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The Role of Hyperinsulinema and the Vagus Nerve in Hypothalamic Hyperphagia Reexamined

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Summary. Three series of experiments investigated the role of hyperinsulinemia and the vagus nerve in the hyperphagia and obesity syndrome produced in female rats by knife cuts in the ventromedial hypothalamus (VMH). The findings of the first series revealed that VMH cuts do not produce hyperinsulinemia when the rats are prevented from overeating, but insulin levels are elevated in rats allowed to overeat. The second series of experiments demonstrated that VMH-cut rats overconsume sweet sugar solutions during daily short-term tests, and that pharmacological blockade of vagal efferent activity with atropine methyl nitrate fails to inhibit this overconsumption. The third study revealed that subdiaphragmatic vagotomy completely blocks VMH hyperphagia and obesity on a chow diet, but does not prevent overeating and rapid weight gain in rats fed an assortment of highly palatable foods. These findings indicate that vagally mediated insulin release is not an essential component to the VMH knife cut syndrome.

Key words: Hyperphagia, obesity, ventromedial hypothalamus, knife cuts, vagotomy, hyperinsulinemia, atropine methyl nitrate, diet palatability, female rats.

Damage to the ventromedial hypothalamic area (VMH) produces overeating (hyperphagia) and obesity in rats and other animals [6]. Considerable evidence suggests that vagally mediated hyperinsulinemia plays a critical role in the development of VMH hyperphagia and obesity. It has been reported, for example, that electrolytic lesions of the VMH produce an immediate increase in plasma insulin levels, that plasma insulin remains elevated even when the animal is prevented from overeating, and that the postoperative increase in plasma insulin is correlated with subsequent weight gain [2, 15, 17]. Since repeated insulin injections increase food intake and body weight in normal rats, it has been argued that the hyperinsulinemia of VMH lesioned animals is responsible for their hyperphagia and obesity [6, 23]. Consistent with this view are the findings that VMH lesions produce little or no overeating and weight gain in insulin-deficient rats [37].

The importance of the vagus nerve to the hyperinsulinemia and hyperphagia of VMH lesioned rats is indicated by reports that subdiaphragmatic vagotomy abolishes the lesion-induced increases in insulin levels, and reverses the overeating and obesity produced by the VMH damage [2, 24]. Furthermore, rats with an intact vagus nerve, but transplanted pancreas, fail to become obese following VMH lesions, although there is a small but significant increase in their food intake [19]. Finally, VMH-lesioned rats have been found to display a potentiated prandial or cephalic insulin response to food, and this effect is mediated by the vagus nerve [22]. Powley [23] and others [21] have postulated that the exaggerated cephalic insulin response is the primary cause of the hyperphagia and diet finickiness displayed by VMH lesioned animals.

In contrast to the above findings, the results of other studies question the importance of vagally-mediated hyperinsulinemia in the VMH hyperphagia syndrome. For example, VMH lesions have been reported to increase food intake and body weight in previously vagotomized rats [20], as well as in rats with controlled insulin levels [11, 35]. Furthermore, procaine injections into the VMH, which increase food intake, fail to increase plasma insulin levels, and in fact, inhibit the cephalic release of insulin to food

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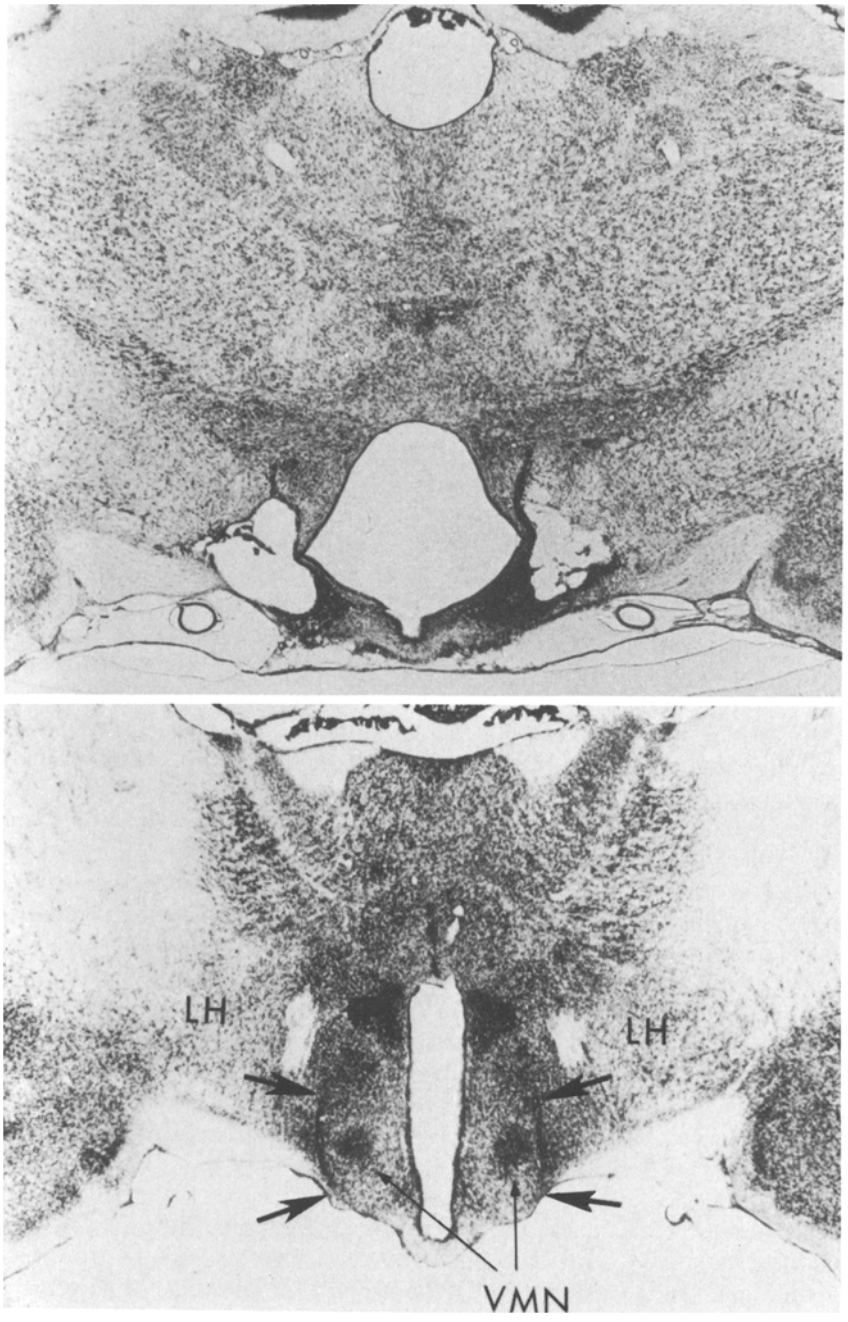

Fig. 1. Photomicrographs of electrolytic lesions (Top) and parasagittal knife cuts (Bottom) in the ventromedial hypothalamus of the rat. The VMH lesions, which represent typical medium size lesions used to produce hyperphagia and obesity, completely destroyed the ventromedial nucleus and immediately surrounding tissue. The VMH knife cuts spared the ventromedial nucleus, and despite their small size produced considerable hyperphagia and obesity. (Body weight increased by 186 g or 75% in 20 days)

stimuli [3, 4]. Recent work in my laboratory also indicates that a reexamination of the role of hyperinsulinemia and the vagus nerve in the hyperphagia syndrome is in order. In our studies hyperphagia and obesity were produced by placing bilateral parasagittal knife cuts through the lateral aspect of the anterior and ventromedial hypothalamus (hereafter referred to as VMH cuts). These knife cuts result in a hyperphagia-obesity syndrome similar to that produced by VMH electrolytic lesions, but produce less neural damage (Fig. 1), less disruption in non-feeding behavior, and less endocrine and metabolic disorders than to VMH electrolytic lesions [5, 27, 33].

Hyperphagia and Hyperinsulinemia

The VMH animal has been described as being hyperphagic because it is hyperinsulinemic, rather than being hyperinsulinemic because it is hyperphagic

Table 1. Mean (±) basal insulin levels in VMH cut and control rats

Experiment	Feeding condition	Days post-op	Hours fasted	Insulin (μU/ml) N	VMH Cut	N	Control
A. Vasselli, Sclafani, & Pi-Sunyer, 1977	Quinine diet ad lib	2	12–14	7	11.3±2.20	7	14.0± 6.63
	Quinine diet ad lib	36	12–14	7	12.9± 2.94	7	15.1± 4.22
	Sweet Milk ad lib[a]	48	12–14	7	65.4±22.76	7	33.4±19.38
B. Bray, Sclafani, & Novin, 1979	Chow, restricted (18 g/day)	14	0	9	61.5±15.75	8	71.0±11.75
C. Sclafani, Faust, & Schneider, 1979	Chow, restricted (22 g/day)	2	2–6	12	53.9± 7.3	7	46.8± 6.17
	Chow ad lib[a]	10	2–6	12	177.4±24.67	7	46.2± 7.80
D. Powley, Cox, & Sclafani, 1980	Sweet milk, yoked-fed to control rat	43	2–7	6	116.0±19.31	5	90.0 6.04

[a] VMH cut rats hyperphagic under this condition

[23]. This description is based on reports that VMH rats have elevated plasma insulin levels even when they are pair-fed with control subjects [15, 17]. In most of these studies electrolytic lesions centered on or near the ventromedial nucleus (VMN) were used. Bernardis and Frohman [1], in fact, observed that only lesions which destroyed the VMN produced primary hyperinsulinemia, i. e., increased insulin levels in the absence of increased food intake. An exception is the finding of Tannenbaum, Paxinos, and Bindra [32] that parasagittal VMH knife cuts, which produced minimal damage to the VMN, elevated plasma insulin levels in four pair-fed male rats. However, in several experiments my associates and I have failed to obtain primary hyperinsulinemia in rats with VMH knife cuts. Conducted in collaboration with four different laboratories, these experiments investigated various aspects of the VMH knife cut syndrome, but only the insulin data are discussed here (see Table 1).

Female rats were used in our experiments and various procedures were employed to prevent the knife cut subjects from overeating, although the hyperphagia-inducing effect of the VMH cuts was confirmed in all cases. Vasselli, Sclafani and Pi-Sunyer ([34], in preparation), for example, took advantage of the fact that VMH rats do not overeat unpalatable diets and fed VMH knife cut and sham-operated control rats a quinine-adulterated diet (see [31]). As expected, the VMH cut rats maintained their food intake and body weight at control levels, and blood samples taken at two and 36 days post surgery revealed that their basal insulin levels also did not differ from control values (Table 1). When subsequently given a palatable sweet milk diet ad libitum, the VMH cut rats were hyperphagic and their insulin levels were now significantly higher than those of the control rats (Table 1).

Bray, Sclafani, and Novin ([5], in preparation) allowed knife cut rats to overeat a regular chow diet for five days after surgery, but then fasted the rats to their pre-operative body weight. (The five-day weight gain of the VMH cut rats was 54.6 g compared to the 4.8 g gain of the controls.) The VMH cut and control rats were then fed restricted amounts of food (18 g/day) so that their body weights remained the same. The daily food ration was equivalent to the mean intake of the controls and one-third was given in the morning and two-thirds in the evening. At sacrifice two weeks after surgery the blood insulin levels of the VMH cut rats were found to be slightly below those of the control rats (Table 1).

In another experiment (Sclafani, Faust, and Schneider, 1979, unpublished findings), VMH cut and control rats were food restricted (22 g/day) for the first two days after surgery and were then given ad libitum access to chow. Figure 2 illustrates that the food intake and body weight of the VMH cut and control groups were similar on Day 2 as were their blood insulin levels (see also Table 1). The VMH cut rats more than doubled their food intake beginning with day 3 and by day 10 after surgery they had gained 68.2 g in weight compared to the controls which gained 3.5 g. Along with their elevated food intake and body weight on day 10, the blood insulin level of the VMH cut rats was almost four times greater than that of the control rats (Figure 2, Table 1). Further analysis revealed that the VMH cut rats' insulin levels on Day 2 did not correlate with their 10-day postoperative weight gain ($r = -0.007$), whereas their insulin levels on Day 10 did correlate ($r = 0.754$, $p < 0.01$) with their weight gain.

In our most recent experiment (Powley, Cox, and Sclafani, 1980, unpublished findings), VMH cut rats were again allowed to overeat for the first five post-operative days and then fasted to their pre-operative

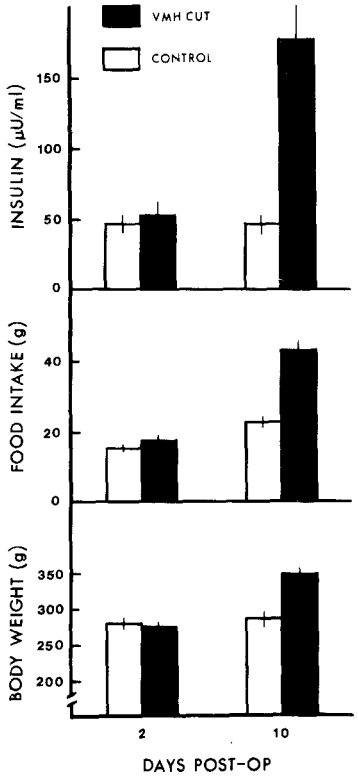

Fig. 2. Mean (±SE) plasma insulin, food intake, and body weight on days 2 and 10 after VMH cut (n=12) or sham (n=7) surgery in female rats. On the first two post-operative days all rats were given 22 g of chow a day, but because of spillage, maximum intake was less than 22 g. Food was available ad libitum after day 2

weight. (The five-day weight gain of the VMH cut rats was 51.8 g and that of the control rats was −1.6 g.) The VMH cut and control rats were then yoked-fed a sweetened milk diet such that when one control animal with ad libitum access to food ate a meal, the remaining VMH and control rats were given a meal of the same size. After four weeks of yoked-feeding the animals were sacrificed and blood insulin measured. As indicated in Table 1, the insulin levels of the VMH cut rats were slightly above that of the controls, but the difference was not statistically significant.

Thus, in four separate experiments we have failed to obtain significantly elevated basal insulin levels in VMH cut rats prevented from overeating, although hyperinsulinemia was obtained in rats allowed to overeat. These results conflict with the findings reported by Tannenbaum et al. [32]. The reason for the discrepancy is not certain but the studies differed in sex and strain of rats, sample size, and restricted feeding procedure. Nevertheless, it can be concluded that hyperphagia-inducing knife cuts, unlike VMH electrolytic lesions, do not *reliably* increase basal insulin levels in food restricted animals. This is not surprising since the knife cuts produce little or no damage to the ventromedial nucleus which appears to be the critical area for the primary hyperinsulinemia effect [1], but not for the hyperphagia syndrome (see [13, 29]). That hyperphagia and hyperinsulinemia are dissociable is further indicated by the findings that VMN lesions in weanling rats, and VMN-arcuate lesions in adult monkeys increase basal insulin levels but not food intake [1, 14].

While VMH knife cuts do not reliably elevate basal insulin levels, they may potentiate the prandial or cephalic insulin response, which, as previously mentioned, has been suggested to be the primary cause of hyperphagia [21, 23]. This possibility is given little support, however, by the results obtained by Vasselli, Sclafani, and Pi-Sunyer ([34], in preparation). The quinine diet fed rats mentioned above were given oral or gastric loads of a palatable food (sweet milk) and blood samples were taken before the load and 15 and 45 min after it. The food stimulated plasma insulin levels of the VMH cut and control rats were nearly identical. Although not strictly a measure of the cephalic insulin response, this finding indicates that the insulin responsiveness of food restricted VMH cut rats does not differ from that of normal rats. As discussed next, other experiments also question the importance of cephalic insulin secretion to the VMH hyperphagia.

Hyperphagia and Anticholinergic Drugs

If vagally-mediated hyperinsulinemia is a primary cause of hypothalamic hyperphagia, then pharmacological blockade of this neuroendocrine response should prevent the overeating and obesity of VMH rats. In independent tests of this prediction, Carpenter et al. [7] and Sclafani et al. ([28], in preparation) treated VMH hyperphagic rats with peripherally acting anticholinergic drugs based on the findings that such drugs prevent the insulin response to oral stimulation with food and to electrical stimulation of the vagus nerve [12, 16]. Carpenter et al. chronically administered high doses of scopolamine methyl nitrate to VMH lesioned and control rats and observed that the treatment reduced but did not reverse static phase obesity, and did not prevent VMH electrolytic lesions from increasing food intake and body weight. The authors concluded that VMH obesity "is independent of vagally mediated insulin secretion and other excess vagal efferent activity." It should be noted, however, that scopolamine treatment did attenuate the hyperphagia of the VMH lesioned animals. Carpenter et al. attributed this

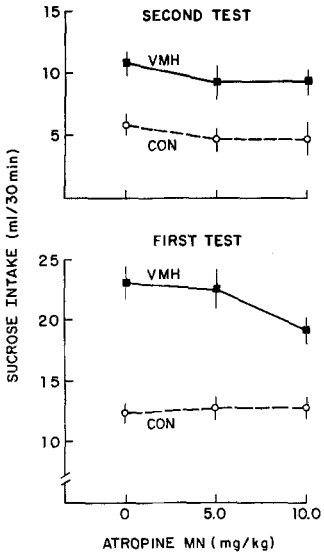

Fig. 3. Mean (±SE) intake of VMH Cut (n=10) and control (n=8) rats during two daily 30-min tests with a 20% sucrose solution. The second test started 90 min after the end of the first test. Saline or atropine methyl nitrate was injected 30 min prior to the first test period. The 0 mg/kg dose refers to the isotonic saline injection (1 ml/kg)

effect to the dry mouth and reduced gastrointestinal motility induced by the drug, but their findings do not rule out a blocked cephalic insulin response as the cause of the suppressed food intake.

Using a different approach, experiments in my laboratory have investigated the effects of acute treatment with atropine methyl nitrate on the intake of sugar solutions in VMH cut and control rats ([28], in preparation). This approach takes advantage of the fact that sugar solutions are particularly potent stimuli for the cephalic insulin response; that VMH cut rats consistently overconsume concentrated sugar solutions during brief daily tests; and that fluid intake is less affected than solid food intake by the effects of atropine on salivary secretion and gastrointestinal motility. Our basic procedure was to deprive rats of food, but not water, for one hour and then give them 30 min access to a sugar solution, usually a 20% sucrose solution. On test days the rats were injected intraperitoneally with saline or atropine methyl nitrate 30 min prior to the presentation of the sugar solution. The results obtained from five different experiments were quite consistent: atropine injections in doses of 1 to 10 mg/kg did not prevent VMH cut rats from overdrinking the sugar solutions relative to controls.

One of our experiments tested the hypothesis that the exaggerated cephalic insulin response of VMH rats results in metabolic changes that promote overconsumption in subsequent meals [23]. The rats in this experiment were given two daily 30 min tests with a 20% sucrose solution separated by 90 min. Food was removed 1 hr prior to the first test and was not returned until the end of the second test, but water was always available. As illustrated in Figure 3, the VMH cut rats consumed more of the sucrose solution than did the controls during both the first and second test and continued to do so following injections of 5 and 10 mg/kg of atropine. The failure of atropine to reduce appreciably the sugar solution intake of VMH cut and control animals cannot be attributed to a thirst-inducing effect of the drug. An additional experiment revealed than when only water was available to drink during the 30-min test period, the rats consumed little or no fluid and their intake did not increase following injections of atropine.

The findings of our experiments along with those of Carpenter et al. [7] seriously challenge the view that vagally-mediated insulin secretion is critical for the expression of the VMH hyperphagia and obesity. The results do not exclude the possibility that non-vagal or non-cholinergic visceral responses are essential to the hyperphagia syndrome, but certainly scopolamine or atropine-sensitive responses do not appear to be involved.

Hyperphagia and Vagotomy

Following the initial report of Powley and Opsahl [24] that subdiaphragmatic vagotomy completely abolishes VMH obesity, a number of studies have obtained mixed results. Most experiments report that vagotomy either before or after VMH lesions or knife cuts prevents overeating and obesity [10, 18, 24, 26], but other studies have reported that vagotomy had only a partial or no effect on the hyperphagia syndrome [9, 20, 36]. Furthermore, in those cases in which vagotomy blocked VMH hyperphagia, some investigators have argued that this is a result of the eating difficulties (dysphagia) produced by the surgery [8, 18, 20, 36], while others contend that vagotomy specifically interferes with the neuroendocrine events responsible for the hyperphagia syndrome [19, 24, 25]. This has been a difficult issue to resolve because of the multiple effect of vagotomy on visceral function, the variability in the vagotomy surgical procedures used in different laboratories, and the lack of a definitive test for the completeness of the vagotomy.

Powley [23, 24, 25] has been among the strongest proponents of the view that the effects of vagotomy on the VMH hyperphagia syndrome are specific and selective. Even his findings, however, indicate that vagotomy does not block all aspects of the VMH

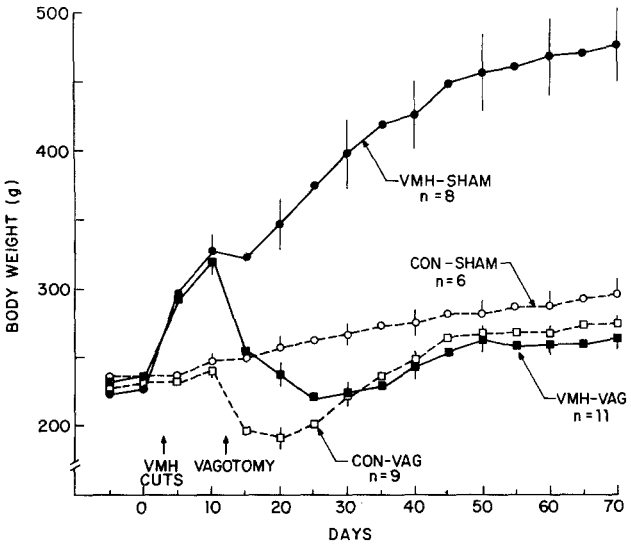

Fig. 4. Mean (±SE) body weight before and after VMH cut or sham surgery, and after subdiaphragmatic vagotomy or sham vagotomy. The female rats were maintained on Purina lab chow

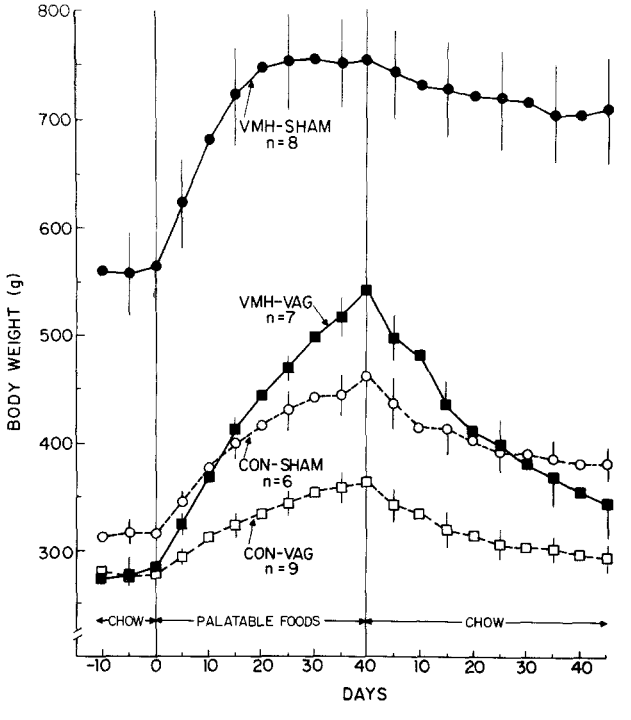

Fig. 5. Mean (±SE) body weight of VMH cut-vagotomized, VMH cut-sham vagotomized, control-vagotomized, and control-sham vagotomized groups on lab chow and palatable food diets. The palatable foods included sweetened condensed milk, chocolate chip cookies, and high fat chow, and were introduced (Day 0) 120 days after vagotomy surgery

syndrome. Powley and Opsahl [24] observed that VMH-vagotomized rats, although they maintained normal food intake and body weight on a chow diet, overate and outgained control-vagotomized rats when fed a high fat diet. The authors proposed that vagotomy spares the finickiness component to the VMH syndrome. Powley's [23] subsequently formulated cephalic phase hypothesis, however, postulates that VMH finickiness is in fact due to vagally-mediated, lesion-exaggerated cephalic reflexes.

We have recently obtained additional evidence that vagotomy spares an important diet-related aspect of the VMH hyperphagia syndrome ([28], in preparation). In our experiment, female rats fed a Purina chow diet were given VMH knife cuts or sham cuts followed 10 days later by vagotomy or sham vagotomy. Figure 4 illustrates that the vagotomy completely reversed the weight gain produced by the VMH knife cuts, and this replicates previous findings obtained with VMH cuts and electrolytic lesions [10, 18, 24]. The hyperphagia of the VMH-vagotomized rats was also totally blocked and the animals maintained their food intake and body weight at the level of the control-vagotomized group until 120 days post vagotomy. At this time all animals were given ad libitum access to three palatable foods (chocolate chip cookies, sweetened milk, high fat chow) in addition to lab chow. We have previously observed that such an assortment of foods induces greater weight gains in rats than does access to a high fat diet alone [30]. As illustrated in Figure 5, all groups gained weight during the 40 day period on the palatable foods, but the most pronounced weight increase was achieved by the VMH-vagotomized group. That is, the VMH-vagotomized rats outgained not only the control-vagotomized animals (260 vs 85 g), but also the control-sham (145 g) and the VMH-sham (195 g) rats. Food intake measures further revealed that the VMH-vagotomized group increased their caloric intake more than did the other groups when the palatable diet was available. These changes were not permanent, however, and when only the chow diet was again available the VMH-vagotomized animals ate less food and lost more weight than did any other group. Their body weight eventually returned to the level of the control-vagotomized subjects.

These results clearly demonstrate that the overresponsiveness of VMH cut rats to diet palatability, which many consider the hallmark of the syndrome, is not dependent upon an intact vagus nerve. Vagotomy, in fact, appears to increase the diet finickiness of VMH rats, since the food intake and body weight of the VMH-vagotomized group were more affected by the changes in diet than that of the VMH-sham group.

Conclusion

In view of the findings reviewed here, it is difficult to maintain that vagally-mediated hyperinsulinemia is the primary means by which VMH damage increases food intake and body weight. In VMH cut rats hyperinsulinemia does not consistently precede the onset of hyperphagia, and appears to be the consequence rather than the cause of overeating. Pharmacological blockade of vagal motor activity does not prevent the hyperphagia of VMH animals, nor does vagotomy prevent VMH animals from overeating and gaining weight on highly palatable diets. It is reasonable to suspect, therefore, that VMH damage increases food intake primarily by altering the central neural control of energy regulation, although the exact nature of this alteration remains to be elucidated. Nevertheless, peripheral neuro-endocrine responses play an important, albeit secondary, role in the VMH hyperphagia syndrome, and a fully functional vagus and pancreas are necessary for the maximal development of the syndrome.

Finally, it should be emphasized that the present discussion has focused on the hyperphagia effects of VMH damage, and it is not denied that hypothalamic manipulations can have direct effects on vagally mediated insulin secretion. The analysis of the hypothalamic control of ingestive behavior and metabolism has been complicated by the use of large electrolytic lesions which damage separate but overlapping neural and neuro-endocrine systems. Only with the use of more discrete lesion techniques (electrolytic, knife cut, neurochemical) will continued progress be made in the understanding of neural-metabolic interaction.

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Discussion after Sclafani's Presentation

Powley: In your most recent experiment, where you were fattening the rats with the high-fat diet, did you obtain insulin values?

Sclafani: Unfortunately not, but insulin levels presumably increased along with body weight.

Steffens: When you give the rats a more palatable diet such that your rats gain weight and secrete more insulin, aren't you actually changing more than palatability?

Sclafani: Yes, for example, when we use chocolate chip cookies, the rats are eating a high-fat diet as well as a diet which tastes better to them. So there may well be several factors operating in that instance.

Bray: It might be that what is actually important is the ability to secrete excess insulin when the high fat diets are consumed, and that it is this exaggerated insulin which causes the weight to be stored. A high carbohydrate diet wouldn't be as efficient because the food requires more processing and conversion to fat before it can be stored.

Sclafani: That's true, but you must remember that these rats actually had a choice and did not overeat foods with an even higher fat content (around 33%). Rather, they overate the cookies and the milk, so palatability seems to be more of a factor than fat content.

Woods: Did you measure glucose levels in these experiments? Hustvedt and Lovo, as well as other investigators, have reported, like you, that rats may have apparently normal insulin levels for a while after the lesion is made, but the glucose levels are lower than normal at that time. This means that what appears to be a normoinsulinemia may actually be an elevated insulin given the low glucose.

Sclafani: Yes, blood glucose levels were measured and were found to be normal in the VMH knife cut animals.

Woods: Is bulk a factor in your vagotomized, knife-cut animals? It may be that your animals don't overeat the diet with the highest fat content because of problems of digestion. When you change your diets, you also change the caloric density of the foods, so ease of passage and digestibility may be important. Did you perform pyloroplasties?

Sclafani: No we didn't. But I'm not sure that you can apply that argument since chocolate chip cookies and normal rat chow have approximately equal caloric density.

Woods: That's true, but your rats also had milk in addition to the cookies and its consumption might have made a combination which was more palatable on physical grounds.

B. Jeanrenaud: Aren't the data concerning the effects of lesions which are restricted to only the ventromedial nucleus somewhat contradictory?

Sclafani: As far as I know, such animals are never hyperphagic. The way these studies are typically done is that the lesions are made and then the rats are screened for hyperphagia. Those that don't eat are discarded, and their data never count in the analyses. You're right in that more work needs to be done investigating the possibility of hyperinsulinemia without hyperphagia, especially in adult rats.

F. Jeanrenaud: Have you looked at islets morphology in your animals?

Sclafani: No, we haven't collected any morphological data.

Goldman: I would like to ask both Dr. Sclafani and Dr. Powley whether they have any data on carcass fat after vagotomy, because we've found that weight gain alone should not be used as an index of adiposity.

Sclafani: We have no data on that, but I believe Dr. Powley does.

Powley: Yes, we've found that the vagotomy does reverse the increased adiposity. We've also found that vagotomy reverses the islet hypertrophy, but the experiments we did were relatively crude.

Berthoud: Do you think that the lesions restricted to the ventromedial nucleus somehow release the lateral hypothalamus from inhibition and thereby increase insulin secretion?

Sclafani: Well, we don't really know, but the direct fibers that interconnect the two nuclear areas cannot be involved since they are severed in our knife-cut animals and they don't become hyperinsulinemic. Little has been done concerning other possible pathways which might be involved. Those of us interested more in the behavioral than the metabolic consequences of these lesions have recently turned our attention to more rostral areas such as the paraventricular nucleus. We find that small lesions, totally restricted to that nucleus, also cause hyperphagia, but the increased eating is less than we see after knife cuts.

Nicolaidis: I'm confused as to the differential effects of various knife cuts. Could you clear this up for us?

Sclafani: When we make bilateral coronal cuts, either behind, through or rostral to the ventromedial nucleus, we observe hyperphagia, but it isn't as great as when we make bilateral parasaggital cuts. We tend to think that the coronal cuts sever all of the important fibers which normally inhibit feeding, but that something else occurs as well which cancels the effect. That's why, in our hands, the asymmetrical combination of a coronal cut on one side and a parasagittal cut on the other is the most effective (J Comp Physiol Psychol (1977) 91: 1000).

Porte: Do your rats which are hyperphagic but not hyperinsulinemic ever reach a weight plateau, or do they keep on overeating forever? If they reach a plateau, can you overfeed them and see evidence for weight regulation?

Sclafani: They do stabilize their weights, but I don't take this as evidence for regulation. Obese VMH rats do not show normal body weight regulation under a number of test conditions (J Comp Physiol Psychol (1974) 86: 28; Physiol Behav (1976) 16: 631; Behav Biol (1978) 22: 244).