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Excessive gastric retention by vagotomized rats and rabbits given a solid diet

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Rats and rabbits were subjected to bilateral subdiaphragmatic vagotomy or laparotomy (sham vagotomy) and maintained on a diet of solid food. Measurement of stomach size was done following fasting for 0, 4, 8, or 12 h in rats or 0, 12, or 24 h in rabbits. Comparison of data from vagotomized and laparotomized animals that underwent an electrophysiological verification procedure indicated that the stomachs of vagotomized animals declined only slightly in size across the full range of fasting intervals, whereas the stomachs of fasted laparotomized animals decreased to a minimum size within 0-4 h in rats and 12-24 h in rabbits. This effect of vagal destruction on gastric function provides a partial explanation for changes in the feeding pattern observed subsequent to vagotomy. In addition, measurement of stomach size provides a reliable means of verifying the completeness of vagal damage produced by a vagotomy procedure.

In recent years, peripheral physiological mechanisms in feeding regulation have been heavily investigated (Novin, 1976). Subdiaphragmatic vagotomy has proved to be a particularly valuable technique for elucidating peripheral neural and hormonal contributions to the control of food intake. Vagotomy has been shown to alter meal patterns of rats maintained on a liquid diet (Snowdon & Epstein, 1970) and rabbits with solid diet (Sanderson & VanderWeele, 1975), abolish anorexic effects of duodenal and hepatic-portal infusions of glucose (Novin, Sanderson, & VanderWeele, 1974), and reduce the increased feeding produced by hepatic-portal infusion of the glucose antimetabolite, 2-deoxy-D-glucose (Novin, VanderWeele, & Rezek, 1973). In general, these studies have focused on the theorized role of afferent vagal fibers in transmitting information concerning visceral homeostasis to the central nervous system and deficits in feeding behavior resulting from subdiaphragmatic transection of the vagus nerves.

However, to fully understand the contribution of the vagus to the regulation of feeding, it is necessary to recognize that vagotomy also interrupts efferent fibers. Vagotomy drastically impairs the motor activity of the gastrointestinal system (Alvarez, 1948), and, in fact, the inability of electrical stimulation to elicit gastric contractions subsequent to vagal transection is the basis of an electrophysiological verification technique (Hollanders, 1971). In addition, such denervation alters intestinal absorption of macronutrients (Tucker, Barnett, & Goodrich, 1963), produces extensive loss of intestinal villi (Ballinger, Iida, & Aponte, 1963), and alters pancreatic secretion (Pincus, Thomas, & Lachman, 1948). The impairment of efferent gastric function by vagotomy might be expected to have direct consequences on feeding.

Further, Snowdon and Epstein (1970) reported that vagotomy resulted in very rapid gastric emptying in rats that were maintained on a liquid diet (suggestive of the clinically described "dumping syndrome"). Stomachs of vagotomized animals maintained on a solid diet, however, are excessively distended due, at least in part, to decreased gastric emptying (Meek & Herrin, 1934; Ellis & Pryse-Davies, 1967; Kilby & Griffith, 1971).

The present study investigated the effect of bilateral subdiaphragmatic truncal vagotomy on gastric retention in rats and rabbits maintained on a solid diet and then fasted for different intervals. These two species were selected because they are frequently used in research concerning the regulation of feeding, and yet the effect of vagotomy on gastric function has not been systematically evaluated. In the present study, stomach size was measured in animals that had fully recovered from the surgical trauma resulting from vagotomy or the control surgery. In contrast to previously cited studies, where

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the extent of vagal damage was typically not assessed, vagal destruction was carefully evaluated in all rats and rabbits using an electrophysiological method. The results of this investigation provide a basis for understanding some of the effects of vagotomy on the feeding pattern of animals fed a solid diet and demonstrates the validity of using fasted stomach size to verify vagal destruction.

METHOD

The subjects that met the electrophysiological verification criterion were 66 New Zealand albino female rabbits and 89 male and female rats of the Long-Evans and Sprague-Dawley strains. Thoughout the experiment, these animals were maintained on ad-lib tap water and Purina chow, and housed in individual cages. The subjects were kept in rooms with a 12:12-h light-dark cycle.

Prior to surgery, the rabbits and rats were anesthetized with sodium pentobarbital (30 mg/kg IV and 50 mg/kg IP, respectively). The procedure used to vagotomize the rabbits involved removal of all connective tissue from the vertex of the stomach and along the proximal esophagus for a distance of 30-40 mm. Residual nerve fibers were then dissected from the esophageal musculature. Rabbits and rats that constituted the control group received laparotomies that involved manipulation of the esophagus prior to suturing the abdominal wound.

The vagotomy procedure used in rats differed slightly from that described for rabbits. The esophagus was stripped of connective tissue for 15-20 mm from its point of junction with the stomach; the left gastric artery was ligated and then cut. The distribution of the abdominal vagi has been described in the rat by Legros and Griffith (1969) and consists of an anterior and posterior trunk that parallel the esophagus. The esophageal branch of the left gastric artery accompanies the anterior trunk of the vagus and facilitates its identification. Also, the posterior vagal trunk and its continuation, the posterior gastric division, accompanies the left gastric artery. Completely dissecting the nerves from this vessel has proved to be very difficult to accomplish, and therefore the ligation and sectioning of both nerve and artery have been used to insure the destruction of the vagal branches. Ligation of the left gastric artery of rats has been reported to cause antral ulceration of the stomach (Berg, 1947). However, it was also reported that within weeks of the ligation, healing occurred and was attributed to the development of collateral circulation. No signs of gastric ulceration were noted upon superficial examination of the stomachs removed from animals 1-4 months after surgery in the present study.

This vagotomy procedure probably destroyed both anterior and posterior vagal trunks, as well as their component divisions, which do not accompany the left gastric artery. Most of the rats and rabbits were surgically implanted with a silastic cannula into either the duodenum or the hepatic-portal vein, and nutrients were infused in some of the animals to minimize weight loss. Palatable foods were also provided, as necessary, to facilitate recovery from surgical trauma.

Following convalescence for 1-4 months, measurements of stomach size were made. The rats (0, 4, 8, and 12 h) and rabbits (0, 12, and 24 h) were fasted for various intervals and then anesthetized with sodium pentobarbital. Vagal function was assessed in both vagotomized and laparotomized subjects by electrically stimulating the cervical vagi while monitoring gastric contractions with a balloon inserted into the stomach and attached to a pressure transducer (Statham Laboratories). Stimulation parameters were 15- to 20-Hz, 1- to 25-V, biphasic dc pulses of .2-msec duration in 5- to 10-sec stimulus trains produced by a Grass Model S4GR stimulator. The pressure transducer was connected to a Grass Model 5D polygraph to provide a permanent record. During a series of verifications, control animals were interspersed with vagotomized animals. Following the electrophysiological verification procedure, subjects were sacrificed with an overdose of sodium pentobarbital. The stomach was tied off at the esophagus and the duodenum, removed, and its weight and volume measured. These values were divided by body weight to control for the wide variation in body size.

RESULTS

Bilateral subdiaphragmatic truncal vagotomy produced excessive gastric distension in rats and rabbits (Figures 1 and 2). Analysis of variance yielded an overall significant difference in stomach weight divided by body weight for vagotomized and laparotomized rabbits across the different fasting intervals [$F(1,60) = 40.6$, $p < .01$]. Due to significant heterogeneity of variance, it was necessary to analyze the stomach ratio data with the Kruskal-Wallis test. Comparison of these stomach-weight ratios in vagotomized and laparotomized rats revealed significant differences following food deprivation for 0 h ($p < .05$), 4 h ($p < .01$), 8 h ($p < .01$),

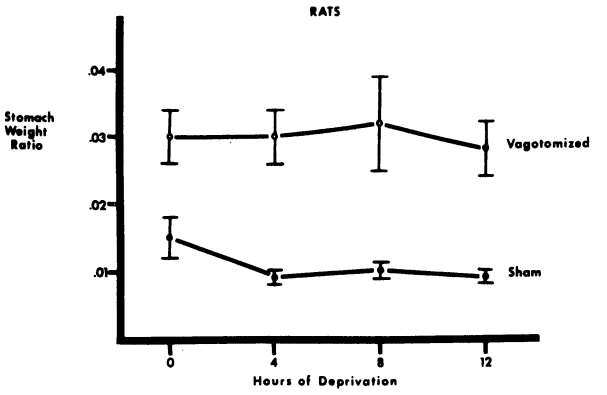

Figure 1. Change in stomach weight after different fasting intervals in vagotomized and sham (laparotomized) rats. Values shown are stomach weight divided by body weight (mean ± MSe).

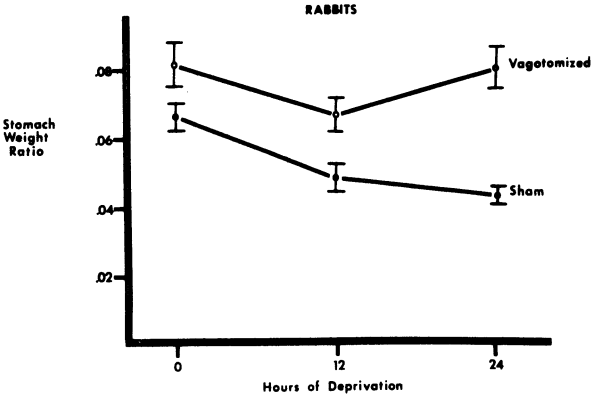

Figure 2. Change in stomach weight after different fasting intervals in vagotomized and sham (laparotomized) rabbits. Values shown are stomach weight divided by body weight (mean ± MSe).

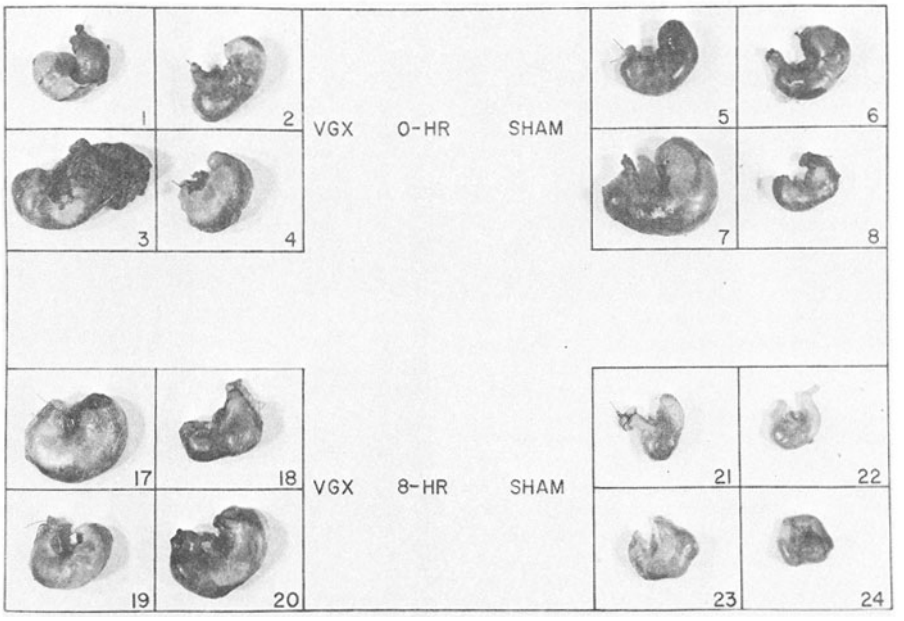

Figure 3. Stomachs removed from 0-h and 8-h fasted rats following complete recovery from either vagotomy or laparotomy. Photograph includes all stomachs from animals rapidly sacrificed without anesthesia to permit an hepatic glycogen assay for another study.

and 12 h ($p < .01$). Figure 3 shows the stomachs removed from vagotomized (unverified) and laparotomized rats following a 0- or 8-h fast. Data concerning stomach volume showed the same trends as those seen for stomach weight and, thus, were not statistically analyzed.

Using data collected in this investigation, confidence intervals have been computed to permit verification of vagal destruction on the basis of stomach weight. This analysis resulted in the following decision rules for rats and rabbits that have undergone the vagotomy procedure: (1) A 24-h fasted rabbit can be classified as vagotomized, with 95% confidence, if its stomach ratio exceeds .065, and (2) a 12-h fasted rat can be identified as having sustained vagal destruction, with 95% confidence, if its stomach ratio exceeds .020. Again, stomach ratio is simply weight of the stomach (grams) divided by weight of the animal (grams). Applying these decision rules to the present data resulted in accepting as vagotomized 10 of the 11 rabbits fasted for 24 h and 9 of 11 rats fasted for 12 h that had met the electrophysiological criterion for verification. Stomach ratios for five vagotomized rats (similarly fasted) that failed to meet the electrophysiological criterion ranged from .005 to .011. Similarly, the stomach ratio of one 24-h fasted vagotomized rabbit in which gastric contractions could be elicited by cervical vagus stimulation was .048. The stomach ratios of 12-h fasted, laparotomized rats, all of which exhibited evoked gastric contractions, ranged from .005 to .016, and those for 24-h fasted, laparotomized rabbits ranged from .026 to .056. The absence of any difference in the stomach ratios of 12-h fasted laparotomized and naive rats [$t(23) = .87$, n.s.] also provides evidence that the laparotomy procedure used in this study does not impair vagal function. Thus, it is not necessary for such control animals to be routinely verified.

DISCUSSION

The present investigation was undertaken to assess gastric retention subsequent to bilateral subdiaphragmatic truncal vagotomy in rats and rabbits that were maintained on a solid diet. In contrast to the rapid gastric emptying that follows ingestion of liquid food by vagotomized animals (Meek & Herrin, 1934; Snowdon & Epstein, 1970), vagotomized rats and rabbits that consume solid food exhibit excessive retention of gastric contents. As a consequence of this chronic distended condition, chyme would be expected to empty into the duodenum at a fairly constant rate, unaffected by the pattern of feeding. Excessive retention of stomach contents could account for the irregular meal pattern and the prolonged but small meals observed in vagotomized animals consuming solid food (Rezek, VanderWeele, & Novin, 1975; Sanderson & VanderWeele, 1975), as well as the inability of such animals to greatly increase food intake subsequent to a 24-h fast (VanderWeele, Skoog, & Novin, 1976). The reduced body weight and the low concentration of hepatic glycogen characteristic of vagotomized animals (Martin, Novin, & VanderWeele, Note 1) may also be attributable to the limited flow of nutrients through the stomach. It should be noted that the increased gastric retention cannot readily explain the relative insensitivity of vagotomized animals to intraportal infusion of both glucose and 2-deoxy-D-glucose

substances that, respectively, decrease or increase feeding in sham-operated subjects (Novin et al., 1973, 1974). That is, it is not clear how delayed stomach emptying could account for both the failure of blocking glucose utilization to increase feeding and infusions of glucose (which would increase glucose utilization) to suppress feeding. These effects have been attributed to the interruption of afferent vagal fibers linking a peripheral gluco-sensitive mechanism to a central integrative center modulating feeding.

The grossly distended stomach that characterizes vagotomized rats and rabbits provides a convenient indicator of the completeness of vagal destruction. Measurement of stomach size to verify vagotomy is particularly valuable in those experiments that require rapid sacrifice of an animal without anesthesia in order to assay the concentration of blood chemicals, hepatic glycogen, or other labile substances. Confidence intervals (95%) have been constructed to permit a conservative judgment of whether an animal that has undergone surgical transection of the vagi should be classified as vagotomized or intact. Rabbits (24-h fasted) and rats (12-h fasted) that have a stomach-to-body weight ratio greater than .065 and .020, respectively, can be assumed to have sustained extensive vagal destruction. Animals that have received laparotomy can be assumed to have undamaged vagi, since the electrophysiological verification procedure failed to detect any evidence of vagal impairment. Although electrophysiological verification is considered the most reliable of the several techniques we have used to detect residual vagal function following vagotomy, the results of this study indicate that fasted stomach weight can also be used.

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