THE RELATION BETWEEN WATER INTAKE AND FOOD INTAKE IN NORMAL RATS AND IN RATS WITH HYPOTHALAMIC HYPERPHAGIA*

JACK LEONARD STROMINGER

The obesity described by Babinski,[2] Fröhlich,[18] and Erdheim[16] in patients suffering from lesions at the base of the brain has now been produced experimentally in the dog,[20, 24] cat,[32] monkey,[9] and rat.[6, 8] Moreover, the long-existing controversy as to whether the primary lesion is in the hypophysis[4, 12, 18] (as originally suggested by Fröhlich[18]) or in the hypothalamus[16, 22, 30] (as Erdheim[16] first proposed) seems to have been settled when Hetherington[21] showed that the pituitary is not involved in the development of the obesity which follows the production of discrete, bilaterally symmetrical lesions in the ventromedial hypothalamus of the rat. Hetherington and Ranson[23] had previously shown that following the placing of these lesions no conspicuous changes could be detected in the pituitary.

Thus far no primary disturbance in the intermediary metabolism of these animals has been discovered, since the alterations observed seem to be the consequence of the hyperphagia rather than the result of the lesion.[7, 31] Present work tends to emphasize the hypothesis that the obesity is a result of a fundamental disturbance of energy exchange.[5] The mechanism of the hyperphagia is at present unknown, and, while it is possible that some metabolic disturbance may be responsible for it, the nature of such a disturbance is wholly conjectural. Clinical investigators also have emphasized the importance of hyperphagia in the pathogenesis of human obesity.[11, 13, 25, 29]

Since the supra-optic nucleus (lesions of which produce diabetes insipidus[17]) lies just anterior to the region where the lesions are

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placed in order to produce hyperphagia, some controversy has existed as to the possible co-existence of diabetes insipidus in the animals exhibiting hyperphagia. Bailey and Bremer[3] noted that in their series the two dogs which showed "permanent diabetes insipidus" also become obese. Heinbecker, White, and Rolf,[20] also working with dogs, suggested that adiposity develops more quickly in the presence of diabetes insipidus. However, several other groups of workers[9, 10, 23] have reported that there are no disturbances of water exchange in animals which develop obesity as the result of hypothalamic lesions. In the course of experiments in this laboratory it was noted that rats with hypothalamic lesions which produced hyperphagia drank large amounts of water. It was thought advisable to investigate the possibility that these animals might have diabetes insipidus, or, at least, that they might be using unusually large amounts of water in their metabolic processes. One manifestation of such a disorder would be an increased water intake. The present study was set up to determine whether the water intake of these animals was inordinately large. When a close relationship between food intake and water intake became evident, this study was extended in order to define further that relationship.

I. *Investigation of food intake and water intake of normal control rats and of rats with hypothalamic lesions producing hyperphagia.*

Method

Twelve female rats of the Yale strain were used. Throughout the experiment, both pre- and post-operatively, all of the animals were maintained in a constant temperature room (82° F.) on a "Purina dog chow" diet, ground and mixed with an equal part (by weight) of water. The animals had an additional source of water from graduated drinking tubes.

Using the Horsley-Clarke instrument, the hypothalamic lesions producing hyperphagia were placed in six of the animals by the method previously described by Hetherington.[22] The other six animals were reserved as controls. The animals were used and operated upon in two groups. The first group of four (two operated, two controls) was used from their thirty-eighth through their forty-ninth post-operative day, records of food intake and of water intake being kept during this period. At this time they weighed 364 grams and 374 grams, while their control rats weighed 212 grams and 224 grams. The second group of eight was similarly used from their twenty-second through their twenty-seventh post-operative day. The four operated animals weighed 310, 322, 350, and 358 grams, as compared with control animals weighing 264, 266, 280, and 286 grams.

Food was given to each rat at the same hour. At this time uneaten food from the previous day was measured, the animal was weighed, the amount of water taken from the tube was recorded, and the tube was refilled. Food intake was computed as follows: the weight of food returned was subtracted from the amount of mixed food (dog chow plus water) given to the animal, the remainder was divided by two, and the result was taken to be the intake of dry food for the day. Because of the fact that the food returned had lost water by evaporation, the results obtained by this method gave dry food values which were slightly higher than the actual amount of food eaten by the animal. To reduce this error to a minimum, the food given to the animal was measured so that a minimal amount of palatable food would be returned. More accurate observations would require a greater consideration of this source of error. Appropriate corrections were made for spillage of food. Water intake was taken to be the amount of water drunk from the tube plus the amount obtained in the food; the latter quantity was computed as half the loss of weight of the food cup minus an appropriate correction for water evaporation. For the conditions of this experiment a correction factor of 5 ml. of water loss per day per food cup containing 35 grams of mixed food was used. A correction factor of 2 ml. of water loss per day was also made in computing the water drunk from the tube. Several factors influenced the correction for water lost from the food, viz: Initially the animal consumed a diet which was actually composed of the equal parts of food and water presented to it; later, as water evaporated, the water: food ratio was decreased. Moreover, as the animal ate, it was constantly presenting a fresh surface of the food to the air for evaporation. Finally, the animal ate the greatest portion of the mixed diet during the first 6 to 12 hours after the food had been presented to it.

In graphing the results of this experiment it was found that two-day averages gave greater uniformity and less dispersion, especially with regard to values for water intake, than did single-day values. For this reason graphing was done with two-day averages for both water intake and food intake.

Results

The correlation between food intake and water intake was exceedingly close, both in the normal rats and in the hyperphagic operated rats. For the conditions of this experiment the average water intake of all the animals, in milliliters per day, was equal to 203 per cent of the average food intake in grams per day, and since the caloric value of the food used was about 3 kcal. per gram, for these conditions the average water intake in ml. per day was equal approximately to two-thirds of the food intake in kcal. per day. Moreover, this relationship was not different in the ravenously hungry animals from that found in their normal controls. The average daily water intake (ml.) of the operated animals alone averaged 200 per cent of their daily food intake (gm.), while that of the controls was 213 per cent of the food intake, but the individual dispersion is great enough so that this is not a significant difference. It made no difference at which absolute level of food intake the animal was eating or whether it changed its food intake from day to day. This ratio of water intake to food intake was maintained quite constantly, providing all environmental conditions were maintained as constants.

These results may be presented graphically (Fig. 1). Each point on the graph represents an average of two consecutive days of the observation period for one animal. It is seen that the points representing the relation between the food and water intake of the operated animals lie on the same line as the points similarly obtained from the control animals alone. Water intake in ml. per day for both groups of animals is shown to be approximately 200 per cent of the food intake in grams per day. During the period reported on, one of the operated animals was recovering from some disturbance which temporarily had greatly depressed its food intake. During the period of recovery as the animal's food intake increased, its water intake rose in almost exact proportion. On the graph the points representing this animal are underscored.

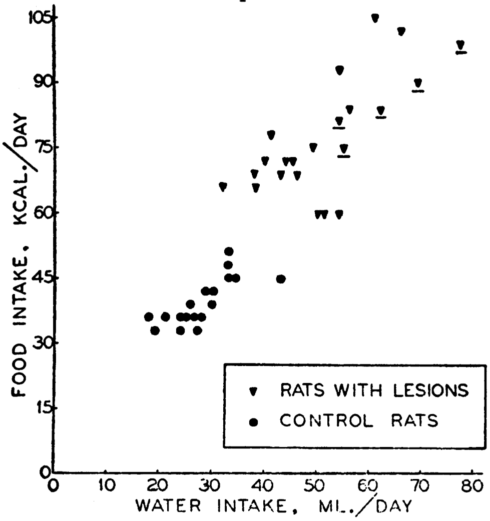

FIG. 1. Correlation between food and water intake in normal control rats and in rats with lesions of hypothalamic hyperphagia. Water intake (ml.) is approximately 200 per cent of food intake (gm.) in both groups. Two-day averages were used for both water intake and food intake. Underscored points are those of an animal whose food intake was rising during the observation period. Its water intake rose correspondingly.

II. *A further definition of the relationship between food intake and water intake in normal animals.*

Method

A. Effect of restriction of water intake upon food intake. Twenty-four Sprague-Dawley male rats were maintained on G.L.F. calf meal ad libitum and water ad libitum in large cages at 85° F. Once each week twelve of these animals were moved to individual cages. For a period of six hours water was not supplied to them although they had free access to food. For the next eighteen hours water was supplied in measured limited amounts, food ad libitum, and during this period both water intake and food intake were recorded. Water was withheld for six hours prior to the experiment because it was found that, while it did not greatly influence the major results, it did greatly increase the uniformity of the various groups. This was probably because, if an animal had drunk water a few minutes before the experiment was initiated (without prior deprivation), it must have influenced the data being collected.

B. Effect of restriction of food intake upon water intake. Twenty-four Sprague-Dawley male rats were maintained under the conditions outlined above. Once each week they were moved to individual cages and fasted for twenty-four hours although supplied with water ad libitum during this period. For the next eighteen hours food was supplied in restricted amounts, water ad libitum, and during this period both food intake and water intake were recorded. Pre-fasting was carried out for the same reasons as deprivation of water in the preceding experiment.

Results

Restriction of water intake in unoperated rats caused marked depression of food intake so that the water: food ratio was approximately maintained, although animals which received no water did eat some food. Figure 2 represents the summary of three experiments using the same groups of 24 animals, 12 at a time. Four other similar experiments involving 48 rats gave comparable results. It was also true that the animals whose food intake was restricted showed a similar depression of their water intake, even though animals which received no food did drink a significant amount of water. A total of seven experiments in which 137 animals were used is the basis for these statements. Figure 3, a single experiment involving 24 animals, is representative. While these experiments were not carried out with operated animals, there is no reason to believe that the results would have been essentially different. The example presented above of the operated animal which maintained its water: food ratio when its food intake was restricted by illness bears this out, and personal experience has indicated that failure to fill water cups severely limits the food intake of operated animals.

Discussion

It was possible to observe a large number of animals maintaining widely different food intakes under ad libitum conditions. It is evident from these results that the large water intake of those animals with the lesions of hypothalamic hyperphagia is not larger than would be expected from their huge food intakes. Their water intake bears the same quantitative relation to food intake as does the water intake of control animals, and on the basis of this relationship their hyperphagia entirely accounts for their polydipsia. Indeed, when Bailey and Bremer[8] described polydipsia preceding polyuria in a dog in which they were trying to produce diabetes insipidus by hypothalamic puncture and which eventually became obese, this polydipsia may well have been related to the animal's hyperphagia rather than to any lesion of the supra-optico-hypophysial system. It cannot be said that the animals with lesions producing hypothalamic hyperphagia have diabetes insipidus nor can it be said that they are using inordinately large amounts of water in their metabolic processes.

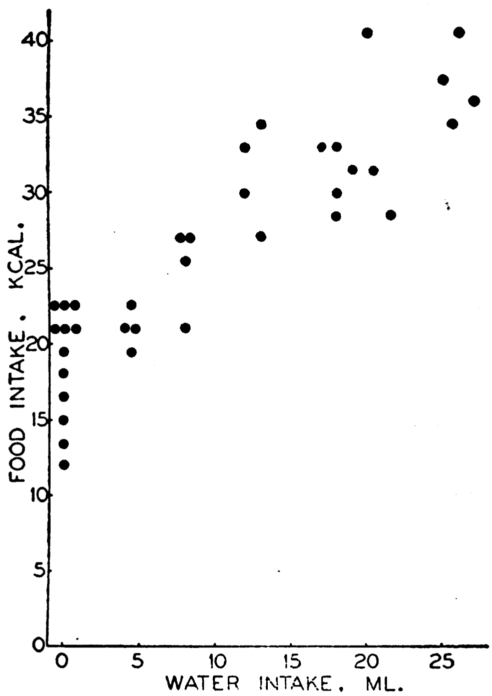

FIG. 2. Effect of water restriction upon food intake (18 hours, at 85° F.). Rats were deprived of water for 6 hours prior to experiment. A positive correlation between food intake and water intake is apparent.

Robinson and Adolph,[28] working with dogs, have reported that the pattern of water drinking closely follows that of eating, and they state that this water is drunk within ten minutes after eating. During fasting periods their animals did not drink amounts of water sufficient to restore the body weight lost through elimination and evaporation. They conclude that "body weight is only a rough criterion of water balance since addition of food and loss of catabolic products complicates its relations." Gregersen[19] also has shown that periods of drinking in dogs are associated with periods of eating. He explains this great thirst during and after periods of eating as due to a state of dehydration resulting from the withdrawal of fluids from the body for the digestive juices. The work of Robinson and Adolph, however, suggests that the largest part of the water intake after feeding occurs in a period sufficiently short so that it may not be accounted for solely by adjustments operating over a long period of time, such as those which might bring about the intake of water because of the continual withdrawal of water from the blood for the formation of digestive juices.

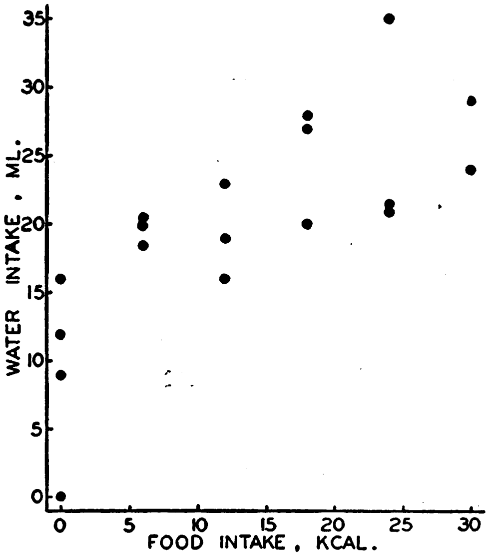

FIG. 3. Effect of food restriction upon water intake (18 hours, at 85° F.). Rats were deprived of food for 24 hours prior to experiment. A positive correlation between water intake and food intake is evident.

There appears to be a threshold of water deprivation to which animals respond by drinking. Robinson and Adolph's dogs[28] responded to a loss of water amounting to minus 0.5 per cent of the body weight. This is not dependent upon the absolute amount of water lost nor upon the lapse of time during which the loss occurred. As yet unexplained is Adolph's observation[1] that dehydrated dogs will drink within a few minutes an amount of water which is quantitatively equal to the amount of their dehydration. The data herein presented suggest that rats also possess an unexplained mechanism regulating water intake. This mechanism operates to relate quantitatively the intake of water to food intake. Such a relationship might be considered to be an additional means by which the animal maintains osmotic and ionic equilibrium in the face of a great increment of particles at the time of eating. The dogs of Robinson and Adolph[28] apparently have a similar mechanism. The data obtained by these workers under similar temperature conditions (75° F.) and using similar diets (dried whole milk and fox chow mixed with an equal part of water) indicate that the water intake of their dogs was also in the region of 200 per cent of the food intake. When the food intake of their dogs was 0.18 per cent of body weight, the water intake was 0.38 per cent of body weight, but lack of knowledge of the exact method by which they computed water intake prevents exact comparisons. In addition, Peters[26] has presented in a young woman a case of diabetes insipidus which could be controlled by starvation. He states that the intake of food by this patient was associated with the intake of inordinately large amounts of water and "as her diet increased, her fluid intake rose out of proportion," an observation which perhaps suggests the presence of an imbalance of a regulation of the sort herein described. During starvation, when she apparently had a normal water intake, she had a normal urine volume. Dogs,[14, 15] cats,[33] and rats[27] with experimental diabetes insipidus resulting from lesions of the supra-optico-hypophysial system also show marked limitation of water intake in response to limitation of food intake. Restriction of water intake also produced cessation of eating in these animals,[15] just as in the normal animals of our series.* The dependence of water intake in part upon food intake seems to be undisturbed by lesions producing diabetes insipidus.

The supra-optic nucleus apparently functions as an internal sense organ of the central nervous system. It is richly supplied with capillaries and is said to be sensitive to changes in the water content of the blood. Fibers emanating from this nucleus descend in the infundibulum and thence reach the posterior pituitary gland where they control the secretion of the antidiuretic hormone.[17] No other mechanism of hypothalamic control of water metabolism has been substantiated, and no other connections of the nucleus are well known. It exists in close anatomic relation to a center exerting an influence on food intake, the center whose destruction produces hyperphagia. Does it have connections with this center or with other centers con-

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* This apparent diminution of hunger in all animals upon restriction of water intake is somewhat difficult to explain by existing theories of hunger.

trolling thirst? Does it truly function alone as a "sense organ"? Are there thirst centers in the brain? The close relationship between water intake and food intake demonstrated herein and the existence of a center regulating food intake in some as yet undetermined manner might suggest such a possibility, but the answers to these questions are now unknown.

Summary

1. The water intake of normal rats and of obese rats with the lesions of hypothalamic hyperphagia is quantitatively related to the food they eat. Under the favorable conditions of this experiment the average daily water intake (ml.) was approximately 200 per cent of the average daily food intake (gm.). Since this quantitative relation was not disturbed in the obese rats, the polydipsia of these animals is attributed entirely to their large food intake.

2. In normal animals restriction of water intake produced depression of food intake and restriction of food intake produced depression of water intake, thus approximately maintaining the water: food ratio, although animals receiving no food drank some water and animals with no water ate some food.

3. These results suggest the existence of a physiological regulation by which water intake is quantitatively related to food intake.

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