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PHARMACOLOGIC CONTROL OF FEEDING

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Several forces have combined to focus research on phenethylamines. Modern research in neuroscience has concentrated on the neuroanatomy and neurochemistry of brain monoamines and their roles in psychosis, schizophrenia, anorexia nervosa, and hyperphagia. Phenethylamines such as amphetamine, fenfluramine, propanolamine have the same basic structures as the monoamine neurotransmitters; therefore they have become useful tools in research and therapy. Phenethylamines are well known—some are infamous—for the treatment of obesity which has become prevalent in food-rich nations. Because amphetamine is now illegal in many countries, other anti-obesity drugs such as fenfluramine

Amphetamine is primarily catecholaminergic and fenfluramine
tonergic; therefore it was our working hypothesis that somewhere in the brain, catecholamine and serotonin neurons participate in the inhibition of feeding. Depleting the appropriate neurotransmitters should release feeding from inhibition and thereby lead to obesity.

Our work has led to several findings including the following: (*a*) experimental obesity can follow adrenergic depletion with 6-hydroxydopamine; (*b*) obesity can also follow serotonergic depletion with parachlorophenylalanine; (*c*) adrenergic depletion causes a decrease in amphetamine anorexia, and this may be coupled with an increase in fenfluramine anorexia; (*d*) phenylpropanolamine may influence feeding in part by altering glucose utilization, and (*e*) electrical self-stimulation and stimulation-escape at certain brain sites can be used to assess the arousal and anorectic properties of anti-obesity drugs.

These findings provide new models for the study and treatment of obesity. There has developed a distinction between two kinds of hyperphagia based on monoamine

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neurochemistry, and two corresponding kinds of anorexia based on phenethylamine pharmacology. This suggests that there are different kinds of obesities that require different treatments (1, 2).

So far, these models have revealed very little about the actual brain circuitry that controls feeding. Gross depletion techniques disrupt the innervation to large areas of the brain, and it is not known whether the obesity results primarily from neural, hormonal, or metabolic alterations.

From the therapeutic point of view it might be preferable to find drugs that act to suppress appetite and hunger through a natural physiological route rather than by an action on brain neurotransmitters. The physiological route is more likely to be behaviorally specific. Therefore this review also deals with homeostatic control of feeding.

We discuss three topics: (*a*) amphetamine and adrenergic systems, (*b*) fenfluramine and serotonergic systems, and (*c*) phenylpropanolamine with reference to glucostatic systems.

The author previously compiled a handbook review of feeding pharmacology and neurochemistry with references by the hundred (3); therefore this review presents only selected recent work. Conference summaries of this work, including figures, are also available (1, 4, 5).

TERMINOLOGY AND ABBREVIATIONS

All researchers who have made lesions in and around the ventromedial hypothalamic nucleus agree that the medial area, not just the nucleus itself, is an effective region for inducing hypothalamic obesity; therefore we refer to these as *medial hypothalamic* (MH) lesions. The neurotoxin, 6-hydroxydopamine, is abbreviated as a dopamine (DA) analogue, 6-OH-DA, although it can kill adrenergic as well as DA neurons. *Adrenergic* refers to either or both norepinephrine (NE) or epinephrine (E) neurons; in this paper it will be important to make a distinction between the two. Unfortunately, it is often impossible to make the distinction given the state of the art at the time the research was done. The ventral bundle (VB) was originally thought to be just a NE bundle. The VB is now known to carry E, as well as NE, neurons as it travels with the medial forebrain bundle from the midbrain to the lateral hypothalamus (LH). Traversing almost the same path is part of the serotonin (5-HT) system projecting from the raphe nuclei to the hypothalamus. Our goal was to find out whether these three monoamines play a role in the normal control of food intake and in the anorexia caused by amphetamine (AMPH), fenfluramine (FEN), and phenylpropanolamine (PPA).

AMPHETAMINE AND ADRENERGIC SYSTEMS

Local Injections of Adrenergic Drugs

It was long known on the basis of brain lesion and stimulation studies that the LH is involved in initiating feeding and the MH in suppressing it (4, 6, 7). Then Grossman (8) discovered that the feeding behavior of a fully awake animal could

be influenced by direct injection of drugs into the brain. Crystalline NE injected in the hypothalamus caused feeding. The effect has been confirmed with fluid low as 10 nmole of the l-isomer (9). This is strictly an α-adrenergic effect, although E is more potent than NE (9, 10).

Margules (11) found that adrenergic drugs could also suppress feeding. Most of these studies used a "perifornical" injection site midway between the LH and MH. Recently Leibowitz (9) has reviewed her evidence that shows the main α-adrenergic feeding effect to be medially located, specifically, in the paraventricular nucleus; whereas the β-adrenergic synapses for satiety effects are centered in the LH.

The simplest way to incorporate this new picture with the old is to imagine that in the medial region an α-adrenergic system excites feeding by inhibiting part of the classical MH satiety system; in the lateral region a β-adrenergic system causes satiety by inhibiting part of the classical LH feeding system. The picture that will be painted in this review is more complicated than this simple outline, but compatible with it.

In accord with this view, AMPH, which has both α and β effects, elicits feeding when injected into the MH and suppresses feeding when injected in the LH (9). This may partially explain why AMPH injected systemically can increase in anorectic potency after VM lesions (12) which would block its feeding effect, and conversely, why systemic AMPH may actually induce feeding after LH lesions (13) which partially block its anorectic effect (14). However, to understand the complicated behavioral effects of AMPH more fully we need to know the anatomy of the systems it influences and the behavioral significance of these systems.

The actions of AMPH are primarily indirect via release and inhibition of uptake of endogenous catecholamines (15, 16). When Leibowitz (9) injected AMPH directly into the LH to suppress feeding, the effect was blocked by either dopaminergic or β-adrenergic blockers. Midbrain lesions also blocked the effect, presumably by killing the neurons from which AMPH would release transmitter. The same lesions did not block the anorectic effects of DA or E injected in the LH, which must have acted directly on intact postsynaptic effectors. Therefore some of the catecholamine subsystems necessary for AMPH anorexia apparently are dopaminergic or adrenergic and arise in the midbrain with terminals in the LH.

Neurochemical Depletions

When DA and NE pathways were discovered ascending from the midbrain to the hypothalamus and forebrain, Ungerstedt (17) reported a major breakthrough in the study of feeding; destruction of the DA path caused anorexia. DA depletion was like an LH lesion in many regards.

Several investigators have now proposed that the DA bundle plays a role in initiating feeding, although it is not clear which of several DA projections is responsible (18). AMPH may initiate feeding in DA depleted animals by stimulating the reticular formation or releasing the remaining stores of DA and thereby providing the behavioral arousal and sensory-motor activation necessary to eat (19, 20). The right amount of environmental or physiological stimulation may accomplish the same thing. Even in normal animals, chronic tail pinch apparently activates DA

systems and can lead to obesity (21, 22). Systemic AMPH in a normal rat could release excessive amounts of DA and thereby overactivate the animal and interfere with feeding. Perhaps this is another of the reasons DA depletion reduces AMPH anorexia (23).

Recent electrophysiological evidence suggests another possibility. Excessive DA release by AMPH might overstimulate neuronal feedback that inhibits DA cells of the substantia nigra (24). The behavioral significance of this feedback system is unknown, but it is conceivable that AMPH causes diffuse DA effects at striatal DA synapses, and, at the same time by the resultant negative feedback to the substantia nigra, leads to reduced sensitivity of the DA system to its natural inputs. Thus the animal experiences a large quantity of DA stimulation which not only masks, but also actively inhibits, the natural patterns of sensory input.

Following Ungerstedt's discovery that the DA path is necessary for feeding, we reasoned that a NE pathway might be necessary for normal satiety because NE fluorescent varicosities are especially profuse in the LH where lesions block AMPH anorexia. The problem was to deplete NE but not DA. Ahlskog (25) tested the concept of an ascending NE satiety system by injecting 6-OH-DA locally into the ventral and dorsal NE bundles in the midbrain. This caused a nearly complete depletion of NE in the projection areas of the two bundles as judged by histofluorescence. Assays also showed that forebrain NE was reduced to less than 15% of normal. The animals became hyperphagic and obese. Injections that depleted only the dorsal bundle projections did not cause hyperphagia or obesity, suggesting that VB neurons were crucial (25, 26).

After 6-OH-DA injections or electrolytic lesions in the VB, an increased dose of AMPH was necessary to produce its usual anorectic effect; the dose-response curve was shifted to the right (25). We concluded that NE neurons, or recently discovered E neurons (27), in the VB are necessary for normal satiety and for a part of AMPH anorexia.

Gold (28) extended these findings to explain why MH lesions produce progressively greater hyperphagia and obesity as lesion size is increased. He suggested that lesions or knife cuts which interrupt the appropriate ascending NE system cause hyperphagia proportionate to NE damage. The same logic could apply to any other neurotransmitter necessary for satiety which is distributed in the MH region. But if the lesions or knife cuts were so big that they damage the DA system necessary for eating, then the effects would be reversed and the animal would starve, as seen after large lesions in the original studies of Anand & Brobeck (6).

We find that midbrain injections of 6-OH-DA cause a type of hyperphagia which is different from typical MH hyperphagia. First, I must warn the reader that hypothalamic hyperphagia is itself a syndrome of many faces (4, 29–31). Some MH lesions cause hyperreactivity to taste and some do not (5). Females show MH hyperphagia more readily than males, and the degree of overeating depends not only on lesion size and exact placement, but also on hormonal conditions (31, 32). Moreover, weight gain depends on preoperative weight (33). As a further complication there are chemoreceptors, such as glucoreceptors, in the hypothalamus as shown by the histotoxic effects of gold-thio-glucose in the mouse (34) and unit

recording in the rat (35). The MH is also a site of pituitary control through hormone-releasing factors (36), and lesions are known to affect endocrine functions including changes in metabolism (30, 37). Some MH lesion locations are more likely to destroy these chemoreceptors and secretory cells than others.

The typical MH lesion produces overeating leading to obesity, sensory enhancement known as finickiness, larger meals, and a shift from normal circadian feeding toward feeding both day and night (4).

Our 6-OH-DA–treated VB rats depleted of NE were different than typical MH–lesioned rats. The VB rats were not finicky (38). In studies now involving hundreds of animals, they did not usually become as obese as MH rats, although some did. In a study specifically comparing the two procedures, VB rats depleted of NE by 6-OH-DA overate only at night. Unlike VB rats, the rats made obese by MH lesions were not significantly depleted of NE according to assays of the whole forebrain. Rats that were subjected to both types of neural damage, first 6-OH-DA in the VB followed later by MH lesions, showed a level of hyperphagia equal or exceeding the sum of the separate effects (39).

The pharmacology of VB obesity was also different. In MH-lesioned rats, Epstein (12) found no change or even an increase in AMPH anorexia, whereas we found a loss of AMPH anorexia in VB rats (25, 26). By all these measures MH hyperphagia and VB hyperphagia are different phenomena.

Our conclusion that hyperphagia and obesity can result from depletion of NE, or possibly E, suffers from several criticisms. The phenomenon has not yet been completely confirmed in any other laboratory although several investigators have similar findings using different techniques. Hyperphagia has been reported in rats after electrolytic lesions in the VB region (40–43). Gold (28) suggests that knife cuts that caused hyperphagia did so by transecting the VB at various levels between the mammillary bodies and hypothalamus. Ungerstedt (17) mentions hyperphagia following midbrain injections of 6-OH-DA. In geese and pigs 6-OH-DA injected intraventricularly caused hyperphagia (44) perhaps by depleting NE but not DA, whereas in rats this procedure produced NE depletion without causing hyperphagia or a reduction in AMPH anorexia (19). Panksepp (29) mentions data confirming that 6-OH-DA injections in the midbrain VB can induce hyperphagia up to a 30% increase in daily food intake.

Lorden, Oltmans & Margules (42) could not replicate 6-OH-DA obesity following VB injection, unless they used procedures designed to cause nonspecific damage (43). They suggested that the hyperphagia and obesity we obtained might not be related to NE depletion because some of their rats had NE depletion as great as we reported. Extensive NE depletion did not necessarily cause hyperphagia; however, all rats that showed hyperphagia did have some NE depletion (G. A. Oltmans, personal communication).

Perhaps different subsets of adrenergic neurons were killed in the two studies, or else nonspecific damage caused obesity in our study or blocked obesity in theirs.

It is difficult to use 6-OH-DA selectively. It readily oxidizes and must be handled with care under a nitrogen atmosphere and with ascorbic acid as an additive. In high doses, 6-OH-DA causes nonspecific damage, and even when it does not, the ascorbic

acid may. Some investigators demonstrate gross damage and nonspecificity from local injections of 6-OH-DA; others demonstrate that a high degree of specificity can be obtained (43, 45, 46). This makes behavioral experiments difficult to interpret unless extensive controls are performed.

We doubt that nonspecific damage caused obesity in our study because the ascorbic acid vehicle did not cause obesity by itself; moreover desmethylimipramine, DMI, given i.p. to block 6-OH-DA uptake into adrenergic neurons prevented NE depletion and prevented the obesity. Nonspecific damage from 6-OH-DA and its vehicle should be the same with or without DMI, which leads us to the conclusion that nonspecific damage is not responsible for the phenomenon unless it occurs in conjunction with adrenergic depletion. The results strongly suggest that specific destruction of adrenergic neurons was responsible for the hyperphagia and obesity we observed.

The depleted neurotransmitter responsible for 6-OH-DA hyperphagia may be E instead of NE (9, 39, 42). Immunohistochemical studies show that a small E pathway follows the same VB path as the NE neurons (27). The experiments did not distinguish between the two because 6-OH-DA can deplete both and DMI can protect both. Leibowitz (9) also suggests that the β-adrenergic transmitter that suppresses feeding in the LH may be E. If 6-OH-DA destroys NE and E neurons in different proportions or in different subsystems depending on dose and injection site, this could explain different findings in different laboratories (46).

There is much evidence for multiple adrenergic influences
obese rats have hypothalamic NE (or E) concentration that is lower than normal in the paraventricular nucleus and higher than normal in the median eminence (47). These regional differences suggest that ascending NE pathways have subsystems that function independently. Montgomery & Singer (48) report that NE injected in the amygdala modulates the feeding effects of NE injected in the hypothalamus. Given the evidence for both adrenergic feeding and adrenergic satiety, the evidence for differential changes in adrenergic localization in genetic-obese rats, and the behavioral evidence for adrenergic modulation of adrenergic function, it seems quite possible that the relative balance of adrenergic supplies to the hypothalamus and related areas determines whether hyperphagia is or is not observed after depletion.

Experimental obesity can sometimes be blocked. Powley & Opsahl (49) blocked MH hyperphagia with vagotomy. Coscina (50) blocked it with midbrain raphe lesions. We prevented 6-OH-DA obesity by hypophysectomy (51). It is conceivable, as one more possible explanation, that 6-OH-DA lesions in the Lorden et al (42) experiments produced some such block that prevented the 6-OH-DA obesity observed by Ahlskog & Hoebel (26).

A different approach to the problem is to deplete NE by blocking dopamine-β-hydroxylase with FLA-63. The depletion produced with this drug reduced food intake and failed to affect AMPH anorexia (52). Conversely, long-lasting activation of α-adrenergic receptors with clonidine caused overeating, and reduced AMPH anorexia (53, 54). Both the FLA-63 and clonidine findings are consistent with the classical α-adrenergic feeding theory. Clonidine given intraventricularly would also inhibit adrenergic neurons that had α-adrenergic autoreceptors (55), including,

perhaps, inhibition of the neurons for β-adrenergic satiety. This might contribute to the overeating.

Perfusate Collection In Vivo and In Vitro

Myers and his colleagues (56) injected perfusate from one monkey's brain into the brain of another. The state of hunger or satiety in the first monkey was reflected in the behavior of the second. They also microinjected H^3NE into the MH of a rat and then found it was preferentially released into push-pull perfusion fluid when the rat was offered food and ate a meal. A correlation between the uptake of H^3NE in vitro and the feeding pattern in rats has also been reported (57). Uptake correlated positively with feeding rate. These studies combine three valuable features: the analysis of neurotransmitter turnover, anatomical localization, and behavior. They have been difficult to interpret, however, because of their correlative nature.

Another step in analyzing E or NE systems in feeding is to study the actual membrane receptor properties in localized areas. So far this has not been done with any specific tie to feeding. It is noteworthy that pretreatment of forebrain slices with 6-OH-DA to cause neuronal damage can enhance adenylate cyclase response to NE, suggesting that at least part of NEs effect is on denervated, supersensitive, postsynaptic receptors, not just glial material (58). β-adrenergic adenylate cyclase that is more sensitive to NE than E has been isolated from homogenates of the anterior hypothalamus and other limbic forebrain structures (59). Thus it is conceivable that NE can be a β-adrenergic, as well as α-adrenergic, transmitter in the brain. There may be no necessity to say that the adrenergic suppression of feeding is mediated by endogenous E just because the effect is β-adrenergic; either NE or E could play the β role. Judging by in vitro (58) or in vivo (9) studies, some "DA blockers" can block β-adrenergic functions; therefore NE or E might also play roles sometimes attributed to DA.

Summary and Conclusion

α-Adrenergic agonists, including AMPH, induce feeding in the medial portions of the hypothalamus. AMPH probably induces feeding by releasing either NE or E; it is not clear which. Starvation has never been produced by selective, adrenergic depletion; therefore all the evidence for adrenergic feeding is based on agonist-antagonist injections and push-pull perfusion studies. This suggests that activation of the α feeding system is sufficient for feeding, but not necessary for feeding.

AMPH injected in the lateral hypothalamus suppresses feeding and the effect is β-adrenergic or dopaminergic. This agrees with the finding that systemic AMPH loses anorectic potency after dopaminergic or adrenergic depletion with 6-OH-DA.

Hyperphagia can follow adrenergic depletion. This was not the same pattern of hyperphagia or depletion seen after classical MH lesions. An overview of work from several laboratories suggests that it is possible to obtain obesity without depleting NE or vice versa, to deplete NE without obtaining obesity, or even to deplete NE to produce obesity but then block it.

We conclude from work in this laboratory that 6-OH-DA injected in the VB reduces the anorectic potency of AMPH. This procedure also depleted endogenous

NE and/or E, but not DA or 5-HT, and the procedure caused obesity. It is therefore a likely possibility that part of AMPH anorexia in the normal animal is the result of the release of endogenous NE or E at adrenergic terminals which have as one of their normal functions a suppressive effect on food intake and body weight.

FENFLURAMINE AND SEROTONERGIC SYSTEMS

Systemic Injections

FEN is structurally related to AMPH (Figure 1), but its anorectic action does not depend on catecholamines (60). For example, midbrain injections of 6-OH-DA reduced AMPH anorexia, but enhanced FEN anorexia (39), and LH lesions produced the same dissociation (14).

FEN is serotonergic. Its anorexic effect was diminished by 5-HT antagonists (61, 62), by 5-HT synthesis block with systemic parachlorophenylalanine (PCPA) (63), by depletion with an intraventricular neurotoxin, 5,6-dihydroxytryptamine (5,6-DHT) (64), or by raphe lesions (65). However, in other studies PCPA (66), 5,6-DHT (66), 5,7-DHT (63), or raphe lesions (66) failed to diminish FEN anorexia. The authors suggested that FEN can have a direct postsynaptic effect, although this has since been challenged (69), or a nonserotonergic effect, such as DA block (70), or simply that a greater degree of 5-HT depletion was needed. It is also possible that some techniques cause depletion in the wrong areas to affect FEN anorexia. It is known that systemic PCPA and various raphe lesions can have differential effects on locomotor activity, pain reactivity, and avoidance behavior (71); clearly, serotonin depletion cannot be spoken of as a unitary concept (72). Another possibility is that some of the 5-HT depletion procedures also caused catecholamine depletion which would potentiate FEN anorexia and counteract any loss of anorexia. Feeding

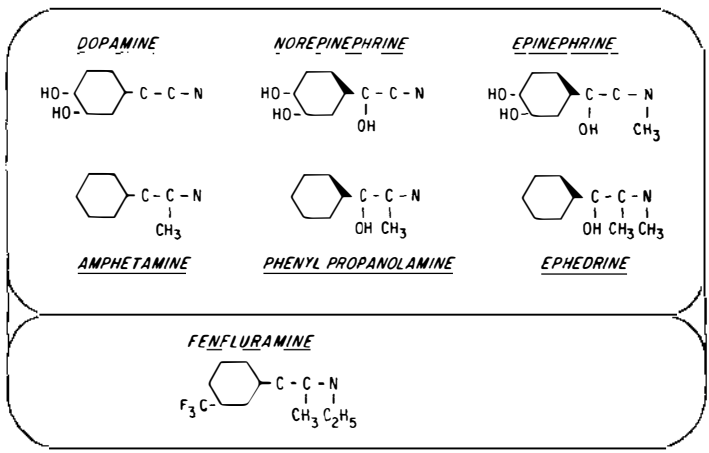

Figure 1 Structural comparison of some monoamine neurotransmitters and phenethylamine anorectics.

schedules used in anorexia tests can also influence
is that high doses of FEN can cause such extensive 5-HT release that FEN, itself, leads to depletion and loss of physiological function (60). In the concentrations generally used, FEN is properly considered to be a 5-HT agonist if one judges by the positive results rather than the negative. This does not necessarily mean that FEN has a straightforward action on a neural system which regulates feeding. FEN might possibly cause anorexia in part by increasing glucose utilization, enhancing lipolysis, or releasing hormones, but in any case a serotonergic basis for a major part of FEN anorexia is well established even though we do not know where it acts.

The effects of FEN on brain metabolites of monoamines suggest an action on serotonergic systems in the central nervous system (73). On the other hand a recent study of 5-HT antagonists failed to find changes in brain metabolites (74). This might have argued against a central action, except that there appears to be no neuronal feedback in brain serotonin systems to cause a compensatory change in 5-HT turnover (75). Therefore 5-HT turnover studies leave open the likelihood of central effects.

FEN injected systemically can be expected to have complicated effects in the CNS because there are many serotonin cell assemblies. Serotonin cells in the hypothalamus have recently been reported (76). Within the midbrain raphe nuclei 5-HT neurons inhibit other 5-HT-containing cell bodies (75, 77). Thus, FEN inhibits neurons in the raphe. It follows that systemic FEN may produce a 5-HT effect at 5-HT terminals in the forebrain, but at the same time inhibit the same 5-HT neurons at their source in the midbrain and render them unresponsive to normal physiological inputs. Similarly a depletor like PCPA could have a variety of effects. It becomes essential to consider factors that affect drug entry into various parts of the brain.

The usual effect of 5-HT agonists is anorexia. Hypothalamic injection of 5-HT (78), FEN to release 5-HT, a 5-HT uptake blocker to prolong synaptic action (29), or 5-HT precursor (80) all can produce anorexia, although controls for sedation are a problem.

Taken together, these facts suggest that somewhere in the chains of serotonergic neurons there may be synapses that lead to the suppression of food intake. If so, depletion of the appropriate 5-HT neurons should disinhibit food intake and cause obesity.

Neurochemical Depletions

We find that parachlorophenylalanine (PCPA) delivered into the ventricles depleted forebrain 5-HT to 25% of normal and consistently caused hyperphagia to develop (81). Brain 5-HT can be depleted with PCPA given systemically, but this failed to cause hyperphagia in many studies (81–83). The experiments may have been confounded by malaise caused by peripheral 5-HT depletion particularly in the gut, or perhaps systemic PCPA caused the wrong pattern of brain depletion.

Our PCPA-treated rats displayed hyperphagia starting three days after injection. They sometimes became overweight and continued to overeat for about two weeks. By then 5-HT levels had been partially restored. Significant changes in forebrain catecholamine levels did not occur during the period of maximum hyperphagia.

The function of 5-HT in feeding could take many forms. It is too soon to speculate whether 5-HT neurons control food intake by a direct action on a final common path for feeding, or through some circuitous neuronal or hormonal route. Another question is whether the effect is specific to feeding, or has to do with overall behavior inhibition, arousal thermoregulation, or locomotor activity (67, 84).

To begin to examine these questions, we have found that rats treated with intraventricular PCPA tend to overeat both day and night, particularly in the day when they should be sleeping (unpublished observations). The same PCPA treatment increased sexual behavior as measured by a female's tendency to assume the lordosis posture when mounted. This confirms with intraventricular PCPA an effect on mating seen earlier with systemic injections (85). Thus in female rats, only intraventricular PCPA causes hyperphagia, but either intraventricular or intraperitoneal PCPA causes hypersexuality. As confirmation that 5-HT underlies the change in sexual behavior, *p*-chloroamphetamine, which releases 5-HT and gradually depletes it, caused a corresponding biphasic effect on behavior. First lordosis frequency decreased, then increased (86).

Confirmation of hyperphagia following PCPA has not yet appeared; however, Saller & Stricker (87) report that serotonin depletion with the neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT) given intraventricularly to young male rats caused hyperphagia and increased bone growth. PCPA and 5,7-DHT each have their own penumbra of side effects involving false transmitters, metabolites, multiple actions, and nonspecific effects. Each drug has a different set of associated problems, so it is encouraging that both produced hyperphagia. We will feel more certain of the effect if and when 5,7-DHT is shown to produce hyperphagia and obesity in females as well as males, and when the effect of PCPA and 5,7-DHT is obtained with localized injections. We have succeeded in mitigating PCPA-induced hyperphagia with systemic 5-HTP to bypass the block of 5-HT synthesis (unpublished observations). One would also expect supersensitivity to develop for serotonergic agonists after 5-HT depletion with 5,7-DHT; this has been done for simple neurological signs (88), but not for feeding behavior.

If it is true that 5-HT neurons play an important role in feeding suppression then a number of intriguing avenues are opened for exploration. Quantity and quality of food intake can cause large shifts in 5-HT levels in the brain. Theoretically, dietary additives or deficiencies or physiological imbalances that prevent tryptophan from entering the brain could deplete 5-HT and possibly cause overeating (89). The same speculation applies to sexual behavior. These behavior changes might also be caused by any environmental pollutants, genetic characteristic, or brain lesion leading to a PCPA-type action.

MH lesions can cause hyperphagia with little forebrain 5-HT depletion (39, 90) and no loss of FEN anorexia (91); nevertheless a comparison of MH hyperphagia and ventricular-PCPA hyperphagia suggests that they might have something in common. Both caused overeating that predominated in the daytime, thereby flattening the diurnal feeding cycle (5). We also have preliminary evidence that VM lesions plus intraventricular PCPA applied to the same rat produces nonadditive hyperphagia (unpublished observations). This is consistent with the possibility that a

major part of the classical VM effect is similar to the action of ventricular PCPA. This is unlike the 6-OH-DA hyperphagia described earlier that occurred at night and was superimposed on the MH effect.

Summary and Speculation

FEN suppresses feeding in people as well as animals and is sold by prescription for that purpose even though it is a mild sedative. Its counterpart, cyropheptadine, a 5-HT antagonist, is marketed to promote feeding and weight gain (3).

There is no doubt that FEN anorexia depends on a different mechanism than AMPH anorexia. The FEN effect seems to be serotonergic. Some procedures designed to deplete 5-HT lead to hyperphagia but so far there is no unequivocal demonstration that any particular brain structure is necessary for FEN anorexia.

Disinhibition of feeding with midbrain 6-OH-DA and ventricular PCPA revealed different types of hyperphagia. This suggests at least two different systems that somehow suppress feeding under normal circumstances. One is adrenergic, and a normal function in the rat is to suppress feeding at night; the other is serotonergic, and it acts to suppress feeding day and night. Presumably the adrenergic one is activated by amphetamine; the serotonergic one, by fenfluramine.

Behavioral studies of AMPH and FEN also suggest a dichotomy between two feeding suppression systems. Blundell, Latham & Leshem (2) found that AMPH inhibited the initiation of meals whereas fenfluramine
meals. In other words, AMPH caused fewer meals, and FEN caused shorter meals. In another dissociation, tail pinch reversed AMPH anorexia but not FEN anorexia (92, and personal communication).

These results offer a hint that adrenergic and dopaminergic substrates control the initiation and maintenance of meals during the half of the day when most meals are taken, and that serotonergic substrates control the cessation and suppression of meals around the clock, particularly during the sleep period.

PHENYLPROPANOLAMINE AND GLUCOSTATIC SYSTEMS

PPA is intriguing for several reasons. As shown in Figure 1 it is closely related to AMPH with the addition of a hydroxyl group (β-hydroxy-AMPH). It is less potent as an anorectic by about 20-fold, but has an even greater loss of psychomotor stimulation. Because it is less stimulating it is less abused and can be sold over the counter for both weight reduction (e.g. Permathene,® Appedrine® and X-11®), and nasal decongestion (e.g. Propadrine® Allarest®, and Contac®). It was useful for studying feeding and self-stimulation in rats because some doses inhibited feeding without causing hyperactivity like AMPH or sedation like FEN (93). Therefore it was the drug of choice for our laboratory studies.

In rats with implanted electrode-cannulas, injection of crystalline PPA in the LH, but not the MH, suppressed electrically induced feeding. This suggested a possible LH site of action. However in 6-OH-DA–treated rats, PPA failed to lose anorectic potency like AMPH, or to gain potency like FEN. Therefore, if PPA acts in the brain, the mechanism is a mystery.

Ideally, an anorectic drug would act on a specific receptor system controlling feeding instead of acting on brain neurotransmitters that might be involved in many behaviors.

The glucostatic theory of feeding control suggests that anorexia could be caused by a drug with an insulin-like action or a direct excitatory action on glucoreceptors. To explore this possibility with PPA, we gave the drug to alloxan diabetic rats in a pilot study and obtained a decrease in blood sugar. Then in collaboration with Dr. Charles Hamilton, rhesus monkeys received PPA at approximately the same mg/kg dose used in humans. In normal monkeys, PPA caused anorexia with accompanying weight loss. In mildly diabetic, but not severely diabetic, monkeys PPA reduced glucosuria significantly more than could be accounted for by decreased food intake. Apparently PPA somehow increased glucose utilization. It is already known that some phenethylamines, including FEN, increase glucose utilization (94). Evidence that PPA, an over-the-counter drug, might act in this fashion is new. It is conceivable that this effect suppresses feeding.

There is currently a controversy in the United States over the issue of PPA efficacy in humans. The Post Office, Federal Trade Commission, and Food and Drug Administration want to know whether this widely sold drug produces the benefits claimed for overweight people. We found that PPA suppressed intake of a liquid lunch, and in another study that it reduced snacks and caused a statistically significant weight loss. There were no consistent reports of side effects. Average subjects lost roughly a pound in anticipation of the study, then in a one month cross-over design they lost another pound on placebo, and a third pound attributed to PPA. It is a matter of judgment whether or not this is medically significant or advisable for any given individual. It is not known whether statistical significance would be obtained in another age, economic, ethnic, educational, or racial population, or in subjects unaware of the nature of the study (3).

Given the present evidence that (*a*) PPA is effective as an anorectic in humans, (*b*) effective at the human dose in monkeys, (*c*) effective at relatively high doses in rats, and (*d*) effective in altering bronchial and nasal secretions, we conclude that there is a great need for information about this drug's effects on other behavioral and physiological systems. At the present time the millions of consumers who take PPA as a decongestant are not well informed that it may affect their appetite. We do not know what, if any, other behaviors are affected. If PPA acts primarily to facilitate energy utilization and thereby suppresses feeding, then its physiological effects on metabolism may be rather widespread and its behavioral effects rather specific. If, on the other hand, PPA turns out to be a catecholaminergic drug in the CNS at the common dose, then it can be expected to affect many behaviors that depend on brain catecholamines.

The only test of behavioral specificity for PPA so far is an indirect assessment using brain self-stimulation and stimulation-escape. This procedure for measuring "reward" and "aversion" in rats has a built-in control for overall activity changes. AMPH elevates response rates for both self-stimulation and stimulation-escape, whereas FEN lowers both. Presumably a drug that lowers self-stimulation but raises stimulation-escape is acting on behavioral reinforcement rather than on overall

arousal or sedation. That is what we found with PPA; it lowered self-stimulation and raised escape rates. Tests that are independent of response rate have not yet been used to confirm this result. Instead, we repeated the experiment using two different electrodes in each rat. LH self-stimulation, which tends to vary directly with feeding, was decreased by PPA. Stimulation-escape, which tends to vary inversely with feeding, was increased by PPA. In the posterior hypothalamus, on the other hand, where self-stimulation tends to vary with sexual appetite, PPA had no effect on self-stimulation or escape (1, 93). Thus under these selected testing conditions there was evidence that PPA affected the reinforcement produced by stimulation of one part of the hypothalamus, but not another. Hernandez and I (95) obtained the same result with injections of small doses of insulin. Thus we again find PPA and insulin may have something in common.

The evidence from animal research described above suggests an application that is exciting, but untested. This over-the-counter drug could be useful in treating some mildly diabetic people. It might help them control hyperglycemia in two ways, by helping them lose weight and by increasing glucose utilization. At the present time PPA is officially contraindicated for diabetics. It might have adverse sympathomimetic effects, particularly on the cardiovascular system. Therefore it is not safe for the suggested new use until long-term tests of cardiovascular effects and controlled clinical trials are published.

SUMMARY

It has become clear that anorectic drugs vary a great deal. They act in a variety of ways and have a variety of side effects. The evidence that has been reviewed suggests that some drugs might be more appropriate than others for a given overweight individual. No one drug has emerged as best or safest for everybody. The issues raised involve central monoamine balance and peripheral metabolic state.

New neurochemical procedures for producing experimental obesity have suggested possible neurotransmitters underlying anorectic drug action. These chemical procedures are supposed to deplete only selected neurotransmitters. This has allowed research on anorectic pharmacology to be tied in conceptually with research on the neurochemistry of brain systems involved in feeding. This is a substantial advance over the state of the art when classical medial hypothalamic lesions were our best tool. However, the new techniques still have many problems and the old questions remain. For example, when we observe chemically induced hyperphagia, to what extent is it behaviorally specific (feeding versus emotion), physiologically specific (glucostasis versus lipostasis), anatomically specific (terminals versus pathways), or neurochemically specific (known transmitters versus the unknown)? In the face of these problems we have arbitrarily delved into the relation between AMPH and adrenergic systems, FEN and serotonergic systems, and PPA and glucostatic systems. Although neither the drugs nor the systems are specific to our arbitrary categories, a number of interesting relationships between the drugs, the brain, and feeding have become evident and have led to the discussion of new ideas in the pharmacologic control of feeding.

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