< 0·01	—	—	—	—	—	10·6	4	9·8	2
3	4·7	29	3·8	7	< 0·2	126	27	89	7	n.s.	9·1	28	8·9	7
4	4·7	26	3·4	10	< 0·001	133	27	96	10	< 0·025	8·2	27	8·4	10
5	4·1	29	2·5	10	< 0·001	108	23	71	6	n.s.	7·4	30	7·3	8
6	4·6	28	2·2	9	< 0·001	108	25	137	10	< 0·01	6·8	28	5·7	10

TABLE 4. Food intake after duodenal infusion of urea or hexoses. *n*, number of recorded observations available for the rat. * Reliable difference from meal size after urea infusion ($P < 0.05$ by two-tailed Mann–Whitney U test)

	Size of first meal (g) on re-feeding after the end of infusion													
	After urea			After glucose			After fructose			After galactose			After 3-methylglucose	
Rat	Mean	S.E.	*n*	Mean	S.E.	*n*	Mean	Range	*n*	Mean	S.E.	*n*	Mean	*n*
7	8·1	0·54	12	5·9	0·54	4	5·5	—	1	8·1	0·78	5	9·0	1
8	5·1	0·11	14	3·7	0·66	3	2·9	0·0	2	5·3	0·56	6	6·2	1
9	5·2	0·33	13	3·6*	0·27	3	4·6	2·1	2	—	—	—	—	—
10	4·2	0·44	15	3·8	0·39	4	2·3*	0·6	2	—	—	—	—	—

TABLE 5. Effects on food intake in the first meal following intravenous infusion. * Difference in size from the meals which followed infusion of 0·9 % NaCl. † One rat in each of these groups showed an individually significant depression of meal size following sugar infusion ($P < 0·05$ by two-tailed Mann–Whitney U test). In five rats receiving hepatic glucose infusions early, the individual effects approached significance ($P < 0·1$). n.s., not significant ($P > 0·05$ by two-tailed Wilcoxon paired comparisons test)

	Hepatic portal vein infusion								Jugular vein infusion			
	During early part of dark period				During middle of dark period				During early part of dark period			
		Change in meal size*				Change in meal size*				Change in meal size*		
Solution infused	No. of rats	Mean (g)	S.E. of mean (g)	P	No. of rats	Mean (g)	S.E. of mean (g)	P	No. of rats	Mean (g)	S.E. of mean (g)	P
None	4	−0·52	0·32	n.s.	5	0·18	0·48	n.s.	—	—	—	—
1·8 % NaCl	6	0·37	0·56	n.s.	8	−0·02	0·49	n.s.	4	0·05	0·96	n.s.
10 % Glucose	8	−1·03	0·24	< 0·01	11	−0·57	0·18	< 0·02†	4	−0·63	0·40	n.s.†
10 % Fructose	2	−2·33	0·13	—†	3	−0·50	0·56	—†	1	−1·3	—	—
10 % Galactose	2	−0·05	0·04	—	4	0·58	0·33	n.s.	1	1·2	—	—
10 % 3-*O*-Methyl-glucose	1	−0·1	—	—	1	0·35	—	—	—	—	—	—

had no inhibitory effect on feeding. There was a substantial hyperglycaemia during infusion of glucose, with hypoglycaemia ensuing in the absence of food after the end of infusion (Fig. 5). Fructose infusion produced a delayed and transient rise in blood glucose concentration during infusion and no hypoglycaemic reaction after infusion. Galactose produced no visible change.

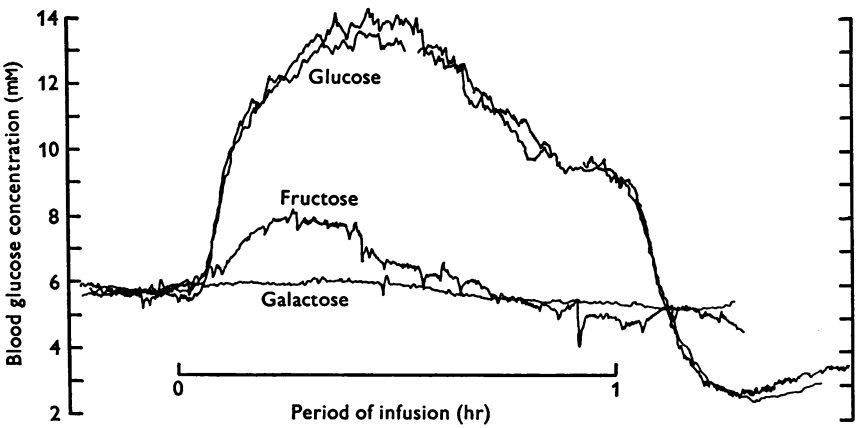

Fig. 5. Blood glucose concentration during and after hepatic portal infusion of sugars into a representative 4 hr food-deprived rat in the dark phase. The lines are tracings of the record from an auto-analyser which was on line to the rat's jugular vein.

Another group of rats was deprived and infused 3–4 hr later in the dark phase of the circadian cycle. Although reliable inhibitory effects followed infusions of glucose and fructose (Table 5), on average they appeared to be smaller than the effects seen in the early part of the dark phase when most of the present experiments were performed. In the 5 rats with hepatic portal cannulae infused in either part of the dark period with 0·9 % NaCl, 1·8 % NaCl, glucose, fructose and galactose, a Friedman analysis of variance by ranks (Siegel, 1956) showed significant variation between treatments ($P < 0{\cdot}05$).

Infusion of glucose into the jugular vein, under the usual conditions in the early part of the dark phase, was followed by rather variable changes of food intake (Table 5). Nevertheless, meals following glucose infusion were generally smaller than meals following saline infusion (nine out of ten occasions in four rats). The average depression of intake did not differ reliably from that following portal infusion ($P > 0{\cdot}1$), but it was less than that seen after duodenal infusion ($P < 0{\cdot}05$).

Signs of a small conditioned suppression of feeding were seen on the

days after hepatic portal infusion of glucose early in the dark phase. On occasions when the same non-nutritive infusion had been given on the day before and the day after glucose infusion, the size of the first meal was 0·37 g lower on the day after infusion (seven rats, $P < 0·05$). Intake recovered by 0·20 g on the second day after infusion, a change which was not reliable in itself ($P > 0·1$) but did differ significantly from the change between the day before and the day after glucose infusion ($P < 0·02$).

DISCUSSION

The present experiments established for the first time that the entry of normal amounts of readily utilized carbohydrate into the circulation by the physiological route is followed by an inhibition of feeding, and that this post-absorptive inhibition can be sufficiently strong to explain much of normal satiation.

Suppression of feeding by gastrointestinal or systemic administration of nutrient has hitherto often been attributed to colligative or bulk effects (Janowitz & Grossman, 1948, 1949; McCleary, 1953; Smith & Duffy, 1957; Smith, 1966; Yin, Hamilton & Brobeck, 1970; Baile, Zinn & Mayer, 1971; Ehman, Albert & Jamieson, 1971; Yin & Tsai, 1973). Such conclusions depend on experiments which have been run under inappropriate conditions. Feeding tests have been given at times when concentrated solutions of both free glucose and control non-nutritive substances are likely to have marked osmotic or bulk effects in the stomach, intestine or intraperitoneal cavity, which would obscure differences in effect following absorption. The post-absorptive differences themselves have probably been attenuated by testing animals after long periods of food deprivation, with a pattern of nutrient utilization very different from that under *ad libitum* feeding conditions. Le Magnen & Tallon (1968) found that regularly starved animals show attenuation of the satiating after-effects of feeding, and, furthermore, they learn to overeat. In the present experiments, the inhibition of feeding following complete absorption of a gastric load of glucose did not occur when the rat was deprived of food for a total of more than 6 hr of the dark period.

Nevertheless, some experiments have indicated that chemospecific properties of hypertonic nutrients given to deprived rats do contribute to satiety (Miller, 1957; Jacobs, 1964). In experiments where rats have been feeding freely, tube-fed nutrients have consistently been found to produce marked inhibitory effects on food intake which could not be attributed to osmotic or distension factors, particularly over the dark period (Booth, Lovett & Simson, 1970; Panksepp, 1971; Booth, 1972*a*, *b*). Rats sleep more and absorb food more slowly in the light part of the circadian cycle,

and might not be so sensitive to the effects of nutrient loads in the daytime tests made in previous work.

The effects of intravenous infusions on food intake are probably no less sensitive to the physiological state of the animal. Absence of a detectable reduction of food intake during glucose infusion (Janowitz, Hanson & Grossman, 1949; Adair, Miller & Booth, 1968) has been attributed to insufficiency of insulin (Rowland, Meile & Nicolaïdis, 1973; Booth & Jarman, 1975) or the distribution of glucose from an inappropriate infusion site (Russek, 1970; Campbell & Davis, 1974*b*). The rate of infusion can be too low (Strubbe, 1975) in relation to current absorption rate and the sensitivity of the satiety measurements (Pruvost, Duquesnel & Cabanac, 1973; Scharrer, Thomas & Mayer, 1974; VanderWeele, Novin, Rezek & Sanderson, 1974). It must be noted that the effect on food intake in the present study was little or no greater than the energy equivalent of the infused glucose.

Mechanism of post-absorptive satiation

During the dark period, rats showed a depression of food intake at time intervals up to 1·5 hr after a 1 g dose of glucose had been completely absorbed. In the light period, although depression of intake did not occur after complete absorption of the load, it was observed under conditions in which too little glucose remained in the gut to be likely to exert a bulk effect. Gastrointestinal analyses showed that glucose was absorbed quickly in the dark period and confirmed (Hunt & Knox, 1968) that absorption was fast in the early stages of absorption, by day as well as night. Absorption and the hepatic and cerebral uptake of glucose begins within a few minutes of ingestion, even when starch has to be digested first (Pilcher, Jarman & Booth, 1974; Steffens, 1970). A high rate of nutrient absorption during and soon after a meal may activate the post-absorptive satiation mechanism while there is still much food remaining to be absorbed. An intensifying satiation of systemic origin has been detected in the first half hour after a meal, as the utilization of rapidly absorbed nutrients progresses (Davis, Campbell, Gallagher & Zurakov, 1971; Davis, 1973).

Carbohydrate metabolism in the liver may be important in the observed depression of food intake. The hypothesis is consistent with the effectiveness of glucose relative to other hexoses when infused into the duodenum of the liver.

First, fructose was at least as effective as glucose in suppressing feeding. Although fructose is not actively transported as is glucose, it can leave the intestine almost as rapidly (Bogdanove & Barker, 1950; Holdsworth & Dawson, 1965) with little conversion to glucose (Kiyasu & Chaikoff, 1957). Administered systemically, fructose is utilized in the liver more exclusively

(Sols, 1968) or more rapidly (Baron, Griffaton & Lowy, 1969) than is glucose.

In contrast, secondly, galactose was ineffective at suppressing feeding, even though it is actively absorbed from the intestine by the glucose transport mechanism (Fisher & Parsons, 1953). Galactose is metabolized mainly in the liver (Bollman, Mann & Power, 1935) but adult rat liver consumes galactose, and produces CO_2 from it, in poor yield – unlike infant rat liver (Segal, Roth & Bertoli, 1963), in which galactokinase activity is much higher (Cuatrecasas & Segal, 1965).

Finally, 3-*O*-methylglucose was ineffective. This analogue enters cells in the same manner as glucose (Morgan, Regen & Park, 1964) but it is not metabolized (Csáky & Glenn, 1957).

There is evidence for glucose-sensitive neural elements in the liver or portal vein which may be important in satiety (Niijima, 1969; Russek, 1970, 1971; Schmitt, 1973). A metabolic rather than merely chemospecific action of glucose is indicated by its effectiveness relative to 3-*O*-methylglucose in suppressing feeding when small doses are injected intraperitoneally in the rat (Booth, 1976), and by the elicitation of feeding by a low dose of 2-deoxyglucose infused into the hepatic portal vein of the rabbit (Novin, VanderWeele & Rezek, 1973). The supply of energy-yielding metabolites to the liver activating a receptor system that inhibits feeding (Booth, 1972*b*) can largely account for observed spontaneous feeding patterns (Booth, 1976). It remains to be determined by concurrent behavioural, neurophysiological and biochemical measurements whether the neural elements responding to metabolism are located in the viscera or whether some or all of them are in specialized regions of the brain (Oomura, Ooyama, Sugimori, Nakamura & Yamada, 1974; Debons, Krimsky, From & Pattinian, 1974).

The inhibition of feeding following hepatic portal infusion of glucose was not statistically less than that following an identical duodenal infusion. Therefore it seems that consequences of absorption other than parenteral action of the absorbed glucose were not critical to the suppression of feeding after absorption has been completed. Nevertheless, the possibility was not excluded that release of a hormone from the gut, a central memory for afferent neural activity, or some other consequence of the process of absorbing glucose, contributed to the effect in a minor way.

Function in the control of feeding

The amounts of free or combined sugar administered in this study ranged from 0·5 to 1·5 g. Such amounts are yielded by the digestion of the carbohydrate content of a meal of the size typical for the freely fed rat (approximately 1·5–3 g: Le Magnen & Tallon, 1966; Levitsky, 1970;

Booth, 1972*c*). Thus the effects observed in the present experiments may well play a major role in the control of feeding and the maintenance of energy balance close to null point under normal conditions.

Under the conditions of these experiments, inhibition of feeding was expressed as a reduction in meal size. The effect is likely to explain much of the increase in size of the first meal on re-feeding which is seen when the period for which food has been withheld is lengthened to 6–8 hr, an increase which is most of that seen with longer durations of deprivation imposed on unadapted rats (Miller, 1957; Le Magnen & Tallon, 1968). The rat delayed the start of the meal in our experiments on only a small minority of occasions, and then for merely a few minutes (20 min at most). The sudden return of food after several hours' absence may have prevented the expression of the inhibitory effect of absorbed glucose as a reduction in the likelihood that contact with food would initiate a meal, which could appear in the continuous presence of food. That is, the present results are consistent with earlier findings (Booth, 1972*a*) indicating that metabolic effects of orally administered carbohydrate increase the intensity and duration of satiation between meals as well as the suppression of appetite during a meal seen here.

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