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Decreased Weight Gain and Food Intake in Vagotomized Rats[1] (39917)

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The effects of subdiaphragmatic vagotomy on feeding behavior have been recognized for some time. In rabbits (1, 2) it leads to an initial profound anorexia lasting for days, followed by a gradual return to the baseline state. In rats fed a liquid diet (3) it produces marked alteration in feeding patterns. These studies do not, however, report weights. In rats, a considerable body of evidence has shown that vagotomy in all cases leads to a loss of weight, or, in the case of growing animals followed for a long period of time, a slower rate of gain than in controls. Powley and Opsalh (4) showed that in obese ventromedial hypothalamic (VMH) rats vagotomy causes a precipitous fall in weight to the level of nonlesioned vagotomized animals. This effect was so dramatic as to overshadow the clear fall in weight of the nonlesioned vagotomized animals. In a second experiment Opsahl and Powley (5) studied the effect of vagotomy on Zucker rats and found a very much smaller effect, which they interpreted as not significant. More recent studies by them (6) have shown that in lateral hypothalamic (LH) lesioned rats the effect of vagotomy is additive to that of lesioning, and again showed that the vagotomized nonlesioned controls lost weight relative to normal animals. In all of these studies, however, the well-recognized (7) gastric distension and delay in gastric emptying that accompany vagotomy served to confound the results.

In view of these earlier findings, we sought further to define the most basic effects of subdiaphragmatic vagotomy on food intake and weight gain. We first wished to confirm the earlier observations of diminished weight gain following vagotomy. In addition we wished to eliminate the confounding effect of gastric distension and retention by employing surgical drainage procedures (pyloroplasties). Because of recent interest in hepatic glucostatic mechanisms (8), we sought also to investigate selective parasympathetic denervation of the liver in order to determine if this branch was exclusively responsible for the effects of subdiaphragmatic vagotomy. Finally, because increased metabolism has been reported in the LH rat (9), we wished to pair-feed a group of normal and vagotomized animals in order to determine if decreased food intake alone could account for the effects of vagotomy.

Methods. In the first set of experiments, 27 female CD rats (Charles River Laboratories) weighing 115 ± 1 g (mean ± standard error) were randomized into normal, sham operation, and vagotomy groups. All animals undergoing surgery were fasted for 12 hr and anesthetized with intraperitoneal pentobarbital (50 mg/kg). A longitudinal midline incision was made, a stay suture was placed in the gastric serosa, and the stomach was delivered. Using a Zeiss operating microscope, the falciform and gastrohepatic ligaments were divided and the lesser omentum was visualized. In vagotomized animals, the hepatic branch and its accompanying vasculature were ligated and divided. The anterior and posterior trunks were then identified and doubly ligated; the segment of nerve between the ligatures was excised. The esophagus was examined under high power to assure that all nerve branches had been severed. The abdomen was closed with resorbable sutures and the skin was apposed with steel clips. Sham operations were identical, except that, after

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visualization, the vagi were subjected only to gentle traction applied to their fascial investiture.

In a second set of experiments, all operated animals underwent a pyloroplasty to facilitate gastric drainage. The pyloric channel was identified and two stay sutures were placed transversely 3 mm apart. A longitudinal incision was made between the stays and then closed transversely with interrupted 6-0 silk ties, thereby disabling the sphincter. In these experiments, 13 females, weighing 107 ± 1 g, and 9 males, weighing 267 ± 2 g, were randomized into normal, pyloroplasty alone, and vagotomy with pyloroplasty groups.

In a third set of experiments, 30 females, weighing 111 ± 1 g, were arranged into normal, sham operation, and selective hepatic branch vagotomy groups. Rats in this last group underwent ligation and division only of the hepatic branch of the anterior vagus nerve. In a fourth experiment, 8 normal males were matched with 8 vagotomy and pyloroplasty males in a pair-feeding experiment initiated 1 week prior to surgery. Initial weight of normals was 303 ± 10 g, and of rats with vagotomy and pyloroplasty was 293 ± 6 g.

The rats were housed in individual cages and weighed twice weekly. For 24 hr postoperatively, all animals were fed Carnation Instant Breakfast. Thereafter, animals in the first experiment were fed Purina rodent chow pellets. Animals in the other experiments were fed ground chow from containers designed to minimize spillage. Food consumption was measured twice weekly, except in the pair-feeding experiment, where the intake of the males with vagotomy and pyloroplasty was measured daily and that quantity of chow then fed to the matched normal rat. Contrast X-ray studies were carried out on all but pair-fed animals to evaluate qualitatively both gastric size and gastrointestinal motility. Following a 12-hr fast, animals were given access to a mixture of 60% barium sulfate and 40% rodent chow for 15–30 min. X rays were taken immediately and 5 and 12 hr after feeding. Growth curves were fitted by the method of cubic splines (10) and differentiated to yield growth velocity curves. Cumulative food consumption was integrated and fitted by the same method. All comparisons were evaluated using *t* tests.

Results. No significant differences with regard to weight gain or food intake were found between normal and sham or normal and pyloroplasty alone in any experiment. In the first experiment, the weight gain and growth velocity of the vagotomized animals were significantly reduced (Fig. 1). During the first 10 days after operation, vagotomized animals grew less rapidly than did either control. Thereafter, the growth of vagotomized rats briefly paralleled that of control groups. Later, however, the growth velocity of vagotomized rats again slowed slightly but persistently, with consequent gradual divergence from the growth curves of control rats. Final weights were 325 ± 9 g for normals and 317 ± 12 g for sham-operated rats, compared with 271 ± 9 g for vagotomized rats ($P < 0.01$ in both cases). Overall weight gains for Days 0 to 110 were 216 ± 9 g for normals and 199 ± 13 g for shams, compared with 152 ± 13 g for vagotomized rats ($P < 0.001$ and $P < 0.05$, respectively). In addition, comparing either control group with the vagotomized

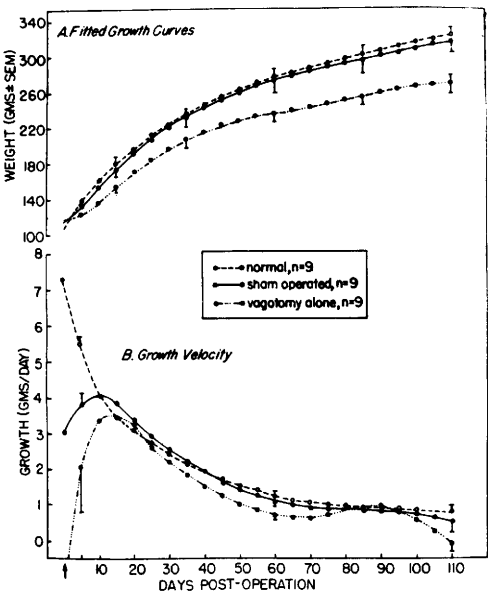

FIG. 1. (A) Growth curves fitted by the method of cubic splines for the first 110 days after surgery. (B) Growth velocities computed by differentiation of the growth curves.

animals, the difference in weight gain from Day 40 to Day 110 is also significant ($P < 0.05$ in both cases). There were no differences in weight gain between Days 10 and 40. These relationships are evident in the growth velocity curve (Fig. 1B). The contrast X-ray studies of this first experimental group revealed that about half of the truncally vagotomized rats had some degree of either gastric distension or delay in gastric emptying.

Addition of pyloroplasty in the second experiment eliminated all radiologic evidence of distension or delayed emptying, but did not cause diarrhea. Growth curves for females (Fig. 2) are essentially the same as in the first experiment. Overall weight gains for Days 0 to 70 were 178 ± 13 g for animals with pyloroplasty alone and 121 ± 14 g for animals with vagotomy with pyloroplasty ($P < 0.02$). Males with vagotomy and pyloroplasty, operated on at a higher initial weight, showed immediate and persistent alteration of the growth curve (Fig. 2). Weight gains for Days 0 to 80 were 301 ± 9 g for rats with pyloroplasty alone and 198 ± 24 g for rats with vagotomy with pyloroplasty ($P < 0.02$).

Food consumption was reduced in vagotomized animals throughout the period of observation. Between Days 5 and 65, females with vagotomy and pyloroplasty ate 950 ± 64 g, as contrasted with 1176 ± 56 g for normals ($P < 0.05$) and 1210 ± 53 g for rats with pyloroplasty alone ($P < 0.02$). Males with vagotomy and pyloroplasty consumed 1645 ± 62 g, while normals ate 2049 ± 115 g ($P < 0.05$) and rats with pyloroplasty alone ate 1931 ± 25 g ($P < 0.02$). The ratio of weight gain to food consumed did not differ significantly among normal, pyloroplasty alone, or vagotomy and pyloroplasty groups.

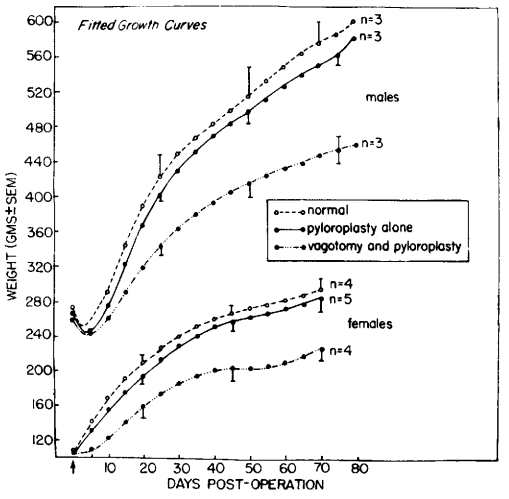

FIG. 2. Fitted growth curves for both male and female rats in the second experiment (see text).

The results of the third experiment show that, over Days 0 to 90, there were no differences among the weight gains of normals (183 ± 11 g), sham-operated rats (172 ± 7 g), or rats with hepatic branch vagotomy (184 ± 9 g). With regard to pair feeding, over the first 80 postoperative days, the weight gain of rats with vagotomy and pyloroplasty (193 ± 12 g) does not differ significantly from the weight gain of pair-fed normals (182 ± 14 g). These gains are not significantly different from the Day 0 to 80 weight gain of the three vagotomy and pyloroplasty males described earlier (198 ± 24 g).

Discussion. These data suggest that the subdiaphragmatic vagus plays a role in the regulation of food intake and weight gain; the abolition of "catchup" growth is particularly notable. The data do not permit conclusions as to the mechanisms responsible for the effect of vagotomy on food intake and weight gain. Malabsorption is unlikely to be the explanation, given the absence of diarrhea and the results of metabolic studies in other species (11). The X-ray findings with pyloroplasty argue against gross disturbances of gastrointestinal motility, but a subtle derangement cannot be excluded. It is possible that vagotomy deprives central regulatory mechanisms of afferent data pertinent to eating behavior (12). Alternatively, sectioning of the vagus may alter metabolic processes under efferent vagal control. Hepatic metabolic pathways are known to be influenced by sympathetic, parasympathetic, and hypothalamic stimulation. Vagotomy could, for example, result in a net increase of sympathetic tone, thus favoring glycogenolysis and inappropriate satiety. Our results with hepatic branch vagotomy argue against this, however.

Given the present observations of vagal

influence on food intake regulation, the reversibility of VMH obesity by vagotomy, and the behavioral similarities reported between the VMH lesioned animal and obese humans (13), it would appear that the role of the autonomic nervous system in human obesity merits additional attention.

Summary. Subdiaphragmatic truncal vagotomy, alone and with pyloroplasty, was performed in intact rats. In all instances, vagotomized animals ate less and gained less weight than controls during a prolonged period of postoperative observaton.

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