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Effects on Hypothalamic and Telencephalic NE and 5-HT of Tegmental Knife Cuts that Produce Hyperphagia or Hyperdipsia in the Rat[1]

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GROSSMAN, S. P., L. GROSSMAN AND A. HALARIS. *Effects on hypothalamic and telencephalic NE or 5-HT of tegmental knife cuts that produce hyperphagia or hyperdipsia in the rat.* PHARMAC. BIOCHEM. BEHAV. 6(1) 101–106, 1977. – Knife cuts in the coronal plane through various aspects of the midbrain tegmentum produced hyperphagia, hyperdipsia, or no effect on ingestive behavior. All of the cuts significantly depleted NE and 5-HT from hypothalamus and forebrain. The brains of hyperphagic or hyperdipsic animals did not differ from those of normophagic and normodipsic animals with respect to hypothalamic NE or 5-HT or telencephalic NE. Both hyperphagic and hyperdipsic animals had significantly lower concentrations of 5-HT in forebrain than rats which sustained similar cuts in the tegmentum which did not affect ingestive behavior.

Tegmentum, knife cuts Hyperphagia, norepinephrine Hyperphagia, serotonin Hyperdipsia, norepinephrine Hyperdipsia, serotonin Norepinephrine, hyperphagia Serotonin, hyperphagia Serotonin, hyperdipsia Serotonin, tegmental knife cuts Norepinephrine, tegmental knife cuts

MOST of the investigators that have reported hyperphagia or hyperdipsia after midbrain lesions in recent years have noted that such lesions result in significant depletions of serotonin (5-HT) and/or norepinephrine (NE) from hypothalamus and forebrain. A number of them have suggested that this might reflect causal relationships.

Ahlskog and Hoebel [1] reported hyperphagia after electrolytic lesions in portions of the tegmentum that are traversed by the ventral noradrenergic bundle (VNB) as described by Ungersgedt [27] and others [16,26]. Microinjections of the neurotoxin 6-hydroxy-dopamine (6-OHDA), which preferentially, although not exclusively, destroys catecholaminergic neurons and their processes, into the same aspects of the tegmentum also produced overeating. Both the electrolytic and the chemical lesions resulted in a reduction of noradrenergic varicosities from the hypothalamus and Ahlskog and Hoebel [1] concluded that the behavioral effects of the lesions might be due specifically to an interruption of noradrenergic projections to the hypothalamus. Gold [10] proposed that the ventromedial hypothalamic (VMH) lesions which produce hyperphagia invariably involve the ventral noradrenergic bundle but offered no biochemical data in support of his hypothesis. Ahlskog *et al.* [2] replicated the behavioral and biochemical effects of 6-OHDA injections into the tegmentum and provided quantitative data indicating very severe (6% of normal) depletions of NE from the hypothalamus of hyperphagic rats. Ahlskog *et al.* [2] also succeeded in demonstrating important differences between the effects of medial hypothalamic and tegmental lesions, which suggest that Gold's hypothesis may not be tenable. We [11, 13, 15] have observed hyperphagia in rats with coronal cuts through the posterior hypothalamus, particularly in the perifornical portion that is traversed by components of the medial forebrain bundle. This supports earlier [6] suggestions that the effects of ventromedial hypothalamic lesions on food intake might well be due to an interruption of caudal connections of the diencephalon rather than the destruction of cellular components of the area but does no provide specific support for Gold's [10] hypothesis.

Two recent publications have suggested that the effects of tegmental lesions on food intake may be due entirely or in part to an interruption of ascending serotonergic pathways which originate mainly in the medial and dorsal nuclei of the raphe. Breisch *et al.* [5] reported that intraventricular injections of p-chlorophenylalanine (p-CPA), which reversibly depletes serotonin by inhibiting

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tryptophan hydroxylase activity, resulted in transient hyperphagia with a time course that appeared to correlate with the drug's effects on brain serotonin. Saller and Stricker [24] observed increases in food intake and body size after intraventricular injections of 5, 7-dihydroxytryptamine which produced irreversible depletions of brain serotonin. Saller and Stricker suggested that the hyperphagia seen after 5-HT depletions might be secondary to peripheral metabolic disturbances because the 5, 7-DHT treated animals continued to grow without depositing abnormal quantities of abdominal fat. On the basis of these and related observations, Saller and Stricker suggested that the syndrome of mild hyperphagia and obesity which was seen in their animals might be different from that seen after either VMH lesions or 6-OHDA induced damage to the tegmentum.

The ascending noradrenergic or serotonergic projections to the hypothalamus and forebrain have also been implicated in the regulation of water intake. Osumi *et al.* [21] have reported that electrolytic lesions in the region of the locus coeruleus which gives rise to the dorsal noradrenergic bundle (DBN), or in portions of the tegmentum that are traversed by this important noradrenergic projection to the forebrain, produced transient hyperdipsia. Damage to the region of the locus coeruleus resulted in abnormalities in renal functions that may have contributed to their effects on water intake but the equally effective tegmental lesions did not, leading Osumi *et al.* to the conclusion that noradrenergic projections to the forebrain may contribute importantly to the regulation of water intake.

Osumi *et al.* [21] unfortunately did not measure the effects of their tegmental lesions of forebrain or hypothalamic serotonin although several earlier publications report correlations between water intake and forebrain 5-HT after serotonin-depleting brain lesions. Hyperdipsia has been observed [14] after serotonin-depleting lesions in the septal area of rats. More transient increases in water intake have been reported [19] after large lesions in the dorsal tegmentum which depleted the forebrain of serotonin to 15% of control values. Lorens *et al.* [19] argued against a causal relationship between the serotonin-depleting and hyperdipsic effects of these lesions because damage to the nucleus accumbens also reduced forebrain 5-HT [18] but did not increase water intake. The logic of this argument is however not compelling because the increased water intake might well be related to an interruption of serotonergic fibers which are not affected by nucleus accumbens lesions.

We [8] have observed delayed and transient hyperdipsia after serotonin-depleting tegmental lesions and demonstrated that this effect did not appear to be the result of impairments in kidney functions. More recently, Grossman and Grossman [12] have reexamined the effects of tegmental lesions on ingestive behavior in 74 rats with bilaterally symmetric cuts in various portions of the tegmentum. Cuts in medial aspects of the tegmentum consistently and reliably produced hyperdipsia whereas cuts of similar size and rostrocaudal location in dorsolateral portions of the tegmentum reliably resulted in hyperphagia. In view of the proximity of these cuts to ascending noradrenergic and serotonergic projections, the present experiments were designed to examine their effects on hypothalamic and forebrain serotonin and norepinephrine and to attempt to correlate their biochemical and behavioral effects on an individual basis.

METHOD

Animals

Adult male albino rats (Holtzman, Madison, Wisconsin), weighing 300–350 g at the beginning of the experiment were used. Fourteen of the rats were hyperphagic and/or hyperdipsic following tegmental knife cuts, twelve rats ate and drank normally after similar cuts, and ten rats which received similar surgical treatments except that no lesions were made served as controls. The animals were maintained in individual cages in an air-conditioned (21 ± 2°C) vivarium with a 12 hr light/dark cycle (0700 to 1900 hr light). Food (Teklad Rat and Mouse Pellets, 6% fat) and tap water were available ad libitum throughout the experiment. Daily food, water, and body weight records were maintained. The experiments were conducted during the months of May and June. The histological and behavioral data of these animals have been presented in detail elsewhere [12].

Procedure

Surgical. In all experimental animals, surgical knife cuts in the coronal plane were made, using an encephalotome that was similar, in principle, to that described earlier [25]. The specifics of the surgical procedure has been described in detail elsewhere [12]. Briefly, the encephalotome was used to position a 27 gauge stainless steel guide in the brains of all experimental animals. A 125 micron tungsten steel wire was then extended from the slightly curved tip of the guide cannula so that it projected medially for approximately 2.0 mm, at an angle for 90° to the guide. The entire assembly was then lowered for 1.5 to 3.0 mm so that the wire knife transected all fibers which crossed the coronal plane of the knife cut (AP=1.0 to -1.0, using coordinates from the de Groot [9] atlas of the rat brain). The wire knife was then withdrawn into the guide cannula and the entire assembly removed from the brain. The procedure was repeated on the contralateral side of the brain.

Histological All animals were killed by decapitation four weeks after surgery. The brains were removed from the calvaria as rapidly as possible and dissected on ice into (a) hypothalamus, (b) forebrain (including the basal ganglia, brainstem rostral and dorsal to the hypothalamus, hippocampus and cerebral cortex) and (c) lower brainstem and cerebellum. Items a and b were weighed and immediately immersed in liquid nitrogen for subsequent biochemical analysis (see below). Item c was placed into a 10% formol-saline solution for several weeks. It was then frozen and 25 micron sections cut through the area of the tegmentum where knife cuts had been made. The sections were stained with cresyl violet to emphasize the glial cell formation that occurs in the area of our cuts.

Biochemical. For each brain the concentration of norepinephrine (NE) and serotonin (5-HT) were determined for hypothalamus and forebrain, using an ion exchange, chromatography procedure described by Barchas *et al.* [4] with minor modifications by Halaris (unpublished). For this purpose, the brain regions were homogenized in 15 ml of ice-cold 0.4 N perchloric acid with 0.25 ml of 4% disodium (ethylenedinitrilo) tetraacetate and 0.2 ml of 2% ascorbic acid in each tube. After centrifugation, the supernatant was adjusted to pH 6.5 and passed onto Amberlite (CG-50) columns. The amines were eluted from the columns in 4 ml 1N hydrochloric acid.

TABLE 1

CONCENTRATIONS (MICROGRAM/G) OF NOREPINEPHRINE (NE) AND SEROTONIN (5-HT) IN HYPOTHALAMUS AND FOREBRAIN OF RATS WHICH SUSTAINED KNIFE CUTS IN THE CORONAL PLANE THROUGH THE TEGMENTUM (MEAN ± SE). THE RESULTS OF TWO ASSAYS ARE SHOWN SEPARATELY

	Assay 1		Assay 2	
	Hypothalamus	Forebrain	Hypothalamus	Forebrain
Norepinephrine				
Exptl (n=10;12)*	1.28 ± 0.13‡	0.42 ± 0.03†	0.71 ± 0.09‡	0.25 ± 0.04‡
Control (n=5;4)	1.91 ± 0.11	0.51 ± 0.02	1.45 ± 0.03	0.41 ± 0.02
Serotonin				
Exptl (n=10;12)	0.45 ± 0.04‡	0.25 ± 0.04‡		0.38 ± 0.03†
Control (n=5;4)	0.94 ± 0.10	0.42 ± 0.01		0.47 ± 0.02

†$p<0.05$
‡$p<0.01$

*The numbers in parentheses refer to the number of rats used in the two assays.

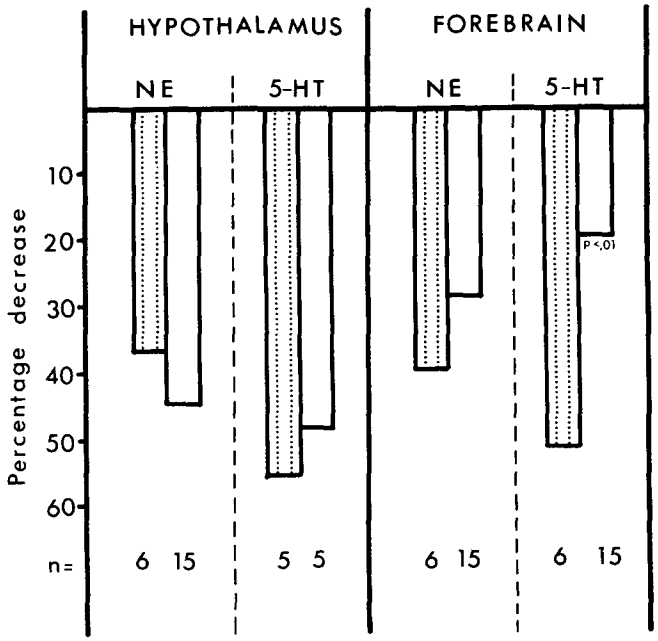

FIG. 1. Decrease in hypothalamic and forebrain norepinephrine (NE) or serotonin (5-HT) in rats with coronal knife cuts through the tegmentum that did (stippled bars) or did not (open bars) produce hyperdipsia, expressed as a percentage decrease from values obtained in intact rats (n=9) of comparable age, weight, and sex. All percentages, except those for hypothalamic 5-HT are the mean of two assays. The baseline control values for all amines are shown in Table 1.

RESULTS AND DISCUSSION

The dorsal tegmental cuts selected for this experiment produced sizeable depletions of hypothalamic and forebrain norepinephrine and serotonin (See Table 1). Attempts to relate the behavioral and biochemical effects of these cuts did not result in compelling evidence for the causal relationships which have been suggested by several investigators.

(a) Hyperdipsic Animals

Six of the experimental animals had been hyperdipsic for varying lengths of time after surgery. The onset of the hyperdipsia and its duration varied considerably between animals. Rats were assigned to the category of hyperdipsic animals if they drank at least 50% more than they had at any time during the ten day control period, prior to surgery, on at least three successive days within the first ten days after surgery. All of the animals included in the present investigations exceeded this criterion. Examination of the histological material from the hyperdipsic animals demonstrated that the cuts which produced hyperdipsia were located in the central portion of the dorsomedial tegmentum (See [12] for further detail). The cuts in the remaining 15 experimental animals that were used in the present experiment were slightly dorsal and/or lateral to that region.

A comparison of the biochemical effects of the two types of cuts (Fig. 1) indicated that both had quite similar significant ($p<0.05$) depleting effects on forebrain norepinephrine, the small difference between the hyperdipsic and normodipsic animals being far from statistically significant ($p>0.10$). In view of the significance of this observation for the hypothesis which Osumi *et al.* [21] have recently advanced, we examined the relationship between the behavioral and biochemical effects in individual animals, and found that (a) the two animals which showed the most severe hyperdipsia had the lowest forebrain NE depletions of the group (a decrease of only 7% and 18% from the average control level); and (b) several normodipsic experimental rats sustained forebrain NE depletions that were larger than the largest seen in the hyperdipsic group. Our depletions were, on the average, as large, or larger than those obtained by Osumi *et al.* with locus coeruleus, DNB or VNB lesions. Our results thus do not support their interpretation that noradrenergic projections to the forebrain play an important role in the regulation of water intake. Our data cannot, however, rule out such an interpretation entirely since it is possible that only a small component of the DNB which projects selectively to a restricted portion of the forebrain might mediate the proposed noradrenergic influence on water

intake. Differences in NE depletion in a small part of the brain would not significantly affect our measure of forebrain NE. An inspection of Osumi *et al.*'s more detailed regional assay data does not offer support for such an interpretation, but we cannot rule out the possibility that an even more detailed dissection might have been required. It should be noted that our results are in excellent agreement with a recent report by Roberts *et al.* [23] who noted hyperdipsia after electrolytic lesions in the region of the locus coeruleus but not after more selective damage to catecholaminergic components of the area due to 6-OHDA injections. Roberts *et al.* [23] specifically confirmed our observation that the appearance of hyperdipsia was not correlated with the effectiveness of their lesion in depleting forebrain NE.

Our assay data demonstrated that hyperdipsia was associated with a significant ($p<0.01$) depletion of NE from hypothalamus ($\bar{X}$ = 63% of control) but this was not peculiar to this group of animals. Fifteen others which were normodipsic after similar tegmental cuts also showed reliable ($p<0.01$) NE depletions from hypothalamus ($\bar{X}$ = 55% of control). These results are in good agreement with other observations from our laboratory (Alheid *et al.* [3]) which have indicated that tegmental knife cuts aimed more specifically for the trajectory of the VNB significantly depleted hypothalamic NE but failed to affect ad libitum food or water intake. Our data thus do not offer support for the conclusion that either the dorsal or the ventral noradrenergic bundle contribute significantly to the regulation of water intake. It should be noted, however, that we (Alheid *et al.* [3]) have observed a correlation between hypothalamic NE and drinking responses to experimental osmotic challenges and discussed the possibility that this might reflect a direct or indirect (renal sodium excretion) influence on water intake that might become apparent only under unusual conditions.

An analysis of hypothalamic and forebrain 5-HT indicated that our cuts depleted both sites significantly ($p<0.01$) (Table 1). This observation is in excellent agreement with earlier reports of 5-HT depletions following electrolytic lesions in the tegmentum that produced transient hyperdipsia [8,19]. Our regional breakdown indicated that the normodipsic animals were as depleted of hypothalamic 5-HT as the hyperdipsic rats but had significantly ($p<0.05$) more forebrain 5-HT (See Fig. 1). These observations suggest a specific association between hyperdipsia and forebrain serotonin but an inspection of the data of individual animals indicates that one must be careful in the interpretation of this observation. Within the small hyperdipsic group, there was no significant correlation between the magnitude of the forebrain 5-HT depletion and the magnitude or duration of the hyperdipsia and three of the normodipsic animals had depletions that were larger than the average depletion seen in hyperdipsic animals. In view of the report by Osumi *et al.* [21] that lesions of the locus coeruleus which should not have affected forebrain 5-HT (although no data were presented) resulted in hyperdipsia, it appears possible that pathways which ascend through the tegmentum in close proximity with the 5-HT projections that arise from the raphe nuclei, might be responsible for the effects of tegmental lesions on water intake.

(b) Hyperphagic Animals

Twelve of the experimental animals were significantly hyperphagic after surgery. To be included in this classification, the food intake of an animal had to remain 20% above a ten-day preoperative baseline for at least ten consecutive days starting on the second day after surgery. Most of our hyperphagic animals exceeded this criterion by 100% or more. Examination of histological data from these animals indicated that the cuts which produced this effect were located in the dorsolateral tegmentum. The ten normophagic animals which were used for comparison purposes in the present analysis had similar cuts through slightly more medial and/or ventral portions of the tegmentum. See [12] for a more detailed description of the behavioral and anatomical consequences of these cuts.

A comparison of the biochemical effects of the two types of cuts (Fig. 2) indicated that both depleted hypothalamic norepinephrine significantly ($p<0.01$). The small difference between the effects seen in hyperphagic and normophagic rats were not statistically reliable. Several aspects of these observations require comment. Firstly, it appears that significant hyperphagia can be obtained by tegmental lesions which produce only small NE depletions from hypothalamus (a decrease of as little as 17% was noted in one hyperphagic animal and the average decrease of 39% is nowhere near the severe depletions reported[2] after injections of 6-OHDA into the area. Secondly, we could not establish a significant correlation between the magnitude of the hypothalamic NE depletion and the magnitude of the hyperphagia (the two animals which overate most dramatically had below average NE depletions for the group.) Thirdly, many normophagic animals sustained hypothalamic NE depletions that were larger than those seen in the majority of the hyperphagic rats.

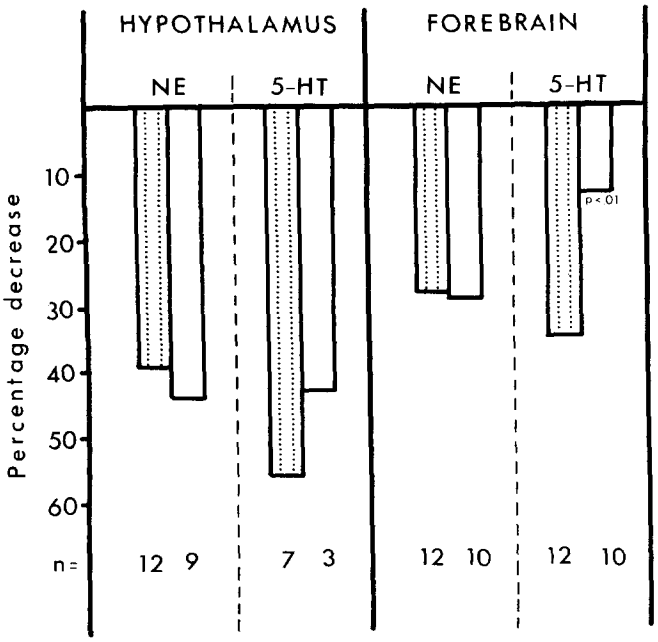

FIG. 2. Decrease in hypothalamic and forebrain norepinephrine (NE) or serotonin (5-HT) in rats with coronal knife cuts through the tegmentum that did (stippled bars) or did not (open bars) produce hyperphagia, expressed as a percentage decrease from values obtained in intact rats (n = 9) of comparable age, weight, and sex. All percentages, except those for hypothalamic 5-HT are the mean of two assays. The baseline control values for all amines are shown in Table 1.

These results do not offer support for Ahlskog and Hoebel's hypothesis [1] that an interruption of noradrenergic projections to the hypothalamus is responsible for the hyperphagia that is seen after some electrolytic or chemical lesions in the tegmentum. Our observations, as well as those of Osumi *et al.* [21], are in agreement with the suggestion by Lorden *et al.* [17] that tegmental pathways which are not catecholaminergic may influence food intake, and that the effectiveness of 6-OHDA injections into the area may be due to the non-specific neurotoxic activity of this compound [7,22]. It should be noted, however, that neither our own observations nor those reported by Osumi *et al.* [21], or Lorden *et al.* [17], entirely rule out Ahlskog and Hoebel's hypothesis since we have not duplicated the near-total depletion of hypothalamic NE which Ahlskog *et al.* [2] accomplished with 6-OHDA injections. Our results demonstrate quite clearly that hyperphagia can be observed in animals which sustained only minor NE depletions from this part of the brain while others with much larger depletions are normophagic. We cannot, nowever, rule out the possibility that the postulated feeding-related NE pathways constitute only a very small proportion of the total NE projections to the hypothalamus. If this component of the ascending NE system were anatomically discrete in the tegmental area under study, it would be possible to destroy it selectively (thus producing hyperphagia with minimal general NE depletion) or sparing it selectively, thus producing no effect on food intake in spite of fairly extensive general NE depletions).

Our cuts depleted norepinephrine not only from the hypothalamus but also, to a lesser extent, from forebrain (Fig. 2). The effects were quite large in some animals but average only 28% and 29% for the hyperphagic and normophagic groups respectively. Both groups contained animals which had forebrain NE levels as large as the average control as well as rats which sustained depletions of NE to 80% of the average control value. A specific relationship between the behavioral effects of our cuts and forebrain norepinephrine thus appears unlikely.

The results of our assays indicate that a loss of hypothalamic serotonin may also not be a critical factor in the effects of some of our cuts on food intake. The hyperphagic animals sustained a slightly greater loss of 5-HT from hypothalamus than the normophagic rats but the difference was small and not statistically reliable (Fig. 2).

Forebrain 5-HT, on the other hand, was differentially affected in the two groups (Fig. 2). Whereas all of the normophagic rats sustained only very slight 5-HT depletions from forebrain, most of the hyperphagic rats showed more severe losses, the difference between groups being statistically reliable ($p<0.01$). It is unfortunately not clear how these observations fit recently published hypotheses that propose a significant role for forebrain 5-HT.

Saller and Stricker [24] depleted brain serotonin by intraventricular injections of 5, 7-dihydroxytryptamine (5, 7-DHT) and reported that ". . . hyperphagia was associated with at least 60–70% depletions of telencephalic 5-HT and was most impressive when depletions were above 80%. Second, for depletions of 5-HT to be effective, the damage to central noradrenergic neurons cannot be substantial." Their published data suggest that average NE depletions of 30% from telencephalon and only 12% from diencephalon sufficed to block the hyperphagia. We, on the other hand, observed significant hyperphagia in animals that sustained 5-HT depletions from forebrain which averaged only 28% and ranged from 0–70%. (Our hypothalamic 5-HT depletion of 56% on the average, on the other hand, was larger than the 45% depletion reported by Saller and Stricker). Our forebrain NE depletions were as large (28% on the average) and our hypothalamic NE losses quite a bit larger than those reported to block hyperphagia in Saller and Stricker's experiment.

The relationship of our finding to the recent report by Breisch *et al.* [5] that intraventricular injections of parachlorophenylalanine (which severely depleted brain serotonin without significantly reducing norepinephrine or dopamine) resulted in hyperphagia is difficult to assess. Breisch *et al.* report a 78% depletion of forebrain 5-HT at the peak of the hyperphagia (five days after the injections) and a much smaller depletion (40% in females and 29% in males) two weeks later when food intake was returning to normal. It is, unfortunately, not clear that one can adduce from these figures that very severe depletions of 5-HT from forebrain are necessary for the hyperphagia. The return of normal intake when 5-HT levels were still low may be influenced by a variety of compensatory mechanisms (including denervation supersensitivity) and the published account unfortunately does not make it clear whether the hypothalamus was included in their sample of forebrain tissue. If hypothalamic tissue was included in their sample, our values are reasonably comparable (although we rarely achieved depletions as severe as those seen during the peak of p-CPA action) but one might ask why many of our rats which sustained severe depletions of hypothalamic 5-HT failed to overeat in our experiment, if serotonergic components of the hypothalamus are responsible for the effectiveness of the p-CPA treatment. If hypothalamic tissue was not included in the forebrain samples assayed by Breisch *et al.* [5], it becomes difficult to understand why our animals displayed hyperphagia although they sustained forebrain 5-HT depletions which were in the range of values which Breisch *et al.* found after food intake had recovered to normal levels.

The results of our experiments should not be interpreted to prove the null hypothesis in any of the individual cases discussed. They do provide data which indicate that any viable and heuristically useful hypothesis concerning the relationship between food or water intake and any of the brain amine pathways cannot be as general as the ones which have been offered so far. Our data clearly show that there are no simple relationships between food and water intake and hypothalamic or forebrain 5-HT or NE which could be used to understand the regulation of these important behaviors better. This does not exclude the possibility that specific components of the serotonergic or noradrenergic projections to the hypothalamus or other regions of the brain may contribute to the regulation of food and/or water intake. A large literature on the effectiveness of pharmacological interventions suggests, in fact, that particularly the NE pathways may be important for the regulation of food intake. What is sorely needed are data concerning the relationship of ingestive behaviors and very much more specific aspects of each of the amine pathways than have been studied in the past and a conceptual framework which explicitly predicts specific roles for particular aspects of the diffuse noradrenergic or serotonergic projections.

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