overeat at night to compensate if that was the only time food was made available.
16. J. E. Blundell and M. B. Leshem, *Eur. J. Pharmacol.* **28**, 81 (1974).
17. Appreciation is expressed to Barry L. Jacobs, Michael E. Trulson, and Patrick K. Randall for help and advice, and to the Alleghany Pharmacal Co. and Mettler Corp. for equipment. F.P.Z. was supported by PHS training grant MH-15767-06. This research was supported by PHS grant MH08493 and NSF grants GB8431 and GB43407 to B.G.H.
* Present address: Rockefeller University, New York 10021.
† Send reprint requests to B.G.H. at Princeton University.
2 December 1975

Hyperphagia and Increased Growth in Rats After Intraventricular Injection of 5,7-Dihydroxytryptamine

Abstract. *Juvenile male rats given intracerebroventricular injections of 5,7-dihydroxytryptamine, following treatment with desmethylimipramine, maintained body weight gains of 5 to 6 grams per day into adulthood and grew much larger than control rats. Biochemical analyses of brain tissue obtained 50 to 140 days after the injections revealed 60 to 86 percent depletions of telencephalic 5-hydroxytryptamine, with catecholamine levels unchanged. Hyperphagia did not develop despite comparable losses of 5-hydroxytryptamine when the pretreatment was withheld, perhaps because substantial depletions of norepinephrine occurred as well.*

There is accumulating evidence that brain monoamines are importantly involved in the control of motivated ingestive behaviors in rats. For example, permanent depletion of greater than 90 percent of telencephalic dopamine (DA) and norepinephrine (NE) in rats by intracerebral injections of 6-hydroxydopamine (6-HDA) can produce prolonged aphagia and adipsia (*1–3*), impaired ability to increase food intake in response to metabolic emergencies such as acute glucoprivation (*2–4*), and maintenance of body weight at significantly reduced levels (*2, 3*). The central catecholamine-containing neurons are not believed to be specifically involved in mediating ingestive behaviors but instead seem to be involved in some general activational component of motivated behavior (*5, 6*). Electrophysiological and neuropharmacological studies both have suggested that the activity of neurons containing the indoleamine 5-hydroxytryptamine (5-HT) is reciprocally related to the activity of catecholaminergic neurons (*7*). Thus, to the extent that central DA- and NE-containing neurons are required for the initiation of ingestive behavior, serotonergic neurons might be expected to be involved in its cessation. The present report provides evidence consistent with this hypothesis by demonstrating that extensive depletions of 5-HT in the brain will induce hyperphagia and considerable body weight gain in rats, but only when NE depletions do not occur.

Twenty-one male albino rats of the Sprague-Dawley strain (Zivic-Miller, Pittsburgh), weighing 200 to 225 g at the beginning of the experiment, were housed in individual wire-mesh cages where they were allowed free access to Purina Chow pellets and tap water. Using ether as anesthesia, we injected 20 μl containing either 100 or 200 μg of free base 5,7-dihydroxytryptamine (creatinine sulfate water complex), or the vehicle (0.9 percent NaCl, 0.1 percent ascorbic acid), into the cerebrospinal fluid by way of the lateral ventricles ($N = 2$, 13, 6, respectively). Because 5,7-dihydroxytryptamine (5,7-DHT) is known to damage both 5-HT- and NE-containing neurons when injected intraventricularly (*8*), we attempted to restrict the drug's action to serotonergic neurons by administering all but four of the intraventricular injections 30 to 40 minutes after an intraperitoneal injection of desmethylimipramine (25 mg/kg) (see Table 1). Desmethylimipramine (DMI), an inhibitor of NE uptake, has been shown to protect central noradrenergic neurons from the cytotoxic effects of 6-HDA when given in this manner (*3*). Convulsions began in some, but not all, of the rats given 5,7-DHT, and were quickly suppressed by intraperitoneal injections of Nembutal (40 mg/kg) (*8*).

Daily food intake decreased by 24 to 90 percent during the first 2 days after

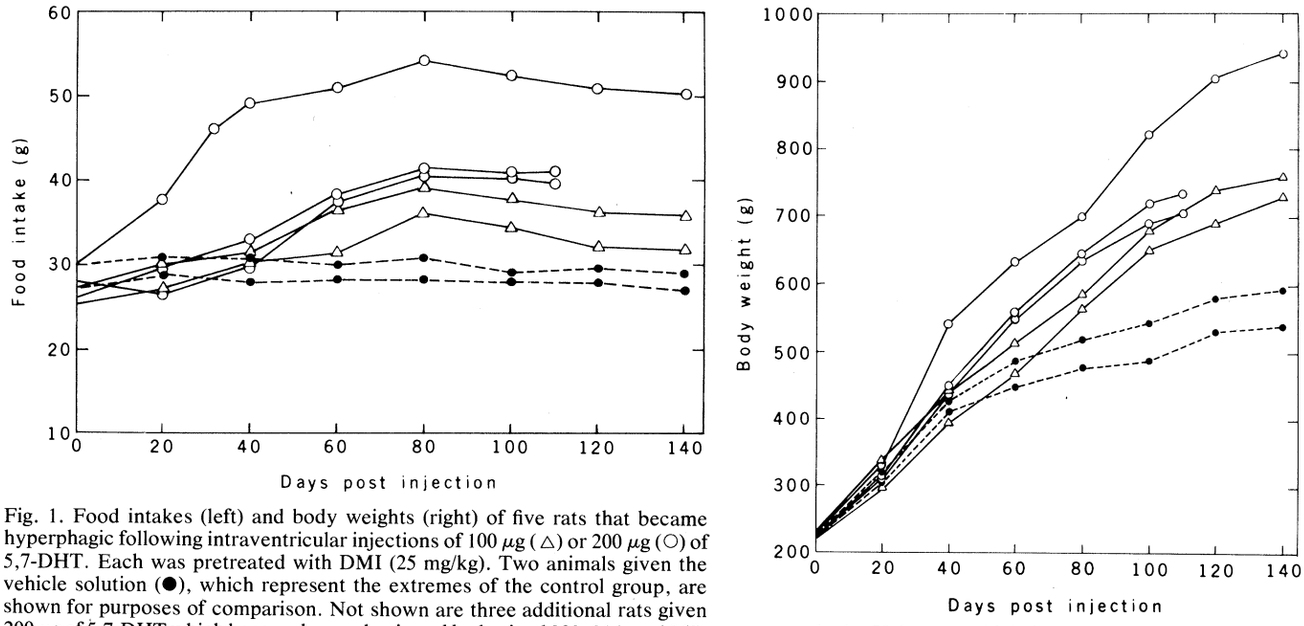

Fig. 1. Food intakes (left) and body weights (right) of five rats that became hyperphagic following intraventricular injections of 100 μg (△) or 200 μg (○) of 5,7-DHT. Each was pretreated with DMI (25 mg/kg). Two animals given the vehicle solution (●), which represent the extremes of the control group, are shown for purposes of comparison. Not shown are three additional rats given 200 μg of 5,7-DHT which became hyperphagic and had gained 309, 314, and 367 g, respectively, by 50 days, at which time they were killed. Transient decreases in food intake and body weight during the first week after 5,7-DHT treatment also are not shown.

Table 1. Effect of 5,7-dihydroxytryptamine (5,7-DHT) on regional levels of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) in the brain. Data are presented as mean micrograms of monoamines per gram of fresh tissue ± standard deviation of the mean. Values are corrected for recoveries (60 to 75 percent). Telencephalic dopamine levels (0.98 ± 0.14 μg/g) were unchanged by the treatments and are not presented. Group A are control animals that received injections of the vehicle (intraperitoneally and intraventricularly). Group B received 100 μg of 5,7-DHT intraventricularly, and groups C, D, and E received 200 μg of 5,7-DHT. Groups B, C, and D were pretreated with 25 mg of DMI per kilogram intraperitoneally. The numbers of rats in each group are indicated in parentheses. Hyperphagia is indicated as present (+) or absent (−). On day 50, two rats from group A, three from group C, and all of group E were killed. On day 110, two rats from group A, two from group C, and all of group D were killed. On day 140, two rats from group A, all of group B, and one from group C were killed. Comparable values were obtained from rats within the same group that were killed at different times after the injections, and thus a single value for the group is presented.

Group	N	Hyperphagia	5-HT (μg/g)			NE (μg/g)		
			Telencephalon	Diencephalon	Brainstem	Telencephalon	Diencephalon	Brainstem
A	(6)	−	.29 ± .03	.40 ± .03	.38 ± .04	.23 ± .01	.50 ± .02	.31 ± .01
B	(2)	+	.14 ± .05*	.30 ± .04*	.31 ± .06*	.29 ± .04*	.51 ± .06	.38 ± .07*
C	(6)	+	.07 ± .05*	.23 ± .04*	.24 ± .04*	.25 ± .05	.51 ± .06	.30 ± .04
D	(3)	−	.06 ± .06*	.22 ± .04*	.25 ± .04*	.16 ± .05*	.44 ± .06*	.25 ± .06*
E	(4)	−	.06 ± .05*	.22 ± .04*	.25 ± .05*	.09 ± .02*	.33 ± .02*	.21 ± .03*

*$P < .001$.

administration of 5,7-DHT and remained low for several days thereafter. Since vehicle-treated rats usually were hypophagic for only 1 day, the 15 rats given 5,7-DHT weighed up to 26 percent less than the controls during the first week. However, by 20 days eight of the lesioned rats (two given 100 μg of 5,7-DHT, six given 200 μg of 5,7-DHT) had body weights similar to control values, and by 50 days the six given 200 μg of 5,7-DHT had gained significantly more weight than controls (mean = 321.8 g, as compared with 245.9 g for control rats; $P < .001$) (*9*). Three of these rats were killed at this time (see below). The other five rats were maintained, became hyperphagic, and continued to gain 5 to 6 g per day during the next 50 days (Fig. 1). In contrast, control rats slowed to an increase of 2 g per day, a rate that is more characteristic of adult male rats. One rat, given 200 μg of 5,7-DHT, was particularly impressive in this regard. This animal gained 366 g in the first 50 days and weighed 823 g by day 100, 279 g more than the heaviest control rat. It was eating 45 to 55 g of food each day during days 25 to 50, whereas the seven other hyperphagic rats ate only 32 to 36 g then (control rats ate still less, 28 to 32 g; $P < .05$). Water intakes were increased in proportion to food intakes in these animals.

In contrast to these findings, the seven other rats given 5,7-DHT ate somewhat less food than controls and gained body weight at a significantly less rapid rate (mean = 154.3 g after 50 days for the three rats pretreated with DMI, and 210.7 g for the four rats not pretreated with DMI; $P < .001$ and $< .05$, respectively, in comparison with controls). Most of these animals were hyperreactive and emotional despite daily handling, whereas the hyperphagic rats were much more like controls. In order to determine the possible basis for these differences among rats given 5,7-DHT, all the rats were killed either 50, 110, or 140 days after injections (see Table 1) and their brains were taken and prepared for fluorometric measurements of regional levels of 5-HT, NE, and DA, using standard neuroanatomical dissections and biochemical assay procedures (*10*). In addition, tibias were taken from all rats killed on days 110 and 140 for measurement of their lengths. There were four findings of note. (i) Each of the eight rats given 5,7-DHT which became hyperphagic showed 60 to 85 percent depletions of telencephalic 5-HT, and no depletion of either NE or DA. (ii) The body weights of the five hyperphagic rats which were maintained past 50 days were arranged in the same rank order as their depletions of telencephalic 5-HT. (iii) These five rats had tibias which measured 4.9 ± 0.1 cm (mean ± standard error), whereas the three rats given 5,7-DHT and DMI which had not been hyperphagic and the four control rats collectively had tibias which measured only 4.5 ± 0.1 cm ($P < .01$). (iv) The seven rats given 200 μg of 5,7-DHT which had not been hyperphagic showed 5-HT depletions comparable to those of the six rats which had gained so much weight, but also showed significant depletions of NE ($P < .001$).

These results indicate that intraventricular injections of 5,7-DHT can produce dramatic increases in food intake and body weight, but appear to do so only when two conditions are satisfied. First, the depletions of 5-HT in the brain must be considerable. Thus, among the eight rats with selective damage to 5-HT–containing neurons, hyperphagia was associated with at least 60 to 70 percent depletions of telencephalic 5-HT and was most impressive when depletions were above 80 percent. Second, for depletions of 5-HT to be effective the damage to central noradrenergic neurons cannot be substantial. In accord with previous work (*8*), 200 μg of 5,7-DHT injected without pretreatment depleted up to 70 percent of NE in the telencephalon and somewhat less in the other regions studied. Neither the four rats so treated, nor the three with smaller NE losses (one of which had only 23 percent depletion of telencephalic NE), became hyperphagic; in fact, these seven animals gained body weight at a less rapid rate than controls (*11*). It was only when DMI completely prevented the 5,7-DHT from exerting its cytotoxic effects on noradrenergic neurons that hyperphagia and increased body weight gain were revealed (*12*). Presumably, accompanying NE depletions have interfered with the development of hyperphagia following other treatments which are commonly used to reduce brain 5-HT levels in rats, such as intraventricular injections of 5,6-DHT, electrolytic lesions of the midbrain raphe nuclei, or repeated intraperitoneal injections of *p*-chlorophenylalanine (PCPA) (*13*).

Hyperphagia and increased body weight gain have previously been reported to occur in rats following three types of brain damage. One, the obesity produced by ventromedial hypothalamic lesions is different from the present results, since rats with such lesions show stunted growth (*14*) and only slight depletions of forebrain 5-HT (*15*). A second, resulting from selective damage to the so-called "ventral bundle" of ascending noradrenergic fibers projecting to the hypothalamus and limbic forebrain (*16*), appears to have a different basis than classical hypothalamic hyperphagia (*17*) and, since no depletions of 5-HT occur, from the feeding produced by 5,7-DHT as well. The third, which follows parasagittal knife cuts lateral to the ventromedial hypothalamus (*18*), closely resembles the present findings and therefore raise the possibility that interruption of 5-HT fibers was the critical event in those studies.

The increases in food intake that follow lesions of either the ventromedial hypothalamus or the ascending noradrenergic fibers have been associated with, and are probably a consequence of, disruptions in peripheral metabolism (*19*).

Some change in peripheral metabolism must also have resulted from the central 5-HT depletions, because juvenile rats continued to grow in size as adults, and showed no remarkable accumulation of abdominal fat at autopsy despite their elevated body weights. Thus, the observed hyperphagia might be secondary, or at least complementary, to an alteration in the secretion, metabolism, or effectiveness of pituitary hormone. In this regard, it is interesting to note that surgical isolation of the basomedial hypothalamus of rats, by knife cuts of areas through which serotonergic neurons might be expected to ascend, have been reported to increase food intake, longitudinal growth, and circulating levels of growth hormone (*20*).

Even if central 5-HT–containing neurons are involved in mediating satiety, there is no reason to restrict their function to the cessation of feeding. That is, serotonergic neurons have also been implicated in sleep (*21*), and the postprandial appearance of synchronized electroencephalographic activity (*22*) suggests a general behavioral inhibition rather than the removal of hunger per se. Thus, an anorexigenic agent like fenfluramine, which appears to increase 5-HT activity in the brain (*23*), may not be acting solely to reduce food intake. Similar arguments have been raised recently regarding the possible nonspecific mechanisms by which amphetamine and related drugs exert their effects on food intake (*24*).

CHARLES F. SALLER
EDWARD M. STRICKER
Psychobiology Program, Departments of Biology and *Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

References and Notes

1. U. Ungerstedt, *Acta Physiol. Scand. Suppl.* **367**, 95 (1971).
2. M. J. Zigmond and E. M. Stricker, *Science* **177**, 1211 (1972).
3. E. M. Stricker and M. J. Zigmond, *J. Comp. Physiol. Psychol.* **86**, 973 (1974).
4. E. M. Stricker, M. I. Friedman, M. J. Zigmond, *Science* **189**, 895 (1975).
5. B. E. Jones, P. Bobillier, C. Pin, M. Jouvet, *Brain Res.* **58**, 157 (1973); U. Ungerstedt, in *The Neurosciences*, F. O. Schmitt and F. G. Worden, Eds. (MIT Press, Cambridge, Mass., 1974), pp. 695–703.
6. E. M. Stricker and M. J. Zigmond, in *Progress in Psychobiology and Physiological Psychology*, J. M. Sprague and A. N. Epstein, Eds. (Academic Press, New York, 1976), pp. 121–188.
7. M. Jouvet, *Ergeb. Physiol.* **64**, 166 (1972); C. Blondaux, A. Juge, F. Sordet, G. Chouvet, M. Jouvet, J.-F. Pujol, *Brain Res.* **50**, 101 (1973); W. Kostowski, R. Samanin, S. R. Bareggi, V. Marc, S. Garattini, L. Valzelli, *ibid.* **82**, 178 (1974).
8. H. G. Baumgarten and L. Lachenmayer, *Z. Zellforsch.* **135**, 399 (1972); H. G. Baumgarten, A. Björklund, L. Lachenmayer, A. Nobin, *Acta Physiol. Scand. Suppl.* **391**, 1 (1973).
9. All statistical comparisons in this report are based on two-tailed *t*-tests.
10. Each brain was separated from the spinal cord at the level of the foramen magnum and was rapidly removed from the skull and dissected on ice. Telencephalons, including olfactory bulbs, were removed following callosal section by peeling them forward and separating them from the thalamus. Diencephalons and brainstems were separated by a cut rostral to the superior colliculus and caudal to the mammillary bodies. Cerebellums and pineal glands were removed and discarded. All telencephalic, diencephalic, and brainstem tissues were frozen separately on Dry Ice, stored at −70°C for not more than 1 week, and later analyzed fluorometrically for 5-HT, NE, and DA using minor modifications of methods that have been described elsewhere [J. Haggendal, *Acta Physiol. Scand.* **59**, 242 (1963); C. Atack, *Br. J. Pharmacol.* **48**, 699 (1973); ——— and M. Lindqvist, *Naunyn-Schmiedebergs Arch. Pharmakol.* **279**, 267 (1973)].
11. This effect is not due to the NE depletions per se, since greater than 90 percent depletions of telencephalic NE do not always retard body weight gain (*3*).
12. It has recently been reported that complete protection of central NE is obtained in rats given 5,7-DHT when DMI is injected 45 to 60 minutes earlier [A. Björklund, H. G. Baumgarten, A. Rensch, *J. Neurochem.* **24**, 833 (1975)].
13. S. A. Lorens, J. P. Sorensen, L. M. Yunger, *J. Comp. Physiol. Psychol.* **77**, 48 (1971); H. G. Baumgarten, K. D. Evetts, R. B. Holman, L. L. Iversen, M. Vogt, G. Wilson, *J. Neurochem.* **19**, 1587 (1972); A. Tagliamonte, P. Tagliamonte, G. U. Corsini, G. P. Mereu, G. L. Gessa, *J. Pharm. Pharmacol.* **25**, 101 (1973); A. Saner, L. Pieri, J. Moran, M. Da Prada, A. Pletscher, *Brain Res.* **76**, 109 (1974). Of course, these treatments have other effects which also may be disruptive. For example, we have recently found that central 5-HT depletions remained in excess of 70 percent for several days after 5-HT synthesis was blocked by a series of daily intraperitoneal injections of PCPA (300 mg/kg), yet rats did not become hyperphagic during that time despite the absence of changes in central NE levels. Increased feeding may have been inhibited in these animals by peripheral factors, since their gastrointestinal tracts often were grossly distended with food. Similarly, in a more recent series of experiments we have found that many rats given 200 μg of 5,7-DHT after DMI treatment would not maintain elevated rates of body weight gain despite the absence of significant depletions of brain NE, and these animals also showed unusual accumulations of food wastes in their intestines. Preliminary data suggest that this decrease in gastrointestinal motility may result from an increase in sympatho-adrenal activity. Thus, minimizing preoperative stress (for example, by handling the animals) may be an important factor in consistently obtaining the phenomenon of increased growth following central serotonin depletions.
14. P. W. Han and A.-C. Liu, *Am. J. Physiol.* **211**, 229 (1966).
15. D. V. Coscina, C. Rosenblum-Blinick, D. D. Godse, H. C. Stancer, *Pharmacol. Biochem. Behav.* **1**, 629 (1973).
16. J. E. Ahlskog and B. G. Hoebel, *Science* **182**, 166 (1973); G. Kapatos and R. M. Gold, *Pharmacol. Biochem. Behav.* **1**, 81 (1973).
17. B. G. Hoebel, in *Hunger: Basic Mechanisms and Clinical Implications*, D. Novin, W. Wyrwicka, G. A. Bray, Eds. (Raven Press, New York, 1976), pp. 33–50.
18. R. M. Gold and G. Kapatos, *J. Comp. Physiol. Psychol.* **88**, 202 (1975). More rapid onset of hyperphagia has been observed in adult female rats, whose rate of body weight gain had already slowed to less than 2 g per day [D. J. Albert and L. H. Storlien, *Science* **165**, 599 (1969); A. Sclafani and S. P. Grossman, *Physiol. Behav.* **4**, 533 (1969); R. M. Gold, *ibid.* **5**, 23 (1970)]. In this regard, we have recently found that intraventricular injection of 200 μg of 5,7-DHT given 45 minutes after DMI (25 mg/kg, intraperitoneally) produced significant increases in food intake and body weight in five adult female rats within 1 to 2 weeks after the drug treatments.
19. B. E. Hustvedt and A. Løvø, *Acta Physiol. Scand.* **84**, 29 (1972); J. E. Ahlskog, B. G. Hoebel, S. T. Breisch, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **33**, 463 (1974).
20. Y. Palka, R. A. Liebelt, V. Critchlow, *Physiol. Behav.* **7**, 187 (1971); J. A. Mitchell, M. Hutchins, W. J. Schindler, V. Critchlow, *Neuroendocrinology* **12**, 161 (1973).
21. M. Jouvet, *Science* **163**, 32 (1969); P. J. Morgane and W. C. Stern, in *Advances in Sleep Research*, E. Weitzman, Ed. (Spectrum, New York, 1974), pp. 1–131.
22. C. D. Clement, M. B. Sterman, W. Wyrwicka, *Electroencephalogr. Clin. Neurophysiol.* **16**, 355 (1964); M. B. Sterman, W. Wrywicka, S. Roth, *Ann. N.Y. Acad. Sci.* **157**, 723 (1969).
23. R. Samanin, D. Ghezzi, L. Valzelli, S. Garattini, *Eur. J. Pharmacol.* **19**, 318 (1972); B. V. Clineschmidt, *ibid.* **24**, 405 (1973). In contrast, intraventricular injections of PCPA have recently been found to cause a transient increase in food intake and body weight [S. T. Breisch, F. P. Zemlan, B. G. Hoebel, *Science* **192**, 382 (1976)].
24. T. G. Heffner, M. J. Zigmond, E. M. Stricker, *Neurosci. Abstr.* **1**, 333 (1975).
25. We thank M. Sippel for her technical assistance, and Dr. M. J. Zigmond for his helpful comments regarding this project and the manuscript. Supported by NIMH grants MH-20620 and MH-25140.

12 January 1976

Anatomical Study of Cerebral Asymmetry in the Temporal Lobe of Humans, Chimpanzees, and Rhesus Monkeys

Abstract. *It is generally accepted that anatomical asymmetries in the temporal lobe language region of humans are associated with the asymmetrical representation of language function in the left hemisphere. Comparative measurements were taken of the length of the left and right Sylvian fissures of human, chimpanzee, and rhesus monkey brains. Measurements confirmed the findings of other studies that the human Sylvian fissure is longer on the left than on the right. The chimpanzee brains had a similar asymmetry but to a lesser degree than the human brains. The rhesus brains, however, showed no significant differences between left and right fissure lengths.*

Anatomical measurements of the adult human brain have shown that the posterior region of the superior surface of the temporal lobe (planum temporale) is larger on the left than its homolog on the right in about 65 percent of the specimens examined (*1*). Since the planum temporale is one of the cortical areas involved in language function (*2*), the asymmetry seen in the planum temporale has generally been interpreted as providing an anatomical basis for the lateralization of language function in one hemisphere (*3*). A recent study found asymmetries in the planum temporale of newborn as well as adult human brains with 86 percent of the newborn and 81 percent of the adult brains having a larger planum temporale on the left than on the right (*4*). The data from the brains