impulse (*17*). Our results cannot be attributed to the experimental procedure itself, since identically treated control animals that received immunoglobulins from nonmyasthenic humans showed none of the myasthenic features. Furthermore, dialysis performed during preparation of the immunoglobulin fraction would remove any residual anticholinesterase medication from the patients' serums.

Our study differs from the many previous attempts to transfer myasthenia gravis to animals over the past three decades (*6*) in at least two important respects which contributed to the present positive results: (i) We exposed the test animals to the serum factor for a relatively prolonged time, in contrast to the minutes or hours previously attempted. (ii) We used more sensitive electrophysiological and radiometric methods to detect the myasthenic abnormalities rather than relying on clinical weakness or decremental responses, which are often absent.

The nature of the myasthenia-producing serum factor has not yet been elucidated, but the 33 percent ammonium sulfate fraction used in these experiments contains the immunoglobulins as well as other serum proteins (*18*). Whether the antibody that binds to ACh receptor (*3*) is itself the transferable serum factor in myasthenic patients remains to be determined. Our experiments may provide the critical link between such an antibody and the pathogenesis of myasthenia gravis as a humorally mediated autoimmune disease.

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19. Supported by NIH grant HD01083 and fellowships from the Muscular Dystrophy Associations of America to K.V.T. and A.P. We thank Drs. H. McFarland, R. Humphrey, and I. Sensenbrenner for helpful discussions.

18 June 1975

Hypothalamic Hyperphagia: Dissociation from Hyperphagia Following Destruction of Noradrenergic Neurons

Abstract. *Major differences were found between classical hypothalamic hyperphagia in rats and the recently discovered hyperphagia syndrome resulting from destruction of the ventral noradrenergic bundle. Traditional medial hypothalamic lesions produced no detectable loss of norepinephrine, and the rats overate both in the daytime and at night, whereas destruction of the noradrenergic bundles with 6-hydroxydopamine depleted norepinephrine to 6 percent of normal and caused overeating only at night. Moreover, the two procedures were additive, not substitutive, in their effects on eating. These results argue against recent suggestions that destruction of the ventral noradrenergic bundle mediates the classical hyperphagia syndrome associated with localized ventromedial hypothalamic lesions. However, damage to noradrenergic pathways may contribute to the hyperphagia after extensive hypothalamic lesions.*

One of the better known phenomena in the study of central nervous system function is the syndrome of overeating and obesity that follows destruction of the ventromedial region of the hypothalamus. We have demonstrated, in the rat, that hyperphagia frequently resulting in obesity also follows neurochemically selective lesions in the ventral noradrenergic bundle (*1*). This is the main noradrenergic pathway to the rat hypothalamus (*2*). Lesser numbers of epinephrine-containing fibers travel with the ventral bundle (*3*). Using somewhat different techniques, Kapatos and Gold (*4*) observed hyperphagia after knife cuts or electrolytic lesions that included the ascending noradrenergic systems within the area of destruction. More recently, Gold (*5*) has suggested that hypothalamic lesions that produce obesity do not appear to be associated with a particular nucleus but rather correspond to the diffuse hypothalamic distribution of ventral noradrenergic bundle; he therefore hypothesized that the destruction of this pathway is responsible for the classical syndrome of hypothalamic obesity.

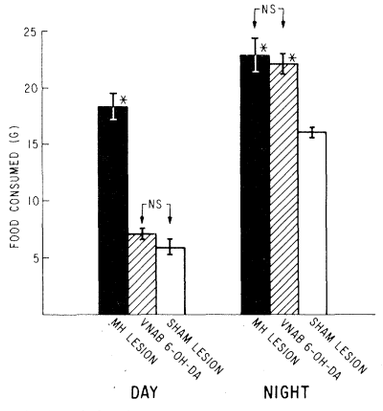

Fig. 1. At night the rats with ventral noradrenergic bundle, 6-hydroxydopamine lesions (VNAB 6-OH-DA) overate; their hyperphagia during the night matched that seen in the rats with medial hypothalamic (MH) lesions. During the day VNAB animals ate no more than the control rats, whereas the MH animals continued to overeat. Values represent 6 days and nights (* = $P < .001$ versus sham lesion group; NS = $P > .10$).

Our experiments suggest that hypothalamic hyperphagia and ventral bundle hyperphagia are actually two different syndromes. Diurnal feeding patterns were different; food intake was quantitatively different; one lesion did not substitute for the other; and rats with medial hypothalamic (MH) lesions became hyperphagic without norepinephrine loss.

Forty adult Sherman female rats were maintained in a room lighted from 8:30 a.m. to 11:00 p.m. They were housed in single cages and had constant access to food (Purina Laboratory pellets) and water. Assignment to one of the three surgical groups was random. (i) Eighteen animals received bilateral, intramesencephalic injections of 8.0 μg of 6-hydroxydopamine (6-OH-DA), an agent that destroys catecholamine neurons (*6*). The injections were made in the vicinity of the ventral noradrenergic bundle (VNAB) (*7*). Our previous studies (*1*) indicate that this procedure consistently destroys nearly all ascending noradrenergic input to the fore-

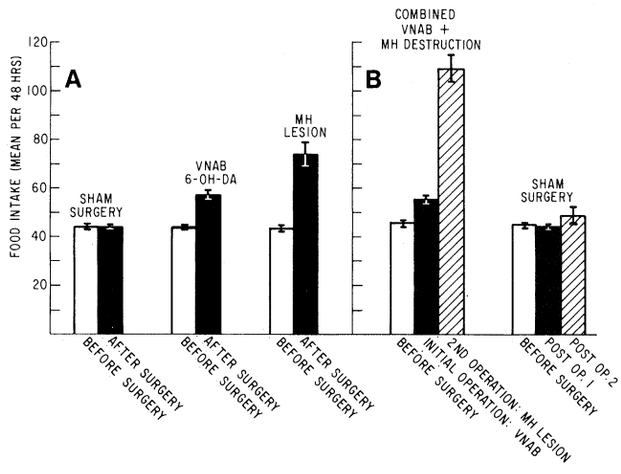

Fig. 2. (A) Norepinephrine depleted (VNAB) rats became hyperphagic, but their postoperative increment was only about one-half that of the group with medial hypothalamic lesions (MH) ($P < .005$). Measurement period: 8 days before and 20 days after surgery. (B) Combined MH lesion, plus 6-OH-DA injection into the VNAB, produced an additive effect; in fact, the combined effect was slightly greater than additive. Food intake is shown as grams consumed per 48 hours.

brain, including both ventral and dorsal noradrenergic pathways. (ii) Twelve other rats received discrete electrolytic lesions of the medial hypothalamus. The procedures were designed to produce maximum obesity in accordance with Bevan's (*8*) localization study. (iii) Ten control animals underwent sham operations in which a skull flap was removed and the dura pricked, but the brain was not invaded. All surgery was done under ether anesthesia.

Food intake and body weight were measured every 48 hours for 8 days before operating and for 20 days after. These measurements did not cover the 48-hour period which included surgery or the next 48 hours, to allow sufficient time for recovery. Body weight tended to parallel food intake in these experiments and will not be reported here. Measurement of daytime and nighttime feeding was begun 5 to 10 days after operating; food and spillage were recorded within 1½ hours after the lights came on at 8:30 a.m. and again within 1½ hours before they went off at 11:00 p.m.; these measurements were taken for six consecutive days and nights.

After completion of the experiments, brain sections from four rats with MH lesions were stained with cresyl violet and studied microscopically to verify correct lesion placement. Norepinephrine and dopamine were assayed (*9*) in the forebrain plus anterior mesencephalon of all the remaining rats in the three groups.

In agreement with other investigators (*10*), we found that rats with MH lesions, unlike normal animals, tend not to display a day-night variation in their food intake. In contrast to the sham-operated group, the animals with MH lesions showed almost no diurnal variation in feeding (Fig. 1), eating 44 percent of their total intake during the day. These rats ate significantly more than the sham-operated animals during both the day and the night ($P < .001$, in each case).

In contrast, the animals with VNAB destruction displayed a normal circadian rhythmicity in feeding. These animals ate only 24 percent of their food during the daytime (compared with 27 percent in the sham-operated group) and thus were clearly not hyperphagic during the day relative to the controls ($P > .10$). However, these animals did consume significantly larger amounts than the control animals at night ($P < .001$). Rats with VNAB destruction ate like normal rats during the day but overate like rats with MH lesions at night (Fig. 1). In sum, rats with ventral bundle destruction differ from those with MH lesions in that they display diurnal changes in food intake by not overeating during the daytime.

As shown in Fig. 2A, animals in both experimental groups ate more food after surgery; however, the postsurgical change in animals with MH lesions was more than twice that of those with VNAB destruction ($P < .005$; + 31.0 g per 48 hours as compared to + 13.7 g per 48 hours, 20-day mean after the operation minus the average of 8 days before the operation). The data from the group with VNAB destruction are quite representative of the syndrome as we have seen it; the 31 percent increment in food intake resembles that found in numerous other groups of rats with similar ventral bundle disruption (*1*). The difference in overall hyperphagia between the two experimental groups is accounted for by the daytime overeating of the animals with MH lesions.

The neurochemical results are shown in Table 1. The midbrain injections of 6-OH-DA reduced norepinephrine to 6 percent of normal. In contrast, the ventromedial hypothalamic lesions, which led to a greater hyperphagia, did not affect forebrain norepinephrine levels. Apparently, discrete hypothalamic lesions can produce significant hyperphagia without altering forebrain norepinephrine; moreover, the hypothalamic hyperphagia was twice that associated with the 94 percent depletion of norepinephrine in the rats injected with 6-OH-DA.

If hypothalamic hyperphagia were due to destruction of the VNAB, hypothalamic lesions in an already hyperphagic, norepinephrine-depleted rat should produce little or no additional increment in food intake; that is, the combined effects should be less than additive. To test this, eight animals injected with 6-OH-DA from the previous experiment were given ventromedial hypothalamic lesions as well. Simultaneously, the eight control animals from the first experiment underwent a second sham operation. Surgery and measurements in both groups were conducted as before.

The hypothalamic lesions in the animals previously depleted of norepinephrine produced a dramatic increment in food intake beyond the already elevated level. The effect of the combined destruction was additive rather than substitutive; in fact, the level of hyperphagia was slightly greater than the sum of the two levels (Fig. 2B). Brain assays verified that the norepinephrine losses in these animals (to 4 percent of normal) were similar to those found in the

Table 1. Norepinephrine levels in rats with medial hypothalamic lesions or destruction (or both) of the ventral noradrenergic bundle. Norepinephrine in rats with lesions in the medial hypothalamus was normal in contrast to the 94 percent depletion in rats with destruction of the ventral bundle. Some rats were subjected to both MH lesions and destruction of the VNAB. Tissue samples included both forebrain and anterior mesencephalon. Data from four animals are not shown because of death of the animal or loss of sample. Values are given in nanomoles per gram of tissue ± the standard error of the means. Abbreviations: NE, norepinephrine; VNAB, rats with destruction of the ventral noradrenergic bundle; MH, rats with lesions of the medial hypothalamus.

Group	*N*	NE (ng/g; ± S.E.M.)	Percent of sham	Dopamine (ng/g; ± S.E.M.)	Percent of sham
		One operation			
Sham	9	283 ± 7		873 ± 44	
VNAB	8	17 ± 3	6.0	700 ± 25	80.2
MH	8	289 ± 16	102.1	775 ± 52	88.8
		Two operations			
VNAB + MH	8	12 ± 3	4.2	812 ± 63	93

norepinephrine-depleted rats in the previous experiment (Table 1).

It could be argued that after a nearly complete depletion of norepinephrine an additional small and undetectable decrease in norepinephrine might surpass some critical threshold and lead to the release of eating. However, if this were true we would also expect this threshold would have been surpassed in at least some of the more than 150 rats in our laboratory which have undergone VNAB destruction via 6-OH-DA injection or electrolytic lesions in previous experiments. In actuality, seven of the eight animals in the combined lesion group ate more food per day than any of the previous VNAB animals studied in this laboratory.

Our results would explain why Gold's (*5*) most effective hypothalamic lesions coincided with the distribution of the ventral bundle. Lesions in the medial hypothalamus that destroy portions of the diffuse projections of the VNAB should lead to exceptional hyperphagia such as that observed with dual lesions in the present study.

Thus, medial hypothalamic hyperphagia and ventral bundle hyperphagia are separable phenomena; the evidence is: (i) norepinephrine loss caused hyperphagia only at night and less hyperphagia overall, (ii) hypothalamic lesions caused overeating without norepinephrine depletion, and (iii) the two forms of destruction combined produced a level of hyperphagia equal to or greater than the sum of their separate effects. In addition, other studies from this laboratory (*1*) indicate that hyperphagia following norepinephrine depletion is dependent on pituitary function, is not associated with finickiness, and decreases rather than increases amphetamine anorexia. In these respects, also, the syndrome is different from classical hypothalamic hyperphagia (*11*). This suggests that classical lesions that produce hypothalamic hyperphagia disrupt other systems involved in satiety besides the VNAB.

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7. A single dose of 8.0 μg of 6-hydroxydopamine hydrochloride, dissolved in 0.8 μl of isotonic saline, was bilaterally, stereotaxically injected through 32-gauge stainless steel tubing into the area of the VNAB at the midbrain level (brain coordinates: 0.6 mm anterior to the interaural line; 1.5 mm lateral to the midsaggital sinus; 6.8 mm below the surface of the leveled cortex); 0.2 μg of ascorbic acid per microliter was added to the vehicle to retard oxidation; injection speed was 0.4 to 0.6 μl/min.
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7 May 1975

Nomenclature of Eukaryotic DNA Polymerases

An international conference on eukaryotic DNA polymerases, organized by David Korn of Stanford University, was held at the Asilomar Conference Center, Pacific Grove, California, 11 to 15 May 1975. This meeting was attended by 48 scientists who discussed recent data concerning various DNA polymerases found in a number of eukaryotic species. Because of the many proposals for systems of naming the DNA polymerases, those attending the conference decided to establish a uniform system of nomenclature. It was decided to include only those enzyme classes for which there is common agreement that they represent distinct entities. Four such polymerase classes were identified. A fifth class of enzyme, the reverse transcriptases or RNA tumor virus–associated DNA polymerases, is distinctive enough not to need further identification (*1*). Other virus-induced DNA polymerases, such as herpes-induced DNA polymerase (*2*) or vaccinia-induced DNA polymerase (*3*), can be referred to by the name of the causative virus.

Consideration was given to devising a nomenclature connoting the size, cellular localization, or template preference of the various DNA polymerases. Such approaches were abandoned because of ambiguities and uncertainties inherent in them. Instead, it was decided that a system of Greek letters, assigned to the DNA polymerases according to the order of discovery, would be the most useful approach because it would differ from any of the systems previously used by ourselves and others.

The nomenclature proposed is as follows (*4*):

1) *DNA polymerase-α* is proposed for the high-molecular-weight (>100,000) DNA polymerase, which was the first to be detected in mammalian cells (*5*). Even though this enzyme is often the major activity in cytoplasmic extracts of growing cells, its actual location in vivo may be in the nucleus. It is particularly active in copying "activated" double-stranded DNA (*6*), and has almost no ability to copy the oligo-homopolymer $A_n \cdot dT_{15}$. The α-polymerase is strongly inhibited by reagents that block sulfhydryl groups, and isoelectric focusing experiments show it to be an acidic protein. It is free of nuclease activity.

2) *DNA polymerase-β* is suggested for the low-molecular-weight (< 50,000) enzyme recovered almost entirely in nuclear extracts (*7*). This enzyme is a basic protein and is resistant to reagents that block sulfhydryl groups. It copies activated DNA well and, to a somewhat lesser extent, the synthetic template $A_n \cdot dT_{15}$. It contains no detectable nuclease activity.

Table 1. Systems of naming DNA polymerases.

New system	Formerly used systems				
	Baltimore (*12*)	Bollum (*13*)	Gallo (*14*)	Korn (*15*)	Weissbach (*10*)
Polymerase-α	C	6*S* to 8*S* (maxi)	I	Cytoplasmic N_2	II
Polymerase-β	N	3.45 (mini)	II	N_1	I
Polymerase-γ	A		III		R