Changes in food intake with electrical stimulation of the ventromedial hypothalamus in dogs

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Six adult dogs were implanted stereotaxically with chronic indwelling Medtronic platinum-tipped electrodes in the left ventromedial hypothalamic area (VMH); two dogs with electrodes placed in the subcortical white matter served as controls. Following 24 hours of food deprivation, VMH-stimulated dogs delayed their next meal for a period ranging from 1 to 18 hours. When not stimulated, however, each dog ate immediately upon receiving its food and consumed greater than average daily intake (p < 0.005). The two control dogs ate immediately upon receiving food regardless of whether they were stimulated or not. Dogs that received 1 hour of VMH stimulation every 12 hours for 3 consecutive days maintained an average daily food intake of 35% of normal baseline levels (range 13% to 51%), and water consumption averaged 50% of baseline intake (range 29% to 67%). Both of these results were statistically significant (p < 0.01). After cessation of stimulation, food and water intake returned to normal within 6 to 9 days, with no observable “rebound hyperphagia.” The two animals that received subcortical electrodes showed no change in food or water intake with stimulation. Blood pressure, pulse, respiration, temperature, and gross behavior were not altered during or after stimulation. These results suggest that the use of electrical stimulation of the VMH may be a useful modality for regulating food intake, and deserves further examination as a potential alternative therapy for human morbid obesity.

KEY WORDS • ventromedial hypothalamic nucleus • stereotaxic technique • electrical brain stimulation • satiety • obesity • food intake

In the early 1940's it was noted that lesions of specific brain areas led to alterations in normal food and water intake: a lesion of the ventromedial hypothalamus (VMH) led to overeating and obesity, whereas a lesion of the lateral hypothalamus (LH) led to anorexia. Anand and Dua then reported that electrical stimulation of the LH induced a pronounced bout of eating in previously satiated cats, and that electrical stimulation of the VMH caused food-deprived cats to stop eating. Since these original observations, a large body of literature has developed examining diverse aspects of the pharmacology, physiology, neuroanatomy, and neurochemistry underlying the central nervous system (CNS) regulation of food intake.

For several reasons the potential clinical application of this technique has received little attention. First, the expense and size of the necessary equipment made routine use impractical. Second, effects of electrical brain stimulation in small animals were frequently transient and/or complicated by undesirable side effects. Finally, a post-stimulation “rebound hyperphagia” was generally observed in animals that had decreased their food intake in response to VMH stimulation. Thus, the effect of VMH stimulation seemed to be compensated immediately after stimulation was terminated. However, recent technological advances in the use of electrical brain stimulation as a therapy for chronic pain syndromes has circumvented at least the first two of these problems. Therefore, the following experiments were conducted: 1) to replicate previously reported acute effects of VMH stimulation on food intake; 2) to determine whether repeated stimulation of the VMH could produce prolonged reduction in food intake; 3) to examine the effects of VMH stimulation on the grossly observable behavior of dogs; and 4) to examine the effects of VMH stimulation on blood pressure, heart rate, respiratory rate, and body temperature.

Materials and Methods

Subjects and Stimulation Parameters

Four adult female and four adult male dogs, each weighing between 8 and 40 kg, were used in these
FIG. 1. X-ray films, anteroposterior (left) and lateral (right) views, showing electrode placement in the dog brain. Arrow indicates the electrode tip.

FIG. 2. Delay until initiating food ingestion following 24 hours of food deprivation and 1 hour of stimulation of the ventromedial hypothalamic area (VMH) or subcortical white matter versus no stimulation. Values represent mean ± standard error of the mean.

experiments. Each dog was housed individually in standard large-animal cages before and during these experiments, and had complete veterinary supervision throughout this period. Food and water ingestion was measured twice daily.

The electrodes* used in this study are identical to those employed in patients undergoing deep brain stimulation for treatment of chronic pain. Each electrode had four stimulation points: “0” (the tip), and “1,” “2,” and “3,” each separated by 3 mm. In all of our experiments, the stimulation was confined to “0” and “1” with negative polarity at “0.”

To calibrate our delivered current intensity, several steps were taken. Electrode resistance was measured in physiological saline, which is the major source of brain tissue resistance; therefore, in vivo resistance should be approximately the same. Voltage output of the transmitter was determined on an oscilloscope, and the actual output of the unit at various dial settings was calibrated. Current delivered was then determined by Ohm’s law: $I = V/R$. Since the resistance in physiological saline was found to be 30,000 ohms, it was estimated that, by setting the transmitter to 3½ volts, a current of 100 μA should be realized. In the present study the stimulation parameters of 3½ volts, 1.0-msec pulse width, and 50 pulses/sec frequency were kept constant for each experiment. These parameters are similar to those used previously by others.⁴

Surgery

After baseline daily food and water intake levels were established, each dog was anesthetized with sodium pentobarbital (30 mg/kg) and secured into a Kopf stereotaxic head frame.† After standard sterile preparation, a skin flap was opened on the left hemicranium, and the temporalis muscle was dissected from the skull with electrocautery. A burr hole was then placed and the dura mater opened to allow appropriate electrode placement. A Medtronic quadripolar electrode was then lowered into the VMH area in six dogs (coordinates AP + 20.0 mm, L + 1.0 mm, DV + 4.5 mm according to

* Electrodes and transmitter manufactured by Medtronic, Inc., 6970 Old Central Avenue North, Fridley, Minnesota.

† Stereotaxic frame manufactured by David Kopf Instruments, 7324 Elmo Street, Tujunga, California.
Hypothalamic control of food intake

FIG. 3. Daily food (left) and water (right) intake during 3 days of stimulation of the ventromedial hypothalamic area (VMH) or subcortical white matter every 12 hours versus daily intake during the 3 days immediately preceding stimulation. Values represent mean ± standard error of the mean.

Experimental Procedure

After each dog had recovered from surgery and returned to baseline food and water intake, the following protocol was begun.

Experiment 1. Each dog was randomly assigned to one of two groups. Group 1 was deprived of food for 24 hours, after which a dog coat, containing a small Medtronic electrical transmitter was placed on the dog. Stimulation wires were connected to the externalized portions of the electrode and the current was turned on for 1 hour (100 μA, 1.0-msec pulse width, 50 pulses/sec). This apparatus allowed the dog complete freedom of movement. Food was presented to the dog immediately upon stimulation. Latency to initiate feeding was then determined and recorded as immediate, during the 1 hour of stimulation, between 1 and 6 hours, and in 6-hour periods after stimulation. One week later, following resumption of normal daily food and water intake, the entire procedure was repeated except that current was not turned on. Group 2 was treated identically to Group 1 except that the stimulation/non-stimulation order was reversed. Data were analyzed using each dog as its own control by paired t-test.

Experiment 2. One week after completion of Experiment 1, and following return to baseline food and water intake, each dog received 1 hour of stimulation, using the same parameters, every 12 hours for 3 consecutive days. Food and water consumption was measured twice daily. Qualitative behavioral observations were made immediately before and after initiating current flow. Following the last stimulation period, each dog's return to baseline daily food and water intake was monitored. Data were analyzed as in Experiment 1.

Experiment 3. Vital signs were monitored through two procedures. Three dogs were monitored for 1 hour immediately after implantation of the electrode, and three dogs were monitored (under anesthesia) for 2 weeks following completion of Experiment 2. An arterial catheter provided blood pressure and pulse rate information. Respiratory rate was monitored with a pneumatic strain gauge strapped around the dog's thorax, and temperature was monitored rectally. All stimulation parameters were identical to those used in Experiments 1 and 2.

Results

The results of Experiment 1 are illustrated in Fig. 2. In this experiment, the latency to initiate feeding following a 1-hour period of VMH or subcortical white matter stimulation was compared to the same period in the corresponding nonstimulated control dogs. Dogs receiving 1 hour of VMH stimulation delayed their next meal an average of 7.1 ± 2.8 hours (mean ± standard error of the mean) despite 24 hours of food deprivation, whereas nonstimulated dogs resumed eating immediately (p < 0.005). Dogs that had electrodes implanted in the subcortical white matter resumed eating immediately, regardless of the presence or absence of stimulation. Generally, once a dog began eating, it consumed a greater than average daily food intake during the next 24 hours, regardless of its electrode placement or stimulation status. Thereafter, the dogs consumed normal daily quantities of food and water.

Dogs that received 1 hour of VMH stimulation every 12 hours for 3 days decreased their average daily food intake by approximately 65% and their average daily water intake approximately 50% (p < 0.01) over these 3 days compared to the 3 days immediately preceding stimulation (Fig. 3). Stimulation of the subcortical white matter, however, had no apparent influence on...
FIG. 4. Graph showing return to baseline food (closed circles) and water (open circles) intake following 3 days of stimulation of the ventromedial hypothalamic area every 12 hours. Values represent the mean; vertical lines indicate standard error of the mean.

Discussion

These results replicate earlier reports demonstrating acute decreases in food intake during electrical stimulation of the VMH in food-deprived animals.4,14,18 Contrary to these earlier reports, however, the subjects of this experiment typically did not return to eating immediately after stimulation was terminated. In fact, in this experiment the subjects delayed their next meal an average of 7 hours following 1 hour of stimulation. One possible explanation for this difference is the longer duration of stimulation used in this experiment (1 hour compared to 10 minutes or less). Morgane14 demonstrated significant latency to initiate feeding in rats stimulated simultaneously in the VMH and far-lateral hypothalamus, and suggested that the LH feeding mechanism had to "build up sufficient potential" to overcome a constantly resisting satiety mechanism in the VMH. Based on this hypothesis, it seems possible that, in our experiment, stimulation of the VMH for a relatively longer period may lengthen the time required for the LH "feeding mechanism" to overcome this VMH "satiety mechanism." Once these animals (that is, animals stimulated only once) did begin eating, however, the previously described "rebound phenomenon" of food intake was observed. This effect could be explained either as a side effect of stimulation or as a compensation for nutrients lost during the food deprivation period.

One important feature of the longer delay in initiating food ingestion is that it enables the use of chronic intermittent electrical stimulation to delay food ingestion, or at least to decrease the amount of food ingested over more extended periods of time. In this experiment, dogs receiving 1 hour of VMH stimulation every 12 hours for 3 days decreased their average daily food intake to approximately 35% of normal, and their average daily water intake to approximately 50% of normal. This decrease in water intake suggests that dehydration may be an undesirable side effect of VMH stimulation. However, preliminary results in our laboratory of stimulation twice daily in dogs for 60 days indicate that water intake gradually returns to baseline after its initial decrease. Therefore, dehydration will probably not be a long-term problem.

Several other important observations were made during this experiment. First, vital signs were not altered by stimulation. Results published during the late 1960's and early 1970's were the first to suggest that hypothalamic stimulation increased heart rate and blood pressure,16 and that hypothalamic cooling and/or warming altered the body temperature.2,8 Second, no grossly observable alterations in behavior were noted before, during, or after stimulation. Hypothalamic manipulation has been reported to induce a variety of behavioral changes, including rage, aggression, fear, and hypersexuality.1,5,7 Most of the differences between our results and those reported previously reflect differences in electrode placement within the hypothalamus: heart rate and blood pressure are increased by stimulation of the LH,16 temperature is influenced via the medial preoptic area/anterior hypothalamus,6 and most behavioral alterations (except those affecting food consumption) have been elicited by the anterior, dorsal, dorsomedial, lateral, and posterior hypothalamus.1,15,17 Different placement within the VMH itself could also account for the aggressive behavior observed in one previous report,1 although species differences and stimulation parameters could also account for the observed differences. Finally, following termination of stimulation every 12 hours for 3 days, the anticipated rebound hyperphagia was not observed. Instead, baseline food and water intake recovered gradually over several days to weeks. These results can be interpreted to suggest that permanent damage to CNS food-intake regulatory processes had not occurred and that rebound hyperphagia may be a phenomenon that occurs preferentially after acute, short-duration stimulation.

Conclusions

The results of these preliminary experiments on the effect of electrical stimulation of the VMH on food and
Hypothalamic control of food intake water intake in the dog suggest that: 1) food intake can be reliably decreased acutely, 2) food intake can be decreased for at least 3 days with stimulation every 12 hours; 3) this can be done without serious effects on behavior; 4) neither blood pressure, heart rate, respiratory rate, nor body temperature are significantly altered by this treatment. Furthermore, the previously reported “rebound hyperphagia” may not be a problem if repeated intermittent stimulation is used. In light of these results, and because recent technological advances have made electrical brain stimulation an easy and safe procedure to use on a chronic intermittent basis, it seems prudent to suggest that chronic intermittent brain stimulation deserves further examination as a potential means of regulating food intake, and therefore as a potential therapeutic modality for human morbid obesity.

References

1. Abzianidze EV: [Influence of electrical stimulation of the various hypothalamic nuclei on alimentary and defensive reactions in cats.] Sak SSR Mets Akad Moahe 52: 539–544, 1968 (Rus)

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