bees, for one of which a single interpolated visit to the feeding station was substituted for the two visits to the 20 percent color. The color preferences established in these experiments were themselves highly stable, persisting even after intervals of 2 to 3 days during which either no training was given or other experiments with gray papers were conducted.

Not all instances of incentive contrast in vertebrates require the assumption of learning about reward, although that capability has been clearly established in several mammalian species. Instrumental contrast experiments of the so-called simultaneous and successive types must be distinguished on the ground that simultaneous contrast permits an interpretation in sensory terms when training trials are massed (as typically they are), with large and small rewards following each other in close succession (*11*). It is not difficult from this perspective to understand why goldfish should show simultaneous but not successive contrast (*12*) or why under special circumstances simultaneous but not successive contrast may be found in rats (*13*). Nor do the present experiments rule out the possibility that bees learn about reward. Other results might well be obtained in experiments with qualitative rather than quantitative variation in reward or with quantitative variation in some different rewarding substance. It is chastening that results like those for sucrose found in one of the rat studies already cited were not obtained in companion work with saccharin (*10*). We can say now only that such evidence as we have of incentive contrast in bees does not argue against the sufficiency of the reinforcement principle. We should be wary, however, of easy anthropomorphic allusion; the results underscore the danger of mistaking what may be superficial similarities in the behavior of diverse species for commonalities of underlying mechanism.

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Hyperphagia and Obesity Following Serotonin Depletion by Intraventricular *p*-Chlorophenylalanine

Abstract. *Loss of brain serotonin was associated with overeating and increased body weight. Rats injected with* p-*chlorophenylalanine intraventricularly began overeating after 3 days and continued to display marked hyperphagia, primarily in the daytime, accompanied by increased body weight for 1 to 2 weeks. The effect was related to drug dose and to the degree and duration of serotonin depletion. Norepinephrine and dopamine levels were not significantly affected. It is concluded that* p-*chlorophenylalanine disinhibits feeding, as it does a number of other behaviors, by depleting serotonin. This suggests that hypothalamic lesions or dietary deficiencies which selectively and sufficiently deplete serotonin would lead to overeating.*

Attempts to define the neural substrate of satiety began with the clinical study of patients with hypothalamic tumors, and then focused on electrolytic destruction of localized tissue. Recent technological advances include experiments employing radio-frequency lesions: local subcortical anesthetization, and circumscribed knife cuts. All of these provide models of tumor damage and improved brain surgery techniques, but none mimic the neurochemical deficits that might follow genetic enzyme abnormalities, ingestion of neurotoxins, or dietary amino acid deficiencies.

Recent advances in neurochemistry

Table 1. Mean food intake and maximum body weight after intraventricular injection of PCPA or saline. Data for experiment 1 show a dose-related hyperphagia and obesity with PCPA in females; the top line corresponds to Fig. 1. Data for experiment 2 show hyperphagia in males as well as females and an increase in intake during both daytime and nighttime. Experiment 3 confirms the effect in ovariectomized females. The number of rats in each group is given in parentheses. The *P* values indicate a statistically significant change from the saline control.

Sex	Time	Group	Food intake (g)			Body weight (g)		
			5 days baseline	Days 3 to 7 after injection	Change (%)	5 days baseline	Maximum after injection	Difference (g)
			Experiment 1					
Female		PCPA* (7)	20.0	30.3	+52	296	345†	49
		PCPA‡ (6)	22.9	28.9	+26	310	336†	26
		NaCl (6)	20.8	20.8	0	310	325	15
			Experiment 2					
Female	Day	PCPA (5)	2.7	4.9§	+81	346	413†	67
		NaCl (6)	2.7	2.8	+4	338	362	24
	Night	PCPA (5)	14.1	16.1†	+14			
		NaCl (6)	14.9	12.9	−13			
Male	Day	PCPA (8)	2.0	5.7§	+185	392	426	34
		NaCl (7)	2.7	2.5	−7	413	438	25
	Night	PCPA (8)	15.5	13.1	−15			
		NaCl (7)	16.7	14.4	−14			
			Experiment 3					
Female	Day	PCPA (6)	4.4	14.2¶	+223			
		NaCl (7)	5.3	6.7	+26			
	Night	PCPA (6)	21.3	29.0†	+36			
		NaCl (7)	20.8	24.2	+16			

*Three milligrams. †$P < .05$. ‡Two milligrams. §$P < .01$. ¶$P < .001$.

now allow the selective depletion of transmitter systems and the determination of their role in the regulation of food intake and body weight. It has been shown that selective depletion of norepinephrine results in overeating (*1*). Norepinephrine depletion also selectively reduced the appetite suppressant properties of amphetamine (*1*), but potentiated another appetite suppressant, fenfluramine (*2*). This suggests that there is another countervailing satiety system. Fenfluramine is an anorectic drug which primarily affects serotonergic rather than catecholamine systems (*3*). This predicts that the depletion of serotonin might produce overeating.

p-Chlorophenylalanine (PCPA) is a drug which depletes serotonin by inhibiting tryptophan hydroxylase activity (*3*). Prior studies of feeding after PCPA administration report variable and contradicting results (*4*). In all cases PCPA was administered peripherally. When we attempted to replicate these findings with intraperitoneal PCPA (400 mg/kg) it was noted that the rats became ill, presumably the result of serotonin depletion in blood platelets, the gastrointestinal tract, and other peripheral structures, in addition to the brain (*5*). To avoid this, we injected PCPA intracranially into the ventricles. The result was marked hyperphagia and obesity for the duration of serotonin depletion.

p-Chlorophenylalanine-methylesterhydrochloride or normal saline was administered into the ventricles of Sherman albino rats. The first experiment tested two doses of PCPA in females. They were kept on a 12-hour-light, 12-hour-dark cycle with Purina powdered chow and water freely available. The food and water intake was measured daily. While anesthetized with ether the rats received 3 mg of PCPA in 12 μl of saline (seven rats), 2 mg of PCPA in 8 μl of saline (six rats), or 12 μl of saline (six rats) in a split dose delivered bilaterally into the lateral ventricles at 1 μl per minute through an acute, 30-gauge cannula which was held in place for an additional 5 minutes after the injection to allow the drug to diffuse (*6*).

Hyperphagia began a few days after the injection and lasted for 1 to 2 weeks (Fig. 1). Food intake reached a peak on day 4, when intake increased from a baseline of 23 g per day to a maximum of 31 g per day for the group that received 2 mg of PCPA (134 percent ± 1.2 percent, standard error of the mean) and from 20 g per day to a maximum of 34 g per day for the group that received 3 mg of PCPA (170 ± 2.7 percent, S.E.M.). The mean food intake on days 3 to 7 after injection,

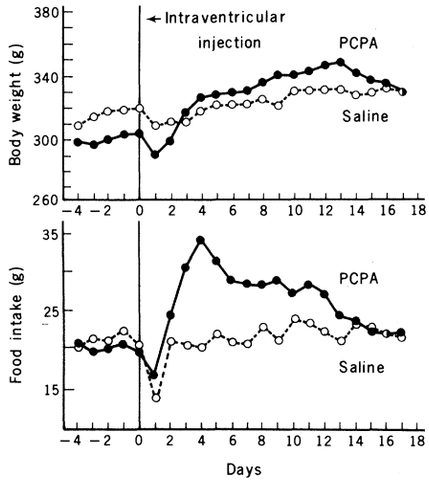

Fig. 1. Hyperphagia and increased body weight induced by 3 mg of PCPA injected intraventricularly in female rats. Curves present group data comparing the mean food intake and body weight before and after injection in experiment 1.

and significance levels, are given in Table 1. A parallel transient increase in body weight resulted from the increased food intake. The mean weight increase for the 3 mg PCPA group on day 13 was triple the controls, 49 g compared to 15 g. Then in the last 4 days they lost 18 g as food intake and body weight normalized (Fig. 1). This first experiment showed a dose-response relationship, finding that after 3 mg of PCPA a significantly greater hyperphagia occurred than after 2 mg; pilot work showed that smaller doses were ineffective.

A second study investigated the effect of PCPA on the diurnal pattern of food intake to determine whether there was a selective effect on either daytime or nighttime feeding. Both males and females were injected intraventricularly with 4 mg of PCPA or saline (*6*). Measurement of high fat diet intake was twice daily, when the lights came on at 7 a.m. and before they went off at 9 p.m.

p-Chlorophenylalanine caused an alteration of the diurnal pattern of food intake. This occurred in both sexes. After PCPA treatment, they ate several extra grams of food in the daytime and another several grams extra at night. Thus the percentage change increased dramatically during the day when rats normally eat very little, whereas feeding during the night was increased by only a moderate percentage (Table 1). An increase in body weight occurred in both males and females; however, only in females was obesity statistically significant. This is similar to the sex difference in obesity seen after ventromedial hypothalamic lesions (*7*).

The third experiment tested the diurnal effect in ovariectomized females. These rats had an elevated food intake baseline. They received 4 mg of PCPA at a neutralized *p*H (*6*). Total daily intake of Purina pellets on a schedule of 14 hours light, 10 hours dark increased from a baseline mean of 25.7 g to an even higher mean of 43.2 g on days 3 to 7. Then food intake began to return to normal. This effect on 24-hour food intake was largely the result of a highly significant doubling of food intake above baseline in the light period ($P < .001$), a mean of 7.5 g more than the control group. In the dark when rats are normally awake, active, and eating, food intake increased 36 percent above baseline ($P < .02$), which was a mean of 4.8 g more than the control group. Before the operation the animals ate 83 percent of their total daily intake at night; after PCPA they ate 67 percent at night. Thus the operative procedure tended to flatten the diurnal feeding cycle, but did not eliminate it.

For monoamine assays, additional groups of male and female rats received 3 mg of PCPA or saline, and 5 or 14 days later the forebrain, anterior to the cerebellum, was removed, weighed, homogenized, and spun, and the supernatant

Table 2. Effect of intraventricular PCPA and normal saline on forebrain monoamine levels. Values, given in micrograms of monoamine per gram of tissue, are means ± standard errors of the means. The number of rats in each group is given in parentheses.

Day	Sex	Treatment	Serotonin	Norepinephrine	Dopamine
5	Female	NaCl	0.20 ± 0.006		
		PCPA (4)	0.052 ± 0.008 (−75%)*		
	Male	NaCl (4)	0.209 ± 0.004		
		PCPA (4)	0.074 ± 0.007 (−65%)*		
14	Female	NaCl (5)	0.207 ± 0.010		
		PCPA (6)	0.124 ± 0.010 (−40%)†		
	Male	NaCl (5)	0.201 ± 0.011		
		PCPA (7)	0.142 ± 0.009 (−29%)†		
5	Female	NaCl (4)	0.212 ± 0.005	0.354 ± 0.034	0.395 ± 0.053
	Male	PCPA (4)	0.046 ± 0.010 (−78%)*	0.348 ± 0.017	0.372 ± 0.054

*$P < .001$. †$P < .01$.

was divided into two parts, one for serotonin determination and one for dopamine and norepinephrine determination (*8*).

A 78 percent depletion of serotonin occurred at the midpoint of the hyperphagia on day 5 ($P < .001$) in females. Dopamine and norepinephrine depletions at this time were slight and not statistically significant (Table 2). In other groups of females and males assayed for comparison, on day 5 serotonin depletion was 75 percent in the females and 65 percent in the males. Two weeks after the operation, when food intake was returning to normal, serotonin depletion was about half as great, 40 percent in females and 29 percent in males.

The correlation between the degree of hyperphagia and serotonin depletion suggests that decreased serotonin levels were responsible for the hyperphagia; however, there exist alternative interpretations. Although forebrain dopamine and norepinephrine levels were not significantly reduced, catecholamine or even nonmonoamine systems could possibly have been influenced by metabolites of PCPA. This is unlikely, judging by Brody's report (*9*) that these effects occur in the first few days, prior to the initiation of the reported hyperphagia. Behavioral effects beginning after this probably reflect decreased serotonin level (*10*).

The mechanism by which serotonin depletion augments food intake is unknown. It could be a direct neural effect on a physiological satiety mechanism, or an indirect effect via some other function such as temperature regulation. It could be a specific or general effect on a reward mechanism measured as increased self-stimulation (*11*). It could also be an effect by way of a general arousal system, as suggested by hyperactivity in tilt cages following systemic PCPA (*12*). We observed a mild increase in tilt cage activity lasting up to a week after intraventricular injections of PCPA (2 and 3 mg/kg). Hyperphagia could also result from hyperreactivity, or by a totally indirect route involving changes in hypothalamic releasing factors and endocrine function (*3*); Saller and Stricker's results suggest the involvement of growth hormone (*10*).

This demonstration that a chemical which depletes brain serotonin can cause overeating and increased body weight has been reported at prior conferences on feeding (*13*). Serotonergic systems in the brain are particularly interesting in regard to feeding control because they depend on dietary factors and are vulnerable to malnutrition (*14*). Unlike other putative neurotransmitters, the rate-limiting factor in serotonin synthesis, under normal circumstances and within certain limits, is the availability of tryptophan, the precursor amino acid. Tryptophan and therefore serotonin in the brain depend on dietary concentration of amino acids and their circadian fluctuations in the blood. Brain serotonin level decreases at about the time of nightfall, when rats eat the most (*14*). Moreover, the concentration of serotonin in the synapses relates directly to the rate of synthesis with very little end-product inhibition of synthesis. Therefore, the activity of serotonergic systems is particularly susceptible to environmental influences over substrate availability. Thus it is possible that the experimental hyperphagia phenomenon that we report here could occur under natural conditions as well.

These findings have several implications:

1) Some of the medical hypothalamic lesions and knife cuts which produce hyperphagia, particularly in the daytime, may interrupt serotonergic neurons (*7, 15*).

2) Fenfluramine and related drugs that cause enhanced anorexia in rats with norepinephrine depletion (*2*) or lateral hypothalamic lesions (*16*) may cause enhanced anorexia by way of serotonergic neurons.

3) Overeating may be promoted by genetic or environmentally induced damage to essential serotonergic neurons, nerve death through aging, or a lack of serotonin precursors in the diet.

We conclude that one aspect of serotonergic function in the brain is to participate in the control of food intake. Serotonin is necessary for normal satiety; it directly or indirectly inhibits feeding. Serotonin is thought to inhibit other behaviors as well. Therefore, there may be an integrated serotonin system that suppresses behavior in general, including feeding, or there may be many serotonergic subsystems, one of which suppresses feeding. This occurs particularly during the half of the circadian cycle when the animal normally eats the least, having recently eaten heavily. It may be that brain damage or even natural conditions that selectively deplete serotonin lead to excessive food intake and obesity.

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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

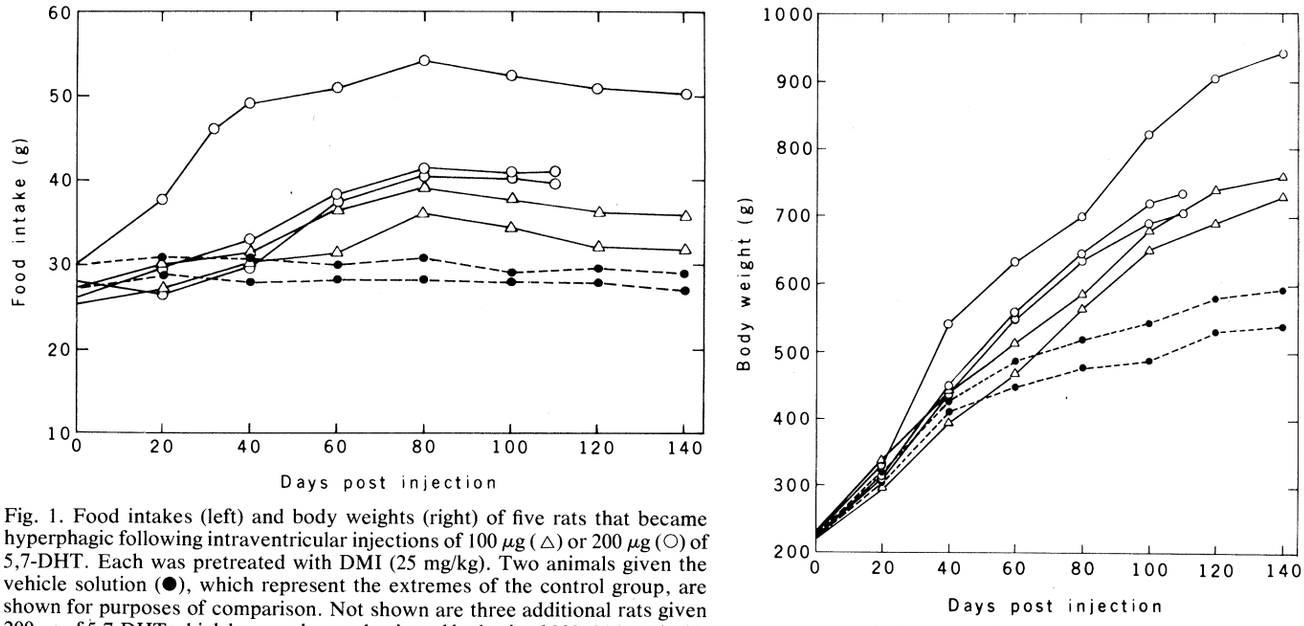

Fig. 1. Food intakes (left) and body weights (right) of five rats that became hyperphagic following intraventricular injections of 100 μg (△) or 200 μg (○) of 5,7-DHT. Each was pretreated with DMI (25 mg/kg). Two animals given the vehicle solution (●), which represent the extremes of the control group, 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.