Feeding pattern of rabbits following intraduodenal glucose infusion as a function of caloric load, fasting interval, and vagal denervation

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Several meal parameters were evaluated during the 3-h period following intraduodenal infusion (3.3 ml/kg BW) of 5%, 10%, or 20% d-glucose, infusion of isotonic saline, or no infusion. Bilateral subdiaphragmatically vagotomized and sham-operated rabbits with chronic intraduodenal cannulas received all infusion treatments following both a 24-h fast and a period of free feeding. When infusions were given after free feeding, cumulative food intake was significantly decreased and latency to initiate feeding significantly increased by infusion of 5% glucose in the sham-operated rabbits, but not by infusion of 10% or 20% glucose. Cumulative food intake and latency were not affected by glucose infusion in the fasted sham-operated rabbits, or in the vagotomized rabbits following fasting or free feeding. The absence of glucose-induced satiety for the higher concentrations indicates that vagotomy does not merely shift the threshold for satiety, but appears to render vagotomized rabbits insensitive to the satiating effects of glucose. Both vagal denervation and a 24-h pretest fast produced dramatic effects on several short-term meal parameters. The nonmonotonic relation between the intraduodenal glucose load and subsequent feeding in sham-operated, free-feeding rabbits may result from the interaction of several factors, including activation of visceral satiety mechanisms, secretion of gut hormones, and visceral malaise.

Administration of glucose directly into the antral duodenum has been reported to produce a decrease in subsequent short-term feeding in rabbits (Novin, Sanderson, & VanderWeele, 1974; Rezek & Novin, 1976; VanderWeele, Novin, Rezek, & Sanderson, 1974) and rats (Booth & Jarman, 1976; Novin, Gonzalez, & Sanderson, 1976; Novin, Sanderson, & Gonzalez, 1979). Furthermore, Campbell and Davis (1974) noted that intraduodenal infusion of glucose

decreased the licking rate of rats given a palatable fluid. Although some investigations have failed to observe nutrient-specific satiety following glucose infusion into the alimentary tract (Ehman, Albert, & Jamieson, 1971; Glick, 1979; Yin & Tsai, 1973), the use of long-fasted animals may have been a reason for the absence of satiety, since the depression in feeding produced by intraduodenal glucose infusion in free-feeding rabbits was absent following a fast (Novin et al., 1974). VanderWeele, Skoog, and Novin (1976) demonstrated that intraduodenal glucose administration decreased feeding in free-feeding rabbits but not in rabbits fasted for even as short a period as 2 h. The magnitude of the glucose load also plays a very important role in determining its modulatory influence on feeding, since a small duodenal infusion (3.5 ml/kg BW) of 5% glucose decreased food intake in free-feeding rabbits, whereas a larger load (10.5 ml/kg BW) of 5% glucose actually increased subsequent short-term food intake (Rezek, Havlicek, & Novin, 1975).

This seemingly paradoxical result casts doubt on the universal applicability of theories that link food

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intake to caloric availability (Booth & Jarman, 1976; Friedman & Stricker, 1976). Thus, one rationale for the present study was to determine the relation between the glucose load (produced by varying glucose concentration) and subsequent feeding. On the basis of our previous report (Rezek et al., 1975), the higher glucose loads used were expected to produce weaker satiating effects than the small isotonic glucose load used in several earlier investigations and found to reliably produce decreased feeding in the rabbit (Novin et al., 1974; VanderWeele et al., 1974; VanderWeele et al., 1976).

A model has recently been proposed to describe the role of visceral mechanisms in the control of food intake (Novin & VanderWeele, 1977). Considerable emphasis was placed on the role of hypothetical vagally innervated visceral glucosensitive cells in modulating short-term feeding. The satiating effect of a small intraduodenal load of isotonic glucose was abolished by total subdiaphragmatic vagotomy (Novin et al., 1979; Novin et al., 1974; VanderWeele et al., 1974). In fact, following recovery from vagal denervation, rabbits typically exhibited a small, but reliable, tendency to increase feeding subsequent to intraduodenal infusion of a small isotonic glucose load (Novin, 1976). No appropriate data exist to indicate whether larger glucose loads would overcome this apparent insensitivity to the satiating effects of glucose resulting from vagotomy or would further enhance the tendency of vagotomized rabbits to consume more food after intraduodenal glucose infusion than after administration of an equiosmotic saline load. Thus, a second rationale for the present study was to determine whether the use of glucose loads greater than previously investigated in vagotomized rabbits would reinstate satiety or, alternatively, perhaps enhance the facilitation of feeding reliably observed in free-feeding vagotomized rabbits following infusion of a small intraduodenal glucose load.

Previous investigations have predominantly evaluated cumulative food intake and the latency to initiate the first meal as measures of feeding. In contrast, the present investigation used a system of load-cell pressure transducers interfaced with a microprocessor data-acquisition system to monitor a number of meal parameters during the 3-h postinfusion test session. A major advantage of this method was that it minimized the disturbance of experimental subjects by eliminating the necessity of periodically removing food containers to permit weighing. In addition to cumulative food intake and latency to feed, the present experiment also evaluated the size of individual meals, hourly number of meals, and the ratio of pre-meal and postmeal intermeal intervals to meal size. Water intake was measured to permit an evaluation of the specificity of the suppressive effect of glucose infusion. The determination of several parameters

related to individual meals, rather than to arbitrarily selected intervals, to characterize the effects of intraduodenal glucose infusions in intact and vagotomized rabbits was expected to result in a better understanding of the mechanisms by which such infusions affect short-term regulation of food intake. Thus, the third important aspect of the present study was its attempt to characterize, in finer detail than hitherto possible, the ways in which intraduodenal glucose infusion acts to modulate feeding in rabbits under a variety of experimental conditions.

METHOD

Animals

Twenty-nine female albino New Zealand rabbits were used. Throughout the experiment, these animals were individually housed in modified plastic canine flight kennels measuring 82 × 45 × 56 cm. A feeding box and a 1,000-ml plastic graduated cylinder were attached to the front of each cage. Prior to surgery, the rabbits were given continuous access to pelleted Purina Rabbit Chow (60% carbohydrate, 16% protein, 2% fat) and tap water. Overhead fluorescent lights were set for a 12:12-h light-dark cycle with light onset at 0600 h. Indirect red illumination was provided from 1800 to 2400 h. Before surgery, the mean body weights of the vagotomy group (N = 14) and the control group (N = 15) were 2.6 and 2.4 kg, respectively; at the start of testing, these groups had mean body weights of 2.7 and 2.6 kg, respectively.

Surgery

All surgery was done under pentobarbital sodium (30 mg/kg, iv) anesthesia. The vagotomy procedure involved the removal of connective tissue from the vertex of the stomach and along the proximal esophagus for a distance of 30–40 mm. The esophagus was closely examined, and all nerve fibers dissected off the surface. Control subjects underwent a laparotomy procedure in which the abdominal cavity was opened and the esophagus manipulated. In addition, all vagotomized and sham-operated rabbits were surgically implanted with an intraduodenal cannula that entered the stomach through an incision located near the pyloric sphincter and was threaded into the duodenum. The cannula (Dow Corning Silastic: 1.02 mm i.d., 2.16 mm o.d.) proceeded from the point of exit in the stomach wall subcutaneously to the skull, where it was attached to a blunted 18-ga needle. Dental acrylic cement bound the blunted needle to four stainless steel screws anchored in the skull. The abdominal incision was closed by continuous suture of the muscle and a second layer of interrupted sutures to close the skin. Physiological saline was infused through each cannula daily to maintain cannula patency. During convalescence, the rabbits were provided with carrots, parsley, and lettuce, in addition to Purina Rabbit Chow and tap water.

Behavioral Testing

Following surgery, all subjects were permitted to recover for at least 2 weeks. When an animal appeared to have recovered from the initial period of hypophagia produced by surgical intervention, daily food intake was monitored until the rabbit consumed a minimum of 100 g of rabbit chow on several successive days. After several days of habituation to the entire infusion procedure, behavioral testing was started and continued for a period of 6–9 weeks. The 3-h test session began at 1700 h (the same time that tests were begun in several previous studies in this laboratory). The infusion consisted of a small volume (3.3 ml/kg BW) of .9% NaCl, or 5%, 10%, or 20% d-glucose (w/v) prepared with distilled water. Infusion of this small volume was done in a period of approximately 20 sec. After infusion of the test solution, the cannula was cleared of any residual infusion fluid by injection of physio-

logical saline. Most animals also underwent a mock procedure that involved neither infusion nor handling. The foodbox and water bottle used in this mock test were merely attached to the front of the cage and data recording begun. All five of these injection conditions were carried out following both 0- and 24-h periods of food deprivation. The 10 resultant infusion-deprivation combinations were presented in randomized order with an interval of 3-6 days elapsing between successive tests.

Data Collection and Analysis

During test sessions, a metal foodbox equipped with a photocell unit was attached to the front of the home cage. Immediately after a test infusion (approximately 3 min), a metal plate blocking access to the food dish was removed. When a rabbit fed, its head interrupted the photocell beam and thus activated the pen of an Esterline-Angus event recorder. In addition to this record of the temporal pattern of meals, the size of each meal was calculated from the output of the system of load cells connected to an Esterline-Angus data acquisition system. Each food dish rested on a load cell that generated an electronic signal proportionally related to that weight. The data acquisition system continuously monitored the output of the load cells and provided a digital print-out at 2-min intervals. Further details concerning this acquisition system are provided elsewhere (Geiselman, Rogers, Jaster, Martin, & Novin, 1979). The size of a meal was calculated as the difference in the weight of the food dish before and after each meal, as determined from the event-recorder paper tape. A meal was defined as consumption of a minimum of 1 g of rabbit chow. A subsequent meal would occur only following a minimum interval of 4 min during which the photocell beam was not interrupted. Water intake was visually determined 1, 2, and 3 h after a test infusion. Food intake was measured to the nearest .1 g, and water intake to the nearest 5 ml.

The statistical analysis of latency data was done with the Mann-Whitney U test for comparisons between surgical conditions and the Wilcoxon matched-pairs signed-rank test for comparisons between infusion conditions. Comparisons were made to determine the effects of vagotomy, fasting interval, and infusion condition. The results of previous experiments in our laboratory (Rezek & Novin, 1976; VanderWeele et al., 1974) provided a basis for expecting that infusion of 5% glucose would increase the latency in the sham-operated rabbits under the free-feeding condition; thus this comparison was based on a directional *p* value. All other comparisons involving latency data were based upon analyses using nondirectional *p* values.

The effects of vagal denervation (Vagx vs Sham) and the fasting interval (0 h vs. 24 h) on the remaining meal-related parameters were evaluated with a 2 × 2 factorial ANOVA design with repeated measures on one factor (fasting interval). Only data from the saline-infusion condition were analyzed in this comparison. The meal-related parameters evaluated included the size of individual meals (first, second, and third), hourly number of meals, deprivation ratio (intermeal interval preceding a meal divided by the size of that meal), satiety ratio (intermeal interval following a meal divided by the size of that meal), cumulative food intake (1, 2, and 3 h), and cumulative water intake (1, 2, and 3 h). To determine the effects of the infusion conditions (saline, 5%, 10%, and 20% glucose, and the mock procedure) on these meal-related parameters, analysis was done with a single-factor repeated-measures ANOVA design. Analysis was done separately on data obtained from (1) undeprived sham-operated, (2) fasted sham-operated, (3) undeprived vagotomized, and (4) fasted vagotomized rabbits. Because only 10 of the 15 sham-operated rabbits underwent testing with the mock procedure, a matched-pairs Student *t* test was used to compare the mock procedure with the saline infusion condition. When the single-factor ANOVA procedure resulted in a significant ($p < .05$) overall effect, individual comparison of each infusion condition with the saline control condition was done with the Bonferroni *t* statistic (Miller, 1966). It was expected that in-

fusion of 5% glucose in undeprived sham-operated rabbits would decrease cumulative food intake (Novin et al., 1974; Rezek & Novin, 1976; VanderWeele et al., 1974; VanderWeele et al., 1976), and, therefore, this comparison was based upon a directional *p* value. All other individual comparisons were based upon nondirectional *p* values.

Verification

At the conclusion of behavioral testing, the rabbits were anesthetized with pentobarbital sodium (30 mg/kg BW, iv). Vagal function was then assessed in all vagotomized and sham-operated animals by electrically stimulating the cervical vagi while continually monitoring gastric contractions with a balloon inserted into the stomach and attached to a pressure transducer. The stimulation consisted of 15-20-Hz, 1-25-V, biphasic dc pulses of .2 msec duration presented in 5-10-sec stimulus trains. The pressure transducer was connected to a polygraph to produce a permanent record. During a series of such verifications, control rabbits were interspersed with those rabbits that had undergone the vagotomy procedure. Vagally intact rabbits exhibit gastric contractions in response to stimulation of the cervical vagi, whereas animals that have sustained extensive abdominal vagal denervation do not. Following completion of this electrophysiological evaluation, each rabbit was sacrificed with an overdose of pentobarbital sodium. Verification of the functioning of the cannula and the duodenal placement of its tip was then done. The surgical and verification techniques are discussed in greater detail elsewhere (Martin, Rogers, Novin, & VanderWeele, 1977).

RESULTS

The infusion condition significantly affected cumulative 2-h food intake; in the free-feeding sham-operated rabbits, infusion of 5% glucose significantly ($p < .02$) reduced subsequent food intake in comparison with the saline condition (Figure 1). The infusion condition failed to have any significant overall effect on cumulative food intake in fasted sham-operated rabbits (Figure 2), or in vagotomized rabbits following a period of free feeding (Figure 3) or fasting (Figure 4). For free-feeding sham-operated rabbits, the latency to the first meal was increased ($p < .05$) by infusion of 5% glucose, in comparison with saline infusion (Figure 5). The other meal parameters evaluated in the vagotomized and sham-operated rabbits, as well as cumulative water intake, were not significantly affected by the infusion condition. There was no evidence that the saline infusion condition differed from the mock procedure in affecting the various meal-related parameters evaluated in this investigation.

The effects of both the denervation condition (vagotomy vs. sham surgery) and the fasting interval (0-h vs. 24-h deprivation) were evaluated for only the saline-infusion condition, with a 2 × 2 factorial ANOVA design with repeated measures on one factor. Vagotomy reduced both 2- and 3-h cumulative food intake ($ps < .05$). However, the latency to initiate feeding following a fast and after a period of free feeding was not different for vagotomized and control rabbits. The size of the second meal was smaller in vagotomized than in control rabbits ($p < .05$). Fasting

Figure 1. Cumulative food intake of free-feeding sham-operated rabbits following infusion of various glucose loads or control procedures.

affected a number of meal-related parameters. Following a 24-h fast, 1-, 2-, and 3-h ($p < .05$) cumulative food intake was increased relative to intake following a period of free feeding. Both vagotomized ($p < .01$) and control ($p < .05$) rabbits exhibited shorter latencies to feed after fasting than after free feeding. Similarly, fasting increased the size of the first, second, and third meals ($p < .05$) postinfusion, and it resulted in a significantly lower satiety ratio for the first meal ($p < .01$). The number of meals occurring within the 1st hour postinfusion ($p < .01$) and within the 3rd hour postinfusion ($p < .05$) was increased by a 24-h fast. During the 2nd hour postinfusion, there was significant interaction between the denervation condition and the deprivation state ($p < .05$) that resulted from the much greater number of meals consumed by fasted sham-operated rabbits in comparison with the number of meals consumed by free-feeding sham-operated rabbits, fasted vagotomized rabbits, or free-feeding vagotomized rabbits.

DISCUSSION

The results of the present investigation demonstrated the effectiveness of a small intraduodenal infusion of 5% glucose (3.3 ml/kg BW), but not glucose loads twice or four times larger, in reducing food intake and increasing latency to initiate the first meal. This satiating effect was observed only in free-feeding sham-operated rabbits and not in fasted sham-operated rabbits or vagotomized rabbits following fasting or continuous access to food. These data are consistent with reports that intraduodenal glucose administration reduced feeding in several species (Booth & Jarman, 1976; Heron & Stephens, 1978; Houpt, Houpt, & Pond, 1979; Novin et al., 1974). The failure of other investigations (Ehman et al., 1971; Glick, 1979; Yin & Tsai, 1973) to demonstrate nutrient-specific suppression of feeding after intraduodenal glucose infusion may be due to the use of long-fasted subjects, which have previously been shown to be less sensitive to the satiating effect of glucose infusion (present experiment; Novin et al., 1974). However, Snowden (1975) also failed

Figure 2. Cumulative food intake of 24-h-fasted sham-operated rabbits following infusion of various glucose loads or control procedures.

Figure 3. Cumulative food intake of free-feeding vagotomized rabbits following infusion of various glucose loads or control procedures.

to observe any nutrient-specific satiety when 18% glucose was intraduodenally infused during spontaneous liquid meals consumed by free-feeding rats. Factors other than the deprivation state also influence the satiating effect of an intraduodenal glucose infusion. In particular, a large glucose load (10.5 ml/kg BW) infused into the duodenum of free-feeding rabbits actually enhanced feeding (Rezek et al., 1975). This paradoxical overeating effect has been shown to be accompanied by the stimulation of prolonged and exaggerated insulin release by such a large glucose load (Rezek, Havlicek, & Friesen, 1979a) and is abolished by pretreatment with somatostatin or cycloheximide, which prevent normal insulin release (Rezek, Havlicek, & Friesen, 1979b). Thus the satiating effect of a 5% glucose load and the absence of significant effects of either 10% or 20% glucose loads in the present experiment may be due to the possibly differential patterns of insulin release generated by infusion of these different glucose loads.

Even the relatively large glucose loads infused intraduodenally in the present study failed to overcome

the loss of glucose-induced satiety following fasting or vagal denervation. The vagotomized rabbits exhibited only a slight nonsignificant tendency to feed sooner and to consume more following glucose infusion than after saline infusion, but this weak tendency did not appear to increase with an increased glucose load. The results extend previous findings in the rabbit and emphasize that total abdominal vagotomy abolishes the glucose-induced satiety observed in free-feeding intact rabbits even when a large glucose load is intraduodenally infused. The involvement of the vagus nerves in mediating the satiating action of an intraduodenal glucose infusion has also been reported for rats (Novin et al., 1979) and pigs (Houpt, Houpt, & Pond, 1979). Other reports have demonstrated the alteration of spontaneous daily meal pattern by total abdominal vagotomy in rabbits (Geiselman, Martin, VanderWeele, & Novin, 1980; Sanderson & VanderWeele, 1975). In the present investigation, cumulative food intake and the size of the second meal were reduced during the 3-h test session following a control infusion of saline in vagotomized rabbits in comparison with control rabbits. Cumulative food intake and latency to feed appeared to be the parameters most sensitive to the effects of glucose infusions, whereas fasting also af-

Figure 4. Cumulative food intake of 24-h-fasted vagotomized rabbits following infusion of various glucose loads or control procedures.

Figure 5. Latency to initiate the first meal (mean minutes $\pm$ SEM) following infusion of various glucose loads or control procedures in vagotomized and sham-operated rabbits under fasting or free-feeding conditions.

fected the size of the initial three meals, the number of meals occurring within the 1st hour and within the 3rd hour after saline infusion, and the satiety ratio for the initial meal postinfusion. Although the failure of infusions of the hypertonic concentrations of glucose to increase drinking is consistent with an earlier report (Snowdon, 1975), the absence of any deficit in spontaneous drinking in vagotomized rabbits (present experiment; Rezek, VanderWeele, & Novin, 1975) contrasts with the severe reduction of spontaneous daily water intake observed subsequent to total abdominal vagotomy in rats (Martin, 1981; Martin, Geiselman, & Novin, 1979).

The results of the present study emphasize that, in the short-term control of feeding in rabbits, the caloric value of a duodenal load is not by itself the sole determinant of the resultant satiety. Increasing the glucose load of an intraduodenal infusion has been found to reduce its satiating effect under certain conditions (present experiment) or may even enhance feeding (Rezek et al., 1975). The nonmonotonic relation between glucose load and satiety observed in sham-operated, free-feeding rabbits is probably a function of several factors, including the

activation of a visceral satiety mechanism, secretion of gut hormones, and possibly visceral malaise at the highest glucose concentration.

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