

Chapter 5

Animal Models of Eating Disorders: Hypothalamic Function

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INTRODUCTION

One of the oldest and most investigated models of food intake disorders is the hyperphagia response to electrical stimulation of the lateral hypothalamic area (ESLH) in sated animals [1]. For decades researchers have been concerned with the possibility that under natural conditions, individual differences in the level of activity of neurons in the LH could override other mechanisms of satiety and contribute significantly to daily food intake and body weight. Particularly attractive was the implication that ESLH might yield a rough approximation of some relatively high level of activity present in the LH of people who eat to excess. Based on the animal research, some clinicians have gone so far as to use ESLH to locate and destroy "feeding sites" in obese humans [2].

ESLH has been the focus of controversy for the last twenty years. The purpose of this chapter is to summarize the background leading up to this controversy, to review the key issues critically, and to outline the current status of ESLH as an animal analog of bulimic behavior.

HISTORICAL BACKGROUND

In 1943, Brugger [3] found that macroelectrode stimulation of the perifornical area of the LH elicited intense eating of both edible and inedible objects in most

cats he tested, and in two of them the stimulation resulted in consumption of edible substances exclusively. In 1949 Hess [4] reported gnawing, biting, and eating responses to ESLH, but it was not until Anand and Brobeck reported that aphagia resulted from the destruction of this same area in rats and cats [5] that reference to a LH center for feeding became prevalent.

In the middle 1950s, Larsson [6], Smith [7], and Miller [8] reported that ESLH of specific points reliably initiated either feeding or drinking in nondeprived animals, and that interruption of the ESLH resulted in a cessation of the stimulation-induced responses. These investigators suggested that the elicited behaviors genuinely reflected the triggering of distinct neural systems or motivational states normally active during deprivation-induced behaviors. Miller and his collaborators [9,10] spent the next decade conducting research that they believed strongly supported this hypothesis. They reported that with the onset of electrical current, mildly thirsty (but not hungry) rats, which were known to be stimulation-induced eaters, would not only actively seek edible objects but would also terminate drinking behavior to engage in food-seeking and eventually feeding behavior. Furthermore, the animals receiving ESLH learned new responses or emitted responses, which had been previously reinforced with food, to gain access to the appropriate goal object, a finding confirmed by others [11].

Miller was concerned that a nonspecific gnawing reflex was being aroused and that the animals might have been responding merely because it would be more reinforcing to chew on a solid substance rather than on nothing at all. However, he showed that water-deprived rats switched from drinking water to lapping milk with ESLH onset, suggesting to him that hunger was the predominant incentive [9]. Miller also predicted that the offset of the current might function as a reward, just as in conventional appetitive behaviors [9]. In support of this prediction, he found that sated rats learned to press a bar or to choose that arm of a T-maze that turned off the current stimulating an LH eating site.

The strength of the motivation to engage in a feeding response to ESLH was indicated by studies showing that rats ate to the point of obesity with frequent applications of the electrical stimulus [12], and tolerated shock [13] or quinine additives [14] to gain access to food during the stimulation.

Misher and Brooks [15] found that stimulation of LH sites that supported stimulation-induced eating also increased the output of gastric acid. This was expected, because gastric activation was known to increase during food deprivation. Stimulation at sites not arousing well-defined feeding responses did not alter gastric acidity. Later, others [16,17] reported that the frequency of stomach contractions increased during and immediately following stimulation of positive but not negative feeding sites.

The well-known antiappetite drug, d-amphetamine, raised the current threshold for stimulation of eating [9,18]. Moreover, free, or intragastric, feeding inhibited stimulation-induced eating, whereas drinking, or intragastric watering, inhibited only stimulation-induced drinking [19]. Thus, ESLH-induced behaviors appeared to be affected appropriately by factors known to influence deprivation-induced behaviors. By 1970, nearly all investigators enthusiastically supported the compelling view that stimulation-induced behaviors reflected the activation of neural system specific to deprivation-induced feeding behaviors [20-22].

CONTROVERSIES

This view, commonly called the "specificity" interpretation of ESLH [23], was challenged aggressively by Valenstein et al [24]. After reviewing the literature pertaining to stimulation-induced behavior and compiling histological results from their own laboratory, they noted that there was extensive overlap of hypothalamic sites at which stimulation yielded widely divergent behaviors [24-26]. They proposed that this lack of anatomical specificity had gone undiscovered because re-

searchers had commonly allowed animals in their experiments to experience a preferred goal object throughout all training sessions, thereby precluding the emergence of less-preferred behaviors.

In an influential series of experiments, they showed that initial performance of either eating, gnawing, or drinking behaviors elicited by ESLH was, in most cases, subject to change without manipulation of stimulation parameters [27]. For example, stimulation-induced eaters might gradually switch to drinking following the removal of food, and in subsequent competition tests, the new behavior (drinking) would be displayed as readily and as vigorously as eating. In fact, when the initial goal object was returned, each of the two stimulation-induced behavior patterns were displayed in most instances. It appeared, then, that behaviors elicited by ESLH were considerably more plastic than was generally accepted and that no circumscribed area of the rat hypothalamus could be identified with electrically-elicited eating or drinking behaviors.

Although the results of Valenstein and his co-workers [24] were consistent with viewing the hypothalamic stimulation as nonspecific in action, the potential contribution of separate but spatially intertwined LH systems could not be ruled out [28,29]. Mogenson and Morgan, even before the work of Valenstein et al [27] conducted similar experiments but had concluded that the LH contained interdigitated and partially overlapping integrative-control systems for both feeding and drinking [30,31; see also 93]. When Mogenson found that the delivery of an electrical stimulus could elicit a single behavior in pretests but a second behavior following various environmental manipulations, he merely inferred that the neural circuit of the first behavior was being influenced to a greater degree initially by the stimulation, after which the influence somehow changed to equally affect the neural circuit of both behaviors. He suggested that the opportunity to engage in a second behavior could directly affect the sensitivity of the LH through an impingement of corresponding peripheral afferents on a select neural system. Indeed, there had been many examples in the literature of studies showing changes in the threshold for stimulation-induced feeding, drinking, or reinforcement brought about by such peripheral influences as deprivation, stomach overloading, appetite whetting, or drugs [9,19,30,32,33].

Wise [34] also countered with the objection that circuits for feeding and drinking appeared to have different elicitation thresholds even before any modification attempts, and that the prolonged stimulation procedure used by Valenstein et al [27] perhaps involved the gradual increase in sensitivity of a system whose inter-

meshed fibers were initially silent to the original stimulation. He argued that had Valenstein et al [27] varied their current levels to begin with, they might have produced switching of behaviors without the further training trials.

The conclusion of Wise [34] was based primarily on the finding that a simple altering of the intensity of ESLH caused a complete behavior replacement. However, Valenstein and his colleagues [35-37] pointed out that Wise had confounded the effects of shifting stimulation intensity with those of removing the initially favored object in this procedure. They found that if the rats were subjected to varying intensities of stimulation during competition trials, a nonpreferred behavior would not be elicited unless the originally selected goal object was removed. Moreover, the new behavior would then only gradually emerge, a result which Valenstein and his colleagues saw as incompatible with the hypothesis that two separate drives were simultaneously competing for satisfaction during ESLH. Furthermore, repeated stimulation in the absence of any goal object would not subsequently produce a change in behavioral tendency [36].

Wise [38] then amended his original viewpoint. Incrementing movable electrodes in 0.113-mm steps, he showed that once a particular behavior from a certain testing site was established in a given rat, any threshold changes brought about by continued stimulation were usually transferred to a range of other positive sites discovered in that animal. A carryover of threshold to remote sites indicated that the neural changes underlying this effect were not peculiar to a single LH locus, as his earlier hypothesis [34] required. Although this confirmed the position of Valenstein et al [24] that frequent stimulation produces some kind of developing tendency in an animal to respond in a particular way, rather than a change in the threshold of neural tissues surrounding the electrode tips, Wise nevertheless continued to view ESLH and food deprivation as essentially similar [39].

Valenstein et al [24] suggested that repeated discharging of a behavior in response to electrical stimulation gradually provides the reinforcement to continue the behavior or to engage in instrumental tasks that are rewarded by the opportunity to elicit the behavior. Any modification of the behavior was seen as related to the reinforcement derived from engaging in a different prepotent behavior.

This assumption of behavior-generated reinforcement was the cornerstone of Valenstein's position from the beginning, and was essential to the "nonspecificity" view of ESLH. Caggua [40] rejected this assumption and favored the specificity hypothesis, because he found that the first behavior to be reliably evoked by the stimulation was not always the first one tested. However, be-

cause Valenstein et al believed that the stimulation-related reinforcing feedback only gradually affected behavior, they did not insist that the preferred ESLH-induced response be established immediately.

The nonspecificity hypothesis did not explain the factors that influenced the occurrence of the initially evoked behavior or the variables that differentially prejudiced the evocation of one of two equally reinforced responses. Valenstein and his colleagues [24,41] could not influence the induction of a particular behavior by imparting selective deprivation conditions on an animal before the first testing experience. They also could not affect the relative frequency of one established stimulation-induced behavior over another in competition testing merely by providing previous experience in a test chamber distinctly associated with the opportunity to display that behavior without ESLH. Valenstein and his colleagues [25,41] briefly noted that the physical proximity of the food or water to the animal at the moment of stimulation seemed to be important in determining which behavior would be exhibited. However, this interpretation was made in the absence of systematic comparisons between the stimulation-induced animals (which were thought by most investigators to resemble hungry/thirsty animals [42]) and animals that were simultaneously deprived of both food and water. It seems likely that if food- plus water-deprived rats had been placed in an environment where a disproportionate balance of food or water existed, a response probabilities even without ESLH would have been influenced by physical proximity to the goal object.

Mogenson [30] and Milgram et al [43] were able to find a small percentage of rats whose initial behavioral preference could not be switched despite many modification sessions, a finding to which Valenstein et al [24,27] also admitted. Valenstein et al emphasized the rarity of this effect, while Mogenson and Milgram et al used this finding to marshal support for stimulation specificity. Valenstein et al [24] further argued that these rare cases of specificity may have occurred because unscored behaviors such as tail preening sometimes developed during the modification sessions and thus precluded the possible emergence of target behaviors.

Some investigators tried to limit the modifiability of behavioral tendency through the use of small-diameter electrodes. Miller [44] expected to obtain greater specificity with the smaller electrodes, but instead found it extremely difficult to elicit any observable behaviors at all. According to Valenstein et al [24] with smaller electrodes, the likelihood of obtaining a specific stimulus-bound behavior was greatly decreased; but if a response was elicited, a second response could be obtained. Others [45,46] did observe some apparently static be-

haviors by reducing the surface area of the electrode tips. The anatomical correlates compared quite favorably to the extensive maps of Olds et al [47] who used even smaller electrodes and low current levels but unfortunately made no attempt to modify the behaviors elicited.

The largest effort to discredit the specificity view included a series of studies in search of dissimilarities between behavior elicited by ESLH and behavior caused by deprivation of food or water. For example, Valenstein and his colleagues found that rats displaying stimulation-bound eating of one kind of food would not readily switch to another food when the first food was removed, though the second was the familiar home cage chow [48]. They and many others [49] reasoned that food-deprived rats should eat the chow in this situation. In the same study [48] the rats would not readily switch from eating standard laboratory pellets to eating powdered chow after removal of the pellets. Again, "these animals certainly did not behave like hungry animals" [50]. However, it was never clear whether the behavior of these stimulation-induced eaters was to be compared to severely food-deprived, to mildly food-deprived or, according to an overlapping systems hypothesis, to food-and-water deprived animals.

There were two features in the study just described that should have weakened its impact in the literature. First, a palatable food had been replaced by less-preferred laboratory pellets in the first situation, and in the second situation, the texture of familiar pellets was changed to powder. Second, water was always available during the competition trials. It should not have been surprising that most of the animals immediately, and all of them eventually, switched to drinking when the preferred food substance was removed. This would be expected of food-and-water deprived animals as well.

In another paper, it was reported that sated rats, which were pretrained under water deprivation to drink from both a water dish and a water bottle and were subsequently exposed to the water bottle alone during ESLH, would not always switch to drinking from the water dish when the bottle was removed during later stimulation tests [51]. Again, however, Valenstein et al failed to emphasize that food was available and that large quantities of it were usually ingested during these later tests. It remained possible that a feeding system had been stimulated simultaneously with a drinking system.

It was further shown that stimulation-induced drinkers preferred a 30% glucose solution to water in a two-choice situation, while the reverse was true for the same animals when they were water deprived [51,52]. However, these animals were called "stimulus-bound

drinkers" rather than "stimulus-bound eaters/drinkers," which others found inappropriate. In fact, rats deprived of food alone or of both food and water preferred a sweet solution to water [39,53]. Moreover the concentration of sucrose required to maintain a consistent feeding bout was found to be related to pulse frequency of ESLH in much the same way as it was known to be related to the level of food deprivation [54,55].

Valenstein and Phillips [56] found that rats reared from birth on a liquid diet alone later displayed stimulus-bound eating of solid food pellets when mature but would not display stimulus-bound eating of the familiar liquid diet despite multiple stimulation sessions in the absence of any other goal objects. Although this was taken as evidence that ESLH could produce a behavior that was topographically similar to, yet fundamentally different from, a deprivation-induced behavior, in some respects the results of this particular study were quite puzzling. One might have asked, for example, why the rats in this study ignored the familiar liquid diet during ESLH when earlier studies describing stimulus-bound behavior had indicated clearly that rats would ingest a variety of liquid foods in response to electrical stimulation [9,12,14,33,44,57].

Moreover, because many researchers had left the impression that it was relatively easy to compel animals to switch from eating to drinking during ESLH [24,27,30,38], there remained the question of why the rats in this study neither drank water nor ate the liquid food when the solid pellets were removed. It may have been relevant that the screening procedure of Valenstein and Phillips required that all animals not displaying stimulation-induced eating of food pellets be discarded even before beginning testing with the liquid diet. It was possible that in doing so they had discarded animals that would have consumed the liquid diet during test sessions, had they been given the opportunity.

Valenstein and his colleagues [24,50,58,59] often concluded that it seemed unnecessary to assume that ESLH reflects the neural substrate for specific regulatory behaviors. They proposed that their nonspecificity hypothesis facilitated a more realistic discussion of stimulation-induced behavior. Because ESLH sometimes produced gnawing, grooming, object carrying, food shuffling, tail preening, and general activity, they argued that it was therefore cumbersome to handle the view that the LH contained neural components directly associated with the motivation to perform all of these behaviors [24]. Likewise, the apparent paradox that animals would turn on stimulation of that same electrode site that elicited hunger or thirst did not demand the additional postulation of an overlapping reinforcement

system [9,60], if one simply assumed that ESLH did not activate hunger or thirst. However, Bergquist [61] felt strongly the opposite way. He found it difficult to conceive of what kind of single organismic state or mood could possibly be commonly related to such a diverse list of behaviors without referring to distinct overlapping systems. Again, there could be no consensus without additional data.

In a further elaboration of his belief that misinterpretations occurred with the view that stimulation-induced behaviors were comparable to the deprivation-induced behaviors, Valenstein [50,58,62] began to emphasize that the behaviors executed by hypothalamically stimulated rats were pre-formed and species-specific. Thus, Valenstein [58] stated that many of the behaviors evoked by hypothalamic stimulation could be better understood by an analysis of the prepotent responses of the species. By itself, this line of reasoning also was unconvincing. However, Valenstein [50,63] went on to make the more influential argument that a variety of species-specific behaviors (including eating or drinking) could be evoked without deprivation by low (presumably stimulating) doses of pentobarbital [64] or non-injurious pain and stress [65-69]. Though this evidence was still indirect, it was important in that it served as a reminder that it was possible for ingestive behavior to emerge from recognized forms of disorganized behavioral activation. However, it had not been disputed that both specific and nonspecific sources of eating existed. Most investigators remained opposed based on the functional reputation of the hypothalamus, the lack of definitive conflicting data, and the specificity of chemical stimulation, which appeared better established than electrical stimulation [61,70,71]. Nevertheless, additional converts entered Valenstein's camp following the demonstration by Antelman and Szechman that tail pinching caused eating and gnawing in some animals [72]. Then Koob et al [73] reported that animals subjected to tail pinching learned to turn into that arm of a T-maze in which there was wood to gnaw, an effect that partially paralleled the well-known work of Coons et al with ESLH [10]. Though the analogous experiment with feeding was never conducted, these data gave Valenstein's view sufficient plausibility that even some of the ardent proponents of the specificity interpretation were no longer so certain, and the controversy seemed to stalemate.

TOWARD RESOLUTION

As noted in the previous section, the key to Valenstein's position was the idea, adapted from Glickman and Schiff [74], that the actual display of a behavior during ESLH is reinforcing, and for this reason it is re-

peated increasingly over subsequent stimulation sessions. For example, as an animal is permitted to eat during ESLH, the eating response gradually strengthens, because eating during activation is reinforcing. It follows that stimuli associated with eating (such as a lever or a goal box) would acquire secondary reinforcement properties (and that gastric activity would increase in anticipation of an eating reaction). A similar proposal was later expressed by Herrnstein [75] to explain the development of "displacement" or related behaviors for which the reinforcer is not obvious. Therefore, to begin to build a bridge between Valenstein's work and the traditional view of ESLH, it was necessary to study the behavior of animals *before* they had the opportunity to eat during stimulation. In all previous experiments, the behavior of stimulation-bound eaters was examined only after they were screened for eating during stimulation (and usually following extensive eating experience during ESLH).

The following experiment was conducted to address this conditioning issue directly [1]: Before any screening, rats were allowed access to familiar food-related odors (but not the food itself) through a small opening at the end of one arm of a T-shaped enclosure. A control odor unrelated to food was present at the other arm. Upon placing their snouts near either opening, the animals activated one of two photocell circuits, which recorded responses and time spent investigating each odor source. It is well known, of course, that food-deprived rats readily approach stimuli related to food [76-80]. Moreover, food odors are pleasant to food-deprived people but become neutral or unpleasant with satiety [81]. The question raised was whether the food odors would be attractive during stimulation to these animals, which had never been given the opportunity to eat during ESLH and thus would not have experienced the putative reinforcement derived from eating during ESLH.

As expected, when the rats were simply food deprived, they appeared highly attracted to the food odors, spending a large percentage of time investigating the region of the enclosure from which the odors emanated and little time at the control region. Also as expected, when the rats were not food deprived and were not subjected to ESLH, they spent little time at either end of the enclosure. However, in the critical test, when the rats received ESLH but were not food deprived, they became very active but appeared unattracted to the food odors, spending little time investigating the food odor region of the enclosure. This same stimulation induced vigorous eating in later screening tests. Only following extensive stimulation-bound feeding experience did it induce great attraction for the food odors. A control condition ruled out the possibility that ESLH excluded

orientation to food odors by, for example, inducing behavior incompatible with odor-investigating responses. When animals received ESLH in the prescreening test while also food deprived, they still appeared highly attracted to the food odors.

Thus, if testing is done before stimulation-induced eating is allowed, food deprivation, but not ESLH alone, yields approach and investigation of food odors. These data are most consonant with the view that ESLH is a nondirected, but directable, activator of behavior [82,94]. Oral manipulation of materials encountered in the environment may reduce the level of cerebral activation by interrupting the long bouts of forward locomotion, rearing reactions, head movements, and postural adjustments forced on the animal by ESLH. If food, for example, is available, eating is channeled by "feedback reinforcement." Eventually with experience the condition caused by ESLH becomes difficult to distinguish from the condition caused by food deprivation (perhaps even from the animal's perspective; see 1,95).

What indication is there that various oral behaviors have a common type of deactivating effect in the brain? Vanderwolf and his colleagues [83-86] have shown in electrophysiological analyses that behavioral activation, including the type produced by ESLH in the absence of goal objects (so-called type-1 behaviors such as forward locomotion, head movements, rearing, turning, and postural adjustments), is associated with a major source of cerebral activation (a noncholinergic, possibly serotonergic, ascending input). When an animal engages in so-called type-2 behavior (including chewing, licking, grooming, or gnawing) the type-1 source of cerebral activation is inhibited. What remains, or what replaces the type-1 source, is a second source (involving a cholinergic input), which appears to be identical to that associated with complete immobility (a behavior that presumably is impossible to achieve during ESLH). This is not meant to imply that a forcibly-induced uninterrupted train of type-1 cerebral activation necessarily is aversive or that type-2 cerebral activation is reinforcing. However, as a step toward understanding stimulation-bound eating, it is important to identify neural correlates shared by the behaviors initially induced by ESLH and then to compare these with neural correlates shared by eating and other behaviors likely to emerge with chronic stimulation.

CONCLUSION

It has been difficult for many to accept the possibility that ESLH does not (at least at first) simulate neural conditions present during nutritional or hydrational

deficits. This difficulty stems in part from a misunderstanding about the concept of homeostasis. A long-established working view in the field of food and fluid intake has been that behavior and physiology are tightly regulated, perhaps by some shared "homeostatic" mechanism in the brain. It was believed that eating, even excessive eating, ought to reflect a change in this mechanism. However, it is critical to realize that behavior can fluctuate relatively independent of homeostatic processes, especially those that protect the brain. Homeostasis is the label Cannon gave to Bernard's physiological processes that evolved to keep the internal environment stabilized against the many forces of nonphysiological equilibrium that would otherwise destroy the fragile cells therein [87]. Homeostasis can correct for behavioral fluctuations, but neither Bernard nor Cannon emphasized that behavior is elicited directly by deviations in the internal environment. Indeed, their point was that homeostatic mechanisms evolved to free the organism from moment-to-moment behavioral maintenance of energy or fluid balance. Obvious examples of the adaptive features of this separation include learned avoidance of a dangerous water hole, and weight regulation despite socially facilitated excessive eating. It is helpful to keep this relationship in mind when developing animal models of feeding disorders. Disorders characterized by aberrations in eating behavior should be distinguished from those in which the primary problem is related to physiological mechanisms of weight regulation [96,97]. ESLH may be a useful method for studying some forms of binge eating, because excessive eating and learning are the predominant features. Moreover, the stimulus, the environment, and the history of the animal can be precisely controlled. However, any animal model is an experimental compromise [88]. It is far from clear how well ESLH resembles some of the conditions underlying eating disorders in people [89-92,98].

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