Food- and ICS-reinforced operant behavior following VMH lesions in conscious rats

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Within-subjects temporal analyses of changes in operant behavior maintained by lateral hypothalamic (LH) self-stimulation and food reward were made following bilateral electrolytic destruction of the ventromedial hypothalamus (VMH) of conscious female rats. LH self-stimulation rates increased immediately following lesioning; however, 24 h postlesion, responding returned to or below prelesion levels. Responding for food did not increase immediately following VMH destruction, but increments occurred 1½ h postlesion. Responding for food reward over 3 days postlesion remained significantly higher than prelesion control data. Significantly increased food intake and body weights were also present 24 h postlesion. Body weights continued to increase over the 30-day posttesting period. It was concluded that increases in ICS leverpressing following VMH destruction may result from possible analgesic or positive affective properties attributed to ICS and that the delayed increase in food leverpressing reflects the rat's increased hunger motivation.

Many physiological and behavioral investigations of food intake are based on the assumption that there is a specific neural system underlying feeding behavior, and that this system can be studied more or less independently of other homeostatic systems of the organism. More specifically, it has been shown that food intake is controlled, at least in part, by the interaction of excitatory and inhibitory hypothalamic mechanisms. Investigators have generally assigned an inhibitory role to the ventromedial hypothalamus (VMH) with excitatory functions assigned to the lateral hypothalamus (LH).

Electrical stimulation of the LH induces feeding in fully sated animals (Delgado & Anand, 1953; Larsson, 1954; Wyrwicka & Dobrzecka, 1960), while stimulation of the VMH of hungry animals decreases food intake (Anand & Dua, 1955). Lesions of the VMH cause hyperphagia (excessive overeating), whereas lesions of the LH induce aphagia and eventually death unless force-feeding procedures are adopted (Anand & Brobeck, 1951; Brobeck, Tepperman, & Long, 1943; Teitlebaum & Epstein, 1962).

Hoebel and Teitlebaum (1962) and Margules and Olds (1962) reported that electrodes placed in the LH that induced stimulus-bound feeding also supported high rates of responding for intracranial self-stimulation (ICS). Hypothalamic sites that regulate feeding thus seem to exert a corresponding control over LH self-stimulation. Changes in hunger motivation have been correlated with the rewarding effects of hypothalamic ICS. Increases in both hypothalamic self-stimulation and feeding occur following VMH destruction or anesthetization (Hoebel & Teitlebaum, 1962). Increases in LH self-stimulation rates also occur during periods of food deprivation (Margules & Olds, 1962; Mount & Hoebel, 1967; Wilkinson & Peele, 1962), whereas decreases follow gastric distension (Hoebel, 1968; Hoebel & Thompson, 1969; MacNeil, 1974). Hoebel (1968) found these decreases in self-stimulation rates regardless of whether the distension was produced by intragastric feeding or by the inflation of a gastric balloon. Electrode preferences have also been shown to shift with shifts in drive states (Gallistel & Beagley, 1971).

Obesity has been produced experimentally by prolonged periods of experimenter-administered LH stimulation in the presence of food (Hoebel & Thompson, 1969; Steinbaum & Miller, 1965). Hoebel and Thompson (1969) also demonstrated that as stimulation-induced obesity progressed, animal disgust reactions increased (such as rubbing the chin on the cage floor) as well as the rate of response to escape from LH stimulation. These experiments suggest that neuronal activity in the LH feeding system becomes aversive in rats that are overfed or overweight. Thus, long-term factors (e.g., obesity) as well as short-term factors (e.g., hours of deprivation) are capable of altering the properties of LH stimulation along a continuum from reward to aversion.

The above attempts have used self-stimulation and leverpressing operants to investigate the consequences of hypothalamic destruction in anesthetized rats that

were permitted several days of postoperative recovery prior to behavioral testing. However, when the time course of appetitive or self-stimulation behaviors immediately following VMH destruction are of interest, alternative procedures must be used. The present experiment attempted to overcome these difficulties by producing VMH lesions in conscious rats.

If VMH hyperphagia is to be explained by increased activity in the LH feeding-reward system, then changes in both feeding and LH self-stimulation behaviors should follow the same postlesion time course. Unfortunately, conflicting outcomes have appeared in the literature regarding the time course changes in feeding behavior following VMH destruction. Hoebel (1965) was the first to note an increase in both feeding and LH self-stimulation immediately (10-20 min) following VMH destruction. Hoebel (1968) suggested that regardless of the means of VMH destruction or anesthetization, changes in feeding and LH self-stimulation behaviors closely parallel each other. Electrical stimulation of sites other than the LH (i.e., septum) were also disinhibited following VMH destruction, but to a lesser degree (Hoebel, 1969), thus giving anatomical specificity to his findings. In addition, Hoebel (1969) found that animals trained to self-stimulate at both an LH site and a septal site switched their preference from hypothalamic to septal self-stimulation after tube feeding, indicating that postingestional stimuli inhibit lateral hypothalamic reward and that all sites are not equally inhibited.

Hoebel's findings regarding the immediacy of food intake following VMH destruction have not been supported by the recent data of Peters and Sensenig (1974). These investigators electrolytically destroyed the VMH in rats via chronically implanted electrodes. Operant responding for food reward (FR-5) was measured 0, 2, or 4 h postlesion. Performance rates significantly increased 2 h postlesion. Destruction of the VMH, however, had no effect on performance immediately following the lesion.

Van Sommers and Teitlebaum (1974), using self-stimulation of the VMH as an index of lesion expression, showed that damage to the VMH produces an initial loss of function, which then progressively increases for several hours after the lesion. These investigators also found that LH lesions produced feeding behavior deficits which extended over a period of 4 to 8 h, with the rapidity of the onset being determined by the size of the lesion. Both these phenomena were interpreted as evidence for a local progressive deterioration of brain tissue following the production of a lesion.

Ferguson and Keesey (1971) have obtained LH self-stimulation rate increases which are more in line with the time course suggested by Peters & Sensenig (1974). These investigators found that both feeding and LH self-stimulation increased following VMH destruction. Increases in food intake continued for several weeks postlesion. Self-stimulation rates, however, returned to or below control levels 24 h postlesion. Furthermore, the degree of hyperphagia and rate of LH self-stimulation were found to be negatively correlated, a finding inconsistent with satiety theory.

The purpose of this research was to provide a within-subjects temporal analysis of the changes in operant behavior maintained by either intracranial self-stimulation or food reward following destruction of the VMH in conscious rats.

METHOD

Subjects

Thirty-three Long-Evans female hooded rats obtained from Blue Spruce Farms, Inc., and weighing approximately 250 g at the time of surgery, were used. The rats were individually housed in conventional rat cages under constant illumination and were maintained under ad-lib food and water conditions except where noted below.

Surgery

Rats were deprived of food approximately 15 h before surgery to reduce bronchial congestion. Under sodium pentobarbital anesthesia (42 mg/kg), each rat was prepared with three chronic indwelling bipolar stainless steel electrodes using standard stereotaxic surgery techniques. The electrodes were obtained commercially (Plastic Products Company, Roanoke, Va., No. MS-303-018-312-SS-008). Each twisted wire electrode was insulated except for an exposed .5-mm conical tip, and the poles were separated by the thickness of the insulation. Two bipolar electrodes were bilaterally implanted in the VMH. The coordinates for these implants were: AP = 5.8, H = −3.5, L = 0.7 (de Groot, 1972). In addition, each subject had a third electrode implanted in the median forebrain bundle (MFB), AP = 5.8, H = −2.0, L = 1.8 (de Groot, 1972). The three electrodes were secured to the rat's skull with aneuroplastic cement and one anchor screw. Food and water were not available until the morning following surgery.

Apparatus

Eight clear sheets of Plexiglas were used to make two 14 × 9½ × 13 cm operant chambers. The top and bottom of each chamber were open. Associated with the first chamber, or "lesion chamber," were two electrode leads which were attached to the rat's VMH electrodes. The other end of the electrode leads were attached to a Lehigh Valley overhead swivel which allowed the animal unrestricted movement about the chamber. The swivel, in turn, was connected to a Heathkit power supply via a double-pole double-throw switch.

The second or "operant chamber" had one electrode lead which was attached to the rat's stimulating electrode. This lead was connected to an overhead commutator (Waldon & Phillips, 1972), which in turn was connectd to an ac power supply. The operant chamber contained a water bottle and a pellet dispenser attached to one of the outside walls of the chamber. The drinking tube and food hopper were situated 6.5 cm apart on the inside of the same wall and 5 cm above the floor. Two levers were attached to one of the adjoining walls, 5 cm above the floor. One lever dispensed 45-mg Noyes food pellets (standard formula) when depressed. The adjacent lever produced a train in intracranial stimulation when depressed. Above the operant chamber was a 7½-W light bulb which systematically changed from a "high" to a "low" intensity. Depression of the food lever resulted in

food reward only when the bulb intensity was low. Depression of the ICS lever under low illumination resulted in no ICS reward. Conversely, ICS was obtainable on the ICS lever only under high illumination.

When ICS was available, each leverpress resulted in an intracranial stimulus of 60-Hz sine waves with a train duration of 200-msec. All responses on the ICS lever were recorded on an electromechanical counter. Responses made during the 200-msec stimulus duration interval were not reinforced. The stimulus intensity was varied for individual subjects but was always between 10 and 60 μA. Peak-to-peak voltage levels were monitored on an oscilloscope. Leverpressing responses on the food lever as well as the number of rewards were also recorded on electromechanical counters. Responses on the "inappropriate" lever were also recorded.

Prelesion Training

Following surgery, 5 days were allowed for postoperative recovery. Each rat was initially shaped to press the right-hand lever for ICS reward. Current intensity was initially set at 25 μA and was increased if the rat was inattentive to the lever. Most rats were shaped during this first training session. However, if a rat failed to press for ICS during this session, the above procedures were continued for several days. If leverpressing was not established at the end of this period, the rat was discarded from the experiment.

After the ICS leverpressing response was established (Day 1), each rat was allowed to leverpress for three 15-min periods a day for 4 days. During this time, current intensity was set at a level such that each rat responded at less than its maximum rate to avoid ceiling effects. After training, on Day 5, each rat was placed on a 23-h food deprivation schedule. During Days 6-10, each rat was permitted to leverpress for ICS for 15 min immediately prior to 1-h access to food in its home cage. The above procedures were used to obtain rates of responding for ICS when the rats were sated and subsequently deprived of food. All rats were also given 20 45-mg Noyes pellets prior to food access on Days 6-10 to familiarize them with this novel food substance.

On Day 11, each rat was trained to press the left lever to obtain food reward. The reinforcement schedule was changed to a FR 5:1 on the following day. All rats were run on this schedule for 15 min on Days 12-16. After testing, on Day 16, all rats were returned to ad-lib access to food.

On Days 17-19, each rat was tested four times daily, with each 15-min session no less than 1 h apart. Food and ICS reinforcement were alternated between each of these sessions such that rats received either Food, ICS, Food, ICS or ICS, Food, ICS, Food. This procedure was used to obtain rates of responding for both ICS and food reward when the rat was again sated.

To this point, whenever a rat was placed in the operant chamber, only one lever was present with the appropriate light stimulus. From Day 20 until the end of the experiment, the rat was confronted with a discrimination task in which it was required to discriminate between two stimulus light intensities and the appropriate reinforcement lever. High illumination was always associated with ICS reinforcement on the right lever, and low illumination was always associated with food reward on the left lever. Responding on the inappropriate lever was never reinforced. Light intensities were changed every 5 min. The light intensity chosen to begin any particular testing session was determined by alternating them daily. All rats were tested in this two-lever situation 3 h per day for 5 days. Immediately prior to testing on each of these days, each rat was attached to the two VMH leads, placed in the lesion chamber, and allowed to roam freely for approximately 1 min. This procedure was used to habituate the rat to the electrode leads before the day the lesions were actually produced.

Lesion Procedure and Postlesion Testing

Upon placement in the lesion chamber on Day 25, each rat was electrolytically lesioned via one of the chronically implanted VMH electrodes (2 mA for 20 sec). Maximal lesion current was obtained

by manually adjusting the rise and decay time for each lesion so as to avoid instantaneous current onset and offset. The contralateral lesion was produced immediately thereafter, using the same current parameters by throwing the double-pole double-throw switch. Animals were able to move freely about the chamber during the lesioning process. No adverse behavioral effects were witnessed during neural destruction. The only noticeable behavior correlating with lesion production was occasional nose rubbing by some rats with both forepaws. The rats were immediately taken to the operant chamber and were allowed to respond in the two-lever situation for 3 h. On Days 26-28, each rat was again tested for 3 h in the two-lever situation. One Days 20-28, the number of leverpresses for each lever was recorded for each successive 5-min time period. This provided information regarding the number of responses on both the appropriate and inappropriate levers. In addition, home-cage food intake was recorded over this same time period.

Following Day 28, each rat was given ad-lib access to food and water for a period of 30 days to assess weight gains.

Histology

Following behavioral testing, each rat was given a lethal dose of sodium pentobarbital and perfused intracardially with physiological saline followed by 10% Formalin. The brains were removed from the skull and placed in 10% Formalin for no less than 24 h. Brains were then frozen, sectioned (150 microns), and photographically enlarged to assess the extent and location of tissue destruction.

RESULTS

Eighteen of the 33 operated rats failed to complete behavioral testing for one of the following reasons: failure to self-stimulate (n = 2), loss of electrode assembly (n = 13), or sickness (n = 3). Also excluded from the data analysis were 2 rats exhibiting a distinct lack of postlesion hyperphagia. Data are reported for the remaining 13 LH implanted rats that finished behavioral testing.

ICS Responding

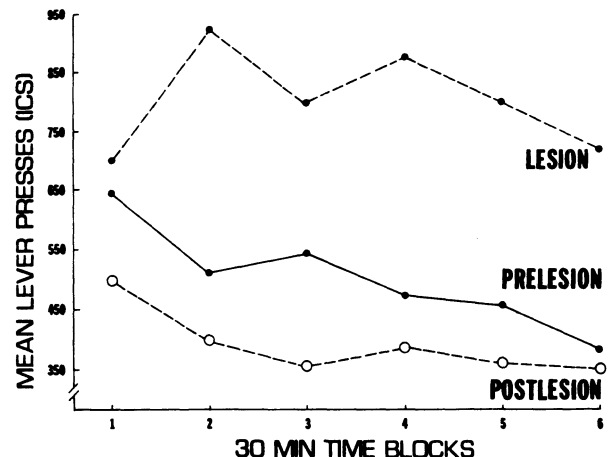Figure 1 represents the mean number of ICS leverpresses collapsed over 30-min intervals for the pre-

Figure 1. Mean number of ICS leverpresses (N = 13) over prelesion (3 days), lesion (1 day), and postlesion (3 days) testing days collapsed into 30-min time blocks.

and postlesion days as well as performance on the day of the lesion.

It can be seen that performance on the day of the lesion was similar to prelesion performance for the first 30-min interval, but ICS responding increased substantially thereafter and remained at this higher level throughout the testing session.

An analysis of variance (ANOVA) between prelesion, lesion, and postlesion performance indicated that both the main effects of treatment and time interval [$F(2,24) = 12.5$, $p < .01$, and $F(5,60) = 2.39$, $p < .05$, respectively] as well as their interaction [$F(10,120) = 2.36$, $p < .05$] were significant.

A second ANOVA, comparing only prelesion and lesion day performance rates, revealed both a significant treatment main effect [$F(1,12) = 13.72$, $p < .01$] and a significant Treatment by Time Interval interaction [$F(5,60) = 2.86$, $p < .05$]. This higher level of ICS responding was not maintained during the subsequent three postlesion testing days, but rather dropped to a level slightly below that of prelesion performance. Analysis of the pre- and postlesion data indicated that this difference was not significant.

Food Responding

Figure 2 presents the mean number of food lever responses collapsed over 30-min intervals for the 3 pre- and postlesion days as well as performance on the day of the lesion. An ANOVA of the food responding data revealed neither a significant treatment or time interval main effect, but did reveal a significant Treatment by Time Interval interaction [$F(10,20) = 2.83$, $p < .01$].

A second ANOVA of the performance on the lesion day with prelesion data revealed a nonsignifi-

cant treatment main effect. These results support the findings of other investigators (Peters & Sensenig, 1974) who report no effect of VMH lesions on operant responding for food reward up to 2 h postlesion. It is evident in Figure 2, however, that responding for food did increase during the third hour postlesion but did not result in a significant Treatment by Time Interval interaction.

It is important to note the contrasting lesion day performance differences between ICS and food-maintained operant responding. It is evident that VMH lesions had a more immediate and profound impact on lesion day ICS responding than on lesion day food responding.

Postlesion food response rates remained significantly higher than prelesion rates [$F(1,12) = 16.49$, $p < .01$], which again was in marked contrast to postlesion ICS responding.

Food Intake (21 h) and Body Weights

VMH lesions produced a significant increase in home-cage food consumption [$t(12) = -40.9$, $p < .001$] across the 7-day behavioral testing period. Consumption jumped from a prelesion average of 19 g per day to a postlesion average of 31 g per day.

A comparison of the postlesion body-weight increases across the 30-day posttesting period were also significant [$t(12) = -11.3$, $p < .001$]. Rat weight gains increased from a 288-g average on the day immediately preceding VMH destruction to a 383-g average recorded on the 30th posttesting day.

Histology

The atlases of de Groot (1972) and König and Klippel (1963) were consulted in establishing the locus of the bipolar electrodes. LH electrode tips were located in the lateral hypothalamic-medial forebrain bundle area within the approximate anterior-posterior limits of the VMH nucleus.

Most rats sustained relatively small and, in most instances, spherical lesions of the VMH and surrounding tissue. Representative photographs are presented in Figure 3 contrasting the VMH lesions of two rats, one exhibiting hyperphagia and obesity and one not exhibiting these behavioral objectives.

Lesions ranged between the following de Groot (1972) coordinates: AP = 6.8 to 5.2; H = -2.0 to -4.5; L = 0 to 1.5. Frequently, the lesions extended to the base of the brain, and dorsally the dorsal medial hypothalamus and fornix were destroyed or interrupted. Only on one occasion did a lesion extend to the mamillothalamic tract.

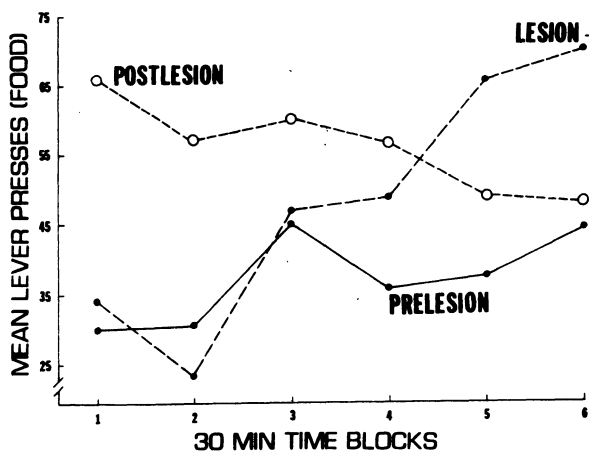Figure 2. Mean number of food leverpresses (N = 13) over prelesion (3 days), lesion (1 day), and postlesion (3 days) testing days collapsed into 30-min time blocks.

DISCUSSION

Previous reports (Hoebel, 1965, 1968, 1969; Hoebel & Teitlebaum, 1962) of increased operant be-
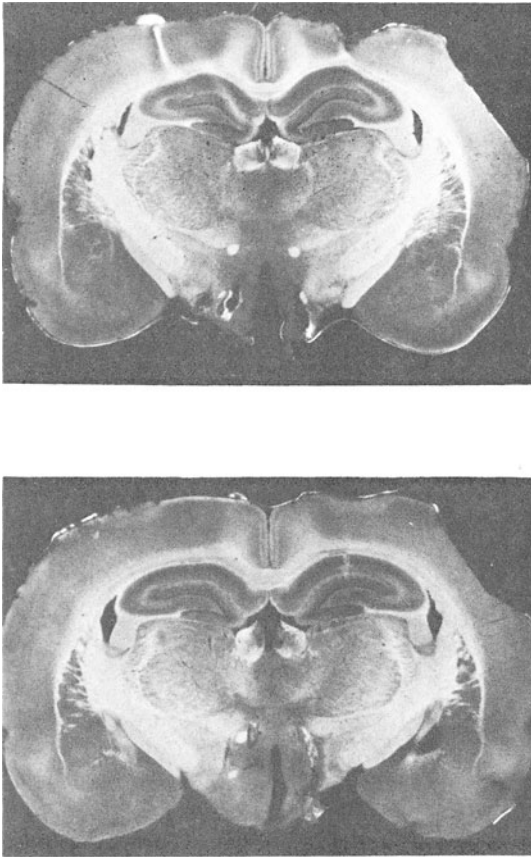
Figure 3. Representative photographs of lesion placements from a hyperphagic obese rat (above) and from a rat that did not display hyperphagia and obesity (below). Stimulation electrode tracks are also visible left of the VMH lesion (above) and left of the ventral midline (below).

havior maintained by ICS or food reward following bilateral destruction of the VMH in unanesthetized rats were substantiated. However, the temporal analysis of these behavioral changes requires some clarification.

Destruction of the VMH in the present experiment did not lead to immediate increases (less than 20 min) in ICS leverpressing, as some investigators have reported (Hoebel, 1965, 1968, 1969; Hoebel & Teitlebaum, 1962). Although lesion day self-stimulation rates never dropped below prelesion control data, it was not until the second 30-min time block that obvious increases in ICS leverpressing appeared. This increased rate of responding was then maintained throughout the remainder of the testing session. However, the increase in ICS responding occurred more rapidly than that reported by Ferguson and Keesey (1971), who found depressed response rates continuing for 1½-2 h postlesion.

Some of these postlesion ICS performance differences may be explained by differences in experimental procedures, such as lesion current parameters, ICS waveform differences, etc. An additional explanation for the absence of the immediate ICS performance increases found by Ferguson and Keesey (1971) and in the present experiment may be explained by the possible noxious aftereffects of the lesioning process. During and immediately after neural destruction, animals may be fearful, stunned, or in some way become disoriented.

This explanation, however, does not appear to be consistent with the present behavioral results. If it is assumed that the delay in ICS performance is a function of neural disruption caused by the lesioning process, one might verify this hypothesis by looking at the number of erroneous or inappropriate barpresses in the two-lever situation on the day of lesioning.

The mean ICS leverpressing rate for all subjects during each of the 18 5-min ICS test periods on the day of lesioning was 270. This compares to a mean leverpressing rate of 7.8 on the inappropriate lever during the same test intervals. If the lesioning process leads to subject disorientation, it is not apparent in the ICS leverpressing data. Unfortunately, many possible effects of the central nervous system (CNS) destruction in conscious animals are as yet unidentified.

The present experiment does not support the contention that increased LH self-stimulation is the result of enhanced sensitivity in the LH feeding-reward system (Hoebel, 1965, 1969; Hoebel & Teitlebaum, 1962; Hoebel & Thompson, 1969). If this hypothesis is tenable, one would expect that changes in responding for food and LH self-stimulation would follow the same postlesion time course. After comparing Figures 1 and 2, one finds this is clearly not the case. In addition, statistical analyses failed to reveal any differences between prelesion and postlesion ICS leverpressing rates, while postlesion food leverpressing rates were found to be significantly higher than prelesion food leverpressing rates. The data suggests a negative covariation between ICS and food responding and not the covariance originally assumed by Hoebel (1969).

What then causes the transient increase in postlesion self-stimulation rates? Ferguson and Keesey (1971) have suggested that this increase reflects an artifact of increased generalized activity. Rats in the present experiment gave no consistent implication of increased activity. In addition, if leverpressing for stimulation does increase after lesioning as an activity artifact, the leverpressing rates for food should also reflect these same temporal increases, but they do not.

A more tenable hypothesis to account for this increase can be derived from the inherent effects of ICS itself. There is general agreement that electrical stimulation of various CNS structures modifies,

masks, or attenuates pain and/or fear states (Buckwalter, Gibson, Reid, & Porter, 1967; Miller, Reid, & Porter, 1967; Yunger, Harvey, & Lorens, 1973). Cox and Valenstein (1965) have also capitalized on this "advantage" of ICS and have reported a significant correlation between the rewarding and analgesic effects of lateral hypothalamic self-stimulation.

More recently, other experimental paradigms have been used to demonstrate the positive affectiveness of ICS. Gordon and Baum (1971) have used positive ICS as a way of increasing the efficacy of extinguishing avoidance behavior through response prevention (flooding). Brief, periodic, positive ICS was used as an extraneous stimulus and was presented to a fearful rat after avoidance behavior had been established through the use of footshock. The availability of positive ICS during response prevention virtually eliminated avoidance behavior.

Thus, it is hypothesized that the increases in ICS responding found up to 3 h following VMH destruction is a result of the analgesic and/or positive affective properties of ICS and not a result of an increase in random activity, disorientation, or neural sensitivity.

On days subsequent to lesioning, the self-stimulation rates tend to be lower than rates prior to lesioning. However, statistical analyses failed to reveal any differences between prelesion and postlesion days of testing. These curves also show a decreasing performance trend which perhaps reflects the effects of the rigorous 3-h testing sessions, or the extension of the VMH lesion necrosis encroaching upon the lateral hypothalamic area (Van Sommers & Teitlebaum, 1974).

Appetitive responding also showed an increase during the 3-h period following VMH destruction. Note, however, that the postlesion performance is delayed before any increase is obtained during the last half of the testing session. Again, this delay in responding could not have been caused by the previously hypothesized debilitating effects of the lesion process, since response rates on the food lever were significantly above the response rates on the inappropriate lever over the lesion day test session [t(233) = 5.98, p < .001].

Although the increase in appetitive response rate was not statistically significant, the trend was certainly in the predicted direction. Lack of significance was attributed to the presence of a negative contrast effect obtained between the alternate sessions of responding for food and ICS. This hypothesis is highly tenable in light of the above suggestion that ICS exhibits strong analgesic properties following VMH destruction. These results are compatible with Peters and Sensenig's (1974) report that operant responding for food (FR-5) is essentially unchanged immediately following VMH destruction.

VMH lesions also increased the food leverpressing performance during the 3 days of postlesion testing. This outcome is consistent with recently reported data that indicates that rats with VMH lesions overeat and become obese because the lesion increases the rat's hunger motivation (Kent & Peters, 1973; Peters & Reich, 1973; Peters & Sensenig, 1974; Wampler, 1973).

This rise in food leverpressing is also associated with a significant increase in hyperphagia and continually increasing weight gain. No support can be given to Hoebel and Thompson's (1969) contention that weight gain following stimulation-motivated hyperphagia is associated with increased LH aversion resulting in a decrease in LH self-stimulation rates.

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