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Glucodynamic Hormones Modify the Recovery Period after Lateral Hypothalamic Lesions

Abstract. *The period of recovery after bilateral electrolytic lesions of the lateral hypothalamus in rats is shortened if insulin is given for 5 days before surgery, and is lengthened if glucagon is given during the preoperative period.*

Eating behavior ceases completely after bilateral destruction of the lateral hypothalamus (LH) (*1*). If the animals are not properly nursed, they die. However, if the animals are maintained by intragastric feeding, their eating behavior resumes in a well-known recovery pattern (*2*). The length of the recovery period after LH lesions is shortened if the animals are maintained at a reduced body weight before surgery (*3*). This has been taken to indicate that LH lesions reduce a regulatory set point for body weight.

We report here on the hormonal influence on the recovery period that follows LH lesions. We have shown that insulin and glucagon, which are known to modify food intake (*4*), respectively shorten and lengthen the recovery period without necessitating a body weight adjustment before LH lesions are made.

Twenty-one male adult albino rats were adapted for 3 weeks to individual cage housing, Purina rat chow feed, and an illumination cycle of 12 hours of light followed by 12 hours of dark (lights on at 0600). Food intake and body weight were recorded daily throughout the experiment. For 5 days before surgery, seven rats were given 0.2-ml subcutaneous injections of glucagon (0.1 mg at 0000, 0600, 1200, and 1800 hours); seven were injected with 0.2 ml of Semilente insulin (3 units at 0000 and 1200 hours and mock injections at 0600 and 1800 hours); and the remaining seven were injected with 0.2 ml of isotonic saline (at 0000, 0600, 1200, and 1800 hours). In order to maintain body weight during the hormone treatment period, the rats were fed an amount equal to the average amount consumed during the preceding 5 days (*5*). The injections were discontinued 24 hours before surgery.

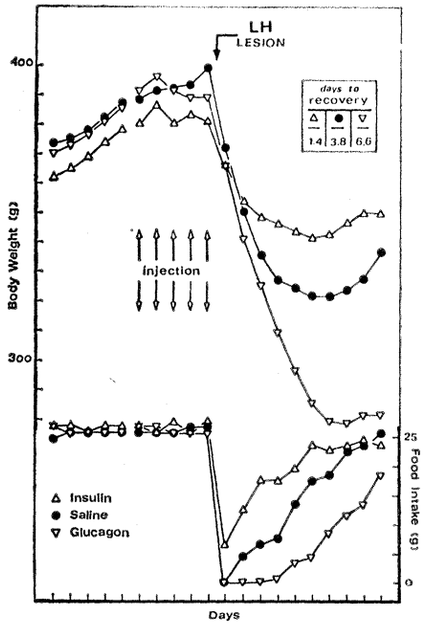

Fig. 1. The influence of injections of insulin, glucagon, and saline on the recovery of feeding after lateral hypothalamic lesions. Recovery of feeding behavior is the time at which animals first begin to eat solid food. Each data point indicates a group mean for 1 day.

Lateral hypothalamic lesions were made under Nembutal anesthesia (50 mg per kilogram of body weight) with the aid of a stereotaxic instrument. Direct anodal current of 1 ma was delivered for 20 seconds through an Insulex-coated stainless steel electrode (0.2 mm in diameter) exposed 0.5 mm at the tip. The stereotaxic coordinates, with the animal's skull in the horizontal position, were 5.6 mm anterior to the interaural line, 2.0 mm lateral to the midsagittal sinus, and 7.7 mm below the dorsal surface of the cortex. The rats were returned to their cages after surgery and their feeding behavior was observed. If an animal had not recovered eating behavior (that is, started to eat solid food) within 7 days, intragastric feeding of milk (5 ml, three times daily) was begun. After recovery of eating behavior, the animals were killed and their brains removed, sliced in sections 60 μm thick, and stained with cresylecht violet for histological verification of the lesion placements.

In every case our lesions encompassed bilaterally the area of the LH and medial forebrain bundle, as well as the most medial edge of the internal capsule at the level of the ventromedial hypothalamus.

Figure 1 summarizes the results. During the hormone treatment, each animal consumed 27 ± 2 g and maintained its preinjection body weight. After LH lesions, the animals that had received saline injections showed the characteristic aphagia and recovered from it in an average of 3.8 ± 2.7 days (*6*). Prior insulin treatment shortened the recovery period to 1.4 ± 1.6 days. Prior glucagon treatment lengthened the recovery period to 6.6 ± 3.1 days. The recovery periods after insulin and glucagon treatments differed significantly in length from that of the saline controls ($P < .05$; two-tailed t-test). An analysis of variance revealed that postsurgical food intake, compared to that of the saline group, was increased by prior insulin treatment and decreased by prior glucagon treatment ($P < .001$; $F = 15.3$; d.f. = 2, 18). The analysis also showed an across-days effect ($P < .01$; $F = 2.5$; d.f. = 9, 162), indicating that the groups reached an eating plateau at different times after the lesion—the insulin group first, the saline

group next, and the glucagon group last. The behavior observed during the immediate postsurgical period was the result of the interaction of hormone treatment and the LH lesion, since hormone administration per se does not cause aphagia (*4, 7*).

The effect of prior hormone treatment on post-LH lesion body weight paralleled the feeding effect. Body weight differed across groups ($P < .001$; $F = 13.2$; d.f. = 2, 18) and across days ($P < .001$; $F = 4.6$; d.f. = 9, 162).

The results obtained were caused by the hormone treatment rather than by differences in the brain lesions. Histological examination of coronal sections revealed no major differences among groups (Fig. 2). These lesions are indistinguishable in size and location from those reported elsewhere to induce aphagia (*2, 3, 8*). The section in Fig. 2a was taken from a saline-treated animal that recovered eating behavior in 3 days. Parts b and c in Fig. 2 are essentially indistinguishable; Fig. 2b is from an insulin-treated animal with less than 1 day of aphagia, and Fig. 2c is from a glucagon-treated animal with 6 days of aphagia.

It has been hypothesized that the shortening of the LH recovery period produced by body weight reduction before surgery is due to a shift in a regulatory set point for body weight (*3*). However, we have demonstrated this phenomenon without altering body weight or food intake before surgery. The effect of the two glucodynamic hormones on the recovery period could be indirectly caused by their action on glucose utilization (*9*) or could be caused by their effects on neurotransmitters.

Reduction of brain norepinephrine by systemic injection of α-methyl-*p*-tyrosine 3 days before LH lesions reduces the recovery period (*10*), probably as a result of denervation supersensitivity. Norepinephrine has been hypothesized to be the neurotransmitter in the neural mediation of feeding behavior (*11*). Little is known of the effects of glucagon on the central nervous system. Insulin, however, has been shown to alter the levels of both tyrosine hydroxylase and dopamine β-hydroxylase (*12*), which are important enzymes in the conversion of tyrosine to norepinephrine. Perhaps, presurgical treatment with insulin, as with α-methyl-*p*-tyrosine, produces denervation supersensitivity in norepinephrine neural systems. Glucagon may also influence the norepinephrine system, but even less is known of its mode of action. However, insulin and glucagon may be influencing the postsurgical recovery in an entirely different manner.

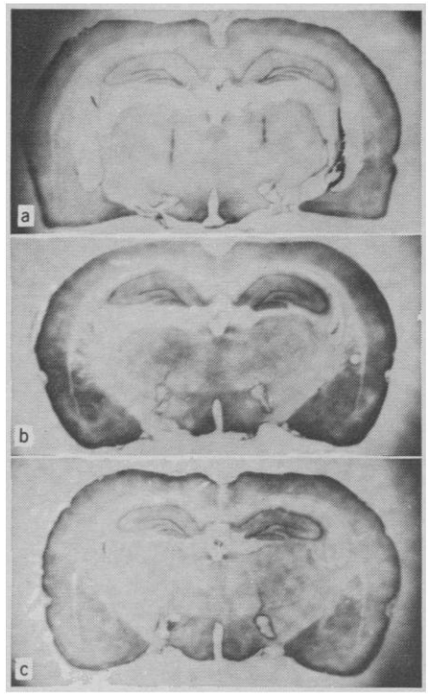

Fig. 2. Coronal sections passing through the midhypothalamus of rats treated with saline (a), insulin (b), or glucagon (c) before surgery. In every case the lesion encompassed the lateral hypothalamus, the inner edge of the internal capsule, and the ventral aspect of the fields of Forel.

Several structural and functional similarities have been observed between insulin and another protein, nerve growth factor (*13*). With this in mind, we would predict that prior administration of nerve growth factor to animals with LH lesions would also shorten the recovery period.

Regardless of the mechanism by which insulin and glucagon alter the recovery period, basically identical lesions to the same brain area in the present experiment led to three quantitatively different recovery periods. This type of phenomenon may underlie the recovery of function after damage to other parts of the central nervous system.

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5. A dose of glucagon comparable to that used in this experiment has been shown to modify the rat's metabolism without greatly altering its caloric intake [J. M. Salter, *Amer. J. Clin. Nutr.* **8**, 535 (1960)]. In our experiment, glucagon-, insulin-, and saline-injected animals consumed all of their allotted food.
6. Lesions of the LH produce aphagia ranging from 3 days [1 ma for 7 seconds (*3*)] to seven or more days [2 ma for 30 seconds (*10*); 2 ma for 10 seconds (*8*)]. The lesion variables in our experiment were calculated to produce about 4 days of aphagia.
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Dopa and Dopamine in Glusulase: Possible Artifact in Studies on Catecholamine Metabolism

Abstract. *Relatively high concentrations of dopa and dopamine were found in Glusulase, an enzyme preparation widely used in studies on catecholamine metabolism. This contamination may be a source of error in some studies, particularly in those measuring the endogenous concentrations of these catechols and their metabolic products.*

Recently, we reported a marked discrepancy between the plasma concentration of dopamine and its cardiovascular effects in man and dog (*1*). We considered the possibility that the major fraction of circulating dopamine might be an acid-labile, biologically inactive conjugate that was inadvertently hydrolyzed during its determination. Our analytical procedure for dopamine in-