Artificial Sweeteners

In their report concerning the palatibility of dulcin and saccharin to monkeys, rats, and men [*Science* **150**, 506 (1965)], Fisher, Pfaffman, and Brown describe these substances as "the sweetest substances known to man," citing as their reference R. W. Moncrieff's *The Chemical Senses* (Wiley, New York, 1944). According to the Merck Index (seventh edition), P-4000 (5-nitro-2-*n*-propoxyaniline) is 4100 times as sweet as sucrose and hence very much sweeter than saccharin or dulcin.

Both dulcin and P-4000 are considered harmful substances by the Food and Drug Administration, and their use as artificial sweeteners in foods or drugs is illegal in the United States.

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Hypothalamic Lesions and Disinhibition of Feeding

Hoebel (*1*) has presented data which he believes contradict recent studies of mine (*2*, *3*) on the nature of hypothalamic hyperphagia. Certain of his statements require comment.

In the first place, the question is not whether one can produce hyperphagia by using a radio-frequency lesion maker. Indeed, I demonstrated that this was possible in my first paper on this subject (*2*). The question is, rather, whether one can successfully remove the ventromedial hypothalamus *without* producing hyperphagia. Aside from my first study and a subsequent (unpublished) replication with 40 animals, I know of three studies in laboratories other than my own confirming my findings. If it is possible to remove the ventromedial hypothalamus without producing hyperphagia, it follows, somewhat tautologously, that hyperphagia is not a necessary result of ablation of the ventromedial hypothalamus, and we must, therefore, find an alternative explanation for the phenomenon. This is what I have tried to do with my "irritative hypothesis," in which I suggest the possibility that the electrolytic method used to induce ventromedial lesions may irritate the lateral hypothalamus and thus stimulate feeding. As I have stated elsewhere (*3*), the use of radio-frequency thermocoagulation does not guarantee that lesions will be nonirritative, but simply reduces the probability of irritation.

Although Hoebel says that all his animals with ventromedial hypothalamic electrocauterization "overate and became obese," the data he presents suggest that at least some of his animals actually were not hyperphagic but simply showed the transient initial weight gain which I had previously reported for animals with large radio-frequency lesions. I have attributed this transient effect to surgical trauma. Hoebel reports that his experimental animals averaged 6 g per day weight gain for the first 2 weeks. This amounts to an average total gain in that period of 84 g. They reached a weight plateau an average of 34 days later (48 days after surgery). Their mean total increase in body weight was 154 g. Thus they gained on the average 70 g during the last 34 days, or approximately 2 g per day after the first 2 weeks following surgery. Since he reports that his normal control animals were gaining at a rate of 1 g per day, with a range of 0 to 2 g per day, this average is just at the upper end of the normal range; and it is quite likely, furthermore, that the gain of many of the animals with lesions was well within the normal range. These data appear to me not to support Hoebel's contention that the lesions consistently produced hyperphagia.

I have previously (*3*) pointed out the paradox in identifying the system subserving intracranial self-stimulation in the ventrolateral hypothalamus with the ventrolateral hypothalamic "feeding center." If these systems were the same, as Hoebel assumes, we would be led to the conclusion that hunger is positively reinforcing, and animals should learn responses which make them hungry. On the empirical level, moreover, Morgane (*4*) has demonstrated that lesions in the medial forebrain bundle, anterior and posterior to the ventrolateral hypothalamic region, eliminate self-stimulation but do not affect feeding induced by stimulation through the same electrode. Miller (*5*) has shown that amphetamine raises the threshold for induced eating but lowers the threshold for self-stimulation through the same electrode in the ventrolateral hypothalamus. These studies suggest that the hunger system is distinct from the self-stimulation system. Hoebel's data on the effect of his lesions on ventrolateral self-stimulation do not, therefore, seem particularly relevant to an examination of the hunger system.

At the beginning of his report Hoebel states that my "series of papers refutes the traditional view that the hypothalamus contains a mechanism necessary for satiety." Later he says that I suggest "that the medial hypothalamus does not inhibit feeding."

The first statement may be his inference from my studies, but I have never made such an assertion, nor have I ever made the suggestion contained in the second statement. What I have said is that destruction of the ventromedial hypothalamus does not necessarily cause hyperphagia. Activation of the ventromedial hypothalamus may indeed have a satiety effect by inhibiting activity in the ventrolateral hypothalamic "feeding center." It may also be the case, however, that some other satiety mechanism intervenes in the absence of the ventromedial hypothalamus, provided that the ventromedial lesions are not chronically activating the "feeding center." There may be an inhibitory mechanism which operates directly on the ventrolateral "feeding center," as has been suggested by Carlisle (*6*). Thus, ventromedial activity may simply be a sufficient but not a necessary condition for satiety. Such a possibility would resolve most of the problems raised by my studies.

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