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Lateral Hypothalamic Stimulation: Stimulus-Bound Eating and Self-Deprivation[1]

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FRANK, R. A., R. L. PRESHAW, R. M. STUTZ AND E. S. VALENSTEIN. *Lateral hypothalamic stimulation: Stimulus-bound eating and self-deprivation.* PHYSIOL. BEHAV. **29**(1) 17–21, 1982.—Research was undertaken in an attempt to clarify the relationship between stimulus-bound eating and self-deprivation produced by electrical stimulation of the lateral hypothalamus. It was hypothesized that if these two phenomena are mediated through a common population of feeding-related neurons, a significant correlation should be observed between these two behaviors. No significant relationship was discovered among the rats tested for both stimulus-bound eating and self-deprivation. Although this finding by itself does not rule out some role for feeding-related neural elements in stimulus-bound eating and self-deprivation, the present results provide no support for this view and suggest alternative explanations should be sought.

Lateral hypothalamic stimulation Stimulus-bound eating Self-deprivation Self-starvation
Rewarding brain stimulation Self-stimulation

THAT electrical stimulation of the same lateral hypothalamic site can evoke both eating (stimulus-bound eating) and reward has never been adequately explained. If, for example, animals eat because stimulation makes them hungry [4,22], then, it seems paradoxical that they should self-stimulate at the same electrode site, unless one assumes hunger is rewarding. On the other hand, if Spies' [16] assumption that rewarding stimulation produces a temporary food drive reduction ("transient satiety equivalent") is accepted then it is equally puzzling that animals eat when stimulated at the brain site. Attempts to resolve the paradox by noting that different stimulation durations are typically used to evoke eating and self-stimulation are not convincing as several investigators have demonstrated both phenomena with identical parameters [2,10].

Earlier work by Margules and Olds [9] and Hoebel and Teitelbaum [8] demonstrated that self-stimulation rates in the lateral hypothalamus are potentiated by food deprivation. Because self-stimulation and eating apparently are both more rewarding when animals are hungry, it was concluded that electrical stimulation of certain hypothalamic regions artificially activates the neural structures that mediate reward associated with food ingestion. This argument, however, never specifically addressed the question of why animals should eat in response to brain stimulation that activates the reward associated with eating.

Valenstein and his co-workers have offered other explanations of stimulation evoked eating which may help to explain the paradox. The numerous differences between eating evoked by stimulation and by hunger and the experiments demonstrating that an animal will display different behaviors in response to the same stimulation raised the possibility that stimulus-bound behavior is a response to a relatively nonspecific activational state [1, 18, 20, 21]. The behavior displayed during brain stimulation seems to depend upon available objects and subject predisposition rather than the activation of a specific drive such as hunger. This interpretation, however, remains controversial [4,22].

It has also been found that electrical stimulation of the lateral hypothalamus can produce food self-deprivation when food and an opportunity to self-stimulate are simultaneously available [15,16]. Although these results are dramatic demonstrations of the relative strength of rewarding brain stimulation, it is not clear why self-stimulation at some lateral hypothalamic sites, but not other, can cause a hungry animal to neglect available food [13]. If it is assumed that brain stimulation at some sites activates a state of hunger while stimulation at other sites produces a reduction in hunger, the behavior of animals in a test involving competition between the opportunity to self-stimulate or eat should differ depending on the motivational consequences of stimulation.

The few incidental reports that exist do not provide adequate data to resolve the issue. For example, Morgan and

[1]We have used the term "self-deprivation" rather than "self-starvation" [14] to acknowledge the fact that some thirsty animals neglect water while self-stimulating [11,13].

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Mogenson [11] reported that three rats who were stimulus-bound drinkers did not make a single lever press for water during a water-brain stimulation competition session despite 71 hours of water deprivation. On the other hand, Olds [12] cited an observation that hypothalamic stimulation that evoked eating failed to produce self-deprivation of food in a competition test. Finally, no stimulus-bound feeding was observed in self-depriving rats with electrodes in the lateral and posterior hypothalamus when repetitive short trains of stimulation were used [13,17].

In the present study, rats were tested for both self-deprivation and stimulus-bound feeding in an attempt to clarify the relationship between these phenomena. If stimulus-bound feeding and self-deprivation are mediated by a common neural substrate, one should expect some relationship to exist between the two phenomena.

METHOD

Subjects, Surgery, Stimulation Parameters and Test Schedule

The experimental subjects were 29 male Long-Evans hooded rats (Simonsen Co., Gilroy, CA) that had completed all phases of the testing and had met a self-stimulation criterion of at least 40 responses per minute. All animals weighed between 250–300 g at the time of surgery. The experimental subjects were implanted with a twisted bipolar stainless steel electrode (Plastic Products Co., Roanoke, VA, MS 303/1 0.25 mm dia.) insulated except at the electrode tip. Equithesin (Jensen-Salsberg Lab, Kansas City, MO) anesthetic (2.7 ml/kg) was used, and the electrodes were fixed to the skull by stainless steel screws and dental acrylic. With the skull held level between bregma and lambda, stereotaxic coordinates were: 3.3 mm posterior to bregma, 1.4 mm lateral from the midline and 8.3 mm below the skull surface. In the stimulus-bound eating tests, animals were stimulated with 20 sec trains of 60 Hz sine waves from a constant current source, alternating with 15 sec interstimulus intervals. The onset and duration of electrical stimulation was always controlled by automatic programming equipment. In the self-stimulation and competition tests a 60 Hz sine wave (train duration 300 msec; intensity 30 μA RMS) was delivered from a constant current stimulator following each lever press.

For 20 of the animals, the stimulus-bound eating tests were administered first followed by the self-stimulation and competition tests. The procedure was reversed for 9 of the animals. The stimulus-bound eating tests were performed in the Neuroscience Laboratory of the University of Michigan while the self-stimulation and competition tests were performed in the Psychology Department Animal Laboratory of the University of Cincinnati. The second test was always performed by experimenters having no knowledge of the outcome of the first test.

In addition to the 29 Long-Evans rats, 11 male Sprague-Dawley rats were tested using a slightly modified procedure. The results of the tests of the Sprague-Dawley rats complement the data obtained from the Long-Evans rats and are described in the Results and Discussion section.

Stimulus-Bound Eating Procedure

Animals were housed in individual cages with food and water available. The animal rooms were temperature regulated and the lights were maintained on a 12-hour light/dark cycle. One week following surgery, animals scheduled to be tested first for stimulus-bound eating were placed in a 20.5×26.5×43.5 cm Plexiglas chamber with a cardboard floor. Food pellets (P. J. Noyes Co., Lancaster, NH, 45 mg) were scattered on the floor. Following 30 min of habituation to the test chamber, animals were screened for stimulus-bound feeding. Animals were initially exposed to a 1.0 μA current that was increased by 1 μA on each subsequent trial until the animal ate, or until the stimulation seemed to agitate the rat excessively. Observations were made carefully to assure that the animals actually ingested food rather than only crumbling it.

If a rat regularly ate during stimulation and did not eat during the intertrial interval, it was designated as "positive." Rats not eating were rescreened within 48 hours using the same procedure. Animals failing to show consummatory behavior after two screenings were classified as "negative."

Positive rats were then given stimulation intensity threshold tests. The threshold test consisted of a modified "stair-case titration" procedure for obtaining the minimum stimulation intensity capable of evoking eating. The current intensity was raised in 1 μA steps from an initial level 3 μA below the animal's screening threshold, until eating occurred. The same current intensity was then repeated on the next trial. If eating did not recur, the intensity was raised. Following two consecutive positive trials at the same intensity, the current was reduced by 3.0 μA and the process was repeated twice. The three intensities at which an animal ate twice in succession were averaged to obtain the threshold intensity.

After the current threshold testing was completed, all positive animals received 20 stimulations at a suprathreshold intensity judged to be at an optimal level for eliciting eating. The number of times stimulation evoked eating was recorded.

Self-Deprivation Procedure

Apparatus. All testing was done in chambers (25×22×34 cm) constructed of wood and Plexiglas. A metal lever was mounted approximately 5.0 cm from a floor constructed of aluminum rods spaced 1.0 cm apart. Brain stimulation was delivered through cables equipped with mercury commutators (Scientific Prototype), which allowed the animal relatively free movement while connected to the stimulation circuit. A food cup measuring 5×4×3 cm was anchored in the rear of the chamber and was filled with 30 200 mg Noyes pellets at the start of each self-stimulation/food competition period. Electromechanical counters were used to record lever presses for the brain stimulation reward.

Self-stimulation screening and baseline feeding procedure. Subjects were trained to lever press for brain stimulation at 30 μA, an intensity previously established to support high self-stimulation rates for most subjects with comparable electrode placements. After animals were pressing at stable rates, a 10 min test was given to obtain a measure of their self-stimulation performance. Two animals that failed to meet the self-stimulation criterion of 40 presses/min were eliminated from the experiment at this point and are not included in the results obtained from the 29 animals that met our self-stimulation criterion and completed all tests.

Following the 10 min self-stimulation test, the 29 experimental subjects were deprived of food for 24 hours and placed in the test chamber where they were given access to 30 200 mg Noyes pellets for 45 min. On four consecutive days, subjects were fed only in the test chamber. During this

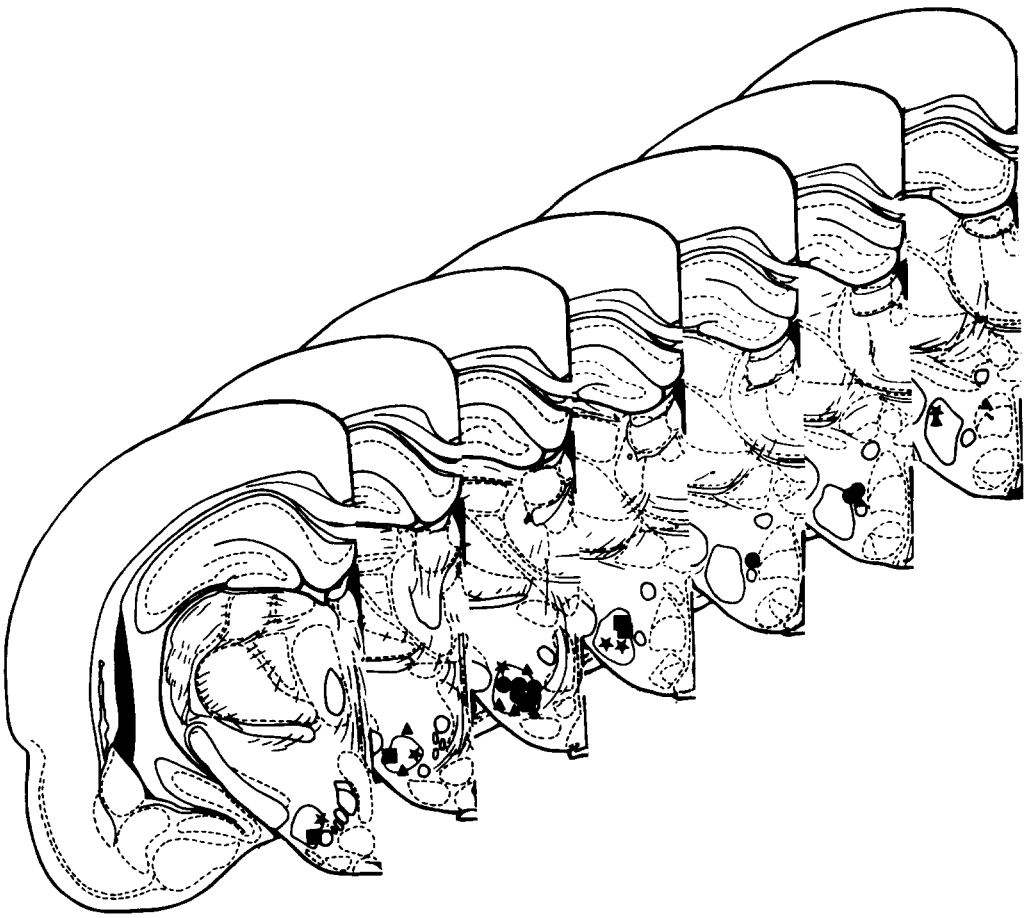

FIG. 1. Electrode placements in the 29 Long-Evans rats. Behavior in the stimulus-bound eating (S-BE) and competition tests is indicated as follows: ● positive S-BE and self-deprivation; ★ positive S-BE and non-deprivation; ■ negative S-BE and self-deprivation; ▲ negative S-BE and non-deprivation. Animals were considered to be self-deprivers if they ate an average of less than 5 food pellets per test.

period, the self-stimulation lever was not available. After the fourth day, animals were given three days of ad lib feeding in their home cages. This free feeding allowed them to regain the weight lost during the preceding deprivation days.

Competition tests procedure. Following the free-feeding period, animals were again deprived of food for 24 hours and placed in the experimental chamber where access to the self-stimulation lever and food were both available during a 45 min competition test. This procedure was repeated on three consecutive days during which time no food was available in the home cage. The number of pellets eaten during the 45 min test was recorded on each day.

Stimulus-bound behavior retest. After the completion of the competition tests, subjects that had received the stimulus-bound eating test first were retested for stimulus-bound behavior using the procedure described above.

Histology

Upon completion of behavioral testing, the animals were overdosed with Equithesin and perfused through the heart with saline and 10% Formalin solution. Frozen sections (60 μm) of the brains were examined to locate the electrode tips.

RESULTS AND DISCUSSION

Fifteen of the 29 Long-Evans animals reliably displayed stimulus-bound eating. Three of the animals initially classified as negative ate consistently in response to stimulation when retested and were reclassified. The behavior of other animals was consistent between the two tests. The average threshold intensity capable of evoking eating was 8.6 μA RMS (range 4.0–15 μA) and the average number of times animals ate out of the 20 stimulations at optimal current intensities was 18.7 (range 15–20).

Self-stimulation rates for the 29 animals ranged between 41 and 110 presses per minute and averaged 76.5 and 72.1 for the 15 positive and 14 negative stimulation-bound feeders, respectively. This difference was not statistically significant.

In the three competition tests the average number of pellets eaten ranged from 0 to 30. Five animals did not eat any food pellets during the three 45 min tests while 3 animals ate all or most (average greater than 23 per test) of the available pellets on each of the tests. The average number of pellets consumed in a single competition test was 8.50 for the 29 animals.

There was a slight tendency for the positive stimulus-bound eaters to consume less food in the competition tests than the non-eaters (average of 6.4 compared to 9.4). This difference was evaluated using a point-biserial correlation test that compared the number of pellets consumed by the positive and negative stimulus-bound eaters. The point biserial was not significant (rpb=.27; $t(27)=1.45$) and supports

FIG. 2. Electrode placements in 8 of the 11 Sprague-Dawley rats. Behavior in the stimulus-bound eating (S-BE) and competition tests is indicated as follows: ● positive S-BE and self-deprivation; ★ positive S-BE and non-deprivation; ■ negative S-BE and self-deprivation; ▲ negative S-BE and non-deprivation. Animals were considered to be self-deprivers if they ate an average of less than 5 food pellets per test.

the conclusion of no relationship between stimulus-bound eating and performance in the competition test.

In addition to the Long-Evans rats tested in this study, 11 Sprague-Dawley rats that had completed an extensive series of competition tests over an 8 week period were later tested for stimulation-bound feeding using the procedure described above. The electrode coordinates differed from those used with the Long-Evans rats only in that they were more posterior (4.5 mm posterior to bregma) in the lateral hypothalamus (compare Figs. 1 and 2). These data also revealed no significant difference in the number of pellets eaten in the competition tests by positive and negative stimulus-bound eaters. The mean number of pellets consumed during their last 3 competition tests was 18.3 for the 7 positive stimulus-bound eaters and 13.6 for the 4 negative animals. The slight trend being in the opposite direction to that seen with the Long-Evans rats supports the conclusion that there is no relationship between behavior in the competition and stimulus-bound eating tests.

An analysis of the relationship between baseline self-stimulation rate during the 10 min test and the number of pellets eaten during the competition test was undertaken in order to determine if animals self-stimulating at the highest rates would be least likely to stop lever pressing in order to eat. For this purpose, we classified the Long-Evans animals as either "self-deprivers" or "non-deprivers" based on their performance in the competition test. The 13 animals that ate less than an average of 5 pellets per test were classified as the "self-depriver" group. The 16 animals that averaged 5 or more pellets per test were considered "non-deprivers." Although the dividing point is somewhat arbitrary, it is likely that animals eating less than five 200 mg food pellets per day would have starved had the tests been continued. The self-stimulation rate averaged 75.3/min and 73.6/min for the "self-deprivers" and "non-deprivers," respectively, a difference which is not significant. Among the highest 6 self-stimulation rates, for example, there were 3 "self-deprivers" and 3 "non-deprivers." A similar overlap in self-stimulation rates was also found between the 7 "self-deprivers" and 4 "non-deprivers" of the Sprague-Dawley strain.

The lack of relationship between self-stimulation rate and performance in the competition test seems to contradict an earlier study [17] reporting a positive relationship based on the data from a relatively small group of Wistar strain rats. In addition to differences in the strains of rats, the two studies also differed in that baseline self-stimulation rates in the earlier study were obtained while animals were food-deprived. The earlier conclusion that magnitude of brain stimulation reward determines behavior in a competition test may ultimately prove correct [5, 6, 13, 17]. However, in view of the shortcomings of self-stimulation rate as a measure of reward strength [7,19] and the extent of the overlap in rate scores in "deprivers" and "non-deprivers" in the present experiment, it is unlikely that even self-stimulation rates obtained under food deprivation conditions would have been correlated with food pellets eaten in the competition tests. Routtenberg and Bulloch [14] also concluded that self-stimulation rate was not related to behavior in their competition tests. It is possible, however, that some relationships might emerge if animals self-stimulating at very low rates were not eliminated.

The histological results for the Long-Evans and Sprague-Dawley rats are summarized in Figs. 1 and 2, respectively. In agreement with earlier reports [1,3] there was no critical focus within the lateral hypothalamus for evoking stimulus-bound eating. A similar conclusion may be drawn for the electrode sites of animals that were classified as "self-deprivers" as noted earlier by Rossi and Stutz [13] and Frank, Preshaw and Stutz [5]. It should be emphasized, however, that this conclusion applies only to the electrode placements within the medial to posterior extent of the lateral hypothalamus as there were no anterior hypothalamic placements and only one medial placement in our sample. Consistent with the difference in stereotaxic coordinates, the electrode placements in the 8 Sprague-Dawley rats for which histology was available tended to be more posterior than those for the Long-Evans rats.

If self-deprivation and stimulation-bound feeding depend upon stimulation of a common population of feeding-related neurons, a consistent relationship between the two phenomena should exist. No such relationship was observed in the present investigation. The behavior of hungry animals self-stimulating with electrodes that differ in their capacity to elicit eating do not differ in the probability that they will neglect food in a competitive situation. Although this finding by itself does not rule out some role for feeding-related neural elements in stimulation-bound feeding and self-deprivation, the present results provide no support for this view and suggest that alternative explanations should be sought.

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