Effect of Dietary Fluoride on Food Intake and Plasma Fluoride Concentration in the Rat [1]

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ABSTRACT The effect of excessive amounts (200–600 ppm) of dietary fluoride on the food intake and plasma fluoride concentration of rats of various ages was investigated. In older animals, the decline in food intake was partially corrected within a week even though the plasma fluoride concentration remained elevated. When the same amounts of fluoride were fed to younger animals, a longer exposure to the diet was required before an improvement in food intake was seen. The ability of the rat to increase its consumption of the high fluoride diet following an initial drop in consumption suggests some type of adaptation to the elevated plasma and soft tissue fluoride concentrations.

The effects of ingestion of excessive amounts of dietary fluoride by animals have been extensively studied and reviewed (1–3), and one of the major physiological responses repeatedly noted is a decline in growth rate. This decline is the result of a marked decrease in food consumption by the animals, and some studies have specifically indicated that the degree to which the consumption is decreased is lessened as the period of exposure is extended (4). It has been shown also that the ingestion of a high fluoride diet by the rat results in an increase in plasma fluoride content (5), and that the decline in food consumption, at least in short-term experiments, is inversely correlated with this increased plasma fluoride.

This study was designed to investigate the response of food intake to dietary fluoride in more detail, and to further study the relationship between dietary fluoride, plasma fluoride, and food intake.

METHODS

Female rats of the Holtzman strain [3] of varying ages were maintained in individual cages in an air-conditioned room with a 12-hour light-dark cycle. They were fed a semipurified diet (table 1) to which fluoride was added as NaF and were given distilled water ad libitum.

Dietary intake was measured daily, and plasma samples for fluoride determination were obtained in the morning by a heart puncture within 1 hour of the end of the night dark period. Fluoride analyses of the plasma were carried out by the method of Singer and Armstrong (6). To clarify the graphic presentation of the data, food intake values for successive 3-day periods have been averaged, and these, rather than individual day consumptions, have been plotted on the figures.

RESULTS

The data presented in figure 1 indicate the response of 120 g female rats to diets containing varying amounts of fluoride. There was an immediate effect on growth at 400 or 600 ppm F, but little if any effect at 200 ppm. At an ingestion level of 400 ppm F there appeared to be a period of about 1 week during which growth was stabilized, followed by a growth rate which was comparable to that of control rats. At 600 ppm F there was an actual loss of weight, and initial weight was not regained for about 2 weeks. The growth rate subsequent to this was only slightly below that of the controls. The graphs of actual food intake at the various ingestion levels indicate that there was a sharp drop in food

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[3] Obtained from the Holtzman Company, Madison, Wisconsin.

TABLE 1

Composition of experimental diet

Ingredient	% of diet
Casein	23.5
Sucrose	66.0
Salts B[1]	5.0
Corn oil	5.0
Vitamin premix [2]	0.5
	100.0

Supplementary additions

1.0 choline·HCl/kg diet in 25% ethanol solution

0.125 g α-tocopherol/kg diet in corn oil

NaF added to the fluoride diets at the level indicated

[1] Harper, A. E. 1959 J. Nutr., *68:* 405.

[2] The vitamin premix contained per kilogram: inositol, 20 g; Ca-pantothenate, 4 g; niacin, 2 g; menadione, 0.8 g; riboflavin, 0.6 g; thiamine·HCl, 1.2 g; pyridoxine·HCl, 0.5 g; biotin, 20 mg; folic acid, 40 mg; vitamin B_{12}, 2 mg; vitamin A, 800,000 IU; and vitamin D, 200,000 IU.

intake which reached its minimum within a few days, and then increased until it was near the control values. It is apparent that after a few weeks on the diets containing 400 or 600 ppm fluoride, food intake, on a body weight basis, was elevated over that of the controls, and was comparable to the intake of the control rats when they were that size.

The results of 2 similar experiments, which indicate that weanling rats appear

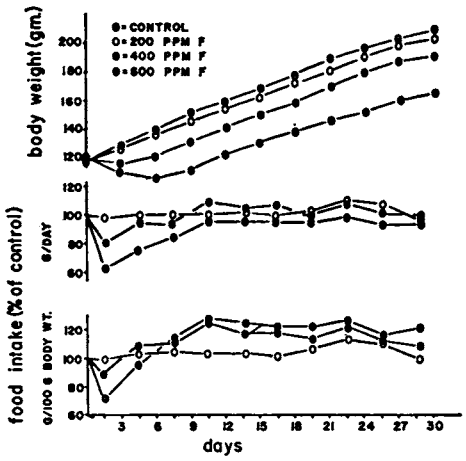

Fig. 1 Growth rate and food intake of female rats (120 g) fed fluoride in the diet, 12 rats/group. Note that in this and subsequent figures, the food intake of the experimental groups is expressed as a percentage of the control group and no curve for the control group is included. The food intake of the control group averaged 11.7 g/day (9.1 g/100 g body weight) at the start of the experiment and 13.3 g/day (6.5 g/100 g body weight) at the end.

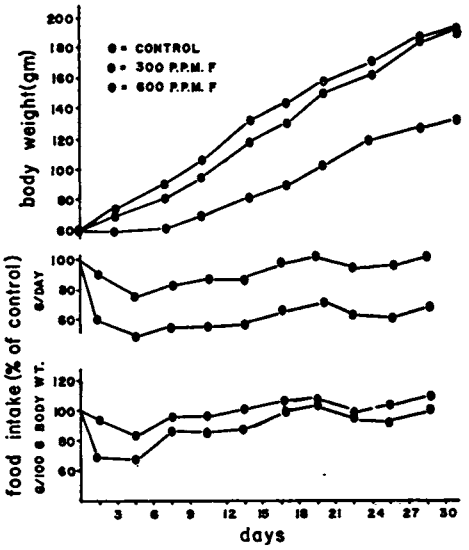

Fig. 2 Growth rate and food intake of weanling female rats fed fluoride in the diet, 10 rats/group. The food intake of the control group averaged 7.9 g/day (10.8 g/100 g body weight) at the start of the experiment and 11.6 g/day (6.4 g/100 g body weight) at the end.

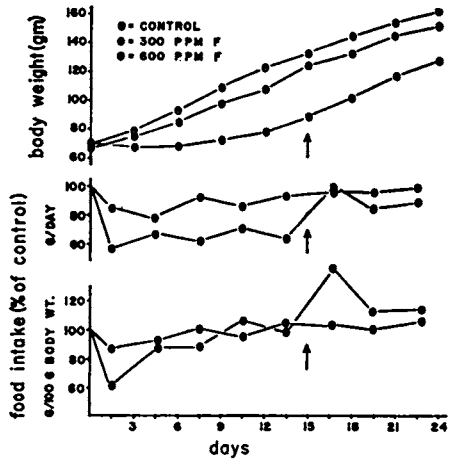

Fig. 3 Growth rate and food intake of weanling female rats fed fluoride in the diet. At day 15, indicated by the arrow, the rats fed fluoride were given the control diet, 15 rats/group. The food intake of the control group averaged 9.6 g/day (12.4 g/100 g body weight) at the start of the experiment and 12.9 g/day (8.2 g/100 g body weight) at the end.

to be more severely affected by the fluoride, are shown in figures 2 and 3. In weanling animals the food intake of those fed 600 ppm F did not recover with time to the extent that it did in the older animals, and even on a body weight basis did not exceed that of the controls. The observation that food intake, on a g/100 g body weight basis, of the animals fed fluoride approached or even exceeded that of the control animals in these experiments did not indicate that fluoride was no longer exerting an appetite-depressing effect. This is illustrated in figure 3, where it can be seen that the removal of fluoride from the diet at day 15 caused a pronounced increase in food consumption of the rats fed 600 ppm F even though they had previously been consuming about the same number of grams of diet/100 g body weight per day as had the controls.

As previous experiments (5) have indicated a close relationship between decreased food intake and plasma fluoride level, it was of interest to follow the changes in plasma fluoride with time. Rats which were 260 g at the start of the experiment were fed the control diet, 300 or 600 ppm F for a period of 42 days. Blood samples were obtained at day 3, day 6, and then at approximately weekly intervals. As the heart punctures were frequent enough to have an effect on food consumption and body weight, only the plasma fluoride data from this experiment are presented in table 2. At all periods sampled, the plasma fluoride concentration of rats receiving either 300 or 600 ppm F was higher than the controls. Although there was some variation from one sampling period to another, the plasma fluoride concentration of the 300 ppm F rats did not appear to increase following the initial sample which was obtained at day 3, and tended to average about 1.2 ppm for the entire experiment. In rats fed 600 ppm F, the plasma fluoride concentration appeared

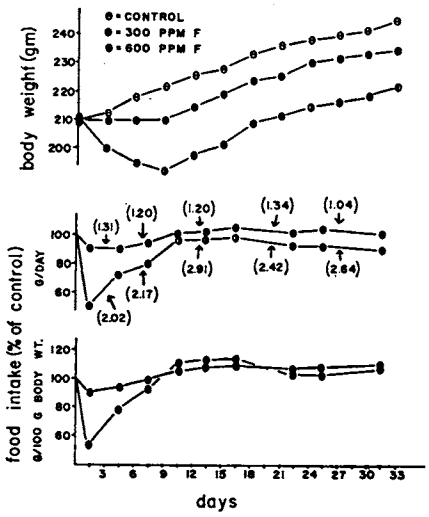

Fig. 4 Growth rate, food intake, and plasma fluoride concentrations in female rats (210 g) fed fluoride in the diet. The food intake of the control group averaged 13.1 g/day (6.1 g/100 g body weight) at the start of the experiment and 13.5 g/day (5.6 g/100 g body weight) at the end. The numbers in parentheses are the plasma fluoride concentrations of 6 rats removed from that group at the times indicated by the arrows. The SE of the mean for the values indicated ranged from 5 to 10% of the mean and the plasma fluoride concentrations determined for the control rats were similar to those seen in table 2. Food consumption and body weight data are based on 36 rats/group at the start of the experiment, and 6 remaining at day 33.

TABLE 2

Plasma fluoride concentrations of rats fed fluoride in the diet [1]

Days on experiment	Control diet	300 ppm F	600 ppm F
		ppm F in plasma	
3	0.31 ± 0.06	1.26 ± 0.10	1.19 ± 0.09
6	—	1.40 ± 0.11	2.10 ± 0.23
13	—	1.28 ± 0.19	2.18 ± 0.18
20	0.40 ± 0.08	1.16 ± 0.07	3.04 ± 0.30
27	—	0.93 ± 0.12	2.61 ± 0.17
35	0.16 ± 0.03	1.13 ± 0.13	2.88 ± 0.21
42	—	1.27 ± 0.07	3.31 ± 0.43

[1] Female rats (260 g) were fed the control or fluoride diets ad libitum. Blood samples were obtained from half of the 16 rats in each group at each sampling period indicated. Values are expressed as mean ± SE.

to increase for about 2 to 3 weeks, and then maintained a concentration near 3 ppm.

This experiment was repeated with sufficient number of rats (200 g) in each starting group so that animals could be removed from the experiment at the time the blood was drawn. This removed the influence of the blood loss on food intake, and growth curves and food intake (fig. 4) can be compared with the data in figures 1–3. It was apparent that the effect of fluoride on these rats was similar to that seen in rats weighing 120 g (fig. 1). The drop in food intake was severe enough to cause a temporary loss of weight in the animals fed 600 ppm F, but when growth was resumed, it was at a rate which was comparable to that of the control rats, and food intake on a g/100 g body weight basis was similar to that of the controls.

The plasma fluoride concentrations seen in the experiment were similar to those shown in table 2. The rats fed the 300 ppm F diet maintained a plasma fluoride concentration of about 1.2 ppm from day 3 to the end of the experiment, while the rats consuming 600 ppm F demonstrated some increase in plasma fluoride concentration for the first 2 weeks and then remained rather stable.

DISCUSSION

These data indicate in some detail the effect of one particular toxic agent, in this case fluoride, on food consumption. It is apparent that the drastic, sharp decline in dietary intake which has often been noted in a fluoride toxicity is in a sense a temporary response, and that food intake returns to more normal levels after a period of reduced consumption. In fact, animals not exposed to fluoride until they were over 100 g were able, after a short period of retardation, to maintain a growth rate which was similar to that of the controls. The data in figure 3 however, show that even though food intake may appear to be stabilized at near the control level in animals fed fluoride, it can temporarily increase to much higher levels if the fluoride is removed from the diet.

Previous work from this laboratory (5) has shown that a concentration of about 3 ppm F in the plasma of the rat was associated with a drastic curtailment of food intake. The rats fed 600 ppm F in these experiments, however, were able to increase their food intake during a period when the plasma F concentration was increasing and approaching this value. The previous studies were of a few days duration only, and the performance of the animals in these current experiments would indicate that there is some type of adaptation to the high fluoride level in the plasma and soft tissues. We have previously postulated (5) that the relationship between food intake and plasma F is an indirect one, mediated through an effect on tissue enzyme activity which results in a shift in the concentration of some metabolite(s), and that this altered balance of tissue metabolites, rather than the increase in fluoride concentration, is the signal for the depressed dietary intake. The ability of the animal to increase its dietary intake in the presence of a continued high tissue fluoride concentration could then be explained by an alteration of metabolic pathways, resulting in a return of metabolite concentrations to more nearly normal. That alterations in at least some metabolic pathways do occur is evident from changes in carbohydrate (7) and lipid [4] metabolism demonstrated in the rat fed fluoride. An alternate explanation would be that the effect of fluoride is on the mechanisms involved in the short-term regulation of food intake only, and that if this is interfered with for a significant period, those factors involved in the long-term regulation of body weight (8) are able to reverse the depression in food intake.

It appears significant that the response of food intake to the inclusion of this toxic agent in the diet is very similar to that which has been observed in an amino acid imbalance (9) and in amino acid toxicities (10). Here again animals adapt to the nutritional disorder, they gradually increase their intake of such diets as they continue to ingest them. Further study of the response of animals to diets such as these might well provide insight into the regulation of food intake in the normal animal.

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