THE FOREBRAIN TASTE SYSTEM : AN EXAMINATION OF THE EFFECTS OF STRIA TERMINALIS KNIFE-CUTS ON FEEDING BEHAVIOUR

BY

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ABSTRACT

Studies examining the etiology of obesity often focus on the relationship between taste, overeating, and the development of obesity. One animal model often used to study obesity, rats with lesions of the ventromedial hypothalamus (VMH), is popular because the degree of overeating and obesity in that animal is particularly sensitive to the taste qualities of the food the rat eats. The exaggerated sensitivity to taste in VMH rats is termed "finickiness" and is thought to contribute to the hyperphagia and obesity of this animal. The present thesis sought to identify the anatomical locus mediating finickiness. The specific hypothesis examined was that interruption of the stria terminalis (ST), a prominent component of the forebrain taste system and a fibre system destroyed in the typical VMH lesion, produces the finickiness characteristic of the VMH syndrome.

A sham feeding paradigm was used to assess finickiness, because sham feeding allows one to measure the extent to which palatability drives feeding. I found that using sham feeding as an index, rats with ST knife-cuts were as finicky as VMH lesioned rats when consuming either sweet sucrose solutions or quinine-adulterated sucrose solutions. However, the degree of finickiness in rats with combined VMH and ST damage was equivalent to the additive effects of VMH and ST damage alone. These results lead to the conclusion

that ST damage was not the locus of VMH lesion-induced finickiness.

Nevertheless, ST knife-cuts did alter feeding; specifically ST knife-cuts produced rats which showed as much of a disturbance of sham feeding as VMH rats. Experiments 2 and 3 investigated whether the overeating of ST animals would generalize to situations when ST rats real feed. Results showed that ST rats ate normal amounts when real feeding, even though VMH rats remained hyperphagic. Thus postingestive signals from the gut, which are activated during real feeding, were sufficient to block or remove the feeding disturbance produced by interruption of the ST. However, signals from food in the gut were insufficient to block the feeding disturbance produced by VMH lesions.

Two more experiments were conducted to determine why the hyperphagia of the ST rat during sham feeding did not generalize to real feeding. Since sham feeding may reflect motivation to eat, it was suggested that the hyperphagia of ST rats when sham feeding may reflect an increased motivation. Therefore, ST rats, VMH rats and controls were tested in a conditioned feeding procedure which provides a direct measure of food motivation. Results indicated that neither ST nor VMH rats demonstrated an increased motivation to eat.

Experiment 5 assessed the contribution of postingestive events from the stomach to the behavioural effects noted with ST and VMH damage. Results showed that ST rats emptied

a liquid meal from the stomach at the same rate as controls. However, the rate of gastric emptying was accelerated in VMH rats. It was argued that the difference in the rates at which food emptied from the stomach could account for the differences between ST and VMH rats when real feeding in spite the similarities of their behaviour during sham feeding.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

TABLE PAGE

Chapter I. INTRODUCTION

A dominant perspective in the study of obesity research has been that overeating is a major cause of obesity (Spitzer & Rodin, 1981). Since the amount eaten is controlled strongly by the palatability of the diet, a prevalent view has been that the overeating seen in obese populations results, at least in part, from an exaggerated reactivity to the flavour of foods, especially sweet (Schachter & Rodin, 1974; Wurtman, Wurtman, Growdon & Henry, 1981; Yudkin, 1973). Studies of overweight and obese humans show a significant interaction between body weight and reactivity to the palatability of foods. While, typically, increases in palatability result in increased consumption, the increased consumption associated with more palatable foods is exaggerated in overweight or obese subjects compared to normal-weight subjects (Hill & McCutcheon, 1975; Nisbett, 1968; Price & Grinker, 1973; Rodin, Slochower, & Fleming, 1977). Spitzer & Rodin (1981, p. 306), in an exhaustive review of the literature examining the interaction between taste reactivity and obesity, concluded a food's palatability has "... a greater effect on its

ingestion for overweight subjects than for normal weight subjects".

Investigations of the mechanisms by which food palatability alters food intake and, specifically, how these mechanisms might be disrupted in obesity, have often depended on studies using animal models of obesity. The animal model of obesity exploited widely has been rats with lesions of the ventromedial hypothalamus (VMH) because damage to the VMH reliably and rapidly produces a dramatic elevation of feeding and body weight (for reviews, see Powley, 1977; Sclafani & Kirchgessner, 1986).

Lesions of the ventromedial hypothalamus produce a wide range of metabolic and behavioural changes in addition to changes in taste reactivity. VMH rats develop an obesity (Han & Liu, 1966; Hirsch & Han, 1969; Inoue & Bray, 1977; Weingarten, Chang & McDonald, 1985), a hyperinsulinemia (Cox & Powley, 1981; Hales & Kennedy, 1964; Weingarten et al., 1985), and a host of physiological changes associated with obesity such as gastric hypersecretion (Chikamori, Fukushima, Yashamita, Sayto, Nishimura & Mori, 1983; Cox & Powley, 1981; Ridley & Brooks, 1965; Weingarten & Powley, 1980a). However, the most outstanding behavioural change following VMH lesioning is a profound increase in food intake and body weight (Brobeck, Tepperman & Long, 1943; Corbit & Stellar, 1964; Gold, 1970).

It is these two later symptoms, hyperphagia and obesity, which have made the VMH animal a popular and useful animal model of human obesity. As Nisbett (1972, p. 443) indicated, "Virtually every aspect of the behavioral parallels between obese and hungry

humans seems also to have a parallel to the behavior of the rat with ventromedial hypothalamus lesions,".

The VMH rat is particularly well suited for studies of the relationship between overeating and taste reactivity since both the VMH rat and obese human demonstrate qualitatively similar overreactivity to the taste qualities of food (Schachter, 1971; Schachter & Rodin, 1974). An overreactivity to the taste of food is one of the defining behavioural characteristics of the VMH syndrome and is viewed as central to the overeating and obesity seen in these rats. VMH rats overeat and become most obese only when they have access to palatable foods (Brobeck et al., 1943; Carlisle & Stellar, 1969; Corbit & Stellar, 1964; Kramer & Gold, 1979; Levison, Former & Vance, 1973; Teitelbaum, 1955). In contrast, maintaining VMH rats on unpalatable foods can block completely overeating and excessive weight gain (Ferguson & Keesey, 1975; Franklin & Herberg, 1974; Levison, Former & Vance, 1973). The initial question guiding this thesis research was analysis of the brain structures involved in VMH lesion-induced changes in taste reactivity, and the effect of changes in taste reactivity on intake. First, the concept of taste reactivity changes in VMH-lesion rats, and issues surrounding this phenomenon, are reviewed in detail.

1.1. FINICKINESS: Taste Reactivity in VMH Lesion Rats

The term "finickiness" was introduced by Teitelbaum to capture what he perceived to be the essence of the disturbance of feeding in VMH rats. He suggested that the amount eaten by VMH rats was modulated disproportionately by sensory properties of the food being consumed, such as its smell, taste or texture (Teitelbaum, 1955). He suggested use of the term "finickiness" to label the exaggerated response to the sensory aspects of a food. Other results were congenial with Teitelbaum's idea. They showed that hyperphagia and obesity developed rapidly when VMH rats were maintained on palatable diets, but that these same symptoms were not manifest when the diet was unpalatable. Examples of palatable diets promoting the expression of hyperphagia were high fat diets (Brobeck, Tepperman & Long, 1943; Carlisle & Stellar, 1969; Corbit & Stellar, 1964; Kramer & Gold, 1979), saccharin flavoured diets (Levison, Former & Vance, 1973), dextrose added to powdered chow (Graff & Stellar, 1962; Teitelbaum, 1955), and sucrose solutions (Beatty, 1973; Sclafani & Xenakis, 1981; Weingarten, 1982; Weingarten, et al., 1985). Unpalatable diets were those adulterated with quinine (Ferguson & Keesey, 1975; Franklin & Herberg, 1974) or diluted with kaolin (Levison, Former & Vance, 1973)).

Two central questions have emerged from the original concept of finickiness. First, the idea that VMH rats overreact to both positive and negative sensory attributes of a food, i.e. that finickiness is bidirectional, has been questioned (e.g. Ferguson

& Keesey, 1975; Franklin & Herberg, 1974; Weingarten et al., 1983). Second, it is unclear whether the exaggerated eating response characteristics of finickiness can be attributed strictly to the sensory aspects of food or whether some other factor also contributes to the dysfunction. These issues are discussed below.

1.1.1. Is Finickiness Bidirectional?

Finickiness was defined originally as a feeding pattern that differed significantly from that of controls fed an identical diet, whether the difference was an increase or a decrease in amount eaten (see Peters & Gunion, 1980). The majority of early work investigating intake adjustments following diet manipulations focused on negative finickiness, i.e. the reduced intake by VMH rats in response to manipulations which made foods less palatable. The initial results were dramatic. When the maintenance diet of VMH rats was adulterated with quinine, VMH-lesioned animals were reported to reduce their intake to a greater extent than did controls and, consequently, VMH animals lost weight more rapidly than did controls (Graff & Stellar, 1962; Teitelbaum, 1955). However, there were two fundamental confounds in these studies.

First, these studies measured intake changes of VMH rats when the diet was switched from a palatable to an unpalatable one. While the amount of intake decrement observed in VMH rats was greater than that of controls, this probably reflected the VMH

rat's excessive eating of the palatable diet, not an enhanced rejection of the unpalatable diet (Weingarten, Chang and Jarvie, 1983).

The second confound was that in many early studies of finickiness, VMH rats weighed more than controls. It is now recognized that obesity can be a major confound in the negative finickiness literature. For example, Franklin & Herberg (1974) found that obese VMH rats initially lost weight more rapidly than controls on a quinine-adulterated diet. However, the weights of VMH rats never fell below those of controls. Rather, VMH-lesion rats came to stabilize and defend their weights at control levels. VMH rats tested at control body weights showed no greater rejection of the quinine adulterated diet than normal rats. Franklin & Herberg (1974) concluded that exaggerated rejection of unpalatable foods did not result from VMH destruction per se, but rather from obesity. This conclusion has been reinforced many times (Ferguson & Keesey, 1975; Gunion & Peters, 1979; Nachman, 1967; Peters & Gunion, 1980; Peters, Luttmers, Gunion & Wellman, 1978; Sclafani & Kluge, 1974; Sclafani, Springer & Kluge, 1976). Thus, negative finickiness appears to develop as a consequence of obesity, not from VMH damage itself. Given this conclusion, it is not surprising that other rat obesity models, e.g. the genetically obese Zucker fatty rat, and rats made obese by exposure to a cafeteria diet (Sclafani & Springer, 1976), also demonstrate negative finickiness.

On the other hand, positive finickiness, the disproportionate reactivity to palatable foods in VMH rats, appears to result directly from the brain damage. Positive finickiness manifests itself immediately post-surgery and, most importantly, even in VMH rats at normal weights (Beatty, 1973; Carlisle & Stellar, 1969; Corbit & Stellar, 1964; Kramer & Gold, 1979; Sclafani & Xenakis, 1981; Weingarten et al., 1985).

1.1.2. Does Finickiness Represent A Sensory Disturbance?

VMH lesion-induced finickiness was conceived originally as a disturbance of taste processing. However, the initial demonstrations leading to this conclusion incorporated a non-trivial confound. The diet manipulations that were used to change the taste of the food also changed the postingestional consequences of the food. For instance, the procedure of adding fat or sucrose to increase the palatability of food also made the diet more energetically dense. Therefore, intake changes following these manipulations could have been due strictly to changes in the food's postingestional consequences (Ramirez, Tordoff & Friedman, 1989).

Various strategies were employed in efforts to resolve whether the intake adjustments used to detect finickiness were due to the altered postingestional or taste characteristics of the food. For example, diet manipulations were made which changed a food's sensory properties but were presumed not to alter the food's postingestional events, e.g. changing diet texture or addition of

non-nutritive adulterants. Corbit & Stellar (1964) showed that VMH rats ate normal amounts of powdered Purina Rat Chow but became hyperphagic when the same food was presented in pellet form. Levison, Former & Vance (1973) added a non-nutritive sweetener, saccharin, to a maintenance diet and obtained results similar to those of Corbit & Stellar (1964). Carlisle & Stellar (1969) demonstrated that the addition of an isoenergetic oil to the diet (which produced no alteration in energy density and so, it was presumed, no alteration in postingestive consequences) also produced a disproportionate increase in consumption in VMH rats compared to controls. However, in all these studies, food did enter the gut and a possible contribution of postingestional events remains.

An alternative strategy to eliminate the possibility that intake adjustments reflect postingestional events was to use a technique which isolated the sensory properties of food. Sham feeding is such a technique. To allow sham feeding, animals are implanted with a gastric cannula which when open, allows liquid diets to drain freely from the stomach (Weingarten & Powley, 1980b). Thus, the sham feeding animal experiences the taste but almost no postingestive consequences of the food. Therefore, intake in sham feeding animals is driven primarily by the sensory properties of the diet. Indeed, sham feeding has been used to isolate the influence of palatability on intake in the absence of postingestional effects (Mook, 1963; Weingarten & Watson, 1982; Young, Gibbs, Antin, Holt & Smith, 1977).

Sham feeding was also used to re-examine positive finickiness in VMH rats. [Sham feeding studies also confirmed that negative finickiness was secondary to the obesity in the VMH rat.] Weingarten (1982) allowed both VMH rats and controls to sham feed sucrose solutions of varying concentrations. VMH rats maintained at control weights sham fed no more 6% sucrose than controls. However, as sucrose concentration increased, VMH rats displayed disproportionately large increases in the amount sham fed compared to controls (Weingarten, 1982; Weingarten et al. 1985). Since sham feeding isolates the effects of taste, and since VMH rats were tested at normal weights, Weingarten (1982) argued that the disproportionate increase in sham intake reflected a lesion-induced change in the ability of taste to drive ingestion, i.e. a confirmation of a direct sensory-based finickiness after VMH lesions.

Cox & Smith (1986) also used sham feeding to study VMH finickiness. They showed that VMH rats sham fed more of a sweet milk diet than did controls. Cox & Smith (1986) also measured intake under real feeding[1] conditions and thus were able to compare intake changes when rats switched from real to sham feeding. They found that the difference between sham and real feeding was greater in VMH rats than controls suggesting that "such exaggerated sham feeding is specific to the VMH syndrome, which is consistent with the proposal that a disturbance of orosensory reactivity underlies VMH hyperphagia" (p. 59).

1. All eating real, except where noted.

1.2. RELATIONSHIP BETWEEN TASTE REACTIVITY, HYPERPHAGIA AND BODY WEIGHT

Theorists have differed on how they conceptualized the relationship among taste reactivity, hyperphagia, and weight gain in the VMH syndrome. One of the earliest views, that of Broebeck, Tepperman & Long (1943), suggested that the weight gain and obesity of VMH rats resulted from overeating, which was the primary effect produced by the lesion, "...the relationship is one of cause and effect - that is, food intake determines weight gain," (p. 836). For Brobeck, Tepperman & Long, taste reactivity was the prime factor governing overeating because they also observed that the more palatable the food, the more VMH rats ate and the more rapidly they gained weight.

Teitelbaum's (1955) view of the relationship between taste reactivity, hyperphagia and weight gain was similar to Brobeck et al. (1943). Teitelbaum proposed that VMH lesion-induced hyperphagia resulted from the ability of palatable food to drive feeding and that this hyperphagia led, in turn, to obesity. Schachter & Rodin (1974), however, argued that VMH lesions produced a generalized hyperreactivity to sensory events, not necessarily only taste.

While all these views regard the enhanced taste reactivity as underlying hyperphagia and obesity, no explanation of <u>why</u> the VMH animal was hyperreactive to taste was offered. One of the first attempts to explain the basis of taste reactivity at the

biological level was Powley's (1977) "Cephalic Phase Hypothesis" (CPH).

Powley, like Brobeck et al. (1943) and Teitelbaum (1955), regarded hyperphagia as a reflection of a VMH lesion-induced finickiness. Powley argued, however, that the biological basis of the taste disturbance was a lesion-induced effect on the cephalic phase of digestion-related events. The cephalic phase is the component of the secretory or motor digestion-related event (e.g. motility, insulin or acid secretion) which is triggered by receptors in the brain and/or oropharynx. Powley suggested that damage to the VMH increased the cephalic phase responses. Most important, Powley argued that the magnitude of the cephalic response directly affected the amount of eating: the greater the response, the greater the amount eaten. Thus, for Powley, finickiness resulted from the ability of palatable foods to elicit a disproportionately large cephalic response. Also, since cephalic responses are vagally mediated (Powley, 1977), the CPH tied finickiness to vagal events.

However, more recent work has indicated that finickiness is not vagally mediated. For example, vagotomised VMH rats <u>are</u> hyperphagic when maintained on highly palatable diets (Powley & Opsahl, 1974; Sclafani, Aravich & Landman, 1981). Cox & Smith (1986) also found that vagotomy failed to block the finicky eating pattern of VMH rats.

Although there was evidence of a strong link among finickiness, hyperphagia and the development of obesity in VMH

rats, the underlying cause of VMH finickiness has remained unidentified.

1.3. POSSIBLE BRAIN MECHANISMS OF TASTE REACTIVITY CHANGES

Finickiness has often been suggested to result from damage to cell bodies in the VMH (e.g. Brobeck et al., 1943; Powley, 1977; Teitelbaum, 1955). However, four sets of observations suggest that finickiness may result from damage to tissue outside the VMH and, more specifically, to neural systems connecting the amygdala and the hypothalamus. These four sets of observations are:
1) Brain damage made to produce the VMH syndrome may sever fibres of passage adjacent to, passing through, or terminating in, the VMH, and destruction of these fibres may lead to VMH finickiness;
2) If destruction of fibres is critical to the development of VMH finickiness, many of these fibres arise from the amygdala (e.g. the stria terminalis and the ventroamygdalofugal pathway);
3) The amygdala is involved in the regulation of food intake and lesions of the amygdala can produce finicky patterns of eating;
4) Finickiness represents a disturbance of sensory processing, and the amygdala is thought to be a neural structure involved in the processing of sensory information.
These few observations are discussed in greater detail below.

1.3.1. Finickiness and Fibres of Passage

The altered taste reactivity characteristic of the VMH syndrome, may not necessarily result from damage to cell bodies in the VMH itself. Rather, finickiness may result from damage to fibre systems arising from other brain areas and running near or through the VMH. For example, Graff and Stellar (1962) found that finickiness resulted from damage in the lateral-posterior portion of the VMH, in a neural area encroaching upon the lateral hypothalamus. Also, taste reactivity changes similar to those seen in VMH-lesioned animals can be produced by knife cuts or lesions of hypothalamic nuclei other the VMH. For example, knife cuts lateral or just posterior to the VMH, produced intake changes similar to those seen in VMH lesioned rats (Aravich & Sclafani, 1983; Sclafani, 1982; Sclafani & Berner, 1977). Similarly, lesions of the paraventricular nucleus of the hypothalamus (PVN), which do not encroach upon the VMH but which may have interrupted the same fibre systems affected by the hypothalamic knife cuts, also produce a finicky pattern of food intake in rats (Aravich & Sclafani, 1983; Weingarten et al., 1985).

1.3.2. Finickiness and the Amygdala

Damage to the amygdala produces a finicky pattern of food intake. For example, rats sustaining amygdaloid lesions spend more time consuming sweet foods (e.g. sultana raisins and

chocolate chip cookies) and less time eating chow than did controls offered the same diet choice (Rolls & Rolls, 1973b). Rolls & Rolls (1973a) showed that rats with amygdala lesions consumed more 25% sucrose than controls (though water intake was no different from control values). They concluded that the lesioned rats were "hyperreactive to the taste of the sucrose solution," (p. 243). From these studies, Rolls & Rolls (1973b) concluded that the amygdala was involved in ingestive behaviour and more specifically in food preferences based upon taste.

Schoenfeld & Hamilton (1981) demonstrated that damage to the medial amygdala resulted in an overconsumption of a 0.1 % saccharin relative to control rats; intake of a 0.025 % quinine solution was equivalent to controls (i.e. an overconsumption of a palatable solution without a heightened rejection of an unpalatable solution). Schoenfeld & Hamilton (1981) concluded that the amygdala was involved in food choice rather than hunger or satiety, and that "the medial pole of the amygdala was associated with an enhanced reactivity to saccharin but had little to do with reactivity to quinine," (p. 574).

Thus lesions involving the amygdala, and lesions involving fibre systems arising in the amygdala, produce a finicky pattern of food intake.

1.3.3. The Amygdala and Food Intake

More generally, the amygdala appears to be involved in the control of food intake. Grossman & Grossman (1963) found that lesions of the posteroventral or anterior area of the amygdala increased food intake (for a review, see Kaada, 1972). Furthermore, increased food consumption in rats has been observed following destruction of the basolateral amygdala (Fonberg, 1968). Finally, similar increases in food consumption have been obtained with 6 hydroxydopamine lesions of the lateral amygdala (Lenard, Hahn & Karati, 1982).

While it is true that many studies involving ablation of the amygdala have found decreases in consumption (e.g Cole, 1974; Fonberg, 1966; Grossman & Grossman, 1963), this is no more surprising than the observation that hypothalamic lesions can also produce either aphagia (lesions of the lateral hypothalamus, Powley & Keesy, 1970) or hyperphagia (lesions of the VMH). Thus a role for the amygdala in taste reactivity is suggested by the results of numerous studies in the literature.

1.3.4. The Amygdala and Sensory Processing

Finickiness is fundamentally a disturbance of sensory processing, and the amygdala is believed to be involved in the processing of sensory information, taste being one example. Based upon the examination of the effect of discrete amygdaloid lesions on the response to aversive and pleasant stimuli,

Schoenfeld & Hamilton (1981) concluded that the amygdala was involved primarily in reactivity to external stimuli, especially unconditioned stimuli like food.

Gaston (1978), in her review of the literature on conditioned taste aversions, suggested that the amygdala had a role in the, "detection of the motivational significance of environmental [i.e. sensory] stimuli". Similarly, in an extensive review of the function of the limbic system, Cormier (1981) hypothesized that the amygdala was responsible for recognition of, and reaction to, external sensory stimuli. This view of amygdaloid function is shared by many others (e.g. Gloor, 1972; Hall, Bloom & Olds, 1977; Henke, 1980a,b,c; Kaada, 1972; Kemble & Schwartzbaum, 1969; Kluver & Bucy, 1939; Nauta, 1963).

In summary, lesion and knife-cut studies implicate a fibre system passing near or through the VMH in taste reactivity. Furthermore, the amygdala appears central to responding to sensory stimuli, such as taste, and lesions of the amygdala produce a finicky pattern of eating similar to that of VMH-lesioned rats. Therefore, it is possible that the taste reactivity changes seen after VMH lesions may involve disruption of amygdalo-hypothalamic connections.

1.4. THESIS QUESTION AND RESEARCH OUTLINE

This thesis examines the hypothesis that destruction of connections between the amygdala and hypothalamus, specifically those the stria terminalis (ST), gives rise to VMH-lesion-induced

taste hyperreactivity after VMH lesions. Four observations support the idea that destruction of amygdalo-hypothalamic connections via the ST contribute to the taste reactivity changes seen following VMH lesions:

· the lesions used to produce the VMH syndrome destroy both of the anatomical pathways linking the amygdala and the VMH;

· the amygdala is known to influence feeding via a neural circuit involving the ST and the hypothalamus;

· the function attributed to the amygdala is control of motivated behaviour, including food selection and intake;

· the ST is in an anatomically strategic position in the forebrain taste system and consequently, damage to the ST should result in changes of taste processing.

These four points are discussed in greater detail below.

1.4.1. Anatomical pathways linking the amygdala and the VMH

The typical lesion used to produce the VMH syndrome destroys the two major pathways linking the amygdala with the VMH -- the ventroamygdalofugal (VAF) pathway and the stria terminalis (de Olmos, 1972; de Olmos, Alheid & Beltramino, 1985; de Olmos & Ingram, 1972; Masco & Carrer, 1984). Both the VAF and the ST originate in the amygdala and terminate in the VMH (de Olmos, 1972; de Olmos, Alheid & Beltramino, 1985; McBride & Sutin, 1977; Saper, Swanson & Cowan, 1976). The VAF is a diffuse fibre system running ventrally from the amygdala to the VMH, while the ST is a discrete fibre bundle which courses under the fimbria, and

descends into the VMH. Most important to the rationale of the current hypothesis, only the ST carries collaterals originating in the medial amygdala, precisely the amygdaloid nucleus which Schoenfeld & Hamilton (1981) concluded was involved in reactivity to taste. Also, stimulation of the medial amygdala activates fibres in the ST which project to the VMH, without any observable activation of the VAF (Watson, Troiano, Poulakos, Weiner, Block & Siegel, 1983). Therefore, as Watson et al. (1983, p. 37) concluded "It would appear that medial amygdaloid stimulation could activate primarily the ST, thus influencing ventromedial neurons directly via its postcommisural component".

1.4.2. Amygdaloid influences on feeding via the ST

The amygdala has already been demonstrated to influence feeding behaviour through a neural circuit involving the ST and the hypothalamus. Grossman (1964) found that cholinergic stimulation of the ventral amygdala in deprived rats decreased food intake, while cholinergic blockade with atropine stimulated food intake . Since Grossman (1964) obtained similar results with sated VMH lesioned rats (in other words, conditions required to observe the effect in VMH rats were not as extreme as those required to observe it in controls), he suggested that the amygdala had a modulatory effect on feeding by influencing hypothalamic activity. Sclafani, Belluzi & Grossman (1970) drew similar conclusions about amygdaloid function, based upon studies of latency to eat in novel situations. They concluded that

amygdala lesions and VMH lesions damaged a common neural system and that the amygdala influenced feeding via modulation of VMH activity.

Box and Mogenson (1975) found that lesions of the amygdala produced either an increase or decrease of intake, depending on the precise location of the lesion. Since the ST is the major projection from the dorsomedial area of the amygdala to the hypothalamus, and since lesions of the dorsomedial amygdala produced a mild hyperphagia, Box & Mogenson (1975) concluded that any amygdaloid influence on feeding behaviour through modulation of hypothalamic activity probably occurred via the ST.

Stimulation studies provide additional evidence that the amygdala influences feeding via the ST to the hypothalamus. White & Fisher (1968) demonstrated that stimulation of the amygdalo-pyriform transition zone suppressed food intake in food-deprived rats. However, this effect was mediated entirely through the ST since bilateral ST lesions eliminated the stimulation-induced suppression of eating. Furthermore, bilateral ST lesions had no effect on stimulation-induced suppression of water intake, indicating that the amygdala-ST-hypothalamus neural circuit was involved specifically with food intake.

1.4.3. The amygdala and sensory control of motivated behaviour

The traditional role ascribed to the amygdala is consistent with the idea that amygdalo-hypothalamic connections may be

involved in VMH lesion-induced finickiness. As reviewed before, the amygdala is typically seen as involved in the processing of sensory information. For example, Gloor (1960) argued that the amygdala was involved in the sensory control of regulated behavior and finickiness is fundamentally a disturbance of the sensory control of eating. Goddard (1964) proposed that the amygdala was involved in the inhibition of feeding specifically and more generally in the inhibition of response to positive stimuli. In their review of the limbic forebrain, Watson et al. (1983, p. 37) suggested that, "...Perhaps, one of the key experimental questions remaining that must now be resolved is the nature and extent of the influence [the ST or VAF] contributes to the overall regulation of both the lateral and medial hypothalamus at the cellular as well as the behavioural level...".

1.4.4. ST and forebrain taste systems

Anatomical studies demonstrate extensive projections from the hindbrain taste system to the forebrain, and the ST occupies a pivotal position within the taste projection system in the forebrain. Gustatory information from the tongue synapses first in the hindbrain, in the nucleus of the solitary tract (NST). The NST projects to the midbrain structure, parabrachial nucleus (PBN), which, not surprisingly, responds promptly to taste stimuli applied to the tongue (Norgren & Leonard, 1971). The PBN then sends extensive projections to the forebrain structures of

the amygdala, hypothalamus and bed nucleus of the stria terminalis (Norgren, 1976; Norgren & Leonard, 1973). The three forebrain areas, amygdala, medial hypothalamus, and bed nucleus of the stria terminalis, receive the majority of taste projections from the hind- and mid-brain gustatory areas (Norgren, 1983; Saper & Loewy, 1980). The ST is the major fibre bundle linking the three main forebrain projection areas (de Olmos, 1972; de Olmos, Alheid & Beltramino, 1985; Watson et al., 1983). Thus, the hypothesis that taste reactivity changes following VMH lesions may involve the ST, receives anatomical support from demonstrations of the strategic position of the ST in the forebrain taste system. Although the extensive forebrain taste system has been described anatomically, at present, little is known about the behavioral function of the forebrain taste systems generally, or the ST specifically (Grill & Berridge, 1981; Grill & Norgren, 1978; Norgren & Grill, 1982).

1.5. EXPERIMENTAL STRATEGY

As reviewed, several observations implicate disruption of the ST in VMH finickiness. First, classic VMH lesions destroy the ST connections with the ventromedial area of the hypothalamus. Second, the amygdala influences feeding via the ST and modulating hypothalamic activity. Third, the amygdala is involved, specifically, in reactivity to food-associated sensory stimuli. Fourth, the ST occupies an anatomically strategic position in the

forebrain taste system. Consequently, ST damage might be expected to affect taste processing.

If destruction of the ST mediates VMH lesion-induced finickiness, then severing the ST at a point remote from the VMH should produce an animal which also overreacts to the taste properties of food. Further, this taste disturbance should be similar both in kind and magnitude to the disturbance seen in the VMH rat. Experiments 1a and 1b examine these predictions using a sham feeding preparation.

The results of Experiments 1a and 1b suggested that the ST was not the substrate of VMH finickiness. However, ST rats did show changes of sham feeding similar in some respects to those seen in VMH rats. Experiments 2 and 3 examined the properties and generalizability of the taste reactivity disturbance of ST rats documented in Experiments 1a and 1b. These experiments showed that ST rats were not hyperphagic when real feeding. In contrast, VMH rats retained their hyperphagia even under real eating conditions.

The hyperphagia of the ST rat when sham feeding, coincident with a normal intake when real feeding, represents the first report of an enhanced sham intake without a concurrent enhancement of real intake. These observations also contrast with the hyperphagia of the VMH rat which is evident under both sham and real feeding conditions. Experiments 4 and 5 attempted to explain these findings.

Experiment 4 used a sensitive behavioural preparation, conditioned feeding, to assess whether elevated sham feeding reflected a heightened motivation to eat.

Experiment 5 examined a stomach satiety factor, gastric emptying, in ST rats, VMH rats and controls, to evaluate whether differences in gastric emptying might account for differences in the feeding behaviour of rats with these different lesions.

CHAPTER II. GENERAL METHODS

Subjects

Subjects were male Long-Evans hooded rats acquired from the McMaster breeding colony (original stock from Blue Spruce Farms, Altamont, NY). For Experiments 1a, 1b, 2, 3,and 5, subjects were individually housed in a colony room maintained at 21^{o} C, and on a 14:10 light:dark cycle. Water was continuously available, and food was available dependent upon experimental protocol.

Gastric Surgery (Experiments 1a, 1b, 2, 3, 5)

A chronically indwelling gastric cannula was implanted into each rat (Weingarten & Powley, 1980b). Briefly, rats were 24 hr food deprived to ensure an empty stomach and then anesthetized with sodium pentobarbital (Somnotol) injected intraperitoneally (ip) at a loading dose of 45 mg/kg. Atropine sulphate (0.2 ml of 0.6% solution, ip) was administered to reduce salivary and mucous secretions. The abdomen was shaved and then cleaned with 70% alcohol. A midline laparotomy (2 - 3 cm) was made and the stomach exposed. Two concentric purse string sutures, 2 to 3 cm in diameter, were sewn into the anterior rumen of the stomach (5-0 silk attached to an atraumatic needle, Ethicon, K880-H) and an

incision was made in the stomach wall encircled by the sutures. One end of an internally threaded stainless steel cannula (8.5 mm OD x 7.9 mm ID x 11 mm long), flanged at both ends, was secured into the stomach. A 2 cm disc of Marlex mesh (Davol Inc., Providence, Rhode Island) cemented to the cannula shaft with dental cement (Dentsply International Inc., York, PA) helped to anchor the cannula in the abdominal cavity. The cannula was exteriorized through a stab wound in the left abdominal wall and skin. A second piece of Marlex mesh was placed around the cannula shaft between the abdominal wall and skin, further anchoring the cannula. The abdominal incision was closed with interrupted catgut sutures (3-0) and the skin closed with 9 mm wound clips (Clay Adams, Parsippany, N.J.) The skin around the cannula was secured with a double stranded 3-0 silk purse string suture. A topical anti-bacterial gel (Furacin, Austin Laboratories, Canada) was applied to the wound. The cannula was kept closed by a stainless steel set screw threaded into the cannula shaft.

Fourteen to twenty days of recovery were allowed after gastric surgery. During this time rats were maintained ad libitum on pellets of Purina Rodent Laboratory Chow (#5001) pellets.

Stereotaxic Surgery

To produce VMH lesions, animals were anesthetized (as previously described) and mounted in a Kopf stereotaxic instrument. Using standard stereotaxic procedures a 2 cm midline cut was made in the scalp to expose the skull. Two 1 mm holes

were drilled in the skull allowing the electrodes to be lowered to coordinates: 2.1 mm posterior to bregma, 0.6 mm lateral to the midline and 9.5 mm below the skull surface (with the incisor bar 3.0 mm below the horizontal). Electrodes were made of #00 stainless steel insect pins coated with Epoxylite except for 0.4 mm at the tip. Lesions were produced by passing a 1.0 mA anodal current between the electrode and a tail cathode for 18 sec. Skull holes were filled with bone wax (Ethicon) and the skin was closed with 9 mm wound clips. For sham lesions, electrodes were lowered to the same coordinates but no current was passed.

Stria terminalis knife cuts were produced using a spring-loaded brain knife (Hamilton, Worsham & Capobianco, 1973). The knife was a 30 ga tungsten wire which passed through a 23 ga guide tube. Animals were prepared for surgery, and the skull exposed, as outlined above. Two holes, 1 mm x 2 mm, were drilled in the skull (with the incisor bar 3.0 mm below the horizontal) to allow the knife to be positioned at 1.3 mm posterior to bregma, 4.7 mm lateral to the midline and 5.2 mm below the skull surface. The tungsten knife was extended 3 mm in a caudal-medial direction, 45^{o} to the midline. The spring-loaded catch was released, allowing the knife to travel 4.0 mm vertically. The wire was retracted and the knife removed from the brain. Skull holes were filled with bone wax and the skin closed with wound clips. For sham knife-cuts, the knife was lowered to the same cocrdinates and the trigger released but the tungsten wire was not extended.

All subjects were food and water deprived for 24 hr following stereotaxic surgery to ensure that none of the animals, especially those sustaining VMH lesions, gorged immediately post-surgery.

Sham Feeding Cages and Procedure (Experiments 1a, 1b, 2)

Animals were tested in individual Plexiglas cages, 10 cm x 10 cm x 20.5 cm with a 1.5 cm x 20.5 cm slot in the center of the floor. The cage was mounted on 19.5 cm high stilts. A 100 ml graduated cylinder with a drinking spout containing the test solution was attached to the front of each cage allowing the spout to enter the cage through a 2.5 cm circular hole in the front wall.

To prepare a rat for testing, it was taken from its home cage and weighed. The set screw was removed from the cannula and the stomach cleaned with lukewarm tap water applied through the cannula. A 19.1 mm long stainless steel collection tube attached to a 150 mm long length of Tygon tubing was threaded into the cannula. When the subject was placed in the test cage, the tube hung freely through the slot in the floor and any ingested material drained out of the stomach, down the collection tube, and into a catch pan under the cage.

A graduated cylinder containing the test solution was attached to the front of the cage and the initial volume recorded. Rats sham fed for 30 min; their intakes were recorded every 5 min. At the end of the test, the rat was taken from the test cage, its

drainage tube was removed, the set screw replaced, and it was returned to the home cage where it immediately received a daily food ration (Purina Rodent Laboratory Chow #5001 pellets) sufficient to maintain the required body weight restriction.

Sham feed training and solutions

For sham feeding, all rats (lesion and controls) were maintained at 95% of their weight prior to stereotaxic surgery, allowing 1 g per day for growth. This procedure ensured that all groups were at similar body weights throughout testing and, therefore, that any behavioural differences between groups could not be secondary to body weight changes induced by the brain manipulations. All rats were reduced to 95% of their ad lib weight over a one week period.

Rats were trained to sham feed reliably prior to testing. Rats that failed to feed reliably by the end of training were not tested further (see Experiments 1a, 1b, 2 and 3). Rats were rejected if, by the end of training, they did not begin to feed within the first 5 min following presentation of the test solution.

Sucrose solutions were prepared on a weight/volume basis, at least 24 hrs in advance, and presented at room temperature. Rats were tested twice at each sucrose concentration.

Histology

At the completion of an experiment, rats were sacrificed using 1.0 ml of 50% chloral hydrate injected ip and were perfused intracardially with 0.9% saline followed by 10% buffered formalin. Each brain was removed and stored in 10% buffered formalin. Brains were frozen at -22° C and sectioned at 40 um in the coronal plane. Every second section through the lesion or knife cut was mounted and subsequently stained with luxol fast blue for fibre tracts and cresyl violet for cell bodies (Kluver & Barrera, 1968).

Subjects were assigned to experimental groups based upon the location and extent of tissue damage, assessed by a rater blind to the experimental results. The criterion for inclusion into the VMH group has been described elsewhere (Weingarten, 1982). Briefly, bilateral destruction of at least 80% of the classically-defined VMH was required. Typically, successful lesions began in the anterior hypothalamus, destroyed the entire ventromedial nucleus, and terminated just anterior to the premammillary bodies. The damage extended laterally from the third ventricle to the fornix and dorsally from the base of the brain to the ventral aspect of the dorsomedial hypothalamic nucleus.

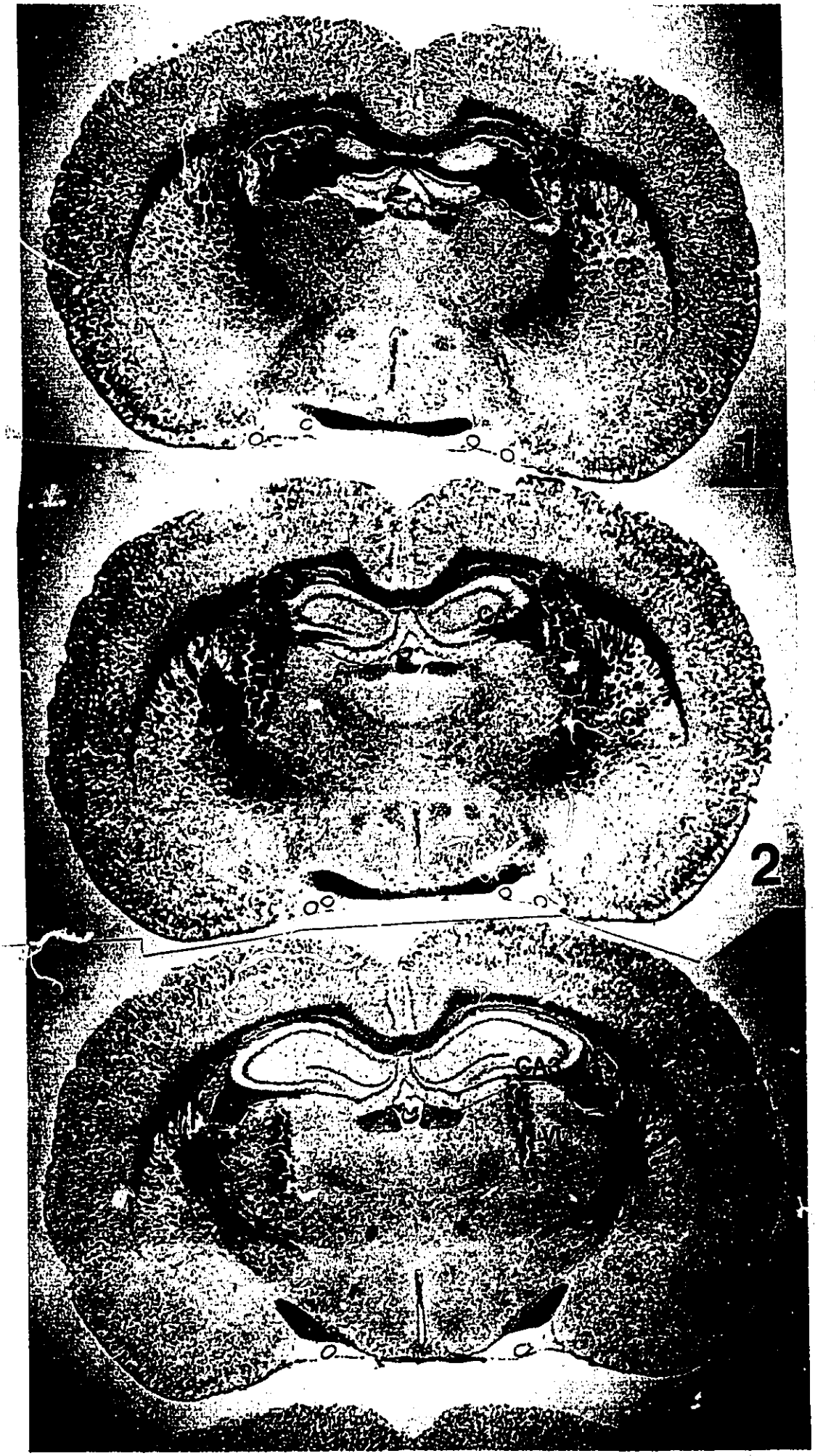
To be included into the ST group, rats needed to sustain complete bilateral transections of the ST. The ST was cut at its most dorsal excursion as it coursed along with the fimbria. At this location, the stria terminalis is a discrete fiber bundle and severing it here interrupts all four of its subsequent

component parts (de Olmos, 1972; de Olmos, Alheid & Beltramino, 1985; de Olmos & Ingram, 1972). A typical successful cut is shown in Figure 1. The cuts extended in a medial-caudal direction from the caudate putamen through the globus palladus to the anterior portion of the lateral-posterior and posterior thalamic nuclei. Typically the fimbria and CA3 layer of the hippocampus also suffered minor damage.

Data Analysis

All data were analyzed using analysis of variance (ANOVA). An alpha level of 0.05 was considered statistically significant. When justified from ANOVA results, post hoc comparisons were conducted using the Newman-Keuls procedure and the Studentized range statistic, q.

Figure 1. Coronal brain slices depicting a successful ST knife cut. The upper cut is, approximately, at A.53401 in the Konig and Kippel (1963) atlas. The middle and lower plates are more caudal. The middle panel shows the knife cut passing directly through the ST. Abbreviations: CA3, CA3 of the hippocampus; CP, caudate putamen; Fi, fimbria; IC, internal capsule; ST, stria terminalis; VL, ventrolateral thalamus.


1
2
CA3

Chapter III. SHAM FEEDING STUDIES

These studies assessed the effects of VMH lesions, ST transections, and the combined manipulation, on reactivity to sweet sucrose solutions and quinine-adulterated sucrose solutions.

Postingestive consequences such as gastric distension, osmotic effects etc., can affect intake even in relatively short (< 30 min) exposures to a diet. Thus, to isolate the influence of taste and to eliminate as many other confounding variables, it is necessary to use preparations which minimize or eliminate the influences of variables other than taste.

Several procedures have been developed to isolate the effects of taste on eating (see Young & Kappauf, 1962). The recent technique of choice is sham feeding since this technique eliminates the accumulation of food in the stomach and thus eliminates (or at least minimizes) activation of postingestive consequences that may affect eating. Sham feeding allows the evaluation of an animal's response to both palatable and unpalatable foods (Weingarten & Watson, 1982) and most relevant, sham feeding has been used successfully to investigate the effects of VMH lesion-induced taste disturbances (Cox & Smith,

1986; Weingarten, 1982; Weingarten et al., 1983; Weingarten et al., 1985). Experiments 1A and 1B each used sham feeding to investigate the influence of oral sensory factors on intake.

The logic of the groups tested is as follows. If the finickiness of VMH rats results from interruption of connections from the amygdala to the VMH via the ST, then rats with ST transections remote from the VMH should be as overreactive to taste as are VMH lesion rats. In addition to this, if ST damage mediates VMH finickiness, then animals with combined VMH/ST damage should be no more hyperreactive to taste than animals with damage to either system alone. In contrast, and this is most important, if ST damage produces effects independent of VMH lesion-induced finickiness, then the combined VMH/ST manipulation should produce additive effects of VMH and ST damage alone.

Experiment 1a. Sham Feeding Sweet Sucrose Solutions

Methods

Thirty rats (mean weight ± 1 SEM at stereotaxic surgery was 443 ± 5 g) were assigned to the VMH (n = 7); ST (n = 8); VMH/ST (n = 9); or control (n = 6) groups. Rats were trained to sham feed using 18% sucrose. Rats were then tested on 6%, 12%, 18%, and 24% sucrose, presented in a random order, one solution per day.

Results and Discussion

Three of the seven rats with VMH lesions sustained criterion damage and comprised the VMH group. Seven of 8 rats met the criteria for inclusion in the ST group. Five of nine rats sustained criterion damage to both the VMH and the ST and constituted the VMH/ST group. Six sham operated rats served as controls.

The food restriction regimen employed was successful in maintaining equivalent body weights among the four groups. Statistical analyses indicated that body weights of the groups did not differ at either the initiation, $F(3,17) = 1.89$, $p > 0.05$, or termination, $F(3,17) = 1.94$, $p > 0.05$, of sham feeding tests.

Figure 2 shows the sham feeding profiles of the four groups at the sucrose concentrations used. Analysis of variance indicated that groups differed in their level of sham feeding, $F(3,17) = 4.78$, $p < 0.01$, and that consumption was influenced greatly by sucrose concentration $F(3,51) = 95.6$, $p < 0.0001$. However, the change in sham feeding profiles with sucrose concentration (Group X Concentration interaction) were not different among groups, $F(9,51) = 1.26$, $p > 0.05$.

Multiple comparisons of mean group intake at each solution concentration were conducted using the Studentized range statistic and evaluated according to the Newman-Keuls procedure

Figure 2. Thirty min cumulative intakes (in mls) of the four groups sham feeding the sucrose solutions indicated (VMH = ventromedial hypothalamic lesion; ST = stria terminalis knife cut).

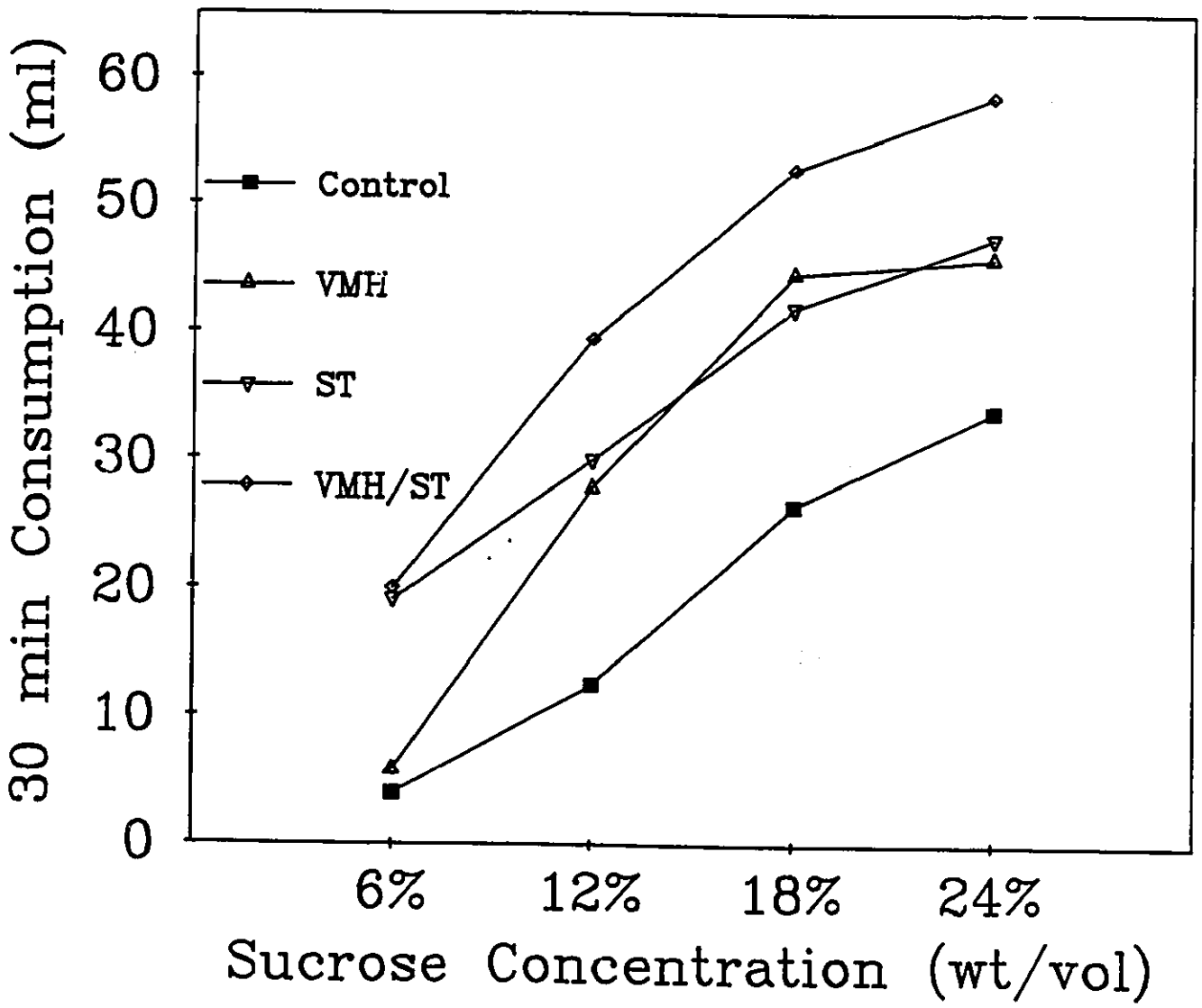

30 min Consumption (ml)
60
50
40
30
20
10
0
Control
VMH
ST
VMH/ST
6%
12%
18%
24%
Sucrose Concentration (wt/vol)

Table 1. This table indicates where significant differences exist between groups sham feeding various sucrose solutions.

TABLE 1

	VMH	ST	VMH/ST
CONT	$q_2 = 0.6^{ns}$ $q_5 = 5.1^{**}$ $q_7 = 6.0^{**}$ $q_5 = 4.0^{*}$	$q_4 = 5.1^{**}$ $q_6 = 5.9^{**}$ $q_8 = 5.2^{**}$ $q_8 = 4.6^{*}$	$q_5 = 5.4^{**}$ $q_6 = 9.0^{**}$ $q_{10} = 8.8^{**}$ $q_8 = 8.3^{**}$
VMH		$q_3 = 4.5^{*}$ $q_2 = 0.8^{ns}$ $q_2 = 0.9^{ns}$ $q_2 = 0.5^{ns}$	$q_4 = 4.8^{*}$ $q_4 = 3.9^{*}$ $q_4 = 2.9^{ns}$ $q_4 = 4.3^{*}$
ST			$q_2 = 0.3^{ns}$ $q_3 = 3.2^{ns}$ $q_5 = 3.6^{ns}$ $q_3 = 3.7^{*}$

KEY: in a given cell, the q values for "column > row" represent comparisons for sham consumption of specific sucrose concentrations in the following manner:

6%	12%
18%	24%

* $p < 0.05$ ** $p < 0.01$

(51 df). These results are summarized in Table 1. VMH rats sham fed control amounts of 6% sucrose ($p > 0.05$), but consumed more 12%, 18% and 24% sucrose than controls. ST animals sham fed more than controls at all sucrose concentrations ($p's < 0.01$). At 6% sucrose, ST rats sham fed even more than VMH animals ($p < 0.05$). ST and VMH rats sham fed similar amounts of 12%, 18% and 24% sucrose ($p's > 0.05$). Animals in the VMH/ST group also sham fed more than controls ($p's < 0.01$). VMH/ST rats sham fed more than VMH rats at all four sucrose concentrations, but this difference was significant only at 6%, 12% and 24% sucrose ($p's < 0.05$). VMH/ST rats ate significantly more than ST rats at 24% sucrose ($p < 0.05$).

This study replicates previous reports of an enhanced sham intake of sucrose by VMH rats (Weingarten, 1982; Weingarten et al., 1985). Also, the results of this experiment demonstrated, for the first time, that rats with ST knife cuts show elevations of sham feeding which can be as large as that of VMH rats. Combined VMH and ST damage resulted in animals with the greatest disturbances of sham feeding, typically greater than those seen in either the VMH or ST rats alone.

Experiment 1b: Sham Feeding Quinine-adulterated Solutions

To determine if the sham feeding disturbance produced by ST knifecuts is qualitatively similar to the disturbance seen in VMH rats, I examined the response of ST rats sham feeding sucrose solutions made increasing unpalatable. While VMH rats do not

show an exaggerated rejection of unpalatable foods when sham feeding (Weingarten et al., 1983), the reaction of the ST rat to unpalatable foods is unknown. Therefore this experiment examines food intake adjustments by ST, VMH and VMH/ST rats in response to a taste manipulations, i.e. quinine adulteration, that render food less palatable.

Methods

Thirty rats, weighing a mean of 359 ± 6 g at surgery were used. The test diet was a 30% sucrose solution adulterated with 0.0%, 0.001%, 0.0025%, or 0.005% quinine hydrochloride (wt/vol). Rats were trained to sham feed using 30% sucrose. Test days alternated between quinine adulterated sucrose and unadulterated sucrose. Diets were presented in an order of ascending quinine concentration.

Results and Discussion

Eight of nine rats with VMH lesions sustained sufficient damage to be included in the VMH group. Five of six rats sustained criterion bilateral transections of the ST. Three of nine rats constituted the VMH/ST group. Of six control rats, two failed to sham feed reliably and were not included in the analyses.

Groups did not differ significantly in weight at either the start, $F(3,16) = 1.30$, $p > 0.05$, or end, $F(3,16) = 0.85$, $p > 0.05$, of testing.

Figure 3 shows the group mean sham feeding profiles across quinine concentrations. As expected, the concentration of quinine significantly affected amount sham fed, $F(3,48) = 19.49$, $p < 0.0001$. Groups also differed in their level of sham feeding, $F(3,16) = 5.28$, $p < 0.01$, although the patterns of intake change among groups across the quinine concentrations were not different from one another, $F(9,48) = 0.82$, $p > .05$.

The results with no quinine adulteration paralleled results of experiment 1a: VMH rats and ST rats sham fed more than controls but were not different from each other, while VMH /ST rats sham fed more than all other groups. Multiple comparisons (48 df) showed that VMH and ST rats sham fed more unadulterated 30% sucrose (0.00% quinine) than controls ($p's < 0.05$); these two groups were not different from each other, ($p's > 0.05$). VMH/ST rats sham fed significantly more than all groups, ($p's < 0.05$) [q values are presented in Table 2].

When the food was adulterated with quinine, ST rats resembled VMH lesioned rats. ST rats showed equivalent declines as VMH rats in sham feeding with increasing levels of adulteration. The difference in intake between 0.00% quinine and 0.005% quinine was 12.5 $\pm$ 3.1 mls for VMH rats; 11.8 $\pm$ 4.1 mls for controls; 15.6 $\pm$ 4.5 mls for ST rats; and 14.2 $\pm$ 9.3 mls for VMH/ST rats. There were no differences in these overall reductions, $F(3,16) = 0.13$, $p > 0.05$.

Figure 3. Thirty min intakes (in mls) of the four groups of a 30% sucrose solution adulterated with increasing concentrations of quinine indicated.

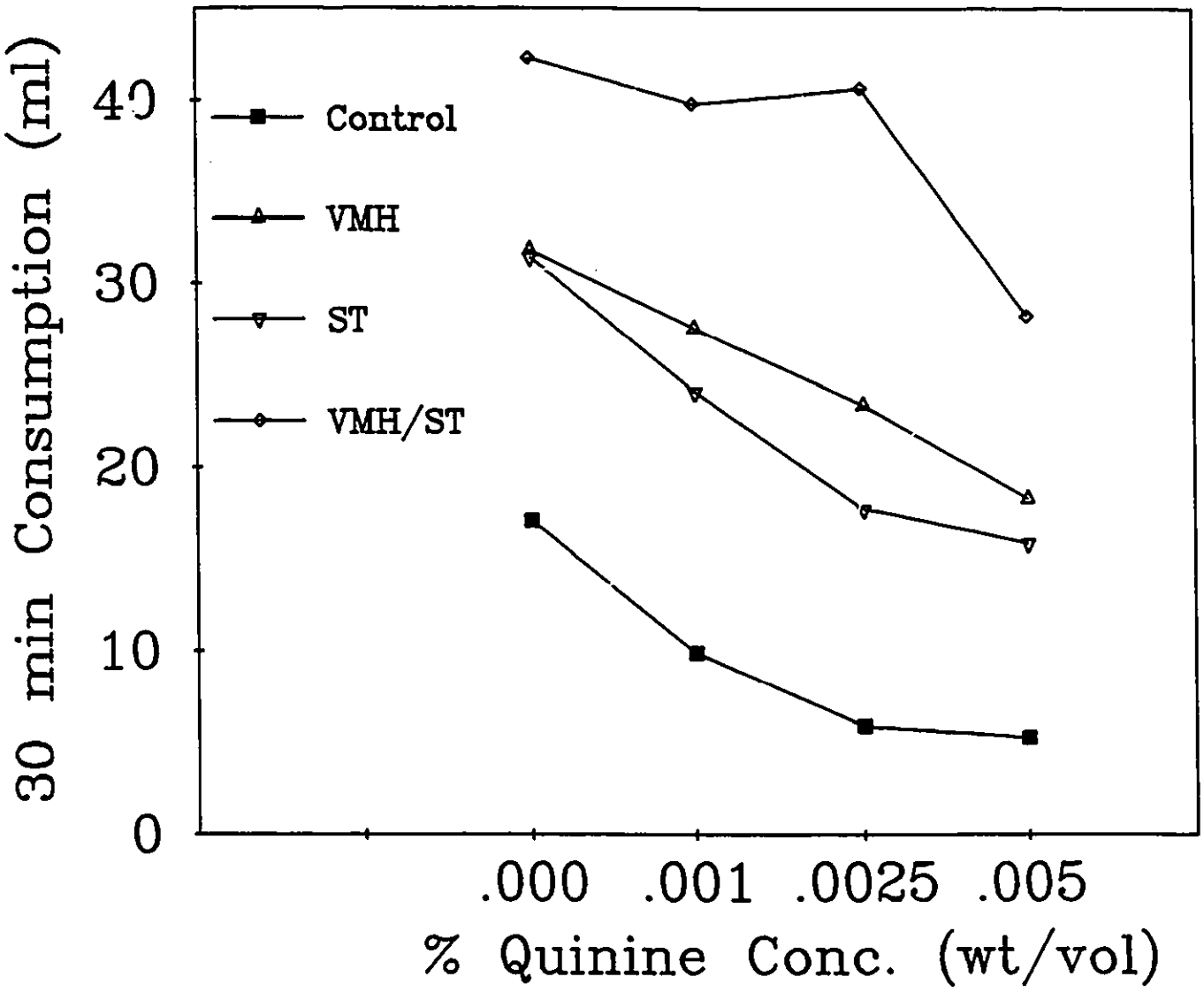

30 min Consumption (ml)
40
30
20
10
0
Control
VMH
ST
VMH/ST
.000
.001
.0025
.005
% Quinine Conc. (wt/vol)

Table 2. This table indicates where significant differences exist between groups sham feeding 30% sucrose solutions adulterated with increasing levels of quinine.

TABLE 2

	ST	VMH	VMH/ST
CONT	$q_8 = 5.6^{**}$ $q_7 = 5.5^{**}$ $q_5 = 4.6^{*}$ $q_4 = 4.1^{*}$	$q_8 = 5.2^{**}$ $q_6 = 6.2^{**}$ $q_7 = 6.2^{**}$ $q_7 = 4.9^{*}$	$q_{12} = 9.8^{**}$ $q_{12} = 11^{**}$ $q_{14} = 13^{**}$ $q_{11} = 8.9^{**}$
ST		$q_2 = 0.4^{ns}$ $q_2 = 0.7^{ns}$ $q_3 = 1.7^{ns}$ $q_4 = 0.8^{ns}$	$q_4 = 4.2^{*}$ $q_6 = 6.1^{**}$ $q_{10} = 8.3^{**}$ $q_8 = 4.8^{*}$
VMH			$q_5 = 4.6^{*}$ $q_5 = 5.4^{**}$ $q_8 = 7.2^{**}$ $q_5 = 4.0^{*}$

KEY: in a given cell, the q values represent comparisons, "column > row", for sham consumption at specific levels of quinine adulteration of 30% sucrose in the following manner:

0.000%	0.001%
0.0025%	0.005%

* $p < 0.05$ ** $p < 0.01$

General Discussion

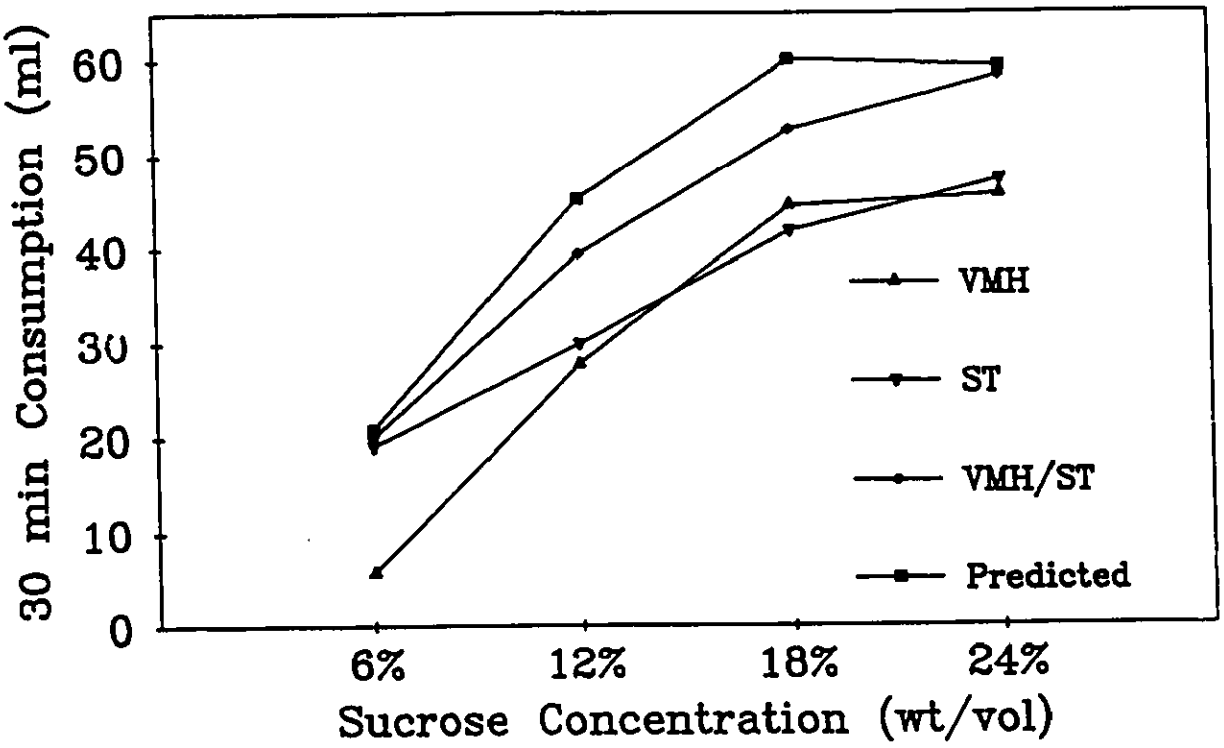
Experiments 1a and 1b evaluated the hypothesis that interruption of amygdalo-hypothalamic connections via the ST produces the taste processing disturbances characteristic of VMH lesions. The logic of these experiments was that if disruption of amygdalo-hypothalamic connections produced VMH finickiness, then interrupting these connections by severing the ST should produce an animal which, when sham feeding, was finicky. Thus, its sham feeding profile should not be different from VMH rats. Also, if the hypothesis is correct, then interrupting the same connections at two points, the ST and the VMH, should produce a rat no more finicky than that produced by VMH or ST damage alone.

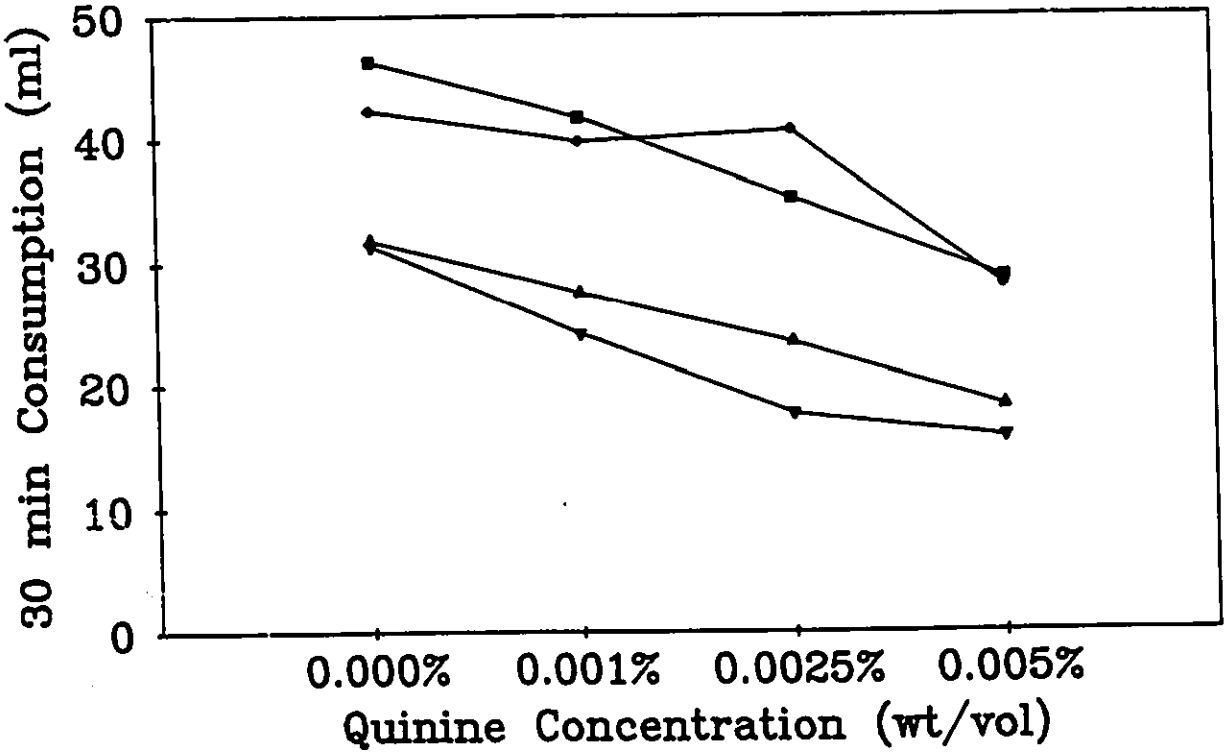
The results did not support the hypothesis since neither prediction was realized. Although the sham feeding profiles of VMH rats and ST rats are superficially similar, an important difference exists between the two at lower sucrose concentrations. As found in earlier studies (Weingarten, 1982), VMH rats sham feedno more 6% sucrose than controls. However, beyond this point their intake rises disproportionately with increases in sucrose concentration. While the sham intake of ST rats is similar to VMH rats above 12% sucrose, ST rats show excessive sham feeding even at 6% sucrose. In fact, the rise in sham intake with sucrose concentration in ST rats parallels that of controls and does not show the disproportionate increase characteristic of VMH rats.

Moreover, the magnitude of sham feeding seen in VMH/ST rats is equal to the sum of the disturbances produced by VMH and ST damage alone. This is shown most clearly in Figure 4, which presents the sham feeding profiles of VMH, ST and VMH/ST groups for Experiments 1a and 1b. Based upon the performance of animals with VMH or ST damage, a curve is calculated which predicts the performance of VMH/ST rats if the effects of VMH lesions and ST knife-cuts were independent and additive. The actual data obtained in VMH/ST rats is compared with this predicted curve. As seen in Figure 4, the sham feeding profile of VMH/ST rats closely matches the predicted values. This observation suggests that the disturbance induced by VMH damage is independent of the disturbance produced by disruption of amygdalo-hypothalamic connections via the ST.

The initial hypothesis guiding this thesis, linking finickiness with damage to amygdalo-hypothalamic connections via the ST is not supported. It is clear, however, that ST knife-cuts result in an abnormal sham feeding profile; the sham fed intake of ST rats is two to three times greater than that of controls. This degree of disturbance is as marked as that seen in VMH lesion rats and is one of the more dramatic demonstrations of an eating-related dysfunction resulting from manipulation of the forebrain taste system (see Introduction, 1.4.4. "ST and forebrain taste systems"). It is also clear that the effects of ST transection on intake are specific to food and do not reflect a generalized increase of appetitive behaviour or licking, since water

Figure 4. Thirty min sham fed intakes from experiments 1 (top graph) and 2 (lower graph). The "Predicted" curve is that generated by adding the effects of VMH lesions and ST knife cuts.


30 min Consumption (ml)
0
10
20
30
40
50
60
6%
12%
18%
24%
Sucrose Concentration (wt/vol)
VMH
ST
VMH/ST
Predicted


30 min Consumption (ml)
0
10
20
30
40
50
0.000%
0.001%
0.0025%
0.005%
Quinine Concentration (wt/vol)

deprived ST rats sham drink no more water than similarly deprived control rats (see Appendix A).

Sham feeding is a useful tool for isolating the contribution of taste on feeding and, given the nature of the initial research question, was ideal for examining the involvement of the ST in VMH finickiness. However, the ultimate aim of feeding research is to understand the mechanisms controlling eating in the intake animal. Given the demonstration of an apparent eating disturbance in ST rats, based upon sham feeding studies, it is important to determine whether the exaggerated eating manifested during sham feeding is apparent when the same animal is real feeding.

CHAPTER IV. REAL FEEDING STUDIES

While the properties of the sham feeding paradigm make it ideal for investigating the effects of taste on intake, sham feeding is only a tool for dissecting mechanisms of food intake. However, real feeding activates a plethora of signals absent in the sham feeding animal and, because of the activation of these signals, intake changes evident when animals sham feed may not be seen when the same animals real feed. There are numerous studies which have demonstrated dissociations between real and sham feeding. For example, peripheral cholinergic blockade by atropine reduces sham feeding (Lorenz, et al., 1978; Weingarten & Watson, 1982), but has no effect on normal intake (Nissenbaum & Sclafani, 1988; Weingarten, 1984b). Similarly, dopamine antagonists reduce sham feeding (Geary & Smith, 1985; Weatherford, Smith & Melville, 1988) but have no impact on real feeding (Blackburn, Phillips & Fibiger, 1987; Weingarten & Martin, 1989).

The hyperphagia of VMH rats when sham feeding is maintained when real feeding (Cox & Smith, 1986; Weingarten, 1982; Weingarten et al., 1985). Similarly, rats with lesions of the area postrema (Edwards & Ritter, 1986) or the paraventricular

nucleus (Weingarten et al., 1985) also show enhanced intake during both normal and sham feeding. To characterize more completely the role of the ST in feeding and to place in perspective the sham feeding disturbances of the ST rat, it is necessary to document the real feeding behaviour of ST rats.

Since the mechanism whereby ST damage produces enhanced sham intake has not been identified, it is not known whether, similar to the VMH rat, the ST rat will also show increased intake when real feeding. I examined the effects of ST knife-cuts on real feeding, in comparison to both VMH rats and controls, in two experiments. In the first, intake during real feeding was measured under the same test conditions in which a sham feeding disturbance had been identified. This demonstrates the effects on short term intake. In the second experiment, subjects were allowed ad libitum access to a series of standard lab diets. This documents effects on long-term intake and body weight. In these studies, VMH rats are maintained to allow comparison of ST rats to controls and to rats with VMH lesions which are known to exhibit marked feeding disturbances.

Experiment 2. Normal Feeding of Sweet Sucrose Solutions

Methods

Gastric cannulae were implanted in a group of eighteen rats, weighing a mean of 375 ± 7 g (mean ± 1 SEM) at surgery. VMH, ST, and control groups were produced following the stereotaxic surgery procedures described.

Animals were tested in a manner similar to Experiment 1a, with the sole exception that the cannula was closed after the stomach was cleaned prior to the feeding test. Because the cannula was closed, the ingested food remained in the alimentary tract, i.e. real feeding. As in Experiments 1a and 1b, all rats were reduced to 95% of their presurgery weight, allowing a 1 g/day growth rate.

Results and Discussion

Based upon the criteria described, 5 of 7 rats comprised the VMH group, and 5 of 6 the ST group. There were 5 controls.

The food restriction regimen maintained equivalent body weights in the three groups. Analysis of variance indicated that groups did not differ significantly in weight at the start, $F(2,12) = 0.62$, or end, $F(2,12) = 0.85$, of testing.

Figure 5 shows the cumulative 30 min intakes for the three groups at each sucrose concentration. There was a significant increase of intake with ascending sucrose concentration, $F(3,36) = 49.8$, $p < 0.0001$. Groups differed significantly in the amount they ate, $F(2,12) = 7.88$, $p < 0.01$. The profile of intake change

Figure 5. Cumulative thirty min intakes (ml) of ST rats, VMH rats and controls real feeding the sucrose solutions indicated.

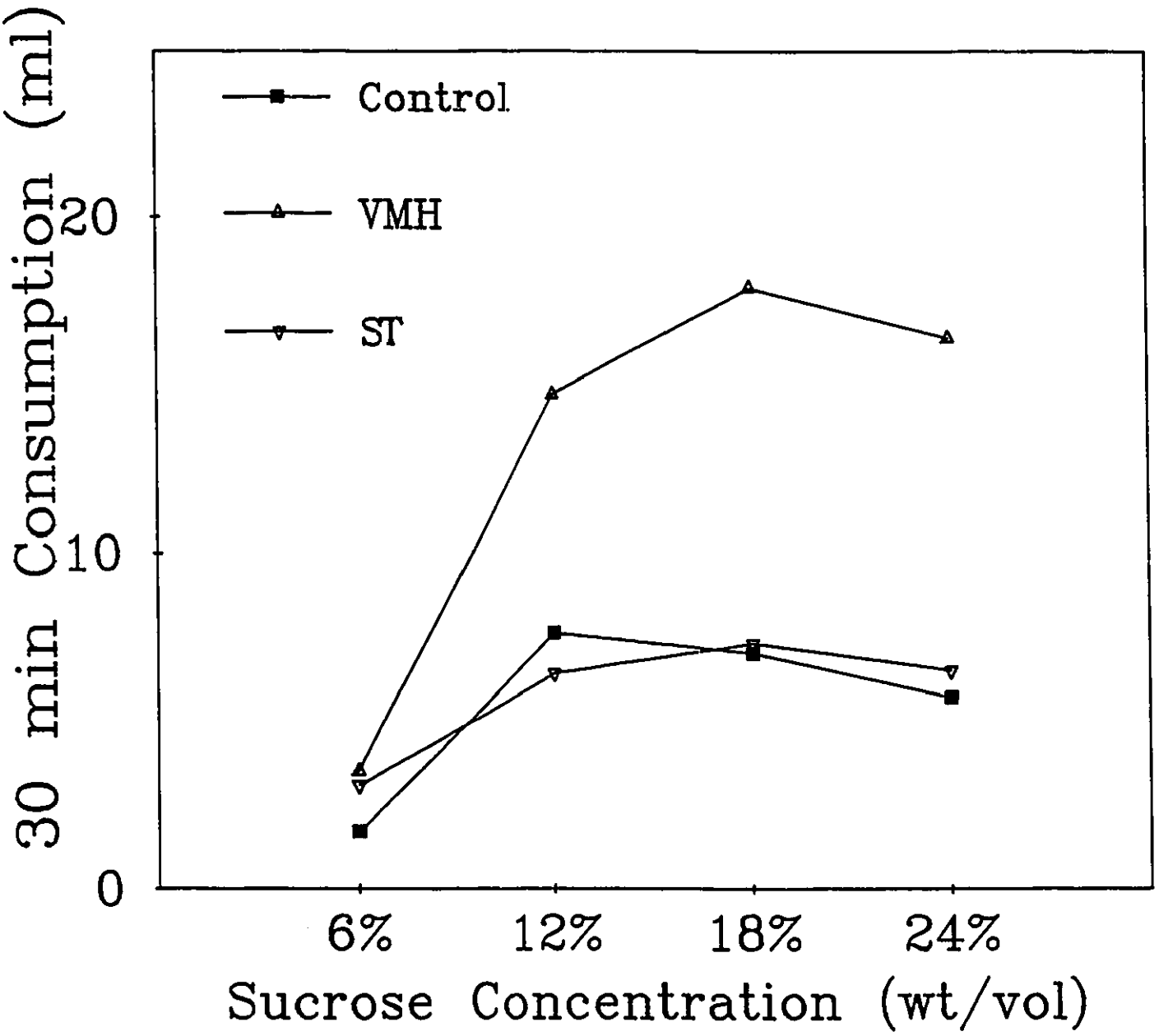

30 min Consumption (ml)
0
10
20
Control
VMH
ST
6%
12%
18%
24%
Sucrose Concentration (wt/vol)

Table 3. The q values for the Newman-Keuls post hoc comparisons of amount consumed when real feeding are presented.

TABLE 3

	ST	VMH
CONT	$q_2 = 0.8^{ns}$ $q_5 = 1.5^{ns}$	$q_3 = 0.9^{ns}$ $q_6 = 6.7^{**}$
	$q_2 = 0.7^{ns}$ $q_3 = 1.5^{ns}$	$q_8 = 11^{**}$ $q_9 = 15^{**}$
ST		$q_2 = 0.4^{ns}$ $q_2 = 8.1^{**}$
		$q_6 = 12^{**}$ $q_8 = 10^{**}$

KEY: in a given cell, the q values represent comparisons, "column > row", for normal consumption of specific sucrose concentrations in the following manner:

6%	12%
18%	24%

* $p < 0.05$ ** $p < 0.01$

across concentrations by the groups, i.e. the group by concentration interaction, was also significant, $F(6,36) = 6.52$, $p < 0.001$.

Multiple comparisons (36 df) revealed that all three groups ate similar amounts of 6% sucrose (all p's > 0.05). At all higher sucrose concentrations tested, however, VMH rats consumed more than both of the two other groups (p's < 0.01). In contrast to sham feeding, ST rats ate no more than controls at any sucrose concentration (all p's > 0.05). (See table 3 for relevant q values.)

Consistent with previous findings (Cox & Smith, 1986; Weingarten, 1982; Weingarten et al., 1985), the enhanced intake of VMH rats was apparent in both real and sham-feed tests. The hyperphagia of the VMH rat during real feeding is generally interpreted as reflecting its hyperreactivity to the positive palatability of the solutions being consumed. From this perspective, the behaviour of the ST rats is enigmatic. In spite of an increased sham intake and, therefore, an apparent hyperreactivity to taste, ST rats show no increased intake when, under similar experimental conditions, they are real feeding. Thus, the excessive eating of ST rats observed during sham feeding is masked or eliminated when food is permitted to accumulate in the stomach and activate gastric and post-gastric mechanisms.

Experiment 3. Ad Libitum Food Intake and Weight Gain

In brief (30-min) real feeding tests, VMH rats, but not ST knife-cut rats, overeat sucrose. The normal level of intake in ST rats when consuming sucrose is in contrast to their marked overeating of these same solutions when sham feeding. It is possible that ST rats would overeat under different experimental circumstances. Experiment 3 explores this possibility by examining food intake and weight gain of ST rats in the long term, when they are maintained on a series of conventional lab diets. This study also permits evaluation of whether ST knife-cuts produce any intake or weight disturbance in the long-term.

Methods

Subjects were 26 rats weighing an average of 342 $\pm$ 7 g at the beginning of the experiment. They were divided into three groups (VMH, ST, controls). After stereotaxic surgery, subjects were maintained ad libitum on the following test diets presented for the days indicated: powdered Purina Rodent Laboratory Chow #5001 (3.61 kcal/g; days 1-15); mash (65% water, 35% chow; 1.26 kcal/g; days 16-34); and high fat (33% Crisco oil, 67% chow; 5.50 kcal/g; days 35-54). Food was available ad libitum in Pyrex food cups placed on the floor of the cage. Daily measurements of food intake and body weight were made beginning on the third day after stereotaxic surgery.

Results and Discussion

Based upon the criteria described, eight of 12 rats were selected to the VMH group, and seven of eight to the ST group. There were six controls.

Figure 6 shows the group mean caloric intakes for the three groups. Groups ate significantly different amounts of powdered diet, $F(2,42) = 76.6$, $p < 0.0001$. Multiple comparisons (42 df) showed that VMH rats ate more than controls, $q_3 = 13.17$, and ST rats, $q_4 = 15.55$ (p's < 0.01). The intake of powdered chow by ST and controls rats did not differ, $q_2 = 2.38$ ($p > 0.05$).

Group intake differences were apparent on mash as well, $F(2,48) = 495.0$, $p < 0.0001$. VMH rats ate more than controls, $q_3 = 9.14$, and ST rats, $q_4 = 34.83$, (p's < 0.01). ST rats ate significantly less than controls, $q_2 = 4.23$ ($p < 0.01$).

Group differences in intake continued on the high fat diet, $F(2,57) = 32.65$, $p < 0.0001$. VMH rats consumed more than control rats, $q_3 = 9.14$, and ST, $q_4 = 10.89$, (p's < 0.01). The intake of ST rats and controls did not differ, $q_2 = 2.02$ ($p > 0.05$).

Differences in food intake were associated with weight changes (Figure 7). At the time of stereotaxic surgery, there were no weight differences among groups, $F(2,18) = 0.23$. However, at the end of 15 days access to powdered chow, groups differed in weight, $F(2,18) = 4.41$, $p < 0.05$. Multiple comparisons revealed that only the VMH versus ST pairwise comparison was significant, $q_4 = 3.93$, $p < 0.05$, although VMH rats also weighed more than controls at this time. At the end of

Figure 6. Average daily intake (kcal) of ST rats, VMH rats and controls when placed on the three diets used in Experiment 4. Values shown represent the group intake averaged over all the days of access to the diet indicated.

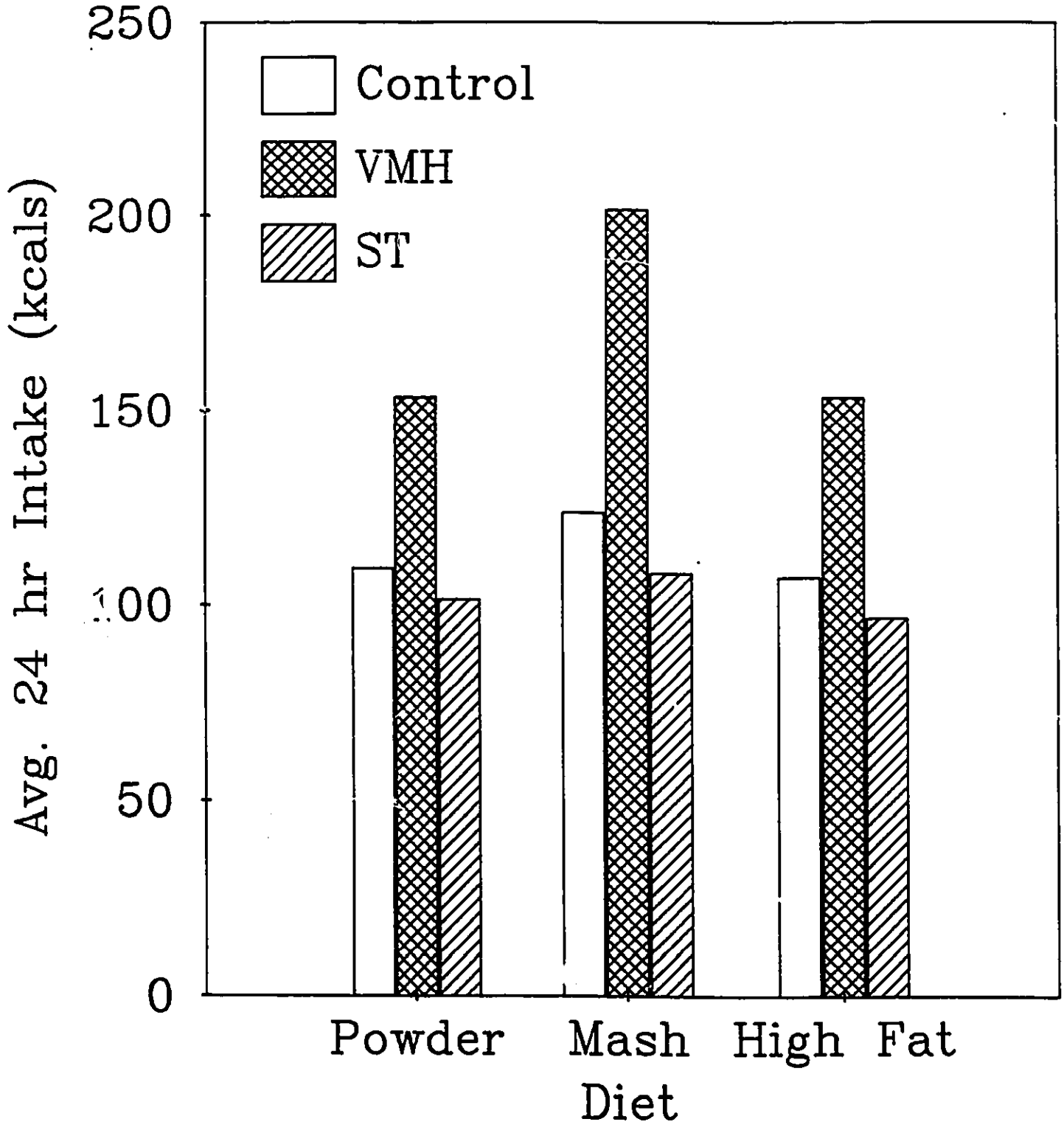
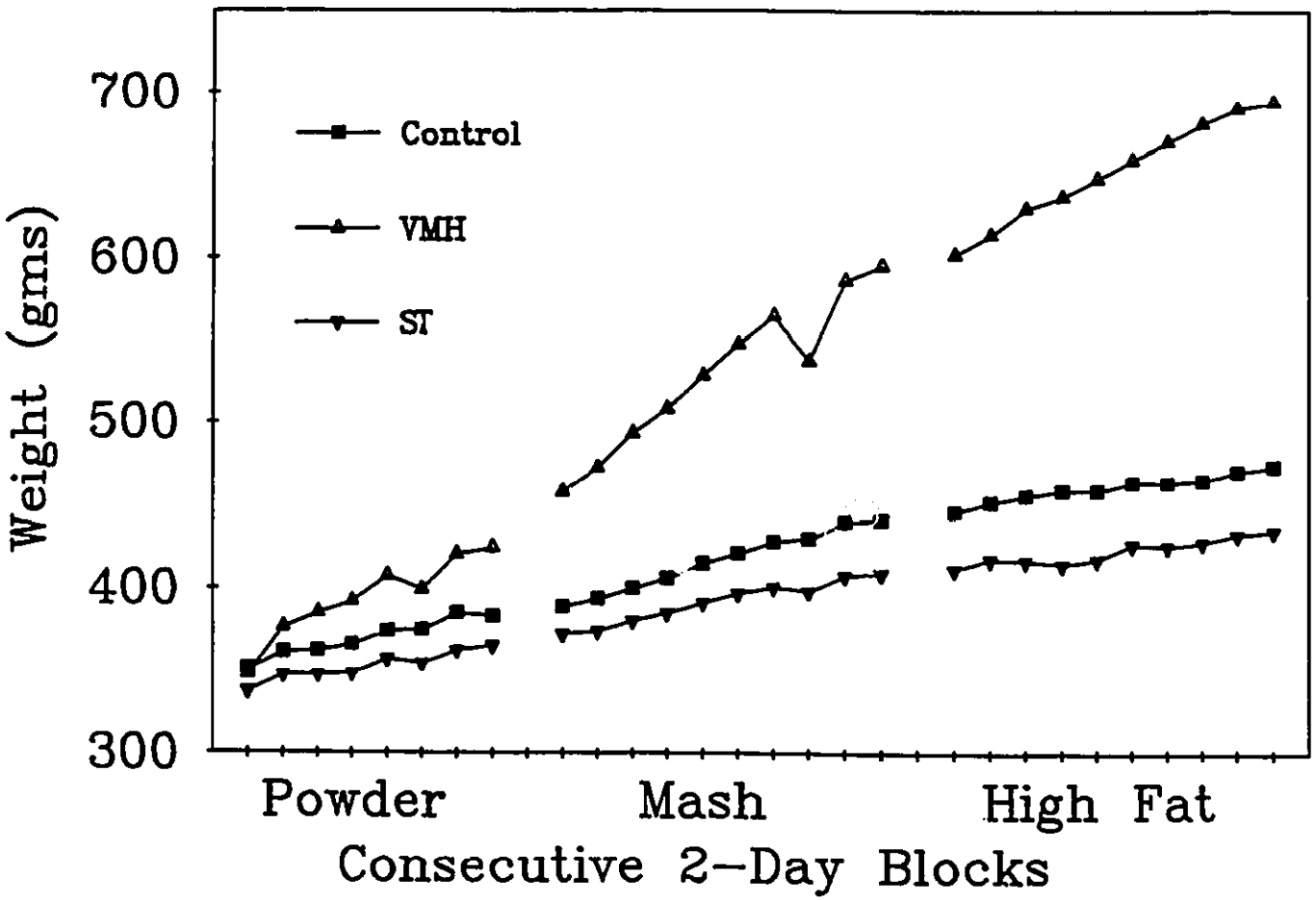

250
200
150
100
50
0
Control
VMH
ST
Avg. 24 hr Intake (kcals)
Powder
Mash
High Fat
Diet

Figure 7. Weight gain (in g) of the three experimental groups when given ad libitum access to the diets presented in Experiment 4.


700
600
500
400
300
Weight (gms)
Control
VMH
ST
Powder
Mash
High Fat
Consecutive 2-Day Blocks

19 days access to mash, large group differences in weight were apparent, $F(2,18) = 26.82$, $p < 0.0001$. VMH rats weighed more than controls, $q_3 = 7.51$, and ST rats, $q_4 = 9.26$, (p's < 0.01). ST rats and controls did not differ in weight, $q_2 = 1.66$. By the end of the high fat period, significant group differences in weight still existed, $F(2,18) = 27.50$, $p < 0.0001$. VMH rats weighed more than controls, $q_3 = 7.03$, and ST rats, $q_4 = 8.39$, (p's < 0.01), but the weights of the latter two groups were not different, $q_2 = 1.27$, $p > 0.05$.

General Discussion

Bilateral transection of the ST produces no change of feeding in either short- or long-term tests. These observations contrast with the results of Experiments 1a and 1b where the elevation of sham feeding in ST rats was as large as that in VMH animals. Although dissociations between real and sham feeding in response to particular manipulations have been reported previously (Lorenz, et al., 1978; Nissenbaum & Sclafani, 1988; Weingarten, 1984; Weingarten & Watson, 1982), all of these cases involve a <u>decreased</u> level of sham feeding in the face of no change in real feeding. The ST rat, however, represents the first instance in which <u>increases</u> in sham intake exist in the absence of similar increases in normal intake. If sham feeding measures the extent to which the taste of a food drives intake, as has been suggested (see Weingarten & Bedard, 1990, for a review of this literature), then it is unclear why an apparent

hyperreactivity to taste does not result in an elevated real feeding in ST rats. Two possibilities exist to explain this dissociation.

Experiments 2 and 3 measured food consumption only, but eating is more than simply consumption. There are also appetitive events which serve to bring the animal into contact with the food. Appetitive behaviour can also be interpreted as an animal's motivation to eat (Blackburn, Fibinger, & Phillips, 1987; Blackburn, Fibinger, Jakubovic & Phillips, 1987; Weingarten & Martin, 1989). It is unclear what aspect of eating sham feeding measures, but it is possible that sham feeding provides a better measure of a rat's motivation to eat than consumption per se. Experiment 4 uses a behavioural preparation, conditioned feeding, which allows the measurement of both appetitive behaviour, i.e. motivation, and consumption. This measure of motivation might uncover a disturbance in real feeding that remained unobserved in Experiments 2 and 3.

An alternative possibility is that gut signals, which are activated during real feeding but which are absent during sham feeding, may block the tendency towards overeating in ST rats. If so, one must hypothesize that relevant gut signals which inhibit eating are exaggerated in the ST rat, or reduced in the VMH rat.

To investigate whether changes in inhibiting gut signals explain the normal intake of ST rats in spite of exaggerated sham intake, I measured a gut signal believed to be involved prominently in meal termination, gastric emptying (Experiment 5)

(for a review of the relationship between gastric emptying and satiety, see McHugh & Moran, 1986a). It is conceivable that this satiety mechanism may be more effective in terminating a meal in the ST rat than in the VMH rat, thus blocking any hyperphagia when the ST rat is real feeding. This could result from a slowed rate of gastric emptying in ST rats. Conversely, the hyperphagia of the VMH rat evident during real feeding may reflect a reduced satiety signal from the stomach involving, perhaps, an accelerated rate of gastric emptying (Duggan & Booth, 1986).

CHAPTER V. CONDITIONED FEEDING

ST knife-cuts increase sham feeding but result in no change of real feeding. Part of the difficulty interpreting this apparent discrepancy is that it is unclear what aspect of eating sham feeding actually measures. It has been suggested that sham feeding reflects motivation to eat and is not an accurate barometer predicting actual consumption. This suggestion is based on demonstrations that manipulations which affect an animal's motivation to eat also change the level of sham feeding but do not necessarily change meal size (Cooper, Van der Hoek & Kirkham, 1988; Weingarten, 1985; Wise, 1974; Wise & Dawson, 1974).

Therefore, increases or decreases in sham feeding may provide a measure of the organisms increased or decreased motivation to eat. Thus, the enhanced sham feeding of the ST rat might reflect an elevated motivation for food, an effect which would not have been detected by the real feeding studies of Experiments 2 and 3 which measured consumption only. To assess this possibility, I used a behavioural preparation, conditioned feeding (Weingarten, 1983,1984a,b), which permits direct

measurement of the animal's motivation to eat as well as the consequent meal size .

In the conditioned feeding paradigm, a neutral cue is paired with food and the opportunity for ingestion. Once rats learn this association, subsequent exposure to the food-associated cue elicits feeding, even in sated rats. Blackburn et al. (1987; Blackburn, Phillips, Jakubovic & Fibiger, 1989) have argued that two measures in the conditioned feeding situation index the animal's motivation to eat: latency to feed when the meal is delivered, and the amount of food related anticipatory behaviour when the meal is expected, but prior to actual delivery of food. The best measure of anticipatory behaviour is the amount of time rats nosepoke into the food cup where food is expected.

If the enhanced sham intake of ST or VMH rats reflects an increased motivation to eat, then this should be evident in the direct measures of motivation permitted in the conditioned feeding paradigm as well.

Methods

Subjects

Thirty one rats, weighing 403 $\pm$ 7 g (mean $\pm$ 1 SEM) underwent stereotaxic surgery to produce VMH (n = 13), ST (n = 10), and control (n = 8) groups.

Housing Conditions

Subjects were individually housed in Plexiglas cages which served as both the home and test cages (29 cm x 29 cm by 46 cm high) in a room maintained at 21° C. A single 25 watt light constantly illuminated the housing room. Water was continuously available.

A food cup was attached to the centre of one wall of the cage, 3 cm above the cage floor. The cup was equipped with a photoelectric beam at its front edge to monitor a subject's nosepoking into the cup. Food was pumped into the food cup by a peristaltic pump (Harvard). Each meal consisted of 8 ml of a liquid diet (385 ml Carnation evaporated milk, 92.5 g sugar, 85 ml water and 0.3 ml Tri-Vi-Sol vitamins).

Conditioning Phase

The conditioning phase started the day following stereotaxic surgery. During conditioning, a Pavlovian conditioning procedure was used to teach rats an association between a neutral cue, a conditioned stimulus (CS+), and food. Each day, rats were given six meals with an average intermeal interval of 3 to 5 hr. [The total intake in the six meals represented approximately 80% of the rats' daily ad lib intake.] Each meal was signalled by preceding its delivery with a 4 1/2 min conditioned stimulus (CS+). The CS+ consisted of illumination of a 60 watt light bulb

presented simultaneously with a buzzer. The meal was delivered during the final 30 sec of the CS+.

Delivery of the food was computer controlled (Commodore PET 2031). The computer also detected when the light beam across the food cup was broken, allowing measurement of the time rats nose-poked into the food cup during the CS+ and the latency to eat the meal once it was delivered. Conditioning continued for 11 consecutive days.

Test Phase

At the completion of conditioning, rats were maintained on ad libitum Purina Rat Chow pellets placed in the home cage. Rats were maintained ad libitum for the duration of the testing. Testing began two days after the end of conditioning. The purpose of the test phase was to assess the motivation to eat, and the amount eaten, by ST and VMH rats in response to the food associated CS+. A test trial consisted of the presentation of the 4 1/2 min CS+ followed by delivery of 24 ml of liquid diet into the food cup. Ten min after meal delivery, the food remaining in the food cup was measured to permit calculation of meal size.

Results

Six of 13 rats sustained criterion VMH damage. Six of 10 rats had criterion ST transections, and eight animals served as controls.

Latency to feed during testing is shown in Figure 8. All rats initiate a meal rapidly in response to the CS+. ST rats and VMH rats were slower to initiate meals than controls, but this difference was not significant, $F(2,17) = 0.49$. However, there were group differences in anticipatory nosepoking, $F(2,17) = 7.55$, $p < 0.005$ (see Figure 9). A Newman-Keuls post hoc test (17 df) showed that control rats nosepoked more than both ST ($q_3 = 5.28$, $p < 0.01$) and VMH ($q_2 = 3.94$, $p < 0.05$) rats. There were no differences in the amount of anticipatory nosepoking between ST and VMH rats ($q_2 = 1.32$).

In spite of the observed differences in anticipatory behaviour, all groups consumed similar amounts of the test meal, $F(2,17) = 0.52$ (see Figure 10).

Discussion

If, as has been suggested (Blackburn et al., 1987; Blackburn et al., 1989), anticipatory nosepoking and latency to eat in the conditioned feeding situation reflect motivation to eat, then the results of this experiment suggest that neither ST nor VMH rats are more motivated for food than control rats. ST rats nosepoke

Figure 8. Latency to feed (sec) following introduction of the signalled meal into the food cup during the test phase. Vertical lines represent 1 SEM.

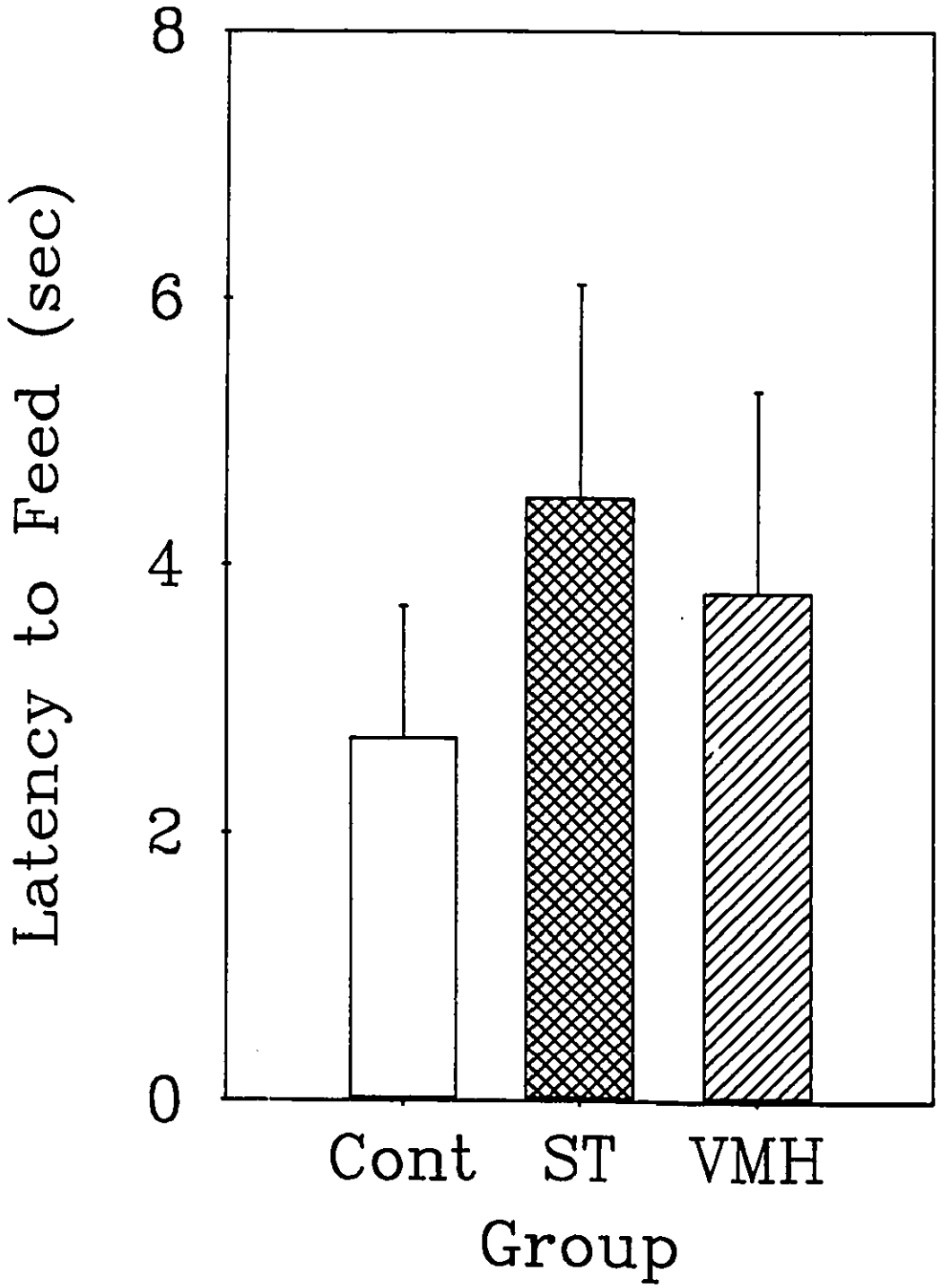

Latency to Feed (sec)
8
6
4
2
0
Cont
ST
VMH
Group

Figure 9. Cumulative time (sec) spent nosing into the food cup during presentation of the CS+, prior to the introduction of the meal, during the test phase. Vertical lines represent 1 SEM.

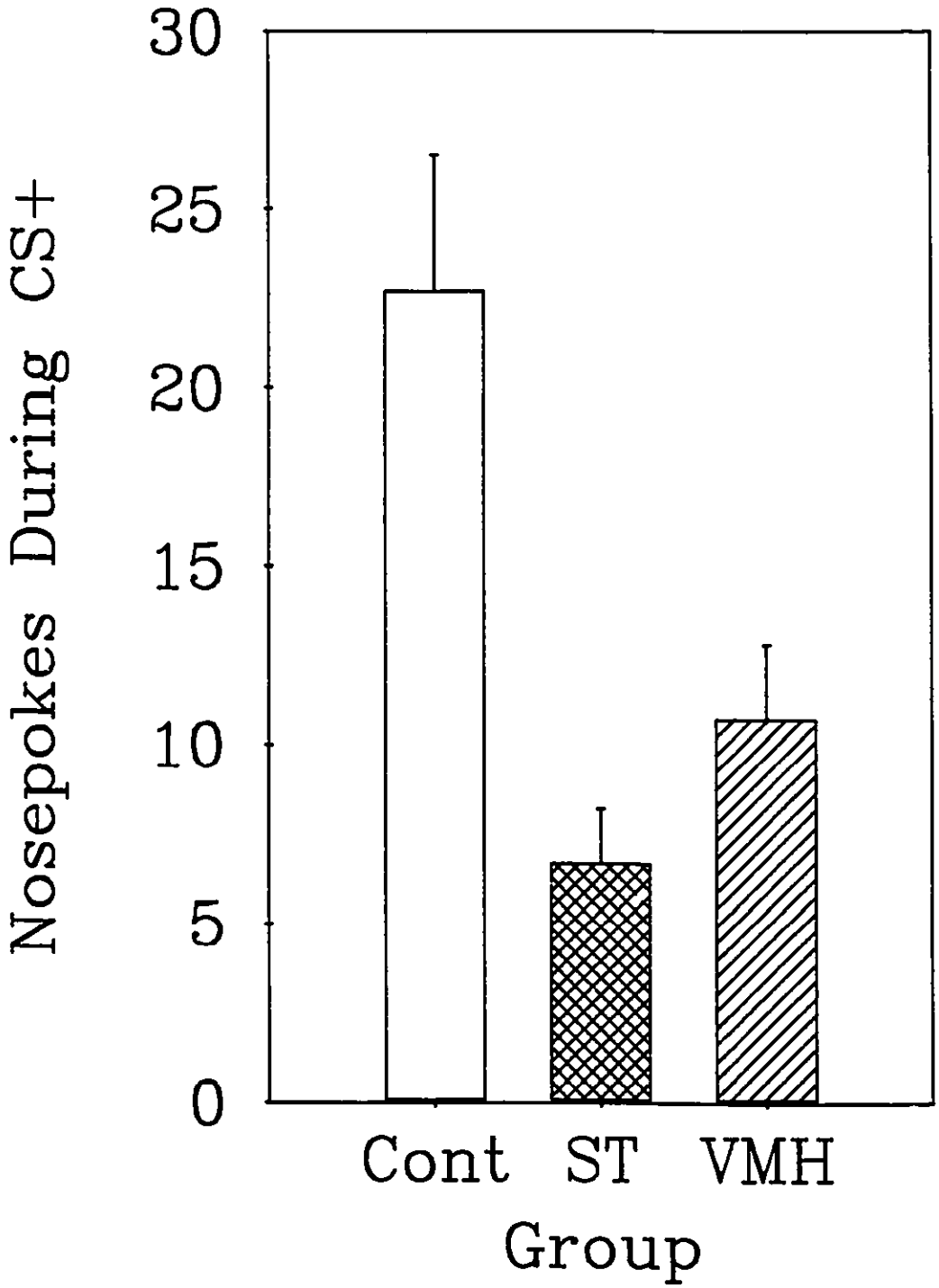
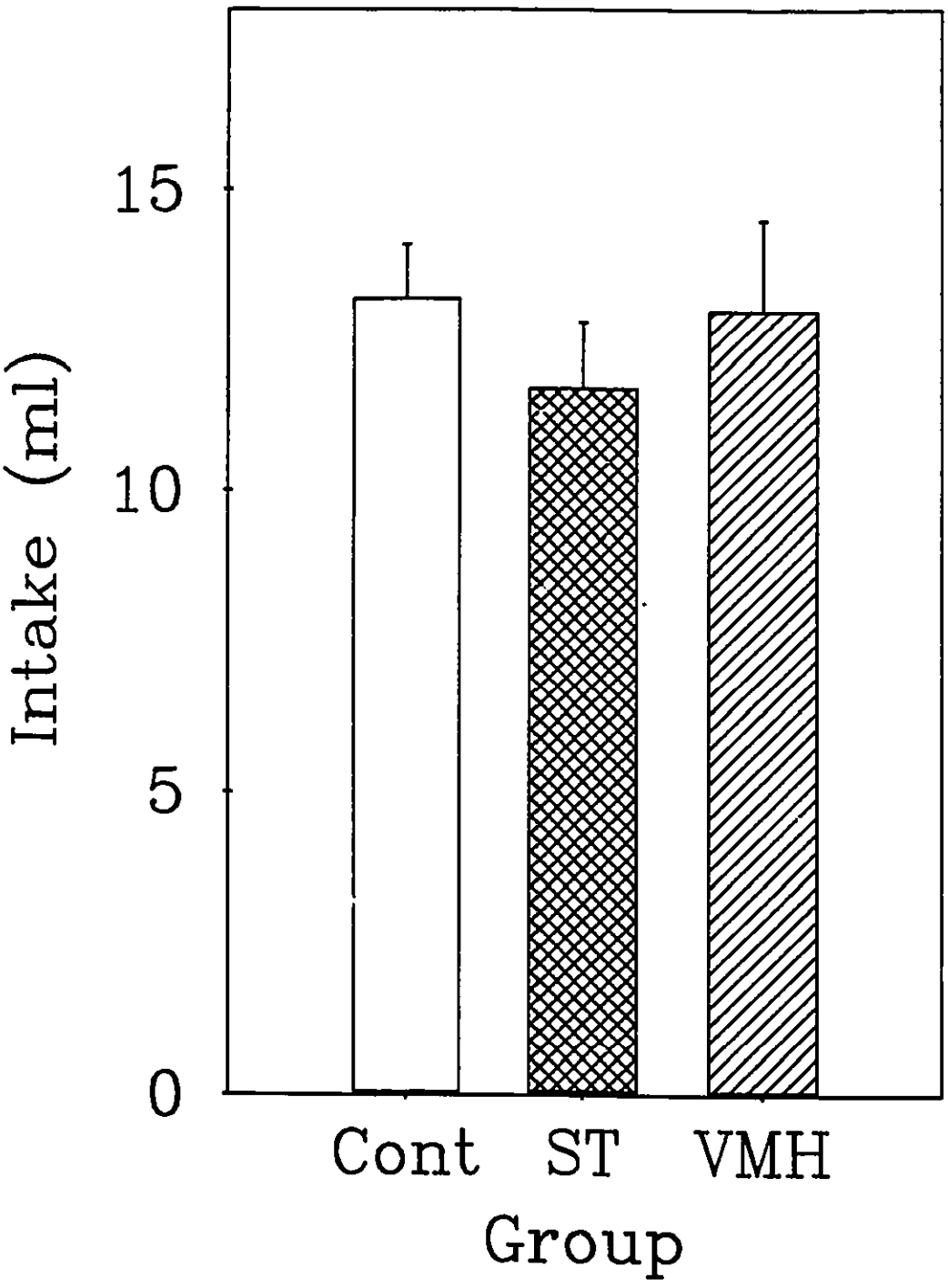

Nosepokes During CS+
30
25
20
15
10
5
0
Cont
ST
VMH
Group

Figure 10. Average 10 min intake (ml) of liquid diet test meal in response to the CS+ during the test phase. Vertical lines represent 1 SEM.


15
10
5
0
Intake (ml)
Cont
ST
VMH
Group

less during the CS+ than controls and show similar latency to feed as controls.

VMH rats also nosepoked less during the CS+, suggesting that they are less motivated to eat than are controls, consistent with other studies (Miller, Bailey & Stevenson, 1950; Teitelbaum, 1957).

An unexpected result was the absence of hyperphagia by VMH rats in response to the CS+. VMH rats were hyperphagic when 24 hr ad libitum intake was measured[1]. It is unlikely that the 12.5 ml average meal consumed by VMH rats in response to the CS+ represents a ceiling on ingestion since, in 10 minutes, controls can eat 20 ml of liquid diet (Weingarten, unpublished data). The absence of excess eating by VMH rats when feeding is consistent with a similar finding by Coover, Welle & Hart (1980), who showed that VMH rats and controls did not differ in amount consumed over the short term when eating was instigated by exposure to a cue associated with food. However, the absence of any discernible hyperphagia in VMH rats when feeding is elicited by a conditioned stimulus, in spite of overeating in VMH rats in other situations, underscores the fact that an adequate explanation of any feeding disturbance requires examination in a set of different eating situations.

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1. At the conclusion of testing, all animals receiving VMH lesions had 24 hr access to a high fat diet (for diet composition, see Chapter 4, Experiment 3). An ANOVA showed that rats with VMH lesions were hyperphagic compared to rats that did not meet the criterion for inclusion in the VMH group, $F(1,13) = 42.9$, $p < 0.0001$.

CHAPTER VI. GASTRIC EMPTYING

Although both ST and VMH rats overeat when sham feeding, only the VMH rat remains hyperphagic when real feeding. It is possible that an exaggerated satiety signal normalizes real feeding in the ST rat, or conversely, that a diminished satiety signal permits overeating in the VMH rat. This experiment evaluates the status of a satiety signal, gastric emptying, in ST and VMH rats.

A large body of evidence points to the involvement of gastric events in satiety, i.e., meal termination. The gastric event most often implicated in meal termination is gastric distension, a physiological signal which depends critically on the rate of gastric emptying.

Stomach distension has long been regarded as a satiety signal (Deutsch, 1985; Deutsch & Gonzalez, 1980, 1981; Deutsch, Gonzalez & Young, 1980). It is believed that once a threshold level of stomach distension is reached, stretch receptors in the stomach (Paintal, 1973) activate satiety. The amount of food in the stomach, and therefore its distended, depends upon the rate not only of eating but also of food emptying from the stomach.

This latter event, gastric emptying, is believed to be key to stomach control of meal size. For example, the predominant theory to explain the mechanism by which cholecystokinin (CCK) induces satiety is that the CCK slows the rate of gastric emptying, thus decreasing the time required for the stomach to reach threshold distension and activate meal termination (Moran & McHugh, 1982; McHugh & Moran, 1986a,b). [Distension may not act in isolation as a determinant of meal termination. Some have argued that distension activates satiety by optimizing chemical and nutritive stimulation of gastric chemo- and nutritive-receptors responsible for signalling the end of a meal (Stricker & McCann, 1985)].

Analysis of gastric emptying in ST and VMH rats is particularly relevant because manipulations of the limbic system, of which the ST is an integral component, alter gastric events. For example, lesions of various nuclei of the amygdala increase gastric motility in the cat (Koikegami, 1964; Shealy & Peele, 1957) and dog (Fennegan & Puiggari, 1966). Electrical stimulation of various amygdala nuclei increase the volume and concentration of gastric acid in response to histamine (Shealy & Peele, 1957). Lesions of the centromedial amygdala reduce fasting gastric acidity (Grijalva, Tache, Gunion, Walsh & Geiselman, 1986) and lesions in the medial amygdala attenuate stress-induced gastric ulcers while lesions of the ST potentiate stress-induced gastric ulcers (Henke, 1980a,b,c, 1981, 1985; Arunabha, Henke & Sullivan, 1988).

VMH lesions are also known to alter gastric events, e.g. increasing gastric acid secretion (Weingarten et al, 1985; Weingarten & Parkinson, 1988; Weingarten & Powley, 1980a) and rate of gastric emptying (Booth & Duggan, 1985; Duggan & Booth, 1986; Duggan, Storlien, Kraegen & Booth, 1988).

To assess the contribution of alterations of gastric emptying to the feeding changes induced by ST knife-cuts or VMH lesions documented in Experiments 1a, 1b, 2 and 3, I monitored effects of these manipulations on gastric emptying. To monitor gastric emptying, I used a technique which provides a valid and sensitive measure of a number of gastric parameters, including emptying, in a single trial -- the double sampling technique (Conover, Weingarten & Collins, 1987).

METHODS

Subjects

Twenty-one subjects were implanted with an indwelling gastric cannula (see Chapter 2). They recovered from surgery for a minimum of two weeks prior to stereotaxic surgery. Subjects were assigned to one of three lesion groups: control (6), ST (6) or VMH (9), such that group mean weights were approximately equal at the time of stereotaxic surgery. Subjects were tested 14 to 21 days post-lesion, in order to allow feeding behaviour to stabilize. During this time, food was provided daily so that all subjects were maintained at 95% of their free feeding body weight measured on the day prior to stereotaxic surgery (allowing a 1 g

per day growth rate). This food restriction procedure ensured that any differences between groups were due to the brain manipulation and did not result from treatment-induced effects on body weight.

Materials and Methods

The materials and protocols for measuring gastric emptying rate have been described in detail elsewhere (Conover et al., 1987).

Briefly, each rat was 6 hr food deprived prior to measurement of gastric emptying. To prepare a rat for testing, it was taken from its home cage and weighed. The set screw was removed to open the gastric cannula and the stomach cleaned with lukewarm tap water applied through the cannula. A sampling catheter was screwed into the cannula and the rat was placed in the test cage (10 cm x 10 cm x 20.5 cm, with a 1.5 x 20.5 cm floor slot, mounted on 19.5 cm stilts); the sampling catheter hung freely through the floor slot.

Gastric emptying was measured using a double sampling technique (Conover et al, 1987). At the beginning of the test session, a test load consisting of 10 ml of 15 % sucrose, containing 2.5 % (v/v) of 0.02 % phenol red (Fisher Scientific), was infused intragastrically. The time of infusion was defined as time 0. Gastric samples were drawn at 2 min, 10 min, and every 10 min thereafter. For each sample, 0.5 ml of gastric contents were removed to determine initial dye concentration. A

probe dye consisting of 1 ml of 15 % sucrose with 0.1 % (v/v) phenol red solution was injected into the stomach and mixed with stomach contents. Finally, one minute after the withdrawal of the first 0.5 ml sample, a second 0.5 ml sample of gastric contents was removed to determine resulting dye concentration.

Double sampling depends upon colourimetric measure of dye concentrations. Dye concentrations of samples were measured by absorption spectrophotometry at a wavelength of 560 nm, using a Bausch & Lomb Spectronic 21 spectrophotometer. Samples were prepared for spectrophotometry by diluting a 0.25 ml aliquot from the sample in 2.75 ml 0.01 N NaOH. Samples were filtered through a 0.2 um cellulose filter (13 mm diameter, Sartorius) to remove particulate matter.

Following gastric emptying tests, subjects were maintained ad libitum on mash diet for 40 days. Subjects were weighed every other day.

Results

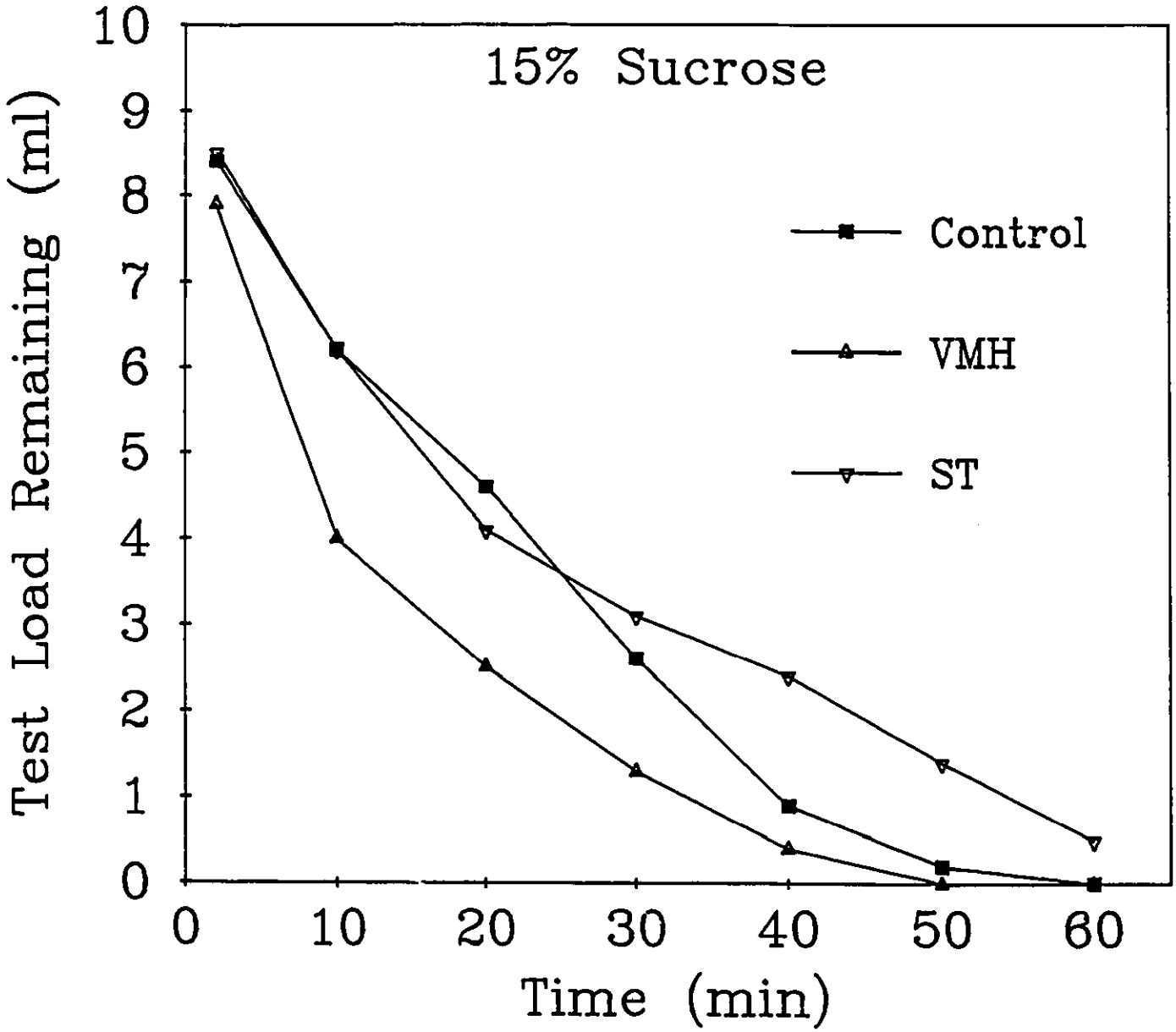
Five of nine rats with VMH lesions sustained criterion neural damage requisite for inclusion into the VMH group. All six rats undergoing ST transection met the histological criterion. Five of the original six rats comprised the control group (the cannula in one control rat failed to remain patent).

The restricted feeding regimen maintained all groups at equivalent weights. There were no significant differences in group mean weights at the time that gastric emptying was

measured, $F(2,13) = 1.44$. After 40 days ad libitum access to mash, however, significant group differences in weight existed, $F(2,13) = 70.66$, $p < 0.0001$. Newman-Keuls multiple comparisons (13 df) revealed that VMH rats weighed more than both controls, $q_2 = 21.0$, and ST rats, $q_3 = 25.7$, (p's < 0.01). There were no significant weight differences between ST rats and controls.

The rate of gastric emptying is documented best by measuring the amount of the original test load remaining in the stomach (which by subtraction from the original test load volume provides the amount that has emptied) (see Figure 11). Analysis of variance applied to the test load remaining data showed significant effects of Group, $F(2,13) = 6.78$, $p < 0.01$, and Time, $F(6,12) = 165.9$, $p < 0.0001$. The Group X Time interaction was also significant, $F(12,78) = 2.21$, $p < 0.05$. For all groups, the amount of original test load remaining in the stomach should decrease with time because the load is being emptied into the duodenum. This stomach emptying accounts for the significant time effect. However, the significant Group and Group X Time interaction indicates that test load emptied from the stomachs of subjects in the three groups at different rates (see figure 11). To determine the nature of the group differences, ANOVA's were performed at each sampling point. At any sampling point where a significant group effect appeared, it was analyzed further with Newman-Keuls post hoc analyses to determine which groups were different from one another. The amount of emptying of test load at 2 minutes was not different among groups, $F(2,13) = 0.811$. By 10 minutes, there were Group differences, $F(2,13) = 10.66$, $p <$

Figure 11. Time course for the emptying of a 10 ml 15% sucrose test load. Test load remaining is the volume in the stomach after a correction for gastric secretion.


15% Sucrose
Control
VMH
ST
Test Load Remaining (ml)
Time (min)
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60

0.01; VMH rats had emptied more the stomach than both controls, q_2 = 5.6, and ST rats, q_3 = 5.71, p's < 0.01. This trend persisted at 20 minutes, a significant Group difference, F(2,13) = 4.44, p < 0.05, with VMH rats' stomachs emptying faster than controls, q_3 = 4.01, and ST rats, q_2 = 3.13, p's < 0.05. By 30 minutes, and for all time points thereafter, all groups had emptied similar amounts from the stomach indicated by the absence of significant Group effects at 30 minutes, F(2,13) = 2.49; 40 minutes, F(2,13) = 2.67; 50 minutes, F(2,13) = 3.32; and 60 minutes, F(2,13) = 1.06).

Analysis of gastric secretions revealed Group differences, F(2,13) = 7.205, p < 0.01, as well as an effect of Time, F(6,12) = 186.8, p < 0.0001. The Group x Time interaction was also significant, F(12,78) = 8.64, p < 0.0001 (see Figure 12). ANOVA's at each time point revealed that by 10 minutes, F(2,13) = 5.09, p < 0.05, and for all other time points, (20 minutes, F(2,13) = 7.38; 30 minutes, F(2,13) = 6.52; 40 minutes, F(2,13) = 7.85; 50 minutes, F(2,13) = 10.48; 60 minutes, F(2,13) = 9.44 (all p's < 0.01)) VMH rats secreted more than both controls and ST rats (Newman-Keuls analyses showed that secretion in VMH rats was greater than controls and ST rats, all p's < 0.05). At no time did the amount secreted by ST rats differ from controls.

Gastric volume, i.e. test load remaining plus gastric secretions, was not different among groups, F(2,13) = 0.1. While there was an effect due to Time, F(6,78) = 54.8, p < 0.001, there was no Group X Time interaction, F(12,78) = 1.02 (Figure 13).

Figure 12. Cumulative volume of gastric secretion following intragastric infusion of 10 ml 15% sucrose solution.

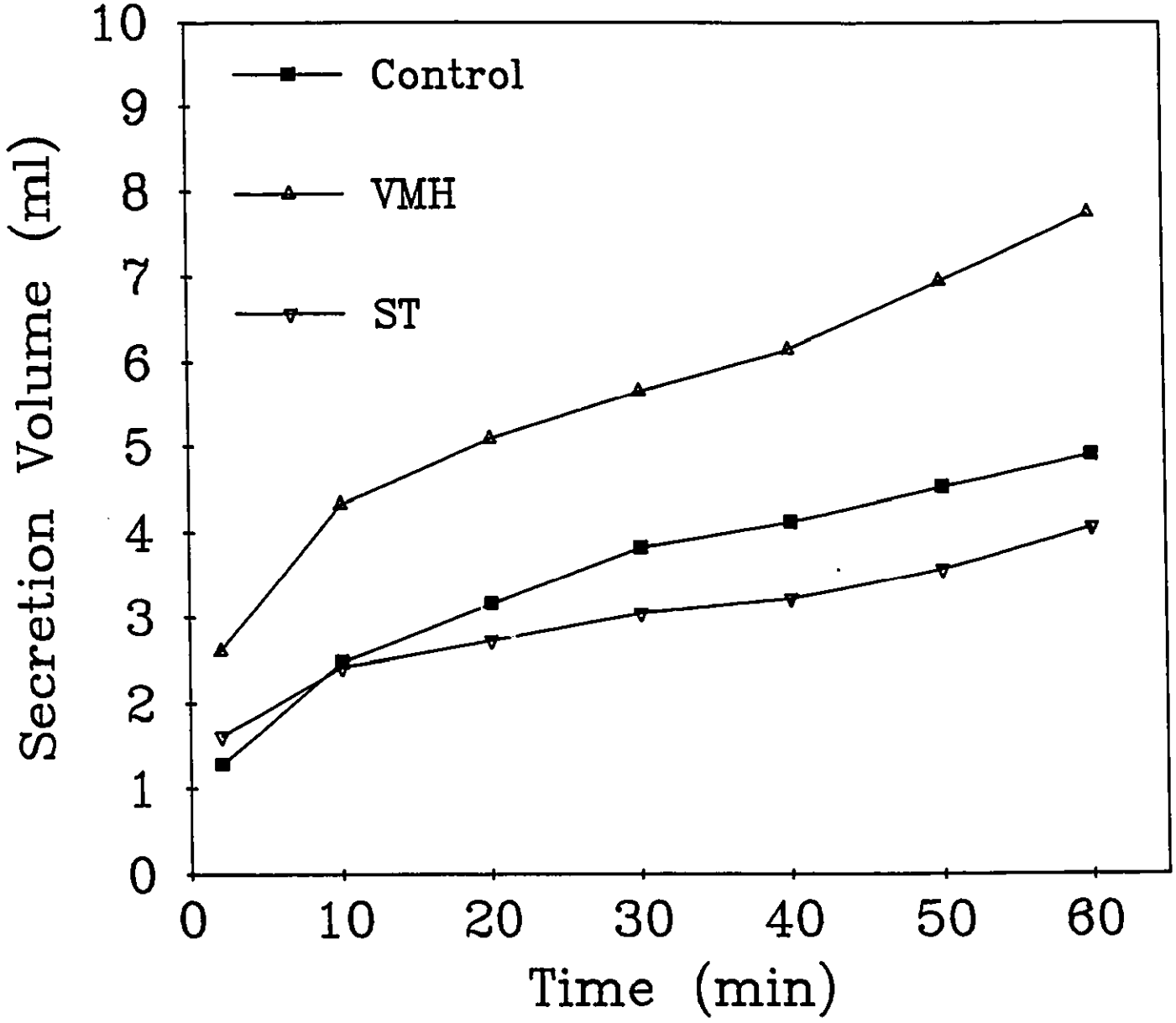
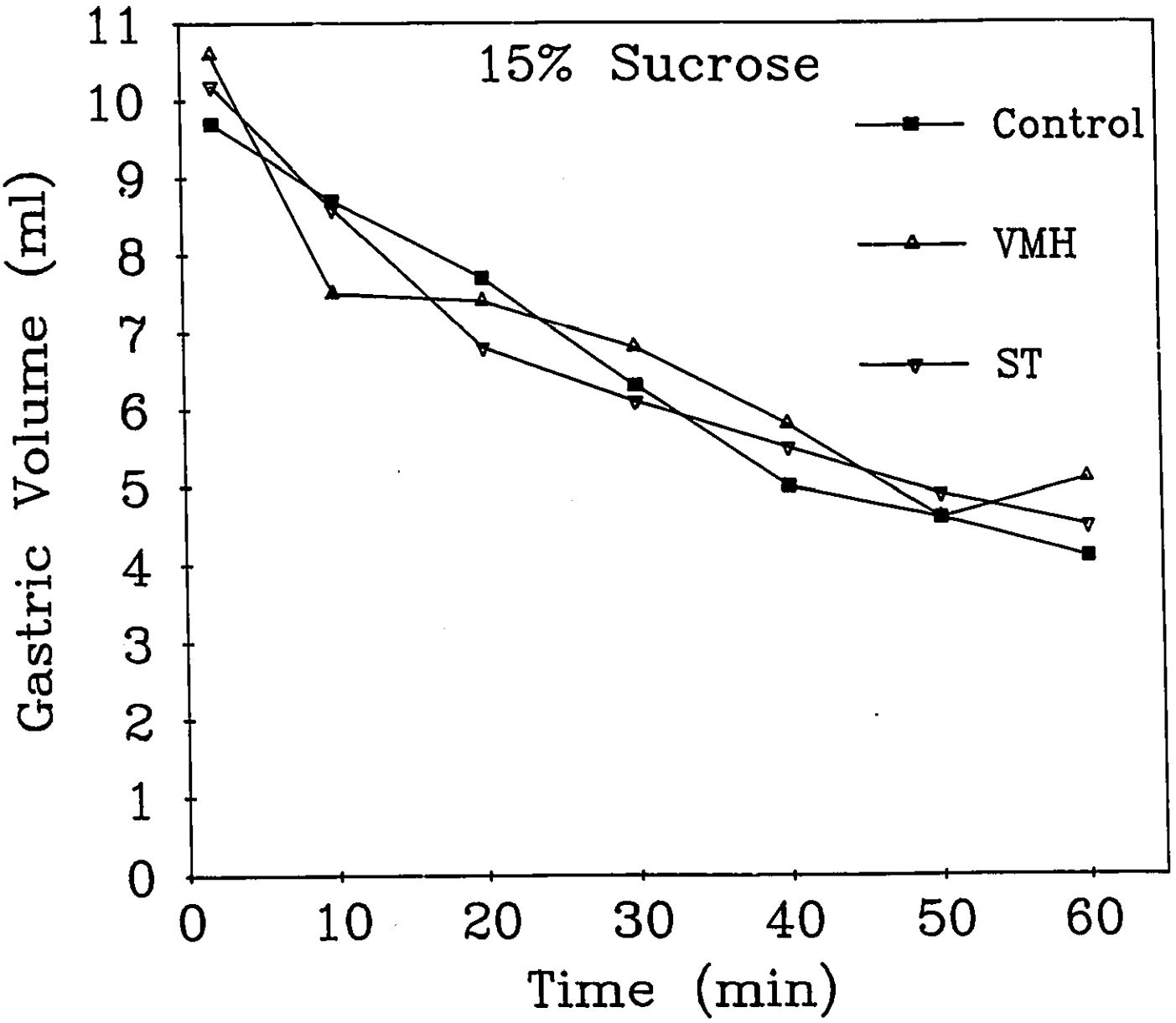

Control
VMH
ST
Secretion Volume (ml)
Time (min)
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60

Figure 13. Time course for change in gastric volume following infusion of a 10 ml 15% sucrose test load. Gastric Volume includes both the test load remaining in the stomach and gastric secretions.


15% Sucrose
Control
VMH
ST
Gastric Volume (ml)
0
1
2
3
4
5
6
7
8
9
10
11
0
10
20
30
40
50
60
Time (min)

Discussion

This experiment was carried out to determine if changes in gastric events could provide an explanation for the absence of hyperphagia in ST rats when normal feeding, or the presence of hyperphagia in VMH rats when normal feeding.

ST knife-cuts did not alter the rate at which a test load of 15% sucrose emptied from the stomach. Furthermore, ST knife-cuts did not alter the rate of gastric secretion or the total gastric volume following infusion of the test load. Thus, this study failed to reveal any amplification of gastric satiety signals which might possibly block the tendency of the ST rat to overeat.

These results do, however, confirm previous reports of an enhanced rate of gastric emptying in VMH rats (Booth & Duggan, 1985; Duggan & Booth, 1986; Duggan, Storlien, Kraegen & Booth, 1988), and an increased volume of gastric secretion (c.f. Ridley & Brooks, 1965; Chikamori, Fukushima, Yashamita, Sayto, Nishimura & Mori, 1983; Weingarten & Powley, 1980a). The combination of the increased rate at which the test load emptied from the stomachs of VMH rats and the increased rate of gastric secretion by VMH rats, resulted in a total gastric volume that was not different from ST rats or controls.

The accelerated emptying of the test load may account for the hyperphagia of VMH rats when real feeding. The difference in emptying rate between VMH rats and control rats exists only for the first 30 minutes following infusion of the test load. It is

during the first 30 minutes of the feeding bout that VMH rats demonstrate their hyperphagia. Furthermore, since the time course of total gastric volume did not differ among the three experimental groups, despite the increased rate at which VMH rats emptied the test load, it is the rate at which nutrient (the test load) empties from the stomach, and not stomach distension, which has the greatest impact on satiety.

CHAPTER VII. GENERAL DISCUSSION

Studies of human obesity emphasize reactivity to taste, especially sweet, in the development of hyperphagia and obesity (e.g. Drewnowski, Brunzell, Sande, Iverius & Greenwood, 1985; Schacter & Rodin, 1974; Wurtman, Wurtman , Growden & Henry, 1981; Yudkin, 1973; for a review see Spitzer & Rodin, 1981). Much of this research has been promoted by anecdotal reports that overweight people have a "sweet tooth" (Drewnowski et al., 1985) and, therefore, seek out and overconsume sweet (high carbohydrate) foods. Some laboratory studies have supported these observations, although the exact stimulus (taste) property to which overweight people respond by overeating is controversial (e.g. Drewnowski et al., 1985), as is the notion that all obese subjects show an exxagerated taste response (James & Trayhurn, 1976, 1981; Jéquier & Schutz, 1986; Jung, Shetty & James, 1979; Ramirez, Tordoff & Friedman, 1989).

An animal model used extensively to study the role of taste reactivity in obesity is the VMH rat (Nisbett, 1972; Schacter, 1971; Schacter & Rodin, 1972) because it has long been recognized that VMH rats demonstrate a profound obesity and an exaggerated response to the taste of food. However, the VMH rat

has a host of additional physiological and behavioural disturbances which make it difficult to study the relationship between taste reactivity, hyperphagia and obesity in isolation (for a review of these disturbances, see Powley, 1977; Sclafani & Kirchgessner, 1986; this thesis, Chapter 1). This thesis attempted to determine the anatomical locus which, when damaged, resulted in taste reactivity changes produced by VMH lesions, in order to determine if it was possible to produce an animal that showed a hyperreactivity to taste similar to VMH rats but which did not possess the assorted other symptoms complicating analysis of the VMH syndrome.

VMH Finickiness

A review of the literature implicated fibre systems between the amygdala and the VMH as a possible locus for VMH lesion-induced finickiness. The experimental strategy for evaluating the role of these connections was to transect the major fibre bundle connecting the amygdala and the hypothalamus, the ST. Also, based on recent anatomical studies of the forebrain taste system, this tactic had the additional benefit of transecting the fibre tract (the ST) which was pivotal in the projection of the taste system in the forebrain and the limbic system.

Experiments 1a and 1b revealed that rats with bilateral ST knife-cuts sham fed in a manner closely resembling VMH rats. For both ST and VMH rats, the magnitude of sham feeding of a sweet sucrose solution was two to three times that of controls. When the sucrose solution was adulterated with quinine, both VMH and

ST rats showed decreases in sham feeding with increasing quinine concentration similar to the decrease exhibited by control rats. However, it was also clear that the enhanced sham feeding of VMH rats did not arise through destruction of amygdalo-hypothalamic connections. Rats with combined VMH and ST damage sham fed more than either VMH or ST rats and, the combined damage was almost perfectly additive with respect to the behavioural disturbance produced by either manipulation alone. Moreover, the sham feeding profile of ST rats differed from that of VMH rats: ST rats had an elevated intake of 6% sucrose while VMH rats did not. Thus, while increasing sucrose concentration led to disproportionate increases in sham feeding by VMH rats, the profile of ST rats paralleled that of controls and was simply elevated compared to control levels.

Nonetheless, ST knife cuts produced animals which displayed a dramatic enhancement of taste-driven intake. This result represents the first demonstration of an intake enhancement following damage to a fibre tract in the forebrain taste system. The remainder of this thesis was devoted to attempts to characterize the feeding disturbance of the ST rat and to understand the mechanism which could explain the behavioural effects observed.

Feeding Behaviour of the ST Rat

Much of the research on the etiology of obesity has derived from the view that an increase in the ability of positive tastes to drive intake could increase overall intake and lead to

obesity. Some studies have failed to find an enhanced reactivity to food in some obese humans (e.g. Grinker, 1975; McKenna, 1972) and animal models of obesity (e.g. Zucker fa/fa fatty rats, Weingarten & Bedard, 1989). The demonstrations of hyperphagia and obesity in the absence of evidence for disturbances of taste processing have generally been interpreted to indicate that obesity can develop in the absence of an altered reactivity to taste. However, data from Experiments 2 and 3 caution that evidence for enhanced taste reactivity can be apparent (when tested for directly (i.e. sham feeding) even if no increased intake is seen in normal eating conditions. This dissociation is apparent in ST rats.

Experiment 2 mimicked experimental conditions identical to the sham feeding studies except that the gastric cannula was closed allowing the rats to feed normally. Under these circumstances, the hyperphagia of the sham feeding ST rat was completely absent. In contrast, the overeating of the VMH rat manifest during sham feeding persisted under these normal feeding conditions.

Experiment 3 showed that the failure to observe overeating in ST rats was not an artifact of the restricted access to food (30 minutes) used in Experiment 2. When 24 hr intakes of three standard lab diets were measured, the intakes and weights gains of ST rats and controls were the same. VMH rats, on the other hand, were hyperphagic on the three diets and became obese. The case of ST rats represents one of the first demonstrations of an <u>increased</u> reactivity to taste coupled with a <u>normal</u> intake, though the opposite has been reported, i.e. <u>normal</u> taste

reactivity coupled with a decreased intake (Berridge, Venier & Robinson, 1989).

Experiments 4 and 5 attempted to explain these apparently dichotomous observations. Experiment 4 used conditioned feeding to assess motivation to eat, independent of amount consumed, in ST and VMH rats. In this preparation, ST and VMH rats displayed no more motivation to eat than controls.

Experiment 5 assessed whether changes in satiety signals, specifically those related to gastric emptying, were relevant to the differences in the sham feeding and normal feeding of ST and VMH rats. Experiment 5 showed that the rate at which ST rats emptied a nutritive liquid from the stomach did not differ from t at of controls. VMH rats, however, displayed an increased rate of gastric emptying.

Synthesis and Implications

Postingestional cues from the gut mask the feeding disturbance produced by ST knife-cuts, but are insufficient to mask the feeding disturbance of the VMH rat. This observation correlates well with the gastric emptying data. Liquid phase gastric emptying is accelerated in VMH rats: this effect increases the rate at which nutrient is delivered to the duodenum, though gastric distension is not affected, and may account for the reduced inhibition of feeding. Accelerated gastric emptying in the VMH rat permits the hyperphagia, resulting from enhanced taste reactivity and evident during sham feeding, to be manifest during real feeding. In contrast, ST rats' stomachs empty at a

normal rate. Consequently, during a meal, nutrients leave the stomach of the ST rat at a normal rate, producing inhibitory signals sufficient to terminate a meal at a normal size, and effectively over-riding any enhanced feeding which might otherwise result from the exaggerated response to sweet characteristic of ST rats.

Results that parallel those obtained in this series of experiments on ST and VMH rats have been reported following ip injection of glucagon, a hormone which retards gastric emptying rate (Murthy & Ganibon, 1988). Geary & Smith (1982) showed that ip glucagon does not affect amount sham fed but reduces amount normal fed, another demonstration that an alteration in gastric emptying rate may not affect sham feeding but can affect real feeding.

It is not clear why ST rats are hyperphagic when sham feeding. However, documentation of this hyperphagia following ST transection is an important first step towards understanding the forebrain taste system.

These results force a rethinking of the manner in which feeding behaviour is studied. Currently, isolation is the guiding principle of most feeding research, where a particular factor or event affecting feeding (exogenous or endogenous) is studied in isolation from other feeding related events. The effect of ST transection underscores the interactive nature of the numerous factors that can affect meal size: when the influence of taste is isolated (sham feeding), ST rats are hyperphagic; when normal digestive processes which follow food

ingestion interact with the ST rat's exaggerated response to sweet taste, intake is normal. These findings indicate that changes in taste reactivity must occur in concert with other physiological or behavioural disturbances, such as those characteristic of the VMH rat, in order that changes in real feeding can materialize.

Studying one factor affecting feeding behaviour, in isolation from all others, permits a thorough and controlled analysis of that one factor. In addition to this, however, it is essential to understand the interdependency of the many factors and events associated with feeding (e.g. the interaction between taste reactivity and gastric distension). Therefore, it is encumbant upon researchers in the area of feeding behaviour to develop experimental protocols which consider and examine the numerous interactions of the components of meal initiation and termination, in order to fully understand the phenomenon of feeding.

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Appendix A

Sham Drinking Water

ST rats are hyperphagic when sham feeding sucrose solutions. It is possible that this elevated sham intake arises through some non-specific increase in motor output, manifested, perhaps, as an increase in lick rate. If true, then ST rats would be expected to be hyperdipsic compared to controls whem sham drinking water following water deprivation. In contrast, if the effects of ST transection are specific to food, then no alteration in sham drinking of water would be observed. Therefore, this experiment examined the effects of water deprivation on sham drinking in ST rats and controls.

Methods

Twenty subjects weighing 372 $\pm$ 8 g (mean $\pm$ 1 SEM) at surgery were used. Once subjects were sham drinking reliably, they were tested following 12 hr, 18 hr an 24 hr of water deprivation (see Chapters 2 and 3 for sham feeding protocol).

Results and Discussion

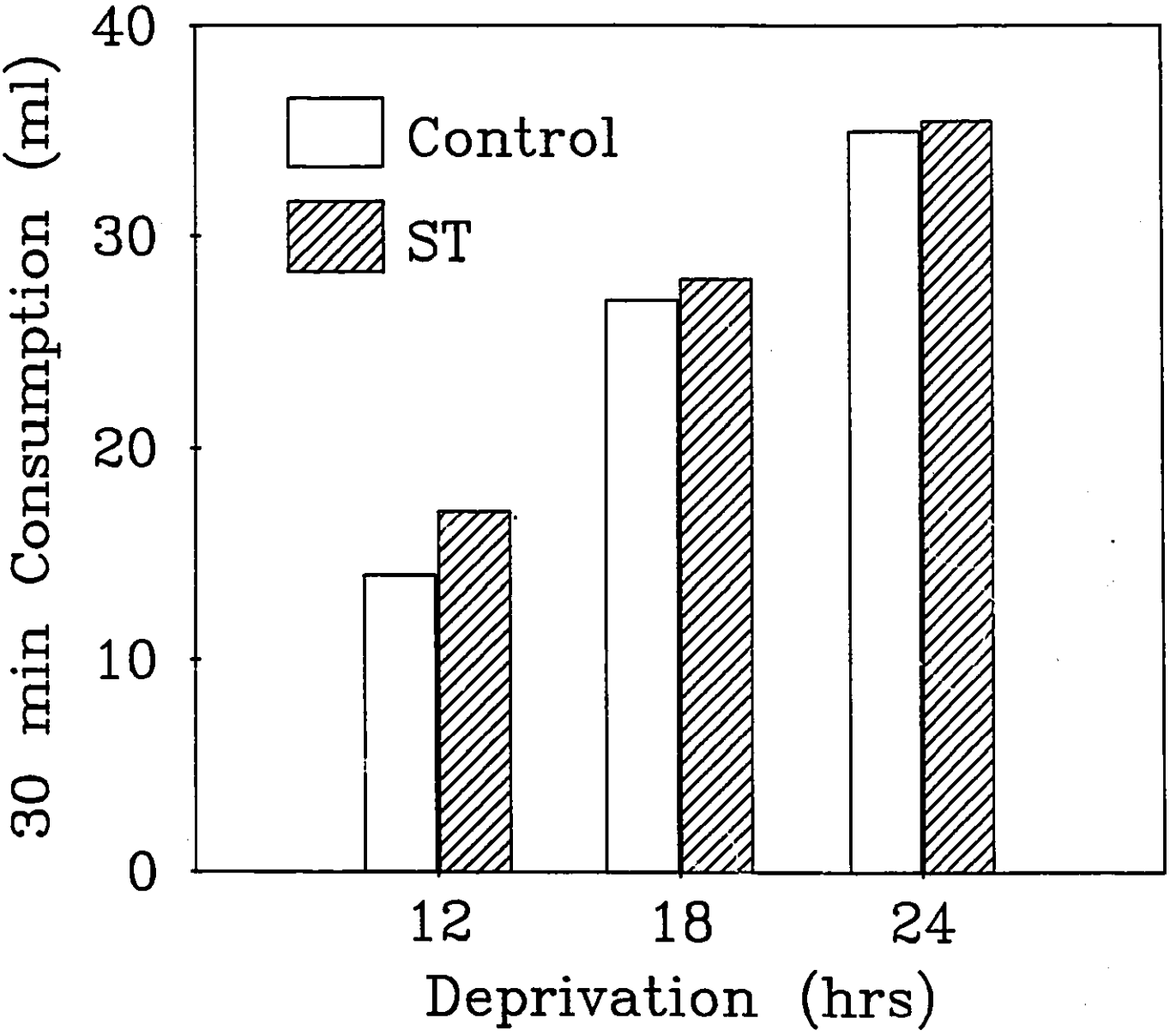
Eight of twelve rats sustained bilateral transections of th ST and were included in this group. Six of eight controls sham drank reliably.

Weights did not differ significantly either at the start, $F(1,12) = 0.34$, or end, $F(1,12) = 0.66$, of testing.

Figure 16 shows amount of water consumed in a 30 minute sham drink following increasing degrees of water deprivation. An ANOVA indicated that there was no Group effect, $F(1,12) = 0.22$, though degree of deprivation had a profound effect on water intake, $F(2,24) = 131.9$, $p < 0.001$.

There were no differences between ST rats and controls when sham drinking water following 12 hr, 18 hr, or 24 hr of water deprivation. The hyperphagia of the ST rat when sham feeding a sucrose solution (Experiments 1a and 1b) is not the result of a non-specific increase in motor output, but rather is tied in some manner to the sensory qualities of the food.

Figure 16. Water intake of ST rats and controls during a 30 min sham drinking test, following 12 hr, 18 hr, and 24 hr of water deprivation.


40
30
20
10
0
30 min Consumption (ml)
Control
ST
12
18
24
Deprivation (hrs)