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City University of New York PH.D. 1983

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THE PARAVENTRICULAR HYPOTHALAMUS AND FEEDING BEHAVIOR

by

PAUL F. ARAVICH

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1983

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

THE PARAVENTRICULAR HYPOTHALAMUS AND FEEDING BEHAVIOR

by

Paul F. Aravich

Adviser: Professor Anthony Sclafani

The role of the paraventricular hypothalamus (PVH) in the feeding behavior of the rat was explored in several experiments. Experiment 1 compared the PVH hyperphagia syndrome to the classic hypothalamic hyperphagia syndrome. PVH lesions and medial hypothalamic (MH) knife cuts produced hyperphagia and overweight on a chow diet although the PVH effect was smaller than the knife-cut effect. Each treatment also produced qualitatively similar ingestive responses to two unpalatable and two palatable diets during the dynamic and static weight-gain phases. The PVH lesions and MH cuts disrupted day/night feeding patterns and elevated water intakes but did not alter water/food intake ratios. PVH lesions, unlike MH cuts, did not increase emotional reactivity. It was concluded that the system responsible for hypothalamic hyperphagia is importantly but not exclusively associated with the PVH.

The relationship between the fiber systems mediating the hypothalamic hyperphagia syndrome and the ingestive

effects following norepinephrine (NE) stimulation of the PVH was explored in Experiments 2-4. Various types of hypothalamic knife cuts in a position to sever the pathway implicated in hypothalamic hyperphagia failed to alter the NE-feeding effect. It was concluded that the output of the NE-feeding system is independent of the system responsible for hypothalamic hyperphagia.

Experiments 5-7 determined if the PVH NE-feeding system mediates the ingestive response to glucoprivation induced by 2-deoxy-D-glucose (2DG). It was found that, in contrast to systemic 2DG injections, injections of alpha-adrenergic agonists (NE and clonidine) into the PVH did not produce a preference for a 20% sucrose diet over a 20% fat diet. It was also shown that injections of the alpha-adrenergic antagonist phentolamine into the PVH or the dorsomedial hypothalamus blocked feeding induced by moderate food deprivation as well as 2DG-elicited feeding. Phentolamine injections into these sites failed to block the sucrose-diet preference effect elicited by 2DG. Finally, it was found that PVH lesions do not impair 2DG feeding. It was concluded that the PVH NE-feeding system is independent of the glucoprivic-feeding system.

Dedication and Acknowledgements

I would like to share the fruits of this effort with my wife Michele, who has shared in all of its costs. It is from her that I have learned the most and because of her that I have lived the most.

I would like to dedicate this effort to:

My parents: for the sacrifices they have made on my behalf; for their unending support and encouragement; and for being their every time I have needed them.

My aunt, Alice Marchiori Pinchock: for the warmth and love she has shown me throughout my life and for teaching me to be proud of who I am and where I come from.

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For over forty years it has been known that destruction of the ventromedial region of the hypothalamus (VMH) produces hyperphagia and obesity (Brobeck, Tepperman, and Long, 1943; Hetherington and Ranson, 1942a). A vast body of experimental literature has been generated attempting to specify the role of the VMH in normal and pathological ingestive behavior. However, it is becoming increasingly evident that at least some of the effects of VMH manipulations on food intake are due to fibers of passage and attention is shifting to the paraventricular hypothalamic area (PVH) as an important integrator of ingestive behavior. While best known for its control of posterior pituitary function (see Defendini and Zimmerman, 1978), the PVH has been associated with two types of alterations in feeding: hypothalamic hyperphagia and noradrenergic-induced feeding.

The Hypothalamic Hyperphagia Syndrome

VMH lesions produce hyperphagia and obesity in a variety of species including rats (see above), humans (Reeves and Plum, 1969), monkeys (Ruch, Patton, and Brobeck, 1942), cats (Wheatley, 1944), mice (Mayer, French, Zighera, and Barnett, 1955), goats (Baile, Mayer, Mahoney, and McLaughlin, 1969), and swine (Khalaf, 1969). In addition to VMH lesions, the syndrome can also be produced by knife cuts through the medial hypothalamus (MH) (Sclafani, 1971). The

hyperphagia and obesity produced by VMH lesions or MH cuts has two characteristic phases. Initially, there is a period of excessive food intake and rapid body-weight gain. Following this period, food intake and rate of body-weight gain become more normal (Brobeck et al., 1943; Brooks and Lambert, 1946; Hetherington and Ranson, 1940). The initial period of rapid body-weight gain and excessive food intake has been termed the "dynamic phase" of the syndrome and the period of more normal weight gain and food intake the "static phase" (Brobeck, 1946). Since the obese weight that is ultimately obtained during the static phase is "defended" under some conditions (Brobeck et al., 1943; Brooks and Lambert, 1946; Hoebel and Teitelbaum, 1966; Kennedy, 1950), the syndrome is sometimes viewed as representing an elevation in the level of regulated body weight (i.e., the "lipostatic" or "body-weight setpoint" views of the syndrome, Hoebel and Teitelbaum, 1966; Kennedy, 1953; Sclafani, 1976). From this perspective, then, hypothalamic hyperphagia fundamentally reflects an alteration in the long-term regulation of food intake and body weight rather than a disruption in the short-term control of satiety (see below).

Another important aspect of the hyperphagia/obesity syndrome is that food consumption is diet dependent (Brooks, Lockwood, and Wiggins, 1946; Hetherington and Ranson, 1942b) particularily during the static phase (Kennedy, 1950; Teitelbaum, 1955). Rats with VMH lesions or MH cuts, for

example, voraciously overeat high-fat diets or high-sugar diets but fail to overeat or actually undereat diets made bitter with quinine or sucrose octa acetate (SOA) (Corbit and Stellar, 1964; Miller, Bailey, and Stevenson, 1950; Sclafani, 1971; Sclafani, Aravich, and Schwartz, 1979; Teitelbaum, 1955). This dietary hyperreactivity is traditionally regarded as representative of a heightened sensitivity to the taste of food and the phenomenon is referred to as "finickiness" (Teitelbaum, 1955). However, this view of finickiness for bitter diets has been challenged by findings that taste hyperresponsiveness alone does not account for SOA diet aversion in the MH-damaged rat (Sclafani et al., 1979) and that it is the obesity rather than the brain damage per se that results in the excessive quinine finickiness of static phase animals (Ferguson and Keesey, 1975; Franklin and Herberg, 1974; Sclafani, Springer, and Kluge, 1976). Some investigators have argued, however, that finickiness to palatable diets is a fundamental aspect of hypothalamic hyperphagia and obesity (e.g., Sclafani, 1976; Sclafani and Kluge, 1974). Regardless of its specific intrepretation, finickiness remains an important hallmark of the syndrome (e.g., Sclafani et al., 1976; Teitelbaum, 1955).

A variety of other effects are also associated with the hypothalamic obesity syndrome. For example, there are alterations in emotional reactivity and in the day/night distribution of feeding behavior. Animals with VMH lesions

or MH cuts are quite irritable and aggressively react to relatively innocuous stimuli (Brooks et al., 1946; Hetherington and Ranson, 1942b; Sclafani, 1971; Wheatley, 1944). Grossman (1966) has argued that VMH damage enhances affective responsiveness to sensory stimuli in general, which accounts for the finickiness as well as the irritability of the animal. MH-damaged rats also consume more of their daily food intake during the daytime than do normal rats (Brooks et al., 1946; Sclafani and Berner, 1976). Le Magnen (1981) has argued that this change is due to metabolic alterations that are essential to the hyperphagia/obesity syndrome, though this point of view has been debated (e.g., Becker and Kissileff, 1974; Gold, Sumprer, Ueberacher, and Kapatos, 1975; Sclafani, 1981).

The hypothalamic hyperphagia syndrome has a number of additional characteristics. For example, there are changes in water consumption (e.g., Stevenson, 1949), carbohydrate and fat metabolism (e.g., Frohman, 1980; Schnatz, Frohman, and Bernardis, 1973; Tepperman, Brobeck, and Long, 1943), insulin secretion (e.g., Powley, 1977), sympathetic activity (e.g., Inoue and Bray, 1979; Schnatz et al., 1973), spontaneous motor activity (e.g., Brooks et al., 1946; Hetherington and Ranson, 1942b), and meal patterns (e.g., Brooks et al., 1946; Teitelbaum and Campbell, 1958). There is also evidence that young rats (Bernardis, 1966; Kennedy, 1957) and male rats (Cox, Kakolewski, and Valenstein, 1969) are less affected by the treatment than are adults or

females.

Several studies have attempted to define the specific anatomical substrate responsible for the hypothalamic obesity syndrome. According to the classic "dual center" theory (Anand and Brobeck, 1951; Stellar, 1954), fiber pathways originating in a VMH "satiety center" project to a lateral hypothalamic (LH) "feeding center" and inhibit food intake; destruction of the VMH destroys the "satiety center" and results in the "disinhibition" of feeding. The dual center theory predicts that destruction of the lateral output of the VMH should also disinhibit food intake. Confirming this prediction, MH knife cuts produce a hyperphagia and obesity syndrome (Albert and Storlien, 1969; Sclafani and Grossman, 1969) qualitatively similar (Sclafani, 1971) to that produced by VMH lesions. However, subsequent studies have questioned the role of the VMH and its lateral projections in hypothalamic hyperphagia. In particular, lesions restricted to the ventromedial hypothalamic nuclei produce little or no overeating (Gold, 1973) and hyperphagia and obesity can be obtained with a variety of hypothalamic and midbrain knife-cut placements that do not damage VMH-to-LH connections (e.g., Gold, Jones, Sawchenko, and Kapatos, 1977; Grossman, 1975; Grossman and Grossman, 1977; Grossman and Hennessy, 1976; Sclafani and Berner, 1977). Rather than the VMH, the placement of hypothalamic lesions and knife cuts effective in producing the hyperphagia syndrome suggests that the PVH may be

critically involved in the syndrome (Gold et al., 1977). According to this interpretation, VMH lesions and MH cuts produce hyperphagia and obesity by disrupting the fiber projections of the PVH. In support of this view, PVH lesions produce hyperphagia and obesity (Eng, Gold, and Nunez, 1979; Heinbecker, White, and Rolf, 1944; Leibowitz, Hammer, and Chang, 1981). However, little else is known about the PVH syndrome and its relationship to the classic hypothalamic hyperphagia syndrome.

The Noradrenergic-Feeding Response

In addition to recent work implicating the PVH in hypothalamic hyperphagia, there has been considerable evidence linking the PVH with the noradrenergic-feeding effect. It has been known for some time that intracranial injections of norepinephrine (NE; also known as noradrenaline) produce feeding in a number of species such as rats (Grossman, 1960), monkeys (Sharpe and Myers, 1969), swine (Jackson and Robinson, 1971), and sheep (Simpson, Baile, and Krabill, 1975). The generality of the response across species is not uniform, though, since cats respond to thalamic NE injections (Avery and Nance, 1970) but not to hypothalamic injections (Milner, Nance, and Sheer, 1971) and since steers do not eat following intraventricular NE injections (Simpson et al., 1975).

The NE-feeding response was first obtained from LH injection sites (Grossman, 1960, 1962a, 1962b) but can also be obtained from other areas including the cerebral

ventricles (e.g., Ritter, Wise, and Stein, 1975), amygdala (Grossman, 1964b), hippocampus, anterior thalamus, reuniens nucleus of the thalamus, lateral septal nucleus, cingulate gyrus, globus pallidus (Coury, 1967; Wagner and de Groot, 1963), and the rostral midbrain tegmentum (Myers and Sharpe, 1968). Booth (1967) obtained NE feeding from a number of brain regions but found that the optimal stimulation site was the anterior portion of the lateral hypothalamus. More recent mapping studies, however, indicate that the brain area most responsive to the stimulatory-feeding effect of NE is the PVH (Davis and Keesey, 1971; Leibowitz, 1978; Matthews, Booth, and Stolerman, 1978). PVH lesions have also been shown to block the feeding effect elicited by intraventricular NE injections (Leibowitz, 1979), which provides further support for the primacy of the PVH in NE feeding.

The pharmacological specificity of the noradrenergic-feeding effect has received considerable attention. The question of nonspecific factors mediating the response has been addressed by intrahypothalamically injecting a number of control substances. It has been shown (e.g., Grossman, 1962a) that general hypothalamic vasoconstriction (via posterior pituitary extracts), vasodilation (via sodium nitrate or barium chloride), neural excitation (via strychnine), tonicity changes (via sodium chloride), and pH alterations all fail to stimulate feeding behavior. On the other hand, nonspecific suppression of

neural activity by MH injections of procaine (Epstein, 1960) or pentobarbital (Maes, 1979; Maes and Callens, 1979a, 1979b) produces feeding behavior. Pentobarbital injections elicit a behavioral pattern that is qualitatively similar to that produced by NE injections not only in terms of food consumption but also with regard to food-reinforced bar pressing, food-carrying behavior, grooming behavior, environmental-scanning behavior, and locomotion though there may be differences in aversion to bright light (Maes, 1979; Maes and Callens, 1979a, 1979b). Nonetheless, for various pharmacological reasons (see below), the effects of hypothalamic injections of NE on food intake are assumed to be the result of specific rather than nonspecific pharmacological actions (but see Harvey, 1973; Hoebel, 1977; Myers, 1974; Singer and Montgomery, 1973).

Several experiments have illustrated that the NE-feeding effect is due to the specific activation of adrenergic receptors. Data obtained with indirect-acting catecholamine (CA) drugs have been important in this context. For example, prevention of the enzymatic degradation of endogenous NE by intrahypothalamic administration of the monoamine oxidase (MAO) inhibitor nialamide will produce feeding when given in conjunction with tetrabenezene which prevents the storage of NE within synaptic vesicles (Slangen and Miller, 1969). It has also been shown that another MAO inhibitor (tranylcypromine) can produce a feeding response on its own when injected

intrahypothalamically and that the response can be blocked by general CA synthesis inhibition (via pretreatment with alpha-methyl-para-tyrosine) (Leibowitz, Arcomano, and Hammer, 1978a). Hypothalamic injections of the tricyclic antidepressants, which potentiate endogenous NE activity by inhibiting the presynaptic reuptake of the CAs, also increase feeding. More particularily, desipramine potentiates both NE feeding (Booth, 1968; Slangen and Miller, 1969) and deprivation-induced feeding (Montgomery, Singer, Purcell, Narbeth, and Bolt, 1971). Further, desipramine, as well as protriptyline and amitriptyline, produces feeding in sated animals offered palatable diets (Leibowitz, Arcomano, and Hammer, 1978b). While many of the indirect-acting NE drugs also potentiate the actions of endogenous dopamine and serotonin, these monoamines are not implicated in the stimulation of feeding since their direct application into the LH or the cerebral ventricles (Grossman, 1964a; Myers and Sharpe, 1968; Ritter et al., 1975; Slangen and Miller, 1969) produce minimal-feeding effects at best. When applied to the perifornical hypothalamus, dopamine can exert inhibitory-feeding effects (see Leibowitz, 1976 and 1980) as does serotonin when applied to the PVH (see Leibowitz, 1980). Finally, a role for dopamine in the feeding response produced by indirect-acting CA drugs does not appear likely since inhibition of the enzyme that converts dopamine to NE (viz., dopa decarboxylase) blocks eating in response to tricyclic

stimulation (Leibowitz et al., 1978b).

According to the classification scheme of Alquist (1948)--which categorizes adrenergic receptor types in the periphery--NE acts on both alpha- and beta-adrenergic receptors though NE's alpha-agonistic properties dominate its beta-agonistic properties. Several studies have sought to determine which central adrenergic receptor type is specifically activated by NE to stimulate feeding. Pharmacological studies using direct-acting adrenergic drugs have indicated the importance of alpha-receptors to the phenomonon. For example, ventricular (Ritter et al., 1975) and intrahypothalamic (Broekkamp and Van Rossum, 1972) injections of the alpha-agonist clonidine are followed by feeding while hypothalamic injections of the beta-agonist isoproterenol do not produce feeding (Booth, 1968). Furthermore, NE eating is blocked by prior hypothalamic treatment with the alpha-antagonists phentolamine and phenoxybenzamine but not by prior treatment with the beta-antagonist propanolol (Booth, 1968; Grossman, 1962b; Leibowitz, 1970; Sharpe and Myers, 1969; Slangen and Miller, 1969).

While the pharmacological and antomical basis of the NE-feeding effect has been extensively studied, less attention has been focused on its functional significance. There is some evidence, however, suggesting that the NE-feeding effect and the hypothalamic-hyperphagic effect are interrelated. As will be discussed in Experiment 2, the

two responses have certain similarities. More specifically, they both produce finickiness to bitter diets, reduce performance in certain operant tasks, stimulate insulin release, and are dependent upon the vagus nerve. Since NE can act as an inhibitory neurotransmitter, it has been proposed that central injections of NE produce a functional lesion of the system responsible for hypothalamic hyperphagia (e.g., Blundell and Herberg, 1970; Coons and Quartermain, 1970; Leibowitz, 1970; Morley, 1980).

Another functional interpretation for the NE-feeding effect is that it mediates the feeding response associated with glucose insufficiency (referred to as "glucoprivation," Smith and Epstein, 1969). Acute cellular glucoprivation can be produced indirectly by insulin or directly by glucose antimetabolites such as 2-deoxy-D-glucose (2DG) (see e.g., Rezek, 1976; Rezek and Kroeger, 1976; Sokoloff and associates, 1977 for reviews). Exogenous insulin injections indirectly produce cellular glucoprivation by diverting circulating blood glucose away from the brain and liver to insulin-sensitive tissues (e.g., adipose tissue and skeletal and heart muscle). The glucose antimetabolite 2DG directly produces cellular glucoprivation by competing with glucose for transport across the cell membrane and, more importantly, by competing with glucose in the Emden-Meyerhoff pathway of glycolysis. However, once 2DG gains access to the glycolytic pathway it is unable to be completely metabolized.

Several lines of evidence indicate that the glucoprivic-feeding effect may be mediated by a hypothalamic NE system (Bellin and Ritter, 1981; Leibowitz, 1980; Muller, Cocchi, and Mantegazza, 1972). As will be discussed in Experiment 5, 2DG feeding is associated with the increased release and turnover of hypothalamic NE and is blocked by intraventricular injections of the alpha-adrenergic anatagonist phentolamine or by depletion of endogenous brain CAs. There is also some evidence indicating that the NE- and glucoprivic-feeding responses are associated with similar changes in dietary responsiveness.

NE-elicited feeding has thus been implicated in both the hypothalamic hyperphagia syndrome and the glucoprivic-feeding response. There does not, however, appear to be a clear link between hypothalamic hyperphagia and glucoprivic feeding since hyperphagia-inducing VMH lesions and MH cuts do not impair insulin- or 2DG-induced feeding (e.g., Epstein and Teitelbaum, 1967; Houpt and Gold, 1975; Sclafani, Berner, and Maul, 1973). The relationship of the PVH NE-feeding effect to the hypothalamic hyperphagia syndrome and to the glucoprivic-feeding effect is not established, however, and is a subject of the present investigation.

Purposes

This investigation had three general objectives: First, to appraise the involvement of the PVH in the classic hypothalamic hyperphagia syndrome. Second, to examine the

relationship between the hypothalamic hyperphagia syndrome and the PVH noradrenergic-feeding effect. Third, to determine the role of the PVH noradrenergic-feeding system in the glucoprivic-feeding response. These objectives were assessed in the following fashion:

1. The involvement of the PVH hyperphagia syndrome in the hypothalamic hyperphagia syndrome was determined by comparing the effects of PVH lesions and MH cuts on food intake, body-weight gain, and measures of finickiness (Experiment 1).

2. The relationship between hypothalamic hyperphagia and noradrenergic feeding was assessed by comparing the fiber systems involved in the two syndromes. In particular, MH knife cuts and posterior hypothalamic knife cuts were used to determine if the output of the noradrenergic-feeding system follows the feeding pathway implicated in the hypothalamic hyperphagia syndrome (Experiments 2-4).

3. The role of the PVH noradrenergic system in the the glucoprivic-feeding response was evaluated in three different ways: a) a dietary preference study compared the feeding responses produced by NE and 2DG stimulation (Experiment 5); b) a pharmacological study determined if PVH alpha-adrenergic receptors are critically involved in 2DG feeding (Experiment 6); c) a lesion study determined if destruction of the PVH disrupts 2DG feeding (Experiment 7).

General Methods

Subjects

Adult female Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA; CD strain) weighing approximately 300 g were used in Experiment 1. Adult male Sprague-Dawley rats (Charles River Breeding Laboratories; CD strain) weighing between 400 and 650 grams were employed as subjects in Experiments 2-7. (The reasons for the gender difference are noted in Experiments 1 and 2.) One hundred fifty one animals successfully completed the experiments and were included in the final data analyses. All animals were individually housed in stainless steel cages (18 cm wide, 24 cm long, and 18 cm high) with ad libitum food and water, except where noted. The vivarium was maintained at 21^{o} C with a 12:12-hr light:dark cycle. The subjects were maintained and tested with either the pelleted form of Purina Rodent Laboratory Chow #5001 (Ralston Purina Co., St. Louis, MO; 3.61 kcal/g) or with various other diets (see specific experiments). All non-pellet diets were presented to the subjects in containers (4-oz glass jars, 6.5 cm high and 5 cm in diameter or metal-feeding cups, LC-306 Wahmann Co., Timonium, MD, 4.5 cm high and 8 cm in diameter) attached to the front corners of the cages with springs. The subjects were adapted to all diet and housing conditions for at least 12 days prior to testing, unless stated otherwise.

Surgeries

The animals were anesthetized with Equi-Thesin (Jensen-Salsbery Co., Kansas City, MO; 3.00 ml/kg, IP) and mounted in a stereotaxic instrument (David Kopf Instruments, Tujunga, CA; model # 1204). As descibed in greater detail in subsequent experiments, either hypothalamic knife cuts were performed with the encephalotomy device of Sclafani (1971) or electrolytic lesions of the PVH were made using anodal DC current and platinum or stainless steel electrodes. Brain cannulation surgeries for the intracranial injection of drugs involved the implantation of stainless steel cannulae (23-gauge tubing, 1.6 cm long, Popper and Sons, New Hyde Park, NY; or 22-gauge tubing, Plastics Products Co., Roanoke, VA, catalog # C313 G). Four stainless steel screws (0-80 x 1/16) and dental cement (Plastics Products Co.) secured the implants to the skull and a postoperative recovery period of at least six days preceded all testing. When not in use, the cannulae were kept patent with flush-fitting inner stainless steel pins.

Drug Injections

NE (l-norepinephrine bitartrate, Sigma Chemical Co., St. Louis, MO), clonidine HCl (Catapres, Boehringer Ingelheim, Ridgefield, CT), and phentolamine HCL (Regitine HCl, CIBA Parmaceutical Co., Summit, NJ) were intrahypothalamically injected. The NE and clonidine were dissolved in isotonic saline while water served as the vehicle for phentolamine. 2DG (2-deoxy-D-glucose Grade II,

Sigma Chemical Co.) was dissolved in physiological saline in a concentration of 100 mg/ml and intraperitoneally injected. Control injections for all drugs consisted of the equivolumetric delivery of the appropriate vehicle. The doses chosen for the various drugs (see specific experiments) were selected to be in the optimal range based on previous research.

Intrahypothalamic microinjections were made through the implanted cannulae using a 30-gauge stainless steel injector cannula that extended 0.0-0.3 mm beyond the tip of the indwelling cannulae. The injector cannula was connected to a 25-µl syringe (Hamilton Co., Reno, NV, model 702-LT) via PE-10 polyethylene tubing (Clay Adams, Parsippany, NJ). The microsyringe was fitted with a mechanical dispenser (Hamilton Co., model PB600) to insure accurate volumetric delivery. Except where noted, the volume of all central injections was 0.5 µl. The animal was removed from its cage and held during all injections.

Histology

Following testing, the animals were transcardially perfused with isotonic saline and fixed with 10% formal-saline. Fifty-micron frozen sections through the hypothalamus were cut and stained with cresyl violet acetate. In some animals, the brains were embedded in albumin/gelatin prior to sectioning. All sections were examined with a Bausch and Lomb Stereozoom 7 microscope (Bausch & Lomb, Rochester, NY) at magnifications of 10-70X.

The sections were traced using an overhead projector (Bausch & Lomb) at magnifications of 6-10X. Photomicrographs of selected sections were taken at magnifications of 25-55X.

Statistical Analyses

Food intake data were corrected for spillage and, unless specified otherwise (Experiments 2-4), converted to kilocalories using the conversion factors applicable to the specific diets (see below). During drug testing, food intake was measured to the nearest 0.1 g; 24-hr intakes were made to the nearest 1.0 g.

Parametric data were analyzed using analysis of variance (ANOVA) or *t* test techniques at the 0.05 level of significance. Higher-level ANOVAs (two-way with repeated measures on one or both factors) with significant tests of interaction effects were followed by tests of simple main effects with the per family alpha error rate held at 0.05 according to the procedure specified by Kirk (1968). (For the sake of brevity, significant simple main effects are denoted by their corrected probability values.) Significant simple-main-effect tests, significant main-effect tests, and significant one-way ANOVAs were followed, when appropriate, by pair-wise comparisons using the Newman-Keuls procedure at the .05 level. A priori orthogonal contrasts using the *F* ratio were also performed, when appropriate, at the .05 level. All differences that are stated to be "significant" or "reliable" refer to differences that are statistically reliable at the .05 level of significance.

Experiment 1

The first report that PVH lesions produce obesity was published by Heinbecker and his colleagues who used dogs as subjects (Heinbecker et al., 1944). Most work with the hypothalamic obesity syndrome, however, has focused on the VMH (see General Introduction; Powley, Opsahl, Cox, and Weingarten, 1980). Currently, there is a renewed interest in the PVH and it has been postulated that the hyperphagia and obesity produced by MH cuts or VMH lesions result from a disruption of fiber projections associated with the paraventricular hypothalamic nucleus (Gold et al., 1977). This hypothesis was based on the anatomical position, relative to the paraventricular nucleus, of knife cuts and lesions effective or ineffective in producing the hyperphagia syndrome. Consistent with this view, it has been reported that PVH lesions produce hyperphagia and obesity in the rat (Eng et al., 1979; Leibowitz et al., 1981). It has not been established, however, if the hyperphagia syndrome produced by PVH lesions is similar to that produced by MH knife cuts or VMH lesions. The purpose of this experiment, therefore, was to compare the behavioral syndromes produced by PVH lesions and MH knife cuts.

An important feature of the hyperphagia/obesity syndrome produced by MH knife cuts or VMH lesions is that it is diet dependent (General Introduction). This feature can distinguish hypothalamic obesity from other obesity

syndromes. For example, the overeating and weight gains induced by ovariectomy (see Wade, 1972) and by ventral noradrenergic bundle (VNAB) lesions (Ahlskog and Hoebel, 1973) were thought to be mediated by the same mechanism as that involved in the hypothalamic hyperphagia syndrome (e.g., Kapatos and Gold, 1973; Wade, 1972). Subsequent research revealed, however, that neither the ovarian syndrome nor the VNAB syndrome is associated with dietary finickiness (Ahlskog, 1973; Gale and Sclafani, 1977). Dietary finickiness is also not associated with genetic obesity (see Sclafani, 1983). If the PVH is involved in the obesity syndrome produced by hypothalamic knife cuts, PVH lesions should produce changes in dietary reactivity similar to those produced by MH knife cuts. This prediction was tested in the present experiment by comparing the effects of PVH lesions and MH cuts on responsiveness to four different diets during both the dynamic and static weight-gain phases. In addition, the effects of PVH lesions and MH cuts on diurnal-feeding pattern, water intake, and emotionality were compared. These variables were chosen because they are known to be affected by MH cuts (see General Introduction) and could be easily assessed without compromising the diet reactivity tests.

Method

Subjects

In order to maximize the effects of PVH lesions and MH cuts, female rats served as subjects in this experiment. Of

the animals that completed the experiment, 11 received MH knife cuts, 16 received electrolytic lesions aimed at the PVH and nine received sham-brain surgery. For the purposes of comparison, the main data analysis included three equal-sized groups (n's = 9) of sham-lesioned (CON), knife-cut (CUT), and PVH-lesioned animals. The subjects included in the CUT and PVH groups were those rats that gained the most body weight postoperatively. In addition, a nonobese PVH group (PVH-N) was formed and included five of the original 16 rats with inadvertently misplaced "PVH" lesions that failed to produce obesity on the lab chow diet (see Results). The behavior of these nonobese PVH rats was of interest in light of recent findings that similar misplaced PVH lesions alter food selection in rats given purified macronutrient diets (Sclafani and Aravich, 1982).

Surgery

Bilateral PVH lesions (A = +6.4, L = +0.4, and H = -1.8; coordinate system of de Groot, 1959) were made by passing an anodal current (1 ma for 20 sec) through a platinum-iridium electrode (0.254 mm diameter) insulated with Teflon except for 0.4 mm of its pointed tip. Bilateral parasagittal knife cuts along the lateral edge of the MH were made at de Groot coordinates A = +8.0 to +5.0; L = +0.8; H = +0.5 to -2.5. Sham-brain surgery consisted of bilateral exposure of the dura at A = +6.4 and L = +0.4

Procedure

The animals were maintained on the powdered form of

Purina Rodent Laboratory Chow #5001 (hereafter referred to as the Plain diet) for nine days prior to and six days following surgery. Diurnal-feeding patterns were assessed on postoperative days four through six by determining food consumption during the 12-hr light and dark phases of the diurnal cycle. Emotional reactivity was evaluated during the first six postoperative days using a reactivity-handling scale modified from Sclafani (1971). According to this scale, each animal was assessed for resistance to capture, resistance to handling, urination and/or defecation during capture or handling, vocalization during capture or handling, and reactivity to a snout poke by a small wooden dowel. The ratings on each factor ranged from zero (i.e., normal) to two (i.e., excessive) and an emotional reactivity score (zero to ten) was computed by summing the scores on each factor. All ratings were done without knowledge of the treatment condition of the animals.

The test diets utilized in the experiment included two unpalatable and two palatable diets. The unpalatable diets were prepared by adulterating the Plain diet with either quinine hydrochloride (QHCL; 0.1% w/w; Sigma Chemical Co.) or sucrose octaacetate (SOA; 1.0% w/w; ICN Pharmaceuticals, Cleveland, OH). The palatable diets were prepared by mixing the Plain diet with either Dextrose (50% w/w; Fisher Scientific, Fair Lawn, NJ) or commercial-grade vegetable shortening (Fat; 33% w/w). These various diets have been previously used for the assessment of hypothalamic

finickiness (see General Introduction). The caloric density of the Plain, QHCL, and SOA diets was 3.61 kcal/g while the caloric densities of the Dextrose and Fat diets were 3.8 and 5.5 kcal/g, respectively (Carlisle and Stellar, 1969).

The dietary reactivity tests involved replacing the Plain diet with a test diet for a 3-day period. Three days of Plain diet exposure preceded all test diets. The animals were tested during the dynamic and static phases in a QHCL-, SOA-, Dextrose-, Fat-diet sequence. The order of the diets was not counterbalanced since previous research (Sclafani et al., 1979) has shown that finickiness to the SOA diet is dependent upon previous experience with the QHCL diet. In addition, since finickiness to bitter diets is substantially affected by obesity, and since body weight increases rapidly during the dynamic phase (see General Introduction), the QHCL and SOA diets were the first diets to be tested. The dynamic phase tests began on postoperative Day 7; the static phase tests on Day 71. During the 43-day period between the end of the dynamic tests and the start of the static tests, the animals were maintained on Plain diet. Following the static phase Fat-diet test, the Fat diet remained as the maintenance diet for an additional 27 days in order to appraise the effects of prolonged Fat-diet feeding on body weight.

Dietary reactivity was assessed in three ways: by analyzing with a one-way ANOVA the percentage change in caloric intake exhibited by the rats when switched from the

Plain diet to a given test diet; by analyzing the absolute intakes of the Plain and test diets with a two-way ANOVA with repeated measures on the diet factor; and by subjecting the Plain- and test-diet scores for the experimental groups to tests of orthogonal contrasts.

Results

Histology

The placements of selected PVH lesions and MH knife cuts are shown in Figure 1. The PVH lesions were bilaterally centered on the caudal aspect of the paraventricular hypothalamic nucleus (PVN) and the area between the PVN, the dorsomedial hypothalamic nucleus (DMN) and the nucleus reuniens of the thalamus (RE). Within the PVN (according to the nomenclature of Swanson and Kuypers, 1980) all lesions were in a position to include the posterior magnocellular component and most of the dorsal-, lateral-, and medial-parvocellar divisions; the lesions also involved caudal portions of the medial magnocellular and periventricular divisions. The anterior magnocellular and anterior parvocellular components were completely or largely spared by most lesions. Beyond the confines of the PVN, the lesions included the anteromedial DMN and zona incerta, the posteromedial anterior hypothalamus (AH), the anteroventral RE, and, occasionally, the rostro-most arcuate nucleus. Except for one instance (Figure 1A), the ventromedial hypothalamic nuclei (VMN) were completely spared by the lesions. The lesions of all animals except one (Figure 1A)

were comparable to each other in size. The most effective lesion (Figure 1A; postoperative Day-66 body-weight gain, 254 g) was also the largest lesion and included the posterior and medial PVN as well as the area between the PVN, DMN, and RE; it involved more of the DMN (and VMN) than did the other lesions. The most well-placed lesion of the paraventricular nucleus itself (Figure 1B) destroyed most of the nucleus including portions of the anterior magnocellular and anterior parvocellular divisions; it minimally damaged the area between the PVN and DMN and did not include the DMN, AH, or VMN. This lesion produced the fifth largest weight gain in the PVH group (Day-66 weight gain, 117 g). The lesions in the five PVH-N animals (i.e., the nonobese PVH group) were either asymmetrical and unilaterally damaged the caudal PVN (n = 3) or were very medially placed and bilaterally spared the lateral PVN (n = 2).

The parasagittal cuts were bilaterally positioned in the medial perifornical hypothalamus lateral to the PVN and lateral to most of the VMN. Longitudinally, they extended from the caudal preoptic area to the mammillary area. Figure 1C illustrates the cuts of the animal gaining the most body weight (Day-66 gain, 301 g).

Behavioral Findings: PVH Group and CUT Group

Prior to surgery the PVH, CUT, and CON groups were equivalent in daily caloric consumption but following surgery (Days 4-6) the PVH and CUT groups ate more of the Plain diet than did the CON group, F (2, 48) = 60.00, $p<$

.025 (Table 1). At this time the CUT group was more ($p < .05$) hyperphagic than the PVH group. Also, the PVH and CUT rats reliably increased their caloric intakes compared to preop levels whereas the control group displayed a small but nonreliable decrease in food intake, PVH F (1, 24) = 34.16, $p < .017$; CUT F (1, 24) = 154.67, $p < .017$.

The hyperphagia of the PVH and CUT groups was associated with a disruption in diurnal-feeding patterns since these groups consumed significantly less of their total caloric intake at night than did the control group, F (2, 24) = 31.21, $p < .05$ (Table 1). The diurnal-feeding pattern of the PVH rats was, however, less disrupted ($p < .05$) than that of the CUT rats. A correlational analysis was performed to determine if there was any relationship between the degree of diurnal disruption and the degree of hyperphagia produced by the PVH lesions and MH cuts. In neither group was the degree of diurnal disruption reliably correlated with the degree of hyperphagia, PVH r (7) = +0.557, $p > .05$; CUT r (7) = +0.056, $p > .05$.

The preoperative water intake of the three groups did not differ but, postoperatively (Days 4-6), the PVH and CUT groups drank more water than the control group, F (2, 23) = 10.13, $p < .05$ (Table 1). The CUT group also consumed more ($p < .05$) water than the PVH group. The postoperative water/food intake ratios, however, for the three groups were essentially equivalent (Table 1). (N.B.: preoperative water intake values were not available for two PVH animals; the

data of one control animal were not included in any water intake analysis since this animal excessively spilled its water on a daily basis.)

Analysis of the emotional reactivity scores of the various groups demonstrated that they were not equivalent, $H' = 16.54$, $p < .05$ (Table 1): the CUT group was significantly more emotional than either the CON or PVH group; the PVH group, on the other hand, did not reliably differ from controls. The nonparametric emotionality scores were six-day medians and were analyzed using the Kruskal-Wallis analysis of variance by ranks procedure followed by post hoc tests with the method of adjusted significance levels for sample sizes greater than eight (Kirk, 1968). The experimentwise alpha-error rate for the post hoc tests was held at the .05 level of significance.

The effects of the surgical treatments on body weight can be seen in Figure 2. Prior to surgery, the body weights of the three groups were statistically equivalent. Following surgery, the PVH and CUT groups out gained the control group. Just prior to the static phase diet tests (Day 66), there were considerable differences in group body weights, $F(2, 48) = 36.89$, $p < .025$, with both the CUT and PVH groups weighing reliably more than the CON group and the CUT group out-weighing ($p < .05$) the PVH group. During the 10-day period that immediately preceded the presentation of the first static phase test diet, the rate of body-weight gain of the experimental groups no longer reliably differed from

that of the control group.

Dynamic Phase Dietary Reactivity (Table 2). The groups were not comparably affected by the QHCL diet as indicated by a significant group by diet interaction effect, F (2, 24) = 29.39, $p < .05$. Further analysis demonstrated that while the PVH group ate more ($p < .05$) of the Plain diet than the control group, and the CUT group ate more ($p < .05$) than the PVH and control groups, F (2, 48) = 4.62, $p < .025$, there were no group differences in the intake of the QHCL diet. The test diet was thus sufficient to block the hyperphagia of the PVH and CUT groups. Furthermore, while all three groups reduced caloric intakes from Plain diet levels when given the QHCL diet [F's (1, 24): 20.72, CON; 142.36, PVH; 228.23, CUT; p's $< .017$], the PVH and CUT groups exhibited comparably greater percentage changes than the CON group, F (2, 24) = 16.96, $p < .05$.

The groups were not differentially responsive to the SOA diet even though the diet caused an overall reduction in caloric intake relative to the Plain diet, F (1, 24) = 23.68, $p < .05$. The ingestive responses of the experimental groups also did not reliably differ from controls in terms of percentage change scores.

There were no group differences in responsiveness to the Dextrose diet. There was an overall increase in caloric intake when the rats were switched to the Dextrose diet, F (1, 24) = 38.20, $p < .05$, and overall caloric intakes differed across groups, F (2, 24) = 13.72, $p < .05$, but there

was no group by diet interaction effect. Also, there were no reliable group differences with respect to percentage change scores. The elevated percentage change for the PVH group was largely the result of one animal that had an unusually low Plain diet intake following the dynamic phase SOA test. With this animal excluded the percentage change of the PVH group was 17.8±3.5%.

There were group differences in response to the Fat diet as indicated by a significant group by diet interaction effect, F (2, 24) = 16.72, $p < .05$. The experimental groups consumed more of both the Plain and Fat diets than did the CON group, F (2, 48) = 20.50, $p < .025$ and F (2, 48) = 60.42, $p < .025$, respectively, and the CUT group also consumed more ($p < .05$) of each diet than did the PVH group. Furthermore, unlike controls, the CUT and PVH animals reliably increased caloric intakes when switched to the Fat diet, F (1, 24) = 96.41, $p < .017$ and F (1, 24) = 74.38, $p < .017$, respectively. The percentage change scores of the CUT and PVH groups were also greater than the CON group's, F (2, 24) = 9.48, $p < .05$.

Static Phase Dietary Reactivity (Table 3). The groups were differentially affected by the QHCL diet as evidenced by a significant interaction effect, F (2, 24) = 10.89, $p < .05$. Whereas the Plain diet intakes of the three groups did not differ and all groups significantly decreased their caloric intake when given the QHCL diet [F's (1, 24): 10.60, CON; 64.34, PVH; 92.00, CUT; p's $< .017$], there were group differences in QHCL diet intake, F (2, 48) = 11.63 $p <$

.025. In particular, the CUT group consumed less ($p < .05$) of the test diet than did either the CON or PVH group; the PVH group did not differ from controls. In terms of percentage changes, however, both experimental groups reduced their intakes more than controls when given the QHCL diet, F (2, 24) = 13.76, $p < .05$, although the CUT group was significantly more affected than the PVH group. One animal in the CUT group refused to eat the Plain diet after the static phase QHCL test; it was therefore excluded from the remaining diet tests.

The groups were not comparably affected by the SOA diet, F (2, 23) = 4.67, $p < .05$. While they did not differ in Plain diet intakes, the CUT group underate the test diet relative to the other two groups, F (2, 46) = 8.86, $p < .025$. Unlike the controls, both experimental groups significantly reduced intakes when given the SOA diet [PVH F (1, 23) = 12.30, $p < .017$; CUT F (1, 23) = 31.55, $p < .017$]. However, in terms of percentage change scores, only the CUT group differed from the CON group, F (2, 23) = 4.82, $p < .05$.

Analysis of the Dextrose diet test revealed a significant interaction effect, F (2, 23) = 11.24, $p < .05$. Each group consumed more calories when given the Dextrose diet than when given the Plain diet [F's (1, 23): 23.62, CON; 120.40, CUT; 82.03, PVH; p's $< .017$] and the groups did not differ in Plain diet caloric intake. There were, however, group differences in the caloric intake of the Dextrose diet, F (2, 46) = 4.18, $p < .025$, with the PVH

group, but not the CUT group, consuming more ($p < .05$) of the diet than controls. Analysis of percentage change scores revealed, however, that the intake change of the CUT group was reliably greater than that of the CON and the PVH groups whereas the PVH group did not differ from controls, F (2, 23) = 6.85, $p < .05$. This elevated percentage change score of the CUT group was due, at least in part, to the group's somewhat lower Plain diet intake following the SOA test.

Presentation of the Fat diet increased the caloric intake of all groups, F (1, 23) = 380.09, $p < .05$, but not to the same degree, F (2, 23) = 39.43, $p < .05$. The Plain diet intake of the three groups did not differ but the CUT and PVH groups ate more of the Fat diet than did the controls, F (2, 46) = 73.24, $p < .025$. The CUT group also consumed more ($p < .05$) Fat diet than did the PVH group. Both experimental groups also had elevated percentage change scores compared to controls, F (2, 23) = 22.14, $p < .05$. During the one-month period on the Fat maintenance diet, the CUT and PVH groups gained more weight than did the CON group [CON gain, 43.9$\pm$7.3 g; PVH gain, 150.7$\pm$13.9 g; CUT gain, 193.4$\pm$14.8 g; F (2, 23) = 39.19, $p < .05$; Figure 2]. The CUT group, in addition, gained more ($p < .05$) weight than the PVH group.

Orthogonal Contrast Assessment of Finickiness. A priori orthogonal contrasts using the F ratio (see Kirk, 1968) compared the magnitude of "finickiness" in the PVH and CUT groups on all diets during both phases of testing. On the dynamic phase QHCL test, for example, this measure

determined if the PVH group altered intakes from Plain diet levels to the same degree as the CUT group. Because it is not subjected to the variability of extreme scores often associated with percentage change or difference measures, this type of analysis is perhaps the most valid way to compare the magnitude of finickiness in PVH and CUT animal. The analysis revealed that the PVH and CUT groups had statistically comparable finickiness responses to all tests except the dynamic phase QHCL test, F (1, 24) = 4.86, $p < .05$, and the static phase Fat test, F (1, 23) = 5.19, $p < .05$.

Behavioral Findings: PVH-N Group and PVH Group

The PVH-N group was initially (Days 4-6) as hyperphagic as the PVH group, F (2, 40) = 25.17, $p < .025$ (Table 1). At this time the PVH-N group was also similar to the PVH group on the other behavioral measures: they had disrupted diurnal-feeding patterns, F (2, 20) = 7.01, $p < .05$, elevated water intakes, F (2, 19) = 4.33, $p < .05$, normal water/food intake ratios, and normal emotionality scores (Table 1). The hyperphagia of the PVH-N group did not persist, however, and the rats in this group failed to gain more body weight than the control rats during the first two postoperative months (Figure 2).

Dietary Reactivity Tests (Tables 2 and 3). When presented with the QHCL diet the PVH-N group no longer differed from the control group in caloric intake. Since the PVH-N group was hyperphagic on the Plain diet, the QHCL diet

produced a greater reduction in percentage intake compared to the controls, F (2, 20) = 13.60, $p < .05$. Following the dynamic phase QHCL test, the PVH-N group was normophagic on all other diets except for the Fat diet: during both the dynamic and static tests they ate more ($p < .05$) of the Fat diet than the CON group although less ($p < .05$) than the PVH group, Dynamic F (2, 40) = 36.75, $p < .025$; Static F (2, 40) = 43.12, $p < .025$. In percentage change terms, however, the PVH-N group did not differ from the CON group in their response to the Fat diet. During the one-month period on the Fat diet the PVH-N group gained reliably more weight than the CON group, though less than the PVH group, F (2, 20) = 27.43, $p < .05$; CON body weight gain, 43.9±7.3 g; PVH-N gain, 84.2±7.3 g; PVH gain, 150.7±13.9 g (Figure 2).

Discussion

This investigation reveals that PVH lesions produce less hyperphagia and overweight than MH cuts but that the two treatments produce qualitatively similar changes in dietary reactivity. The PVH and CUT treatments also have similar effects on diurnal-feeding patterns and water consumption but differ in their effects on emotionality.

In both the dynamic and static phase dietary tests the caloric intakes of the PVH and CUT groups were altered to the greatest extent by the QHCL and Fat diets. Exposure to the QHCL diet during the dynamic phase blocked the hyperphagia of these groups although the groups did not undereat the diet relative to controls. The Fat diet, on the

other hand, caused the two experimental groups to increase their caloric intake to a greater degree than controls. Neither the SOA diet nor the Dextose diet differentially affected the caloric intake of the PVH and CUT groups during the dynamic phase although intake levels were altered by each diet.

When offered the QHCL diet in the static phase both the PVH and CUT groups again reduced their intakes more than the control group. Furthermore, the CUT group, but not the PVH group, now underate the QHCL diet compared to controls. The SOA diet also suppressed the caloric intake of the obese groups more than that of the control group, although only the CUT vs. CON difference was reliable. The PVH rats were thus less reactive to the bitter diets than were the CUT rats during the static phase. This difference may have been due to the fact that the PVH rats weighed significantly less than the CUT rats at the time of these tests. Previous studies have demonstrated that QHCL-diet aversion in VMH-lesioned and MH-cut animals is directly related to the degree of obesity (Ferguson and Keesey, 1975; Franklin and Herberg, 1974; Sclafani et al., 1976). It should be noted that the abnormal QHCL-diet aversion of hypothalamic hyperphagic rats may be due to quinine's noxious postingestive effects rather than to its bitter taste per se, and that SOA-diet aversion may represent the generalization of a conditioned aversion to bitter taste established by the prior consumption of QHCL (Aravich and

Sclafani, 1980; Sclafani et al., 1979). It should also be noted the the F tests on orthogonal contrasts between the PVH and CUT groups during the static phase revealed that they did not differ in the magnitude of their finickiness response to either bitter diet. The only bitter diet difference between the groups, according to this analysis, was during the dynamic phase QHCL test. This difference may be due to the greater hyperphagia of the CUT group at the time of the test.

Regarding the consumption of the palatable diets during the static phase, the obese groups displayed an exaggerated response to both the Dextrose and Fat diets compared to the control group. The magnitude of the response to the Fat diet was, however, more impressive than was the response to the Dextrose diet. The PVH and CUT groups also were abnormally responsive to the Fat diet as evidenced by their greater than normal weight gain during the 30-day period on this diet. According to the F tests on orthogonal contrasts, the PVH and CUT groups differed in the magnitude of their response to the Fat diet during the static phase test. This was despite the fact that the two groups had very similar baseline levels on the Plain diet. This difference may be related to the differing degrees of obesity between the two groups. Alternatively, the difference may be due the fact that the MH cuts more effectively disrupted the system responsible for hypothalamic hyperphagia as evidenced by their greater hyperphagic effects during the dynamic phase

and their greater body-weight effects during the static phase.

The dietary response pattern of the PVH and CUT groups is quite similar to the pattern exhibited by VMH-lesioned animals. In particular, VMH-lesioned and MH-cut rats have been found to display equivalent changes in caloric intake during the dynamic and static phases when presented with the four test diets used in the present experiment (Aravich and Sclafani, in preparation). PVH, CUT, and VMH treatments also produce similar changes in the self-selection of purified macronutrient diets (i.e., pure fat, carbohydrate and protein diets) in that all three treatments preferentially increase carbohydrate consumption over fat and protein consumption (Sclafani and Aravich, 1982). This later finding contrasts with the present observation that PVH and CUT rats overeat the Fat diet more than the Dextrose diet. These inconsistent results may be due to the nature of the diets (purified vs. mixed) and/or the nature of the choice situation (self-selection vs. single diet). This issue has been examined in another study (Sclafani and Aravich, in preparation).

In contrast to the PVH group, the PVH-N group was much less affected by the test diets. This is not unexpected since the rats in the PVH-N group had "misplaced" lesions which presumably only minimally damaged the neural substrate involved in the hyperphagia syndrome. Nonetheless, this small effect of misplaced PVH lesions on finickiness is of

interest in view of the finding that similar lesions produce substantial changes in dietary selection in rats given purified macronutrient diets (Sclafani and Aravich, 1982). That is, PVH-N rats increase their carbohydrate consumption relative to preop levels and relative to brain-intact rats. PVH-N animals also decrease protein intake relative to preoperative levels. Taken together, these data indicate that the intake of purified macronutrient diets is more susceptible to disruption than is the intake of the nutritionally complex diets used in the present experiment.

In addition to their effects on caloric intake and dietary reactivity, both PVH and CUT treatments disrupted diurnal-feeding patterns. More specifically, the PVH treatment and, to a greater extent, the CUT treatment increased the percentage of total food intake consumed during the daytime. The relevancy of disrupted diurnal-feeding patterns to hypothalamic hyperphagia has been debated (e.g., Becker and Kissileff, 1974; Gold et al., 1975; Le Magnen, 1981; Sclafani, 1981). In the present study, the most hyperphagic group (i.e., the CUT group) was also the most diurnally disrupted but the degree of diurnal disruption within this group did not correlate with the degree of hyperphagia. In addition, the PVH-N group had disrupted diurnal-feeding patterns comparable to the disrupted patterns of the PVH group, yet the PVH-N group gained considerably less body weight than the PVH group. These findings suggest that independent mechanisms are

associated with the diurnal and body-weight effects of MH and PVH damage. Other evidence also points to the existance of independent mechanisms in the control of diurnal rhythms and feeding behavior. For example, lesions of the suprachiasmatic (SCN) (van den Pol and Powley, 1979), septal (de Castro, Stoerzinger, Barkmeier, and Ellen, 1978), and dorsomedial hypothalamic (Bernardis, 1973) nuclei all disrupt feeding rhythms without inducing hyperphagia. In keeping with the current emphasis on the SCN in the generation of diurnal rhythms (see e.g., Moore, 1981), the septal and dorsomedial nuclei as well as the paraventricular nuclei all receive SCN projections (e.g., Stephan, Berkley, and Moss, 1981). The PVH and CUT treatments were each in a position to disrupt substantial numbers of SCN efferents, particularly those originating from vasopressinergic-like (Sofroniew and Weindl, 1978) and vasoactive intestinal polypeptide-like (Sims, Hoffman, Said, and Zimmerman, 1980) neurons and such disruptions may be responsible for the alteration in diurnal feeding rhythms (but see Groblewski, Nunez, and Gold, 1981).

Confirming previous findings (Leibowitz et al., 1981), PVH lesions increased daily water intake during the dynamic phase resulting in the PVH group consuming about 40% more water than the CON group. This effect was similar to, but less than that produced by the CUT treatment. Although urine osmolarity was not evaluated, the PVH lesions clearly did not produce the excessive water intakes characteristic of

diabetes insipidus which is consistent with the now-classic emphasis on supraoptic-nuclear dysfunction in the etiology of the diabetic syndrome (see e.g., Fisher, Ingram, and Ranson, 1938; Heinbecker and White, 1941). The PVH and CUT treatments also did not produce an obvious primary polydipsia since neither treatment elevated water/food intake ratios. However, normal water/food intake ratios do not preclude the possibility that PVH lesions or MH cuts disrupt water balance. Various primary water intake deficits have in fact been previously noted to accompany the hypothalamic hyperphagia syndrome (King and Grossman, 1977; Sclafani et al., 1973; Stevenson, 1949) and the paraventricular nucleus has been implicated in the regulation of the renin-angiotensin system (Saavedra, Chevillard and Fernandez-Pardal, 1981).

The present study revealed one clear-cut difference between the behavioral effects of the PVH and CUT treatments: unlike the MH knife cuts, the PVH lesions did not increase emotional reactivity. It may be argued that this difference in emotional reactivity was due to the differing degree of neurological disruption produced by the PVH and CUT treatments as indexed by their differential effects on body weight. However, in another study it was found that small VMH and PVH lesions produced similar weight gains but that only the VMH lesions produced hyperemotionality (Aravich and Sclafani, unpublished observations). It is concluded, therefore, that, contrary to

earlier suggestions (e.g., Grossman, 1966), heightened emotional reactivity is not an essential feature of the hypothalamic hyperphagia syndrome. Since enhanced emotionality, with its attendant autonomic and endocrine effects could obscure the basic mechanism(s) responsible for the hyperphagia syndrome, the lack of hyperemotionality in PVH-lesioned rats confers a definite experimental as well as practical advantage to this preparation.

In addition to emotional reactivity, the effects of PVH lesions differ from those of MH cuts and VMH lesions in other respects as well. First, whereas all three treatments produce carbohydrate overeating in a self-selection paradigm, only PVH lesions have a suppressive effect on protein consumption (Sclafani and Aravich, 1982). Second, the obesity produced by PVH lesions is not invariably associated with elevated basal insulin levels in contrast to the hyperinsulinemia associated with MH cut- and VMH lesion-induced obesity (see General Discussion) (Sclafani and Aravich, 1982 and in preparation). Last, PVH lesions produce less hyperphagia and obesity than do MH cuts (present study; Sclafani and Aravich, 1982). In the present experiment, the initial hyperphagia of the CUT group on the Plain diet exceeded that of the PVH group by nearly 30% and by the static phase the CUT group had gained 55% more weight than the PVH group. Unlike the previously noted differences, however, this difference appears to be quantitative rather than qualitative since the degree of obesity produced by

appropriately placed VMH lesions (Gold, 1973; Hetherington and Ranson, 1942a), MH knife cuts (Sclafani et al., 1973), and PVH lesions (present study; Leibowitz et al., 1981) is positively correlated with the size of the lesion. It should be emphasized that the PVH lesions of the present study were not designed to produce the maximal hyperphagic effect. Instead, they were intended to be relatively restricted in size and placement to the paraventricular nucleus.

The most effective lesions in the present study were centered on the caudal aspects of the nucleus. This emphasis on the caudal PVN in the production of hypothalamic obesity is consistent with the conclusions of other investigators (Heinbecker et al., 1944; Leibowitz et al., 1981). Examination of the effective and ineffective lesions in this experiment and in the experiment of Sclafani and Aravich (1982) suggests further that the most effective lesions are centered on the lateral portion of the caudal PVN and include the region between the PVN and DMN, portions of the perifornical hypothalamus, and perhaps portions of the medial zona incerta. Since the lesions in the present study damaged most of the paraventricular nucleus but produced less hyperphagia and obesity than MH cuts, it is concluded that the neuronal substrate responsible for the hypothalamic hyperphagia syndrome is not confined to the paraventricular nucleus but is more diffusely organized in the medial hypothalamus. Hence, damage to neuronal systems associated with the nucleus (see General Discussion) are only partly

related to the hyperphagic effects of hypothalamic knife cuts and VMH lesions. Nonetheless, an important implication of the present study follows from the fact that lesions largely restricted to the paraventricular nucleus, while not producing maximal hyperphagia, do substantially increase food intake and body weight. Since such circumscribed lesions are unlikely to damage many fibers of passage, their hyperphagic effects would appear to result from destruction of neuronal systems associated with the paraventricular nucleus itself. These systems (see General Discussion), therefore, appear to form an important component of the substrate responsible for hypothalamic hyperphagia.

Experiment 2

The PVH is also associated with the noradrenergic-feeding effect (General Introduction) and several lines of evidence indicate that this effect may be related to the hypothalamic hyperphagia syndrome. For example, both NE feeding (Booth and Quartermain, 1965; Sclafani and Toris, 1981) and hypothalamic hyperphagia (Ferguson and Keesey, 1975; Sclafani et al., 1976) are blocked by quinine adulteration of the diet and are associated with decreased performance on appeitively reinforced operant tasks (Coons and Quartermain, 1970; Teitelbaum, 1957). Furthermore, NE microinjections and MH damage, unlike food deprivation, do not produce food horading (Blundell and Herberg, 1970; Herberg and Blundell, 1970). Finally, both NE feeding and MH hyperphagia are accompanied by enhanced insulin secretion (Martin, Konijnendijk, and Bouman, 1974; de Jong, Strubbe, and Steffens, 1977) and, under certain circumstances, can be blocked by subdiaphragmatic vagotomy (Powley and Opsahl, 1974; Sawchenko, Gold, and Leibowitz, 1981). Because of these functional similarities, several authors have hypothesized that hypothalamic NE injections and MH damagae induce feeding by way of a common feeding system (Blundell and Herberg, 1970; Coons and Quartermain, 1970; Leibowitz, 1970; Morley, 1980).

According to this hypothesis, the NE-feeding response results from inhibition of the system involved in the

hyperphagia syndrome. This hypothesis predicts that lesions producing hypothalamic hyperphagia should remove the substrate upon which NE acts and, hence, block the NE-feeding response. In a previous test of this prediction, it was found that hyperphagia-inducing lesions of the posterior VMH blocked the NE-feeding response (Herberg and Franklin, 1972). However, other hyperphagia-producing lesions located in the more anterior VMH did not block NE eating. Furthermore, lesions which produced the greatest hyperphagia, and therefore most effectively damaged the MH-feeding system, "were not necessarily the most effective in blocking the action of NE" (p. 1032, Herberg and Franklin, 1972).

The relationship between the NE-feeding response and the hypothalamic hyperphagia syndrome thus remains uncertain. Moreover, the emphasis on the VMH as the critical site involved in hypothalamic hyperphagia is no longer warranted since the PVH is now implicated in the syndrome (see Experiment 1). It is possible, therefore, that NE injections and MH damage increase food intake by disrupting a common feeding inhibitory system originating in the area of the PVH. Consistent with this view are the findings that a) microiontophoretic application of NE inhibits the activity of some paraventricular neurons (Moss, Urban, and Cross, 1972), b) PVH lesions produce hyperphagia (Experiment 1; Eng et al., 1979; Leibowitz et al., 1981), and c) PVH lesions block the feeding response induced by

intraventricular injections of NE (Leibowitz, 1979).

Experiments 2-4 assessed the relationship between NE-induced feeding and hypothalamic hyperphagia by combining chemical stimulation of the PVH with hypothalamic knife cuts. (The results of these experiments will be discussed after Experiment 4.) If PVH NE injections elicit food intake by inhibiting the neural system the destruction of which is responsible for MH hyperphagia, then hypothalamic knife cuts of this system should block NE feeding. The advantage of the knife-cut technique is that it allows for the destruction of the fibers, but not the cell bodies, responsible for hypothalamic hyperphagia. This technique has been used to assess the effects of electrical brain stimulation (Aravich and Beltt, 1982; Sclafani and Maul, 1974) but has not been previously combined with chemical stimulation.

A number of knife-cut studies indicate that MH hyperphagia results from damage to a longitudinally oriented fiber pathway which interconnects the anteriomedial hypothalamus with the more caudal brainstem (Gold et al., 1977; Mufson, Sclafani, and Aravich, 1980; Sclafani and Berner, 1977). At the level of the PVH this pathway courses laterally into the perifornical region; it then turns caudally in the perifornical area or the most medial portion of the medial forebrain bundle (MFB) to project to the lower brainstem. While it is not clear if this is an ascending or descending fiber system, the position of this pathway overlaps with many of the known efferents of the PVH (e.g.,

Armstrong, Warach, Hatton, and McNeil, 1980; Conrad and Pfaff, 1976; Saper, Loewy, Swanson, 1976; Swanson, 1977; Sawanson and Kuypers, 1980). In particular, hyperphagia is produced by parasagittal knife cuts in the anterior perifornical hypothalamus which presumably sever a portion of the lateral output of the PVH (Albert and Storlien, 1969; Gold, 1970; Sclafani and Grossman, 1969) and by coronal knife cuts in the posterior hypothalamus which are in a position to sever many of the descending efferents of the PVH (Grossman and Hennessy, 1976; Sclafani and Berner, 1977). If the output of the NE-feeding system is identical to that of the MH-feeding system, then these parasagittal and coronal knife cuts should disrupt the feeding response to PVH injections of NE. Experiment 2 tested this prediction.

Method

Subjects

Male rats were used as subjects in this and all other experiments. Male rats were chosen as subjects for the NE experiments since most of the previously published work with the NE-feeding effect in rats has employed male subjects. Six rats with parasagittal knife cuts and five rats with sham parasagittal cuts, which successfully completed all testing, were included in Part 1. Eight rats with posterior hypothalamic coronal knife cuts and five with sham posterior cuts survived all testing and were included in Part 2. The rats were maintained and tested on the Purina pellet diet.

Surgery

The animals in this experiement were implanted with a unilateral drug cannula aimed at the PVH (0.5 mm posterior to bregma, 7.5-7.8 mm beneath the surface of the skull and 0.3-0.4 mm lateral to the superior sagittal sinus; nose clamp 3.0 mm above the the ear bars). The rats were also implanted with bilateral 18-gauge cannulae to be used for later knife-cut surgery. The cannulae for the parasagittal cuts were positioned 1.0 mm anterior to bregma, 1.0 mm lateral to the sagittal sinus, and 1.8 mm beneath the surface of the skull; for the coronal cuts they were positioned 2.5 mm posterior to bregma, 2.0 mm lateral to the midline, and 1.8 mm beneath the surface of the skull.

In a second surgery, the animals were given either bilateral knife cuts or sham cuts. In Part 1, parasagittal knife cuts lateral to the PVH were made by inserting the knife shaft through the chronic guide cannulae (1.0 mm anterior to bregma; $\pm$1.0 mm lateral to the midline). At a depth of 0.0 mm (ear bar reference), the cutting wire was extended 3.0 mm posteriorly and the knife was lowered to the base of the brain. Each cut was designed to extend from the anterior hypothalamus (rostral to the PVH) to the area just caudal to the ventromedial hypothamic nucleus. In Part 2, bilateral coronal knife cuts were made in the posterior hypothalamus using a spring-loaded knife carrier (Hamilton, Worsham, and Capobianco, 1973). The cuts were designed to extend from the base of the hypothalamus dorsally 3.0 mm and

from the lateral perifornical area (L±2.0 mm) to the midline. Sham-lateral or sham-posterior knife cuts were performed in a fashion identical to actual knife cuts except that the cutting wire was not extended into the brain and the knife shaft was not lowered to the floor of the cranium.

Procedure

Feeding responsiveness to NE was appraised in the following fashion. During a one-hour preinjection period, the animals were given fresh food and were frequently aroused in order to promote feeding and insure satiety at the time of testing. The subjects were then injected with saline and their food intake during the next hour was measured. In Part 1, immediately following the saline injection period, the animals were injected with NE (35 nmoles) and food intake in the following hour was determined. In Part 2, saline and NE tests were conducted on alternate days. A NE-feeding score (in Experiments 2-4) was computed for each animal by subtracting the amount of food consumed after the saline injection from the amount of food consumed after the NE injection. A reliable NE-feeding response for a particular animal was defined as a mean intake of at least 1.0 g above the mean-feeding response to saline. In addition to these NE-feeding score measures, daily 24-hr food intake and body weight were also determined.

The subjects were injected with NE and saline for two to three days to adapt them to the injection procedure. They

were then given three NE-saline feeding tests on successive days. Because of the different designs, Part 1 required three days to complete these tests while Part 2 required six days. Animals which displayed a reliable NE-feeding response were retained for further study. In both parts of the experiment, the animals were then divided into two groups equated for feeding responsiveness to NE: the experimental group was given bilateral hypothalamic knife cuts while the control group was given sham knife cuts. Following a two day recovery period, postoperative NE drug testing was conducted in the same manner as preoperative testing. Thus, postoperative testing for Part 1 was conducted on days 3-5 after knife-cut surgery while postoperative testing for Part 2 was conducted on days 3-8 following knife-cut surgery.

Results

Part 1

The 24-hr food intake prior to surgery for the lateral-cut group was slightly, but not significantly, below that of the sham-cut group (21.8±1.1 vs. 25.5±1.2 g, $p>.05$). Following knife-cut surgery, the cut group increased its daily food intake relative to preoperative levels (+72.9±15.2%) whereas the control group maintained nearly normal intake [-8.4±9.8%; independent t (9) = 4.44, $p<.05$]. The lateral-cut animals were thus hyperphagic compared to the control animals during postoperative drug testing [37.8±4.0 vs. 23.1±2.2 g/day; t (9) = 2.98, $p<.05$] and by postoperative day 18 had gained significantly

more body weight than controls [69.0±10.4 vs. 13.6±5.5 g; $t(9) = 4.44$, $p < .05$].

As illustrated in Figure 3, prior to knife-cut surgery, the NE-feeding score of the lateral-cut group was slightly below that of the control group, whereas, postoperatively, it was slightly above control levels. Analysis of variance indicated that the group effect and the group by surgery interaction were not significant. The feeding response of both groups, however, significantly declined after sham-cut and knife-cut surgery [$F(1,9) = 7.12$, $p < .05$] (see Introduction, Experiment 3). Nevertheless, during postoperative drug testing, all of the knife-cut rats and 4 out of the 5 control animals were reliable NE feeders according to the established criterion.

Figure 4A is a photomicrograph illustrating the knife cut and drug cannula placements of a representative animal from the lateral-cut group. The cannulae for all animals were in or near the PVN. The knife cuts were positioned 0.1 to 0.3 mm lateral to the lateral edge of the drug cannula. They extended 0.5 to 1.0 mm anterior to the cannula and from 2.0 to 2.5 mm posterior to it, terminating in the mammillary region. There was some variability in the height of the cuts at the level of the PVN: in two animals, the cuts extended dorsally 2.5 to 3.0 mm from the base of the brain, whereas in the remaining animals they extended from the base of the brain 1.5 to 2.1 mm dorsally. In the two animals with the tallest cuts, one animal showed no change in its NE-feeding

response following surgery while the other animal demonstrated a slight increase.

Part 2

The daily food intakes of the posterior coronal cut (30.5g±0.7 g) and control (33.4±2.1 g) groups were similar ($p > .05$) during the preoperative drug tests. During postoperative drug testing, the daily food intake of the posterior-cut animals (23.6±1.4 g) was significantly less than that of the controls [30.1±2.7 g; t (11) = 2.31, $p < .05$]. By postoperative day 18 the posterior-cut group had gained less weight than did the control group although this difference failed to reach significance (-4.0±1.8 vs. 10.0±18.5 g).

Figure 5 illustrates the results of the NE tests in the posterior-cut animals and their controls. The pre- and postoperative NE-feeding scores of the posterior-cut group were below those of the control group, although analysis of variance revealed that the group effect was not significant. Also, the posterior-cut group was not differentially affected by the surgery (group by surgery interaction not significant) although both groups reliably decreased their feeding response postoperatively [F (1,11) = 19.75, $p < .05$]. All control rats and 5 of the 8 posterior-cut rats continued to be reliable NE feeders during the postoperative drug tests. The 3 posterior-cut animals which did not display a reliable NE-feeding response during the initial postoperative drug tests were given three additional tests.

In these subsequent tests, 2 of the 3 rats recovered their NE-feeding response. Since the knife cuts in these rats did not differ from those in the other posterior-cut subjects, their initial response decrement was probably due to generalized surgical trauma. (Figure 5 does not reflect these additional data.)

Figure 4B is a photomicrograph of a representative animal from the posterior-cut group. The knife cuts were in the caudal hypothalamus near the mammillary bodies and from 1.0 to 2.5 mm posterior to the cannula tip. They extended from the fornix to the midline and from the base of the brain dorsally 1.5 to 4.5 mm. The drug cannulae in all subjects were in or near the PVN.

Experiment 3

The results of Experiment 2 demonstrate that parasagittal knife cuts in the perifornical hypothalamus and coronal knife cuts in the posterior hypothalamus do not block the NE-feeding response. These findings suggest that the feeding effect following PVH injections of NE does not depend upon the fiber system whose destruction is responsible for MH hyperphagia. (The failure of the posterior cuts to produce hyperphagia is addressed in the Discussion following Experiment 4). These findings also suggest that transections of the lateral and ventroposterior efferents of the PVN are not essential to NE-induced feeding. In Experiment 2, however, the NE-feeding response was attenuated following both knife-cut surgery and sham-cut surgery, perhaps due to the impact of repeated NE testing and the general malaise produced by the second surgery. In the next experiment, therefore, the effects of hypothalamic knife cuts on the NE-feeding response were examined using an experimental paradigm whereby knife-cut surgery was performed prior to hypothalamic cannulation and drug testing. A palatable diet, known to enhance the NE-feeding response (Leibowitz et al., 1978a) was also employed.

Method

Subjects

Five rats with lateral cuts, eight rats with posterior cuts, and six rats with sham cuts successfully completed the

experiment and were included in the data analysis.

Surgery

In the first operation the rats were either given bilateral parasagittal cuts lateral to the PVN, coronal cuts in the posterior hypothalamus, or sham cuts. The lateral cuts were designed to be slightly larger than those employed in Experiment 2. The knife shaft was positioned 2.0 mm anterior to bregma and 0.8 mm lateral to the midline. At a depth of 0.0 mm above ear bar reference, a 3.5 mm length of cutting wire was extended in a caudal direction and the knife lowered to the base of the brain. The bilateral posterior cuts were performed using the procedure described in Experiment 2. Sham cuts were made as in the preceding experiment using the coordinates of either the lateral or the posterior cuts. Following a recovery period of 14 to 19 days, the animals were implanted with a unilateral PVH cannula.

Procedure

The testing procedure was similar to that of Part 1 of Experiment 2 except that a lower dose of NE was employed (20 nmoles) and the animals were tested on a more palatable sweet milk-mash diet [300 ml of sweetened condensed milk (Magnolia brand, Borden Foods), 250 g of the powdered form of Purina laboratory chow, and 250 ml of water]. The subjects were maintained on the Purina pellet diet for 12 to 13 days following knife-cut surgery and were then given the milk-mash diet for the remainder of the experiment. Food

intake measures during the drug tests were corrected for evaporation as well as spillage. Testing began 23 to 25 days after knife-cut surgery and 6 to 11 days after brain cannulation. Daily body weight, but not 24-hr food intake, was recorded throughout the experiment.

Results

By Day 21 after knife-cut surgery (just prior to the onset of drug testing), the lateral-cut animals had gained significantly more body weight than controls [85.8±17.0 vs. 15.7±17.1 g; t (10) = 2.87, p <.05]. The posterior-cut animals also gained more weight than did controls during this time period, although this difference failed to reach significance (31.6±8.7 vs. 15.7±17.1 g).

The results of the NE tests are shown in Figure 6 and analysis of these data indicated that there were no reliable group differences. All animals displayed a reliable eating response to NE. The feeding scores ranged from 6.6 to 9.4 g in the lateral-cut group, 1.4 to 11.9 g in the posterior-cut group, and 4.5 to 13.0 g in the control group. The somewhat lower performance of the posterior-cut group relative to the other groups was largely the result of the low score of one animal that was nearly two standard deviations below the group mean.

Figure 7 illustrates the placements of the knife cuts and cannulae in the experimental groups. Except for the slightly longer caudal projection of the lateral cuts, all cut and cannula placements were similar to those in

Experiment 1. Specifically, the lateral cuts were positioned 0.8 to 1.0 mm lateral to the midline and extended from the posterior portion of the anterior commissure 3.5-4.0 mm caudally to the mammillary region of the hypothalamus. At the level of the PVN, the cuts extended 3.0-3.5 mm dorsally above the base of the brain. In the posterior mammillay region the lateral cuts severed all fibers within 2.0 mm of the base of the brain. The knife cuts in the posterior-cut group were in the mammillary region; they extended from the midline 1.0 to 1.5 mm laterally into the perifornical area, and 2.5 to 3.0 mm dorsally from the base of the brain. In all animals, the drug cannula was positioned in the immediate vicinity of the PVN.

Experiment 4

The results of the preceding experiment replicate those of Experiment 2 and confirm that parasagittal cuts lateral to the PVN, as well as coronal knife cuts in the posterior hypothalamus, do not block NE feeding. The lateral knife cuts in these experiments did not extend to the most dorsal level of the PVN and, therefore, may have spared the more dorsolateral efferents of this nucleus (Conrad and Pfaff, 1976). Even though these dorsolateral efferents are not numerous, it is possible that they may mediate the NE-feeding response. Consequently, disruption of these efferents may disrupt the NE-feeding response. Experiment 4 thus investigated the effects of perifornical knife cuts extending well into the thalamus on NE feeding.

Method

Subjects

Twelve animals with large lateral cuts and eight sham-cut animals survived all testing and were included in the data analysis.

Surgery

The knife shaft was positioned 1.0 mm anterior to bregma, 0.8 to 1.0 mm lateral to the midline, and 2.5 mm above the ear bar reference point. The 3.0 mm cutting wire was then extended and lowered to the base of the brain. Sham cuts were performed as in Experiment 2. In a second operation, which was performed 9 to 13 days after knife-cut

surgery, the animals were implanted with a PVN drug cannula.

Procedure

The subjects were maintained and tested on the Purina pellet diet. Drug testing began 18 days after knife-cut surgery and from 6 to 11 days after implantation surgery. A NE dose of 40 nmoles was employed using a testing procedure identical to that in Experiment 2, Part 1.

Results

In the 18 day period between the knife cuts and the onset of drug testing, both groups lost body weight although the lateral-cut group lost significantly more weight than controls [-46.2 ± 9.1 vs. -19.9 ± 9.4 g; t (18) = 1.95, $p < .05$] (see Discussion, Experiment 4). The reason for the weight loss in the controls is unclear, but, at the start of testing, both groups were consuming a normal amount of food (30.8 ± 3.4 g for the cut group; 29.8 ± 1.6 g for the control group) and their body weights had stabilized.

The results of the NE tests can be seen in Figure 8A. The mean-feeding score of the knife-cut animals was slightly but not significantly less than that of controls. Two cut animals and one control animal did not display a reliable NE-feeding response. There was no correlation between NE-feeding response and 18 day postknife-cut body-weight change in the experimental animals.

A representation of the knife cuts and cannula placements for the experimental subjects is shown in Figure 8B. As in the previous experiments, the cannula placements

were in or near the PVN. The medial-lateral and rostral-caudal placement of the knife cuts were quite similar to the lateral cuts employed in the preceding experiment. The cuts differed substantially, however, from those of the last experiment in terms of their dorsoventral extent since they extended from the base of the brain well into the thalamus or, in some instances, into the lateral ventricles.

Discussion

The results of Experiments 2-4 demonstrate that parasagittal knife cuts in the perifornical hypothalamus lateral to the PVN, which produced hyperphagia and excessive weight gain, did not disrupt the feeding response induced by PVH microinjections of NE. Coronal knife cuts in the posterior hypothalamus, which did not produce hyperphagia, but which were in a position to sever the pathway involved in the hypothalamic hyperphagia syndrome (see below), also did not block the NE-feeding response. The failure of these knife cuts to impair noradrenergic feeding cannot be attributed to regeneration of the relevant fibers since behavioral testing in Experiment 2 began only two days after surgery. It is possible that the lateral cuts did not block the NE-feeding response because of diffusion of the NE to receptor sites in the perifornical area. If this were the case, however, the lateral cuts should have significantly reduced the NE-feeding response since previous work has established that feeding stimulated by NE injections into

the perifornical region is less than that obtained with PVN injections (Leibowitz, 1978; see also Experiment 6). Since the posterior knife cuts were 1.0 to 2.5 mm away from the cannula, it is unlikely that the drug acted on receptors located caudal to these cuts. The findings of these experiments, therefore, indicate that the output of the hypothalamic noradrenergic-feeding system does not follow the feeding pathway implicated in the hypothalamic hyperphagia syndrome (see General Discussion).

As previously discussed, the pathway involved in the hypothalamic hyperphagia syndrome appears to be longitudinally situated in the perifornical region of the hypothalamus. Yet, the posterior coronal knife cuts in Experiments 2 and 3, which should have severed this pathway, did not produce overeating or obesity. Earlier studies have also observed that bilateral posterior coronal knife cuts result in little or no hyperphagia in male rats (Grossman and Hennessy, 1976; Sclafani, 1982). In female rats, on the other hand, such cuts produce hyperphagia although less than that produced by bilateral parasagittal knife cuts in the perifornical hypothalamus (Sclafani and Berner, 1977). Furthermore, in both male and female rats, a unilateral coronal knife cut in the posterior hypothalamus combined with a contralateral parasagittal knife cut in the perifornical hypothalamus has been found to produce as much obesity as do bilateral parasagittal knife cuts (Gold et al., 1977; Sclafani, 1982; Sclafani and Berner, 1977). Based

on these results, it has been proposed (Sclafani, 1982; Sclafani and Berner, 1977) that posterior coronal knife cuts sever the same feeding pathway as do parasagittal knife cuts, but that the coronal cuts also sever additional fibers which, when bilaterally damaged, interfere with the expression of the hyperphagia syndrome. This proposed action of coronal knife cuts is of relevance to the present study because, while the bilateral posterior coronal cuts block the expression of hypothalamic hyperphagia, they do not abolish the feeding response to microinjections of NE.

A similar argument applies to the effects obtained with the large parasagittal knife cuts used in Experiment 4. Since these cuts severed all the fibers damaged by the smaller, hyperphagia-inducing parasagittal cuts of Experiments 2 and 3, their failure to produce overeating and excessive weight gain can be attributed to the additional damage they produced to the more dorsal diencephalon. Yet, while these larger parasagittal cuts inhibited the hyperphagia syndrome, they did not interfere with NE feeding. Therefore, the results obtained with the nonhyperphagia-inducing knife cuts, as well as those obtained with the hyperphagia-inducing knife cuts, indicate that different systems are involved in the NE-feeding response and the hypothalamic hyperphagia syndrome.

Further evidence indicative of a dissociation between the MH hyperphagia syndrome and the noradrenergic-feeding response can be cited: a) high fat diets greatly potentiate

the hyperphagia induced by MH damage (Experiment 1; Carlisle and Stellar, 1969; Corbit and Stellar, 1964), but such diets do not exaggerate the NE-feeding response (Sclafani and Toris, 1981); b) systemic injections of atropine block NE feeding (Sawchenko et al., 1981) but not hypothalamic hyperphagia (Carpenter, Stamoutsos, Dalton, Frohman, and Grossman, 1979; Sclafani and Xenakis, 1981); and c) hypophysectomy inhibits the NE-feeding response (Leibowitz, 1980), but not MH hyperphagia (Cox, Kakolewski, and Valenstein, 1968; Ieni and Gold, 1977).

Thus, while the noradrenergic-feeding response and hypthalamic hyperphagia syndrome share some anatomical and behavioral features (see Introduction, Experiment 2), the present results, and those cited above, suggest that they are mediated by separate neural mechanisms. Although the nature of these mechanisms remains to be identified, they may involve different aspects of energy regulation. For example, the system involved in the hypothalamic hyperphagia syndrome may be related to the long-term regulation of body fat (Hoebel and Teitelbaum, 1966; Kennedy, 1953; Sclafani, 1976), while the noradrenergic-feeding system, as discussed in the next experiment, may be involved in the short-term glucostatic control of feeding.

Experiment 5

A variety of neurochemical, pharmacological, and behavioral evidence suggests that the PVH NE-feeding system may be involved in the feeding response produced by glucoprivation. For instance, 2DG eating is associated with increased NE release (McCaleb and Myers, 1979) and turnover (Ritter and Neville, 1976) in the hypothalamus and alpha-receptor blockade by intraventricular injections of phentolamine reduces eating in response to systemic (Muller et al., 1972) and intraventricular (Berthoud and Mogenson, 1977) injections of 2DG. The feeding response following systemic injections of 2DG is also blocked by depletion of endogenous brain catecholamines with intraventricular injections of the catecholamine neurotoxin 6-hydroxydopamine (Muller et al., 1972); by peripheral injections of the catecholamine synthesis inhibitor alpha-methyl-para-tyrosine (Muller et al., 1972); and by depletion of hypothalamic NE by midbrain lesions of the dorsal noradrenergic bundle (Leibowitz and Brown, 1980). Finally, glucoprivation elevates hypothalamic NE turnover rates, which can be restored to normal by food consumption (Bellin and Ritter, 1981).

If glucoprivic feeding results from the release of NE into the PVH, it would be predicted that similar feeding responses should be produced by administration of NE into the PVH and by systemic injection of 2DG. Some support for

this prediction is provided by the results of one-jar acceptance tests and two-jar preference tests. One-jar tests have indicated that both the 2DG- (Kanarek and Mayer, 1978) and the NE- (Booth and Quatermain, 1965; Sclafani and Toris, 1981) feeding responses are blocked by quinine diets. It has also been reported that, in choice situations, NE injections are associated with a preference for sugar or high-carbohydrate diets over other diets (Leibowitz, 1980) and several studies have shown that insulin-induced glucoprivation produces an enhanced appetite for sugar (e.g., Jacobs, 1958; Le Magnen, 1971). The effects of 2DG-induced glucoprivation on sugar or carbohydrate consumption in the rat have not been previously reported. However, preliminary observations in this laboratory have revealed that, unlike food deprivation, 2DG produces a reliable preference for a high-sucrose diet compared to a high-fat diet. Thompson and Campbell (1977) have also provided evidence that, in the human, 2DG produces an enhanced appetite for sugar. The purpose of this experiment was to compare directly the effects of PVH injections of NE and systemic injections of 2DG on the dietary preference behavior of rats given a choice between a 20% sucrose diet and a 20% fat diet. In addition, the present experiment also examined the effects of the alpha-adrenergic agonist clonidine on the choice of the sucrose and fat diets. Central clonidine injections have been reported to have a more potent stimulatory-feeding effect than NE injections

(Broekkamp and Van Rossum, 1972; Ritter et al., 1975) and, therefore, might be expected to reveal a more pronounced dietary preference effect than NE.

Method

Subjects and Surgery

Eleven rats completed Part 1 of this experiment; eight subjects completed Part 2. The subjects were housed in large stainless steel cages (43 cm wide, 24 cm long, and 18 cm high) throughout the experiment.

All subjects received a unilateral PVH cannula using the procedures descibed in Experiment 2.

Diets

During all phases of the experiment, the subjects were maintained and tested with two diets: a fat diet (20% commercial-grade vegetable shortening in the powdered form of the Purina diet, w/w; 4.74 kcal/g) and a sucrose diet (20% commercial-grade sucrose in powdered Purina chow, w/w; 3.68 kcal/g). The percentage of total kilocalories associated with each macronutrient in the fat diet was: 37.9% carbohydrate, 46.5% fat, and 15.6% protein. The macronutrient breakdown of the sucrose diet by calories was: 70.8% carbohydrate, 9.1% fat, and 20.1% protein. For all test periods, the subjects were given fresh diets and side preferences were controlled by within-subject conterbalancing of side of diet presentation. The rats were adapted to the diets for at least two weeks preceding testing.

Procedure

Part 1. During the week following the postoperative recovery period, the animals were adapted to the testing procedure by exposing them to one moderate food deprivation test and three alternating saline/NE tests (see below). Formal testing commenced immediately after this period.

The testing sequence involved a comparison of the feeding responses following six hours of food deprivation, PVH injections of NE (50 nmoles), systemic injections of 2DG (600 mg/kg), and finally, following another 6-hr fast. The experimental conditions were presented on separate days with the appropriate control condition occurring on the preceding day. Each test phase included two experimental treatments and two control treatments. Food intake across a 3-hr observation period was recorded for each treatment.

The food deprivation phases involved tests following a non-deprived control condition and a 6-hr deprivation condition, which began at the onset of the light cycle (0700 hr). At the start of each of these conditions, the subjects were given control injections. During the first deprivation phase (i.e., the phase preceding the NE tests) the control injections involved central saline injections while during the last deprivation phase (i.e., the phase following the 2DG tests) the rats were given mock intraperitoneal injections (i.e., the needle was inserted but nothing was injected).

The NE- and 2DG-testing procedures were similar to each

other except that the subjects were not tested the day after 2DG injections. These respective phases consisted of four test days during which caloric intake was measured following the administration of the vehicle or drug conditions: On the first and third days of testing, the subjects were given the vehicle treatment; on the second and fourth days, the rats were given the drug treatment. A 1-hr preinjection period preceded each condition. At the beginning of this period the subjects were given fresh food. However, they were not handled during the preinjection period.

The pattern of drinking and eating was recorded during the initial presentation of all treatments except for the deprivation treatments. (This measure was evaluated only during the second phase of deprivation testing.) That is, it was noted whether or not a bout of drinking preceded a feeding response and whether or not a feeding response occurred within ten minutes after the beginning of the test period.

Part 2. Following the postoperative recovery period, the subjects in this condition were tested for feeding responsiveness to clonidine (38 nmoles) in a fashion similar to that employed in Part 1. However, the subjects were given four drug and saline injections in an ABBA-ABBA sequence. A dose of clonidine similar to the dose chosen for this experiment has been previously shown to elicit feeding behavior from the perifornical hypothalamus (Broekkamp and van Rossum, 1972). As in Part 1, the pattern of eating and

drinking following the initial treatments was observed in all animals.

Results

Histology

The cannula placements for all subjects were in the immediate vicinity of the PVH and did not differ from the placements obtained in the previous experiments.

Part 1

In the first test phase, the 6-hr food deprivation condition increased food intake, F (1, 30) = 4.23, $p < .05$ (Figure 9). The rats had no overall diet preference across this test phase nor did the deprivation condition differentially affect the intake of either the fat or sucrose diet (deprivation by diet interaction not significant).

NE also enhanced overall caloric intake above control levels, F (1, 30) = 17.59, $p < .05$ (Figure 9). As with the first deprivation tests, there was no overall diet preference effect and their was no treatment by diet interaction effect. NE thus equivalently enhanced the intake of both diets.

2DG resulted in a significant overall increase in caloric intake compared to control levels, F (1, 30) = 8.50, $p < .05$ (Figure 9). In contrast to the preceding test conditions, there was also an overall preference for the sucrose diet, F (1, 30) = 5.12, $p < .05$, and a tendancy for the 2DG to enhance consumption of the sucrose diet to a

greater extent than consumption of the fat diet. This later tendancy, however, failed to be reliable. Closer inspection of the data indicated that the failure to obtain a significant drug by diet interaction effect during the 2DG test phase was due to one animal with an exceptionally strong fat preference: the caloric intake of the fat diet by this animal following the 2DG treatment was more than three standard deviations above the mean 2DG-fat intake. Exclusion of this animal from the 2DG analysis resulted in a significant drug by diet interaction effect [F (1, 27) = 5.59, $p < .05$]. Examination of this interaction effect demonstrated that the drug and saline conditions did not differ with respect to fat-diet intake but did differ with regard to sucrose-diet consumption, F (1, 27) =14.09, $p < .025$, and that 2DG increased sucrose-diet, F (1, 27) = 410.51, $p < .025$, but not fat-diet intake. Exclusion of the odd animal from the NE analysis had no effect on the NE findings [significant drug main effect F (1, 27) = 19.13, $p < .05$ but no significant diet main effect or drug by diet interaction effect]. Consequently, while NE comparably increased the intake of both the fat and sucrose diets, 2DG selectively increased sucrose diet consumption. Analysis of the percentage of total calories associated with the sucrose diet following the 2DG and NE treatments (n = 10) further substantiated this difference between the two feeding responses. Specifically, the 2DG treatment produced a relatively greater preference for the sucrose diet than did

the NE treatment [75.3±5.2% vs. 54.7±9.0%, respectively; t (9) = 2.38, $p < .05$].

The macronutrient intakes associated with the NE and 2DG treatments and their respective control conditions are shown in Table 4. All data were expressed as a percent of total caloric intake. Each macronutrient was analyzed with a two factor repeated measures ANOVA. The animal with the abnormal 2DG-fat preference was excluded from the analysis. Also excluded from the analysis was an animal that failed to eat following the saline control injection associated with the NE treatment (the failure to eat renders the percent total intake conversion inappropriate). Consumption of each macronutrient was differentially affected by the NE and 2DG treatments as evidenced by significant treatment (NE test vs. 2DG test) by injection (saline vs. drugs) interaction effects [Carbohydrate F (1, 24) = 5.31, $p < .05$; Fat F (1, 24) = 5.31, $p < .05$; Protein F (1, 24) = 5.34, $p < .05$]. Tests of simple main effects on these interaction effects were not, however, significant at the corrected .05 probability levels. Thus the source of the interactions cannot be further specified.

The results of the last deprivation test phase were unlike those of the first phase since there was no reliable deprivation-induced feeding response relative to the no deprivation condition (Figure 9). However, the total caloric intake associated with the deprivation condition (18.98 kcal) was quite similar to that produced by the 2DG

treatment (16.69 kcal). Nonetheless, the rats displayed no diet preference effect following the deprivation condition.

The pattern of eating and drinking associated with the various treatments was analyzed with McNemar tests for the significance of changes, corrected for continuity (Siegel, 1956). Such an analysis revealed that, unlike their respective control conditions, the NE, 2DG, and deprivation treatments all produced a feeding response within ten minutes of the start of testing [NE χ^2 (1) = 9.09; 2DG χ^2 (1) = 9.09; Deprivation χ^2 (1) = 5.14; p's< .05]. The 2DG- and NE-feeding responses were reliably preceded (relative to their control treatments) by a short bout of drinking [NE χ^2 (1) = 9.09; 2DG χ^2 (1) = 9.09; p's< .05]. However, a drinking response did not (p> .05) precede the deprivation-feeding response.

Part 2

The results of the clonidine test are depicted in Figure 10. The total caloric consumption following the clonidine treatment substantially differed from that following the saline treatment, F (1, 21) = 15.79, p< .05. There was also an overall preference for the fat diet, F (1, 21) = 7.80, p< .05, but no drug by diet interaction effect. Thus clonidine did not differentially affect consumption of either diet. As was the case with the NE and 2DG treatments, clonidine, unlike its saline control, evoked a feeding response within 10 minutes of injection, χ^2 (1) = 6.12, p< .05. However, in contrast to the behavioral response pattern

obtained with NE and 2DG injections, the clonidine feeding response was not reliably preceded by a short bout of drinking. In fact, no animal drank during 30 minutes of observation.

Discussion

The results of Part 1 indicate that exogenous injections of NE into the PVH and moderate food deprivation produced similar effects on dietary preference behavior in that both treatments enhanced the intake of both the 20% sucrose diet and the 20% fat diet. On the other hand, systemic injections of 2DG produced a different dietary response profile since they induced a greater increase in consumption of the sucrose diet compared to the fat diet. The sucrose-diet preference effect elicited by 2DG but not by NE replicates unpublished findings with similar diets (see Introduction) and is further supported by the results of the next experiment. The results of Part 2 demonstrate that a sucrose-diet preference effect was also not obtained with the alpha agonist clonidine which tended to produce a stronger feeding response than the NE injections of Part 1 although this difference was not reliable (clonidine response, 18.2$\pm$3.0 kcal above saline levels; NE response, 13.7$\pm$2.9 kcal above saline levels). Systemic clonidine injections in young rats, have also been reported not to enhance carbohydrate intake. Rather, such injections are associated with an enhanced preferences for protein (Mauron, Wurtman, and Wurtman, 1980). Taken together, the findings of

this experiment indicate that the preference behaviors elicited by adrenergic stimulation of the PVH and by 2DG-induced glucoprivation differ and do not support the hypothesis that the glucoprivic-feeding response is due to the activation of PVH alpha receptors.

In contrast to the present findings, Leibowitz and associates have reported that NE and clonidine can produce a shift in preference towards high-carbohydrate diets (Fahrbach, Tretter, Aravich, McCabe, and Leibowitz, 1980; Tretter and Leibowitz, 1980). However, the diets used in these studies, namely purified macronutrients, differed from those employed in the present study and in the study of Mauron et al. (1980). This is an important consideration and the specific nature of the test diets has been found to influence the ingestive response of one other catecholamine agent, viz., amphetamine (Kanarek, Ho, and Meade, 1981; Orthen-Gambill and Kanarek, 1982). Nevertheless, the crucial aspect of the present experiment is that, under identical testing conditions, the preference behavior associated with PVH adrenergic stimulation markedly differs from that associated with systemic 2DG administration.

This investigation reveals that 2DG induces a sucrose-diet preference effect and this is similar to the results obtained with insulin-induced glucoprivation (e.g., Jacobs, 1958; Le Magnen, 1971). The classical interpretation for glucoprivic feeding is that it reflects an effort on the part of the animal to provide specific fuel (i.e., glucose,

e.g., Smith and Epstein, 1969) or general fuel (e.g., Stricker, Rowland, Saller, and Friedman, 1977) for oxidative metabolism. The mediators of this process could be central (e.g., Miselis and Epstein, 1975) or peripheral (e.g., Novin, VanderWeele, and Rezek, 1973) in origin. It should be noted, however, that the classic interpretation of glucoprivic feeding is undergoing revision. One reason for this revision is the observation that the feeding response can occur in the absence of physiological signs of glucose insufficiency (Nonavinakere and Ritter, 1982; Ritter, Roelke, and Neville, 1978); glucoprivic agents also produce many effects in addition to glucoprivation (see Discussion Experiment 6; Friedman, Ramirez, Wade, Siegel, and Granneman, 1982). Therefore, while glucoprivation may be necessary for triggering the sequence of events related to the production of a sucrose-diet preference effect, glucoprivation itself may not be sufficient for the preference effect and alternative explanations are possible (Aravich, in preparation).

Consistent with the differences in dietary preference behavior produced by 2DG and NE, the two drugs also differentially affected macronutrient intake. In particular, while the specific tests of simple main effects were not statistically significant, 2DG tended to increase carbohydrate consumption and decrease fat consumption whereas NE tended to affect carbohydrate and fat intake in the opposite directions.

The findings regarding the feeding and drinking patterns following NE and systemic 2DG injections confirm previous observations with intraventricular 2DG (Berthoud and Mogenson, 1977) and intrahypothalamic (Leibowitz, 1975a; Slangen and Miller, 1969) NE injections: the noradrenergic- and glucoprivic-feeding responses are each preceded by a bout of drinking. This was not the case with the feeding behavior produced by six hours of food deprivation. This difference between the two drug treatments and moderate food deprivation is consistent with the interpretion that NE (Blundell and Herberg, 1970; Booth and Quartermain, 1965; Coons and Quartermain, 1970; Sclafani and Toris, 1981) and 2DG (Blass and Kraly, 1974; Smith, Gibbs, Strohmayer, and Stokes, 1972) feeding differ from deprivation-induced feeding behavior.

Unlike the NE response, the clonidine-feeding response was not preceded by a bout of drinking. It is possible that this NE/clonidine difference is due to NE's mixed alpha-1-, alpha-2-, and beta-adrenergic receptor actions (Wikberg, 1979). Clonidine may fail to elicit a preliminary bout of drinking because it more specifically activates alpha-2 receptors (Wikberg, 1979). Previous studies in which the NE and 2DG drinking/feeding responses have been pharmacologically manipulated support the possibility that the two responses to each treatment reflect the activation of independent substrates. For example, while' the alpha-adrenergic blocker phentolamine (which blocks both

alpha-receptor types although its alpha-1 action predominates; Wikberg, 1979) suppresses both the drinking and eating responses to intrahypothalamic NE (Leibowitz, 1975b) and intraventricular 2DG (Berthoud and Mogenson, 1977) injections, beta-adrenergic antagonists block the drinking response but not the feeding response to NE (Leibowitz, 1975b); a similar type of pharmacological dissociation, vis-a-vis 2DG, is obtained with the serotonergic antagonist methysergide (Berthoud and Mogenson, 1977). Therefore, the drinking responses produced by NE and 2DG injections may reflect the alteration of neural systems independent of those responsible for the respective feeding effects.

Experiment 6

An important role for the NE-feeding system in glucoprivic eating was originally suggested by the findings that intraventricular injections of the alpha-adrenergic antagonist phentolamine block the feeding response produced by 2DG (Muller et al., 1972). The specific site mediating this blocking effect has not, however, been examined. If the release of endogenous NE in the PVH is crucial to the glucoprivic-feeding effect, it would be predicted that PVH injections of phentolamine should block eating elicited by systemic injections of 2DG.

In addition to the PVH, another medial hypothalamic area richly innervated by noradrenergic fibers is the dorsomedial hypothalamic area (DMH) (see e.g., Lindvall and Bjorklund, 1974). DMH lesions have been previously shown to block 2DG feeding (Bellinger, Bernardis, and Brooks, 1978) and NE stimulation of the area stimulates eating (Leibowitz, 1970) suggesting that the DMH may be an important component of the 2DG-feeding system. The participation of the lateral hypothalamus (LH) in the regulation of glucoprivic feeding must also be considered. Lesions in various parts of the LH block 2DG feeding (Miselis and Epstein, 1971; Nicolaidis, 1971; Wayner, Cott, Millner, and Tartaglione, 1971), LH injections of NE promote eating (e.g., Booth, 1967; Leibowitz, 1970), and the ascending CA systems innervate this region (e.g., Lindvall and Bjorklund, 1974). The

present experiment, consequently, compared the effects of phentolamine injections into three different hypothalamic areas on 2DG-induced feeding. The effects of phentolamine injected into these three brain regions on feeding elicited by mild food deprivation were also assessed in order to determine if any obtained blocking effect of phentolamine on 2DG-elicited feeding is specific to this type of feeding or a more general phenomenon. In order to determine if any suppressive-feeding effects of phentolamine were diet dependent, the subjects were tested with the sucrose and fat diets during both the 2DG and deprivation test phases. Finally, if glucoprivation elicits feeding by releasing endogenous NE, this release would be expected to occur bilaterally. As a result of this consideration, intrahypothalamic drug injections were bilaterally administered.

Method

Subjects

Twenty one subjects completed the experiment. Of these animals, seven received PVH cannula placements, eight received DMH cannula placements, and six received LH cannula placements. Eight other rats did not complete testing because of illness while one animals was excluded because of a dislodged implant.

Surgery

The bilateral cannulae in all groups were angled six degrees laterally from the vertical plane. With the nose

clamp at 3.0 mm above the ear bars, the tips of the cannulae in the PVH group were positioned 0.2 mm posterior to bregma, 8.2 mm beneath the surface of the skull, and 0.3 mm lateral to the midline. In the DMH group, the cannula tips were implanted 0.9 mm posterior to bregma, 8.6 mm ventral to the surface of the skull, and 0.5 mm lateral to the midline. Finally, in the LH group, the cannula tips were positioned 0.2 mm posterior to bregma, 8.4 mm beneath the skull surface and approximately 1.2 mm lateral to the midline.

Drugs

A 20 nmole dose of NE was injected into each cannula in a 0.5 µl volume for a total dose of 40 nmoles. Phentolamine (30 nmoles in 0.5 µl) was bilaterally injected for a total dose of 60 nmoles. 2DG was injected intraperitoneally in a dose of 600 mg/kg body weight.

Procedure

The 20% fat and 20% sucrose diets were used throughout the experiment. Side preferences were controlled by between-subject counterbalancing of side of diet presentation. Following the postoperative recovery period, the animals were screened for their feeding responsiveness to central injections of NE using the procedure of Experiment 2, Part 2.

The rats were next tested with 2DG using the following sequence of injections: systemic saline and central water (Vehicle treatment); systemic 2DG and central water (2DG condition); systemic saline and central phentolamine (PHT

condition); systemic 2DG and central phentolamine (2DG+PHT condition). This sequence of injections was then repeated. The systemic injections were given immediately before the central injections and at least one day of no testing followed each 2DG treatment. All tests included a 1-hr preinjection period during which fresh food was available and the animals were handled. Following this period was a 4-hr postinjection period during which hourly food intake was recorded.

In the final phase of the experiment, the feeding response to moderate food deprivation was assessed. The rats were deprived of food for six hours beginning at the onset of the light cycle. The specific treatment conditions included no deprivation and central water injections (no deprivation condition); six hours of food deprivation and central water (deprivation treatment); and six hours of food deprivation combined with central phentolamine (DEP+PHT condition). The dose and volume of the phentolamine injections were the same as those employed during the 2DG phase as was the length of the test period. In addition to the 6-hr deprivation test, some of the animals within each group were also tested following 18 hours of food deprivation prior to the 2DG test phase. The data from these few animals were inconsistent and are not reported here.

Results

Histology

The PVH cannula sites were located near the

anteroposterior midpoint of the paraventricular hypothalamic nucleus; the DMH placements were located near the caudoventral dorsomedial hypothalamic nucleus and were not far removed from the dorsal aspect of the ventromedial hypothalamic nucleus; and the the LH injection sites were situated in the midlateral hypothalamus at the same anteroposterior level as the PVH injection sites (Figure 11). The ventral extent of the LH placements was slightly below the level of the PVH placements.

NE Tests

NE produced a substantial feeding response in the PVH and DMH groups [F (1, 18) = 21.07, $p < .05$, and F (1, 21) = 29.50, $p < .05$, respectively] and a smaller but still reliable feeding response in the LH group, F (1,15) = 6.37, $p < .05$ (Figure 12). Within each group, all subjects ate within 10 min of the injection. In the majority of cases, the feeding response was preceded by a short drinking response. NE tended to increase the intake of the fat diet more than that of the sucrose diet but the diet by drug interaction effect was not significant. In the PVH and DMH groups there were no overall diet main effects. The LH group, however, had an overall bias towards the fat diet, F (1, 15) = 5.95, $p < .05$.

2DG Tests

Figure 13 shows that PVH injections of phentolamine completely blocked the overall-feeding response produced by 2DG. Specifically, the cumulative caloric intake for the PVH

group during the 2DG test phase was associated with a drug by hours interaction effect, F (9,90) = 3.76, $p < .05$. Further analysis revealed that the 2DG condition produced more feeding than the other conditions at both the third hour, F (3, 90) = 11.19, $p < .0125$, and fourth hour, F (3, 90) = 17.03, $p < .0125$. None of the other treatments differed among themselves. Caloric intake reliably increased across the 4-hr observation period for each of the drug conditions except for the PHT condition [Vehicle F (3,90) = 7.20, $p < .0125$; 2DG F (3,90) = 37.26, $p < .0125$; 2DG+PHT F (3, 90) = 10.24, $p < .0125$]. On this later measure then, PHT had a general suppressive effect on food intake. Analysis of the total 4-hr intake of the fat and sucrose diets for the PVH group (Figure 14) showed a significant drug by diet interaction effect, F (3, 42) = 6.87, $p < .05$. More specifically, the PVH rats ate reliably more of the sucrose diet following the 2DG treatment than following the three other conditions, F (3, 42) = 11.84, $p < .025$. Sucrose consumption following the Vehicle, PHT, and 2DG+PHT conditions did not reliably differ from each other. Thus, the overall increase in caloric intake associated with the 2DG treatment was due to a specific increase in the consumption of the sucrose diet. Further analysis revealed that there was no reliable sucrose preference associated with the two control conditions but that both the 2DG and 2DG+PHT conditions were associated with a significant sucrose-diet preference effect [significant diet at

treatment simple main effects: 2DG F (1, 42) = 17.47, $p<$ .0125; 2DG+PHT F (1, 42) = 10.45, $p<$ .0125]. Consequently, while phentolamine suppressed the feeding stimulatory effect of 2DG, it spared the sucrose-diet preference effect induced by the glucoprivic agent.

Figure 13 also shows that DMH injections of PHT completely block the overall-feeding response produced by 2DG. The effects of the various drug treatments in the DMH group were essentially the same as those observed in the PVH group with the exception that there was no significant drug by hours interaction. Nonetheless, there was an overall drug effect, F (3, 105) = 17.68, $p<$ .05, and the overall caloric intake produced by the 2DG treatment reliably exceeded that produced by all other treatments (Figure 13). None of the remaining conditions differed among themselves. Phentolamine thus blocked the 2DG feeding effect in the DMH group. Analysis of the total 4-hr intake of the fat and sucrose diets in the DMH group (Figure 14) demonstrated a treatment by diet interaction effect, F (3, 49) = 6.57, $p<$ .05. Further analysis showed that the 2DG-feeding effect was associated with a specific overconsumption of the sucrose diet relative to all other treatment conditions, F (3, 49) = 6.57, $p<$ .025; none of the other treatments differed in amount of sucrose diet consumed and none of the treatments differed in fat diet consumption. However, both the 2DG condition and the 2DG+PHT condition were associated with a reliable sucrose preference [F (1, 49) = 22.92, $p<$ .0125 and

F (1, 49) = 12.37, $p < .0125$, respectively]. Therefore, while phentolamine blocked the feeding effect of 2DG in the DMH group, it failed to block the glucoprivic-induced sucrose diet preference effect.

The results of the 2DG test phase for the LH group differed from those obtained for the other groups. Analysis of the hourly cumulative caloric intake associated with the treatment conditions revealed that there was no reliable overall 2DG feeding stimulatory effect in the LH group (Figure 13). However, examination of the total 4-hr intake of the fat and sucrose diets (Figure 14) demonstrated a significant drug by diet interaction effect, F (3, 35) = 3.00, $p < .05$. As with the other groups, while the intake of the fat diet did not differ across treatment conditions, there were reliable differences between treatment conditions in the amount of sucrose diet consumed, F (3, 35) = 4.49, $p < .025$. This was due to the fact that both the 2DG and the 2DG+PHT treatments caused the LH rats to overconsume ($p < .05$) the sucrose diet relative to the Vehicle condition (but not relative to the PHT condition). Thus, there was a 2DG feeding stimulatory effect with regard to sucrose consumption compared to the Vehicle treatment. In contrast to the results obtained with the PVH and DMH groups, phentolamine failed to reduce sucrose intake. As was the case in the PVH and DMH groups, the sucrose-diet preference effect induced by 2DG was not blocked by PHT since, unlike the other conditions, the 2DG and 2DG+PHT treatments were

each associated with a reliable sucrose preference, F (1, 35) = 7.52, $p < .0125$ and F (1, 35) = 8.92, $p < .0125$, respectively.

Deprivation Tests

In the PVH group, their was a significant treatment effect on overall caloric intake across the 4-hr test period, F (2, 66) = 29.39, $p < .05$ (Figure 15). Further analysis of this main effect indicated that the deprivation condition produced reliably more feeding than the no deprivation condition. However, this increase was completely blocked by phentolamine since the amount of feeding produced by the DEP+PHT condition did not differ from the no deprivation condition but reliably differed from the deprivation condition. The total 4-hr intakes of the sucrose and fat diets (Figure 16) were each increased following the deprivation treatment although, in this analysis, this overall increase was not reliable. There was also no specific diet preference effect associated with the deprivation condition.

The DMH group also reliably enhanced its overall cumulative caloric intake across the 4-hr test period following the deprivation condition, F (2, 77) = 15.31, $p < .05$ (Figure 15). As with the PVH group, this effect was totally blocked by phentolamine: the DEP+PHT condition and the no deprivation condition did not reliably differ from each other but significantly differed from the deprivation treatment. Analysis of the total 4-hr intake of the sucrose

and fat diets (Figure 16) showed that, while the intake of each diet increased following six hours of food deprivation, the overall increase in food intake (in this analysis) was not reliable. There was also no reliable diet preference associated with moderate food deprivation in the DMH group.

The results of the deprivation tests in the LH group (Figures 15 and 16) were similar to those of the other two groups with one important exception: while moderate food deprivation significantly enhanced caloric intake across the test period, F (2, 55) = 27.98, $p < .05$, phentolamine only partially blocked this effect: the DEP+PHT condition resulted in reliably less food intake than did the deprivation treatment but significantly more intake than the no deprivation condition.

Discussion

The results of this experiment indicate that phentolamine completely suppresses 2DG-elicited eating when injected into the PVH and DMH. These findings are consistent with those obtained with intraventricular phentolamine injections (Muller et al., 1972) and would appear to support the view that PVH as well as DMH alpha-adrenergic receptors mediate the feeding effects of 2DG. However, the results of this experiment further indicate that PVH and DMH phentolamine injections completely suppress feeding induced by moderate food deprivation. This later effect replicates earlier findings with perifornical and DMH injections of phentolamine (Broekkamp, Honig, Pauli, and Van Rossum, 1974;

Leibowitz, 1970). Phentolamine, in addition, has been shown to suppress the feeding response elicited by taste in nondeprived rats (Broekkamp et al., 1974). It is debatable (e.g., Blass and Kraly, 1974; Epstein, Nicolaidis, and Miselis, 1975; Jones and Booth, 1975; Ritter et al., 1978; Smith et al., 1972; Stricker, Friedman, and Zigmond, 1975) if glucoprivic mechanisms are necessarily involved in the feeding response produced by moderate food deprivation and even less likely that such mechanisms are involved in the eating response to a palatable food. Thus, the results of this experiment along with other data (e.g., Broekkamp et al., 1974) indicate that phentolamine has an inhibitory effect on feeding which is not specific to glucoprivation and provide little support for a specific alpha-adrenergic glucoprivic-feeding hypothesis.

The failure of phentolamine to block the sucrose-diet preference effect of 2DG stimulation further questions the role of hypothalamic NE in glucoprivic feeding. One interpretation for the general-feeding enhancement and sucrose-diet preference effects produced by 2DG is that the general increase in feeding following 2DG is more sensitive to disruption than is the sucrose-diet preference effect. Alternatively, it is possible these responses are mediated by independent mechanisms. Whether or not the difference between the feeding stimulatory and sucrose-diet preference effects are quantitative or qualitative in nature, the sucrose-preference effect does not appear to be dependent

upon a PVH or DMH alpha-adrenergic system.

Other recent data also question the hypothesis that the NE-feeding system mediates glucoprivic feeding. For example, while it has been shown that insulin-induced glucoprivation can elevate hypothalamic NE turnover rates until food is consumed (Bellin and Ritter, 1981), the termination of the glucoprivic feeding response is not dependent upon the normalization of NE turnover rates (Ritter, Bellin, and Pelzer, 1981). In addition, glucoprivation enhances the activity of GABA (Kimura and Kuriyama, 1975) as well as NE and in vitro glucose insufficiency affects several putative transmitter systems (O'Fallon and Ritter, 1982). NE is, therefore, not uniquely affected by glucoprivation.

In contrast to the PVH and DMH groups, the LH-cannulated animals failed to display a vigorous 2DG-feeding response. This may have been due to the neural damage produced by the LH cannulae (LH damage impairs 2DG feeding, Miselis and Epstein, 1971; Nicolaidis, 1971; Wayner et al., 1971). It should be noted, however, that DMH lesions also block 2DG feeding (see above) but that the DMH cannulation procedure did not impair the overall 2DG-feeding response. Although 2DG did not produce an overall increase in total calories across the 4-hr test period in the LH group, 2DG still produced an increase in sucrose diet consumption relative to the vehicle condition. Unlike the PVH and DMH placements, this overconsumption failed to be reduced by phentolamine. In addition, unlike its effects

when injected into the PVH and DMH, phentolamine did not completely block deprivation-induced feeding when injected into the LH group. These data thus suggest an anatomical dissociation for the suppressive-feeding effects of phentolamine on both glucoprivic- and deprivation-induced feeding.

The sucrose-diet preference effect of 2DG adds to the list of responses associated with 2DG. Many of these responses, however, may be independent of each other. For example, there is good evidence for a dissociation between the general-feeding effect and the adrenal-mediated glycemic response produced by 2DG (cf e.g., Ikeda, Nishikawa, and Matsuo, 1980; Muller, Frohman, and Cocchi, 1973; Muller, Pecile, Cocchi, and Olgiati, 1974; Ritter and Balch, 1978; Ritter et al., 1978; Stricker et al., 1977). The glycemic effect of 2DG-induced glucoprivation also appears dissociable from its inhibition of insulin secretion (Frohman, Muller, and Cocchi, 1973) and its lipolytic effect (Gunion, Grijalva, and Novin, 1982; Teixeira, Antunes-Rodrigues, and Migliorini, 1973). In addition, the stimulation of gastric acid following glucoprivation has been argued to be independent of the feeding effect (see Epstein et al., 1975). Multiple systems are therefore activated by 2DG and the interrelationship between these systems and the feeding and sucrose-diet preference effects of the drug remains to be established.

Consistent with previous reports (Davis and Keesey,

1971; Leibowitz, 1978; Matthews et al., 1978) NE injections into the PVH produced a more vigorous feeding response than LH injections. The suppressive-feeding effects of phentolamine on deprivation-induced feeding and on 2DG feeding have also been shown in this experiment to be greater from PVH as opposed to LH injection sites.

Unlike previous research (e.g., Leibowitz, 1978), the feeding response produced by administration of NE into to the DMH was comparable to that obtained from the PVH sites. The relatively large cannulae and the variability associated with bilateral placements in this experiment do not, however, allow for the precise localization of the substrate responsible for the NE-feeding response. In support of previous research (Leibowitz, 1970), the suppressive-feeding effect of phentolamine on deprivation-induced feeding was greater from DMH injection sites compared to LH sites. This experiment also reveals that phentolamine injected into the DMH has a greater suppressive effect on 2DG eating than does LH injection of the drug (see Figure 14). Since the PVH and DMH placements were close to the third ventricle, and since the cannula site most distant to the third ventricle (i.e., the LH placement) was the least effective blocking site, the present findings do no exclude the possibility that phentolamine may have diffused into the ventricular system and acted at another site to suppress feeding in response to deprivation and glucoprivation. However, a previous study demonstrating the suppression of 2DG feeding by

lateral-ventricular injections of phentolamine used an effective dose that was nearly three times as large as the dose used in the present experiment in a volume that was almost 20 times larger (Muller et al., 1972).

Experiment 7

A third way to evaluate the hypothesis that the release of endogenous NE into the PVH mediates glucoprivic feeding is to determine the effects of PVH lesions on 2DG eating. Such lesions have previously been reported to effectively block the feeding response elicited by intraventricular NE injections (Leibowitz, 1979). The effects of PVH lesions on the 2DG-feeding response have not been previously explored.

Method

Subjects

Five PVH-lesioned and seven sham-lesioned (CON group) animals survived all testing. Three other lesioned animals were excluded from the analysis because of misplaced lesions (midline thalamus, $n = 2$; unilateral PVH, $n = 1$). Two months prior to this investigation, the rats had participated in an auditory habituation study and had been maintained on a water deprivation schedule (23.5 hr/day) for two weeks. The test diet (Purina pellets) and housing conditions were the same as in Experiment 1.

Surgery

Bilateral electrolytic lesions (1 ma for 10 sec) aimed at the PVH (0.3 mm posterior to bregma; 8.4 mm beneath the skull; 0.3 mm lateral to the midline; nose clamp at +3.0 mm) were made with a stainless steel insect pin (#00) and a rectal cathode. The electrode was insulated with Epoxylite except for 0.4 mm of its tip. A 21-22 day postoperative

recovery period followed surgery.

Procedure

Following the postoperative recovery period, the animals were tested for feeding responsiveness to systemic injections of 2DG using a procedure similar to that employed in the previous experiment. Two doses of the drug (600 and 400 mg/kg) were administered in descending order. Each dose and its respective saline control was given once.

Results

The lesions of the experimental group were relatively small and were restricted to the immediate vicinity of the paraventricular nucleus (photomicrograph, Figure 17). Portions of the medial zona incerta were also involved in these lesions.

The effects of the surgical treatment on body weight and food intake are shown in Table 4. Prior to surgery, the experimental and control groups differed in body weight and food intake though these differences were not reliable. Following surgery, the PVH group initially lost body weight but, by the time of drug testing, did not differ from the CON group in body weight or food intake. Analysis of the preoperative and postoperative differences in the PVH and CON group (two-way ANOVA with repeated measures on the test-phase factor) revealed that there was no group by test-phase interaction on either the body weight or food intake measure. Thus, neither the body weight nor the food intake of the PVH group was differentially affected by the

surgical treatment.

The results of the 2DG feeding tests are shown in Figure 18. The 600 mg/kg dose of 2DG produced an overall feeding response across groups, F (1, 10) = 19.38, $p < .05$. There was, however, no overall group difference in caloric intake nor was there a group by drug interaction effect. The 400 mg/kg dose also resulted in an overall drug effect, F (1, 10) = 60.09, $p < .05$, and no group main effect or group by diet interaction effect. During this later test, both groups had somewhat higher saline baseline scores than during the 600 mg/kg test. The reason for this baseline shift is not readily apparant.

Discussion

The results of this experiment indicate that PVH lesions do not block the 2DG-feeding response. Rather, the PVH lesion group showed a response to the 600 and 400 mg/kg doses of 2DG that did not differ from the control group. The inability of PVH lesions to impair 2DG feeding has also been found in other studies (Aravich and Sclafani, unpublished observations; McCabe, Debillis, and Leibowitz, 1982). Both the PVH and control groups showed a flat dose-response curve, but this is not unusal with 2DG doses above 100 mg/kg (Jones and Booth, 1975; Smith et al., 1972).

The failure of the PVH lesions to block the 2DG-feeding response cannot be attributed to the robust nature of this response since lesions of the DMH, LH (see above), 'globus pallidus (Neill and Linn, 1975), zona incerta (Walsh and

Grossman, 1975), and preoptic area (Blass and Kraly, 1974; Miselis and Epstein, 1971) as well as knife cuts in the dorsolateral midbrain tegmentum (Grossman and Grossman, 1977) and lateral perifornical hypothalamus (Aravich and Sclafani, unpublished observations) all impair 2DG feeding. The small size of the lesions also cannot explain the failure of the PVH lesions to affect the 2DG-feeding response since the DMH lesions that have been reported to block the response (Bellinger et al., 1978) are comparable in size to the PVH lesions employed in the current experiment.

The inability of PVH lesions to alter 2DG feeding contrasts with the suppressive effects of PVH injections of phentolamine on 2DG-elicited eating (Experiment 6). This lesion vs. pharmacological dissociation could be due to various factors. For example, the phentolamine effect may mediated by tissue adjacent to the PVH region not damaged by the lesions of the present experiment. One site near the PVH is the DMH. Since DMH lesions (Bellinger et al., 1978) and DMH injections of phentolamine (Experiment 6) both disrupt 2DG feeding, it is possible that the effects of PVH injections of phentolamine are due to diffusion to the DMH. If this were the case it would be expected that the effects of phentolamine would be less when injected into the PVH than when injected into the DMH. This difference was not, however, obtained. It is also possible that acute pharmacological blockade of PVH adrenergic receptors may be

more disruptive to the 2DG-feeding response than is the chronic disruption produced by surgical damage; that is, there may be a functional compensation associated with the surgical treatment that is not associated with the pharmacological treatment. Further research is needed to explore these possibilities.

Unlike previous studies (Experiment 1; Eng et al., 1979; Heinbecker et al., 1944; Leibowitz et al., 1981), the PVH lesions of the present study were ineffectual as far as hyperphagia and obesity were concerned. The normophagia of these lesioned animals may be related to the small size of the lesions (lesion size is related to the degree of hyperphagia; see Experiment 1) as well as to the sex of the animals (male PVH-lesioned rats are less hyperphagic than female rats; Leibowitz et al, 1981). It has been observed, however, that larger PVH lesions in male animals that do produce hyperphagia also fail to block feeding in respone to 2DG (Aravich and Sclafani, unpublished observations). Thus, neither restricted PVH lesions nor large hyperphagia-inducing PVH lesions block 2DG eating.

While Experiments 5-7 fail to support the hypothesis that a specific PVH NE system mediates the 2DG-feeding reponse, these experiments do not exclude the possible importance of other hypothalamic or extrahypothalamic noradrenergic mechanisms. As previously noted, one hypothalamic area to be considered is the DMH. Even though DMH injections of phentolamine failed to block the

sucrose-diet preference effect of 2DG, it is possible that the DMH is an important link in the noradrenergic/2DG-feeding circuit. It should be noted, however, that DMH lesions fail to block insulin-induced feeding (Bellinger and Bernardis, 1979). Consequently, if the DMH exerts a role in glucoprivic feeding, this role would seem to be limited to feeding induced by glucose antimetabolites. Another potentially important hypothalamic area is the periventricular hypothalamus. It is also richly innervated with adrenergic fibers (see Leibowitz, 1980) and may be important to both the noradrenergic-feeding effect and the glucoprivic-feeding effect. Among the extrahypothalamic noradrenergic mechanisms to be considered are those involved in the regulation of brain glycogen stores. Central glycogen stores have been previously implicated in the 2DG-feeding effect (Ritter et al., 1978). These stores are the largest energy reserves for the brain and are at least partly under the direct control of central NE mechanisms (Harik, Busto, and Martinez, 1982). Thus, noradrenergic mechanisms may affect glucoprivic feeding by influencing central glycogen stores.

General Discussion

This investigation has produced three general findings: Experiment 1 indicates that the PVH hyperphagia syndrome is qualitatively similar to the classic hypothalamic hyperphagia syndrome in several important respects; Experiments 2-4 demonstrate that the output of the PVH NE-feeding system is independent of the system responsible for hypothalamic hyperphagia; and Experiments 5-7 reveal that the PVH NE-feeding system is independent of the glucoprivic-feeding system

The PVH Hyperphagia Syndrome

Experiment 1 established that PVH lesions produce changes in food intake, body weight, dietary responsiveness, and diurnal-feeding patterns that are similar to those produced by MH knife cuts. Since relatively restricted PVH lesions (particularily of the caudolateral PVH) produce a hyperphagia syndrome qualitatively similar to that produced by MH cuts and since these lesions produce less damage to fibers of passage than MH cuts, an examination of the fiber systems mediating the PVH effect may clarify the fiber systems involved in hypothalamic hyperpagia.

The anatomy of the area responsible for the PVH hyperphagia syndrome, i.e., the caudal PVH region, is exceedingly complex. This is particularily true with respect to the number of newly identified neurochemical systems associated with the region. Although the PVN itself is best

known for its projections to the posterior pituitary (see Defendini and Zimmerman, 1978), recent anatomical work demonstrates that PVN efferents are distributed over a remarkably wide extent of the neuroaxis including the external layer of the median emminence and several extrahypothalamic sites. Of particular relevance to the hyperphagia syndrome, many PVN efferents project to the lower brainstem in the vicinity of a perifornical fiber pathway previously implicated in the hyperphagia syndrome (Gold et al., 1977; Mufson et al., 1980; Sclafani and Berner, 1977) and to brainstem areas associated with feeding behavior such as the parabrachial nucleus, the nucleus of the solitary tract, the dorsal motor nucleus of the vagus, and preganglionic neurons of the sympathetic nervous system (i.e., intermediolateral cell column of the spinal cord) (Conrad and Pfaff, 1976; Saper et al., 1976). PVN projections to the dorsal vagal complex and intemediolateral cell column are of special interest in light of the emphasis given to parasympathetic (Powley, 1977) and sympathetic (Inoue and Bray, 1979) disruptions in the etiology of hypothalamic hyperphagia. The caudal PVH region in general gives rise to the majority of monosynaptic hypothalamo-spinal cord projections and a large number of hypothalamo-brainstem projections (Armstrong et al., 1980; Hosoya, 1980; Ono, Nishino, Sasaka, Muramoto, Yano, and Simpson, 1978; Saper et al., 1976; Sofroniew and Schrell, 1980 and 1981; Swanson and Kuypers, 1980). Efferents from

this region may be associated with at least 15 different neuroactive substances. Seven of these systems are in a position to project to the lower brainstem and/or spinal cord: vasopressin and oxytocin (see below), neurotensin (Kahn, Abrams, Zimmerman, Carraway, and Leeman, 1980), angiotensin II (see Hokfelt and associates, 1978), acetylcholine (Jacobowitz and Palkovits, 1974), and methionine- and leucine-enkephalin (DiFiglia, Aronin, Carey, Breslow, and Martin, 1981; Finley, Maderdrut, and Petruz, 1981; Sawchenko and Swanson, 1982; Warnsley, Young, and Kuhar, 1980).

Of these efferents, the most extensively mapped are the neurophysin-associated vasopressin and oxytocin systems (Armstrong et al., 1980; Buijs, 1978; Sawchenko and Swanson, 1982; Swanson, 1977). Neurophysin-containing neurons are scattered throughout the rostral hypothalamus. Notably however, neurophysin-like cell bodies are located in parvocellular and magnocellular portions of the PVN and in the perifornical area (Armstrong et al., 1980; Buijs, 1978; Rhodes, Morrell, and Pfaff, 1981; van den Pol, 1982). The majority of neurophysin projections to the forebrain and midbrain are vasopressinergic (Buijs, 1978) while 75% of the projections to lower levels are oxytocinergic (Sofroniew and Schrell, 1981). Most of the descending neurophysin output of the PVN itself originates in caudal areas of the nucleus (Sawchenko and Swanson, 1982). The majority of this output bends ventrolaterally from the PVN and travels through the

perifornical hypothalamus (Armstrong et al., 1980; Swanson, 1977). The parabrachial nucleus, dorsal vagal complex, and spinal cord all contain neurophysin-like fibers (Sofroniew and Schrell, 1980; Swanson, 1977; Sawchenko and Swanson, 1982). Neurophysin projections account for about 20% of the descending output of the paraventricular nucleus (Sawchenko and Swanson, 1982) and may exert further influence on the sympathetic nervous system by projecting to the A1 cell group in the brainstem (Sladek and Scholer, 1981) which is the primary source of catecholamines to the intermediolateral cell column (see Glazer and Ross, 1980). Although vasopressin and oxytocin neurons and fibers are no doubt damaged by hyperphagia-inducing PVH lesions and MH cuts, these peptides have not been previously implicated in the control of feeding behavior. The role of these peptides, particularily oxytocin, in the hypothalamic hyperphagia sydrome, therefore requires experimental attention.

The five other neurochemical systems noted above have all been implicated in the control of feeding (Hoebel and Leibowitz, 1981; Grossman, 1962a; Leibowitz, 1980; McFarland and Rolls, 1972; Stanley, Eppel, and Hoebel, 1982). However, little is known about the caudal distribution of neurotensinergic, angiotensinergic, and cholinergic fibers from the caudal PVH region and the contribution of enkephalinergic fibers to the descending projections of this area appear to be minimal (Sawchenko and Swanson, 1982). In addition to these various systems, neurons appearing to

contain other types of neuroactive substances have also been localized in the caudal PVH including cholecystokinin (Beinfeld, Meyer, and Brownstein, 1980), dynorphin (Watson and associate, 1981), somatostatin (Bennett-Clarke, Romagnano, and Joseph, 1980; Kahn et al., 1980; Sawchenko and Swanson, 1982), dopamine (paraventricular nucleus, Sawchenko and Swanson, 1982; A13 cell group, Hokfelt et al., 1978), gastrin (Loren, Alumets, Hakanson, and Sundler, 1979), luteinizing hormone-releasing hormone (Marshall and Goldsmith, 1980; Selmanoff, Wise, and Barraclough, 1980), molluskan cardioexcitatory peptide (Weber, Evans, Samuelsson, and Barchas, 1981), and, perhaps, avian pancreatic polypeptide (Brecha, Card, Moore, 1981). Several of these substances have been previously associated with the control of feeding behavior (see e.g., Leibowitz, 1980; Morley, 1980; Morley and Levine, 1981; Woods and associates, 1981). However, because of their small numbers, positions within the PVH region, and/or apparant projection routes, these cell types would not seem to be prime candidates for the hyperphagia syndrome.

Rather than disruption of a PVH efferent system, it is possible that the PVH hyperphagia syndrome results from damage to a PVH afferent system. Neural input to the PVH region originates from many, though not all, of the same areas which it innervates (e.g., Edwards and de Olmos, 1976; Norgren, 1976; McKellar and Loewy, 1981; Ricardo and Koh, 1978; Silverman, Hoffman, and Zimmerman, 1981; Tribollet and

Dreifuss, 1981). There is evidence, albeit indirect, for at least 18 different neurochemicals contained within fibers projecting to or passing through the caudal PVH. Some of these neurochemicals also form components of the output of the PVH.

One of the most prominant afferent systems to this area contains the catecholamines norepinephrine (NE) and epinephrine (e.g., Leibowitz and Brown, 1980; Lindvall and Bjorklund, 1974; Palkovits and associates, 1980; Sawchenko and Swanson, 1981). There is considerable evidence that NE acts in the PVN to influence feeding behavior (General Introduction), and it has previously been proposed that damage to ascending noradrenergic pathways may be responsible for the hypothalamic hyperphagia syndrome (Kapatos and Gold, 1973). However, while both the PVH and CUT treatments were in a position to disrupt much of this ascending system, such disruption would not seem implicated in the hyperphagia syndrome since depletion of PVN norepinephrine can produce hypophagia rather than hyperphagia (O'Donohue, Crowley, and Jacobowitz, 1978). Furthermore, the present investigation (Experiments 2-4) indicates that the feeding response to PVH microinjections of NE and the hyperphagia syndrome produced by MH cuts are mediated by different fiber pathways.

Several other types of neurochemical systems traveling to or through the PVH may also be damaged by either PVH lesions or MH cuts. The neurochemicals include serotonin

originating from the raphe complex (Azmitia, 1978), cholecystokinin (Loren et al., 1979), substance P (Cuello and Kanazawa, 1978), thyrotropin releasing hormone, gamma-aminobutyric acid (GABA) (see Hokfelt et al., 1978), the enkephalins (Finley et al., 1981), avian pancreatic polypeptide, bovine pancreatic polypeptide (Brecha et al., 1981; Olschowka, O'Donohue, and Jacobowitz, 1981), and molluskan cardioexcitatory peptide (Weber et al., 1981). Some of these substances have been previously shown to influence feeding behavior (see e.g., Leibowitz, 1980; Morely, 1980; Woods et al, 1981) and their potential involvement in the PVH hyperphagia syndrome cannot be excluded. However, other input systems to the PVH region do not seem to be prime candidates. For example, neurons within the area of the arcuate nucleus and median eminence putatively project serotonin (Kent and Sladek, 1978), motilin (Jacobowitz, O'Donohue, Chey, and Chang, 1981), adrenocorticotrophic hormone, alpha-melanocyte stimulating hormone, beta-endorphin, and/or beta-lipoprotein (see Jacobowitz and O'Donohue, 1978; Kreiger, 1980) fibers to or near the PVH region. While some of these fibers project periventricularily, others may project perifornically (see Jacobowitz and O'Donohue, 1978) and could be in a position to be damaged by CUT and PVH treatments. However, this perifornical projection route does not conform to the longitudinal inhibitory-feeding pathway (Gold et al., 1977; Mufson et al., 1980; Sclafani and Berner, 1977) implicated

in the syndrome. A similar argument applies to vasoactive intestinal polypeptide and vasopressenergic fibers to the PVH since their source of origin is primarily the SCN (Sims et al., 1980; Sofroniew and Weindl, 1978).

In summary (see Figure 19), the PVH lesion syndrome is qualitatively similar to the classic hypothalamic hyperphagia syndrome with regard to changes in food intake, water intake, body weight, dietary reactivity, and diurnal feeding patterns. The PVH syndrome is not identical to the knife-cut syndrome in all respects, however, nor, for that matter, is the knife-cut syndrome identical to the VMH lesion syndrome (e.g., Bray, Sclafani, and Novin, 1982; Sclafani, 1971). The PVH lesion syndrome, in particular, differs from the knife-cut and lesion syndromes in terms of emotionality, protein consumption, insulin secretion, and obesity levels. The failure of PVH lesions to produce hyperemotionality but their ability to produce qualitatively similar changes in food intake and dietary reactivity suggests that alterations in emotionality are not critical to the hypothalamic hyperphagia syndrome. The differential effects of PVH lesions and MH damage on protein consumption indicates that PVH lesions and MH cuts affect other regulatory-feeding systems in addition those responsible for hypothalamic hyperphagia.

PVH lesions also seem to differ from MH cuts and VMH lesions in their effects on insulin secretion. It has been observed that static phase PVH rats self-selecting purified

macronutrient diets do not have elevated resting insulin levels in contradistinction to MH-cut and VMH animals (Sclafani and Aravich, 1982). However, static phase PVH animals have elevated resting insulin levels when maintained on a Purina chow diet (Sclafani and Aravich, in preparation). The chow diet is lower in fat content and higher in carbohydrate content than the diet self-selected by the PVH rats. Hence, the obesity produced by PVH lesions, unlike that produced by MH cuts or VMH lesions, is associated with a diet-dependent hyperinsulinemia. Since elevated insulin levels do not appear to be essential for the maintenance of obese body weights in PVH animals, the importance of hyperinsulinemia to the maintenance of obese body weights in MH-cut and VMH-lesioned animals is open to question. In support of this possibility, York and Bray (1972) have shown that destruction of pancreatic beta cells in static phase VMH rats by streptozotocin reduces but does not block their obesity. Regarding dynamic phase PVH animals, it has been reported that they have elevated stimulated insulin levels when maintained on a chow diet (Steves and Lorden, 1982). It remains to be established if the hyperinsulinemia of dynamic phase PVH animals is diet dependent. If, however, this is proven to be the case the role of hyperinsulinemia in the etiology of hypothalamic hyperphagia (Powley, 1977) would also be open to serious question.

The fact that PVH lesions produce less obesity than do

large perifornical knife cuts suggests that the substrate responsible for hypothalamic hyperphagia is diffusely organized and is not localized exclusively within the PVH. Further parametric studies utilizing small lesions are needed to more precisely define the anteriomedial hypothalamic components responsible for the syndrome. Nonetheless, the neurochemical organization of the PVH region allows us to consider the possible involvement in hypothalamic hyperphagia of various biochemical systems either not previously associated with the syndrome in particular or with feeding behavior in general. In addition, because PVH lesions are less disruptive to fibers of passage than are MH knife cuts and because such lesions fail to produce hyperemotionality, the PVH hyperphagia syndrome may be a more tractable model of hypothalamic hyperphagia. Finally, it should be noted that the PVH has been considered to subserve important autonomic and endocrine functions (Krieg, 1932; Sawchenko and Swanson, 1981) and has been implicated in such disparate activities as cardiovascular regulation (e.g., Ciriello and Calaresu, 1980), the neural control of the testes (Nance, 1981), adenohypophysiotrophic regulation (e.g., Baertschi, Beny, and Gahwiler, 1982), and insulin stimulation (Vonderhae, 1937), as well as in posterior pituitary function (see Defendini and Zimmerman, 1978) and feeding behavior (Heinbecker et al., 1944). Further explication of the PVH hyperphagia syndrome therefore requires consideration of the functional and

biochemical complexity of this region.

The PVH Noradrenergic Feeding Effect

Experiments 2-4 demonstrate that various hypothalamic knife cuts in a position to sever the pathway implicated in the hypothalamic hyperphagia syndrome fail to disrupt the PVH NE-feeding effect. Consequently, the output of the PVH NE-feeding system does not follow the fiber system involved in the hyperphagia syndrome. Experiments 5-7 show that the PVH NE-feeding system is also independent of the system mediating the glucoprivic-feeding effect. In particular, it was found that that the dietary preference behaviors elicited by PVH injections of NE and by systemic injections of 2DG substantially differ; that the feeding response elicited by mild food deprivation as well as by systemic 2DG injections can be blocked by phentolamine injections into the PVH and DMH; that central phentolamine injections do not reduce the sucrose-diet preference effect elicited by 2DG injections; and that PVH lesions fail to alter 2DG feeding. The functional significance of the NE-feeding system thus remains to be established

Initially, the NE-feeding effect was regarded as representing the activation of a normal, generalized type, hunger drive (Grossman, 1964a; Miller, 1965). Certain data are consistent with this hypothesis. For example, food deprivation may enhance NE activity as indexed by its depletion of hypothalamic NE stores in general (Glick, Waters, and Milloy, 1973) and medial-zone NE stores in

particular (Stachowiak, Bialowas, and Jurkowski, 1978). In the PVH, food deprivation reduces alpha-receptor-binding sites and increases NE turnover (Jhanwar-Uniyal, Fleischer, Levin, and Leibowitz, 1982). However, caudal hypothalamic NE uptake (Van der Gugten and Slangen, 1975) and anterior hypothalamic NE release (Martin and Myers, 1975) are highest during feeding rather than before it. This suggests that hypothalamic NE may normally function in the maintenance rather than in the initiation of feeding behavior. Supportive of this view, small doses of hypothalamic NE, which are inadequate to elicit feeding in sated animals, are sufficient to substantially promote the size of a spontaneously initiated meal (Grinker, Marinescu, and Leibowitz, 1982; Ritter and Epstein, 1975). While a number of factors--including satiety alterations--can influence meal size (see e.g., Le Magnen, 1971), the maintenence of feeding is importantly influenced by diet palatability (see e.g., Peck, 1978).

Another hypothesis for the functional significance of the NE-feeding system, therefore, is that it mediates the rewarding quality of food (Ritter et al., 1975). This hypothesis is an extension of the view that reward in general is mediated by NE (see Stein, Wise, and Belluzzi, 1977) and specifically postulates (Stein and Wise, 1969) that the consumption of good-tasting foods is due to activation of the NE-feeding system. Consistent with this hypothesis, hypothalamic injections of NE fail to stimulate

consumption of unpalatable quinine diets (Booth and Quartermain, 1965; Sclafani and Toris, 1981). Saccharin diets, on the other hand, have been reported to potentiate the NE-feeding response (Booth and Quartermain, 1965). However, NE eating is not potentiated by a palatable high-fat diet (Sclafani and Toris, 1981). This would seem to indicate that the rewarding qualities of all foods are not mediated by NE and recent attention has been focused upon dopaminergic and endorphinergic mechanisms (see e.g., Sclafani, Aravich, and Xenakis, 1982; Wise, 1982; Xenakis and Sclafani, 1981). Nonetheless, a role for NE in the mediation of other aspects of reward that may influence feeding behavior cannot be discounted (see Leibowitz, 1982).

In addition to providing data on the relationship between the hypothalamic hyperphagia syndrome and NE-elicited feeding, Experiments 2-4 provide information on the output fibers of the PVN which are <u>not</u> involved in the NE feeding response. Among the laterally projecting efferents of the PVN are fibers which form the supraopticohypophysial tract (Armstrong et al., 1980; Defendini and Zimmerman, 1978; Haymaker, 1969; Swanson, 1977; Swanson and Kuypers, 1980). These PVN efferents pursue a circuitous route as they loop laterally through the perifornical area (or even the internal capsule) to the supraoptic nuclei. Together with fibers from the supraoptic nuclei, they then travel medially along the floor of the hypothalamus into both layers of the median eminence and

into the neurohypophysis. Since the perifornically positioned parasagittal knife cuts of the present study did not block the NE-feeding response, but presumably redundantly damaged many of these fibers, these PVN efferents do not appear to be essential to the feeding effect of NE. However, the knife cuts spared more medially oriented PVN efferents to the median eminence and neurohypophysis (Armstrong and Hatton, 1980; Armstrong et al., 1980; Conrad and Pfaff, 1976; Swanson and Kuypers, 1980). Since hypophysectomy blocks NE feeding (Leibowitz, 1980), the hypothalamo-pituitary axis in general, and these medially directed PVN pituitary projections in particular, would seem to be implicated in the NE-feeding effect. On the other hand, the finding (Leibowitz, 1980) that corticosterone replacement therapy restores the noradrenergic feeding response in hypophysectomized rats suggests that the pituitary exerts only a permissive influence on NE eating.

According to Swanson (1977), most of the neurophysin-containing autonomic projections of the PVN descend to the lower brainstem in the MFB, ventral and lateral to the fornix. The knife cuts employed in the current study were in a position to significantly impinge upon this projection system but failed to alter NE feeding. This suggests that PVN efferents in the MFB are also not essential to NE feeding. On the other hand, it is unlikely that the knife cuts severed all of the descending output of

the PVN. In particular, while the various cuts severed PVN efferents in the medial and perifornical hypothalamus, they produced little or no damage to the more dorsally situated periventricular tract and dorsal longitudinal fasiculus (Krieg, 1932; see also Nauta and Haymaker, 1969), which may also contain caudally directed PVN efferents to lower brainstem autonomic nuclei (compare Krieg, 1932 with Conrad and Pfaff, 1976). The NE-feeding effect may also be related to five other brain systems involving GABA, the endophins, CCK, neurotensin, and/or vasopressin.

Kelly and Grossman (e.g., 1980) have argued that the output of the NE-feeding system is directed to PVH GABA interneurons and that these GABA neurons inhibit satiety. Consistent with this view, central injections of GABA agonists stimulate feeding (Grandison and Guidotti, 1977) particularily from the the PVH (Kelly, Rothstein, and Grossman, 1979). This stimulatory-feeding effect is blocked by the GABA anatagonist bicuculline methiodide but not by the alpha-adrenergic antagonist phentolamine (Grandison and Guidotti, 1977; Kelly et al., 1979). The NE-feeding response, on the other hand, is blocked by both phentolamine and by the GABA antagonist (Grandison and Guidotti, 1977).

The PVH NE-feeding system has also been related to an endorphinergic system (see Leibowitz and Hor, 1982). Hypothalmic injections of opiate agonists stimulate feeding behavior (Grandison and Guidotte, 1977; see also Leibowitz, 1982). The feeding effect which follows endorphinergic

stimulation of the PVH is blocked not only by the opiate antagonist naloxone but also by the alpha-antagonist phentolamine (Leibowitz and Hor, 1982). The feeding effect which follows NE stimulation of the PVH, however, is blocked by phentolamine but not by naloxone (Leibowitz and Ho, 1982). The relationship of the endorphins to the PVH NE-feeding system would therefore seem to be the reverse of the GABA relationship: the endorphinergic system may modulate NE input; the postsynaptic effects of NE may be mediated by a GABA system. The GABAergic and endorphinergic theories of NE feeding are therefore not mutually exclusive. It has recently been reported that the the opiate-feeding effect unlike the NE-feeding effect, does not depend upon the glucocorticosteriods (McLean and Hoebel, 1982). Thus, despite the pharmacological evidence noted above, there may be a dissociation between the NE- and opiate-feeding systems. Additional research is clearly required to explore the interactions of these various systems. Also to be further evaluated is the behavioral specificity of the various treatments.

Considering the neurochemical complexity of the PVH region, it is not unlikely that other systems may also be involved in the NE-feeding response. McCaleb and Myers (1980) have suggested that CCK may interact with the NE-feeding system. They have found that CCK injections given systemically or into the PVH prior to PVH NE injections block the NE-feeding response. However, little other data

are available concerning the specificity of the CCK effect to NE feeding and further research is required before these results can be adequately interpreted. Levine and associates (Levine, Kneip, Grace, and Morley, 1982) have suggested that the NE-feeding system interacts with a neurotensinergic system. The neurotensin effect appears to be more convincing than the CCK effect since neurotensin was reported to suppress feeding elicited by ventricular injections of NE but not feeding in response to insulin or intraventricular injections of the GABA agonist muscimol. Feeding elicited by intraventricular injections of the opiate agonist dynorphin was also blocked by neurotensin. The effects of neurotensin can be incorporated into the model outlined above in the following fashion: since it blocks the feeding effects of both an opiate and a noradrenergic agonist but not of a GABA agonist, neurotensin may exert its effects on the NE-GABA link of the chain. However, interpretation of these neurotensin data requires caution since the basic findings have only been reported in abstract form and since neurotensin also suppresses deprivation-induced feeding which may be unrelated to NE feeding (see above).

A possible role for vasopressin (VP) in the NE-feeding effect can also be considered. There is an intimate and reciprocal anatomical relationship between the noradrenergic and vasopressinergic systems of the PVH (Sladek and Scholer, 1981; Swanson, Sawchenko, Berod, Hartman, Helle, and Vanorden, 1981; Sawchenko and Swanson, 1981). Among the

fiber projections spared by the knife cuts in Experiments 2-4 were those to the external layer of the median eminence (e.g., Armstrong and Hatton, 1980; Armstrong et al., 1980; Conrad and Pfaff, 1976; Swanson and Kuypers, 1980). Many of these projections may contain VP (Vandesande, Dierickx, and DeMey, 1977). While VP has not been previously implicated in the NE-feeding effect, its effects on feeding behavior have not been sytematically studied.

In summary, the output of the PVH alpha-adrenergic feeding system does not follow the feeding pathway implicated in the hypothalamic hyperphagia syndrome. The output of the noradrenergic feeding system is also not directed to the lower brainstem via PVN efferents in the medial or perifornical hypothalamus, nor to the pituitary by PVN efferents in the supraopticohypophysial tract. The results of this investigation do not exclude the possibility that other caudally directed fiber pathways not transected in the present study (e.g., in the dorsal periventricular stratum), may mediate the NE-feeding response. The results also do not exclude the possibility that the output of the NE-feeding system is directed to the median eminence by VP neurons. It is conceivable, however, that the noradrenergic feeding effect involves a diffusely directed fiber system which cannot be sufficiently interrupted by a knife cut confined to a single plane. The possibility of a humoral rather than neural output for the noradrenergic-feeding system also cannot be discounted in light of the fact that

the rich capillary network of the PVN is importantly innervated by adrenergic receptors (Swanson, Connelly, and Hartman, 1977; but see Olschowka, Molliver, Grzanna, Rice, and Coyle, 1981).

Conclusions

The PVH is important to both the hypothalamic hyperphagia syndrome and the noradrenergic-feeding effect but does not appear to be important to the glucoprivic-feeding effect. While PVH mechanisms are involved in both hypothalamic hyperphagia and noradrenergic feeding, these mechanisms do not appear to be directly related.

Since hypothalamic hyperphagia and noradrenergic feeding can be obtained from other hypothalamic and extrahypothalamic areas, the PVH is not the center for either effect but rather one important link in an integrated neuronal and hormonal chain. That the PVH should exert an important role in feeding behavior is not surprising in light of its phylogenetic age (Krieg, 1932), rich vascularization (Krieg, 1932; van den Pol, 1982), neurochemical complexity, and various autonomic, endocrinological, and circumventricular associations. But the PVH is not unique in these respects, and the median eminence and MH in general are as neurochemically and anatomically diversified.

In the past decade our knowledge of the role of the hypothalamus in feeding behavior has undergone a kind of

Copernican revolution: for many years the hypothalamus was regarded as the center for feeding behavior with other neurological and hormonal mechanisms revolving around it. Now it is seen as but one planet in a complex and elegant galaxy. Exploration of this galaxy requires the appropriate anatomical, physiological, and pharmacological tools. Its stars will never be mapped, however, without the appropriate behavioral tools. The behavioral specificity and functional significance of various treatments that affect food intake and body weight must therefore receive greater attention as should the contribution of classical and instrumental conditioning to ingestive behavior. But, hypothetical constructs such as "satiety" and "finickiness" must also become more firmly rooted in their physiological substrates. Further advances in the field of ingestive behavior will be obtained only with such an intergrated and cautious approach.

Table 1.

Mean (+SEM) Food Intake (Kcal), Percent Total Food Intake Consumed at Night (ZNight), Water Intake (Ml), Water/Food Intake Ratio (Ml/Kcal), and Median Emotionality (Em) Scores For the Various Groups.

		Food Intake		ZNight	Water Intake		Ml/Kcal	Em
Group	N	Preop	Postop	Postop	Preop	Postop	Postop	Postop
CUT	9	77.7+2.6	143.2+7.1†	51.8+1.2†	50.8+2.5	98.5+7.7†	0.69+0.04	4.0†
PVH	9/7	80.0+3.6	110.7+5.9*	59.1+2.1*	51.5+6.5	74.7+8.4*	0.67+0.06	0.0
CON	9/8	80.1+2.3	75.0+2.1	71.2+1.9	50.3+4.7	53.0+3.2	0.72+0.05	0.5
PVH-N	5	82.5+5.0	101.1+1.9*	61.9+4.6*	54.0+4.9	79.2+5.0*	0.78+0.04	0.0

Note. Postop refers to the period between surgery and the first dynamic phase diet test (i.e., the first week after surgery).

* Differs from CON ($p < .05$)

† Differs from both CON and PVH ($p < .05$)

TABLE 2.

Mean (+SEM) Caloric Intake (Kcal) of the Plain and Test Diets During the Dynamic Phase Tests For the Various Groups.

		QHCL			SOA		
Group	N	Plain	Test	ZChange	Plain	Test	ZChange
CUT	9	143.2+7.1 †	53.6+6.1	-62.7+3.4 *	127.8+8.2	86.4+19.1	-35.6+12.8
PVH	9	110.7+5.9 *	39.6+3.5	-62.6+4.8 *	96.1+3.5	73.9+6.8	-23.1+5.7
CON	9	75.8+2.1	48.8+3.8	-36.8+3.8	92.5+3.1	77.4+4.6	-15.8+5.1
PVH-N	5	101.1+1.9 *	36.8+5.7	-63.4+6.8 *	97.5+5.1	68.8+8.6	-30.4+6.5
		Dextrose			Fat		
CUT	9	126.9+9.6	149.3+6.9	+20.8+5.8	143.5+6.9 †	198.4+9.6 †	+39.3+6.3 *
PVH	9	94.6+9.8	120.4+4.6	+59.8+11.3	109.9+6.4 *	158.1+8.2 *	+45.1+4.9 *
CON	9	87.8+3.2	100.4+2.8	+15.7+2.4	83.4+2.2	95.7+3.6	+15.1+4.8
PVH-N	5	89.5+3.9	105.9+4.8	+18.4+2.5	90.7+4.6	113.3+4.4 †	+25.4+3.8

* Differs from CON ($p < .05$)

† Differs from both CON and PVH ($p < .05$)

TABLE 3.

Mean (+SEM) Caloric Intake (Kcal) of the Plain and Test Diets

During the Static Phase Tests

For the Various Groups.

		QHCL			SOA		
Group	N	Plain	Test	%Change	Plain	Test	%Change
CUT	9/8	84.7+5.4	25.2+4.8 †	-71.2+4.4 †	78.3+6.8	25.3+11.1†	-64.9+15.2*
PVH	9	93.8+4.6	44.1+5.2	-51.1+6.7 *	82.4+2.2	55.9+9.1	-33.8+10.6
CON	9	76.1+2.8	55.9+4.8	-25.3+7.1	76.7+3.5	64.9+6.8	-16.1+7.8
PVH-N	5	76.5+2.3	41.6+6.1	-46.1+7.8	97.5+5.1	68.8+8.6	-16.2+7.4
		Dextrose			Fat		
CUT	8	67.2+7.7	104.5+7.6	+64.2+13.7†	87.5+4.8	178.6+7.8 †	+95.7+5.8 *
PVH	9	88.7+4.4	109.7+3.8 *	+38.1+5.7	85.7+2.9	152.3+5.6 *	+78.5+6.4 *
CON	9	75.4+2.8	91.8+2.8	+21.8+2.8	78.6+2.3	92.1+5.6	+31.5+8.8
PVH-N	5	84.7+3.4	105.4+9.3	+24.1+8.7	79.6+3.5	112.6+9.9 †	+42.8+13.9

* Differs from CON ($p < .05$)

† Differs from both CON and PVH ($p < .05$)

Table 4.

Macronutrient Intake (% Total kcal) Associated with the NE and 2DG Tests and Their Respective Saline Control Conditions (n = 9).

	NE Test		2DG Test	
Nutrient	Saline	Drug	Saline	Drug
Carbohydrate	61.8±2.9	55.9±3.8	56.9±4.1	62.8±1.9
Fat	19.4±3.3	26.8±3.4	24.9±4.6	18.2±2.2
Protein	18.9±0.4	18.1±0.4	18.2±0.6	19.0±0.3

Table 5.

Mean (+SEM) Body Weight (g) and Food Intake (Kcal) for the PVH-Lesioned (PVH) and Sham-Lesioned (CON) Groups Prior to Surgery (Preop) and Prior to Testing (Postop).

		Body Weight		Food Intake	
Group	N	Preop	Postop	Preop	Postop
PVH	5	564.6+24.6	558.8+26.2	99.6+3.4	96.5+7.3
CON	7	604.3+30.6	616.1+32.3	114.5+8.8	112.7+5.1

Figure Captions

Figure 1. (Experiment 1) Schematic representations of the largest PVH lesion (A), the most circumscribed PVH lesion (B), and the most effective knife cuts (C) (page 126). (Based on the atlas of Pellegrino, Pellegrino, and Cushman, 1979; AP level of each section indicated on left.)

Figure 2. (Experiment 1) Mean (±SEM) body weights for the various treatment conditions as a function of postoperative days.

Figure 3. (Experiment 2, Part 1) Mean (+SEM) norepinephrine-feeding score (g) before and after knife-cut surgery for the control (CON) and lateral-cut (LAT CUT) groups.

Figure 4. (Experiment 2) A: Photomicrograph illustrating the cannula placement and knife cuts of an animal in the lateral-cut group. B: Photomicrograph illustrating the cannula placement and knife cuts of an animal in the posterior-cut group. (Arrows indicate the knife cuts.)

Figure 5. (Experiment 2, Part 2) Mean (+SEM) norepinephrine-feeding score (g) before and after knife-cut surgery for the control (CON) and posterior coronal-cut (POST CUT) groups.

Figure 6. (Experiment 3) Mean (±SEM) norepinephrine-feeding score (g) for the control (CON), lateral-cut (LAT CUT) and posterior-cut (POST CUT) groups.

Figure 7. (Experiment 3) Schematic representation of the knife-cut and cannula placements in Experiment 3. The left panel represents the parasagittal cuts (LAT CUT) while the right panel represents the coronal cuts (POST CUT). [Based on Pellegrino et al. (1979) atlas; AP level of each section indicated by number in extreme right.]

Figure 8. (Experiment 4) A: Mean (±SEM) norepinephrine-feeding score (g) for the control (CON) and large lateral-cut (LAT CUT) groups. B: Schematic representation of the knife-cut and cannula placements; based on Pellegrino et al., (1979) atlas.

Figure 9. (Experiment 5, Part 1) Mean (±SEM) 3-hr intake (kcal) of the fat and sucrose diets following the deprivation, NE, and 2DG treatments and their respective saline (SAL) or no deprivation (NO DEP) control conditions.

Figure 10. (Experiment 5, Part 2) Mean (±SEM) 3-hr intake (kcal) of the fat and sucrose diets following clonidine (CLON) or saline (SAL).

Figure 11. (Experiment 6) Schematic representation of the cannula placements in the PVH, DMH, and LH groups. (Based on atlas of Pelligrino et al., 1979; AP level of each section indicated in right corner).

Figure 12. (Experiment 6) Mean (±SEM) 1-hr intake (kcal) of the fat and sucrose diets by the PVH, DMH, and LH groups following NE or saline (SAL).

Figure 13. (Experiment 6) Mean (±SEM) 4-hr cumulative intake (combined kcal from both test diets) by the PVH, DMH, and LH groups following the 2DG, 2DG+PHT, PHT, and Vehicle treatments.

Figure 14. (Experiment 6) Mean (±SEM) 4-hr intake (kcal) of the fat and sucrose diets by the PVH, DMH, and LH groups following the 2DG, 2DG+PHT, PHT, and Vehicle treatment conditions.

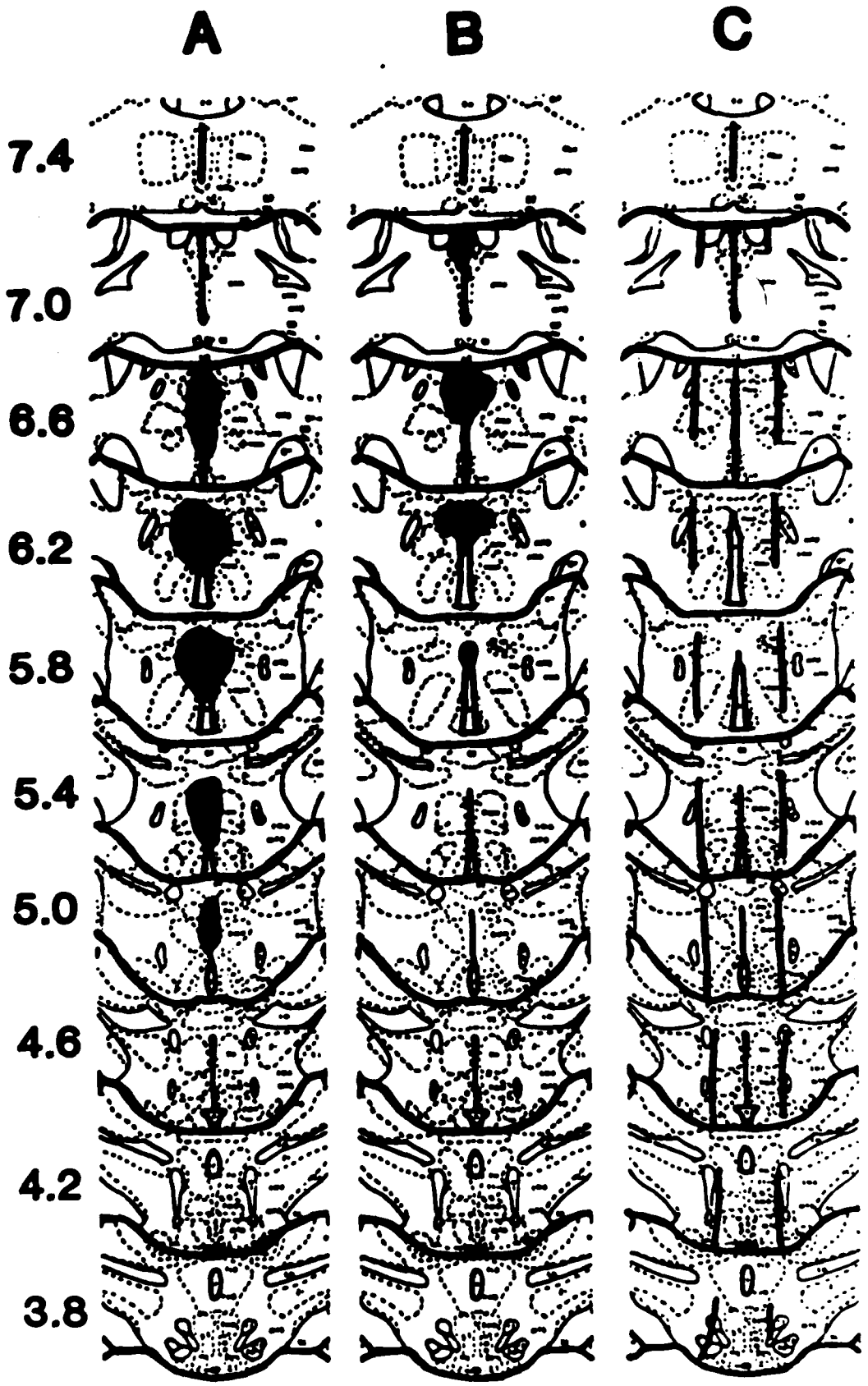
Figure 15. (Experiment 6) Mean (±SEM) 4-hr cumulative intake (combined kcal from both test diets) by the PVH, DMH, LH groups following the deprivation (DEP), deprivation+PHT (DEP+PHT), and no deprivation (NO DEP) conditions.

Figure 16. (Experiment 6) Mean (±SEM) 4-hr intkake (kcal) of the fat and sucrose diets by the PVH, DMH, and LH groups following the deprivation (DEP), deprivation+PHT (DEP+PHT), and no deprivation (NO DEP) treatment conditions.

Figure 17. (Experiment 7) Photomicrograph of a representative PVH-lesioned subject.

Figure 18. (Experiment 7) Mean (±SEM) 4-hr intake (kcal) of a Purina pellet diet by PVH-lesioned (PVH) and sham-lesioned (CON) animals following two doses of 2DG or the saline control conditions (SAL).

Figure 19. (General Discussion) Relationship of the PVH-lesion syndrome to the VMH-Lesion/MH-Cut syndrome.


A
B
C
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8

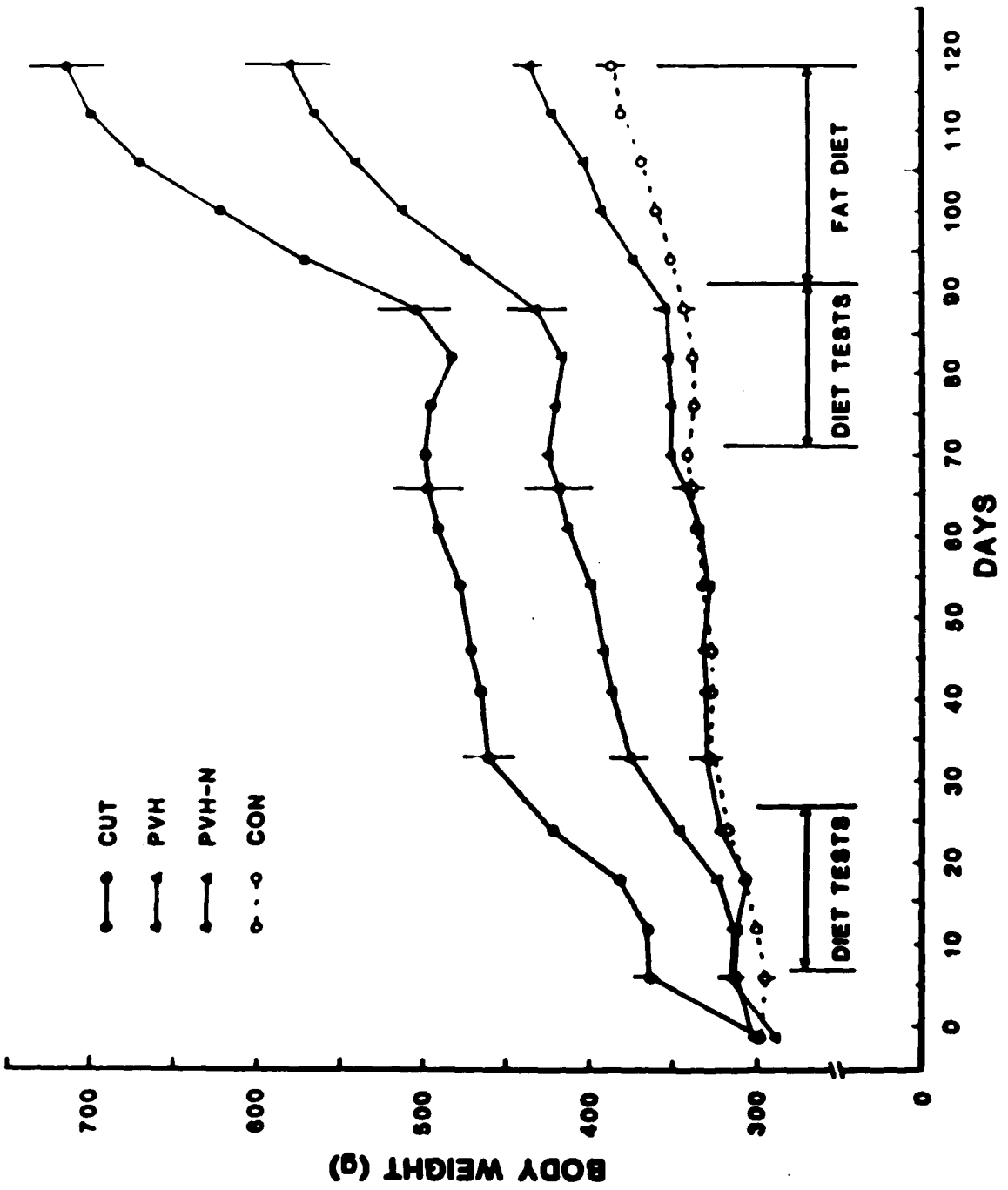

BODY WEIGHT (g)
700
600
500
400
300
0
10
20
30
40
50
60
70
80
90
100
110
120
DAYS
DIET TESTS
DIET TESTS
FAT DIET
CUT
PVH
PVH-N
CON

Figure 2

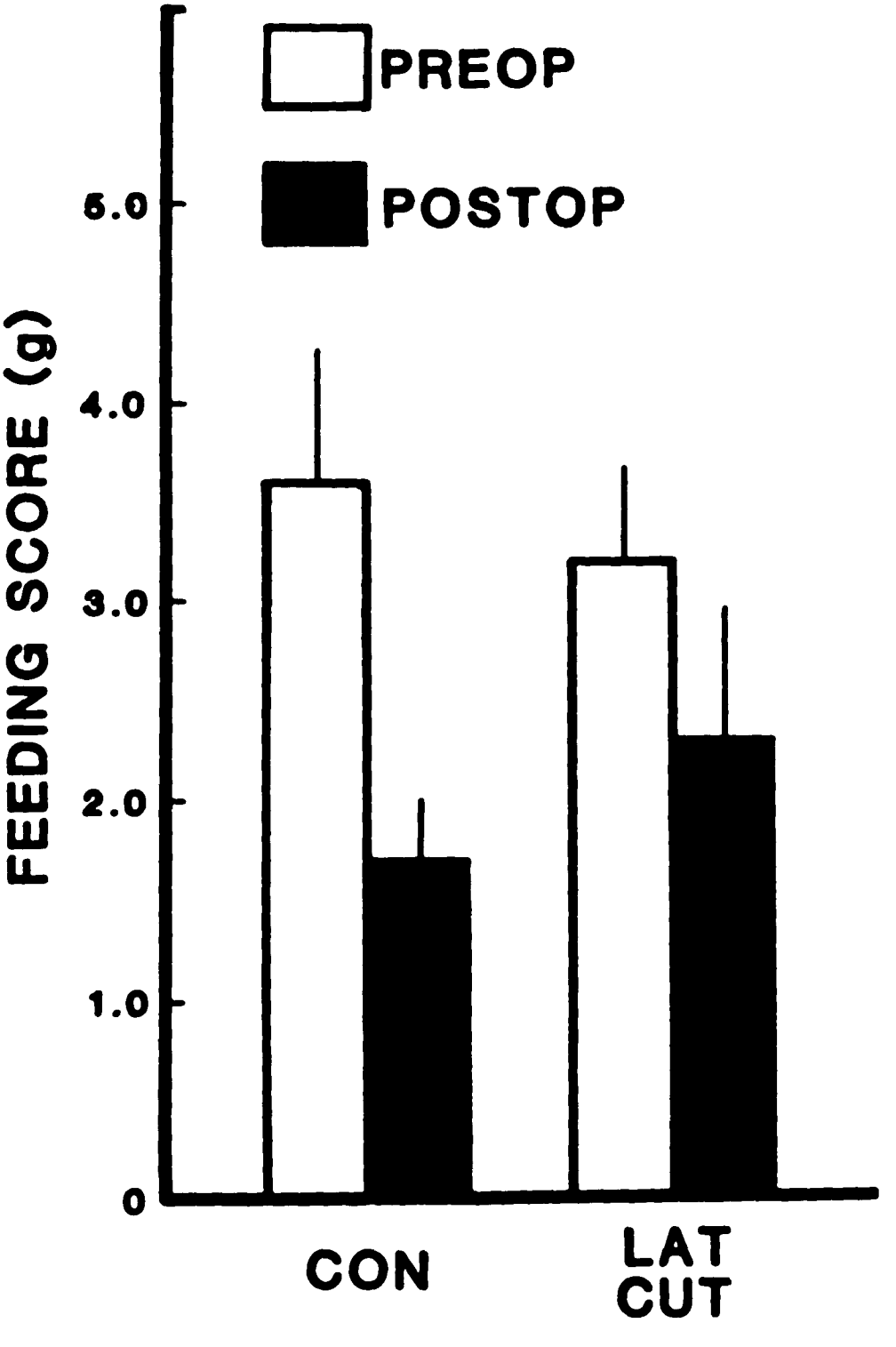


Figure 3

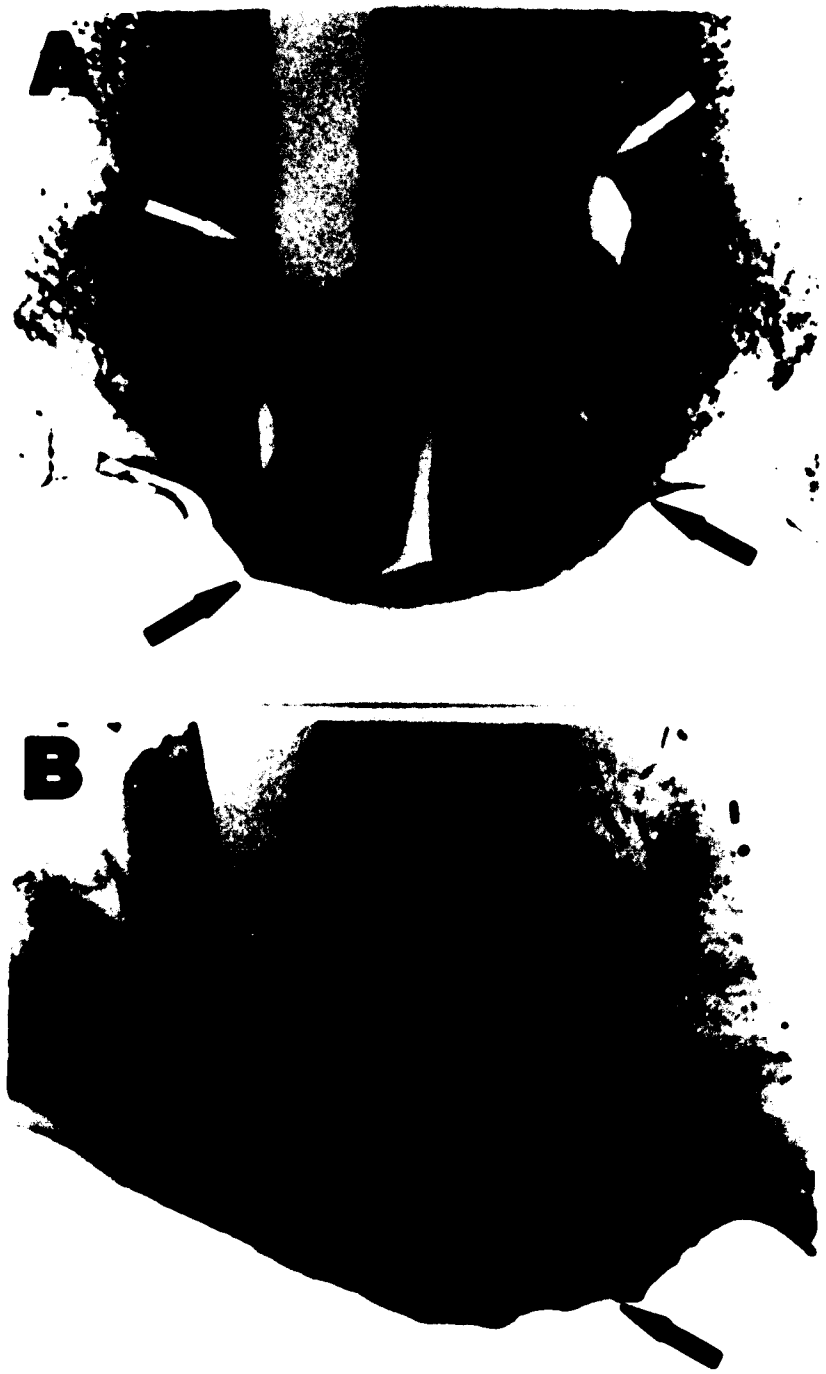


Figure 4

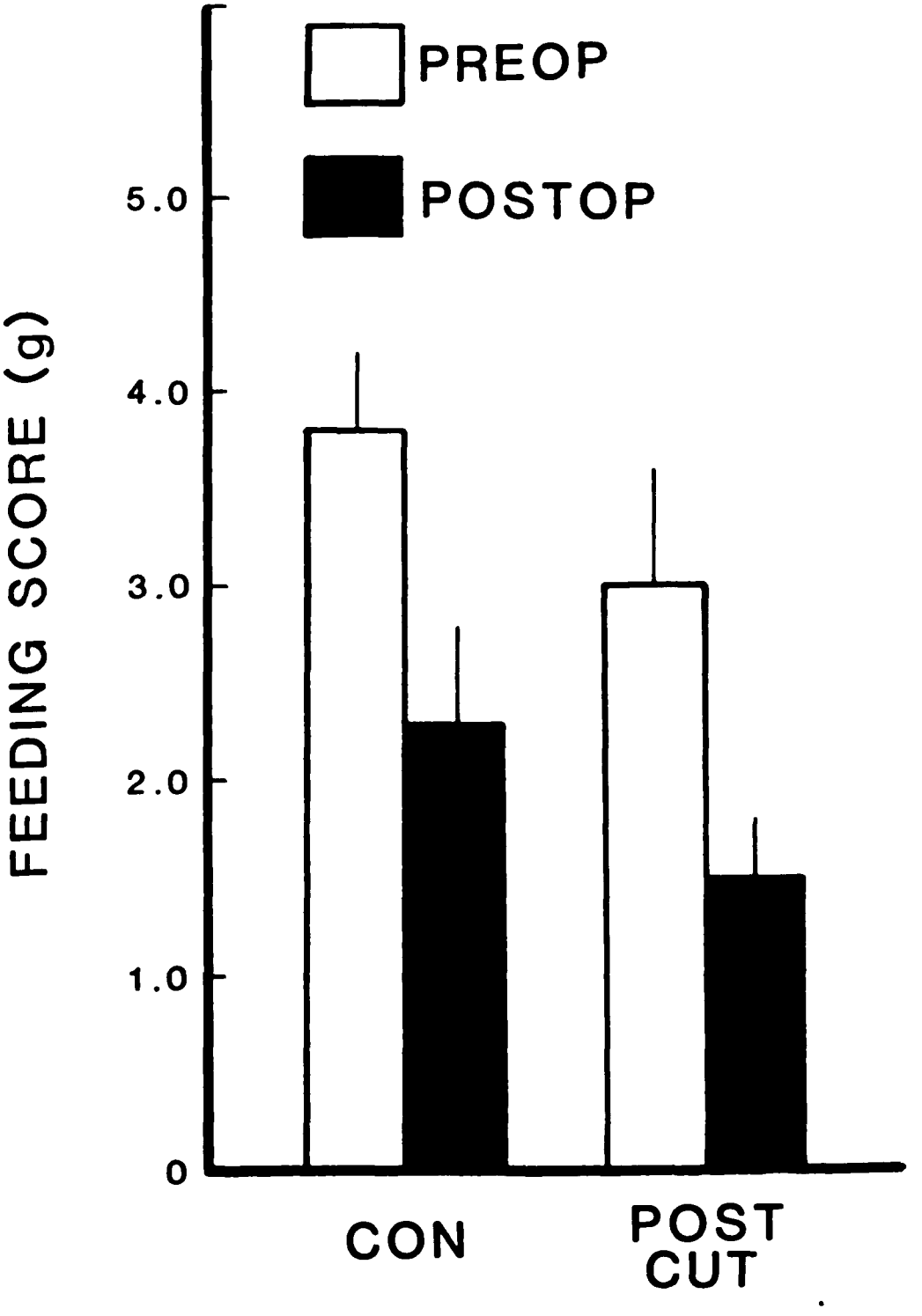
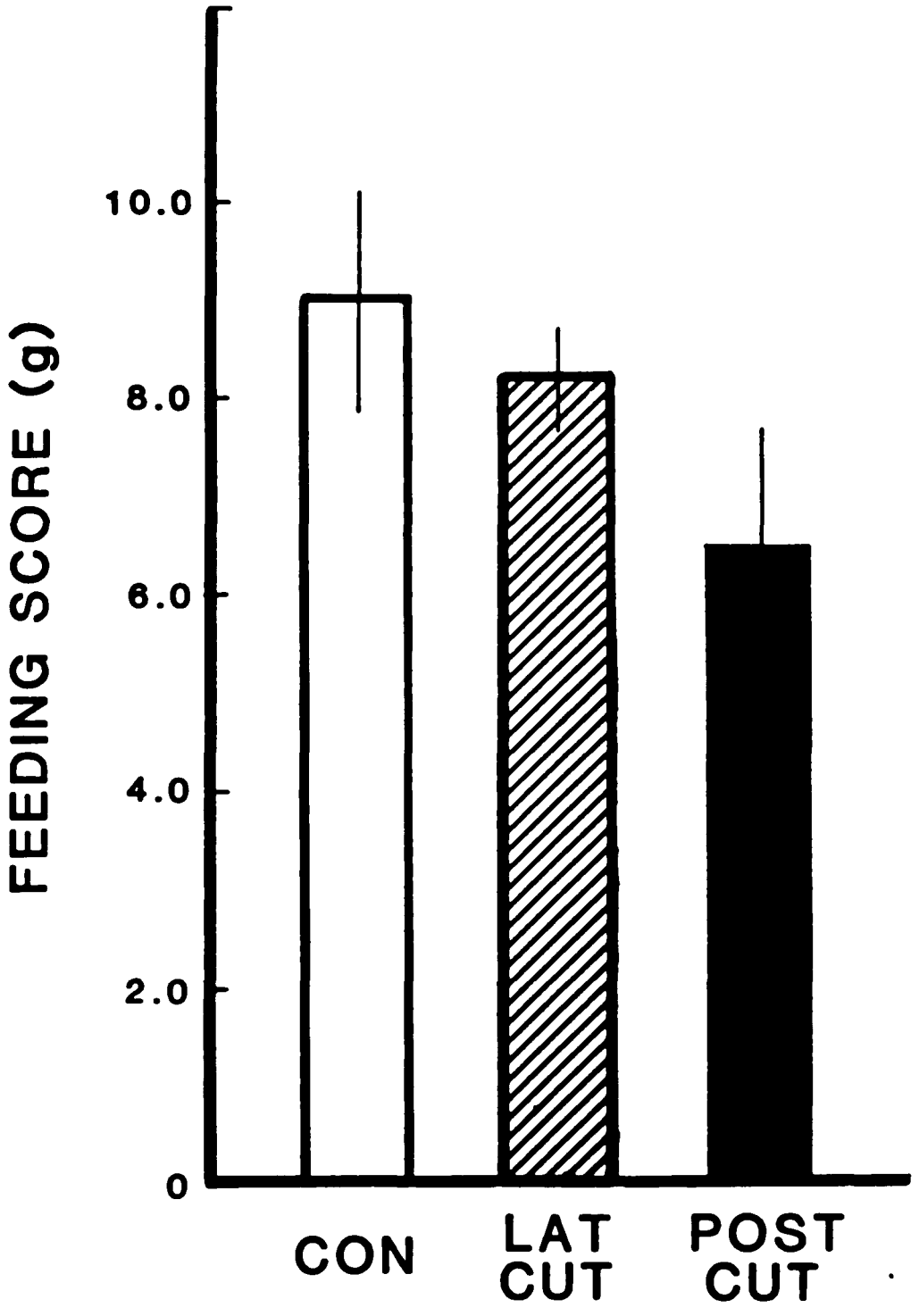


Figure 5



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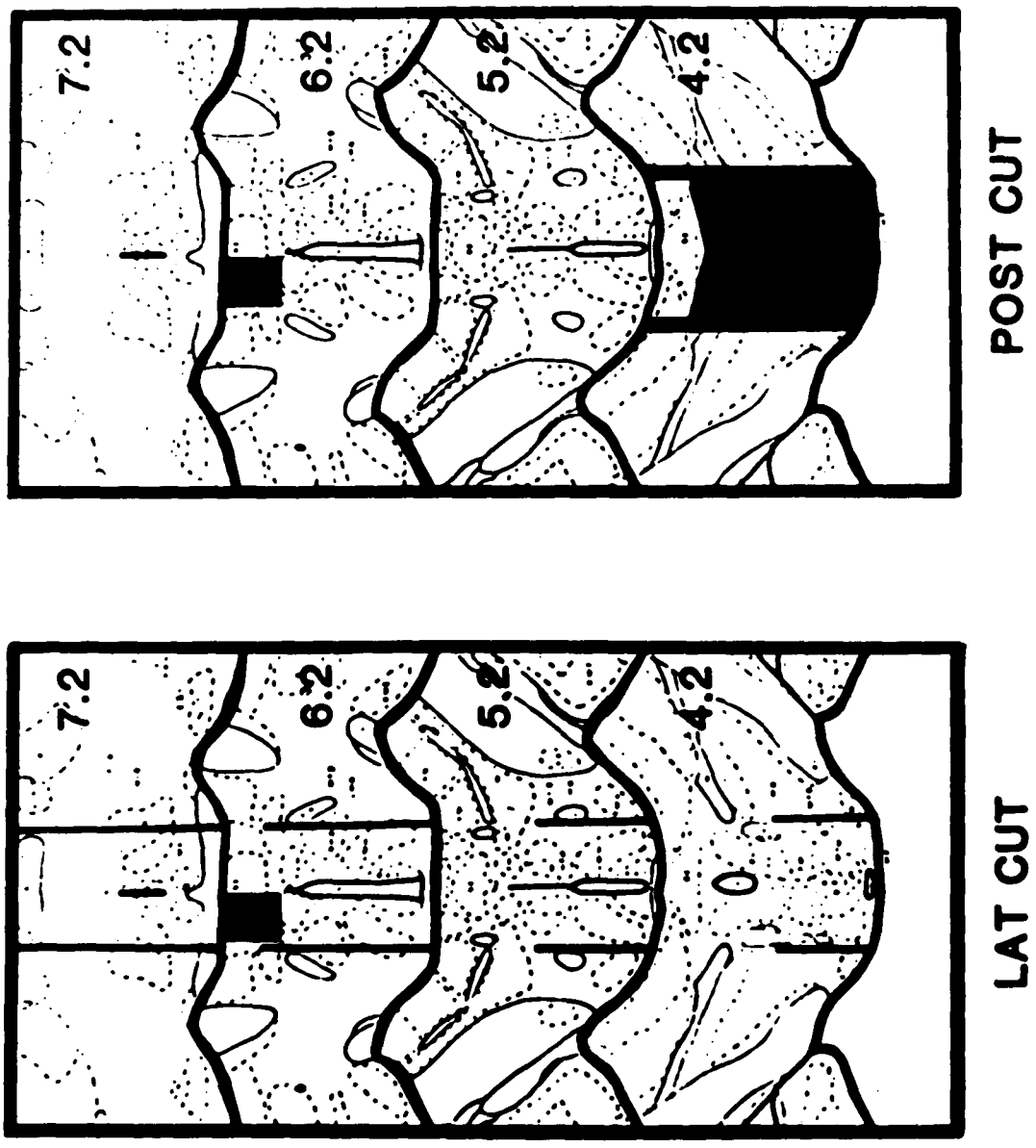

Figure 7

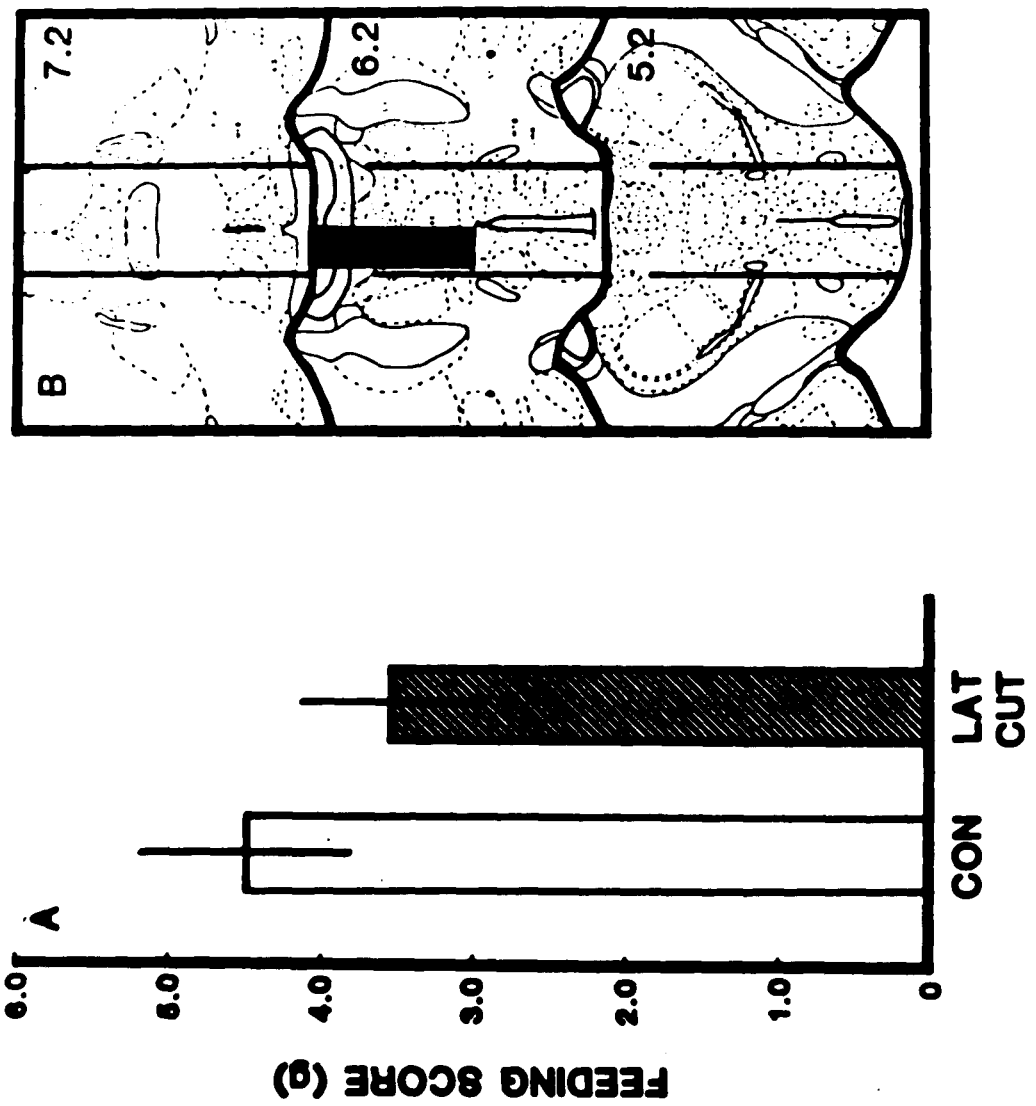

Figure 8

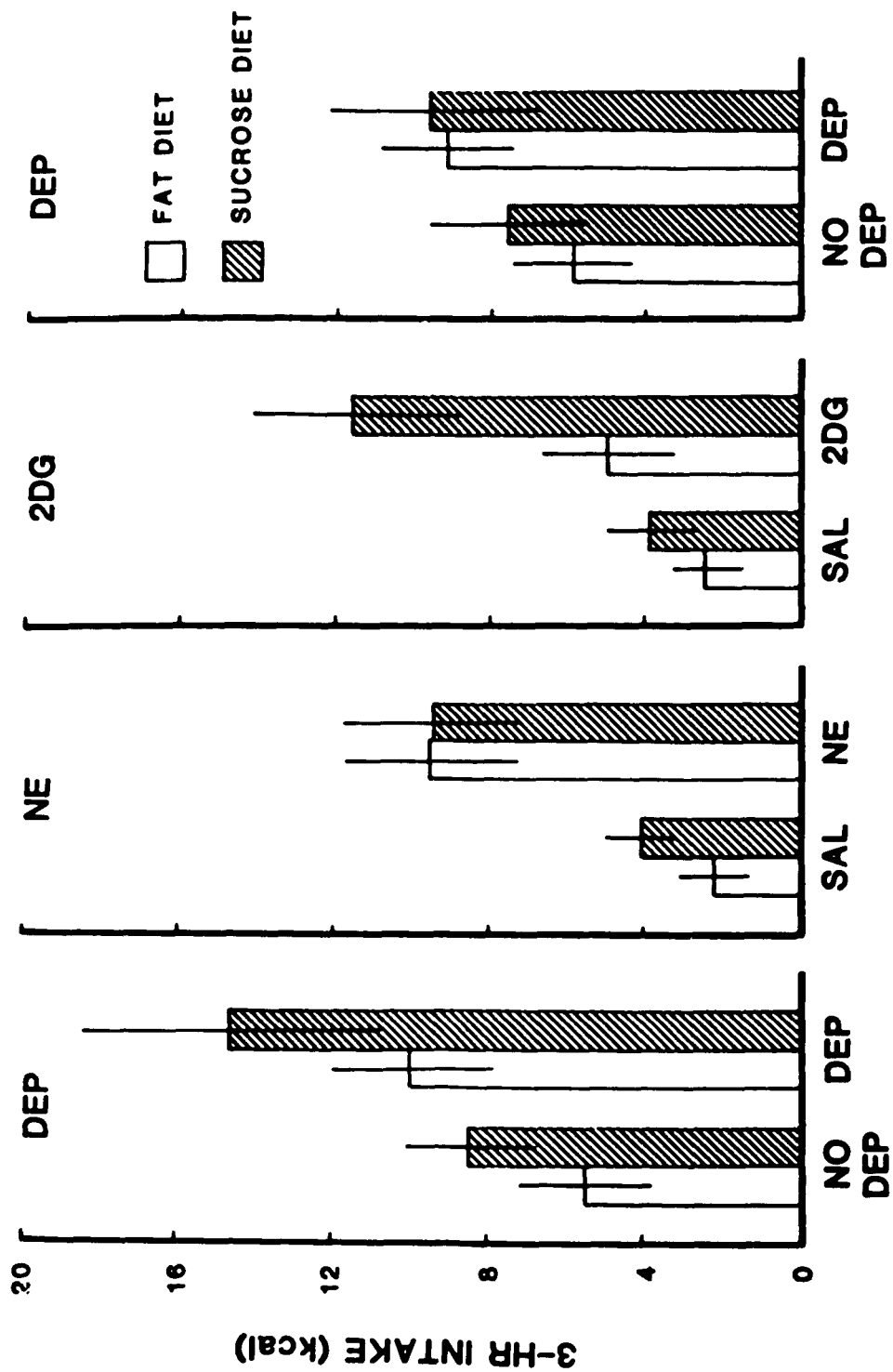
3-HR INTAKE (kcal)
20
16
12
8
4
0
DEP
NO DEP
NE
SAL
2DG
SAL
DEP
NO DEP
FAT DIET
SUCROSE DIET

Figure 9

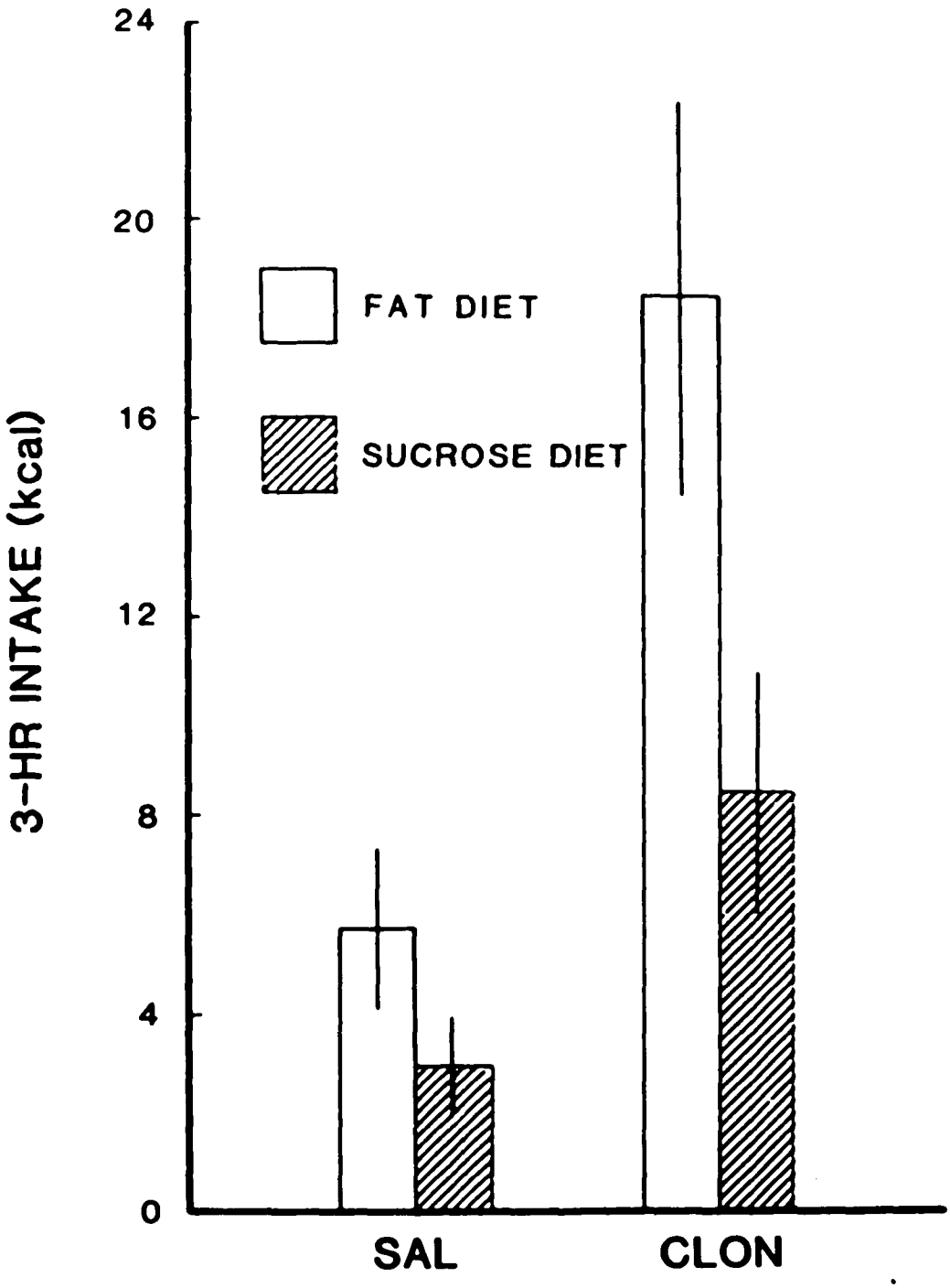

Figure 10

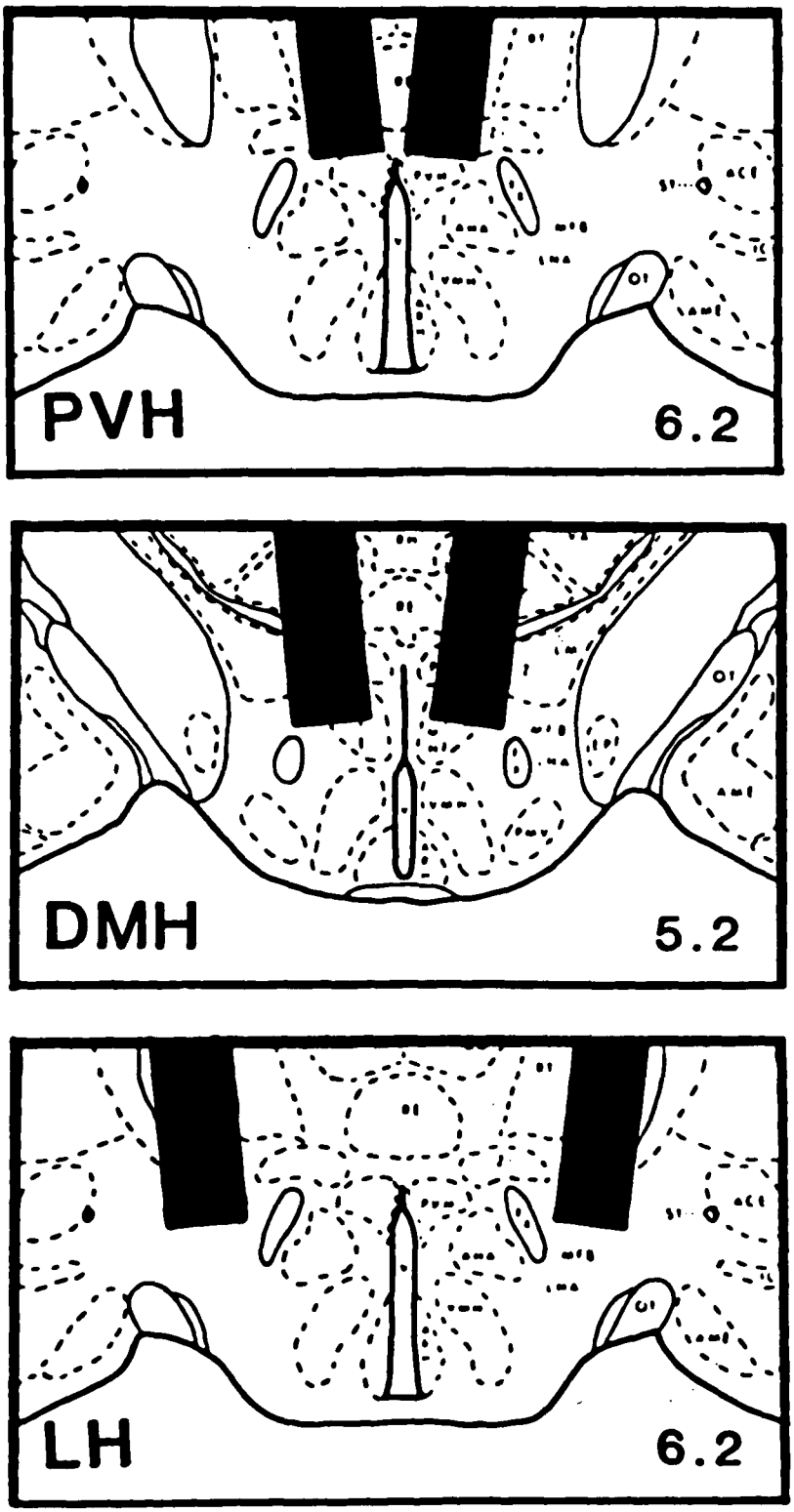

Figure 11

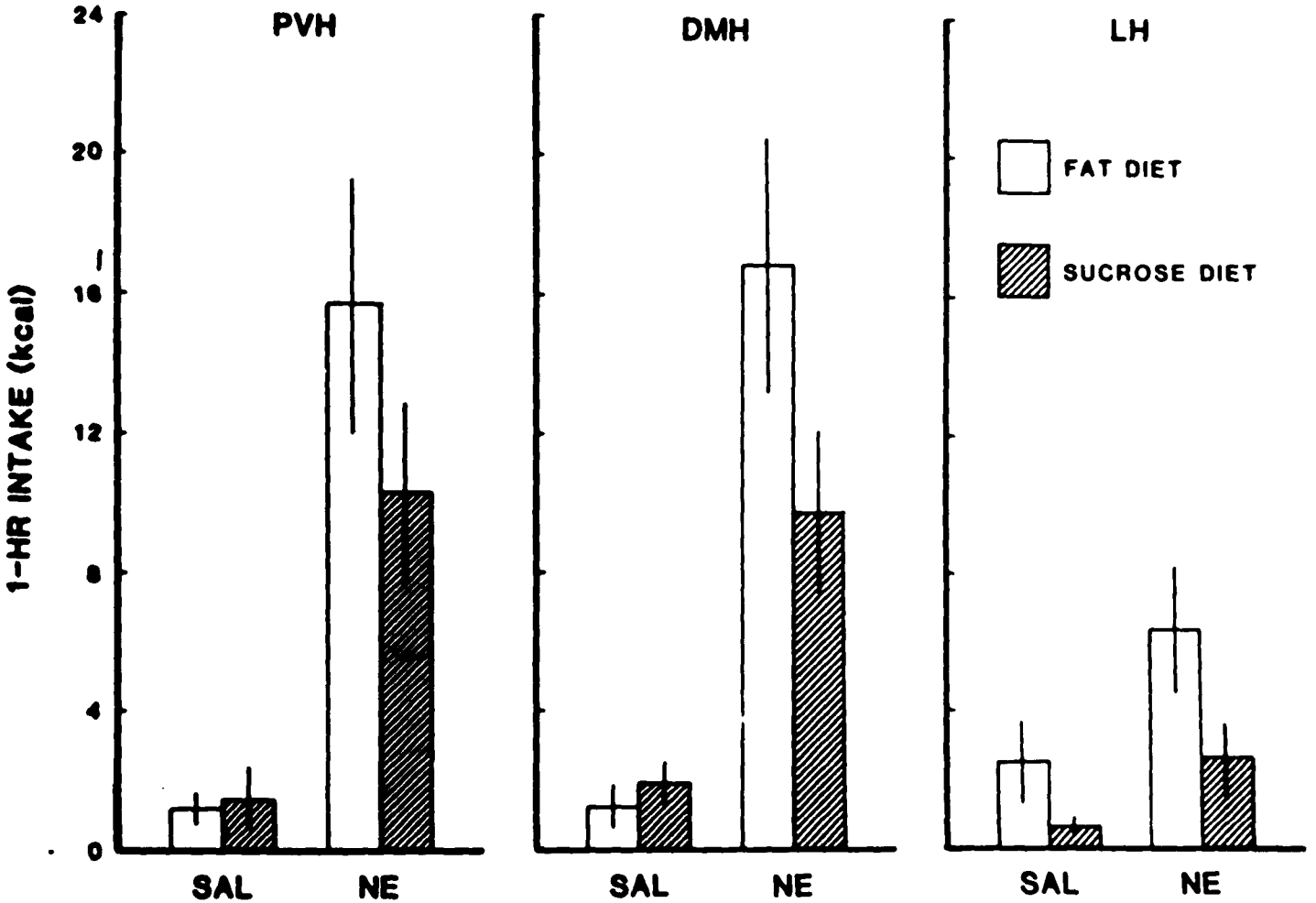
PVH
DMH
LH
1-HR INTAKE (kcal)
24
20
16
12
8
4
0
FAT DIET
SUCROSE DIET
SAL
NE
SAL
NE
SAL
NE

Figure 12

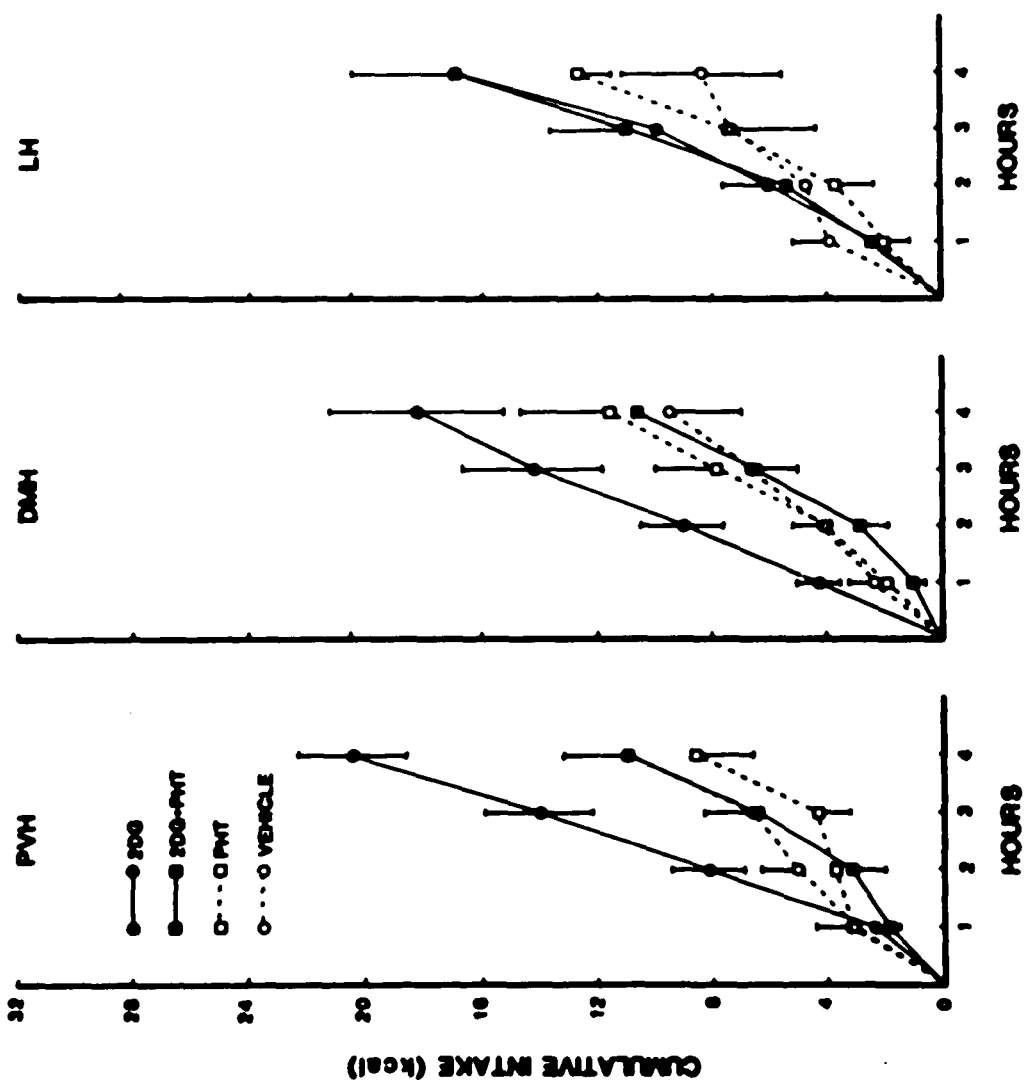
PVH
DMH
LH
HOURS
CUMULATIVE INTAKE (kcal)
0
4
8
12
16
20
24
28
32
1
2
3
4
2DG
2DG+PNT
PNT
VEHICLE

Figure 13

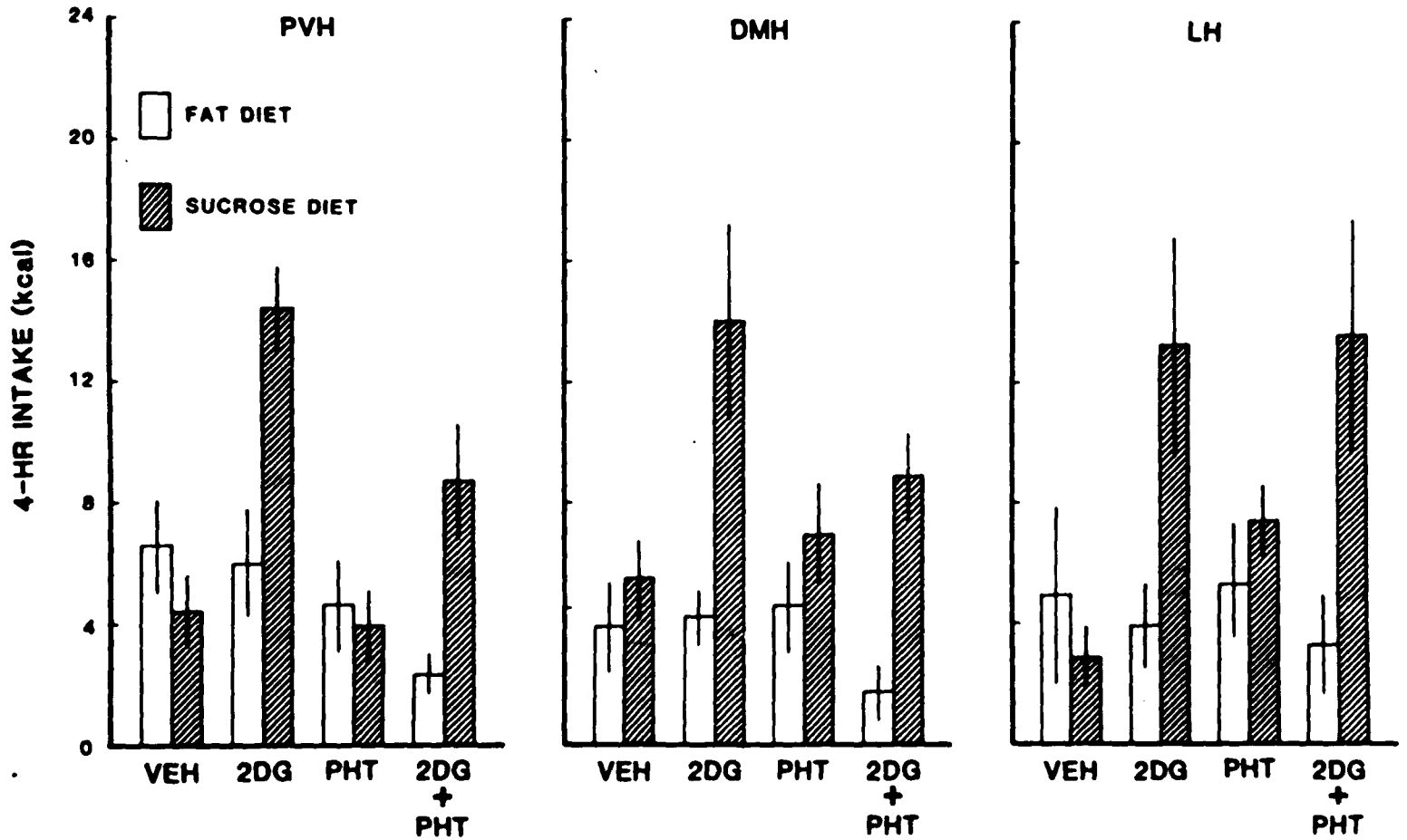
PVH
DMH
LH
FAT DIET
SUCROSE DIET
4-HR INTAKE (kcal)
0
4
8
12
16
20
24
VEH
2DG
PHT
2DG + PHT

Figure 14

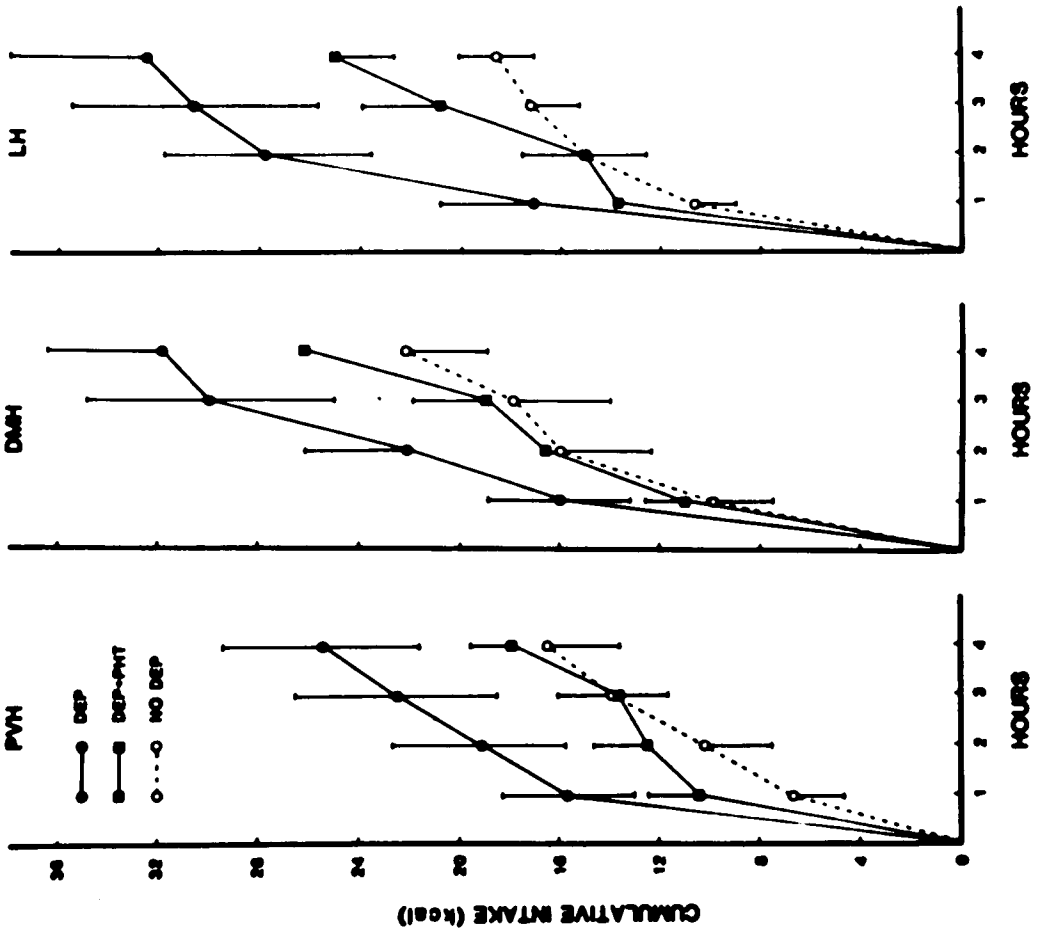
LH
DMH
PVH
DEP
DEP-PHT
NO DEP
HOURS
HOURS
HOURS
CUMULATIVE INTAKE (kcal)

Figure 15

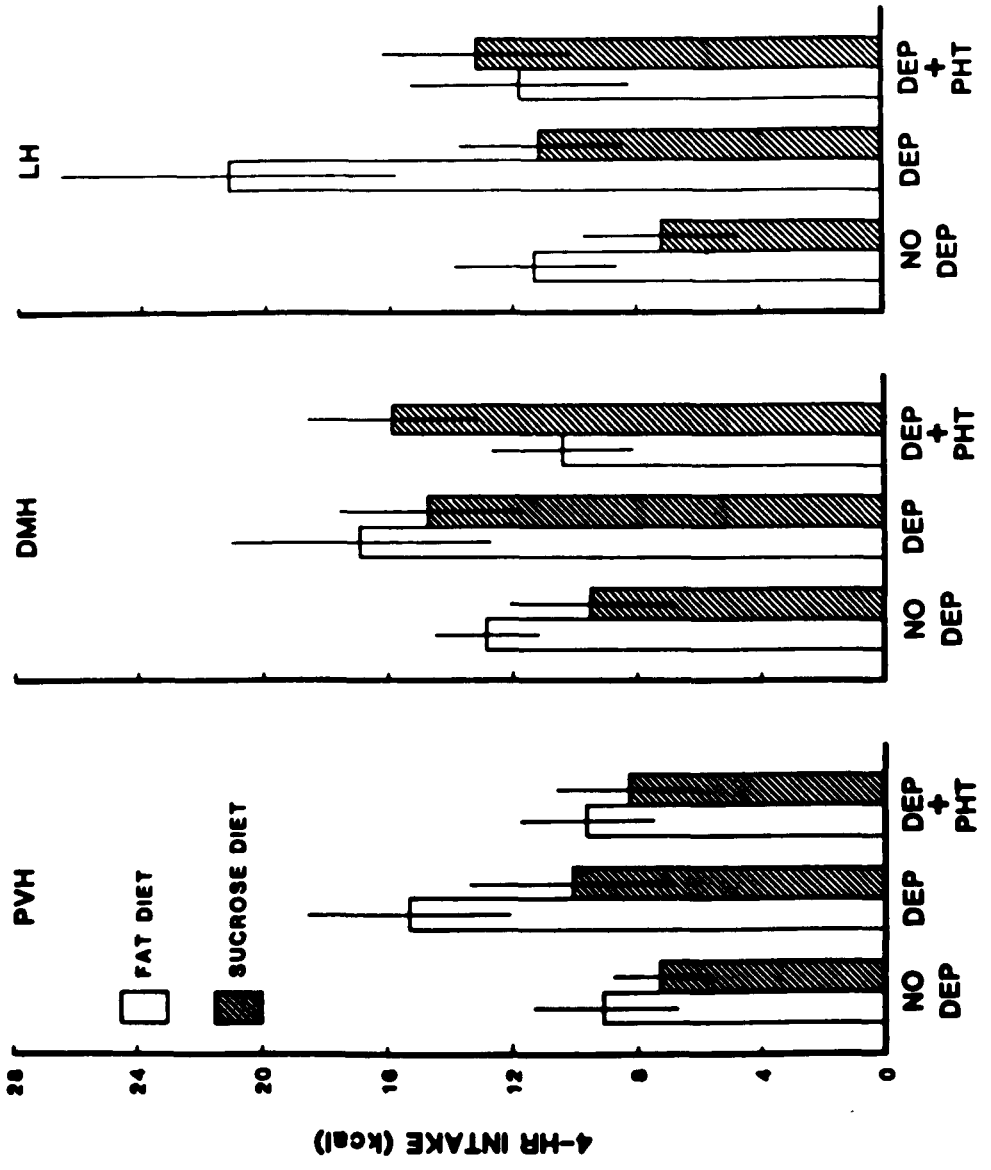
4-HR INTAKE (kcal)
0
4
8
12
16
20
24
28
PVH
DMH
LH
FAT DIET
SUCROSE DIET
NO DEP
DEP
DEP + PHT

Figure 16

Figure 17

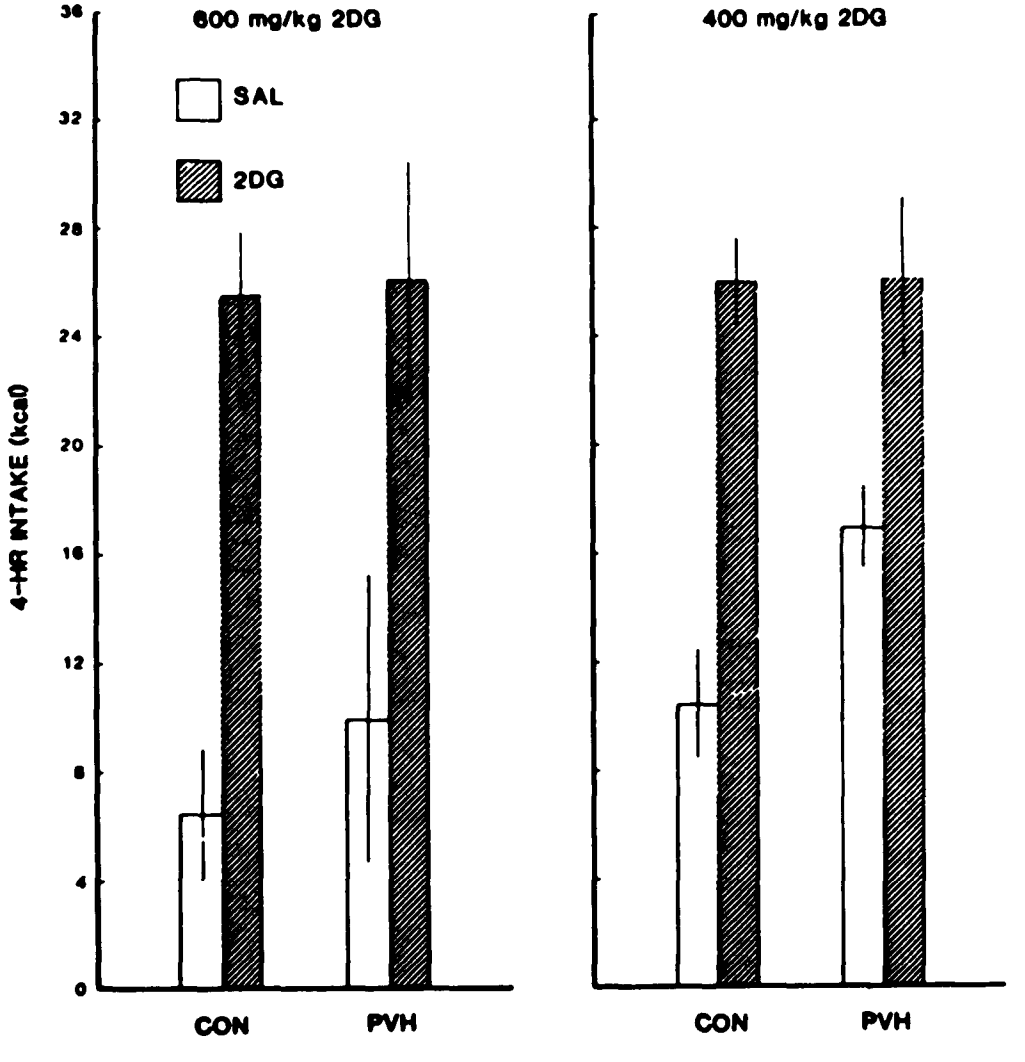
600 mg/kg 2DG
400 mg/kg 2DG
SAL
2DG
4-HR INTAKE (kcal)
36
32
28
24
20
16
12
8
4
0
CON
PVH
CON
PVH

Figure 18

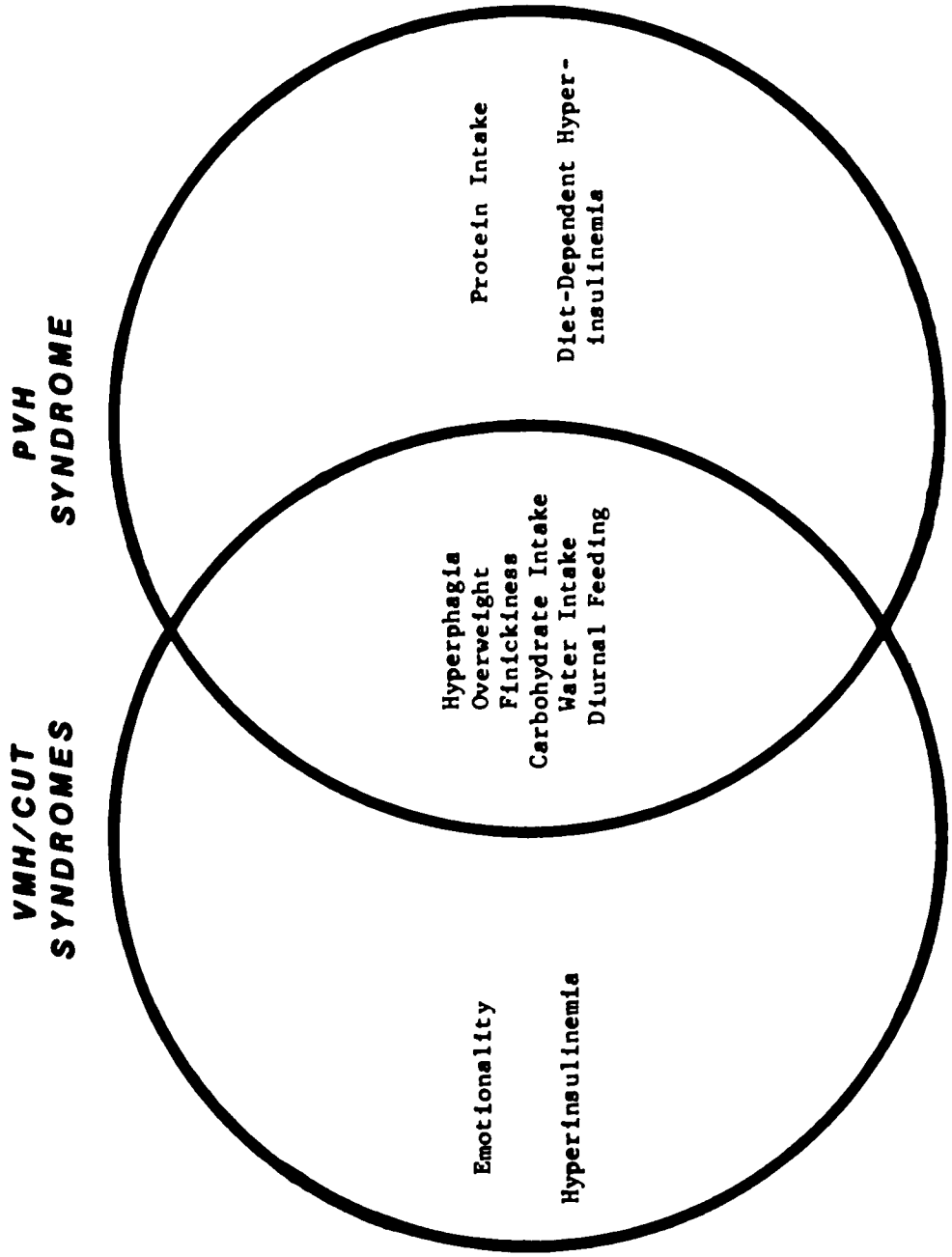
VMH/CUT SYNDROMES
PVH SYNDROME
Emotionality
Hyperinsullinemia
Hyperphagia
Overweight
Finickiness
Carbohydrate Intake
Water Intake
Diurnal Feeding
Protein Intake
Diet-Dependent Hyper-insullnemia

Figure 19

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