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Appetitive Determinants of Self-Stimulation

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Previous reports have pointed to a biologically meaningful relationship between brain-stimulated reward and appetitive motivation such as feeding. The present experiments further examined this relationship in chronically self-stimulating Sprague–Dawley rats. In Expt 1 restriction of *ad libitum* food produced a subsequent increase in self-stimulation in the substantia nigra. In Expt 2 restriction of *ad libitum* self-stimulation, from the same sites, produced a subsequent gain in body weight. In Expt 3 restriction of *ad libitum* self-stimulation produced subsequent increases in responding for stimulation.

Soon after the initial discovery of self-stimulation of the brain (ICS; Olds and Milner, 1954) the results of several experiments suggested that the same central nervous system (CNS) circuits subserving electrically elicited reward might also be involved in biological reinforcement. Brady and co-workers (1957) noted increases in self-stimulation rates subsequent to food and water deprivation in rats and cats. This finding was independently confirmed by both Olds (1958) and Hodos and Valenstein (1960).

The possible interrelationships between feeding and self-stimulation have since been extensively investigated. Hoebel and Teitelbaum (1962), Margules and Olds (1962), and Wilkinson and Peele (1962) simultaneously reported a behavioral and anatomical identity for hypothalamic feeding and self-stimulation loci: Other CNS sites involved with taste, oral sensation, and ingestive behavior may also support self-stimulation (Micco, 1974; Ritter and Stein, 1973; Van Der Kooy and Phillips, 1977). Finally, the concurrent availability of reinforcing tastes may alter ongoing self-stimulation performance (Hoebel, 1971; Poschel, 1968). These and other related studies have been summarized in a number of recent reviews (Hoebel, 1969, 1974; Mogenson and Phillips, 1976).

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While feeding–ICS interrelationships have now been unequivocably demonstrated behaviorally and anatomically, the procedural limitations of many studies to date have produced only a partial description of the many possible means by which one process may affect the other. Prior studies have manipulated feeding (through force feeding, *ad libitum* food access, or food restriction) and maintained a standard (predominantly limited) access to ICS. Clearly, if food and ICS were both continuously available a number of additional motivational interrelationships might be demonstrated. The following experiments examined the appetitive determinants of reward under the latter condition. Experiment 1 examined the effects of restricting *ad libitum* food upon self-stimulation. Experiment 2 examined a converse case, in which *ad libitum* self-stimulation was restricted and subsequent weight regulation was altered. A final experiment examined the effects of restricting *ad libitum* brain stimulation upon later self-stimulation patterns. While it is well established that animals maintain a fairly constant level of weight and attempt to compensate for food restriction by later increases in food intake (e.g., Le Magnen, 1971), procedural limitations in establishing a chronic continuous access self-stimulation task have heretofore limited the opportunity for examining a parallel case of "thymic homeostasis," i.e., attempts to maintain behaviorally a specific level of reward through self-stimulation just as weight is maintained at a given set point. If the motivational determinants of feeding and brain-stimulated reward are fundamentally similar, then animals should compensate for deprivation of normally available reward with subsequently greater reward seeking.

EXPERIMENT 1—EFFECTS OF FOOD DEPRIVATION UPON ICS

The present report was intended to replicate, to supplement, and to extend previous reports by examining the effects of food restriction using a chronic self-stimulation task. Sites which did not directly elicit stimulation-bound feeding or drinking or offset rebound feeding or drinking (e.g., Huston *et al.*, 1975; Phillips and Fibiger, 1973) were employed. Electrodes were aimed at a site in or adjacent to the substantia nigra. This area has been implicated in the control of food intake (e.g., Ungerstedt, 1971; Phillips and Fibiger, 1974). The decision to use sites which were related to feeding but from which feeding was not elicitable allowed a test of the generality of the feeding–ICS relationship. Most lateral hypothalamic sites and some other limbic sites show a feeding–ICS relationship. The substantia nigra has been shown to control many aspects of feeding and to have a limited similarity to hypothalamic sites with regard to the elicitation of stimulus-bound behavior. The present choice of sites allowed an additional investigation of the determinants of feeding and reward within this system.

Methods

Subjects. The subject pool consisted of 15 adult male Sprague–Dawley rats, each 300–500 g in weight. Rats were obtained locally (Charles River Farms, Portage, Michigan) and were maintained upon normal day/night cycles of 12 hr of light/12 hr of darkness. Water was continuously available and, with the exception of experimental manipulations, food (a standard diet of 0.4% fat Teklad laboratory Chow; S-0836, Teklad, Madison, Wisconsin) was also available *ad libitum.*

Surgery. Subjects were anesthetized with 35 mg/kg sodium pentobarbital (Nembutal) administered intraperitoneally. Each subject received a stereotaxic implant with a single unipolar stainless steel electrode made of 0.1-mm wire insulated to the tip. The electrode was attached to a head-mounted brushing identical in design to that employed by Wolf *et al.* (1973). Initial coordinates for implantation were +2.5, −2.5, −2.5 using the coordinate system of Konig and Klippel (interaural 0) (1963). All electrodes were aimed at the substantia nigra, and subjects were allowed 1 week of recovery prior to training.

Apparatus. All testing was carried out in the subjects' home cages. The cages consisted of 28 × 20 × 18-cm chambers with wire mesh floors and hinged, overhead mounted 14 × 16-cm stainless steel plates which served as both manipulanda and contacts for the delivery of current. Displacement of the overhead plate resulted in the delivery of a 0.3-sec train of monopolar 60 cps sinusoidal current, 50 to 300 μA in intensity via the head-mounted brushing. Self-stimulation was therefore continuously available 24 hr/day without external leads. Additional details of this stimulation procedure have been published elsewhere (Katz *et al.*, 1977; Wolf *et al.*, 1973).

Procedure. Subjects were shaped to perform the panel displacement task using standard operant techniques. After 3 days of initial shaping sessions, subjects were allowed 2 additional weeks of *ad libitum* responding in which rates stabilized. Week 3 served as a behavioral baseline and all results are expressed in terms of mean values obtained during this week. At the close of the third week normally available food was removed for 2 days, beginning at approximately 16:00 hr, and then was reinstated.

Statistics. All self-stimulation scores were based upon stimulations/24 hr. Mean values obtained during Week 3 served as a baseline for the evaluation of all change. Statistical comparison of deprivation-induced changes were based upon Friedman analysis of variance (Siegel, 1956).

Histology. At the close of all testing (Expts 1, 2, and 3) all subjects were injected with an overdose of Nembutal and perfused initially with normal saline and later with formalin–alcohol–acetic acid fixing solution (Luna, 11960). The brains were removed, sliced in 20-μm sections and stained with cresyl violet. All placements were within or immediately adjacent to the substantia nigra. Histology for all experiments may be found in Fig. 4.

Results

The effects of food deprivation are presented in Fig. 1. It may be seen that after free feeding (i.e., the PRE period), food deprivation resulted in concomitant increases in self-stimulation and decreases in feeding for 2 days of food restriction (R_1, R_2). Both changes (i.e., weight, ICS) were significant and were reversed by the reinstitution of *ad libitum* feeding ($POST_1$, $POST_1$) ($\chi^2_r = 10.9, df = 4; \chi^2_r = 8.3, df = 4; P < 0.05$ in both cases).

We have also examined the normal supradian fluctuations of weight and ICS during a period of unrestricted access to both reinforcers. The second and third weeks of ICS training were examined using a nonparametric contingency analysis based upon the McNemar test for the significance of changes (Siegel, 1956). The analysis was based upon nominal changes in the signs of weight and ICS rate. Contingency analysis of the signs of daily changes indicated that weight and ICS normally were inversely related within subjects on a daily basis ($X^2 = 7.2$; $df = 1, P \leq 0.05$), i.e., on days when weight increased (ICS decreased,) and on days when weight decreased, ICS increased.

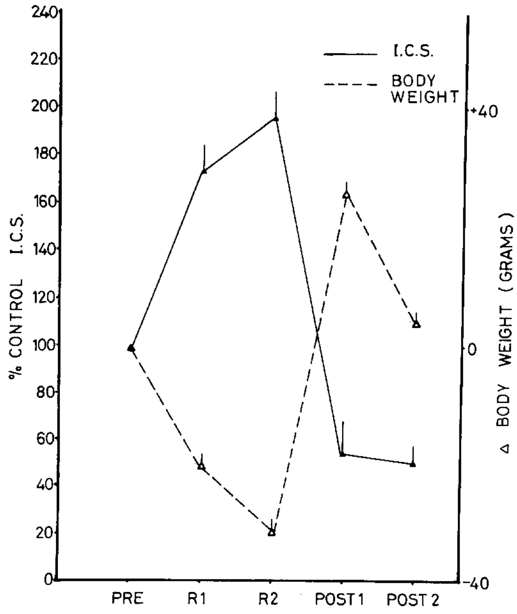

FIG. 1. Effects of food deprivation upon body weight and self-stimulation (mean ± SEM). PRE = predeprivation (control) rate of response; R_1 = 24 hr of deprivation; R_2 = 48 hr of deprivation; $POST_1$ = reinstitution of *ad libitum* feeding; $POST_2$ = second day of *ad libitum* feeding. In all experiments deprivation began and ended at approximately 16:00 hr.

Discussion

Food deprivation of self-stimulating rats produced concomitant increases in self-stimulation rate and weight loss. This was reversed by reinstitution of *ad libitum* feeding. The present results suggest that the sites employed in the present experiments were sensitive to altered patterns of food access and thus confirm previous results using a novel site, measurement period, and operant response. The results of normal daily weight and ICS rates further confirm and expand these and prior observations and suggest that they are not limited to conditions of experimental intervention. A second question might be asked of the feeding–self-stimulation relationship, i.e., would restricting *ad libitum* self-stimulation affect feeding? Experiment 2 examined the effects of ICS deprivation upon weight regulation.

EXPERIMENT 2

Methods

A total of 16 subjects identical in description to those employed in Expt 1 were used, and these included all animals used in the first experiment. Apparatus, shaping procedures, and stimulation parameters were identical to those reported previously. After 3 weeks of *ad libitum* self-stimulation and feeding eight subjects were placed into cages from which the operant panels were absent and eight were maintained in working stimulation boxes. Deprivation was instituted at approximately 16:00 hr. *Ad libitum* food and water were available throughout.

Results

The results are presented in Fig. 2. During the 24 hr succeeding ICS deprivation the experimental (EXP; i.e., deprived) group gained 6.3 ± 1.4 g, while the group with continued access (CTL) gained 2.7 ± 1.2 g (all measurements are the mean ± the standard error). This increase was highly significant in comparison to the control ($U = 9, P < 0.01$, Mann–Whitney U test). Upon return of *ad libitun* ICS the experimental group experienced a weight loss of -6.0 ± -2.0 g while the control group gained an additional 3.1 ± 0.6 g.

Discussion

Experiment 2 demonstrated a feeding–ICS relationship converse to the initial deprivation study. Restricting subjects from a normally available source of reward resulted in an increase in body weight. Experiments 1 and 2 taken together demonstrate consistent and complementary phenomena. Formal and informal observations suggest that the feeding system is under fairly strong homeostatic control; weight loss or excessive weight gains are compensated for by later changes in food intake. It might

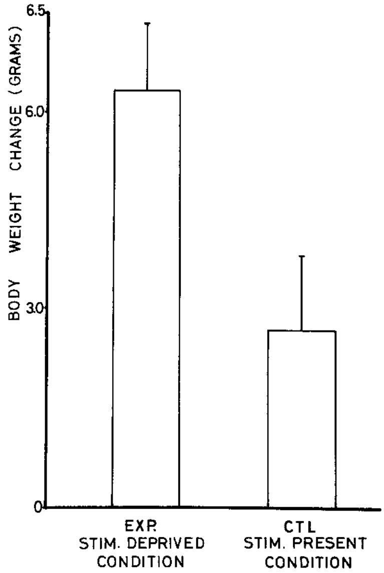

FIG. 2. Effects of self-stimulation deprivation upon weight (mean + SEM). EXP = group deprived of ICS for 24 hr; CTL = group with continued access to ICS.

be questioned if the self-stimulation system is also under homeostatic control, as is feeding. For example, would restricting access to normally available reward produce a motivation for later increased seeking of stimulation?

EXPERIMENT 3

Methods, subjects, and apparatus were identical to those reported in Expt 2. After 2 weeks of *ad libitum* access to food and ICS, subjects were either placed into the inoperative boxes described previously or allowed continued access to ICS. Food and water were continuously available. Testing continued for 3 weeks and periods of 1, 2, or 3 days of stimulation deprivation were employed. In all cases deprivation began at approximately 16:00 hr. Subjects were allowed at least 1 week between tests and all comparisons were based upon concurrently run control animals. At the close of testing subjects were sacrificed for histology.

Results

The results are presented in Fig. 3. It may be seen that stimulation deprivation produced a roughly monotonic increase in later rates (EXP = deprived group, CTL= continued access group). This increase in turn was followed by a return to normal response patterns. Friedman analysis of variance indicated a significant effect of deprivation upon rate ($X_r^2 = 11.1$,

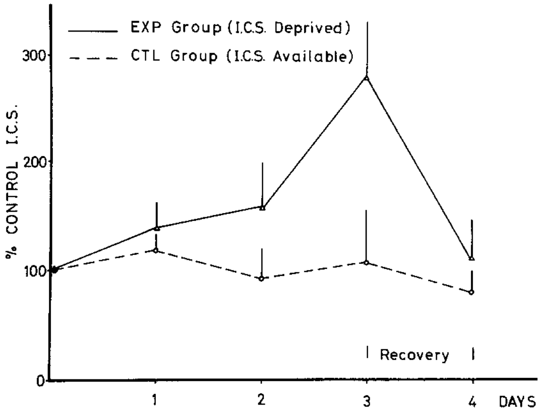

FIG. 3. Effects of self-stimulation deprivation upon later self-stimulation (percentage mean ± SEM). The X-axis shows days of deprivation for experimental group EXP.

df = 3). The histology for all subjects is presented in Fig. 4. It may be seen that placements were located in or near the substantia nigra.

GENERAL DISCUSSION

The present results describe a number of biological relationships between feeding and self-stimulation, and also demonstrate an appetitive drive for ICS. Other reports, which have already been reviewed, further support a feeding–ICS relationship. Two recent reports, however, suggest that such a relationship may need to be modified to include also satiety/ICS systems. Both Ball (1972) and White (1973) report sites which simultaneously suppress feeding and support self-stimulation. The report of Ball is of particular interest since it suggests a direct correlation between ICS threshold and threshold to inhibit feeding. This finding is in turn complicated by still more recent reports which suggest that many of the medial hypothalamic sites initially identified as involved in satiety may have a role in facilitating feeding under specialized circumstances. Davies *et al.* (1974) reported a ventromedial hypothalamic stimulation which typically produced satiety (e.g., Ball, 1972) and actually increased food intake under conditions of low current and limited food access. Thus, the notion of a satiety–ICS site may itself require additional parametric investigation to assure it may not also potentially involve some inherent food motivation-related properties.

Recent studies by Hoebel and colleagues have demonstrated elegantly that a single hypothalamic electrode may mediate reward under conditions of high food motivation and aversion under conditions of satiety (Hoebel, 1974). Therefore, the feeding–self-stimulation relationship may

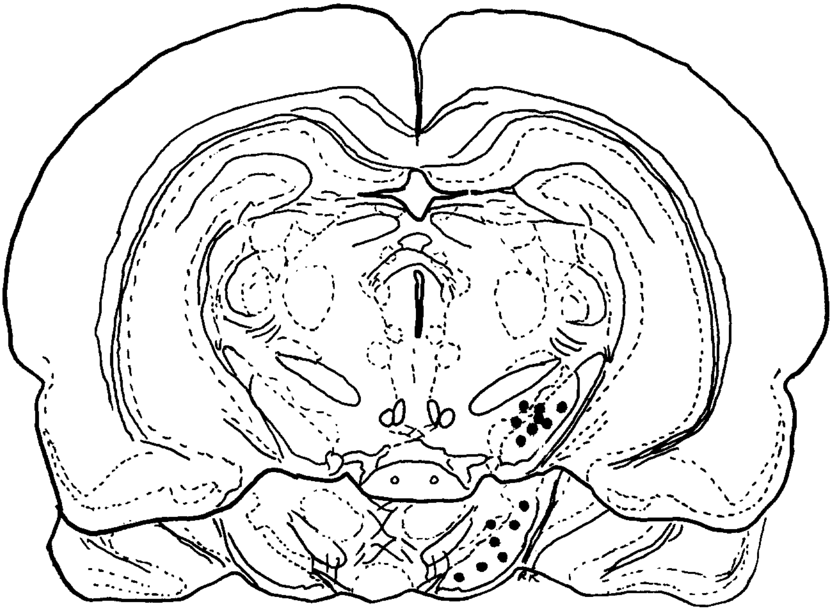

FIG. 4. Composite histology (redrawn from Konig and Klippel, 1963). Sections are 2580 and 2420 μm from frontal (earbar) 0.

be multiply determined—electrode site and degree of hunger may interact to yield either reward or aversion.

The present studies, by using *ad libitum* feeding and ICS availability, demonstrated a number of novel psychobiological relationships. A feeding–ICS relationship was demonstrated as a novel site. A second relationship between feeding and ICS was also demonstrated for the first time. Also, a long-term drive to maintain reward which had not previously been demonstrated was shown to exist. We feel the technique of chronic *ad libitum* self-stimulation offers an interesting alternative to other traditional ICS techniques and may aid in clarifying questions related to both brain stimulation and biologically occurring reward.

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