Abnormalities in taste preference in hypothyroid rats

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Rivlin, Richard S., Martha Osnos, Susan Rosenthal, and Robert I. Henkin. Abnormalities in taste preference in hypothyroid rats. Am. J. Physiol. 232(1): E80-E84, 1977. - Rats made hypothyroid by administration of radioactive iodine and age-matched controls were individually caged and offered a choice between either water or varying concentrations of sweet (sucrose), bitter (quinine sulfate), salty (NaCl) or sour (HCl) solutions to drink ad libitum for 48 h periods. Comparative measurements were made of the volume of test solution consumed to that of total volume consumed and were expressed as taste preferences. Throughout a wide range of concentrations, taste preferences for sucrose were significantly lower (P < 0.001) and those for quinine sulfate in hypothyroid animals than in controls. Taste preferences for NaCl were generally similar in both groups. Daily intraperitoneal injections of thyroxine, 10 μg/100 g body wt, to hypothyroid rats for 18-24 days eliminated completely the difference between hypothyroid and control rats in taste preference for quinine sulfate. These studies show that significant and reversible changes in taste preferences occur in rats rendered hypothyroid with radioactive iodine.

THE OBSERVATION that the sense of taste in man may be disturbed in hypothyroidism was made by physicians more than fifty years ago (16). Later, drugs used in the treatment of hyperthyroidism were noted to reduce and to alter taste acuity (9, 15, 25), but whether these effects were due to the drugs themselves or to the production of hypothyroidism was not clarified. Recently (17), defects involving each of four taste qualities have been demonstrated to occur in the majority of a group of patients with hypothyroidism, and these changes were improved by treatment with thyroid hormones.

In order to investigate taste defects in hypothyroidism in man, taste preference studies were performed with laboratory rats made hypothyroid after radioactive iodine administration and the results compared with those of controls. Taste preference studies in both groups of rats consisted of offering them a choice between distilled water and graded concentrations of either sucrose, quinine sulfate, sodium chloride (NaCl) or hydrochloric acid (HCl) to drink ad libitum. From these investigations, the pattern of fluid consumption was determined. This report presents the results of these studies and also of the effects of administration of thyroxine to hypothyroid rats upon taste preference for quinine sulfate.

MATERIALS AND METHODS

Male Holtzman rats initially weighing 100-150 g were divided into two groups and used in all experiments. One group of 40 rats received a low-iodine diet (General Biochemicals Corp.) for 3 wk, after which they were rendered hypothyroid by a single intraperitoneal injection of 131I, 300 μCi/100 g body wt. Hypothyroidism has been reliably produced by this technique (24). Forty-eight hours after receiving 131I, these animals were switched to a diet of Purina rat chow pellets which they received ad libitum throughout the experimental period. Rats were used in these experiments at least 12 wk after treatment with 131I, at which time they weighed 160-320 g, and were 4-9 mo of age. Hypothyroidism was confirmed by demonstrating lower than normal levels of serum thyroxine concentration by radioimmunoassay (21). The range of serum thyroxine levels in hypothyroid rats was 1.1-2.1 μg/dl, compared to 6.1-7.6 μg/dl in controls.

The second group of 20 age-matched rats served as controls and received the same diet of Purina rat chow pellets ad libitum throughout. Control rats did not receive a low-iodine diet at any time. These rats weighed from 370-600 g at the time of testing. During the course of experimental testing with the four taste qualities, 1-2 hypothyroid and 0-1 control rats died. Each of these rats was replaced with similarly treated animals of the same age from the original pool of either hypothyroid or control rats. The number of animals to which each taste quality was presented is shown in RESULTS.

All animals were individually housed. Each cage was supplemented with a fully accessible food hopper. Two 250-ml drinking bottles were provided, one mounted on the left and the other on the right side of each cage. The room temperature was maintained constant at 70°F, and continuous lighting was provided for 12 h each day.
The procedure for determining taste-preference percentages was based upon a modification of the two bottle choice technique initially described by Richter (22, 23). One 250-ml bottle containing 150-250 ml of the test solution and a similar bottle containing water were presented to each animal for two consecutive 48-h periods. The left-right positions of the bottles were reversed during the second 48-h period. At the termination of each 48-h testing period, the volumes of water and of test solutions remaining in each bottle were measured and refilled to their original levels. Taste preference was expressed as follows

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\text{preference, %} = \frac{\text{volume (ml) test solution consumed}}{\text{volume (ml) test solution + water consumed}} \times 100
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The data were expressed as means ± SE of the two 48-h experimental periods combined.

After the two 48-h test periods had been completed, all rats received water in both bottles for 48-72 h. At the end of this period, a new test solution was presented.

In order to exclude "right-left preference" as a possible factor influencing the experimental observations, each animal was tested beforehand to determine whether it drank predominantly from a bottle on one side or the other side of the cage. This procedure was performed by placing two identical bottles of water on either side of the cage and determining the volumes consumed during several 48-h testing periods. An animal was considered to exhibit right-left preference, and was therefore excluded from the study if the volume of fluid consumed from a bottle on one side of the cage exceeded that from the other side by 25% or more on 3-4 successive trials.

Taste preference was determined in both hypothyroid and control animals for sweet (sucrose), bitter (quinine sulfate), salty (NaCl) and sour (HCl) solutions. The concentration ranges tested were as follows: sucrose, 1-20 mM; quinine sulfate, 0.067-6.7 mM; NaCl, 0.001-0.60 M; and HCl, 2-12 mM. Each quality was tested sequentially with increasing concentrations of solute.

In further experiments, preferences of hypothyroid rats for quinine sulfate (0.67 mM) were determined both before and during a 28-day period of treatment with daily intraperitoneal injections of thyroxine, 10 \( \mu \)g/100 g body wt, dissolved in isotonic saline. Hypothyroid animals served as their own controls. In addition, a group of age-matched normal animals simultaneously received daily injections of isotonic saline of the same volume and pH as that received by the thyroxine-treated group.

RESULTS

In control rats, preference for sucrose was significantly greater than 50% throughout the concentration range of 2.5-20 mM (Fig. 1), indicating that controls drank more sucrose than water at each concentration tested, particularly in the range of 16-20 mM. By contrast, sucrose preference in hypothyroid rats was not consistently greater than 50% and was significantly \((P < 0.001)\) lower than that of controls in the range of 12-20 mM.

Quinine preference in control rats was significantly reduced \((P < 0.001)\) below 50% at a concentration of 0.33 mM quinine sulfate and was reduced even further in the range of 0.67-6.7 mM (Fig. 2). By contrast, in hypothyroid rats, preference at a concentration of 0.33 mM quinine was barely decreased below normal levels. At higher concentrations of quinine sulfate, preference in hypothyroid rats decreased below 50% but always remained significantly greater \((P < 0.001)\) than in controls.

Preference for increasing concentrations of NaCl in controls was greater than 50% in the range of 0.001-0.01 M, but less than 50% at concentrations of 0.035 M or greater (Fig. 3). NaCl preference in hypothyroid rats was elevated well above 50% at low concentrations and remained above 50% up to a concentration of 0.2 M. Only at concentrations of saline greater than 0.2 M was preference reduced below 50%. Except at the single most dilute concentration of saline, preferences of
hypothyroid rats were significantly greater ($P < 0.001$) than those of controls.

Both control and hypothyroid animals exhibited preferences for HCl of less than 50% throughout the concentration range tested (Fig. 4). The preference curves for both groups of animals were generally similar. HCl was increasingly rejected by hypothyroid and control rats as the concentrations were increased.

In order to determine the reversibility of the abnormal taste preferences described above, hypothyroid animals were tested with quinine sulfate (0.67 mM) both before and during a period of daily treatment with thyroxine. Controls were tested similarly with quinine sulfate both before and during daily injections of isotonic saline. Quinine sulfate was selected for this study because its detection by the rat is presumably less dependent upon metabolic factors such as blood sugar level and adrenal function than are the other taste qualities. The results of these experiments are shown in Fig. 5. Prior to treatment, preferences for quinine sulfate in hypothyroid rats on repeated trials were reproducibly elevated over those in controls. Exogenous thyroxine administration to hypothyroid rats produced a progressive decrease in preferences for quinine sulfate. In these hypothyroid rats after 18–24 days of daily treatment with thyroxine, preferences for quinine sulfate did not differ significantly from those observed in control rats injected with saline.

**DISCUSSION**

The present studies show that rats rendered hypothyroid with radioactive iodine differ from controls in their patterns of consumption of solutions of several taste qualities. When offered a choice between water and a test solution, hypothyroid rats consume relatively less of a sweet-tasting solution and relatively more of a bitter-tasting solution than do controls. In addition, hypothyroid rats have increased preference for NaCl compared to controls, similar to that shown by other investigators in rats made hypothyroid with the antithyroid drug, propylthiouracil, or after surgical thyroidectomy (6, 7). In a study of renal hypertensive rats, radioactive iodine administration did not result in increased NaCl preference (4). In the present study, only for HCl was there no consistent difference in preference found between hypothyroid and control rats.

Taste thresholds, as well as taste preferences, have been shown to be affected by hypothyroidism; these effects have been shown in mice (13), rats (8) and man (17). In mice made hypothyroid with radioactive iodine, increased thresholds were observed for the taste of saccharin at a concentration considered sweet, phenylthiocarbimide (a bitter-tasting substance), and acetic acid (a sour-tasting substance), but not for sodium chloride (13). In rats treated with propylthiouracil, taste thresholds for NaCl were reported to be lower than in controls (8). In hypothyroid patients, abnormalities in the detection and recognition thresholds of salty, sour, and bitter stimuli were observed in one-half to three-quarters of 18 individuals studied, whereas abnormalities with respect to sucrose were detected in 17% only (17). Although the bases for these...
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... differences among species have not been determined. It is apparent that the effects of hypothyroidism upon modifying taste thresholds are not confined to a single species.

In previous reports (5), differences between hypothyroid and control rats in taste preferences, taste thresholds, and total fluid intakes were corrected after the administration of exogenous thyroxine. Similarly, in hypothyroid human patients, elevated taste thresholds were significantly improved, and in many instances were completely restored to normal by treatment with thyroid hormones (17). In the present studies, elevated taste preferences for quinine sulfate returned to control levels within 20 days after initiating daily administration of exogenous thyroxine. These results indicate that thyroid hormones play a significant role in determining taste preference and taste acuity in rats and in human subjects.

The mechanisms by which thyroid hormones influence taste sensations and food consumption have not been defined clearly. Little is known of any morphological alterations that may occur in the taste buds in hypothyroidism either in experimental animals or in man. Infiltration with myxedematous deposits could interfere mechanically with taste perception (19), as has been observed in other tissues. Similarities in taste preference behavior between hypothyroid and adrenalectomized rats have been noted (5), and both histological (2, 3) and functional (5) abnormalities in adrenal glands have been noted in hypothyroid rats. These findings have been observed in particular in the zona glomerulosa of the rat adrenal gland, the region associated with the production of aldosterone. The decreased aldosterone secretory rates in hypothyroid rats were corrected by treatment with thyroxine (5). Altered adrenal function in hypothyroidism could influence salt preferences, but seems unlikely to explain abnormalities in quinine preference. Diminished blood-sugar levels observed in hypothyroid rats (14) could potentially influence the consumption of sucrose; it is of interest in this connection that in the present study hypothyroid rats consumed relatively less rather than more of the sucrose solution compared to controls.

The manner in which thyroid hormones influence zinc metabolism may also play a role in the development of abnormalities of taste preference in hypothyroidism. Zinc deficiency in rats has been associated with anorexia and abnormalities in taste preference (1, 18). An increase in preference for NaCl, HCl, and quinine sulfate has been noted only 3 days after feeding a zinc-deficient diet to laboratory rats (18). Similarly, zinc deficiency in man has been associated with loss of taste acuity, and structural and functional abnormalities in the taste buds (10-12). The status of zinc metabolism in thyroid gland disorders is currently under active investigation. Initial studies suggest that, in hypothyroidism in man, zinc concentrations in erythrocytes are normal (20, 26), but, in serum and in parotid gland saliva, appear to be reduced (12, 17). A comprehensive understanding of zinc metabolism and its possible relevance to taste abnormalities in hypothyroidism needs to be established firmly.

Whatever the mechanism of these complex effects may be, hypothyroidism has a wide range of actions upon nervous system activity, as recently reviewed (17). Whether the observed changes in taste preference are related to abnormalities in the central or peripheral nervous systems, changes in receptor function, or to some combination of these possibilities is unclear at present. The data in their entirety are most compatible with some kind of abnormality in taste sensation that remains to be elucidated.

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