1973

Effects of Ventromedial Hypothalamic Lesions on Food-Reinforced Fixed Ratio Responding

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EFFECTS OF VENTROMEDIAL HYPOTHALAMIC LESIONS ON FOOD-REINFORCED FIXED RATIO RESPONDING

by

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A thesis submitted to the Faculty of The Rockefeller University
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

April 9, 1973

The Rockefeller University
New York

PREFACE

The experiments described here began as a laboratory project in a Physiological Psychology course at The Rockefeller University. In that phase, as well as in Experiments I and V, Harry Kissileff was advisor, collaborator, and incisive critic. His help then and his advice since then are gratefully acknowledged. I am also grateful for the advice of Ralph Norgren, who has given help and encouragement during the latter parts of the project. Carl Pfaffmann has watched over the entire project and provided laboratory space and resources. I thank him for these direct forms of assistance, but especially for the strong, interdisciplinary program of behavioral science he has brought to The Rockefeller.

I am grateful to Emil Becker for technical assistance during Experiments I and V, to Rosanne Blair for typing and retyping, to Robert Schor for expert diagnosis of computer problems, and to my wife Pat for gentling the rats and other tasks. The facilities at Rockefeller are always available to a student and their use is always appreciated. The Electronics and Computer Laboratory and the histologists in the Pfaffman Laboratory were most generous with their indispensible services.

ABSTRACT

Previous research has shown that rats with experimental lesions in the ventromedial area of the hypothalamus become obese due to hyperphagia. This striking effect on ad libitum food intake is sometimes accompanied by an increase and sometimes by a decrease in other measures of propensity to eat such as food-rewarded lever pressing. The current experiments attempt to discover the conditions under which these opposite effects on "food-motivated" behavior occur.

Rats with ventromedial lesions made with steel electrodes showed a decrease relative to controls in lever pressing on a fixed ratio schedule. This effect was also seen in rats which had extensive pretraining on the fixed ratio task. Nonpretrained rats with lesions made with platinum electrodes showed a smaller, more variable deficit. However, rats with both platinum lesions and extended pretraining pressed reliably more than controls on schedules up to fixed ratio 256. The type of metal used in the lesion-producing electrode and the degree of pretraining are critical variables influencing the fixed ratio performance of rats with ventromedial hypothalamic lesions. The importance of these variables will necessitate a reinterpretation of the role of the hypothalamus in operant and consumatory behavior.

In further experiments, procaine anesthetization was found to also have disparate effects on eating and lever pressing. Eating was elicited within two minutes. Lever pressing on continuous reinforcement was less readily elicited and lever pressing on fixed ratio 64 appeared to be disrupted by a nonspecific increase in activity.

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Chapter 1. INTRODUCTION

In the early 1940's a series of reports appeared in the medical literature which marked a turning point in the study of food intake. Hetherington and Ranson (1942) discovered that lesions produced by direct current in the ventromedial part of the hypothalamus caused extreme obesity in albino rats. The principal mechanism of this effect was quickly elucidated by Brobeck, Tepperman and Long (1943), who established that the rats became obese for the simple reason that they were chronic overeaters. Prior to this time, most investigators had assumed that "hunger" had its origin in the gut and had concentrated their efforts on chemical and neural signals originating in the stomach. Though interest in peripheral mechanisms has continued, the hypothalamus has become a focal point of research on the control of food intake.

The "hypothalamic hyperphagia" which these researchers discovered is a dramatic effect. Immediately after recovery from the stereotaxic surgery usually required to produce the lesion, the animal commonly begins to consume large quantities of food. It continues to overeat and gain weight for several weeks, until its body weight and food intake asympote at a stable level. The stage of rapid weight gain is known as the "dynamic" phase of the hyperphagia and the stage of asympote is known as the obese or "static" phase (Brobeck et al., 1943). Unlike animals with damage to many other parts of the brain, hypothalamic hyperphagic rats do not show physiological or behavioral recovery of function; if an animal in the static phase is starved until its weight drops to the level of control rats and then given ad lib food again, a new dynamic phase occurs and the animal quickly regains the lost weight (Brooks and Lambert, 1946; Hoebel and Teitelbaum, 1966). The fact that no other nervous tissue is capable of compensating for the damage to the ventromedial hypothalamic area indicates that the area is of crucial importance. Ability to maintain a constant weight, however, is not lost in the hyperphagic rat as evidenced by the static phase.

An important step in understanding the behavior of hypothalamic hyperphagic animals was taken by Miller, Bailey and Stevenson (1950), who sought to determine "Whether the marked increase in food intake...is accompanied by increased performance in a variety of behavioral tasks

motivated by hunger." Using a battery of tests which required rats to work or to overcome "resistance" to obtain food, they found that hyperphagic rats performed poorly in comparison with controls on all the measures. This paradox of "decreased hunger but increased food intake" (Millet et al., 1950) has had a great influence on current concepts of motivation; in particular it has stood as a major argument against the idea of a unitary hunger drive (Miller, 1957; Hinde, 1970).

The experiments which I have performed are concerned with this apparent contradiction between decreased instrumental food-getting behavior and increased food intake. Instead of using the term "hunger," however, I have reformulated the problem so that it is more directly testable. I shall attempt to determine whether the hypothalamic hyperphagic rat behaves as if it were food-deprived and, if not, whether the differences can be accounted for by the experimental conditions. In order to compare deprivation with ventromedial lesions, it is necessary to review the behavior of animals under each condition.

Behavioral Effects of Food Deprivation

In a normal, unoperated rat overeating can be easily induced by depriving it of food for several hours to several days, providing that the distensibility of the stomach is maintained (Hamilton, 1969). Interpretation of such an experiment is not straightforward, however, since the animal mobilizes stored calories and loses weight. Numberous studies have attempted to distinguish the effects of the duration of deprivation from the effects of the accompanying weight loss. The consensus is that performance on a task which is rewarded with food correlates better with weight loss than with length of deprivation *per se* (Bolles, 1967; Weinstock, 1972). Since an endotherm cannot endure a substantial interval of food deprivation without losing weight, the distinction may not always be essential. When using the term "deprivation" in this regard, I will not be excluding the possibility that weight loss is the actual causal agent.

A large number of measures have been found to vary as a function of deprivation (or weight loss). Since the measures may not always

food. Electrified grid crossing, lid lifting, pulling on a harness, and speed of running down a long alley correlate postively with length of food deprivation (reviewed in Miller et al., 1950).

"Activity" has been extensively studied as a function of deprivation. On a 23-hour deprivation cycle (one hour/day access to food) "activity" as measured by running wheels and stabilimeter cages increases during the period preceding feeding (Bolles, 1963; Bolles and Stokes, 1965; Hetu, 1971). Running wheel revolutions/hour also increase when food is removed (Moskowitz, 1959; Treichler and Hall, 1962), but sensory deprivation abolishes the increase (Campbell and Sheffiedl, 1953). "Activity" is a difficult variable to study, since intercorrelations between various measures of "activity" are low (Tapp, 1969).

Six of these measures are used in the present experiments. Number of presses per session is the principal variable. Data are also taken on ad lib consumption, latency to eat, size of the first meal, post-reinforcement pause duration, and quinine tolerance. Since each of these measures has been shown to be sensitive to deprivation, no effort is made to replicate the literature reports concerning them. The work reported here concentrates on comparing the behavior of hypothalamic hyperphagics to that of sham-operated controls using these seven measures.

Behavioral Effects of Ventromedial Lesions

Hypothalamic hyperphagic rats exhibit a number of behavioral abnormalities, some related to feeding behavior but some apparently not.

The correlation of these behavioral abnoramlities with each other is often difficult to determine from published data, especially since lesions seldom allow precise, selective localization of anatomical structures. In the following review of some behavioral characteristics which are reported for dynamic hyperphagic rats, those investigators who are cited without qualification employ steel electrodes to make bilateral direct current lesions and verify histologically that the lesions are located in the region of the ventromedial nuclei. No

vary together, one should use as many of them as possible (Miller, 1957; Hinde, 1970).

Ad lib consumption of food (amount which disappears from a container of food in a specified period of time) is a critical variable. Within limits presumably imposed by stomach distensibility and by palatibility of the food, rats eat more when deprived (Hamilton, 1969).

Similarly, number of lever presses per session in an operant situation is increased by deprivation (Johnson and Thatcher, 1972).

The latency to eat in either a familiar or an unfamiliar situation decreases following deprivation (Chance and Mead, 1955; Bolles, 1962; Sclafani, 1972). This variable has the advantage of being virtually unaffected by the amount of consumption and it can be measured in both the ad lib and operant situations.

The size of the first meal following deprivation is usually large, reflecting an influence of deprivation on mechanisms which stop eating as well as those which initiate it (Ehrenfreund, 1959; LeMagnen, 1969; Levitsky, 1970; Wiepkema, 1971).

On a fixed ratio schedule the duration of post-reinforcement pauses is longer in satiated than in deprived rats, although the response rate within fast trains of presses is virtually unaffected (Sidman and Stebbins, 1954).

I investigated some microbehavioral parameters which have been reported to change during the course of a meal of liquid diet (Allison and Castellan, 1970; Allison, 1971), and found that deprivation per se has no effect, nor do ventromedial lesions; this work will not be presented here.

Deprived rats will eat more quinine-adulterated food than non-deprived rats (Miller, 1956; Williams and Campbell, 1961). Quinine tolerance tests should last several days in order to allow adaptation to the bitter diet (Gentile, 1970).

Instead of the chemical obstruction imposed by quinine, physical obstructions can be employed to assess the rat's tendence to approach

comparison of hyperphagics with deprived rats is made here; this comparison will be made in the Discussion section (Chapter 4).

Hyperphagia, the most noticeable effect of ventromedial lesions, does not invariably follow bilateral destruction of the ventromedial nuclei themselves (Reynolds, 1965a; Rabin, 1972). This is not particularly surprising since rigorous studies have failed to find strict anatomical localization of hyperphagia within these nuclei (Brobeck et al., 1943).

On the contrary, the most effective site for making lesions may be lateral to the ventromedial nuclei (Kennedy, 1950; Satinoff, 1970, using Citellus). I shall refer to the "ventromedial area" or the "ventromedial region" without specifying which particular anatomical structures, if any, are crucial in hypothalamic hyperphagia.

Most well-controlled studies indicate that hyperphagia will result from lesions made using any of several electrical techniques. (Knife cuts (Sclafani, 1971) and gold thioglucose (Liebelt and Perry, 1967; Smith and Britt, 1971) are also effective.) Electrical methods of lesion production involve current passing between a small electrode located in the brain and a large electrode elsewhere. The current can be cathodal or anodal direct-current (DC) or radio-frequency (RF). The brain electrode is usually steel, nichrome, or platinum (90% platinum, 10% iridium). Although lesions through platinum electrodes can produce substantial hyperphagia (Teitelbaum, 1955; Hoebel, 1965), Rabin and Smith (1968) report that steel electrode lesions produce greater obesity than platinum electrode lesions (no current parameters mentioned). Cathodal DC lesions made with steel electrodes also cause obesity (Rabin and Smith, 1968; Dahl and Ursin, 1969; Grossman, 1972). RF lesions, which appear to differ in shape from those made by other techniques (Herrero, 1969), nevertheless produce approximately equal weight gain compared to that produced by steel anodal DC lesions (Herrero, 1969; Stevenson, 1969; Marks and Remley, 1972), providing that female rats are used and that the lesions are bilateral (these two factors are discussed by Valenstein et al., 1969, and Herrero, 1969).

Early failures to produce obese rats using RF lesions (Reynolds, 1963) led to the development of an "irritative" hypothesis to explain why animals lesioned with steel electrodes become obese (Reynolds, 1965b, Rabin, 1972). Iron deposits from the steel anode, which can be clearly seen in most such lesions, were said to "irritate" the lateral feeding area, thus causing chronic overeating. The central link in this chain of reasoning, the assertion that iron "irritates" nervous tissue, is virtually unsupported. An EEG recording experiment seeking to demonstrate "irritation" (Rabin, 1968) is reported without description of currents used to make the lesions, conditions under which the EEG recording was carried out, or behavioral or body weight evidence of hyperphagia. Unexplained contralateral activity changes were noted using unilateral lesions. Because of the "irritative" hypothesis, however, a considerable effort has been expended to document the presence of iron near various types of ventromedial hypothalamic damage. Special staining techniques have indicated the presence of iron ions after platinum-electrode lesions (Dahl and Ursin, 1969, Prussian Blue stain), RF lesions (Herrero, 1969, Prussian Blue; Marks and Remley, 1972, Turnbull's Blue), and parasaggital knife cuts (Gold, 1970; "modified" Perl stain). The relative amounts of oxidized hemoglobin and exogenous iron are unknown in all these cases; even so, the effect of the iron on surrounding tissue may be independent of the source of the iron. It is agreed that anodal DC lesions with steel electrodes deposit more iron than other techniques--often to the extent that the tips of the steel electrodes are visibly eroded after the electrodes are used; platinum electrodes do not erode (Loukes et al., 1959). The chronic effects of iron deposits on nearby cells and fibers, if any, are unknown. With this possible exception, there is no consistent evidence of differences among steel electrodes, platinum electrodes, platinum electrodes, and electrodes used with RF current in the amount of hyperphagia or weight gain which follows ventromedial damage.

Normal albino rats kept under a light cycle of about 12 hours light and 12 hours dark consume about 70% of their daily intake during the dark part of the cycle (Brooks et al., 1946; Bare, 1959). Following

ventromedial hypothalamic lesions, intake during the light part of the cycle increases so that the daily cycle of food intake is abolished (Balagura and Devenport, 1970). In many laboratories, however, the diet is changed in the morning--near the beginning of the light part of the cycle--and the rats respond to the taste of the fresh diet by taking a large meal (DeCaire, 1968). This tendency to take a large meal following servicing is exaggerated in the rat with ventromedial lesions and may be responsible for much of the alteration in daily feeding rhythms which has been observed on some diets (Brooks et al., 1946; Pi et al., 1964; no histology in either study). The "first meal" phenomenon may be related to the hyperphagic rat's increased reactivity to the stimulus qualities of the diet (see below).

Dynamic hyperphagics eat larger meals than controls (Brooks et al., 1946; Thomas and Mayer, 1968, no histology; Balagura and Devenport, 1970). Since they consume more food per day, it follows that ratio of mean meal size to mean intermeal interval also increases.

The latency to eat in a familiar environment (Sclafani, 1971; Marks and Remley, 1972) or in an unfamiliar environment (Sclafani et al., 1970; Grossman, 1972) is shorter in hyperphagics than in controls.

Following a fast of several days hyperphagic rats have been reported to eat less on the first day of refeeding than controls (Hamilton, 1969; Miller et al., 1950; no histology, electrode unspecified). This phenomenon has been named "post-starvation anorexia."

The designation "ad lib food" includes a variety of diets. Many characteristics of the diet seem to have an effect on the amount of food a hyperphagic eats or on its asymptotic weight level. In studying the qualities of the diet to which a hyperphagic rat is responding, great care is necessary to avoid confounding texture, taste, caloric density, and method of presentation of food (Balagura, 1972). Rats with ventromedial lesions prefer (or gain more weight on) a high-fat or greasy-textured diet than on dry laboratory chow (Brobeck et al., 1943; Corbit and Stellar, 1964; Carlisle and Stellar, 1969, electrode metal unspecified), but they gain more weight on dry pellets than on dry powdered food (Corbit and Stellar, 1964; Herrero, 1969, nichrome

electrodes; Sclafani, 1971). However, dynamic hyperphagics with platinum-electrode lesions may prefer powdered food to pellets (Teitelbaum, 1955, no histology). When pellets are scattered on the floor, more are consumed than if they are available in a food hopper (Herrero, 1969).

Adding quinine to food is a potent way to alter taste without affecting texture, etc. Rats with ventral hypothalamic lesions consume less quinine-adulterated diet than controls in a quinine-tolerance test (Miller et al., 1950, no histology, electrode metal unspecified). However, this effect may be uncorrelated with the degree of hyperphagia (Strominger et al., 1953, no histology, electrode metal unspecified; Graaf and Stellar, 1962, electrode metal unspecified). Teitelbaum (1955) has shown that obese hyperphagics respond to dietary changes differently from hyperphagics which have been reduced in weight to the level of controls, indicating that weight level may be important in determining intake on various diets.

In spite of the apparent complexity of the hyperphagic's response to taste and other qualities of the diet, one can say with some assurance that many rats with ventromedial lesions will gain weight on a diet which is calorically dense, not powdered, and palatable.

"Activity" of several kinds has been shown to be affected in hyperphagic rats on ad lib food. A period of "hyperactivity" is reported by many early investigators (Hetherington and Ranson, 1942; Brobeck et al., 1943; Brooks, 1946, Anand and Brobeck, 1951). Details of methodology are generally lacking in these reports. Within a few days after surgery running-wheel activity decreases almost to zero in dynamic rats (Hetherington and Ranson, 1942; Sclafani, 1971). In at least one report (Kennedy and Mitra, 1963) running-wheel activity decreased immediately following surgery, before excess weight could account for the decreased activity. Similar decreases in activity were recorded in a stabilimetric device by Teitelbaum (1957, no histology). Gnawing also disappears following ventromedial lesions (Sclafani, 1971; Beatty, 1972). Histological verification is especially

important in evaluating effects of lesions on activity, since a small amount of damage to the lateral hypothalamus can have a larger effect on activity than a large ventromedial lesion (Gladfelter and Brobeck, 1962).

Docility when being handled by humans, the hallmark of the albino rat, is sometimes affected by ventromedial hypothalamic lesions. As has been shown by Candland and co-workers (Candland et al., 1962), handling is aversive to normal rats, but they merely struggle to escape. Rats with ventromedial lesions made with steel electrodes are reported to bite when handled or when prodded with a finger (Brooks et al., 1946; Marks and Brown, 1971; Sclafani, 1971). But Herrero (1969) using nichrome electrodes and Pool (1967) using suction lesions found no significant changes in reactivity following ventromedial damage. In addition to this possible effect of lesion method one would suspect that the degree of habituation to being handled is an important consideration.

Ventromedial lesions affect the response of rats to electric shock. In a two-way shuttlebox (active avoidance) situation, rats with ventromedial lesions learn to avoid shock more quickly (Levine and Soliday, 1960) and make more crossings during the intertrial interval (Grossman, 1972) than controls. Shock-elicited fighting between rats is also increased following ventromedial lesions (Adams, 1971, electrode metal unspecified; Grossman, 1972). Grossman (1966) has hypothesized that rats with ventromedial lesions are "hypersensitive" to shock and other stimuli. However, if such rats are shocked in the act of drinking (passive avoidance) they drink at higher currents than controls (Green, 1967, nichrome electrode; Kaada et al., 1962). This result renders Grossman's attractively simple explanation implausible.

As Schacter (1971) has remarked, there are few unchallenged behavioral observations on ventromedially lesioned rats. No one theory adequately accounts for the generally accepted data. The numerous exceptions to most generalizations are usually ignored by theory-builders unless they happen to be useful. Undoubtedly, the inhomogeniety

of hypothalamic tissue, with its many nuclei and fiber tracts, combined with the crude methods of attack used by physiologists, is responsible for much variability in the results of lesion studies. Still more variability arises from disparities in technique and from incompleteness in reporting the details of techniques.

Even if such considerations are overlooked, however, extreme caution is justified in working with ventromedial rats and in drawing conclusions about their behavior. Without strong evidence to the contrary, one must suppose that rats with ventromedial lesions are hyperphagic, obese, anorexic following deprivation, finicky about food, hypoactive (although sometimes hyperactive), and hyperreactive to aversive stimuli such as being handled. Such rats are delicate subjects. Obtaining valid measures of behavior from them requires arranging experimental conditions to minimize undesired effects of the rats' abnormalities.

The Fixed Ratio Schedule of Reinforcement

The principal measure of behavior used in these experiments is common in psychological experiments: presses on a small lever are intermittently rewarded ("reinforced") with food and the number of presses per session is recorded. The schedule used to determine which lever presses are rewarded is known as a "fixed ratio"; a lever press is reinforced "upon completion of a fixed number of responses counted from the preceding reinforcement" (Ferster and Skinner, 1957). The schedule is abbreviated by the letters "FR" followed by the number of responses/reinforcement.

Animals trained on an FR schedule exhibit a highly stereotyped pattern of responding which is characterized by trains of responses in rapid succession alternating with periods of no responding; the latter are most probable following the delivery of reinforcement (Sidman and Stebibins, 1954; Powell, 1970). Fig. 31 shows a cumulative record of typical FR responding. This characteristic pattern develops slowly in a manner suggesting that the animal must learn to perform efficiently on the schedule (Ferster and Skinner, 1957). In fact,

after sufficient training, rats on FR 4 to FR 16 appear to count their responses (Mechner, 1958). In view of the changes in responsivity to noxious stimuli sometimes found in hyperphagic rats, it should be noted that pigeons find high FR's aversive (Thompson, 1964, 1965a, 1965b).

Teitelbaum's 1957 Experiment

The conclusion of Miller et al. that hyperphagic rats show a reduced "hunger drive" was supported in an experiment by Phillip Teitelbaum (1957). This experiment warrants detailed description, since it forms the basis for the experiments reported here. Teitelbaum produced ventromedial lesions in female Wistar rats and later trained them to press a lever for small pellets of food. When tested in 12-hr sessions on steadily increasing fixed ratio schedules (two days each on FR 1, 4, 16, 64, and 256), both obese and dynamic hyperphagics responded differently from unoperated control rats (Fig. 1). At low FR's (FR 1 and 4) the dynamic hyperphagics pressed more times per session than the normal rats, on FR 16 the means were nearly identical, and on high FR's (FR 64 and 256) they pressed much less. Obese hyperphagics pressed fewer times than dynamics at all ratios and pressed more than controls only on FR 1. No histological material is presented. Teitelbaum concludes that "hyperphagic animals, especially obese animals, show a lower-than-normal drive to obtain food."

This experiment (Teitelbaum, 1957) is difficult to interpret because of several deficiencies. The diet used as food reward, which is not described, may have been rejected by the hyperphagics when many presses were required to obtain it. The electrode material and the time of day when the experiments were conducted are not reported and may have had important effects. Also, Teitelbaum employed unoperated controls but subjected the lesioned rats to stereotaxic surgery and probably damaged their ears, preventing them from hearing the sounds of the pellet dispenser. The operated rats may have been deprived of secondary reinforcement in this fashion, affecting their performance on any intermittent schedule of reinforcement (Kimble, 1961). Finally, the performance effect demonstrated by Teitelbaum could easily be

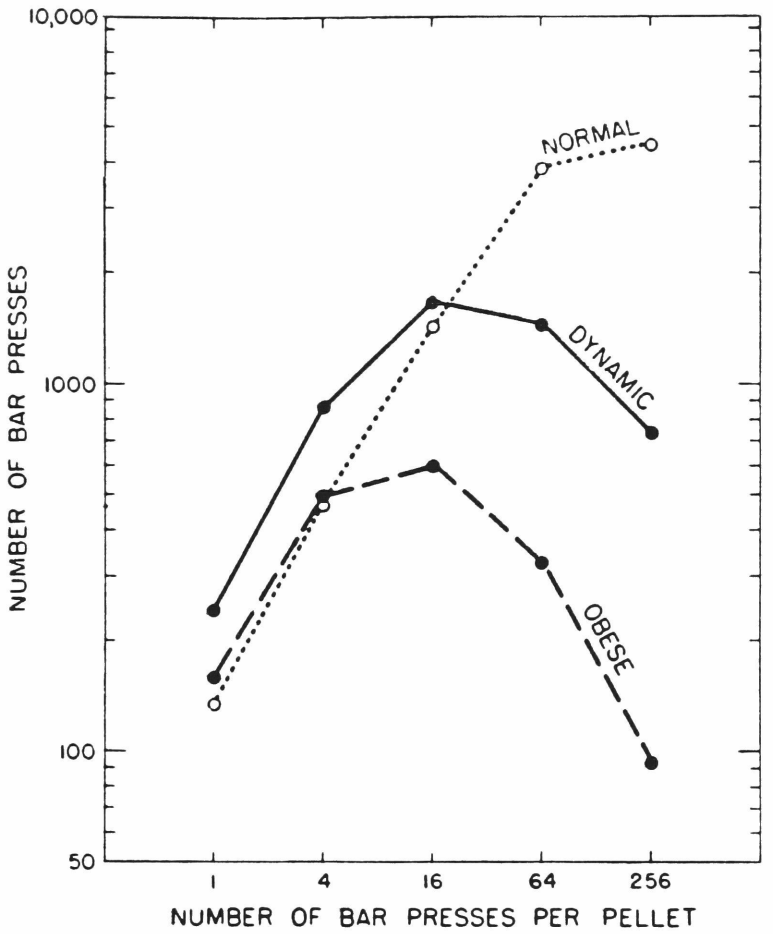

Fig. 1. (From Teitelbaum, 1957) Mean number of lever presses (per 12-hr period) of normal, obese hyperphagic, and dynamic (nonobese) hyperphagic animals as a function of the number of lever presses required to obtain each pellet.

interpreted as an inability to learn the fixed ratio pattern of lever pressing, instead of a lowered "drive." As it stands, Teitelbaum's study is provocative but contains defects which make it impossible to draw firm conclusions. Many other experiments have since been published on the effect of ventromedial lesions upon instrumental food-getting behavior; they will be reviewed in the Discussion (Chapter 4) along with the results of my experiments.

Overall Description of the Experiments

The five experiments involve the manipulation of two parameters not heretofore recognized as important in determining the level of instrumental responding for food in ventromedial rats. These are (1) the type of electrode used to produce the hypothalamic lesion and (2) pretraining on the instrumental task. The methods generally follow Teitelbaum (1957) except that control rats were sham-operated and palatable diets were used. Lesion size and placement were verified histologically. Other data such as latency to eat, quinine consumption and temporal patterns of lever pressing were collected when appropriate. The five experiments were:

I Nonpretrained rats, steel electrodes
II Pretrained rats, steel electrodes
III Nonpretrained rats, platinum electrodes
IV Pretrained rats, platinum electrodes
V Pretrained rats, platinum electrodes, 24-hr sessions.

These experiments were conducted in the order I, V, II, III, IV. They are more fully summarized in Appendix IV.

Chapter 2. METHODS

Animals

The rats were virgin female albinos (R. norvegicus) of the Wistar (CFN) strain obtained from Carworth Farms, New City, New York. They were shipped when they reached a weight of 190-230 g (nominal 8-12 weeks of age) and were allowed at least 2-3 weeks of habituation to the laboratory regime before being used in experiments. Except when they were tested in Skinner boxes, the rats lived singly in standard laboratory cages which had wire mesh fronts and bottoms and measured 18 cm high, 20 cm wide, and 25 cm deep. Flourescent ceiling lights provided illumination on a regimen which varied from Light-Dark 12:12 to LD 15:9. The animals used in Experiments II, III, and IV were handled for about a minute three times per week during the two or three weeks prior to being introduced to the Skinner boxes. In Experiment IV substantial weight differences between rats necessitated pairing lesioned and control rats on the basis of body weight at the time of surgery. In the other experiments, animals were assigned on the basis of a coin flip at the time of surgery.

Electrodes and Surgery

Two materials were used as anodes in producing electrolytic lesions. Experiments I and II employed steel dental broaches (Asko round smooth broach, fine, no. 12 1/2, manufactured by A. S. Koch and Sons, Lancaster, Pa.). The metallurgical content of these broaches could not be determined, although they rapidly rusted in physiological saline, indicating that they are not high quality stainless steel. The broaches were shortened so that the tip diameter was about 0.4 mm, dipped repeatedly in insulating material (Insl-x E-33, Insl-x Corp., Yonkers, N.Y.), and sharpened by twirling against a spinning abrasive grinding disc at an angle of 45-60°. They were inserted into the brain singly (Experiment I) or in pairs (Experiment II).

Experiments III, IV, and V employed platinum wires 0.38 mm in diameter (platinum-10% iridium wire, factory straightened, Matthey Bishop, Inc., Malvern, Pa.). These wires were soldered into shafts of 22 ga (0.60 mm) stainless steel hypodermic tubing so that the platinum

protruded 4 mm. This assembly was then insulated and sharpened as above. For chronic implanatation of these platinum-tipped electrodes, the shafts were 12 mm long and the electrodes were cemented into a pair, using dental acrylic, before insertion into the brain. For acute lesions, the electrodes were lowered into the brain in pairs. The method of making platinum electrodes is modified from Hoebel, 1964.

Surgery was performed under sodium pentobarbitol anesthesia in order to permanently implant electrodes (implanted condition) or to produce DC lesions during the surgical procedure without implanting the electrodes (acute condition). Nembutal (0.19 to 0.24 cc) and atropine sulfate (0.07 cc) were injected intraperitoneally, the rats' heads were shaved, and the vibrissae were cut to a length of about 1 cm. The animals were positioned in a standard stereotaxic apparatus so that the frontal bones were level. Insertion of each ear plug was normally accompanied by an audible pop, indicating that the tympanum was ruptured. Using clean but not sterile technique, the dura and midsaggital sinus were exposed and the electrodes lowered into the brain. The stereotaxic coordinates for lesioned rats were 8.5 mm down from the dura, 0.75 mm bilateral to the midsaggital sinus, and 6.0 mm anterior to the ear bars. All control rats had electrodes lowered to or implanted at the same coordinates as lesioned rats except that the depth was only 4.5 mm from the dura. Implanted electrodes were affixed to the skull using stainless steel screws and dental acrylic. The rats were sutured and given 0.1 cc of Longicil-S or a similar antibiotic.

The hypothalamus of the "lesioned" rats was damaged using a commercial Lesion Producing Device (C. H. Stoelting Co., Chicago, Ill., cat. no. 58040). Implanted rats were briefly (2-5 min) etherized for this procedure. One electrode at a time was the anode and a banana plug connector inserted in the rectum served as the cathode. Lesions were made bilaterally; a current of 1 ma was passed for 15 sec through steel electrodes and 1-2 ma was passed for 20-25 sec through platinum electrodes. The difference in Coulombs required between steel and platinum is discussed in Appendix III. No current was passed through the electrodes of control rats, although they were similarly connected

and etherized. In the experiments involving pretraining, lesions and sham-lesions were made at the time when an FR session would otherwise start.

Diets

Except during periods of deprivation, the animals were fed one of two types of food: laboratory chow in the form of pellets (Purina Rat Chow) or a palatable liquid diet. Except for Experiment I, the liquid diet was composed of three parts by volume Borden Magnolia Brand Sweetened Condensed Milk to 1 part tap water, supplemented with vitamins and minerals (Kissileff, 1972). Milk supplemented with minerals has been found adequate to grow rats from "weaning" to maturity (Kemmerer et al., 1932) and has kept rats healthy in my laboratory for periods exceeding one year. The mixture is a viscous syrup with a specific gravity of 1.15 to 1.20 and a nominal caloric value of 2.91 kcal/g. Although I have conducted no tests of the 3:1 milk diet's palatability to rats, it appears to be highly preferred over laboratory chow by both normal and hyperphagic rats and causes immediate weight gains when rats are transferred from ad lib chow to ad lib milk. The mixture was kept for up to several days at 8°C and served daily at this temperature either as reinforcement in the dipper apparatus described below or as an ad lib maintenance diet in 100 ml capacity Richter tubes. In order to test the result of mild spoilage, the milk was once purposely kept for four consecutive 12-hour sessions (48 hours) without replacement (Experiment II, pre-lesion FR 64) with the result that four out of six rats took more reinforcements during their second session on the milk than during their first, indicating that the milk did not decrease in palatability over this two day period.

In Experiment I, the reinforcement was either undiluted Magnolia brand milk or, for one hyperphagic and one control, a slurry of 60 g Sunshine Chocolate Chip Cookies in 40 ml tap water, prepared in a food blender. The liquid ad lib diet was Magnolia brand milk diluted 1:1 with tap water, supplemented as above. Since the exact liquid diet used did not appear to affect any of the results except intake volumes, the word "milk" will be used to describe all these diets. The rats had

ad lib water available from metal spouts at all times.

Apparatus

Lever pressing sessions took place in clear Lucite Skinner boxes which were individually enclosed in large, lightproof, sound-deadening chambers of wood and fiber insulation. Ambient light in Experiment I was provided by a small incandescent lamp of unmeasured intensity. In Experiment V a 4 watt lamp produced a mean photopic illuminance of 4.9 lux on the walls of the chambers; this lamp was reduced to a glow by a series resistance for 12 hours a day. In the other experiments the ambient illumination was a 25 watt 110 v red-coated incandescent lamp operated at 80 v and mounted in a Kodak Model A Safelight housing and covered by a Wratten no. 1A deep red filter. This red light was probably equivalent to darkness for the rat but allowed observation of the rat's activity from windows in the large chamber. A blower provided continuous air flow and masked external sounds.

The Skinner boxes measured 20 x 20 x 39 cm high, with floors of stainless steel bars placed 1.3 cm apart and 10 cm round holes in the ceiling. A 100 ml graduate with a metal spout protruding through one wall provided water; on the opposite wall were a lever and a dipper feeder manufactured by Ralph Gerbrands Co. The lever end measured 5 cm wide by 1.1 cm high, was mounted 4 cm above the cage floor, and required 16-21 g moving through an arc of 4 mm to be actuated. Beside the lever at a distance of 2.5 cm was a recessed food well, a circular stainless steel concavity 5.8 cm in diameter. When the animal pressed to criterion, a small dipper brought milk up through a 1.3 cm diameter hole in the food well and held it for nine seconds. The dippers (nominal capacity 0.2 ml) were measured to deliver 0.187 ml plus or minus 0.005 ml of the 3:1 milk diet. The dipper was powered by a solenoid which gave a loud click when the dipper rose and during the nine seconds when the dipper was raised a 7.5 watt overhead lamp was illuminated, providing an additional 145 lux. Electromechanical programming equipment controlled the schedules and recorded the data.

The pulse formers in this equipment were periodically tuned so that a 50 msec closure followed by 50 msec period between closures was required to register a lever press. The rats' effective pressing rate was thus limited to a maximum 10/sec. In all experiments except Experiment I the programming equipment was located in a distant room and was not audible from inside the sound-deadening chambers.

Training and Testing

In order to minimize and equate the effects of handling, a stereotyped daily routine was adopted. The rat was carried from the animal quarters to the testing room in its home cage and transferred by hand to a basket on a pan balance by grasping base of the tail with a black neoprene rubber glove. Body weight was taken to the nearest 1 g and the covered basket containing the rat was picked up, tilted 90°, and placed so that the rat could walk out of the basket and into the Skinner box. After the lever pressing session, the rat was removed from the Skinner box using the glove and placed immediately in its home cage. A rat was not removed from the Skinner box unless two minutes had elapsed since the last lever press, insuring that a bout of pressing was not interrupted. Except in Experiment V, the lever pressing sessions were a nominal 12 hours in length and always took place during the dark period of the animals' daily cycle.

Most rats used in these experiments learned to press the lever for continuous reinforcement during their first 12 hour session, usually without any manipulation on the part of the experimenter. Those which did not learn themselves were shaped by the method of successive approximation within an additional one or two sessions. After the rats had pressed on FR 1 for two full sessions, they were placed on steadily increasing fixed ratio schedules of reinforcement: two days each on FR 4, 16, and 64 (and 256 for Experiments I and III). In Experiments II, IV, and V, the schedule was held at FR 64 for an additional 11 to 15 days--the "pretraining" condition. Three to eight days following placing of lesions or sham lesions, the schedules were usually further increased to FR 256, 512, and sometimes to FR 1024 and FR 2048. These schedules, the "high" ratios, resulted in highly variable responding

and sometimes extinction. If an animal obtained 5 or fewer reinforcements/day for 2 consecutive days on these schedules it was removed from the experiment. An animal was also removed if the equipment malfunctioned such that the effective schedule became extinction.

Data Collection and Analysis

Basic records kept of each rat's daily performance consisted of total presses and reinforcements accumulated on digital counters and cumulative records of presses taken at a speed of 30 cm/hour. In Experiments II-V the cumulative records indicated if the dipper was not touched during the 9-sec reinforcement period. Such unconsumed reinforcements were rare on all schedules greater than FR 1. More detailed data were taken in one of two forms. In Experiments I and V, printout counters printed the time in 0.1 min units whenever a rat started to press and cumulated the number of presses during each bout of pressing. After one minute elapsed without a press, the time and the cumulated number of presses was printed. Each "bout" or "meal" was thus defined by a one minute criterion and its size, duration, and time of occurrence were recorded. These printout counter records were then key punched and processed using a digital computer. This method of analysing lever pressing patterns was replaced during Experiments III, IV, and part of II by a paper tape punch which recorded the time of each press to one second. Both of these methods were periodically verified using a computer-driven incremental plotter to generate "imitation cumulative records" which could be compared to the actual cumulative records taken by the electromechanical equipment.

Post-test Period and Histology

Except for some short quinine adulteration tests and further lever pressing tests in some groups, the rats remained on ad lib food following the fixed ratio sessions. In Experiments I and V the rats were given milk until their weight stabilized and then were switched to laboratory chow. In the other experiments, the reverse order was followed--first laboratory chow, then milk. The rats were weighed at least twice weekly and a ten-day period of stable weight (less than

0.5 g/day total change in weight) determined when a hyperphagic was switched to a new diet. Since the control rats in all cases reached a stable weight before the hyperphagics, each control rat was paired with a neighboring hyperphagic during this period and the diets of both rats were changed when the hyperphagic's weight stabilized.

After the rat's weight had stabilized on its final diet, it was killed with an overdose of anesthetic, perfused with 10% formalin in 0.9% NaCl, and the brain removed and placed in the formol-saline. After hardening, the brain was transferred to formol-saline with 30% sucrose added and kept under refrigeration. The brain was then imbedded in gelatin-albumin and sectioned at 50 micron intervals in the transverse plane. Sections were mounted and stained with cresyl violet and Weil stains in alternation. Several sections of brains of rats in Experiments II and IV were selected before mounting and were stained for ionic iron with potassium ferro- and ferricyanide according to the procedure given in Lilly, 1965, p. 407. These special sections were counterstained with pyridine red. The maximum transverse cross-sectional extent of the lesion was drawn to scale using the atlas of Koenig and Klippel (1963) and the anterior-posterior extent of each side of the lesion was recorded.

Criterion for Hyperphagia

A rat is called "hyperphagic" if it attained or maintained a body weight of 400 g on laboratory chow. This criterion has been used previously (Graff and Stellar, 1963; Thomas and Mayer, 1968). In addition, hyperphagic rats in the nonpretrained condition (Experiments I and III) gained at least 4.5 g/day, satisfying another criterion which has been used to identify hyperphagic rats (Thomas and Mayer, 1968; Herberg and Blundell, 1970). Since ad lib diets in the period following the FR sessions varied, rates of weight gain during this period were not used.

Chapter 3. RESULTS OF LESION EXPERIMENTS

The data of the five lesion experiments are presented in two parts. First, the experiments are described one-by-one in terms of the crucial variables of body weight, food intake, presses per session, and histology. Then other variables such as rate of lever pressing are covered, grouping the data by variable.

Body Weight, Food Intake, Presses per Session, and Histology

Experiment I. Eight rats averaging 265 g were fed milk diet for 6 days, given acute lesions with steel electrodes (5 rats) or sham lesions (3 rats) and again fed ad lib milk for 13-15 days until rates of weight gain were stable. They were then trained to press the lever and placed on increasing FR schedules from FR 1 to FR 256. Except for the diet and sham-operated controls, this experiment is a replication of Teitelbaum (1957).

The three rats which met the criterion for hyperphagia (400 g) averaged 433 g in weight at asymptote. Controls averaged 313 g. These weights were maintained when the rats were fed laboratory chow.

Quinine aversion scores and data collected previous to the FR sessions are summarized in Table 1. The three hyperphagic rats showed rapid weight gain on milk and sharp reduction of intake on quinine adulterated milk.

In the lever pressing sessions the dynamic hyperphagic rats pressed slightly more than controls on low schedules (FR 1 and 4) but fell behind on high schedules (FR 64 and 256) (Fig. 2). The results of Teitelbaum (1957) (Fig. 1) were thus fully replicated.

Each hyperphagic rat had sustained bilateral damage to the ventromedial region, however, the poor quality of histology on these brains did not permit accurate measurements of the extent of the lesions. Black areas presumed to be iron deposits coated the horizontal surfaces of the lesions.[1]

[1] i.e. the lateral anterior, and posterior borders of the lesion were rich in black material, but the dorsal and ventral borders frequently were not.

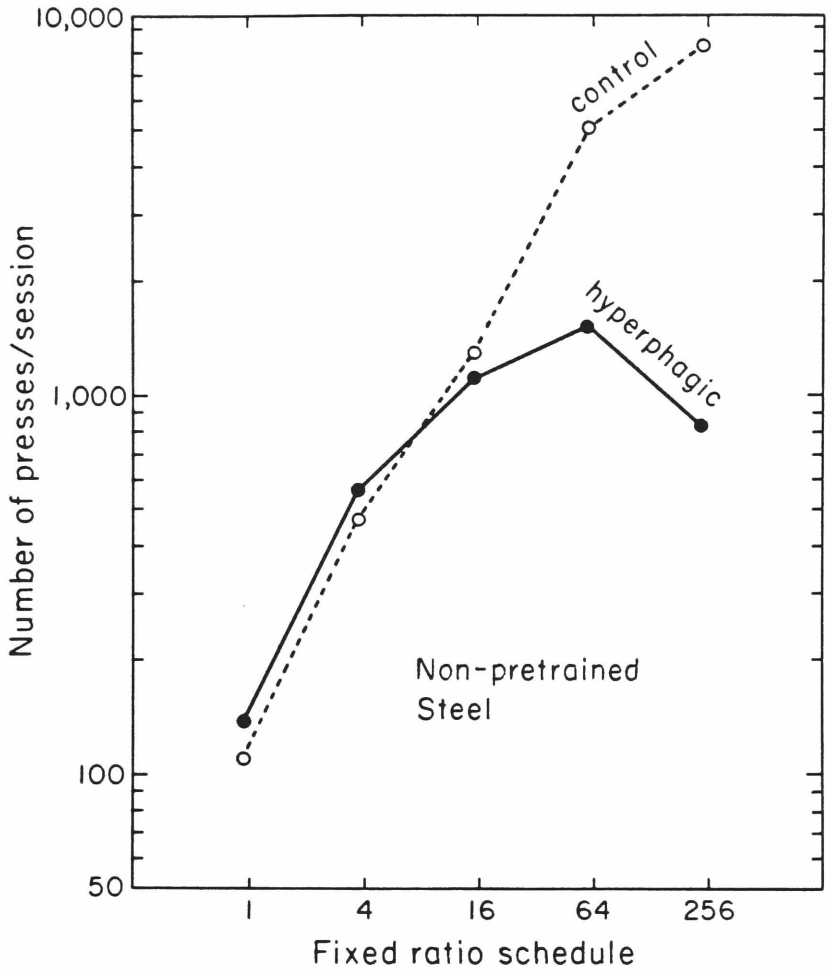

Fig. 2. Experiment 1: Log number of presses per 12-hr session on each fixed ratio schedule. Means of 3 hyperphagics and 3 controls. $p = .05$ for FR 64 and 256 (Mann-Whitney U-Test).

Table 1

	Rat	Weight Gain (g/day) Pre	Post	Change in Intake Post-Lesion	Quinine Score
Hyperphagics	H-4	0.8 (6)	-0.1 (11)	-6%	54%
	H-6	2.8 (5)	0.7 (13)	-11	84
	H-8	0.5 (6)	0.0 (15)	-12	31
Controls	H-3	1.7 (7)	4.5 (14)	28	2
	H-7	0.8 (6)	8.3 (15)	79	1
	H-10	2.3 (6)	5.3 (10)	35	3

Individual weight gain and food intake data, Experiment I. Mean daily weight gain on milk diet pre- and post-lesion, mean percent change in daily food intake post-lesion, and quinine score. Number of days is in parentheses. Quinine test was three days on 0.1% quinine HCl in 1:1 milk diet. Quinine score is the mean intake for the three days preceding the quinine test. The quinine test was conducted when the hyperphagic rats' mean weight was 400 g and the controls' 307 g.

Experiment II. Twelve rats were trained to press on FR 64 and the FR schedule was held at 64 for 13-19 days. (During this period six rats were deprived of food for 36 hours once as described below under "Rates of Pressing.") Ten of the rats were given acute lesions with steel electrodes and two were given sham lesions. On the following day the rats were replaced in the Skinner boxes on FR 64. Asymptotic weight levels on ad lib laboratory chow were: five hyperphagics 424-519 g (mean = 464), two controls 306 and 289 g. Asymptotic weights of the hyperphagics on ad lib milk were 541-580 g (mean = 568).

The sham-operated rats pressed slightly fewer times on FR 64 following the operation (Fig. 3). Placed on FR 256-1024, they maintained high performance. Even at FR 1024 these controls obtained 20-30 reinforcements in a 12-hr session.

One rat with a lesion appeared debilitated following surgery and died a few days after the FR testing sessions; its data were discarded. Another (H-42) increased pressing on FR 64 following the lesion but fell much below controls on FR 256 and above (Fig. 4). The other 9 rats with lesions behaved similarly to those whose performance is summarized in Figs. 5 and 6. On FR 64 one to three days following surgery the rats pressed few or no times/session. Since it was obviously meaningless to increase the FR schedule at this point, I manipulated the rats' access to food, trying to induce them to press the lever. When briefly presented with a small Petri dish of milk in the Skinner box, the rats with lesions began to eat immediately. Placed on ad lib milk or laboratory chow after 2-3 sessions on FR 64, they invariably displayed hyperphagia and gained 5-9 g/day. Some rats did not press even on FR 1 at this time (day 3-6). After a varying period of time the rats began to maintain their weight on low FR schedules and were tested to ascertain if they would press on FR 64. When FR 64 performance appeared to have recovered three final days' data were collected on FR 64 from each rat. The result of this procedure for individual rats is presented in Table 2 and the mean FR 64 and FR 256 performance for the 5 criterion hyperphagics is shown in Fig. 7. Weights of the hyperphagic rats at the start of the final FR 64 test were within 26 g of preoperative weights.

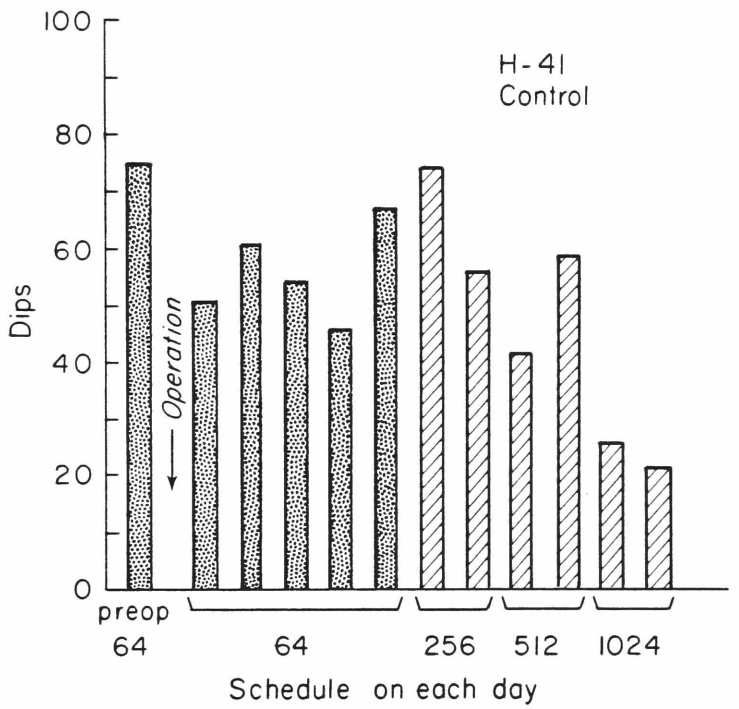

Fig. 3. Experiment 2: Number of dips (reinforcements) obtained by control H-41 before and after sham operation. Preoperative FR 64 value is mean of 13 days. Following the operation, the animal was held on FR 64 for 5 days, then 2 days each on FR 256, 512, and 1024.

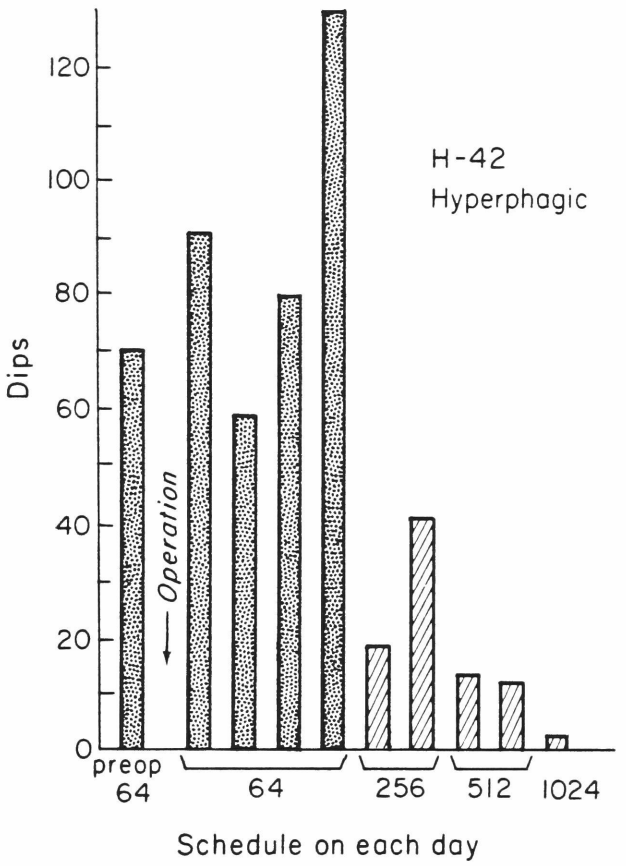

Fig. 4. Experiment 2: Number of dips (reinforcements) obtained by hyperphagic H-42 before and after placement of ventromedial lesions. Preoperative FR 64 value is mean of 14 days. The animal had extinguished by the second day on FR 1024. This was the only one of 10 rats with lesions to increase pressing immediately following the lesion.

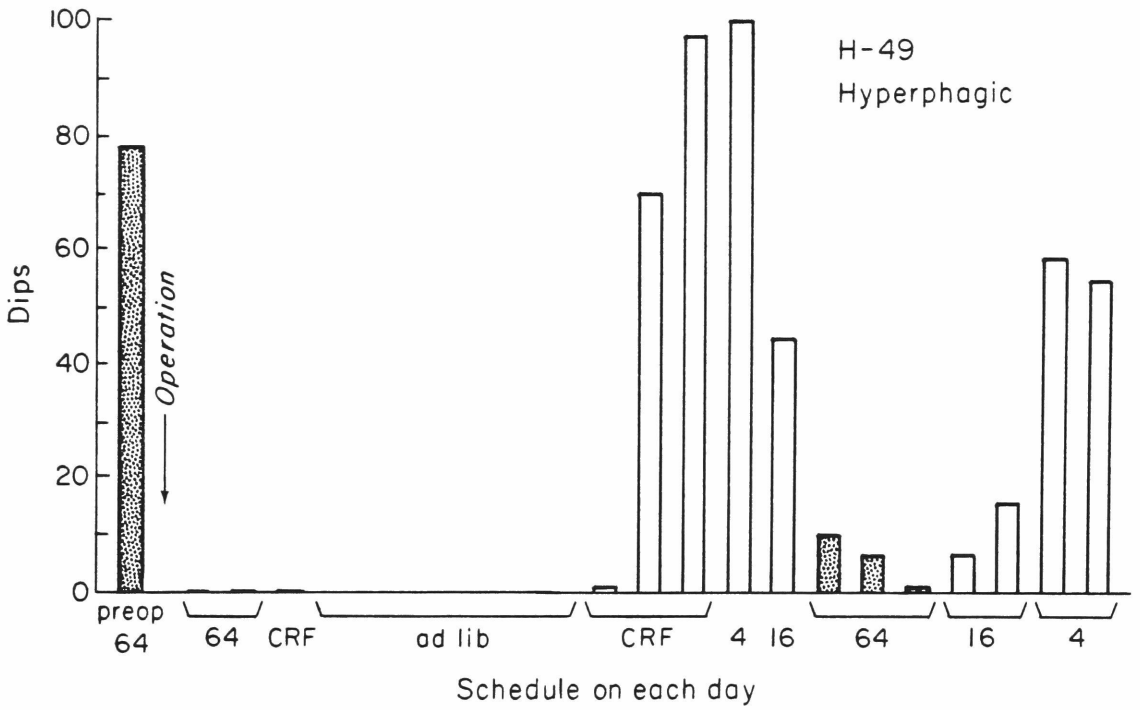

Fig. 5. Experiment 2: Number of dips (reinforcements) obtained by hyperphagic H-49 before and after placement of ventromedial lesions. Preoperative FR 64 value is mean of 17 days. No reinforcements were obtained on FR 64 and CRF (FR 1) during the first 3 postoperative days. The rat was then given ad lib milk diet 12 hr per day for 5 days; during this time it gained 6 g/day. It was then returned to the Skinner box and the schedule was held at CRF for 3 days. At the beginning of the first of these 3 CRF days its weight was 11 g above the level at the time of operation. On FR 4-64 the rat obtained fewer reinforcements on higher schedules.

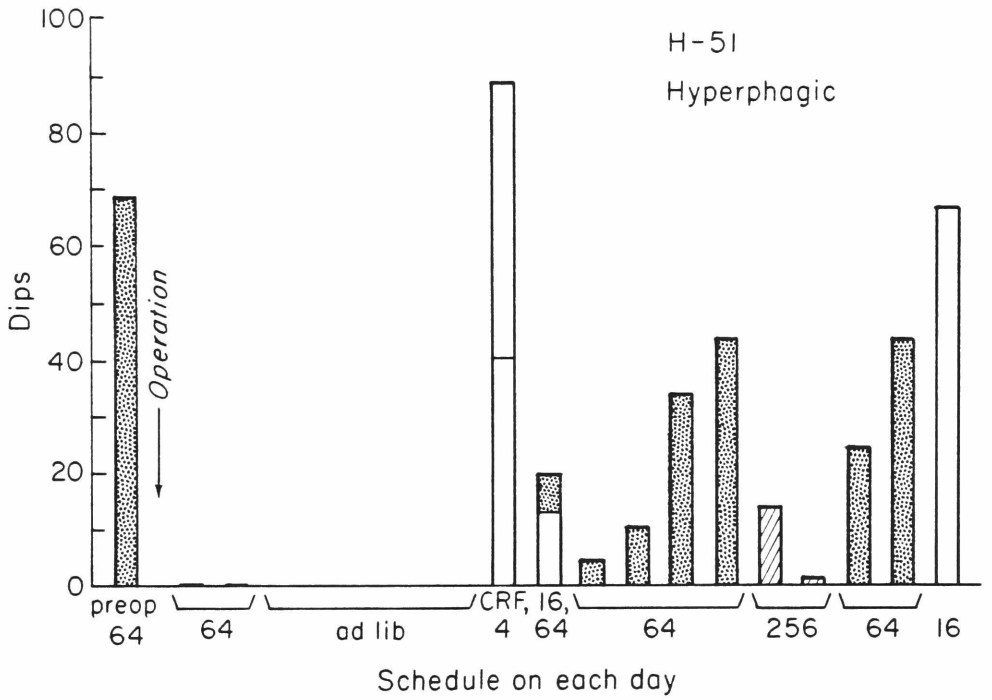

Fig. 6. Experiment 2: Number of dips (reinforcements) obtained by hyperphagic H-51 before and after placement of ventromedial lesions. Preoperative FR 64 value is mean of 19 days. Performance is similar to H-49 (Fig. 5) and most other hyperphagics. Transition from ad lib to FR 64 was accomplished by increasing the fixed ratio each half-session (6 hr).

Table 2

	Rat	Mean FR 64 Presses/Day Pre-lesion	Day 1-3	Final	No. Days Intervening	Hyperphagic
Control	H-41	4761	4761	-	-	-
	H-45	5980	5859	-	-	-
Lesioned	H-42	4771	5744	-	-	Yes
	H-43	4337	4	2624	2	No
	H-46	3627	0	3918	2	Yes
	H-47	4593	1	5765	9	Yes
	H-48	6293	0	1584	7	No
	H-49	5123	19	406	12	Yes
	H-51	4495	0	2463	10	Yes
	H-52	4831	2327	-	-	No
	H-53	3861	4	288	11	No

Individual FR 64 performance, Experiment II. Means of presses/session for the last 12 pre-lesion days on FR 64, day 1-3 post-lesion, and final (best) 2-3 days on FR 64. The number of days intervening between day 3 and the first day of the final sessions is also listed; these were days on ad lib food or low fixed ratios.

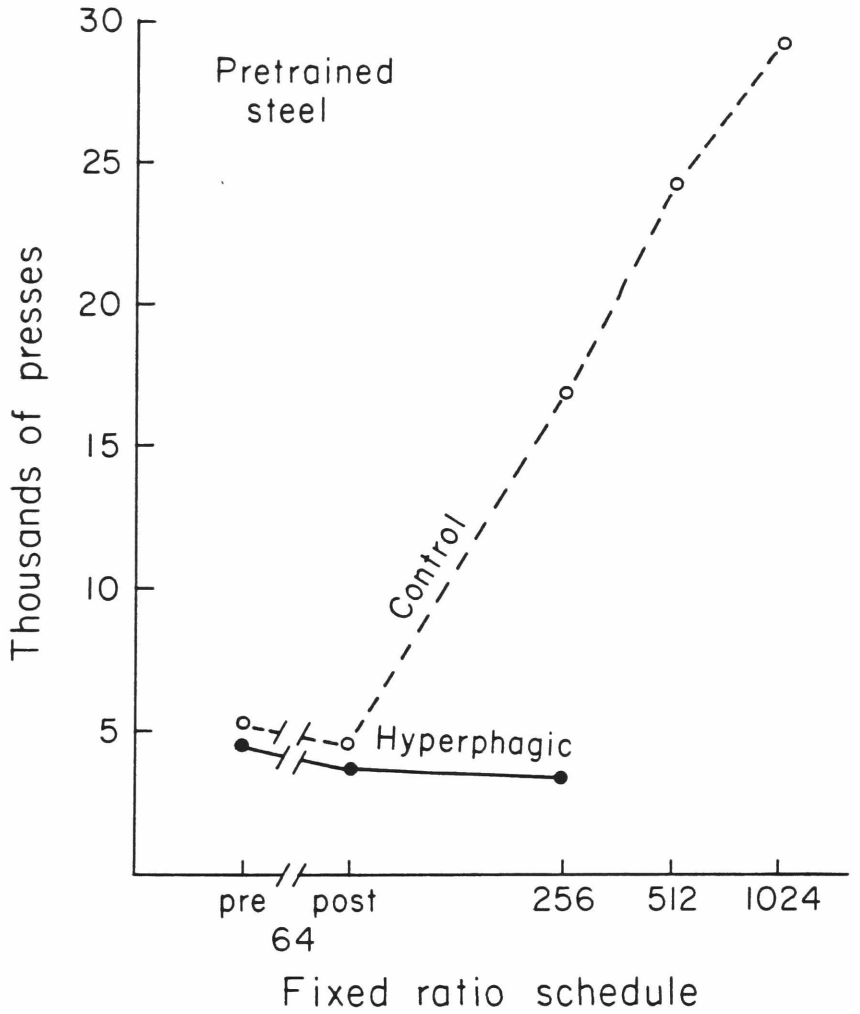

Fig. 7. Experiment 2: Number of presses (in thousands) per 12-hr session on each fixed ratio schedule. Means of 2 controls; means of 5 hyperphagics preoperatively; means of best 3 days of 5 hyperphagics on FR 64 postoperatively; means of 2 days of 4 hyperphagics on FR 256 postoperatively. One lesioned rat (H-42) pressed 6552 times/day on FR 512; all other lesioned rats extinguished at FR 512 or below. $p = .067$ on FR 256.

In spite of the ad hoc nature of postoperative testing in this experiment, two generalizations are possible:

(1) Immediately following the placement of lesions, most of these rats ate food ad lib but did not press for food. (2) Fixed ratio performance eventually improved but usually did not reach pre-lesion levels on FR 64.

Cresyl-violet stained transverse sections through the maximum extent of damage of two rats are shown in Fig. 8. H-51 (Fig. 8a) sustained symmetrical damage which spared the ventralmost part of the ventromedial nuclei. The lesion proper does not involve the lateral area. This rat performed poorly on FR 64 after surgery. H-47 (Fig. 8b), in contrast, eventually exceeded preoperative levels in FR 64 performance. Its lesion damages the lateral area on both sides. Both sections contain copious amounts of black material similar to that seen in Experiment I. Quantitative measurements of these lesions from Experiments II-V are tabulated in Appendix II and drawings of the lesions are presented in Appendix V.

Potassium ferrocyanide stain, which reacts with the Fe^{+++} ion (Lillie, 1965), reveals the presence of large amounts of iron near the lesion (Fig. 9a). Potassium ferricyanide (reacts with Fe^{++}) stains only lightly (Fig. 9b). Additional sections, mounted completely unstained, were rusty red in this area. These observations apply to the five brains which were examined using these stains. They are consistent with the hypothesis that oxides of iron, rich in Fe^{+++}, are present at the horizontal borders of lesions made with steel dental broaches.

A small lesion was purposely produced in one rat, H-48, by using a current of 0.5 ma instead of 1 ma for 15 sec. This rat did not become hyperphagic, and was found to have a discrete lesion centered just above the ventromedial nuclei; its level of FR 64 pressing was nevertheless decreased following the lesion.

Experiment III. Experiment I was repeated using implanted platinum electrodes. Lesions were produced under ether anesthesia after 7 days on ad lib milk. After 6-11 days, each hyperphagic had gained weight equal

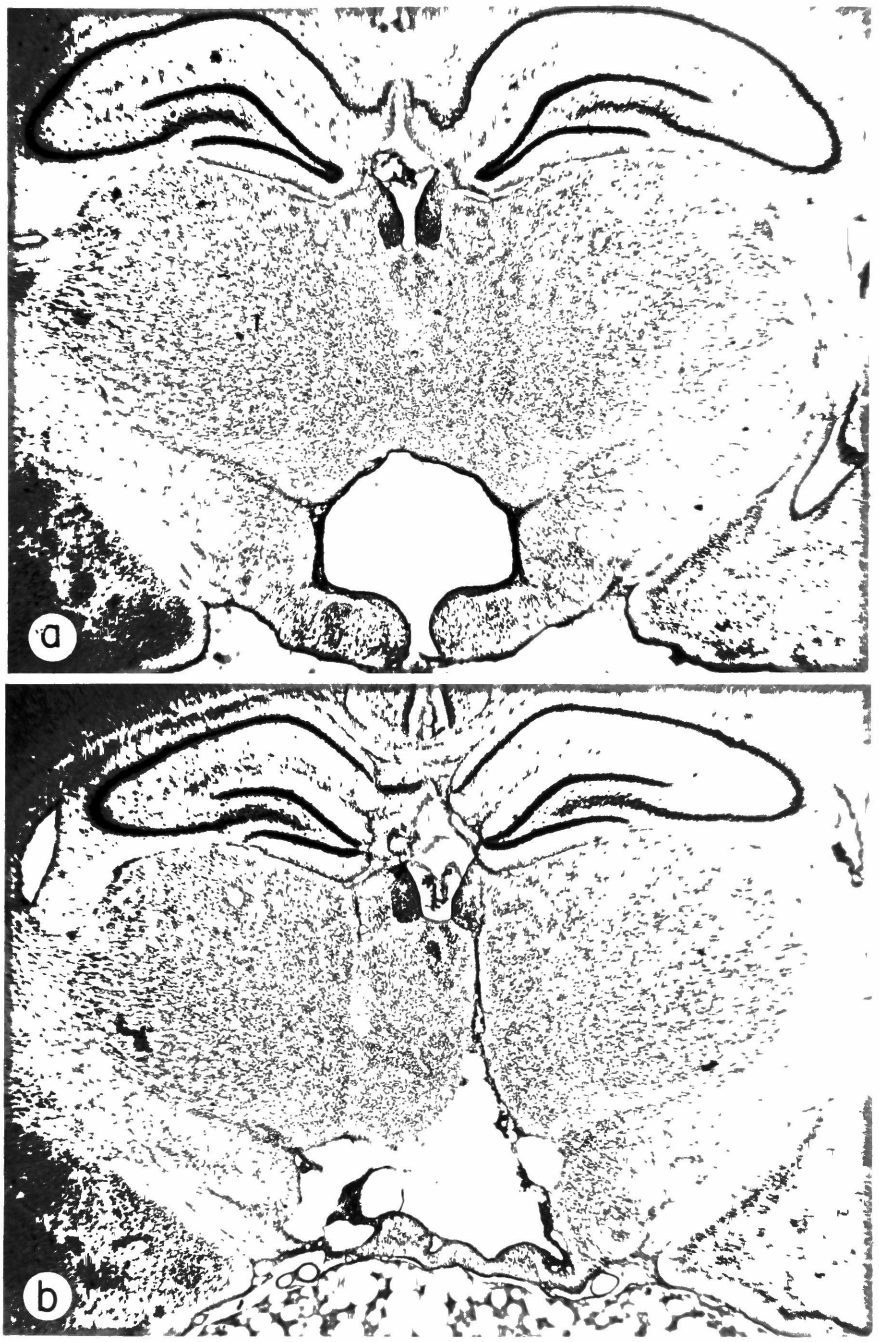

Fig. 8a. Cresyl-violet stained transverse section through the maximum extent of damage of rat H-51. Section is 4620 μ anterior to the interaural line.

Fig. 8b. Rat H-47. Section is 4230 μ anterior.

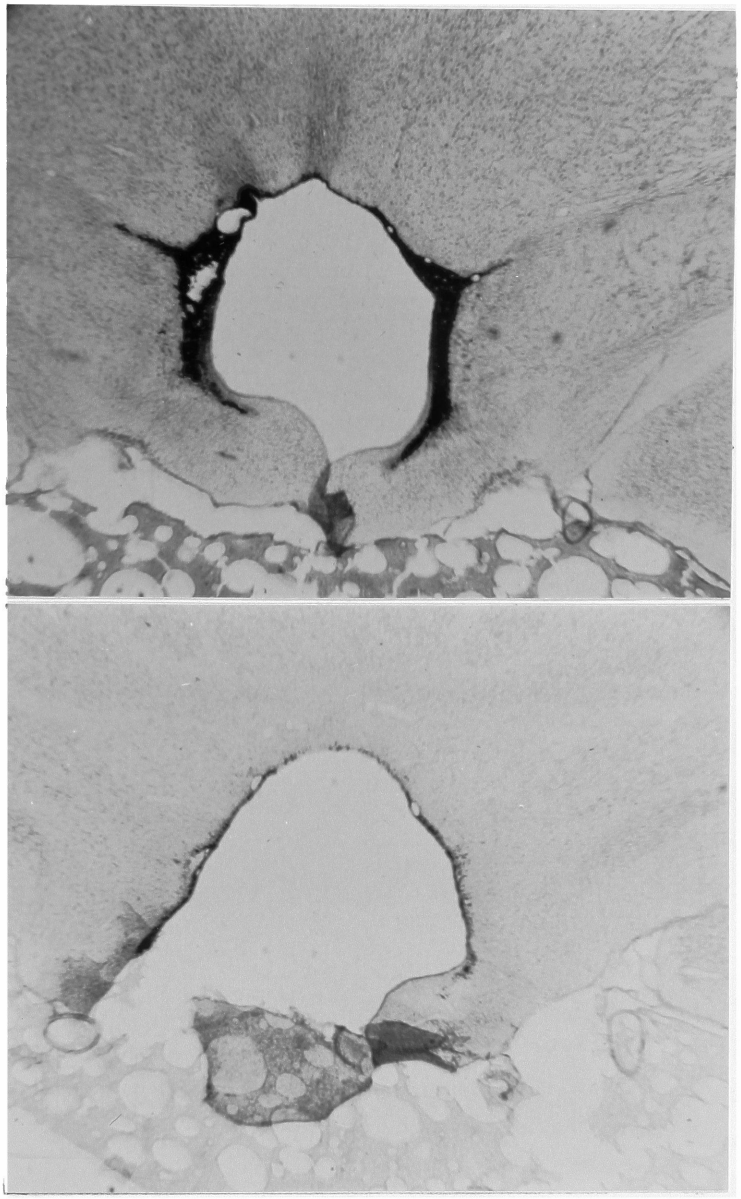

Fig. 9a. Potassium ferrocyanide (Prussian blue) stain of a lesion made with a steel electrode. Blue and black areas indicate the presence of ferric ions around the horizontal borders of the lesion. Pyridine red is used as a counterstain in these sections; distortion of the sections is due to handling them during the staining and washing procedure (Lillie, 1965).

Fig. 9b. Potassium ferricyanide (Turnbull's blue) stain of a steel electrode lesion. Blue and black areas indicate the presence of ferrous ions around the horizontal borders of the lesion.

to the mean weight gain of hyperphagics in Experiment I (79 g). At this time, therefore, the five rats with lesions (mean 342 g) and the three with sham lesions (mean 273 g) were trained to press the lever and placed on the increasing series of FR schedules.

One rat in the group with lesions did not reach the criterion for hyperphagia (400 g) and its data were discarded. Another (H-55) was accidentally killed two weeks following the FR sessions. It was nevertheless included in the hyperphagic group on the basis of ad lib weight gains of 11.3 g/day during the immediate postoperative period on ad lib milk and of 10.1 g/day on laboratory chow following the FR sessions. The three other hyperphagics reached asymptote at 470, 470, and 478 g on laboratory chow and the controls at 317, 327, and 347. On ad lib milk the hyperphagics reached 496, 506, and 538 g; two controls reached 355 and 362 g. One control rat became "hyperphagic" on ad lib milk, losing a large amount of weight when again fed laboratory chow (Fig. 10). This was the only control rat in these experiments which exceeded 375 g on any diet.

Data collected previous to the FR sessions are summarized in Table 3. Weight gains and increases in food intake are slightly higher than those found in Experiment I, possibly because the animals did not suffer from the effects of stereotaxic surgery during the post-lesion period.

Fixed ratio performance of these non-pretrained, platinum electrode rats was superior to that of either of the steel-lesioned groups (Fig. 11). The mean performance of the hyperphagic rats was above that of the controls on FR 1 to FR 64. At FR 256, most of the hyperphagic rats failed to increase the number of presses/session and by FR 1024 they had extinguished. The control rats maintained increasing levels of pressing. One hyperphagic (H-58) did not fall below the level of controls on any schedule.

Each hyperphagic rat sustained bilateral damage to the ventromedial nuclei. In one rat (H-55) the ventralmost part of these nuclei was left intact. As can be seen in potassium ferro- and ferricyanide-

Fig. 10. Body weight of the one sham-lesion rat which became obese on ad lib milk. Day 0 is the day of the final fixed ratio session. Arrows mark the initial day of ad lib laboratory chow or ad lib milk.

Table 3

	Rat	Weight Gain (g/day) Pre	Post	Change in Intake Post-Lesion
Controls	H-56	0.3 (7)	3.6 (7)	-1%
	H-57	3.4 (7)	1.7 (9)	-3
	H-63	1.1 (7)	0.9 (7)	-3
Hyperphagics	H-54	1.7 (7)	5.8 (12)	55
	H-55	2.6 (7)	11.3 (7)	71
	H-58	0.9 (7)	8.3 (9)	80
	H-59	0.3 (7)	5.2 (11)	37

Individual weight gain and ad lib food intake data, Experiment III. Mean daily weight gain on milk diet pre- and post-lesion and mean percent change in daily food intake post-lesion. Number of days is in parentheses.

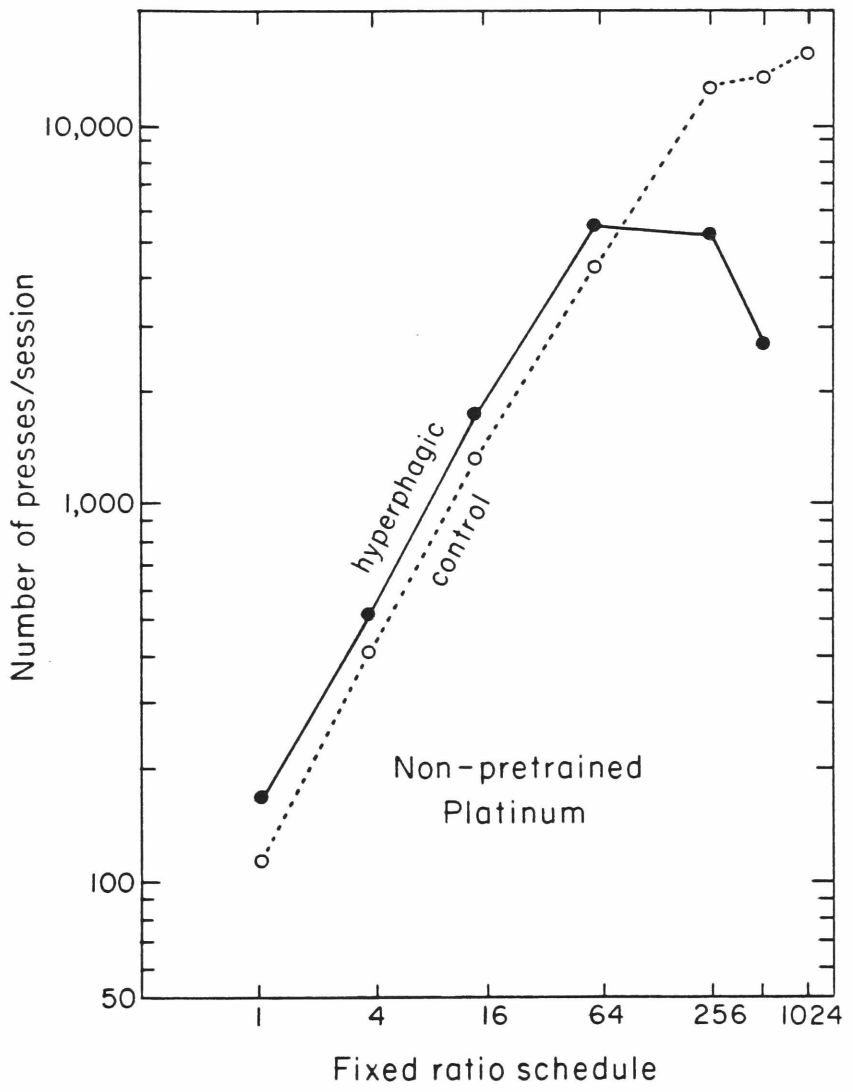

Fig. 11. Experiment III: Log number of presses per 12 hr session on each fixed ratio schedule. Means of 4 hyperphagics and 3 controls. p = .057 on FR 256 and 512.

treated sections (Fig. 12), little or no ionic iron is detectable surrounding platinum electrode lesions. (Note that these sections do not transect the maximum extent of H-58's lesion.)

Experiment IV. Experiment II was repeated using platinum electrodes. After 12-15 days' pretraining on FR 64, ten rats received acute lesions, four received sham lesions, and two rats received "double bilateral lesions"--a bilateral pair 5.5 mm anterior to the ear bars and another bilateral pair 6.5 mm anterior (cf. Hetherington and Ranson, 1942). Since most of the animals with lesions showed immediate hyperphagia on FR 64, the schedule was increased to FR 256 on the third day following surgery to prevent the rats from gaining weight before they could be tested at higher schedules.

Asymptotic weight on laboratory chow was: controls 286-344 g (mean = 312), single bilateral lesion hyperphagics 424-516 g (mean = 479), and double bilateral lesion hyperphagics 579 and 539 g. Asymptotic weight on milk was: controls 290-374 g (mean = 340), single bilateral lesion hyperphagics 514-551 (mean = 534), and double bilateral lesion hyperphagics 587 and 550.

Mean FR performance of the control rats and the single and double bilateral lesion hyperphagics is illustrated in Fig. 13. As in Experiment II, the sham-lesion controls decreased pressing slightly on FR 64 postoperatively, presumably due to the general effects of surgery. They then pressed more times per session as the FR schedule was increased. In contrast to Experiment II, however, both groups of hyperphagics pressed more than controls on all schedules in the postoperative period. There was no overlap between the control group and both single and double bilateral lesion hyperphagics on FR 64 and 256; on FR 512 variability became large in all groups and all groups overlapped.

Mean weight of the sham-lesion rats was 247 g on the first preoperative day on FR 64; single bilateral lesion rats 243; double bilateral lesion rats 237. Weight changes were:

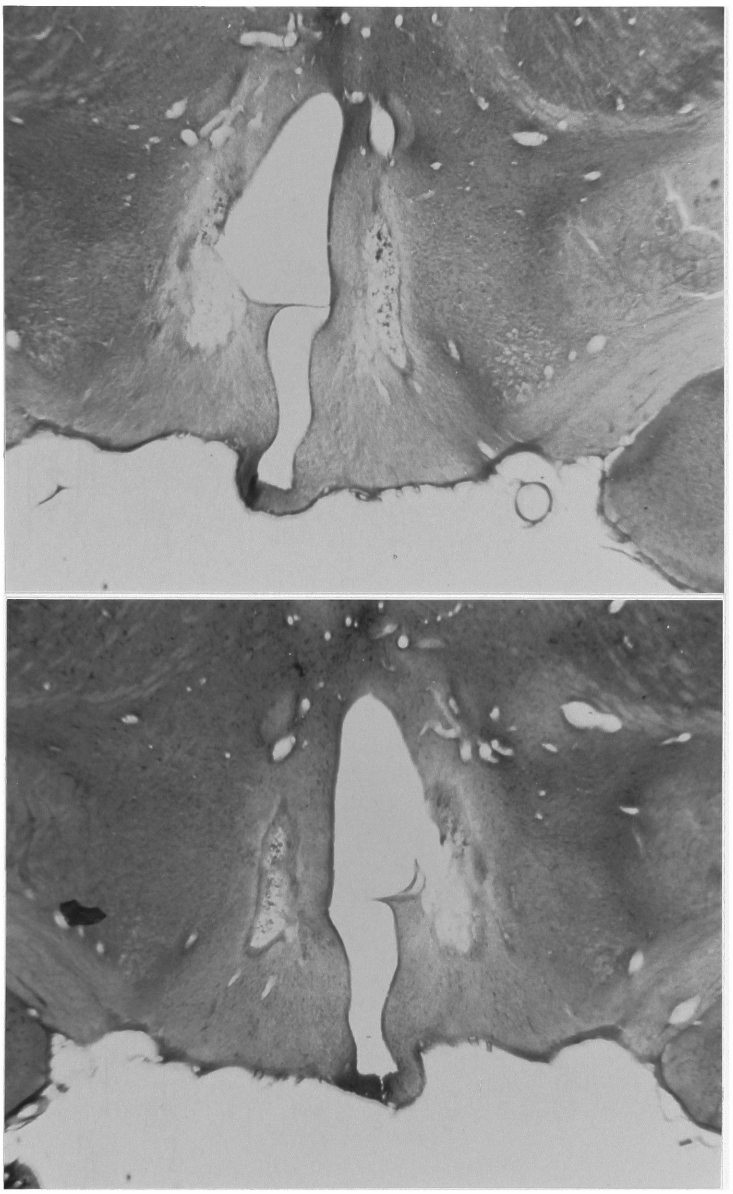

Fig. 12. (a) Potassium ferrocyanide stain of a lesion made with a platinum electrode. The blue grains indicate minute amounts of ferric ions in the lesion. These sections are from the posterior portion of the lesion of rat H-58. More iron is present in this section than occurred in almost any other rat in the platinum group. (b) Potassium ferricyanide stain of an adjacent section. No ferrous ions are indicated by the stain.

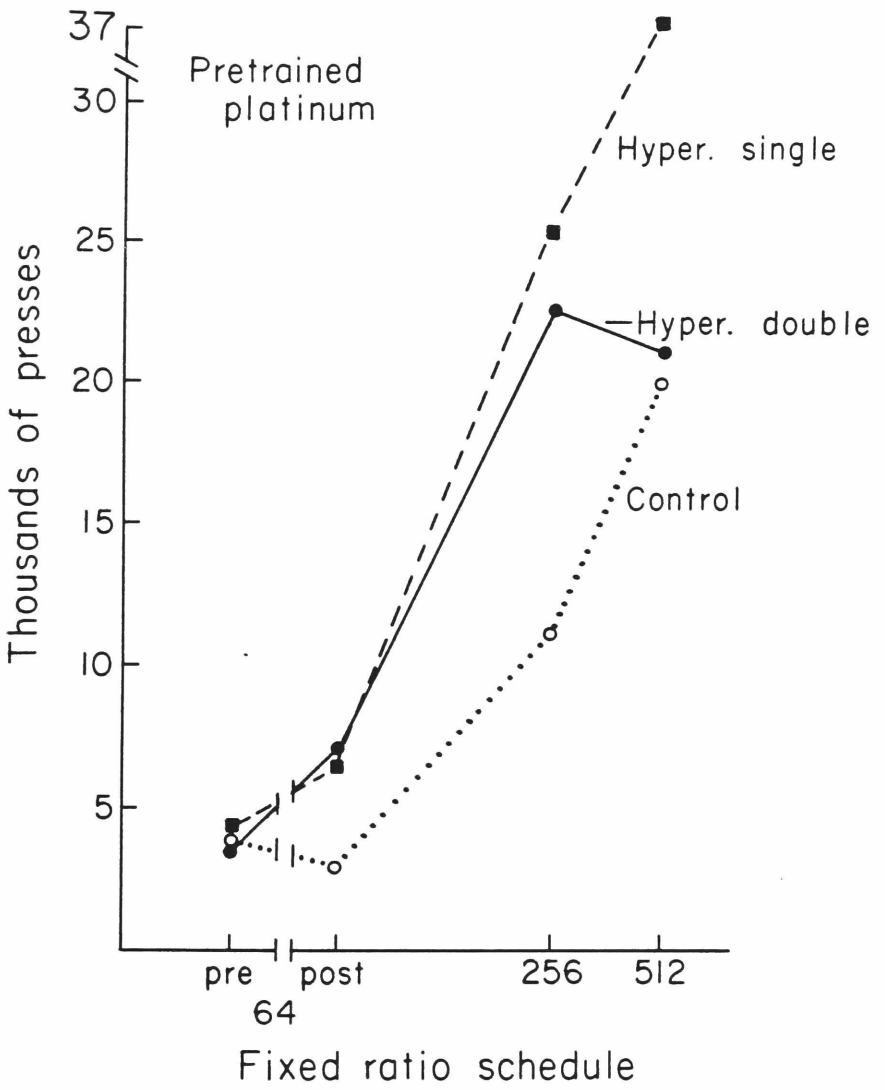

Fig. 13. Experiment IV: Number of presses (in thousands) per 12-hr session on each fixed ratio schedule. Preoperative values are means for 12-15 days; postoperative values are means for 2 days/schedule. Data are for 5 single bilateral lesion hyperphagics, 2 double bilateral lesion hyperphagics, and 5 sham lesion controls. For controls and singles: $p = .008$ on FR 64 post and FR 256; $p = .1$ on FR 512.

Table 4. Mean Weight Change per Day, FR 64

	Preoperative	Postoperative
Controls	0.5 g	0.6 g
Single bilateral	1.0	9.0
Double bilateral	0.6	16.5

All rats lost weight on FR 256 and FR 512.

The hyperphagic rats in Experiment IV sustained bilateral damage to the ventromedial area. The brains of the rats with double bilateral lesions (Appendix II, H-71 and H-77) had a continuous region of damage similar in extent and placement to that of the steel electrode rats in Experiments I and II. Histological material was not available from the brains of two of the single bilateral lesion rats.

Experiment V. Rats with implanted platinum electrodes were tested in continuous, 24-hr sessions after 13-16 days of FR 64 pretraining. Etherization and lesion or sham-lesion production were performed at the time of daily servicing, at 1030-1200. The rats were returned to the Skinner boxes as soon as they were able to walk, always within 7 min of the time current was passed through the electrodes. Four of the nine rats with lesions received 1 ma for 20 sec, and five received 2 ma for 25 sec. There were five sham-lesion controls. The schedule of reinforcement was kept at FR 64 for 5-8 days postlesion before increasing to FR 256 for 3 days and FR 512-2048 for 2 days each.

Three of the rats in the 1 ma-10 sec group and one rat in the 2 ma-25 sec group failed to exceed a weight of 400 g on ad lib milk. The other five rats with lesions became hyperphagic (409-730 g, mean = 526). Controls weighed 247-336 g (mean = 310). One hyperphagic rat (H-32) was hyperdypsic, drinking 90-130 ml of water per day while on milk diet. This rat lost 47 g when placed on dry laboratory chow and one control (H-36) lost 35 g; all other hyperphagics and controls maintained or increased the weights attained on ad lib milk.

Quinine tolerance scores were: controls 59-68%, hyperphagics 2-35% (computed as in Table 1, 0.2% quinine hydrochloride in 3:1 milk).

FR 64 performance of one hyperphagic rat is shown in Fig. 14. Pre-lesion pressing is steady, with a suggestion of a four day rhythmicity possibly due to the estrus cycle. Following the lesion, presses/day (and therefore intake) immediately doubled and stayed at this high level for the 8-day post-lesion period. This rat's post-lesion FR 64 performance was median among the five hyperphagics. Its weight at asymptote was 730 g.

Mean presses/day on FR 64-2048 are shown in Fig. 15. No overlap between the five hyperphagic and the five control rats' means occurred at FR 64; at FR 256 one hyperphagic, the lightest in asymptotic weight, fell in the range of controls. The number of presses/day was erratic on schedules above 256; for instance, H-34 pressed 4193 times during the first 24 hours on FR 512 and 30174 times during the second.

Mean weight of the sham-lesion rats was 266 g on the first preoperative day on FR 64; hyperphagics' was 272 g. Weight changes were:

Table 5. Mean Wegiht Change per Day, FR 64

	Preoperative	Postoperative
Controls	0.6 g	0.5 g
Hyperphagics	0.4	7.1

Mean weight changes were negative for all rats on FR 256 and above; hyperphagics and controls did not differ in rate of weight loss on these high schedules.

Cresyl-violet sections from the brain of H-34 indicate that the ventromedial and arcuate nuclei were completely destroyed but adjacent structures were almost entirely intact (Fig. 16, a-f). Electrode tracks from the implanted electrodes are visible. This lesion was one of the largest in this group (Appendix II). The lesion of H-32, the hyperdypsic rat, extended to the ventral dura bilaterally, unlike other platinum electrode lesions.

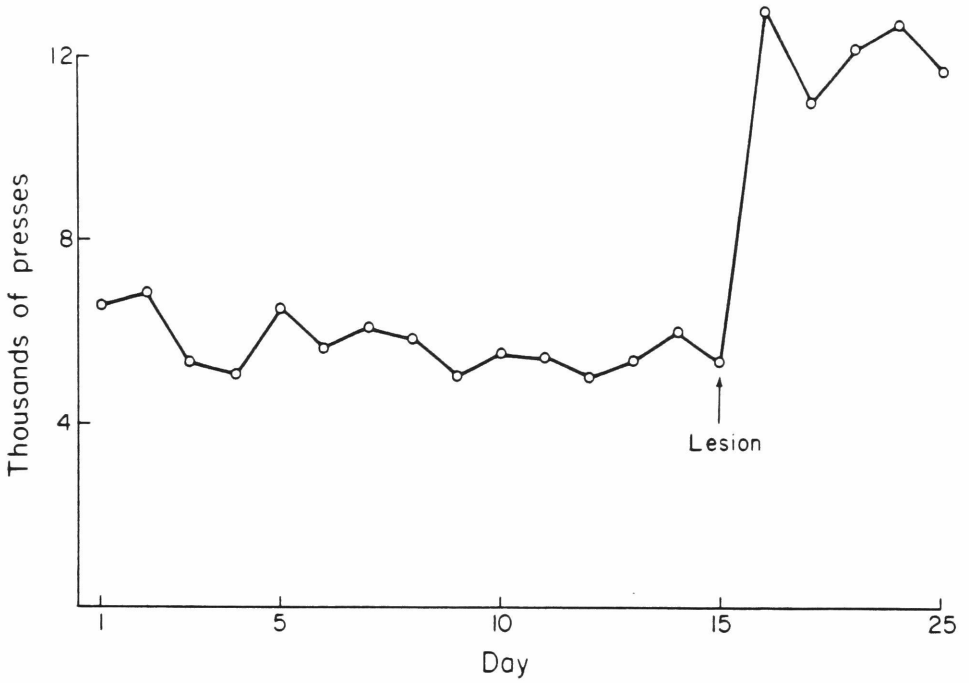

Fig. 14. Experiment V: Number of presses per 24 hr session on FR 64, before and after acute platinum electrode lesion. Lesion was made at the beginning of session 16. Data for the rat (H-34) which pressed the median number of times on FR 64 postoperatively.

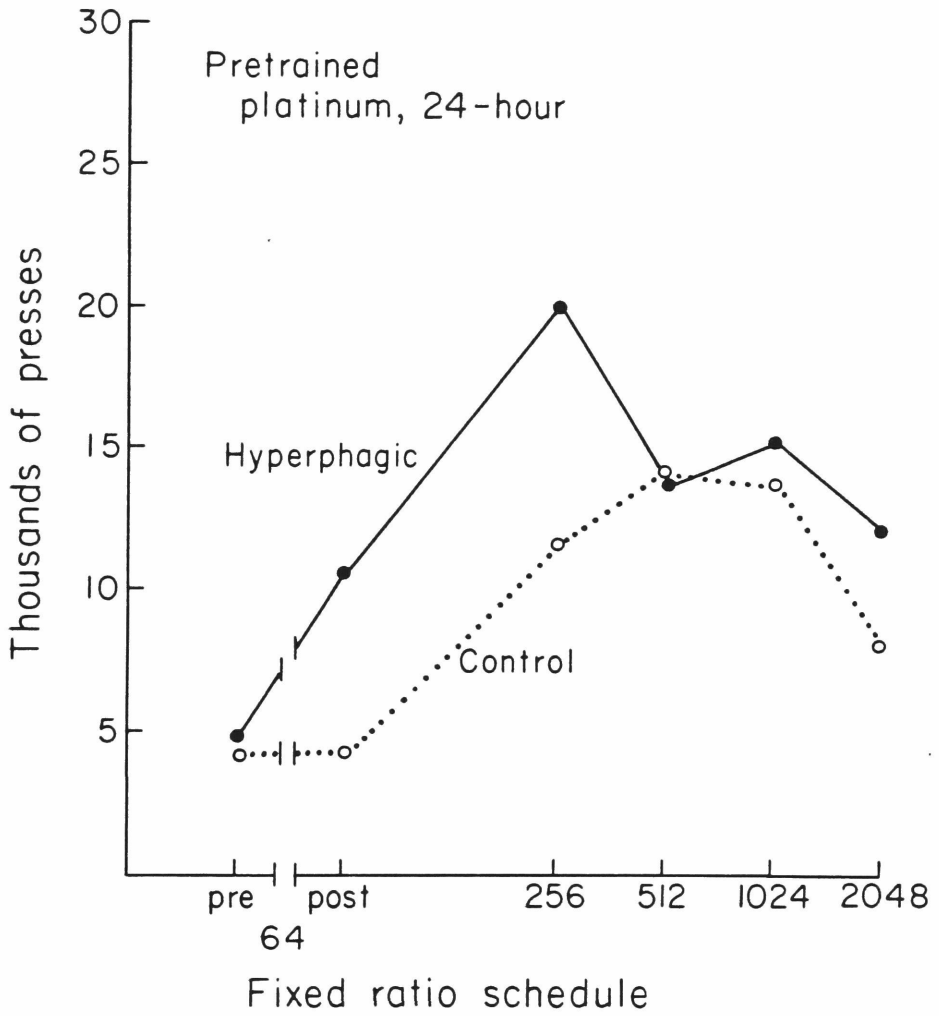

Fig. 15. Experiment V: Number of presses (in thousands) per 24-hr session on each fixed ratio schedule. Preoperative values are means for 13-16 days; postoperative values are means for 5-8 days on FR 64, 3 days on FR 256, and 2 days each on FR 512-2048. Data are for 5 hyperphagics and 5 controls. $p = .004$ on FR 64 post op. $p = .05$ on FR 256.

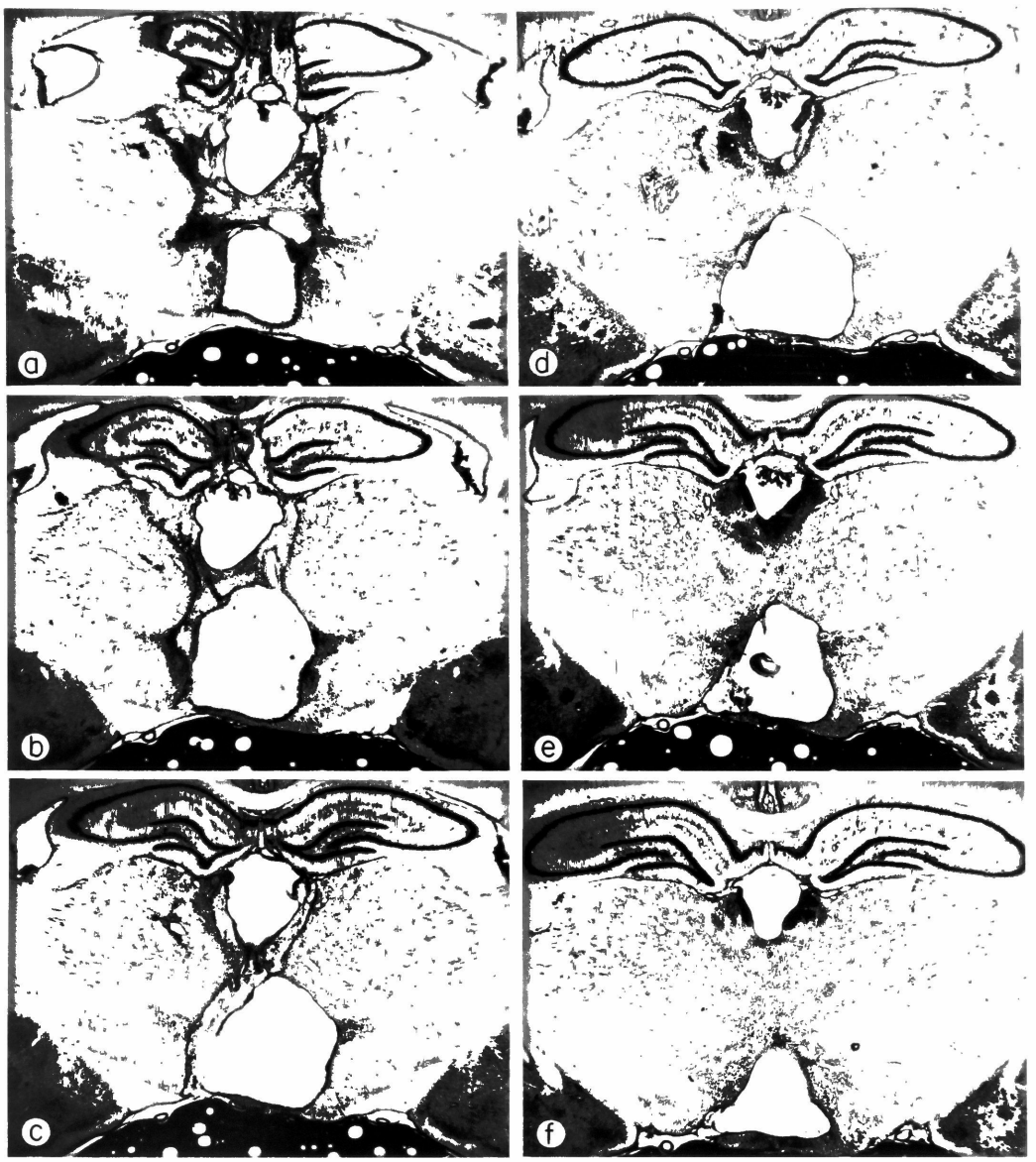

Fig. 16. Cresyl-violet stained transverse sections through the ventromedial lesion of rat H-34. a-f are arranged anterior-to-posterior at 200 μ intervals. Section a is 5660 μ anterior to the interaural line.

Other Variables

"Rate" of pressing. Cumulative records obtained during Experiment I (nonpretrained, steel electrodes) showed differences between hyperphagics and controls in the local rate of fixed ratio 64 responding (Fig. 17). Controls rarely paused except following reinforcements and pressed at a fast, steady pace, often taking several reinforcements in succession. Hyperphagics, on the other hand, paused frequently for short periods during the fixed ratio run and reinforcements were separated by long intervals. An attempt to quantify the difference in response "rate" is illustrated in Fig. 18a. Total duration of bouts (1 min criterion) of pressing for one day is divided into total presses for that day, giving an average "rate" of responding in presses/minute. Hyperphagics clearly pressed slower than controls on FR 64 and FR 256, the same schedules on which they pressed fewer times per day than controls (Fig. 2).

Hyperphagics in Experiment III (nonpretrained, platinum electrodes) did not press slower than controls on any schedule (Fig. 18b). In fact, it appears as if the hyperphagics pressed faster than controls on FR 64 and FR 256 in Experiment III. This apparent increase is due to the fact that hyperphagics took many reinforcements without pausing longer than one minute. The hyperphagics' shorter post-reinforcement pauses (p. 54) are thus confounded with local rate producing a spurious increase in this measure of "rate." (Such a confounding was not present in the analysis the hyperphagic group in Experiment I, due to the wide separation between reinforcements.) In Experiments II, IV, and V (all pretrained on FR 64), this measure of "rate" gave no significant differences between hyperphagics and controls.

In order to more accurately measure the local rate of pressing, I devised a method of representing the median fixed ratio run for a session using 1-sec resolution paper tape records. The method is based on the intuitively attractive procedure of measuring the slope of a cumulative record. Paper tape data is loaded into the memory of a digital computer and each reinforcement is located by counting modulo the FR schedule (i.e. FR 64). The median amount of time between Press 64

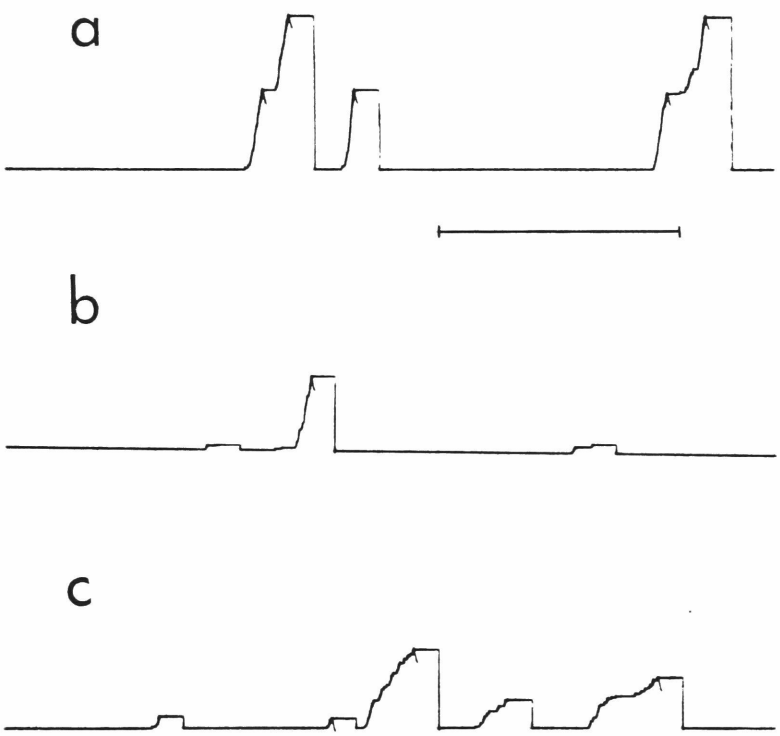

Fig. 17. Experiment I: Representative cumulative records on FR 64. A control rat (a) and hyperphagics with high (b) and low (c) rates of response. Records are reset after one minute without responding; all records are from beginning part of second FR 64 session.

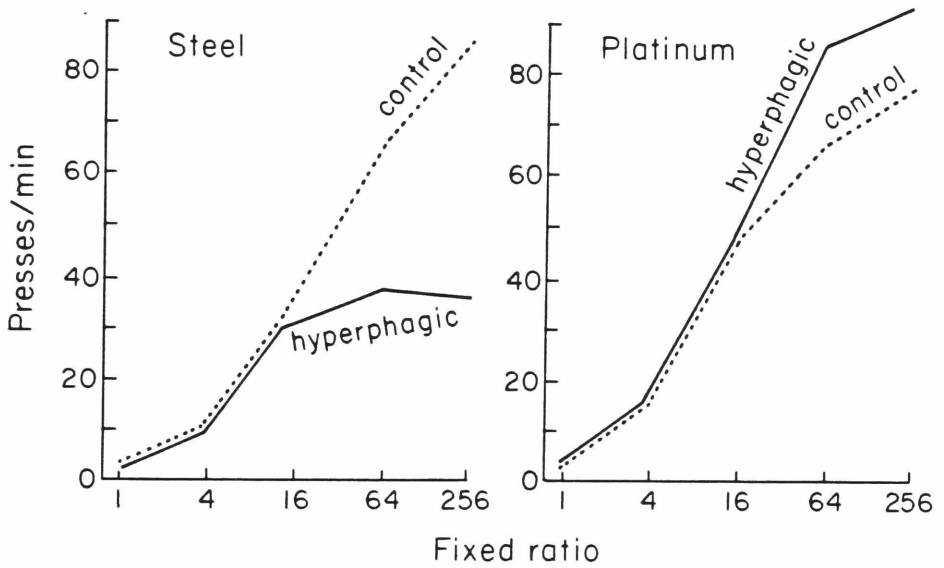

Fig. 18a (left). Experiment I: Mean "rate" of pressing as a function of fixed ratio. "rate" was derived by totalling the time the animal was engaged in bouts of pressing during a session and dividing into the total number of presses for that session. Data for 3 hyperphagics and 3 controls.

Fig. 18b (right). ExperimentIII: Same as 18a. Data for 4 hyperphagics and 3 controls.

(the one which is reinforced on FR 64) and Press 63 is determined, then the median time between Press 64 and Press 62. This process is repeated for each press, working backward to Press 1. Since the median is used, infrequent long pauses have little effect on the result.

Median FR runs for FR 4 to FR 1024 are plotted in Fig. 19. In each case, the press which satisfied the criterion is located at the upper right and the presses which precede it extend back in time. In this manner the cumulative record of the "typical" (i.e. median) FR run for each day is plotted. The curves, especially those for FR 64 and FR 256, have an initial, postively accelerating portion and a final, nearly linear portion. The slope of the linear portion, expressed in presses/sec, provides a measure of rate of pressing which is free of arbitrary assumptions, free of post-reinforcement pauses, and which is highly reproducible on succeeding days on a given schedule. As can be seen in Fig. 19, no effect of ventromedial lesions on bar-press rate is evident from the median FR runs of nonpretrained, platinum electrode rats of Experiment III. Similar lack of effect was seen in Experiments II and IV.

In order to quantitatively compare the slopes of the median FR runs of controls with those of rats with lesions in Experiments II, III, and IV, the slope of the latter one half of each median FR run was determined by the least squares technique. Slopes varied from 3.2 presses/sec to 6.0 presses/sec. In no case did the central tendency of the change in slope, postoperative minus preoperative, differ from zero. The slope of the rats with lesions was more variable than that of controls, but sometimes increased and sometimes decreased following the lesion.

In summary, no effect of ventromedial lesions on any measure of FR local rate was seen in any experiment except Experiment I, the non-pretrained, steel electrode condition.

In order to ascertain the effect of deprivation upon rate of fixed ratio responding under the conditions of extensive pretraining

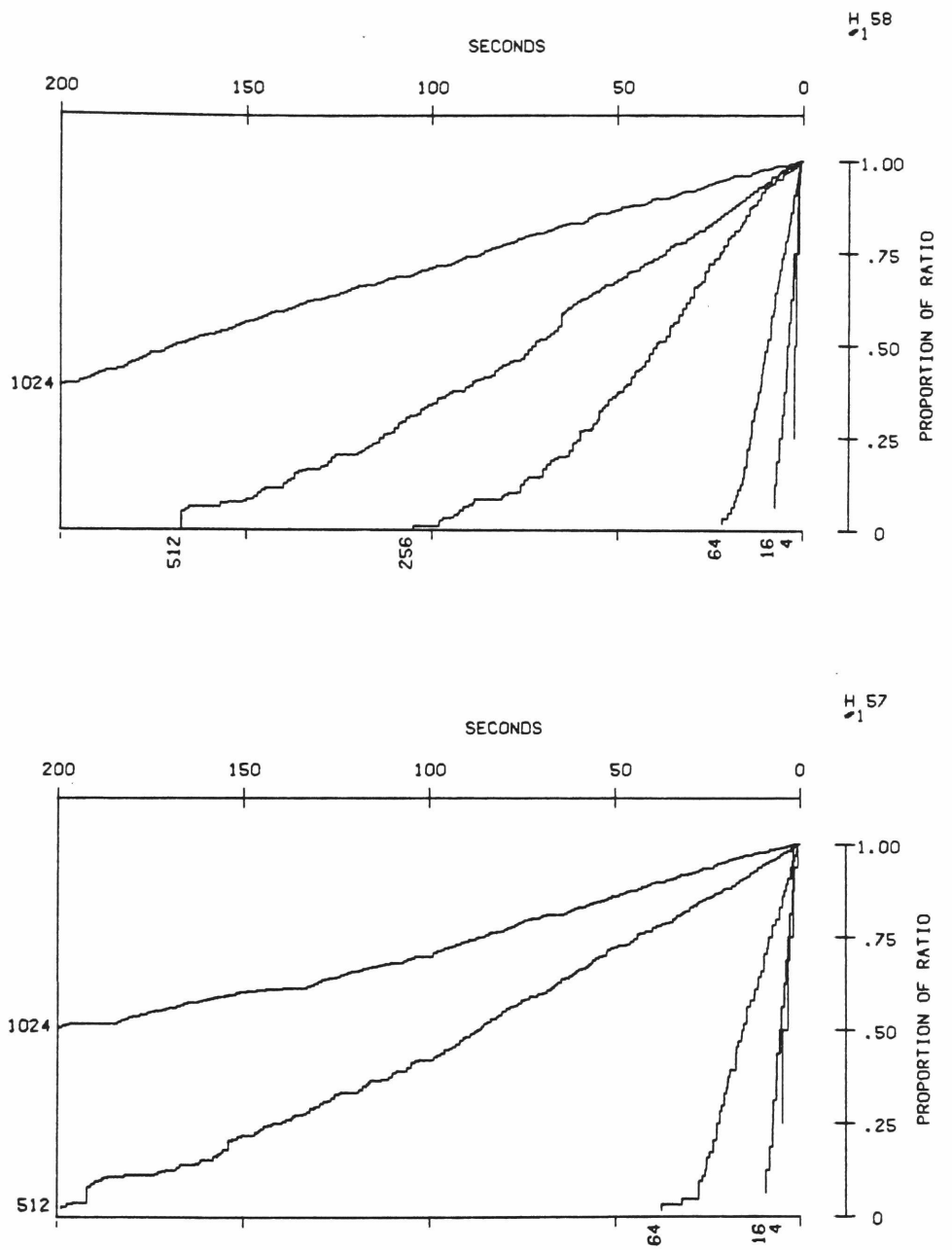

Fig. 19. Experiment III: Median fixed ratio run for the first day on each FR schedule for a hyperphagic (H-58, top) and a control (H-57, bottom). No data are available from the first day of FR 256 for H-57.

imposed in these experiments, six rats were deprived for 36 hours and rates of pressing were measured before and after the period of deprivation. This was done during the FR 64 pretraining period of Experiment III. Since paper tape equipment was not available at this time, presses were recorded to 2 msec resolution on audio tape (Larkin, 1972). Pressing rates were summarized for individual bouts of pressing and for the entire session before and following the 36 hour deprivation period. No differences in pressing rates were observed. Fig. 20 (top curve) shows a typical IRT histogram for the post-deprivation day and (bottom curve) the difference between the pre- and post-deprivation day. Deprivation does not affect pressing rate.

Post-reinforcement pause duration is longer in satiated than in deprived rats. In order to determine the effect of ventromedial lesions on this parameter, median post-reinforcement pause durations were computed for Experiments III and IV. (Insufficient reinforcements were acquired by hyperphagics in Experiment II to allow meaningful conclusions to be drawn.) The minimum post-reinforcement pause was also computed and showed the same trends as the median. Post-reinforcement pauses were corrected by subtracting the 9-sec duration of the reinforcement presentation, since presses in this period were without effect.

Durations for the four rats in Experiment III for which complete data could be obtained are shown in Fig. 21. Duration and variability of duration increases above FR 16 in both hyperphagics and controls. Durations in these nonpretrained rats were not affected in any obvious way by the lesion.

It seems likely that pretraining might stabilize post-reinforcement pause durations and allow a clearer comparison of hyperphagics with controls. This proved to be so in Experiment IV (Table 5). Hyperphagics decreased post-reinforcement pause durations on FR 64 following the lesion; controls increased following the sham-lesion. FR 256 and FR 512 showed similar trends of shorter durations in hyperphagic rats.

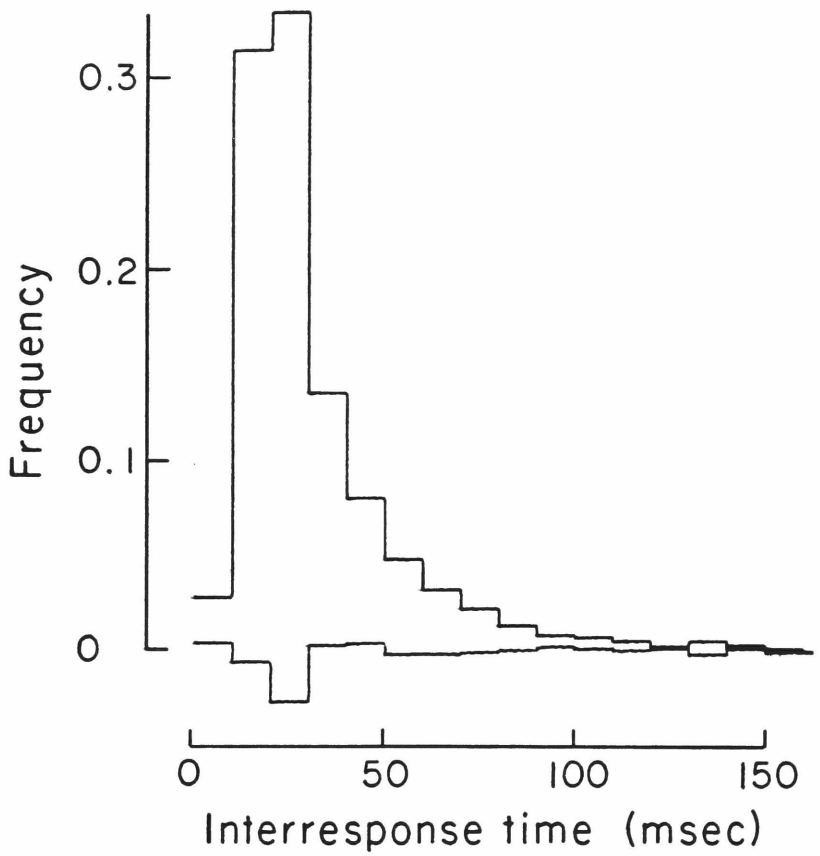

Fig. 20. Interresponse time (IRT) histogram and difference histogram, FR 64. The top curve is an IRT histogram of 100 msec binwidth taken for an entire 12-hr session on 3/16/72. The bottom curve is the result of subtracting a similar histogram taken on 3/14 from the 3/16 histogram. On 3/15 the animal was food deprived in the home cage. The bottom curve shows that no significant differences in interresponse time distributions result from deprivation.

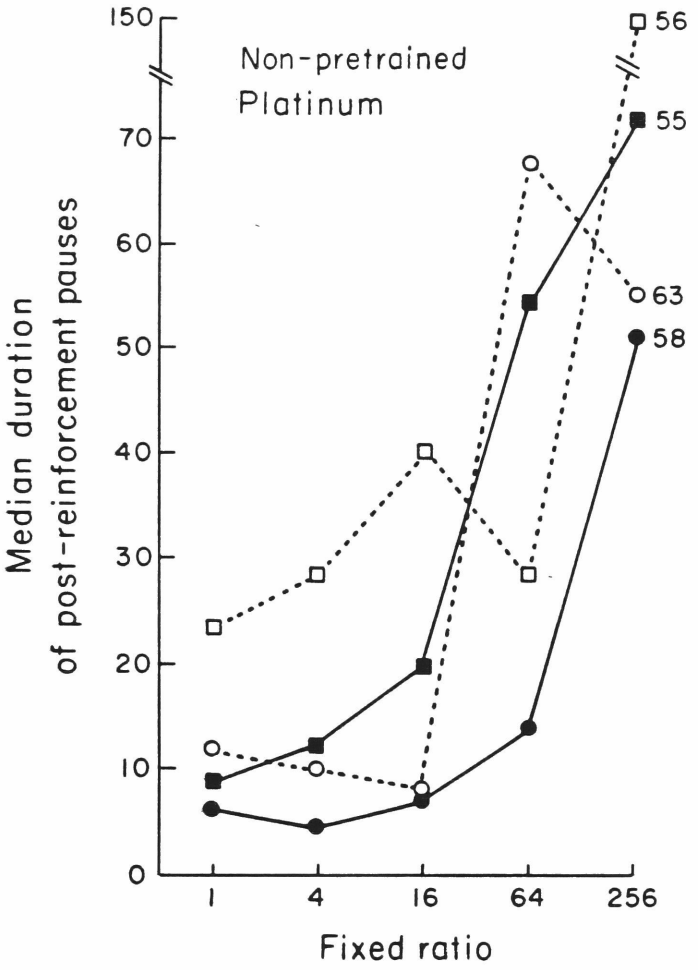

Fig. 21. Experiment III: Median post-reinforcement pause duration as a function of fixed ratio for four individual rats. Solid lines (H-55 & H-58) are hyperphagic rats, dotted lines (H-56 & H-63) are controls.

Table 5. Median Post-reinforcement Pause Durations, Experiment IV: FR 64.

	Preoperative	Change (pre-post)
Controls	11 to 14 sec	+14 to +22 sec
Single bilateral lesion Hyperphagics	7.5 to 21	-0.5 to -8.0

Day-night distributions of reinforcements in Experiment V showed the increased daytime eating which others have reported for ad lib feeding. Preceding the lesions, four hyperphagics obtained 21-27% (mean 24.3%) of FR 64 reinforcements during the 12-hour illuminated period. During the 5-8 day postoperative FR 64 period this proportion increased to 42-51% (mean 46.8%). Furthermore, this increase was not due to the "first meal" phenomenon discussed on page 8. Preoperatively, the mean percentage of reinforcements obtained during the first hour after servicing was 4.60%; postoperatively 4.55%. This close match is similar to the value expected if the rats distributed their feeding randomly throughout the 24-hour cycle: 4.16%. As shown in Fig. 22, both hyperphagic rats (H-25) and non-hyperphagic rats with lesions (H-26) alter the day-night distribution of pressing following the lesion. I conclude that increased daytime feeding occurs in rats with platinum-produced lesions and that the increase is unrelated to a "first meal" phenomenon.

Presses in the first hour provide an indication of the effect of 12-hour deprivation in Experiments I-IV. If "post-starvation anorexia" is significant, this measure should decrease postoperatively in lesioned rats. Nonpretrained hyperphagics, the steel group as well as the platinum group, pressed proportionally more in the first hour of the 12-hour session than controls (Fig. 23). The pretrained, steel electrode rats (Experiment II) usually pressed in an intermittent fashion and their data are not readily amenable to summarizing. The pretrained, platinum electrode rats (Experiment IV) showed an increase in the proportion of pressing in the first hour on FR 64:

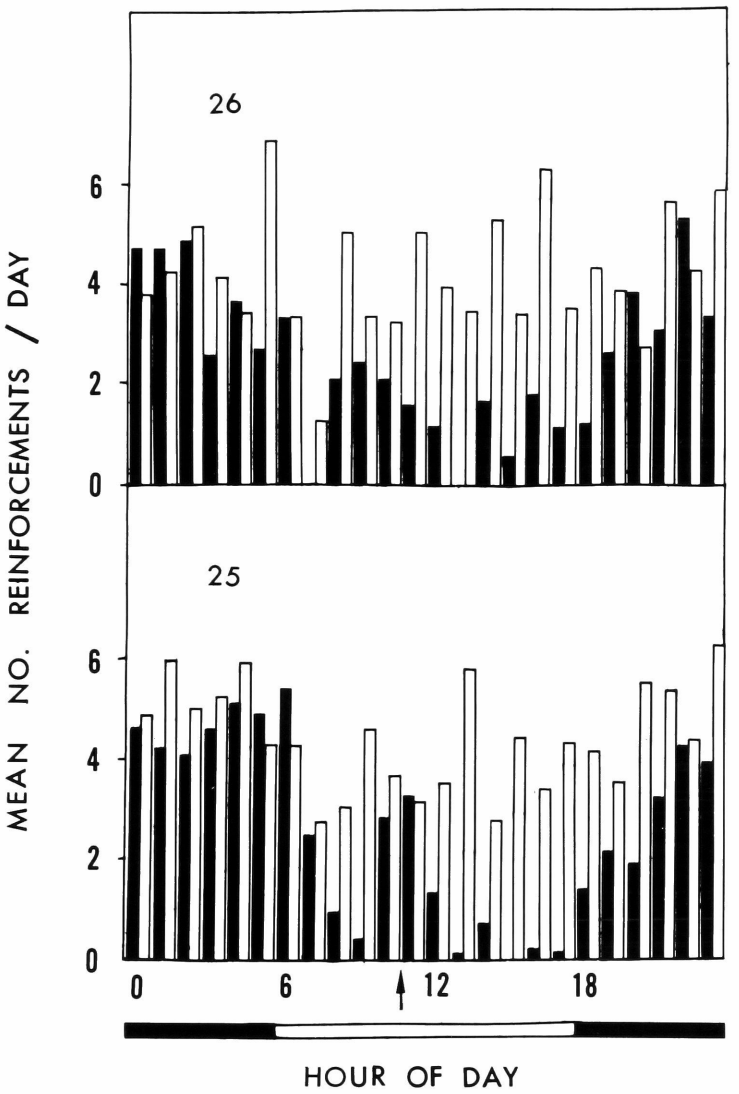

Fig. 22. Experiment V: Mean number of reinforcements for each hour of the day for 12 preoperative days (solid bars) and 8 postoperative days (open bars). H-25 (bottom) is a hyperphagic, H-26 (top) is a non-hyperphagic rat with small ventromedial lesions.

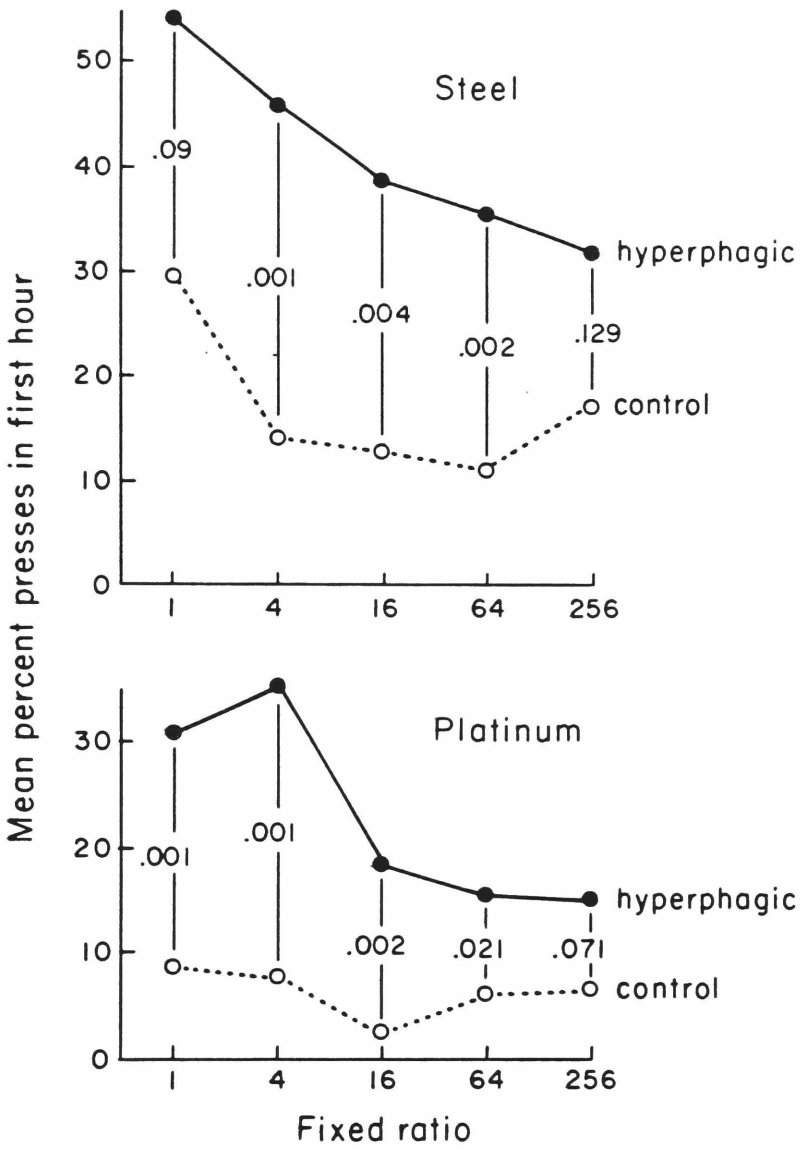

Fig. 23. Mean percent of presses occurring in the first hour of 12-hr sessions as a function of fixed ratio. Top: Experiment I, nonpretrained rats with steel electrodes (3 hyperphagics, 3 controls). Bottom: Experiment III, nonpretrained rats with platinum electrodes (4 hyperphagics, 3 controls). Probabilities are computed from daily sessions by the Mann-Whitney U Test (Siegel, 1956).

Table 6. Mean Percent Presses in First Hour after Servicing

	Preoperative	Postoperative
Controls	16.3%	14.7%
Single bilateral lesion hyperphagics	17.5	34.7

One of the double bilateral lesion hyperphagics, H-71, was especially prone to press in the first hour. Postoperatively this rat usually began to press with its forefeet before its hind feet had left the scale pan used to transport the rats to the Skinner boxes.

Hyperphagics press (and eat) proportionally more in the first hour of 12-hour session than controls. Instead of the subnormal level of feeding after deprivation seen in the "post-starvation anorexia" effect, the hyperphagics responded to deprivation by supernormal feeding. Since the presses in the first hour almost always corresponded to the first meal following deprivation, these hyperphagics, like animals deprived for a long period, ate a large first meal at the start of a lever pressing session.

Meal sizes increase following ventromedial lesions made with steel electrodes when animals are fed ad lib food. In Experiment V (pretrained, platinum electrodes, continuous sessions), data on meals (bouts of pressing) were taken in order to ascertain the effect of platinum electrodes and the effect of the FR 64 contingency. In this analysis it is important to specify a suitable criterion for the separation of adjacent meals (Kissileff, 1970). Such a criterion was found by constructing intermeal interval survivorship curves (Cox and Lewis, 1966) for each rat, using meal data gathered at a 1 min criterion (Fig. 24). These curves could be approximated by two straight line segments in all cases, with a sharp junction occurring at 3.5-10.5 min. This point, where the slope suddenly changes, demarcates the rapid process of taking successive reinforcements within a meal from the slower process of initiating successive meals (cf. Cox and Lewis, 1966).

Survivorship curves of intermeal intervals were constructed at 0.1 min resolution for each of five animals, one control and four

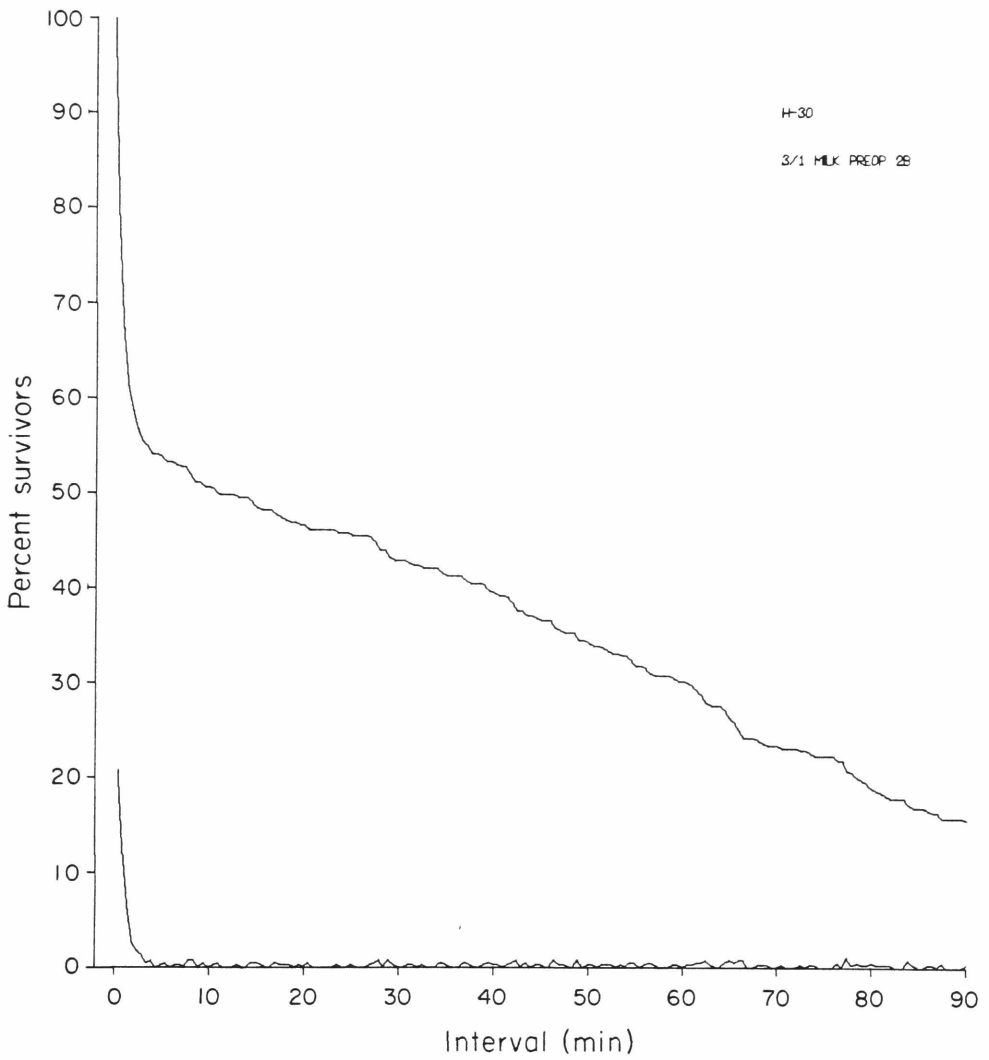

Fig. 24. Interval survivorship curve for the meals of one hyperphagic rat (H-30) during the 13 day preoperative period. Since 1.0 min is the shortest interval measured, 100% of intervals between meals are at least 1.0 min; 54% of intervals are at least 6.5 min; at this point the absolute derivative of the interval survivorship curve (a histogram, shown along the bottom of the plot) reaches zero and remains at zero for 0.1 min. This value (6.5 min) is the meal criterion used for H-30. Time resolution is 0.1 min.

hyperphagics, on FR 64 in Experiment V. The first point at which the derivative of each survivorship curve remained zero for two consecutive 0.1 min bins was chosen as the optimum meal criterion; this point was always close to the abrupt change in slope. The optimum criterion varied between rats but did not change more than 0.5 min following lesion or sham-lesion production in any individual rat. The same criterion was employed for the preoperative and postoperative days.

Since mean meal size may not be sensitive to changes in meal size distribution under some conditions (Kissileff, 1970), distributions of meal sizes were plotted and both mean and modal meal size values were computed. Table 7 shows that meal sizes increased following the lesion in 3 or 4 hyperphagic rats and that sham-lesions did not affect meal sizes. Day, night, and total distributions of meal sizes were not different.

Size-interval correlations are of possible interest with respect to the integration of feeding behavior following ventromedial lesions. If "satiety," defined as the propensity for ingested food to inhibit eating, is diminished following ventromedial lesions (Miller et al., 1950), then a large meal should inhibit eating no longer than a small meal. The correlation between meal size and succeeding interval (Appendix I) should become more negative following ventromedial lesions. Preceding and succeeding correlations were performed on day, night, and total meals for five rats from Experiment V. All correlations were low (only 2 of 60 were greater than 0.5); such low correlations are similar to those seen in normal rats feeding ad lib (Appendix I). Both preceding and succeeding correlations became more positive following ventromedial lesions, indicating that this aspect of "satiety" is not diminished following ventromedial lesions.

Latency to eat following the production of ventromedial lesions with chronically implanted electrodes has not previously been reported. In Experiment III latencies to eat were obtained using a standard procedure. Rats were etherized to immobility during the lesion producing procedure, then placed on a table and watched. 1 min ± 5 sec following the first head movement or other bodily movement they were returned to

Table 7

Rat	Criterion (min)	Mean Size (dips)			Modal Size (dips)		
		Day	Night	Total	Day	Night	Total
25 pre	10.0	2.4	2.8	2.6	2	2	2
post	10.0	4.1	4.2	4.1	4	4	4
30 pre	6.5	5.8	4.5	4.7	6	7	7
post	6.5	10.9	9.3	9.9	10	11	11
31 pre	6.5	3.1	2.8	2.9	2	2	2
post	6.5	6.9	5.6	6.4	8	7	8
34 pre	7.0	4.0	5.8	5.3	7	7	7
post	7.0	6.5	6.2	6.3	7	7	7
36 pre	4.0	2.2	3.5	3.2	3	6	3
post	4.0	2.6	2.7	2.7	4	3	3

Meal sizes, Experiment V. Means and modes of pre- and post-operative meal size distributions for four hyperphagic rats and one control rat. N is between 42 and 355 in each cell. When bimodal distributions occurred, the value was chosen which was nearest to the mean. Hyperphagics 25-31 increased meal size following the lesion. Hyperphagic 34 did not significantly change. Control 36 and other sham-lesion rats did not change following sham-lesion.

the home cage and given a fresh tube of milk. Latencies were measured from the time of introduction of the home cage until the time of initiation of the first coordinated (rhythmical) burst of licks. Latencies greater than 600 sec were not recorded. Meal sizes were recorded using a criterion of 5 min.

One hyperphagic rat (H-59) showed severe ataxia following lesion placement; it was not included in the latency measure. Latencies were shorter and meal sizes were greater in hyperphagics (Table 8).

Table 8. Latencies and meal sizes, Experiment III.

		Latency to eat (sec)	Meal size (ml)
H-56	control	405	1
H-57	control	325	1
H-63	control	600	0
H-54	hyperphagic	225	12
H-55	hyperphagic	55	17
H-58	hyperphagic	90	16

Differences between hyperphagics and controls are significant on both measures (Mann-Whitney U Test, $p = .05$). The differences are not due to disparities in the time taken to recover from the anesthetic--hyperphagics usually began to eat as soon as they began to stagger around the cage, but controls usually groomed and explored for several minutes before eating.

Biting the experimenter was an infrequent behavior for almost all rats in Experiments II-V. Three rats with lesions (2 steel, 1 platinum) bit regularly; no other rat with or without a lesion bit more than two times total. "Irritability" was not a general characteristic of these ventromedial rats.

Chapter 4. DISCUSSION OF LESION EXPERIMENTS

Comparison of Rats with Ventromedial Lesions with Food Deprived Rats

Does the operation of producing a lesion in the ventromedial area have an effect on an animal's behavior similar to the effect of depriving it of food? If so, then it may be profitable to regard the hypothalamus as a site where information about the body's caloric stores is integrated and used to influence different kinds of food-related behavior (Powley and Keesey, 1970; Nisbett, 1972). If not, then perhaps hypothalamic hyperphagia is simply a "side effect" of a more general affective disturbance (Grossman, 1966).

Table 9 provides a summary comparison of deprived rats with steel and platinum electrode hyperphagics. With two exceptions, the effects of deprivation and of both types of ventromedial lesions are uniformly in the same direction. Generally, we can conclude that ventromedial lesions affect food-related behavior in a manner similar to deprivation. For most of these behaviors, the paradox of "decreased hunger but increased food intake" is resolved, provided that appropriate experimental conditions are chosen. This conclusion is compatible with most data on the physiology of the ventromedial region. Its very acceptability, however, occasions our interest in the two exceptions to the generality: decreased quinine tolerance in hyperphagics and reduced lever pressing in steel electrode hyperphagics.

Both steel electrode lesions and platinum ones appeared to decrease quinine tolerance. (Especially in light of the disparaties which appear in published work (page 9), it should be noted that quinine tolerance was somewhat higher in platinum lesion hyperphagics than in steel lesion ones.) Several possible factors may account for the decreased quinine tolerance seen in these experiments. First, the weights of the hyperphagics at the time of testing were as much as 50% greater than those of the controls. Quinine tests immediately after the lesions are placed would be necessary to completely control this type of confounding, which is common to almost all published reports of "finickiness." Second, hyperphagics may require "pretraining"

Table 9

Measure	Deprivation	Effect of Pt Lesion	Steel Lesion
Ad lib intake	+	+	+
Number of presses (pretrained animal)	+	+	-
Latency to eat (inverse)	+	+	+
Size of first meal	+	+	+
Post-RF pause duration (inverse)	+	+	n.a.
Quinine tolerance	+	-	-
Local rate on FR schedule	0	0	0

Effect of Deprivation and of Ventromedial Lesions on some Behavioral Measures. Effects on deprivation were taken from the literature as summarized in Chapter 1. Effect of lesions made with steel electrodes on latency to eat is work of Sclafani, 1971 and Marks and Remley, 1972. Other effects are from present experiments. Effects are arranged so that the direction of the effect on deprivation is positive.

or habituation to quinine in order to show increased quinine tolerance. The lever pressing results in the platinum groups support such an interpretation, as does the partial habituation of young guinea pigs to SOA (Warren and Pfaffmann, 1958). Third, there may be specific quinine-responsive neurons near the ventromedial nuclei. Such cells may or may not be distinct from the main neural system controlling food intake, but they could be anatomically located such that they are usually damaged by ventromedial lesions which produce hyperphagia. This line of reasoning is supported by the work of Graff and Stellar (1962). It is also in agreement with work showing that quinine-responsive neurons are present near the ventromedial nuclei but are not found elsewhere in the hypothalamus (Norgren, 1970).

Variables Influencing Operant Responding for Food by Hyperphagic Rats

Since the influential studies of Miller et al. (1950) and Teitelbaum (1957), further research has demonstrated that the second exception, the paradoxical observation of decreased operant responding but increased food intake, occurs in some conditions but not in others. Fourteen studies not including the present one are summarized in Table 10. They include all published and unpublished experiments known to me on food-reinforced responding following electrical damage to the ventromedial area. (Three experiments, Knott et al., 1960; Balinska, 1967; and Helms and Kuenzel, 1969 are so unconventional as to prohibit meaningful comparison with those in Table 10.) Most of the studies present one or more serious methodological difficulties which hamper one's ability to make general conclusions. There is enough work, however, to allow tentative identification of a few critical variables.

The characteristics of the operant task have received little experimental treatment in spite of their obvious importance. Is the energy expenditure involved in performing the task of significance? Is resistance to extinction greater following ventromedial lesions? Investigators appear to have chosen operant measures relying on guesswork or precedence.

STUDY	TASK	PRETRAINING	SESSION	DEPRIVATION	REINFORCEMENT	WT. DIFF.	SEX	SHAM?	METAL	CURRENT
INCREASED RESPONDING										
Falk, 1961	VI 1'	several days	3.17 hr.	75-80% wt.	Noyes	0	♀	-	?	? (1)
Hamilton & Brobeck, 1964	FR 1-64	30 days total	1 hr.	22 hr.	0.7 g. pellets	?	♂(2)	no	steel	3 ma. 30"
Beatty, 1971	FR 1-32	repeated testing	30 min.	manipulated	sucrose solutions	manipulated	♀	yes	?	1.6 ma. 10"
Kent & Peters, 1971	VI 1'	24 sessions	1 hr.	80-110% wt.	Noyes	0	♀	no	?	2 ma. 20"
	runway	some	5 trials/day	same	Noyes	0				
Brittain, et al. 1972	mult FR 5 VI 1'	some	weekly sessions	?	?	0-150 g.	♀	yes	steel	2 ma. 20"
Porter & Allen, 1972	VI 1'	10 sessions	30 min.	(3)	Noyes	0 & 155 g.	♀	-	steel	1.5 ma. 15"
Wampler, 1972	VI 2'	14-48 days	50 min.	85% wt.	Noyes (?)	0	♀	-	platinum	DC, 3 sets of parameters

(1) Few details given.
(2) Macaca.
(3) 5, 10, 15, & 20% body wt.

STUDY	TASK	PRETRAINING	SESSION	DEPRIVATION	REINFORCEMENT	WT. DIFF.	SEX	SHAM?	METAL	CURRENT
DECREASED RESPONDING										
Miller, et al., 1950 (1)	FI (VI ?) 5'	some	20 min.	0-96 hr.	"pellet"	10 g.	♂	½	?	2 ma. 20"
	alley run	"thorough"	1-4 trials	0 & 72 hr.	"food"	30 g.				
	lid lift	none	continuous	none	high-fat diet	100 g.				
Teitelbaum, 1957	FR 1-256	none	12 hr.	12 hr.	lab chow pellet	20 g.	♀	no	?	1 ma. 15"
Singh, 1970	FR 1,16,64	FR 1 only	12 hr.	12 hr.	Noyes + cellulose	50 g. 80 g.	♂♀	yes	steel	3 ma. 20"
Sclafani, 1971	FR 1-256	none	30 min.	85% wt.	Noyes	0	♀	yes	steel	2 ma. 10-30"
Storlein & Albert, 1972	FR 1-128	none	1 hr.	22 hr.	Noyes	?	♀	yes	steel	2 ma. 15"
MIXED RESULTS										
Hamilton, 1963 (2)	FR 4-256	confounded with wt. & temp.	2 hr.	1 pellet/day	Noyes	122 g.	♂	no	steel	2 ma. 30"
Marks & Remley, 1972	VI 2'	some	2 hr.	90% wt.	Noyes	0	♀	no	steel	2 ma. 20" or RF 25-30 ma. 15" double

(1) Contrary results mentioned in later (1955) paper.
(2) Pretrained animals pressed more; non-pretrained ones pressed less.

A few variables are of only minor importance in most conditions. As seen in Table 10, session length need not be great to obtain good operant responding from rats with ventromedial lesions. This is in agreement with my results--neither handling the rats nor "post starvation anorexia" hinders them from taking 20-50% of their daily intake within an hour of being placed in the Skinner box. Implanted electrodes were also of minor importance, except that responding on days 1 and 2 following surgery was sometimes decreased when implanted electrodes were not used.

Four variables emerge as critical to the operant responding of hypothalamic hyperphagic rats. Palatability of the food reward has been investigated in two experiments. An experiment by Singh (1970) is difficult to interpret because the rats appeared to be hypophagic for a long period following the lesion. But a study by Beatty (1970), using two sucrose solutions, found reliable differences in FR responding by hyperphagic rats. The highly palatable diets used in the present study may have facilitated the performance of the hyperphagic rats.

Weight differences between hyperphagics and controls have been cited to account for decreased responding by hyperphagics. Porter and Allen (1972) tested rats with ventromedial lesions immediately following surgery and again as obese rats and found that they pressed fewer times when obese. Brittain et al. (1972) found that VI pressing decreased as body weight increased in hyperphagic rats. The decreased ability of obese rats to maintain normal body temperature when exercising (Han and Brobeck, 1961) has been suggested as an explanation of the decreased responding of obese hyperphagics (Hamilton, 1963; Barfosky et al., 1970). In the present experiments, responding at FR 256 and above may have been higher in hyperphagics if they had not been heavier in body weight than controls.

Pretraining appeared necessary for the platinum electrode groups in the present study to exceed the FR performance of controls at high ratios. Animals in Experiment III fell behind controls on FR 256 and above, but those in Experiments IV and V did not. This variable has not been mentioned as significant; however, some studies have used

pretrained animals and some have not (Table 10). Since no author mentions a reason for using pretrained or nonpretrained rats, this parameter may vary virtually randomly with respect to other parameters. (However, the experimenters who pretrained their animals may have been more careful in other respects than those who did not.) Eleven studies on rats specify the amount of pretraining, if any, given postoperatively.[1] Of these, five report deficits in operant performance by hyperphagic rats; none use pretrained animals. Six report increased operant performance in hyperphagics; all use pretrained animals. Hamilton (1963) confounded postoperative practice with environmental temperature; nevertheless the practiced hyperphagics performed better than controls. No other variable allows such an easy distinction to be made: pretrained hyperphagics respond more than controls, nonpretrained ones less.

I have encountered no published work concerning the possibility of a learning deficit in rats with ventromedial lesions. One study (Balinska et al., 1961) found impaired discrimination performance in hypothalamic hyperphagic rabbits. It is possible that "hyperreactivity" to a learning situation (Grossman, 1966) or "disinhibition" similar to that seen in rats with septal lesions (McCleary, 1966; Singh and Meyer, 1968; Singh, 1972) somehow impairs the ability of hyperphagic rats to adapt to a partial reward schedule.

The type of electrode used to produce the lesion proved to have a powerful effect upon lever pressing on high FR schedules. A discussion of published work bearing on this point will appear in Chapter 6, following presentation of results on procaine anesthetization of the ventromedial area (Chapter 5). Meanwhile, let us examine some possible explanations for the steel-platinum difference.

It could be argued that platinum electrodes do not produce "typical" hypothalamic hyperphagic rats. Examining the results of the

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[1] I do not consider CRF to be "pretraining" when animals are tested on more demanding schedules.

present experiments, we see that the platinum electrode rats are hyperphagic (i.e. overeat and become obese), eat larger meals, show marked flattening of the light-dark food intake rhythm, are finicky, and have a decreased latency to eat. If differences in other factors (i.e. "hyperreactivity") occur, they were not apparent from the data.

Perhaps the steel electrode rats were debilitated following the lesion. Since decreased operant responding is essentially a negative result, one might suspect that many different kinds of injury to the animal could be responsible. The relatively specific nature of the deficit found in Experiments I and II belies this line of reasoning. The animals were hyperphagic when placed on ad lib food before and after the lever pressing tests; furthermore, the deficit usually appeared at high ratios and not at low ones. This occurred in Experiment II in spite of the fact that all rats had pressed the lever at least 50,000 times on FR 64 during the preoperative training period.

One can also pose the opposite argument. Perhaps the steel lesions produce such a ravenous animal that its "hunger drive" is elevated past the point where increasing deprivation produces increasing lever pressing for food--the far end of an inverted U-shaped function. Such an interpretation, suggested by the Yerkes-Dodson Law (Bolles, 1967) appears highly improbable; lever pressing for food remains an increasing function of deprivation even at 84 hours' deprivation (Miller, 1956).

Size differences in the lesions produced by the two types of electrodes could account for the lever pressing results. (Greater currents are required to produce platinum lesions, cf. Appendix III.) For instance, tissue which mediates FR responding could be situated near the border of a small platinum lesion, but be destroyed by a larger steel one. Quantification of lesion sizes (Appendix II) shows that, although steel lesions are generally larger than platinum ones, some overlap exists. In particular, the animals with the largest platinum lesions (H-34) and with double bilateral lesions (H-71 and H-77) responded much above controls on high FR schedules, whereas the animals with smallest steel lesions (H-48) nevertheless pressed fewer

times than controls. Sheer volume of tissue destroyed does not appear to be important in determining lever pressing.

Even if lesion size is not critical, possibly steel lesions damage different tissue than platinum ones. Microscopic examination of the Weil and Cresyl-violet sections failed to reveal consistent differences in damage to large fiber tracts in the region of the ventromedial nuclei. Although steel electrodes produced more damage anterior and posterior to the ventromedial nuclei (Appendix II), double-lesion platinum animals, which have extensive damage in these areas, behaved similarly to single lesion groups on FR 64 and 256. A vast amount of data would be required to disconfirm the hypothesis of differential tissue destruction by the two types of electrode.

One consistent difference between platinum and steel lesions has appeared in the present experiments: the presence of large amounts of ionic iron around the horizontal borders of only the steel electrode lesions. These iron deposits, which are largely Fe^{+++}, emerge as the most likely causal agent of the decreased FR responding of the rats on which steel anodes were used to produce lesions. Whether these iron deposits "irritate" surrounding tissue, depress the function of surrounding tissue, or have specific effects on the neurochemistry of the hypothalamus is not known.

To summarize, four variables, palatability of the diet, weight differences, pretraining, and type of electrode, appear to be important in facilitating food-reinforced operant responding in hyperphagic rats. If appropriate conditions with respect to these, and probably other, variables exist, then hyperphagics will outperform controls. Moreover, performance on other deprivation-sensitive measures, such as latency to eat, also increases following ventromedial lesions. (Quinine tolerance is a notable exception.) Given certain conditions, hyperphagic rats behave as if they were food deprived.

Chapter 5. CHEMICAL INJECTION EXPERIMENTS

The experiments so far described are consistent with a pair of complementary hypotheses: A. Damage from DC current in the region of the ventromedial hypothalamic nuclei results in increased food intake on ad lib food coupled with increased lever pressing on fixed ratio schedules. B. Iron deposits around the horizontal edges of a ventromedial hypothalamic lesion have an additional, profoundly depressing, effect on performance on high fixed ratio schedules. If these hypotheses are correct in this simple form, then depression of the ventromedial region by chemical means (without iron) should elicit feeding on ad lib food and it should elicit lever pressing for food on fixed ratio schedules. The work described in this chapter offers a test of these two assertions.

The first assertion receives qualitative support from reports of the effect of neural depressants injected directly into the ventromedial region of rats through chronic indwelling cannulae. In the first and most thorough such study, Epstein (1960) discovered that satiated rats began to feed on wet Purina mash "several seconds to several minutes" after bilateral injections of procaine (1-3 µl, 50 mg/cc) were made via the cannulae through long PE-10 tubes. Hypertonic NaCl had an opposite effect, suppressing the feeding of deprived rats for "several minutes." This basic work on the effect of single ventromedial injections was confirmed by Wagner and deGroot (1963) using lidocaine, epibarbitol, and pentobarbitol and by Reynolds and Simpson (1969) using procaine HCl.

These experiments unfortunately furnish only qualitative data with regard to the important question of the time course of the eating which follows a procaine injection. As suggested by Reynolds and Simpson (1969) and by Rabin (1972), an effect which occurs "several minutes" following direct application of a chemical to the hypothalamus might be a result, not of ventromedial hypothalamic suppression, but of action on a distant site in the brain. In the ventromedial area, a chemical could be transported in both blood and cerebrospinal fluid (reviewed in Routtenberg, 1972).

I have found no published work bearing on the second assertion, which predicts that ventromedial procaine injection will elicit lever pressing for food.

Method

In order to directly test the assertions, the techniques of Epstein (1960) were adapted to the apparatus, tasks, and rats described in Chapter 2. The cannulae, which are fully described by Epstein, were of 23 ga hypodermic tubing and were stereotaxically implanted at the coordinates named in Chapter 2. Injections were made through lengths of 29 ga tubing which could be inserted so that their tips were flush with the tips of the cannulae. Unlike Epstein, I found it necessary to disturb the animal by inserting the injectors into the cannulae at the time of each injection. I removed the animal from the Skinner box, restrained it with one gloved hand, removed the obdurators, injected or sham-injected into the left, then the right cannula, replaced the obdurators, and returned the rat to the Skinner box. After a week of this routine the rat displayed no discomfort and usually it was not necessary to hold the rat's head, but only to block head movements with a finger. The procedure required 70-80 sec.

I prepared two stock solutions at the beginning of the experiment, boiled them, divided them into labeled vials, and froze the vials. I thawed one vial each day and discarded it after use, ensuring fresh and uniform chemical solutions. The solutions were those used by Epstein (1960): isotonic NaCl (145 mEq/l) and procaine HCl (50 mg/cc) in isotonic NaCl.

Test sessions were composed of three one-hour (minimum 50 min) periods: at the end of hour 1 the rat was injected with a chemical, at hour 2 it was injected again with the same amount of the same chemical, and at hour 3 it was returned to its home cage. The tests took place at the same time each day for a given rat--within three hours before or after the beginning of the dark part of the daily cycle. In ad lib tests, the rats licked 3:1 milk from a metal spout on a 100 ml graduate. In FR 1 and FR 64 tests the rats pressed a lever for 3:1 milk

after training as described in Chapter 2. A lickometer circuit or microswitch transduced the respective responses and a paper tape punch recorded the time of each lick, lever press, and (right cannula) injection to 1.0 sec. Except during tests the rats had ad lib 3:1 milk available in Richter tubes at all times.

Four weeks after surgery, the six rats were trained on FR 1 and adapted to 3 hour tests under FR 1 and ad lib conditions. They were then given a series of ad lib and FR 1 tests on succeeding days in a counterbalanced order, using 1 µl injections. This was followed by a similar, but shorter series using 2 µl. The animals were then given training in continuous sessions as described in Chapter 2 until they had each had at least 72 hours practice on FR 64 and were pressing in the stereotyped fixed ratio pattern. A series of 2 µl injections was then administered using the usual 3-hour sessions. Until this time, the animals had been without food only during their initial session (0-10 hr) on FR 1, before they had learned to press the bar. After the FR 64 tests followed one saline and one procaine injection test on FR 64 after 21 hours food deprivation. After several days on ad lib food, one final procaine injection test was made in the ad lib condition to verify that the response had not diminished.

Histological Results

Each of the six rats had cannulae implanted bilaterally at the level of, or slightly posterior to, the ventromedial nuclei (Koenig and Klippel, 1963, plates 33-39). With cresyl-violet stain, considerable gliosis can be seen at the tip of each cannula (Fig. 25). The locus of cannula placement did not appear to be related to ad lib or fixed ratio performance in these rats. For example, P-8, the one rat which did not eat or lever press following procaine injection, had a quite normal cannula placement immediately dorsal to the ventro medial nuclei (Fig. 25b).

Licking and Lever Pressing

Since each rat was permitted 50 min following an injection to eat or lever press, this standard interval provided a natural basis to

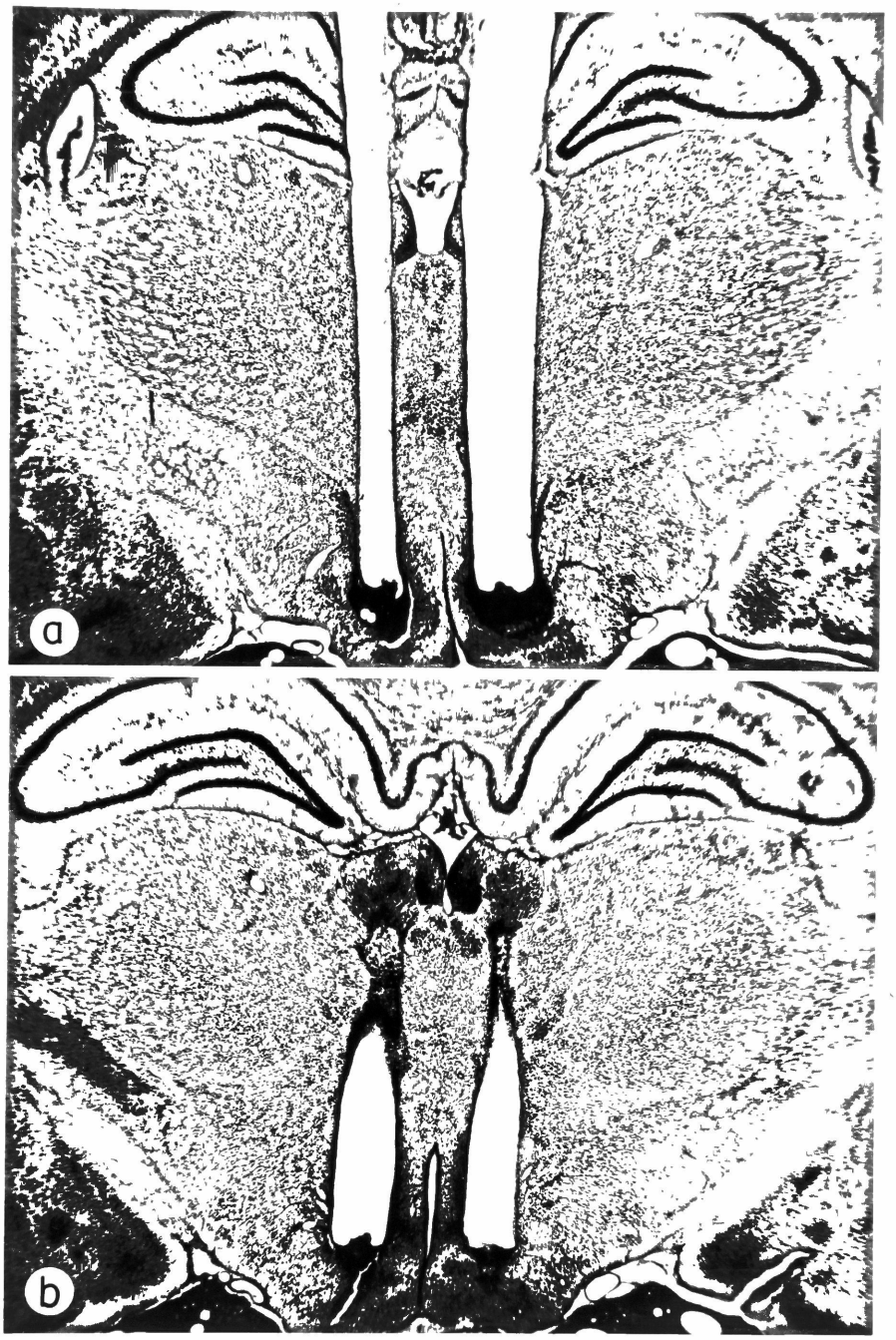


Fig. 25. Cresyl-violet stained transverse sections through the maximum diameter of the cannula tracks of P-6 (25a) and P-8 (25b). P-6 responded to procaine injections by eating, P-8 did not.

compare different rats and injections. The post-injection period was divided into 50 one-min bins and a "post-injection histogram" was constructed by summing across injections. The resulting averaged response to the injections is wholly analagous to the post-stimulus histogram used in neurophysiology. The first and second injections of each day's test were not different and so they were pooled. One rat (P-8) showed no response and its data are omitted. All other tests having valid paper tape records are included.

Average post-injection histograms for all five rats licking ad lib food are presented in Figs. 26 and 27. There is no substantial difference between 1 µl and 2 µl. Procaine injection produces a period of increased eating lasting about 10 min, followed by a period of decreased eating. NaCl injection depresses eating for about 10 min and then eating resumes at a low and fluctuating level.

FR 1 tests (which were interspersed with the above ad lib tests) are shown in Figs. 28 and 29. Injection of 1 µl of either procaine or NaCl or 2 µl of NaCl sometimes resulted in a small bout of presses. Injection of 2 µl of procaine produced a substantially larger bout of presses peaking at an average of one press/min or 0.19 ml/min, an amount comparable to the peak intake elicited by procaine on ad lib food. Automatic recording equipment established that the rats contacted the dipper during each reinforcement, and therefore probably consumed the milk each time. A period of depressed intake was not evident in the FR 1 condition.

FR 64 tests were conducted with 2 µl injections only (Fig. 30). The post-injection histograms show that there was no difference between NaCl and procaine in the average number of presses/min during the first 9 min, but that some increases occurred during minutes 9-19. Examination of the cumulative records from these sessions indicates that the pressing which occurs during the first 10-12 min following NaCl injection is typical of FR responding--fast runs of responding terminating in reinforcements, with a few isolated presses interspersed. During the same time following procaine, however, the presses were scattered in bouts of 1-4 and only one reinforcement was obtained during all of the 46 tests.

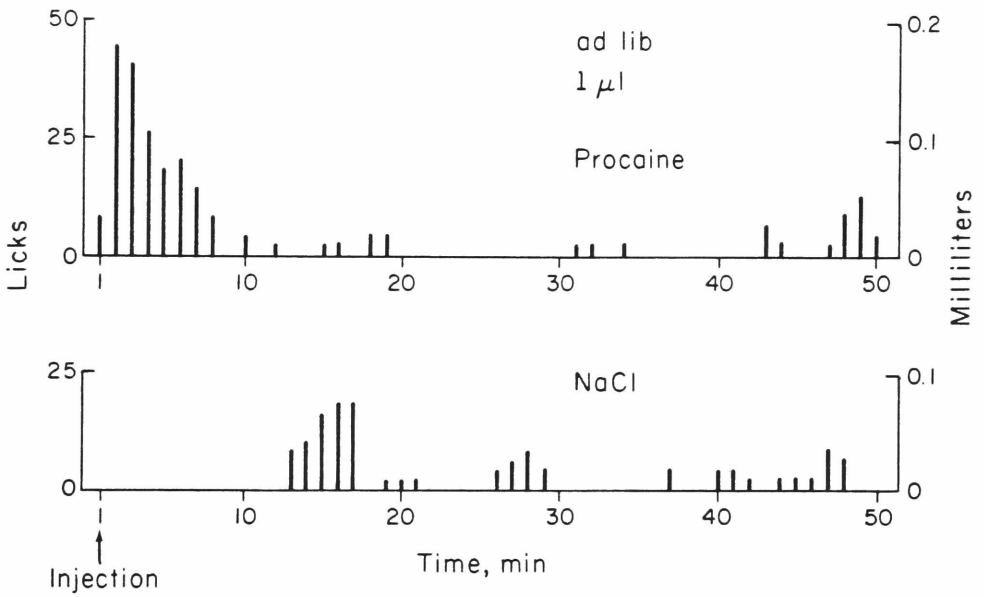


Fig. 26. Post-injection histograms for 1 µl procaine and 1 µl NaCl, ad lib condition. Injections were made at time = 0. Vertical bars represent mean licks/min across 5 rats for N = 49 injections of each solution. An approximate scale in milliliters is given on the right.

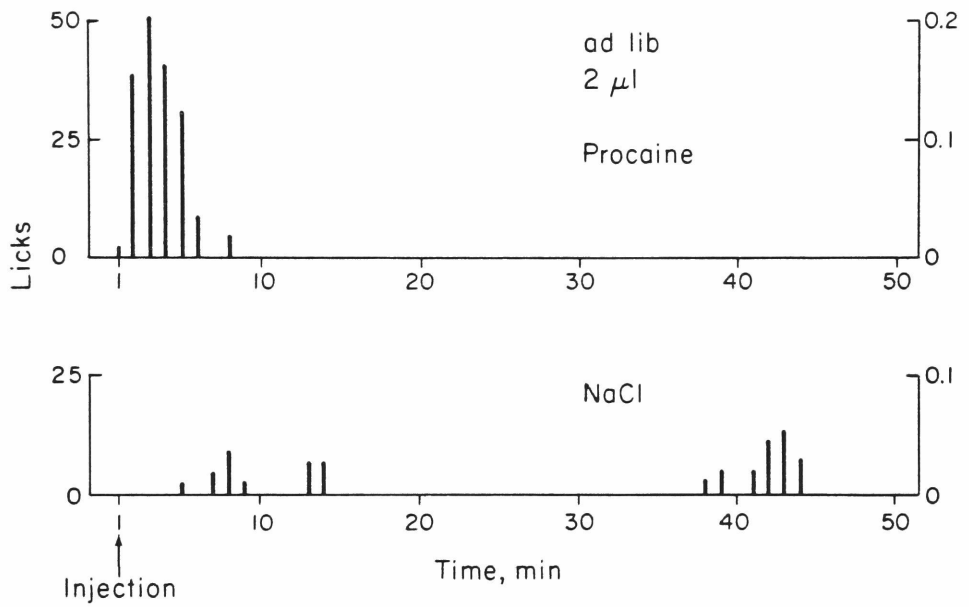


Fig. 27. Post-injection histograms for 2 µl ad lib. N = 21.

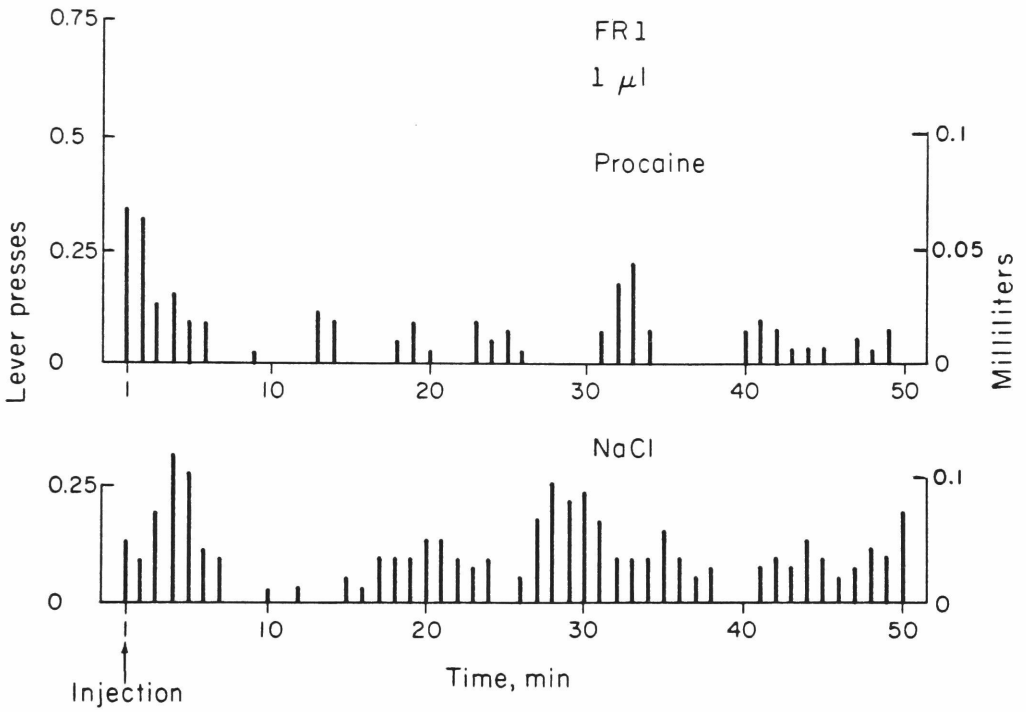


Fig. 28. Post-injection histograms for 1 µl procaine and 1 µl NaCl, FR 1 condition. Bars represent mean lever presses/min across 5 rats for N = 59 injections of each solution. Approximate milliliter scale, on left, is not the same scale used in the ad lib histograms (Figs. 26 and 27).

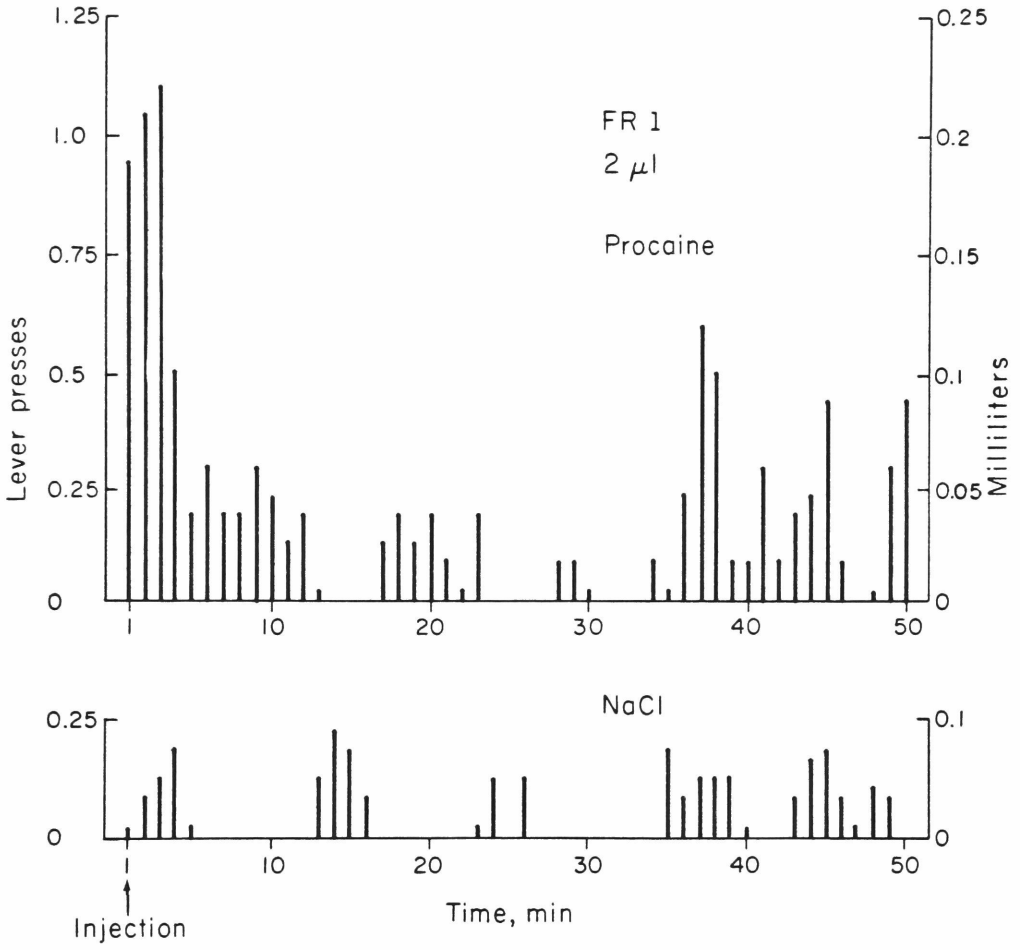


Fig. 29. Post-injection histogram for 2 μl FR 1. N = 20.

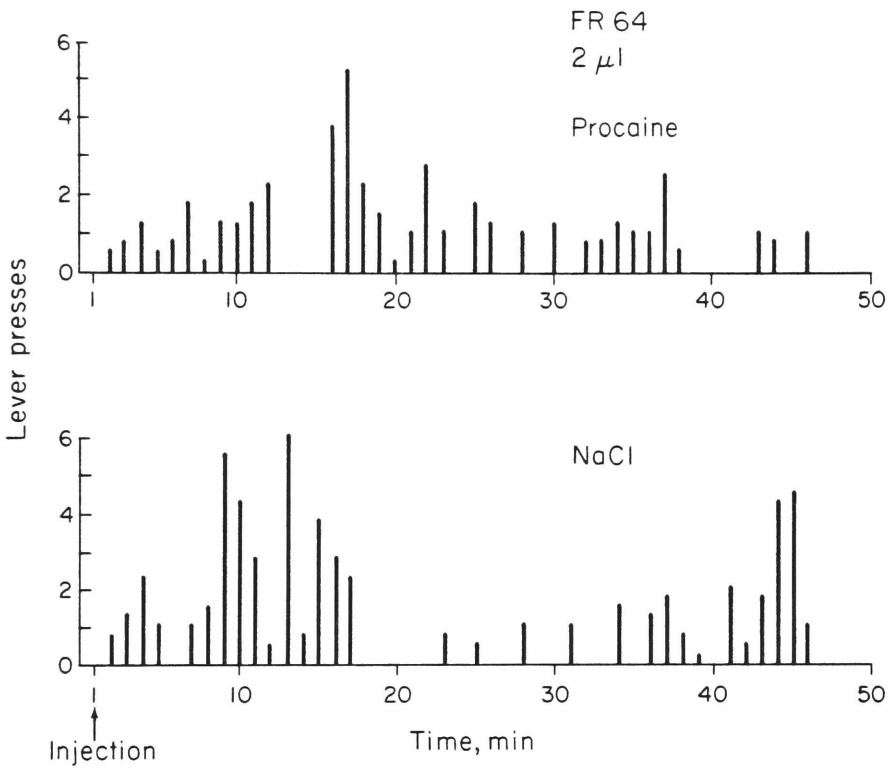


Fig. 30. Post-injection histograms for 2 μl FR 64. N = 46.

(This disruption of pressing is treated in detail in the section of "Visual Observations" below.)

The five rats behaved alike when tested on FR 64 following 21 hours food deprivation. As seen in Fig. 31, animals injected with 2 µl NaCl quickly began to press and consumed a substantial meal. Animals injected with 2 µl procaine (Fig. 32) pressed in small bouts at irregular intervals for 8-10 min, then began to press in the normal fixed-ratio pattern and continued to take a large meal. The meal size was not different from the NaCl condition (Mann-Whitney U test, $U = 9$, $p = 0.27$).

In the final ad lib procaine test all rats ate a large meal within 2 min, indicating that the effect of procaine on eating had not waned.

Although the post-injection histograms show increased ad lib licking during the first 1-2 min after injection of procaine, the averaging technique provides inadequate information on the latency of the eating. Accurate measurement of this latency must take into account the fact that a few licks usually occur whenever an animal is placed into the Skinner box, during an initial few seconds of exploring the chamber. Accordingly, the first meal (2 min criterion, 10 lick minimum size) was identified from the computer records and a straight line was fitted to the lick number/lick latency pairs of the meal using the least squares technique. Solving the resultant linear equation for Lick #1 gave the estimated latency of the first meal following injection. This technique was used on injection 1 only for NaCl and procaine injections and the results were the same for 1 µl and 2 µl doses. Fig. 33 gives the log estimated latency vs. log meal size for each of the 15 meals in the procaine condition and the 12 meals in the NaCl condition following 1 µl injections. The median meal size (600 licks or about 2.5 ml) is similar in the two conditions; the latencies, however, are virtually nonoverlapping. A meal begins as soon as 16 seconds following procaine injection and all such meals begin within 200 sec. In contrast, meals usually begin no sooner than 700 sec following NaCl injection.

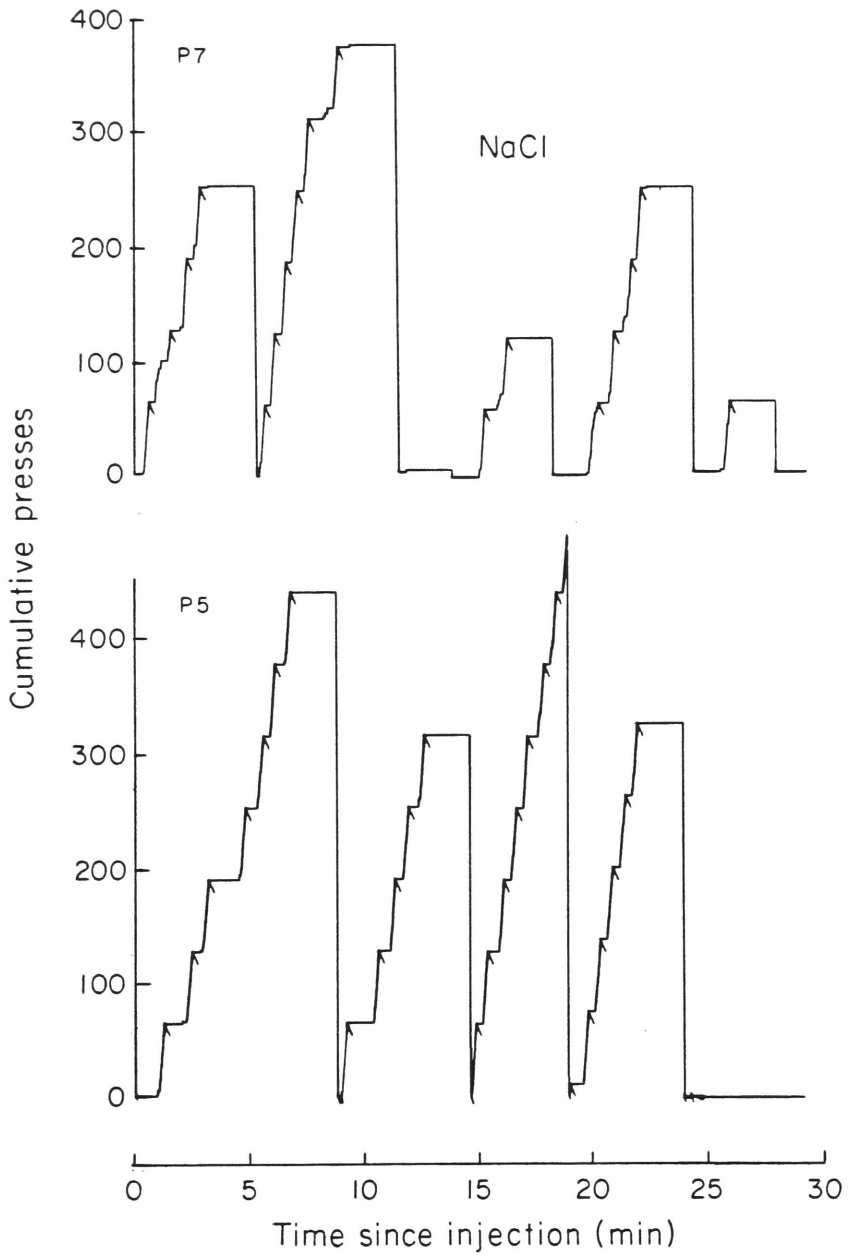


Fig. 31. Cumulative records of two rats deprived of food 21 hours and injected with 2 μl NaCl. The 1.5 min delay before pressing shown by P-5 was the longest recorded for the 5 rats after NaCl injection.

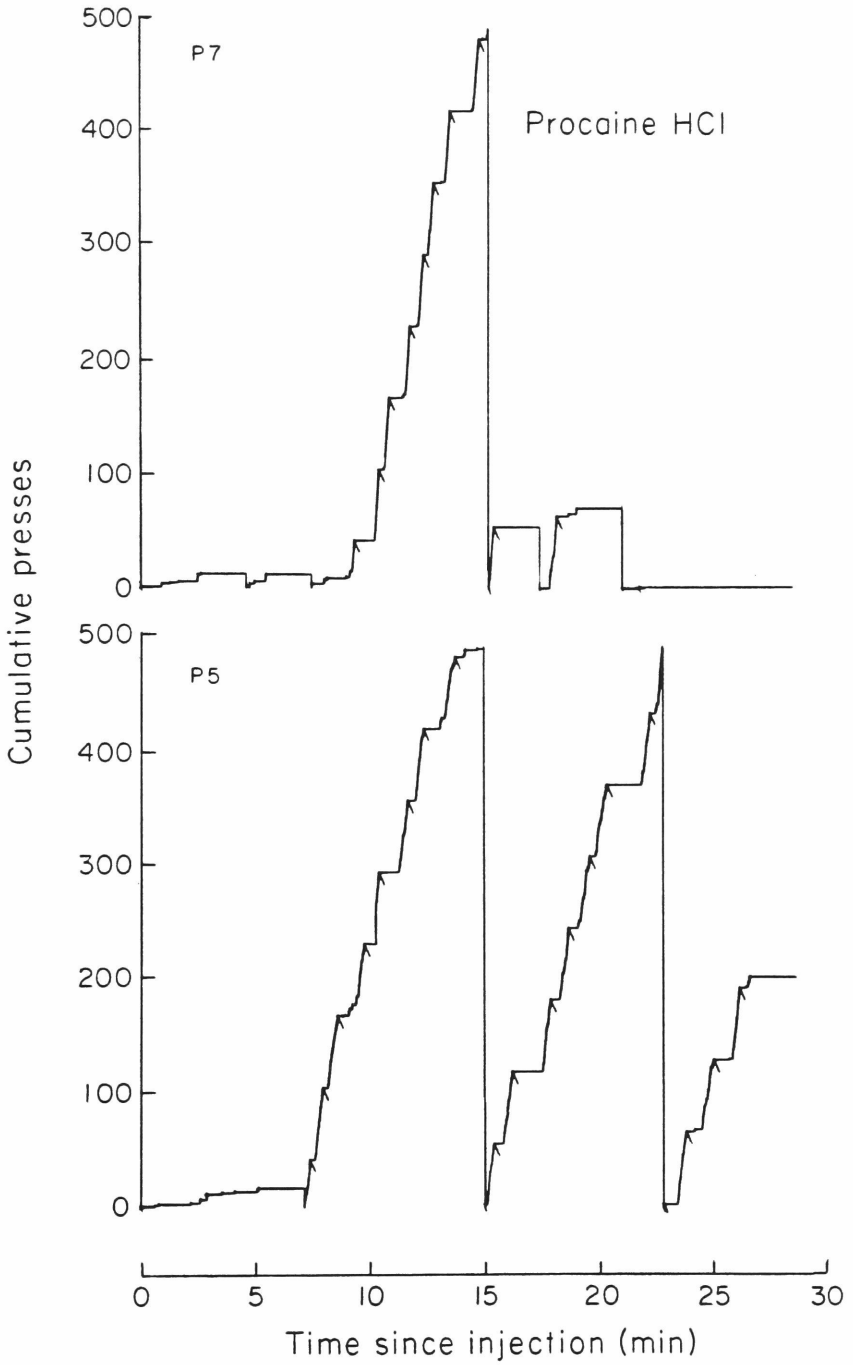


Fig. 32. Cumulative records of two rats deprived of food 21 hours and injected with 2 µl procaine. Delays between injection and the first reinforcement were always at least 7.5 min in the procaine condition.

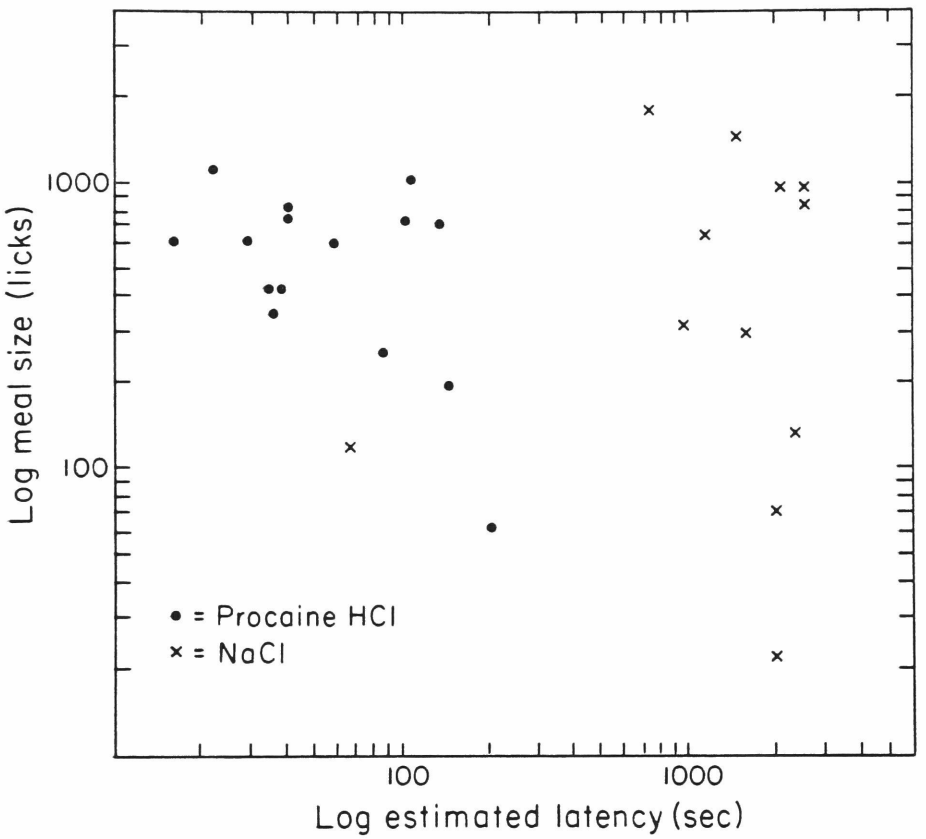


Fig. 33. Size-latency scattergrams of individual ad lib meals following 1 µl procaine and NaCl injections. Only data from Injection 1 are included. No eating occurred within 50 min of 5/20 procaine and 9/22 NaCl injections.

Visual Observations

In contrast to NaCl injections, procaine injections disrupt the fixed ratio pattern of pressing during the 8 to 10 min following injection. This effect occurs in both the nondeprived and deprived tests on FR 64. The records are characterized by short bouts of pressing alternating with periods without pressing, instead of the usual long runs of pressing terminating in reinforcement. Two questions arise concerning the nature of this effect: (1) Are other patterns of the animals' behavior disrupted as well? (2) Are the lever presses which are emitted singly or in short bouts following procaine injection a result of increased general activity, or are they part of an organized sequence of behavior? I attempted to answer these questions by observing the rats during a 14-min period following procaine or NaCl injection and applying stochastic methods of analysis to the records.

Preliminary observations showed that eight distinct behaviors dominated the repertoire of the rats during the post-injection period (Table 11). The eight behaviors seemed to be well-coordinated following both procaine and NaCl injections--no motor deficits were noted. Three rats were selected for scoring these eight behaviors. Each time one of the eight behaviors occurred during the 14 min post-injection period, I wrote a symbol for that behavior. No records were kept of the time of occurrence or duration of the behaviors, but only of their temporal sequence. For purposes of analysis, successive instances of one behavior were ignored (self-transitions were deleted). Observations of 14 procaine and 14 NaCl injections were pooled and tables of the first-order behavior transitions were constructed (Wiepkema, 1961; Blurton-Jone, 1968). These tables (Tables 12 and 13) show the number of times, expressed as a percent of the total, that each behavior followed each other behavior, giving an overall picture of the sequential patterning of the animals' activity. Three times as many transitions occurred following procaine as following NaCl injections, indicating an increase in the general level of "activity."

To determine whether the distribution of activity among the eight behaviors was the same in the two conditions, a Spearman Rank Correlation

Table 11. Behaviors used in sequence analysis

Activity	Definition
Lever press	One or more movements of the lever, including movements insufficient to actuate the programming logic.
Reinforcement	The last press before reinforcement + approach food cup + lick the dipper.
Groom	Buccal or limb movements directed at the fur or tail.
Rear	Both forepaws raised off the floor; at least one forepaw contacts the wall of the chamber.
Paw wipe	Forepaw movements in a rostrocaudal direction on or beneath the floor bars.
Eat object	Object from floor or beneath brought to mouth and nibbled. Includes pica and coprophagy.
Food cup approach	Nose extended past the chamber wall into the food cup.
Water drinking	Licks at water spout.

Table 12

		Following							
		L	X	G	R	P	E	F	W	
Preceding	L	-	4.19		0.60			9.58	1.20	Lever press
	X	1.80	-	1.80	0.60					X reinforcement
	G	0.60		-	8.38	0.60	1.80	3.00	9.60	Groom
	R	3.60		7.20	-		0.60	2.40	3.60	Rear
	P					-		0.60		Paw wipe
	E			2.40			-			Eat object
	F	9.00		3.00	4.80			-	2.40	Food cup approach
	W	0.60		9.00	4.19			3.00	-	Water drinking
Total		15.57	4.19	23.35	18.56	0.60	2.40	18.56	16.77	

Transitions Between Behaviors, 2.0 µl NaCl. Percent occurrences of each transition 14 minutes following an injection. N = 167 transitions.

Table 13

		Following							
		L	X	G	R	P	E	F	W	
Preceding	L	-	0.51	2.73	1.87	0.51		7.16	1.02	Lever press
	X		-	0.51						X reinforcement
	G	3.41		-	12.10	0.51	1.02	4.60	5.11	Groom
	R	3.41		9.37	-	1.02		4.77	4.98	Rear
	P	0.17		0.51	1.53	-	0.51	0.51	0.17	Paw wipe
	E	0.17		0.68		0.68	-		0.17	Eat object
	F	5.62		6.99	4.26	0.34	0.34	-	1.53	Food cup approach
	W	0.85		6.30	2.73	0.34	0.17	1.70	-	Water drinking
Total		13.63	0.51	27.09	22.49	3.41	2.04	18.74	12.10	

Transitions Between Behaviors, 2.0 µl procaine. Percent occurrences of each transition 14 minutes following an injection. N = 587 transitions.

was used on the total distributions. The resulting correlation of 0.89 indicates that the rats' activity was indeed distributed similarly and that there was no strong effect upon just one or a few behaviors. Furthermore, examination of the entire matrix reveals few substantial differences between the two chemicals which are not related to the lever pressing effect. (There is no ordinary nonparametric statistical technique which can be used on a matrix with many empty cells.) I conclude that lever pressing is disrupted far more than other behaviors by procaine injection.

In order to ascertain whether the short bouts of lever presses which occur following procaine administration are integrated into organized sequences of behavior, I examined the behaviors which occur immediately before and after lever presses. In the NaCl condition, as in undisturbed animals, trains of presses are usually interrupted at least once by approaches to the food cup. Food cup approaches are, in fact, the most common behavior before or after lever presses (Table 12). Approaching the food cup is obviously a food-related response, reflecting the fact that the animals' pressing is maintained by the reinforcement contingency. The procaine-injected animal also follows this pattern (Table 13). Lever press-food cup and food cup-lever press transitions are significantly more likely than chance (p's less than .001, chi square test), whereas no other lever press transition is significantly different from chance (p's all greater than 0.1). The lever presses of the procaine-injected rat are therefore not emitted solely as a result of hyperactivity but are preceded and followed by responses which can be said to be "food-seeking."

Discussion of Chemical Injections

These experiments confirm the first assertion and the work of previous investigators: procaine injected into the ventro-medial region of the hypothalamus elicits ad lib eating in non-deprived rats. In addition, the time course of the elicited eating can now be estimated. Eating begins within two minutes of procaine injection, sometimes in as little as 16 seconds. Eating is suppressed after NaCl injection for about 11 minutes, possibly due to upsetting the rats by handling them.

Procaine-elicited eating lasts no longer than 10 minutes and is followed by a period of depressed eating. The depression of eating is interesting in itself because it suggests the identity of the mechanism by which eating is stopped following procaine injection. Since no period of decreased eating is evident in the FR 1 condition, and since in this condition the rats consume much less food in the first 10 minutes, the depressed intake in the ad lib condition may be a result of physiological satiation. If this is so, then neural structures mediating short-term satiety are functioning 10 minutes after procaine is injected.

The second assertion, that rats injected with procaine should show increased fixed-ratio lever pressing for food, is confirmed only at a dose of 2 1 in the FR 1 condition. Procaine at a dose of 1 µl does not elicit more lever pressing than NaCl. FR 64 pressing is clearly disrupted for 8-10 min following procaine administration but not following NaCl administration; the disruption appears to be accompanied by a general, nonspecific increase in the level of activity.

The time course of the eating which followed these procaine injections is short, but not so short that the possibility of action on distant sites in the brain is completely excluded. The spread of material injected into the ventromedial area has been estimated using cresyl violet stain (Wagner and DeGroot, 1963); however, the large difference in molecular size between this stain and procaine makes the technique of doubtful value. Studies of the spread of radioactively labeled procaine would resolve the problem; the present work shows that two minutes is an appropriate period of time to allow the procaine to spread.

Procaine depression of the ventromedial area produces some effects similar to electrical stimulation of the lateral hypothalamus. Lateral stimulation can elicit feeding behavior (Akert, 1961). Behavior which is thus elicited is modifiable, however, and elicited eating may not generalize from one diet to another (Valenstein et al., 1968; Valenstein et al., 1970). When stimulated animals are not showing "stimulus-bound" eating, or when the food is removed, they typically show exploratory behavior and hyperactivity during stimulation (Valenstein, 1969). This

hyperactivity may be similar to the behavior of procaine injected rats on FR 64. It is possible that both the eating and the hyperactivity which follow procaine injection are due to disinhibition of the lateral feeding area, supporting the venerable "dual center" theory of hypothalamic function (Stellar, 1954). One attractive prediction which arises from such an interpretation is that ventromedial anesthetization, like lateral stimulation, should have rewarding properties. This prediction is afforded ancillary support by the finding that procaine applied to the ventromedial area increases lateral hypothalamic self-stimulation (Hoebel and Teitelbaum, 1962).

Chapter 6. GENERAL DISCUSSION

The experiments using anodal DC lesions uncovered two variables which had not previously been considered important in determining the performance of hyperphagic rats on a food-reinforced operant task. Using platinum anodes it was found that pretraining improves the performance of hyperphagics relative to that of controls. Pretraining appears to have played an unsuspected role in determining the outcome of previously published experiments on operant responding in hyperphagics. Interpretation of the effect of pretraining awaits data concerning the influence of ventromedial lesions on the learning of tasks other than the fixed ratio schedule employed in the present experiments.

The type of electrode used to produce the lesion also had a marked effect on the performance of the hyperphagics. Rats with lesions produced by steel anodes showed a decrease in fixed ratio lever pressing relative to controls, whether or not they had been pretrained. In examining the brains of these animals it was found that, although lesion size and shape differed between steel- and platinum-produced lesions, the presence of large amounts of iron at the horizontal borders of the steel electrode lesions provided the clearest distinction between the two types of lesion.

A procaine anesthetization study was performed in order to depress the function of the ventromedial region by chemical means, without iron. This study showed that feeding is elicited in a short time when procaine is injected into the ventromedial region, but that procaine has a relatively specific disruptive effect on fixed ratio responding. The disruption appears to be unlike any deficits seen following ventromedial lesions and may be a result of actions of the drug on neural networks which are separate from those controlling food intake. Useful knowledge could be gained on this question if extent and sites of the drug were accurately determined and if more localized techniques of depressing function, such as cooling, were attempted.

The two hypotheses which were proposed in Chapter 5 remain essentially unaltered. Each of them has interesting implications for current theories of the function of the hypothalamus in feeding behavior.

A. Damage from DC current or anesthetization of the ventromedial region results in increased food intake on ad lib food; in addition, increased lever pressing on fixed ratio schedules occurs following DC lesions.

Miller et al. (1950) suggested the possibility that ventromedial lesions "interfere seriously with the mechanism of stopping eating and somewhat less seriously with the mechanism of hunger." The first named function, that of stopping eating which has been initiated by other brain centers, has been called "satiety." ("Satiety" has also been loosely used to indicate lack of "hunger.") The concept of a ventromedial "satiety center" has had immense influence on theories of hypothalamic function. The specific function of terminating a meal was ascribed to the ventromedial area largely as a result of three behavioral observations.

(1) Rats with ventromedial lesions were thought to be less "hungry" than normal rats because they did not as readily perform operant responses for food. Since they ate more but were less "hungry," it was hypothesized that the ventromedial lesion interferred with satiety rather than the onset of feeding behavior.

(2) Ventromedial stimulation during a bout of eating causes an animal to stop eating.

(3) Hyperphagics eat larger meals than controls. The mechanism which stops eating must be damaged.

It should be noted that stopping eating is a specific behavior related to a more general function of decreasing the propensity to eat. I shall now examine the evidence that the latter function is influenced by the ventromedial region. First, consider the three observations supporting the satiety center theory:

(1) Hyperphagics are less "hungry." The present results (Hypothesis A) show that some hyperphagics respond much more than controls in an operant situation, in fact they resemble deprived animals in most respects. It is no longer accurate to say that hyper-

phagics are less "hungry" than controls.

(2) Ventromedial stimulation stops feeding. It is difficult to determine whether the observed suppression is specific to feeding behavior or whether the stimulation simply punishes whatever behavior is occurring when the stimulation begins (Krasne, 1962; Ball, 1962; Atrens and von Vietinghoff-Riesch, 1972). As Ball (1972) has observed, ventromedial stimulation may "distract" the animal from feeding even if it does not actually punish feeding. Mrosovsky (1971) reviews this topic and justly concludes that the rebound eating often seen following ventromedial stimulation is far better evidence for a direct suppression of feeding behavior than is the cessation of eating itself. At the time the electrical stimulation ceases, the animal is specifically not eating; it then initiates eating. The evidence here appears to be at least as strongly supportive of the decreased-propensity-to-eat concept as of the satiety concept.

(3) Hyperphagics eat larger meals. This observation has not been contested; however, it does not provide direct evidence for a satiety deficit. Other equally simple explanations come to mind: Possibly a hyperphagic eats a larger meal because the positive feedbacks maintaining feeding behavior--such as taste--are more effective following ventromedial lesions. Also, I have given evidence that the correlation between meal size and intermeal interval becomes more positive following ventromedial lesions (Chapter 3). This may indicate that the hyperphagic is attending to satiety cues more than the normal animal. Experiments by Panksepp (1971b) on stomach loading in hyperphagic rats indicate that they do, in fact, respond at least as well as normal to satiety cues.

There appears to be a dearth of evidence specifically supporting the satiety center concept. The alternative, more general, idea that the ventromedial region acts to decrease the propensity to eat, however, receives strong support from present findings. Hyperphagic animals press a lever more than controls when up to 256 presses are required to obtain a small amount of food. After eating the food, they resume pressing the lever sooner than controls. In addition, I have shown

that an animal begins to eat within a very short time following either a lesion through implanted electrodes or anesthetization with procaine. This observation complements published work demonstrating that the latency to eat in a familiar or unfamiliar environment is shorter in hyperphagic rats than controls.

I conclude that the initiation of eating as well as the cessation of eating must be influenced by the ventromedial nucleus. The general function of decreasing the propensity to eat subsumes both of these ideas. It appears to account for much of the data on feeding behavior and the ventromedial region which cannot be explained by the more restricted concept of a satiety center. It is premature to conclude, however, that the ventromedial region plays no role at all in post-prandial satiety. (See Panksepp, 1971a, for a statement of this rather extreme position.)

B. Iron deposits around the horizontal borders of a ventromedial lesion have an additional, profoundly depressing effect on performance on high fixed ratios.

This hypothesis receives only indirect support from published work. Although several experiments have found increased operant performance following lesions made with steel electrodes, none document the presence of iron deposits. Since a variety materials can be called "steel," the insect pins and stainless steel wires which other investigators use may deposit much less iron than the dental broaches used in the present experiments.

Lesions made with radio frequency current, like those made with platinum electrodes, contain little or no iron around their borders (Reynolds, 1963; Herrero, 1969). Marks and Remley (1972) found that rats given DC lesions with stainless steel electrodes or given RF lesions pressed at an equal rate to that of controls when all groups were deprived to 90% of preoperative weight. In this situation, however, both controls and hyperphagics were perhaps pressing at the maximum rate which the VI2' schedule elicits under the conditions employed. A later experiment performed when the hyperphagics were at 90% of static (not

preoperative) weight levels showed that the RF group pressed more than the steel DC group, supporting the hypothesis that iron deposits decrease operant pressing for food.

Knife cuts also damage tissue without appreciable iron deposits (but see Gold, 1970). An experiment performed by Sclafani (1971) sought to determine if knife cuts decrease FR performance for food reinforcement. He found that rats with steel electrode lesions pressed far fewer times than controls and that hyperphagics with long parasaggital knife cuts pressed more than the steel electrode group but fewer times than controls. All groups were deprived to 85% of preoperative body weight. No pretraining was employed. This experiment is subject to the objection raised above with respect to the deprivation level; also, both groups of hyperphagics responded fewer times than controls even at FR 1, indicating that the conditions are not comparable to those in other experiments such as the present ones or those of Teitelbaum (1957). Knife cuts may also produce lesions indirectly by cutting large blood vessels (Grossman and Grossman, 1971), complicating the interpretation of experiments involving knife cuts.

These two studies using non-iron-depositing techniques (Marks and Remley, 1972; Sclafani, 1971) provide equivocal evidence concerning the effect of iron deposits on operant responding for food. In both cases, the deprivation condition of the experiment may or may not account for the results. Further evidence on the deprivation question is presented by Kent and Peters (1971), who produced lesions using an unspecified electrode material and tested hyperphagics and controls in a lever pressing and a runway situation. The hyperphagic and control groups showed equal performance at 80-90% preoperative body weight but the hyperphagics pressed more and ran faster than controls at 100-110% weight. The animals had been pretrained on both tasks. This finding may help account for the results of Marks and Remley (1972) and Sclafani (1971). It also provides evidence that the hyperphagic behaves as if it were food deprived--no difference occurs if a hyperphagic is compared with a deprived rat. The RF and knife cut experiments should be repeated using hyperphagics and undeprived controls.

What might be the mechanism of the hypothesized effect of iron deposits on operant responding for food? With respect to the steel electrode animals, the paradox of animals which eat but do not press for food remains as real as it was in 1950. A few related phenomena have appeared in the literature. Margules and Stein (1969) found that atropine implants in the ventromedial area produce a syndrome which is the reverse of that occurring in the steel electrode rats in the present experiment. Lever pressing (VI 2') was increased following application of atropine, but the rats frequently did not consume the resulting reinforcements.

Of more immediate relevance are two studies which implicate the lateral or mid-lateral hypothalamus as a possible site mediating operant but not consumatory food-getting behavior. Morgane (1961a, 1961b; Morgane and Jacobs, 1969) used combinations of lateral and mid-lateral lesions and discovered that lesions in the two areas have different effects. Lateral lesions at the plane of the ventromedial nuclei, and only in this plane, produce decreased eating and decreased lever pressing for food. However, lesions in the mid-lateral area (1.7 mm from the midline) "seemed to interrupt those systems more concerned with 'motivation' of feeding behavior" than with eating per se. Following lesions in the mid-lateral area, rats resume apparently normal feeding but do not work for food.

Wampler (1972) came to the same conclusion from the opposite anatomical direction. Using implanted platinum electrodes (3 current parameters) he found that some hyperphagics increased VI 2' pressing and some decreased following ventromedial hypothalamic lesions. In all cases decreased responding was associated with unilateral or bilateral damage to the "lateral" hypothalamus. In most cases the area involved was the same region implicated in Morgane's work, the mid-lateral hypothalamus.

The experiments of Morgane (1961a, 1961b, Morgane and Jacobs, 1969) and of Wampler (1972) suggest a mechanism for the depression of operant responding observed in the present experiments following steel

electrode lesions in the ventromedial area. Since there is no substantial evidence that adjacent tissue is "irritated" by iron deposits, one might assume that adjacent tissue is functionally depressed by iron deposits. The adjacent tissue in this case is partly the mid-lateral hypothalamus. If its normal function is impaired by iron deposits at the borders of a ventromedial lesion, then decreased operant responding for food should indeed result. One need not specify the specific manner in which the hypothesized impairment of normal function occurs, nor the universe of behaviors affected. If iron deposits depress the mid-lateral hypothalamus, and if the mid-lateral hypothalamus mediates operant responding for food, then the steel electrode effect can be accounted for. This hypothesized mechanism is attractive because it is testable and is based on some empirical evidence, not because other imaginable mechanisms have been disproven.

APPENDIX I

Meal size-interval "correlations": What evidence is there that they are strongly positive?

The feeding behavior of some animals is clustered in time into discrete meals of varying size which are separated by intervals of varying length. It is stated by some authors that the "correlation" between the size of a given meal and the interval succeeding that meal is high and positive but that the "correlation" between size and the preceding interval is near zero. Some regard these "correlations" to be of fundamental physiological importance (LeMagnen, 1971). I will show here that most succeeding "correlations" are in fact low or near zero.

There are at least 11 publications which provide data on size-interval "correlations." All agree that the meal size-preceding interval "correlation" is near zero. Five studies (Baker, 1953; Premack, 1965; Levitsky and Collier, 1968; Wiepkema, 1968; Zeigler et al., 1971) find near zero succeeding "correlations." Five studies (LeMagnen and Tallon, 1966; Thomas and Mayer, 1968; Snowdon, 1969; LeMagnen and Devos, 1970; Lemagnen, 1971) appear to find strong positive succeeding "correlations." One study (Balagura and Coscina, 1968) finds positive correlations in the dark but not in the light phase of the day. These reports taken together make any general statement on succeeding "correlations" questionable at best.

Of the five studies which find strong positive meal size-succeeding interval "correlations," one (Thomas and Mayer, 1968) does not describe the mathematical method of computing the "correlation." Another (LeMagnen and Devos, 1970) probably uses standard methods to find a high positive correlation. The other three (LeMagnen and Tallon, 1966; Snowdon, 1969; LeMagnen, 1971) use a method which is apparently employed to speed computation. The meals are ranked according to meal size, divided into decades, and a "correlation" is done on a list of the ten average sizes and intervals. <u>This "correlation" is not the correlation coefficient</u>, r. Averaging within decades has the effect of reducing

the variance of the data in a nonlinear fashion, thus automatically inflating the resulting number which the authors call a "correlation." "Correlations" generated using this technique will be higher than correlations computed using the normal technique.

In order to estimate the effect of decading the data on the correlation, I have computed both normal and decade correlations on artificial data. The values were produced using a tested random number generator on a digital computer. Thirty to 200 pairs of points were generated for each of 100 varying values of r between 0 and 1. The resulting 100 normal and decade correlations were then plotted against one another and each was found to lie close to a curve which intersects (0,0) and 1,1). The curves were fitted using a Gaussian elimination least-squares procedure for a third-order polynomial; these curves are shown in Fig. 34 for N = 30 to N = 200. It can be seen that, for intermediate values of r, the decade "correlation" value is considerably greater than r and that the effect increases with N. Depending, of course, on the actual distributions of the sizes and intervals, the value of r for the decade "correlations" of 0.7 to 0.8 reported by LeMagnen and coworkers is likely to be 0.30 or 0.35 for N = 100. Such a correlation, although statistically significant, does not go far in accounting for the variance in meal patterns.

Data gathered during the course of an experiment on licking behavior confirm the generalization that meal size-succeeding interval correlations are generally low. Five female albino rats were kept in a sound-deadening and lightproof chamber on a 12:12 light cycle for at least four days, then meal pattern data were taken by a method described elsewhere (Larkin, 1972). The rats had continuous access to 3:1 sweetened condensed milk (Kissileff, 1972) from a metal drinking spout and tongue contacts were detected electrically. Size-interval correlations (Pearson's r) for the rats are given in Table 14. Only one succeeding interval correlation and no preceding interval correlation is as high as those reported using the decade "correlation" technique. These results offer further reason to question the importance of size-interval correlations.

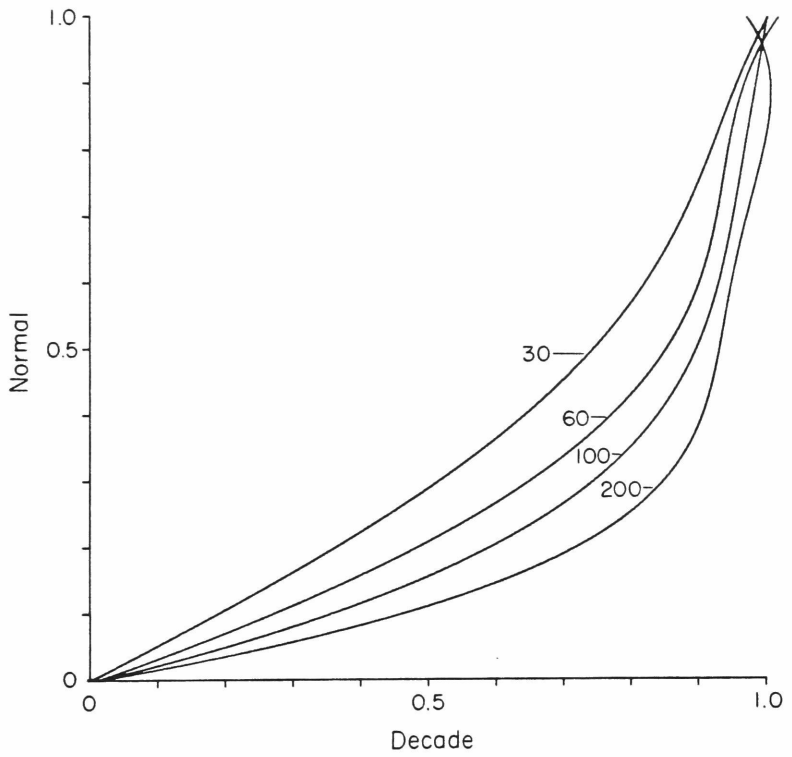


Fig. 34. Decade "correlation" vs. normal (r) correlation. Decade "correlations" and r were computed on 30 to 200 pairs of numbers with randomly varying degrees of correlation. If decading the data had no effect, the curves would be straight line segments intersecting (0,0) and (1,1).

Table 14

Correlations between meal size and preceding and succeeding intermeal interval (10 min criterion).

Number of Meals	Correlation	
	Preceding	Succeeding
44	-0.08	0.83
51	-0.16	0.41
63	-0.16	0.18
64	-0.06	0.05
240	0.20	0.27

In conclusion, only two studies (LeMagnen and Devos, 1970; Balagura and Coscina, 1971, dark phase) find a high positive correlation coefficient between meal size and succeeding interval, five find no correlation, and four use an erroneous technique. Correlations on four out of five rats were found to be low. The succeeding interval correlation appears to be of little use in explaining meal patterns in most experimental conditions.

(Note: Independent work has just been published (Pankseep, 1973) which duplicates most of the points raised in this Appendix.)

APPENDIX II

Quantification of Lesion Size and Placement

Several parameters were measured from the stained transverse sections in order to allow a comparison of steel- and platinum-produced ventromedial lesions. The results of these measurements are presented in Table 15; all dimensions are in mm. A general comparison of the steel electrode and the platinum electrode lesions follows, then a detailed description of the procedure for computing the estimates of lesion size. Columns of Table 15 are referenced in capital letters, e.g. "AP."

Differences Between Platinum and Steel Electrodes

Lesions made with steel electrodes tend to be larger in most dimensions than platinum electrode lesions. Amount of damage inside the fornices (IN), total area of the lesion (TOTAL), and transverse diameter (A) show considerable overlap between the steel and platinum anodes. Anterior-posterior plane (AP) is not different. Damage outside the fornices (OUT) is greater in steel electrode lesions, but some platinum electrode lesions extend well into this area (H-30, H-31). The dimension of least overlap is the anterior-posterior diameter of the lesion (B); this results in a larger overall volume for the steel lesions (VOLUME). Only the one-half current steel electrode lesion of rat H-48 is as small in the anterior dimension as the platinum lesions.

In summary, I find two ways in which the geometry of lesions produced by steel electrodes (current 1 ma, 15") differs from that produced by platinum electrodes (current 1-2 ma, 20-25"). (1) Steel electrode lesions are larger in volume. (2) They differ in shape in that they are always larger in the anterior-posterior dimension but not in the transverse plane. Because of the clear opposite effects on lever pressing performance produced by the two types of electrodes, I feel that the anterior-posterior difference is the only one sufficient to account for the behavioral results.

Table 15

Rat	Wt. (g)	Area In	Area Out	Area Total	A	B	Volume	AP Plane
			Steel electrodes					
H 46	519	38.5	9.6	48.1	3.9	1.1	20.4	4.4
H 47	515	39.0	26.6	65.6	4.6	1.5	42.4	4.2
H 51	426	28.1	4.3	32.3	3.2	1.0	12.3	4.6
H 42	424	35.2	5.8	41.0	3.6	1.3	27.5	4.0
H 10	400	28.5	4.6	33.1	3.2	1.0	12.4	4.1
			Platinum electrodes					
H 34	730	36.3	1.3	37.6	3.5	0.9	10.8	4.6
H 77	579	37.3	5.5	42.7	3.7	0.9	13.4	4.0
H 71	539	51.3	1.6	52.9	4.1	1.2	23.7	4.6
H 31	530	42.9	5.0	47.9	3.9	0.6	5.3	4.4
H 30	520	34.6	9.0	43.6	3.7	0.7	7.1	4.2
H 74	516	49.9	4.9	54.8	4.2	0.3	1.7	5.3
H 54	478	31.8	1.5	33.3	3.3	0.7	6.8	5.1
H 58	470	44.4	2.0	46.4	3.8	0.7	7.4	4.9
H 68	454	34.4	1.5	35.9	3.4	0.4	2.9	4.4
H 65	424	17.4	1.0	18.4	2.4	0.3	0.7	4.6
H 25	409	17.2	5.1	22.3	2.7	0.3	1.1	4.2
H 32	401	19.0	0.0	19.0	2.5	0.5	2.7	4.4
			Platinum electrodes--weight data unavailable					
H 55	--	29.5	2.4	31.9	3.2	0.8	8.1	4.2

Size and location of ventromedial lesions of hyperphagic rats. Weights are asymptotic weights on laboratory chow following the experiment. See text for explanation of other parameters. All brains are listed for which the quality of histological preparation permitted measurements of the lesions.

Procedure for Computing Lesion Size

By visual microscopic inspection I located the section containing the largest amount of bilateral damage (column AP, in mm anterior to the interaural line). I then reconstructed the cross section of the lesion at this AP plane using the atlas of Koenig and Klippel (1963). On this reconstruction I delineated a region below the ventral boundary of the mammalothalamic tract (at the anterior-posterior level of the ventromedial nuclei). Within this region, I bilaterally localized two subregions of the lesion by counting on millimetric graph paper. Column IN is the subregion medial to the fornices, OUT is lateral to the fornices, and TOTAL is the maximum cross sectional area of the sub-mammalothalamic part of the lesion (all expressed in mm^2).

I then located the sections containing the rostralmost and caudalmost extent of necrotic or missing tissue for right and left sides separately. The rostalmost and caudalmost sections were usually almost equidistant from the section of maximum damage.

In order to estimate the volume of the lesions, I approximated the shape of the single hole normally created by the bilateral lesions with a simple geometrical figure, an oblate ellipsoid symmetrical about the anterior-posterior axis, with a major axis (column A, in mm) of length equal to one-half the distance between the mean rostral and caudal extent of the two sides of the lesion. The minor axis (column B in mm) was given a length equal to the radius of a circle equal in area to the maximum total cross sectional area. The volume of this ellipsoid (column VOLUME, in mm^3) gives a rough approximation to the volume of tissue destroyed by the bilateral lesion.

APPENDIX III

The Use of Platinum Electrodes for Producing Lesions

In a pilot experiment three rats received the same current and time of current passage through platinum electrodes as is usual in making ventromedial lesions with steel electrodes. None of these rats gained weight following the placement of the lesions and histological examination revealed that only a small amount of damage had occurred around the tip of the electrodes. This requirement for higher current x time when using platinum electrodes is implied (e.g. Teitelbaum, 1955) but is apparently not documented in literature on brain lesions. Reactive substances such as steel and copper produce monotonically increasing lesion sizes with increasing coulombs applied through them (MacIntyre et al., 1959), but nonreactive substances such as platinum appear to require substantially greater coulombs for the same amount of visible damage. Therefore, nonreactive substances may be hypothesized to damage nervous tissue by a fundamentally different mechanism.

Another problem encountered using platinum electrodes bears upon the biophysics of their use in producing lesions. Approximately half the individual lesions of hyperphagics and non-hyperphagics reported in this thesis terminated before the normal 20 or 25-second duration of current passage due to the stopping of the lesion producing device--the milliammeter suddenly registered zero. At these times, the device was working adequately when tested across artificial resistances of 5×10^4 ohms or across physiological saline. This "electrode blockage phenomenon," occurred some times after only 5 seconds of current passage and appeared to be more frequent with electrodes having unusually small areas of bared tip. The problem did not occur with steel electrodes.

Electrical resistance between the electrode and the rectal cathode was measured after disconnecting the lesion producing device and found to be greater than 1.5×10^5 ohms, rather than 5×10^4 ohms which is normal for the preparation before passage of current. By raising and lowering the electrode, a pocket of high resistance could be located at the lesion coordinates. Observation of the voltage being

produced by the lesion maker (a constant-current circuit) on a slow-sweep oscilloscope display showed that the voltage rose sharply but smoothly from 10-20 volts to an unmeasurably high value just before the milliammeter needle dropped to zero. I conclude that a pocket of a high resistance material, almost certainly a gas, is created during the production of a platinum electrode lesion and that the pocket of gas is large enough to affect both the lesion making technique and the tissue damage which results.

Calculation of the amount of an ideal divalent gas (ideal O_2 or Cl_2) generated by 2 ma of anodal current shows that about 6-7 mm^3 will be generated in 25 sec at standard pressure and at a temperature 1-2 times that of body temperature. Steam formation and dissolution of the gas would, of course, alter this estimate greatly. In any case, it is perfectly reasonable that a volume of gas of the same order of magnitude as the volume of the lesion would be generated at the tip of a platinum electrode when making such a lesion.

These two phenomena, the increased current required when using platinum electrodes as compared to steel and electrode blockage using platinum electrodes suggest that steel and platinum produce tissue damage by fundamentally different means. Characterization of the events occurring at the electrode tip during the passage of current and of the subsequent course of degeneration and gliosis will be necessary to evaluate the role of iron deposition, gas formation, heat damage, etc. in what is loosely called "brain lesions."

APPENDIX IV

Summary of Procedures in the Five Lesion Experiments

	Experiment				
	I	II	III	IV	V
Animals handled before training?	no	yes	yes	yes	no
Surgery	acute	acute	implanted	acute	implanted
Electrodes	steel	steel	Pt	Pt	Pt
Session length	12 hr	12 hr	12 hr	12 hr	continuous
Testing diet	100% milk or slurry	3:1 milk	3:1 milk	3:1 milk	3:1 milk
Pretraining?	no	yes	no	yes	yes
Temporal resolution of data	6 sec	1 sec or 6 sec	1 sec	1 sec	6 sec

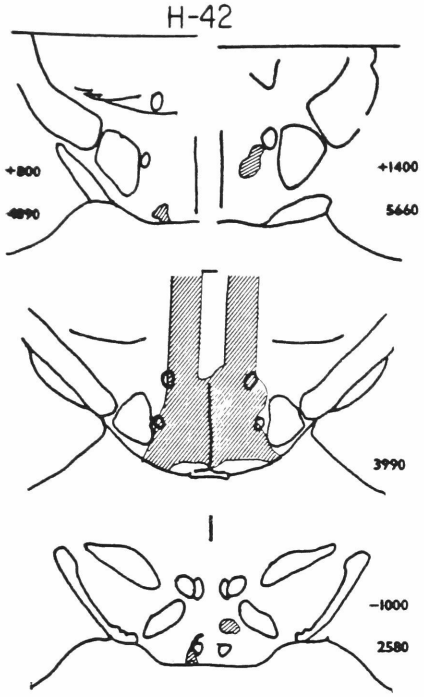
APPENDIX V

Reconstructions of Ventromedial Lesions

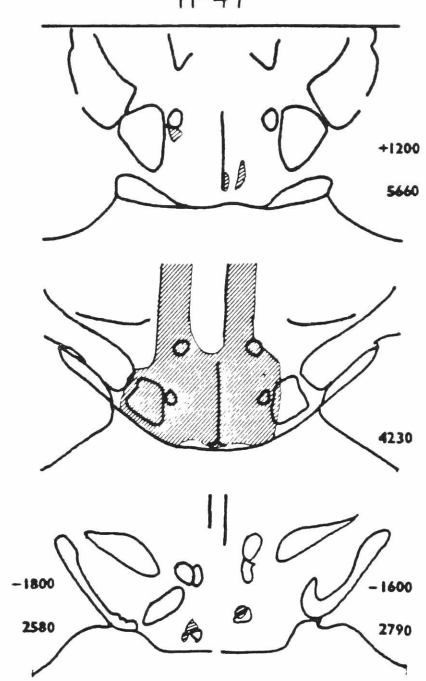
Reconstructed drawings of all lesions for which adequate histology was available are presented. For each rat, three sections are shown (four are shown for double-lesioned animals H-71 and H-77). The top section transects the anteriormost extent of the lesion, the middle section(s) the maximum transverse area of the lesion(s), and the bottom section the posterior extent of the lesion. For each section, nominal anterior distances in microns from the interaural line are given according to the Kownig and Klippel (1963) atlas. For the anterior and posterior sections, actual distances in microns are given, measured in 50 micron sections from the center section.

Figure	Animal(s)	Experiment
35	H-42, 46, 47, 51	II
36	H-10	I
36	H-54, 55, 58	III
37	H-65, 68, 74	IV
37	H-31	V
38	H-71, 77	IV
39	H-25, 30, 32, 34	V

H-42



H-47



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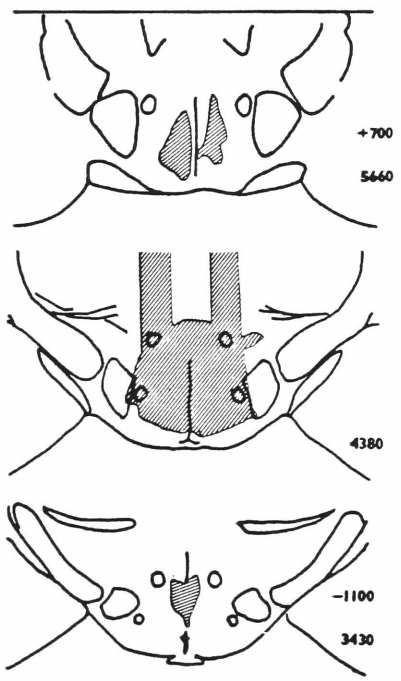

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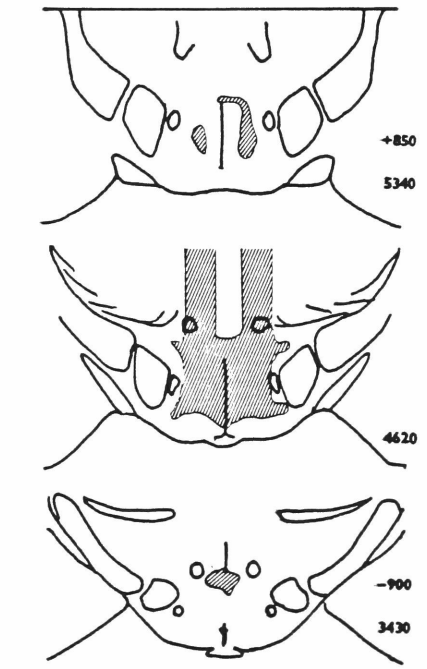

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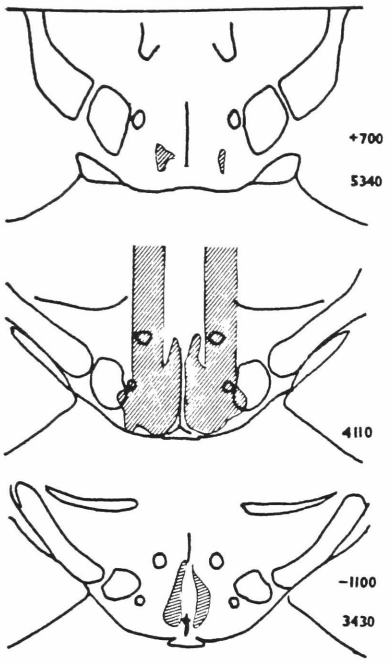

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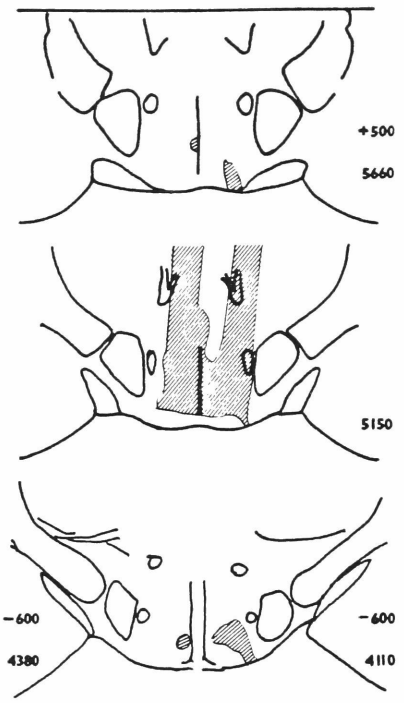

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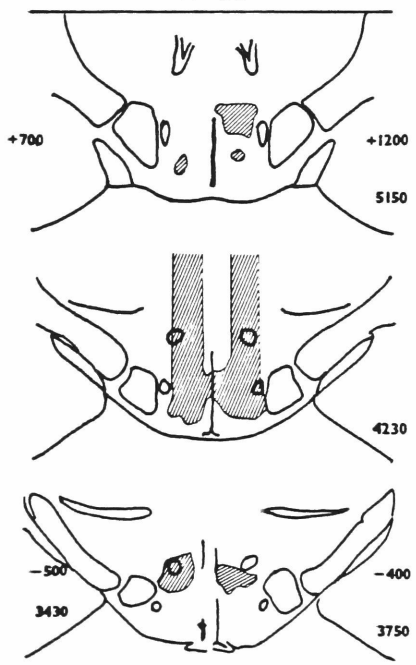

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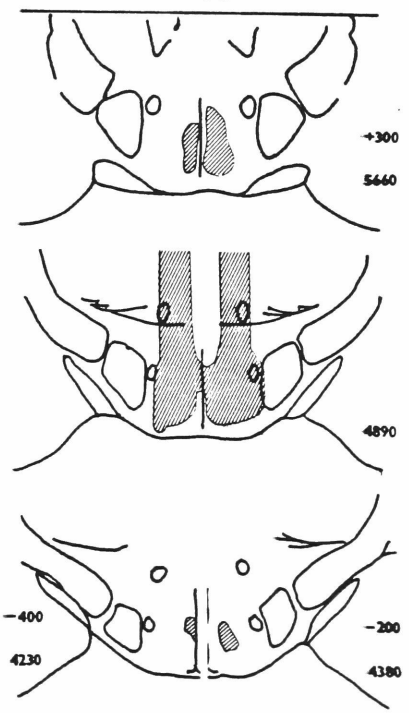

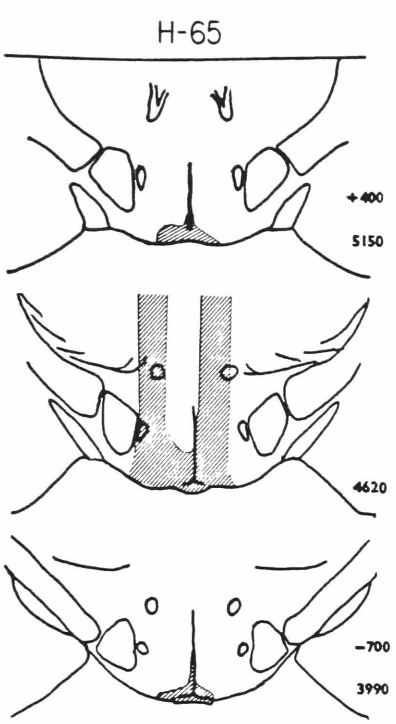
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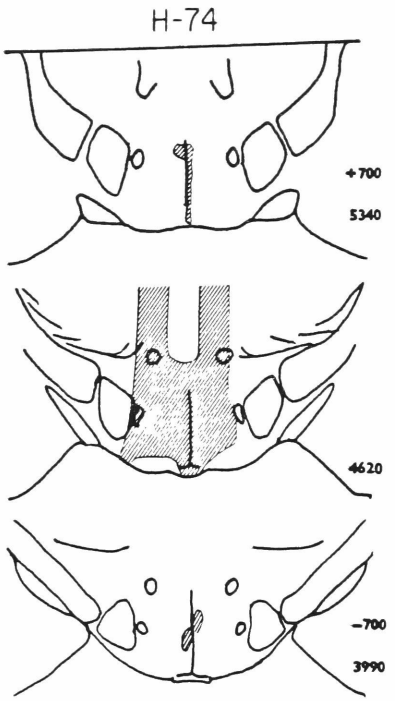
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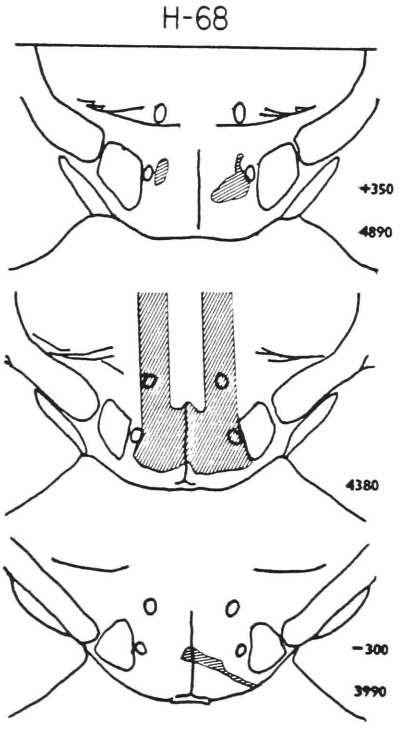
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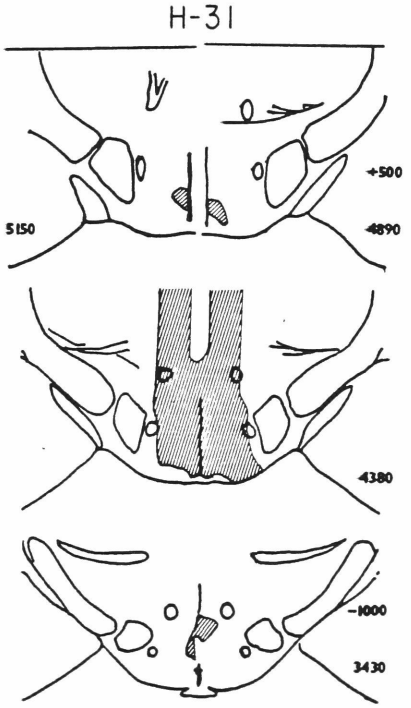
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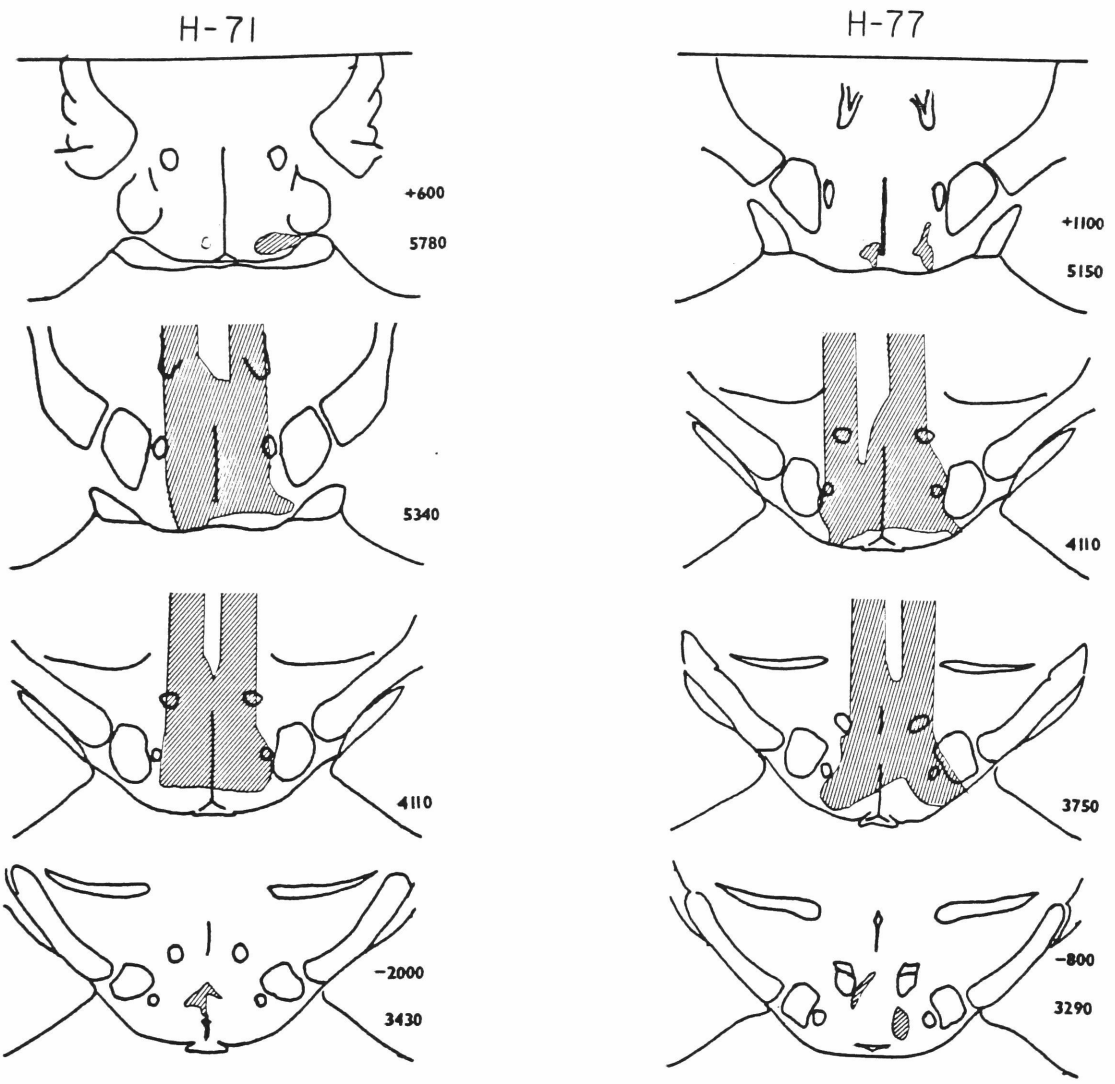
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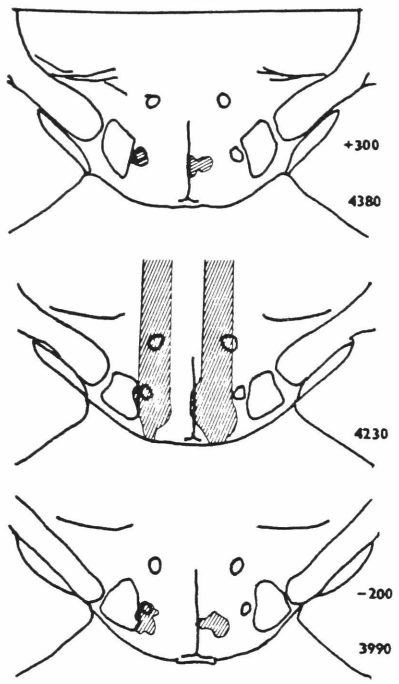

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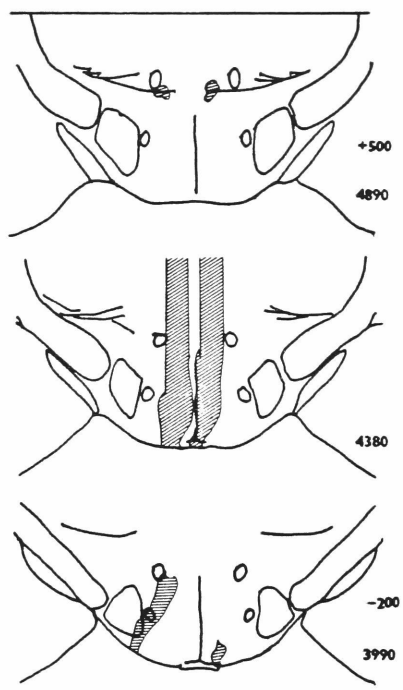

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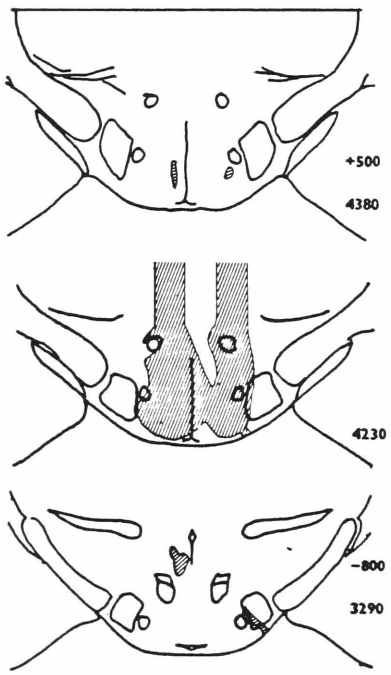

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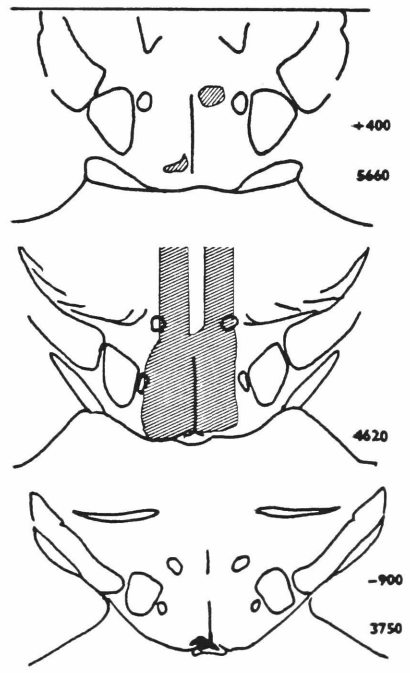

REFERENCES

Adams, D. B. Defence and territorial behaviour dissociated by hypothalamic lesions in the rat. Nature, 1971, 232, 573-4.

Akert, K. Neurophysiological correlates: Diencephalon. In D. E. Sheer, ed., Electrical stimulation of the brain. Univ. Texas Press, 1961, 288-310.

Allison, J. Microbehavioral features of nutritive and nonnutritive drinking in rats. Journal of Comparative and Physiological Psychology, 1971, 76, 408-417.

Allison, J. and Castellan, N. Jr. Temporal characteristics of nutritive drinking in rats and humans. Journal of Comparative and Physiological Psychology, 1970, 70, 116-125.

Anand, B. K. and Brobeck, J. R. Hypothalamic control of food intake in rats and cats. Yale Journal of Biology and Medicine, 1951, 24, 123-140.

Atrens, D. M. and von Vietinghoff-Riesch, F. The motivational properties of electrical stimulation of the medial and paraventricular hypothalamic nuclei. Physiology and Behavior, 1972, 9, 229-235.

Baker, R. A. Aperiodic feeding behavior in the albino rat. Journal of Comparative and Physiological Psychology, 1953, 46, 422-426.

Balagura, S. Neurophysiologic aspects: hypothalamic factors in the control of eating behavior. Advances in Psychosomatic Medicine, 1972, 7, 25-48.

Balagura, S. and Coscina, D. V. Periodicity of food intake in the rat as measured by an operant response. Physiology and Behavior, 1968, 3, 641-643.

Balagura, S. and Devenport, L. D. Feeding patterns of normal and ventromedial hypothalamic lesioned male and female rats. Journal of Comparative and Physiological Psychology, 1970, 71, 357-364.

Balinska, H. Studies on feeding behavior in rabbits. Activitas Nervosa Superior, 1967, 9, 11-18.

Balinska, H., Lewinska, K., Romaniuk, A., and Wyrwicka, W. The effect of lesions of the medial hypothalamus on internal inhibition in the alimentary reflexes type II. Acta Biol. Exptl. Warsaw, 1961, 21, 189-197.

Ball, G. G. Self-stimulation in the ventromedial hypothalamus. Science, 1972, 178, 72-73.

Bare, J. K. Hunger, deprivation, and the day-night cycle. Journal of Comparative and Physiological Psychology, 1959, 52, 129-131.

Barfosky, I., Robinson, S. M., and Horwitz, D. A. The effect of elevated temperature on food and water reinforced fixed ratio performance. Physiology and Behavior, 1970, 5, 1243-1248.

Beatty, W. W. Influence of type of reinforcement on operant responding by rats with ventromedial hypothalamic lesions. Physiology and Behavior, 1973, 10, 841-846.

Beatty, W. W. Persistent depression of wood-gnawing following ventromedial hypothalamic lesions in the rat. Physiology and Behavior, 1972, 8, 383-384.

Blurton Jones, N. G. Observations and experiments on causation of threat displays of the Great Tit (Parus major). Animal Behavior Monographs, 1968, 1, 1-158.

Bolles, R. C. The readiness to eat and drink: the effect of deprivation conditions. Journal of Comparative and Physiological Psychology, 1962, 55, 230-234.

Bolles, R. C. Effect of food deprivation upon the rat's behavior in its home-cage. Journal of Comparative and Physiological Psychology, 1963, 56, 456-460.

Bolles, R. C. Theory of Motivation. N.Y., Harper and Row, 1967.

Bolles, R. C. and Stokes, L. W. Rat's anticipation of diurnal and a-diurnal feeding. Journal of Comparative and Physiological Psychology, 1965, 60, 290-294.

Brittain, W. P., Knowles, P. and Remley, N.R. Some effects of VMH lesions on bar-press activity in rats using Mult FR 5 VI 1'. Proceedings of the 54th Midwestern Psychological Association, May 4-6, 1972.

Brobeck, John R., Tepperman, J., and Long, C. N. H. Experimental hypothalamic hyperphagia in the albino rat. Yale Journal of Biology and Medicine, 1943, 15, 831-853.

Brooks, C. Mc and Lambert, E. F. A study of the effect of limitation of food intake and the method of feeding on the rate of weight gain during hypothalamic obesity in the albino rat. American Journal of Physiology, 1946, 147, 695-707.

Brooks, C. M., Lockwood, R. A., and Wiggins, M. L. A study of the effect of hypothalamic lesions on the eating habits of the albino rat. American Journal of Physiology, 1946, 147, 735-741.

Campbell, B. A. and Sheffield, F. D. Relation of random activity to food deprivation. Journal of Comparative and Physiological Psychology, 1953, 46, 320-322.

Candland, D. K., Horowitz, S. H. and Culbertson, J. L. Acquisition and retention of acquired avoidance with gentling as reinforcement. Journal of Comparative and Physiological Psychology, 1962, 55, 1962-1064.

Carlisle, H. J. and Stellar, E. Caloric regulation and food preference in normal, hyperphagic, and aphagic rats. Journal of Comparative and Physiological Psychology, 1969, 69, 107-114.

Chance, M. R. A. and Mead, A. D. Competition between feeding and investigation in the rat. Behaviour, 1955, 8, 174-181.

Collier, G., Hirsch, E. and Hamlin, P. H. The ecological determinants of reinforcement in the rat. Physiology and Behavior, 1972, 9 705-716.

Collins, E. Localization of an experimental hypothalamic midbrain syndrome simulating sleep. Journal of Comparative Neurology, 1954, 100, 661-697.

Corbit, John D. and Stellar, Eliot. Palatability, food intake, and obesity in normal and hyperphagic rats. Journal of Comparative and Physiological Psychology, 1964, 58, 63-67.

Cox, D. R. and Lewis, P. A. W. The statistical analysis of series of events. New York, Wiley, 1966.

Dahl, E. and Ursin, H. Obesity produced by iron and tissue destruction in the ventromedial hypothalamus. Physiology and Behavior, 1969 4, 315-317.

de Caire, E. The distribution of feeding behavior in the albino rat and the effects of disturbance. South African Journal of Medical Science, 1968, 33, 71-74.

Ehrenfreund, D. The relationship between weight loss during deprivation and food consumption. Journal of Comparative and Physiological Psychology, 1959, 52, 123-125.

Epstein, A. N. Reciprocal changes in feeding behavior produced by intra-hypothalamic chemical injections. American Journal of Physiology, 1960, 199, 969-974.

Ferster, C. B. and Skinner, B. F. Schedules of reinforcement. New York, Appleton-Century-Crofts, 1957.

Gentile, R. L. The role of taste preference in the eating behavior of the albino rat. Physiology and Behavior, 1970, 5, 311-316.

Gladfelter, W. E. and Brobeck, J. R. Decreased spontaneous locomotor activity in the rat induced by hypothalamic lesions. American Journal of Physiology, 1962, 203, 811-817.

Graff, H. and Stellar, E. Hyperphagia, obesity, and finickiness. Journal of Comparative and Physiological Psychology, 1962, 55 418-424.

Green, P. Effects of early vs. late lesions on cognitive-affective behavior in rats: VMH. Psychonomic Science, 1967, 7, 11-12.

Grossman, S. P. The VMH: A center for affective reactions, satiety, or both? Physiology and Behavior, 1966, 1, 1-10.

Grossman, S. P. Aggression, avoidance and reaction to novel enviornments in female rats with ventromedual hypothalamic lesions. Journal of Comparative and Physiological Psychology, 1972, 78, 274-283.

Grossman, S. P. and Grossman, L. Food and water intake in rats with parasaggital knife cuts medial or lateral to the lateral hypothalamus. Journal of Comparative and Physiological Psychology, 1971, 74, 148-165.

Hamilton, C. L. Interactions of food intake and temperature regulation in the rat. Journal of Comparative and Physiological Psychology, 1963, 56, 476-488.

Hamilton, C. L. Problems of refeeding after starvation in the rat. Annals of the New York Academy of Sciences, 1969, 157, art. 2, 1004-1017.

Hamilton, C. L. and Brobeck, J. Hypothalamic hyperphagia in the monkey. Journal of Comparative and Physiological Psychology, 1964, 57, 271-278.

Han, P. W. and Brobeck, J. R. Temperature regulation of rats with hypothalamic hyperphagia. American Journal of Physiology, 1961, 200, 703-706.

Helms, C. W. and Kuenzel, W. J. Operant responses of a White-throated Sparrow to fixed ratio reinforcement for food and water before and after lesion of the ventromedial area of the hypothalamus. American Zoologist, Nov. 1969, 4.

Herberg, L. J. and Blundell, J. E. Non-interaction of ventromedial and lateral hypothalamic mechanisms in the regulation of feeding and hoarding behavior in the rat. Quarterly Journal of Experimental Psychology, 1970, 22, 133-141.

Herrero, S. Radio-frequency-current and direct-current lesions in the ventromedial hypothalamus. American Journal of Physiology, 1969, 217, 403-410.

Hetherington, A. W. and Ranson, S. W. Hypothalamic lesions and adiposity in the rat. Anatomical Record, 1942, 78, 149-172.

Hetu, R. Deprivation-feeding cycle and locomotor activity of the albino rat in a complex maze. Psychological Record, 1971, 21, 125-130.

Hinde, R. A. Animal behaviour. 1970. (2nd ed.), New York, McGraw-Hill.

Hoebel, B. G. Electrode-cannulas for electrical or chemical treatment of multiple brain sites. Electroencephalography and Clinical Neurophysiology, 1964, 16, 399-402.

Hoebel, B. G. Hypothalamic lesions by electrocauterization: disinhibition of feeding and self-stimulation. Science, 1965, 149, 452-453.

Hoebel, B. G. and Teitelbaum, P. Hypothalamic control of feeding and self-stimulation. Science, 1962, 135, 375-377.

Hoebel, B. G. and Teitelbaum, P. Weight regulation in normal and hypothalamic hyperphagic rats. Journal of Comparative and Physiological Psychology, 1966, 61, 189-193.

Johnson, D. A. and Thatcher, K. Differential effects of food deprivation on the fixed-ratio behavior of normal rats and rats with septal lesions. Psychonomic Science, 1972, 26, 45-46.

Kaada, B. R., Rasmussen, E. W., and Kueim, L. Impaired acquisition of passive avoidance behavior by subcallosal, septal, hypothalamic, and insular lesions in rats. Journal of Comparative and Physiological Psychology, 1962, 55, 661-670.

Kemmerer, A. R., Elvehjem, C. A., Hart, E. B., and Faro, J. M. The nutritive value and efficiency of mineralized milk. American Journal of Physiology, 1932, 102, 319-324.

Kennedy, G. C. The hypothalamic control of food intake in rats. Proceedings of the Royal Society, B, 1950, 137, 535-549.

Kennedy, G. C. and Mitra, J. Hypothalamic control of energy balance and the reproductive cycle in the rat. Journal of Physiology, London, 1963, 166, 395-407.

Kent, M. A. and Peters, R. H. Effects of ventromedial hypothalamic lesions on hunger motivated behavior in rats. Journal of Comparative and Physiological Psychology, 1973, 83, 92-97.

Kimble, G. A. Hilgard and Marquis' conditioning and learning. 1961, Appleton-Century-Crofts, New York.

Kissileff, H. R. Manipulation of the oral and gastric environments. In: R. D. Myers (ed.) Methods in Psychobiology, 1972, New York, Academic Press, 125-154.

Knott, J. R., Ingram, W. R. and Correll, R. E. Effects of certain subcortical lesions on learning and performance in the cat. Archives of Neurology, 1960, 2, 247-259.

Koenig, J. F. R. and Klippel, R. A. The rat brain, Baltimore, 1963, Williams and Wilkins Co.

Krasne, F. B. General disruption resulting from electrical stimulus of ventromedial hypothalamus. Science, 1962, 138, 822-823.

Larkin, R. P. How hard will hyperphagic rats work for food? Eastern Psychological Association meetings, 1971, N. Y.

Larkin, R. P. Detailed recording of spontaneous rapid events. Behavior Research Methods and Instrumentation, 1972, 4, 32-33.

LeMagnen, J. Advances in studies on the physiological control and regulation of food intake. Progress in Physiological Psychology, 1971, 4, 203-261.

LeMagnen, J. Perpheral and systemic actions of food in the caloric regulation of intake. Annals of the New York Academy of Science, 1969, 157, 1126-1156.

LeMagnen, J. and Devos, M. Metabolic correlates of the meal onset in the free food intake of rats. Physiology and Behavior, 1970, 5, 805-814.

LeMagnen, J. and Tallon, S. La periodicite spontanee de la prise d'aliments ad libitum du rat blanc. Journal de Physiologie (Paris), 1966, 58, 323-349.

Levine, S. and Soliday, S. The effects of hypothalamic lesions on conditioned avoidance learning. Journal of Comparative and Physiological Psychology, 1960, 53, 497-501.

Levitsky, D. A. Feeding patterns of rats in response to fasts and changes in environmental conditions. Physiology and Behavior, 1970, 5, 291-300.

Levitsky, D. A. and Collier, G. Effects of diet and deprivation on meal eating behavior in rats. Physiology and Behavior, 1968, 3, 137-140.

Liebelt, R. A. and Perry, J. H. Action of gold thioglucose on the central nervous system. In: Handbook of Physiology, Sect. 6, American Physiological Society, Washington, D. C., 1967, 1, 271-285.

Lillie, R. D. Histopathologic technic and practical histochemistry. 1965, New York, McGraw-Hill.

Loucks, R. B., Weinberg, H. and Smith, M. The erosion of electrodes by small currents. Electroencephalography and Clinical Neurophysiology, 1959, 11, 823-826.

Margules, D. L. and Stein, L. Cholinergic synapses in the ventromedial hypothalamus for the suppression of operant behavior by punishment and satiety. Journal of Comparative and Physiological Psychology, 1969, 67, 327-335.

Marks, H. E. and Brown, G. E. The effects of VMH lesions in Charles River rats. Psychonomic Science, 1971, 23, 117-118.

Marks, H. E. and Remley, N. R. The effects of type of lesion and percentage body weight loss on measures of motivated behavior in rats with hypothalamic lesions. Behavioral Biology, 1972, 7, 95-111.

McCleary, R. A. Response-modulating functions of the limbic system: Initiation and suppression. In: E. Stellar and J. M. Sprague (eds.), Progress in Physiological Psychology, New York, Academic Press, 1966.

Mechner, F. Probability relations within response sequences under ratio reinforcement. Journal of the Experimental Analysis of Behavior, 1958, 1, 109-121.

Miller, N. E. Experiments on motivation. Science, 1957, 126, 1271-1278.

Miller, N. E. Shortcomings of food consumption as a measure of hunger: results from other behavioral techniques. Annals of the New York Academy of Sciences, 1955, 63, 141-143.

Miller, N. E. Effects of drugs on motivation: The value of using a variety of measures. Annals of the New York Academy of Sciences, 1956, 65, 318-333.

Miller, N. E., Bailey, C. J. and Stevenson, J. A. F. Decreased "hunger" but increased food intake resulting from hypothalamic lesions. Science, 1950, 112, 256-259.

Morgane, P. J. Distinct 'feeding' and 'hunger motivating' systems in the lateral hypothalamus of the rat. Science, 1961 (a), 133, 887-888.

Morgane, P. J. Medial forebrain bundle and 'feeding centers' of the hypothalamus. Journal of Comparative Neurology, 1961 (b), 117, 1-24.

Morgane, P. J. and Jacobs, H. L. Hunger and satiety. World Review of Nutrition and Dietetics, 1969, 10, 100-213.

Moskowitz, M. J. Running-wheel activity in the white rat as a function of combined food and water deprivation. Journal of Comparative and Physiological Psychology, 1959, 52, 621-625.

Mrosovsky, Nichols. Hibernation and the hypothalamus. 1971, New York, Appleton.

Nisbett, Richard E. Hunger, obesity, and the ventromedial hypothalamus. Psychological Review, 1972, 79, 433-453.

Norgren, R. Gustatory responses in the hypothalamus. Brain Research, 1970, 21, 63-77.

Panksepp, J. Is satiety mediated by the ventromedial hypothalamus? Physiology and Behavior, 1971, 7, 381-384. (a).

Panksepp, J. A re-examination of the role of the ventromedial hypothalamus in feeding behavior. Physiology and Behavior, 1971, 7, 385-394. (b)

Panksepp, J. Reanalysis of feeding patterns in the rat. Journal of Comparative and Physiological Psychology, 1973, 82, 78-94.

Pool, R. Suction lesions and hypothalamic hyperphagia. American Journal of Physiology, 1967, 213, 31-35.

Porter, J. H. and Allen, J. D. Food-motivated performance as a function of weight loss in hypothalamic hyperphagic rats. Psychonomic Science, 1972, 28, 285-288.

Powell, R. W. Probability of reinforcement and fixed-ratio responding: a model. Psychological Record, 1970, 20, 73-80.

Powley, T. L. and Keesey, R. E. Relationship of body weight to the lateral hypothalamic feeding syndrome. Journal of Comparative and Physiological Psychology, 1970, 70, 25-36.

Premack, D. Reinforcement theory. In: Nebraska Symposium on Motivation, 1965, 8, ed. by David Levine, 123-180.

Rabin, B. M. Effect of lesions of the ventro-medial hypothalamus on the electrical activity of the ventrolateral hypothalamus. Electroencephalography and Clinical Neurophysiology, 1968, 25 344-350.

Rabin, B. M. Ventromedial hypothalamic control of food intake and satiety: a reappraisal. Brain Research, 1972, 43, 317-342.

Rabin, B. M. and Smith, C. J. Behavioral comparison of the effects of irritative and non-irritative lesions in producing hypothalamic hyperphagia. Physiology and Behavior, 1968, 3, 417-420.

Reynolds, R. W. Ventromedial hypothalamic lesions without hyperphagia. American Journal of Physiology, 1963, 204, 60-62.

Reynolds, R. W. Hypothalamic lesions and disinhibition of feeding. Science, 1965 a, 150, 1322-1323.

Reynolds, R. W. An irritative hypothesis concerning the hypothalamic regulation of food intake. Psychological Review, 1965 b, 72 105-116.

Reynolds, R. W. and Simpson, C. W. Chronic infusion studies on the hypothalamic regulation of food intake. Annals of the New York Academy of Sciences, 1969, 157, Art. 2, 755-757.

Routtenberg, A. Intracranial chemical injection and behavior: a critical review. Behavioral Biology, 1972, 7, 601-641.

Satinoff, E. Hibernation and the central nervous system. Progress in Physiological Psychology, 1970, 3, 201-236, (ed. by E. Stellar and J. M. Sprague).

Schachter, S. Some extraordinary facts about obese humans and rats. American Psychologist, 1971, 26, 129-144.

Sclafani, A. Neural pathways involved in the ventromedial hypothalamic lesion syndrome in the rat. Journal of Comparative and Physiological Psychology, 1971, 77, 70-96.

Sclafani, A. The effects of food deprivation and palatability on the latency to eat of normal and hyperphagic rats. Physiology and Behavior, 1972, 8, 977-979.

Sclafani, A., Belluzzi, J. P. and Grossman, S. P. Effects of lesions in the hypothalamus and amygdala on feeding behavior in the rat. Journal of Comparative and Physiological Psychology, 1970, 72 394-403.

Sidman, M. and Stebbins, W. C. Satiation effects under fixed-ratio schedules of reinforcement. Journal of Comparative and Physiological Psychology, 1954, 47, 114-116.

Siegel, S. Nonparametric statistics. 1956, New York, McGraw-Hill.

Singh, D. Sex differences in obesity and food-directed activity in normal and hyperphagic rats. Psychonomic Science, 1970, 21, 306-308.

Singh, D. Preference for mode of obtaining reinforcement in rats with lesions in septal or ventromedial hypothalamic area. Journal of Comparative and Physiological Psychology, 1972, 80, 259-268.

Singh, D. and Meyer, D. R. Eating and drinking by rats with lesions of the septum and the ventromedial hypothalamus. Journal of Comparative and Physiological Psychology, 1968, 65, 163-166.

Smith, C. J. U. and Britt, D. L. Obesity in the rat induced by hypothalamic implants of gold thioglucose. Physiology and Behavior, 1971, 7, 7-10.

Snowdon, C. T. Motivation, regulation, and the control of meal parameters with oral and intragastric feeding. Journal of Comparative and Physiological Psychology, 1969, 69, 91-100.

Stellar, E. The physiology of motivation. Psychological Review, 1954, 61, 5-22.

Stevenson, J. A. F. Mechanisms in the control of food and water intake. Annals of the New York Academy of Sciences, 1969, 157, 1069-1083.

Storlien, L. H. and Albert, D. J. The effect of VMH lesions, lateral cuts and anterior cuts on food intake, activity level, food motivation, and reactivity to taste. Physiology and Behavior, 1972, 9, 191-197.

Strominger, J. L., Brobeck, J. R. and Cort, R. L. Regulation of food intake in normal rats and in rats with hypothalamic hyperphagia. Yale Journal of Biology and Medicine, 1953, 26, 55-74.

Tapp, Jack T. Activity, reactivity, and the behavior-directing properties of stimuli. In: Reinforcement and Behavior, ed. by Jack T. Tapp, Academic Press, 1969, pp. 146-177.

Teitelbaum, P. Sensory control of hypothalamic hyperphagia. Journal of Comparative and Physiological Psychology, 1955, 48, 156-163.

Teitelbaum, P. Random and food-directed activity in hyperphagic and normal rats. Journal of Comparative and Physiological Psychology, 1957, 50, 486-490.

Thomas, D. W. and Mayer, J. Meal taking and regulation of food intake by normal and hypothalamic hyperphagic rats. Journal of Comparative and Physiological Psychology, 1968, 66, 642-653.

Thompson, D. M. Escape from S^D associated with fixed ratio reinforcement. Journal of the Experimental Analysis of Behavior, 1964, 7, 1-8.

Thompson, D. M. Punishment by S associated with fixed-ratio reinforcement. Journal of the Experimental Analysis of Behavior, 1965 (a), 8, 189-194.

Thompson, D. M. Time-out from fixed-ratio reinforcement: a systematic replication. Psychonomic Science, 1965 (b), 2, 109-110.

Treichler, F. R. and Hall, J. F. The relationship between deprivation weight loss and several measures of activity. Journal of Comparative and Physiological Psychology, 1962, 55, 346-349.

Valenstein, E. S. Behavior elicited by hypothalamic stimulation. Brain, Behavior, and Evolution, 1969, 2, 295-316.

Valenstein, E. S., Cox, V. C. and Kakolewski, J. W. The motivation underlying eating elicited by lateral hypothalamic stimulation. Physiology and Behavior, 1968, 3, 969-971.

Valenstein, E. S., Cox, V. C. and Kakolewski, J. W. Reexamination of the role of the hypothalamus in motivation. Psychological Review, 1970, 77, 16-31.

Wagner, J. W. and De Groot, J. Changes in feeding behavior after intracerebral injections in the rat. American Journal of Physiology, 1963, 204, 483-487.

Wampler, Richard S. Increased motivation in rats with ventromedial hypothalamic lesions. Journal of Comparative and Physiological Psychology, 1973, 84, 275-285.

Warren, R. P. and Pfaffman, C. Early experience and taste aversion. Journal of Comparative and Physiological Psychology, 1958, 52, 263-266.

Weinstock, Roy B. Maintenance schedules and hunger drive: an examination of the rat literature. Psychological Bulletin, 1972, 78, 311-320.

Wiepkema, P. R. An ethological analysis of the reproductive behavior of the Bitterling (Rhodeus amarus Bloch), Arch. neer. Zool., 1961, 14, 103-199.

Wiepkema, P. R. Behaviour changes in CBA mice as a result of one goldthioglucose injection. Behaviour, 1968, 32, 179-210.

Williams, B. A. and Campbell, B. A. Weight loss and quinine-milk ingestion as measures of "hunger" in infant and adult rats. Journal of Comparative and Physiological Psychology, 1961, 54, 220-222.

Wolf, G. and DiCara, L. V. Progressive morphological changes in electrolytic brain lesions. Experimental Neurology, 1969, 23, 529-536.

Zeigler, H., Green, H. L., and Lehrer, R. Patterns of feeding behavior in the pigeon. Journal of Comparative and Physiological Psychology, 1971, 76, 468-477.

End