mixtures were frozen and lyophyllized. The residues were dissolved in a few drops of ethanol and 0.1*N* hydrochloric acid (1:1) and chromatographed (ascending) on Whatman 3 MM paper with *i*-amyl alcohol saturated with 0.1*N* hydrochloric acid. The autoradiogram (Fig. 1) indicates that most of the C^{14}-simazine is converted to a substance with the R_F of hydroxysimazine by either the aglucone (mixture *A*) or the glucoside (mixture *B*). The results of cochromatography of incubation mixtures in the four other solvent systems mentioned earlier also suggest that the product is hydroxysimazine.

Since hydroxysimazine absorbs maximally at 240 mμ, its formation from simazine by the glucoside and the aglucone was also demonstrated by spectrophotometry. No changes in the ultraviolet spectra attributable to decomposition of the glucoside could be observed when it was incubated with simazine. Hence, a catalytic action for the hydroxamate is suggested.

We have presented evidence of both the in vivo and in vitro conversion of simazine to hydroxysimazine. A cyclic hydroxamate from corn effects this conversion in vitro. This substance may be at least in part responsible for the tolerance of corn to simazine. The reaction can also possibly be mediated by enzymatic or other nonenzymatic systems, or both (*5*, *6*).

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References and Notes

1. H. Gysin and E. Knüsli, in *Advances in Pest Control Research,* R. L. Metcalf, Ed. (Interscience, New York, 1960), vol. 3.
2. W. Roth, *Compt. rend.* **245**, 942 (1957); C. L. Foy and P. Castelfranco, *Plant Physiol. Suppl.* **35**, 28 (1960).
3. R. H. Hamilton, thesis, Michigan State Univ. (1960).
4. Ö. Wahlroos and A. I. Virtanen, *Acta Chem. Scand.* **13**, 1906 (1959).
5. An independent observation which relates hydroxamates with the tolerance of certain plants to simazine has been published recently [W. Roth and E. Knüsli, *Experientia* **17**, 312 (1961)].
6. These studies were cooperative investigations of the Crops Research Division, Agricultural Research Service, U.S. Department of Agriculture and the North Carolina Agricultural Experiment Station. This report is published with the approval of the North Carolina Experiment Station as paper No. 1325. The sample of C^{14}-simazine was supplied by the Geigy Chemical Corporation, Ardsley, N.Y. We wish to acknowledge the support given these investigations by the National Cotton Council of America and the Geigy Chemical Corporation.

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Identical "Feeding" and "Rewarding" Systems in the Lateral Hypothalamus of Rats

Abstract. Electrodes were implanted in the lateral hypothalamic feeding system; animals were subjected to both feeding and motivational tests. All animals that demonstrated stimulus-bound feeding behavior also showed high self-stimulation rates. As it was impossible to produce the feeding response without simultaneously producing the rewarding effect of hypothalamic stimulation, it was concluded that the feeding system of the lateral hypothalamus is one among a larger group of places where stimulation causes primary rewarding effects. With electrodes in these same areas, food deprivation often caused a major increment in the self-stimulation rate.

The so-called "feeding center" of the lateral hypothalamus and the "satiety center" of the medial hypothalamus are well known (*1*). In neither case are we really dealing with centers, as both feeding and satiety involve systems that traverse the brain (*2*). It is also known that rewarding effects, evidenced by self-stimulation, can be obtained from similar areas of the hypothalamus (*3*). The question remains whether the self-stimulation phenomenon is correlated with the eating or the satiety system. Classical drive-reduction theory in psychology has suggested that reward should be correlated with satiety; thus stimulation at a satiety center might be rewarding (*4*). A less doctrinaire approach might suggest, on the contrary, that feeding activity itself should have a hedonic correlate; thus stimulation at a feeding center might be rewarding.

Approaching the problem more empirically, Morgane has recently found evidence that seems to suggest separation of two different *lateral* hypothalamic areas: one correlated with the *hunger motive* and the other with the *feeding reflex* (*5*). It is not immediately apparent whether stimulation of either of these areas should yield defensive or rewarding reactions.

The present experiment was designed to screen lateral points for eating effects, and then to learn whether points which yield the feeding behavior would also yield positive reinforcement.

Single pairs of electrodes were implanted in the lateral hypothalami of 46 albino rats. The animals were allowed 3 weeks to recover from the operation. In satiated conditions, rats were tested for feeding behavior during bipolar stimulation with an alternating current ranging from 7.5 to 40 μa r.m.s. in steps of 2.5 μa. If a rat began to feed within 2 seconds after the onset of current, continued to feed as long as the current remained on, and ceased feeding as the current was turned off, this was considered to be evidence of stimulus-bound feeding. Each rat was tested for stimulus-bound feeding 10 times a day for 5 days. Animals were considered to be stimulus-bound feeders if they demonstrated the feeding in 40 or more out of the 50 trials. Of the 46 animals prepared, 28 were found to be stimulus-bound feeders.

Each rat was then tested for self-stimulation in a simple Skinner box. Tests were run daily at five different electric current levels ranging from just below to just above threshold for the self-stimulators, but in no case above 40 μa. All rats fell either into a chance category of responding with rates of less than 50 responses in any 8-minute test period, or into the high self-stimulation category with more than 350 responses in the suprathreshold test periods.

Every single animal that demonstrated stimulus-bound feeding behavior also demonstrated self-stimulation. Of the 18 nonfeeding rats, only four stimulated themselves (see Fig. 1).

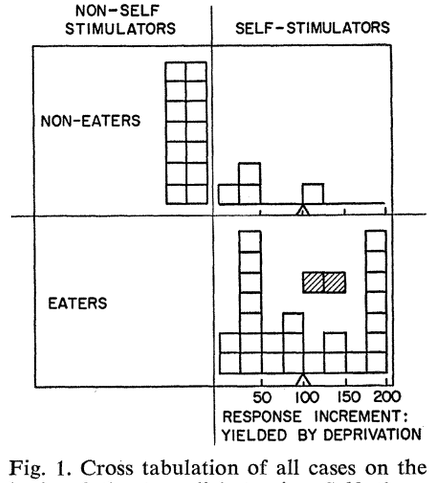

Fig. 1. Cross tabulation of all cases on the basis of the two dichotomies. Self-stimulators are also characterized along an abscissa to indicate the amount of change in self-stimulation output caused by food deprivation. For this latter purpose, animals were run for 8 days; 4 days hungry alternated with 4 satiated. There were five different intervals each day with electric current raised from one to the next. For each animal the mean difference in daily self-stimulation rate was obtained at each current level. For each rat, the highest mean difference was used. Two self-stimulators (see shading) were not tested for drive differences.

Self-stimulators were then tested for the effects of hunger drive on the rate of self-stimulation. In almost all cases, animals stimulated themselves faster after 24 hours of food deprivation. However, deprivation caused a much greater increase in the eaters than the non-eaters (see Fig. 1).

Thus, although there are self-stimulation points which are not also feeding points, when we do get an electrode into the feeding area of the lateral hypothalamus, it appears to be always in a strong self-stimulation area. Furthermore, hunger seems to augment the self-stimulation response derived from this area (*6*).

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References and Notes

1. J. R. Brobeck, *Physiol. Revs.* **26**, 541 (1946); B. K. Anand and J. R. Brobeck, *Yale J. Biol. and Med.* **24**, 123 (1951).
2. B. K. Anand and J. R. Brobeck, *J. Neurophysiol.* **15**, 421 (1952); E. Fonberg and J. M. R. Delgado, *Federation Proc.* **20**, 335 (1961); B. W. Robinson and M. Mishkin, *ibid.* **20**, 327 (1961).
3. J. Olds, R. P. Travis, R. C. Schwing, *J. Comp. and Physiol. Psychol.* **53**, 23 (1960).
4. N. E. Miller, *Science* **127**, 315 (1958).
5. P. J. Morgane, *ibid.* **133**, 887 (1961).
6. This study was supported by research grants from the National Institute of Mental Health and the Ford Foundation.

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Hypothalamic Control of Feeding and Self-Stimulation

Abstract. Hypothalamic sites which control feeding exert a corresponding control over lateral hypothalamic self-stimulation. This was demonstrated in rats bearing four, intrahypothalamic electrode-cannulas for electrical stimulation or chemical injection. Self-stimulation of the lateral hypothalamus was inhibited by ventromedial excitation or by excessive feeding. Both self-stimulation and feeding were accelerated (disinhibited) by ventromedial ablation or anesthetization. Thus food acts via the ventromedial hypothalamus to inhibit not only feeding, but also lateral hypothalamic self-stimulation.

Feeding is under the control of a dual neural mechanism in which the lateral hypothalamus excites feeding and the ventromedial hypothalamus inhibits it (*1*). In the lateral hypothalamus, electrical (*2, 3*) or chemical stimulation (*4, 5*) induces feeding, and anesthetization (*4*) or destruction of this region (*1*) depresses it. In the ventromedial hypothalamus the situation is reversed; stimulation (*3, 6*) suppresses feeding, and anesthetization (*4*) or destruction (*7*) augments it.

Stimulation in certain areas of the brain is reinforcing; in other areas it induces aversion. For instance, a rat will press a lever repeatedly to stimulate its lateral hypothalamus, but will work to avoid stimulation of its ventromedial hypothalamus (*8*). Thus, the tissue in the lateral hypothalamus which excites feeding lies within a system where stimulation is reinforcing, whereas the inhibitory "satiety center" lies within an aversive region. This anatomical overlap suggests that there might be a functional correlation between feeding and self-stimulation. If so, the hypothalamic systems which regulate feeding should exert a similar control over self-stimulation; moreover, food should decrease the rate of self-stimulation as it satiates hunger.

To explore these possibilities, we devised an electrode-cannula assembly which made it possible to excite or depress the medial and lateral hypothalamus, both bilaterally and simultaneously, in waking rats. Monopolar, hollow electrodes, insulated except at the tip, were constructed from 24-gauge platinum tubing (*9*). Four tubes were implanted simultaneously in the hypothalamus of each rat. Implantation was perpendicular to the surface of the cortex in a frontal plane 6 mm anterior to the ear bars of the stereotaxic instrument. The lateral hypothalamic electrode-cannulas were 2 mm lateral to the midsagittal sinus and 7.5 mm below the surface of the cortex (symbolized: A-6, L-2, D-7.5). Ventromedial electrode-cannulas were implanted at A-6, L-0.75, D-8.5. An indifferent electrode was secured under the scalp.

The electrical stimulus was a 0.5-second train of 100-cy/sec, monophasic, negative, 0.1-msec pulses from a Tektronix 161 square-wave generator. The intensities used were between 0.1 ma and 0.6 ma per electrode. Chemical injections were made from a remote microsyringe via a length of PE-10 tubing fitted onto a 31-gauge stainless-steel tube which was inserted inside the full length of the platinum electrode. The chemical injections used were 5 to 10 μl of a 2- to 5-percent solution of sodium chloride for local excitation, and 5 to 10 μl of 1-percent procaine hydrochloride for local anesthetization.

In this report "self-stimulation" always means lever pressing to trigger electrical stimulation of the lateral hypothalamus. Figure 1 summarizes the effects upon feeding and self-stimulation which were obtained by exciting or depressing the hypothalamus. Each arrow represents the results of experiments on five or more female, Sherman albino rats. In brief, when feeding was elicited or increased, so was self-stimulation. When feeding was inhibited, self-stimulation was also inhibited.

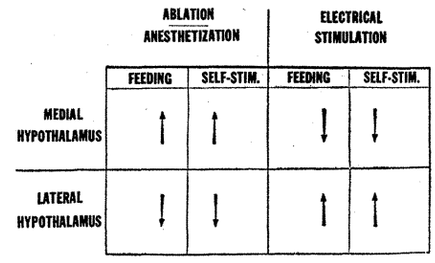

Fig. 1. The relationship between hypothalamic control of feeding and self-stimulation. An upward arrow means start or increase of feeding or self-stimulation, as indicated; a downward arrow means stop or decrease of these activities. Each hypothalamic manipulation that had an effect on feeding had a similar effect on lateral hypothalamic self-stimulation.

The lower-right quadrant in Fig. 1 indicates that unilateral or bilateral electrical stimulation of the lateral hypothalamus caused the rats to eat. This effect was observed from the time stimulation was begun on the day after implantation. Eating was stimulus-bound: satiated rats began to eat within 10 seconds of stimulus onset and continued eating for only a few seconds after the stimulus was turned off. The same rats did not begin self-stimulation until approximately a week after the electrodes were implanted. Once they began, the rate of self-stimulation by rats fed ad libitum was typically 3000 lever presses per hour.

The upper-right quadrant in Fig. 1 indicates that the rats stopped eating when they were stimulated in the ventromedial hypothalamus. They were induced to eat either by 2 days of starvation or by stimulation of the lateral hypothalamus; under both conditions they voraciously ate a liquid diet (*10*) or Purina laboratory chow until medial stimulation was applied. During weak medial stimulation, on either side of the brain, eating slowed or stopped completely. The same was true for self-stimulation; the rats stopped lever pressing when each press stimu-