Influences of Hypothyroidism on the Taste Detection Performance of Rats: A Signal Detection Analysis

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The influences of hypothyroidism on behavioral measures of the taste function in male and female Long-Evans rats were determined. Experimental rats' preferences for and ability to detect NaCl, HCl, sucrose, and quinine sulfate were examined before, during, and after 9 weeks of maintenance on 0.1% propylthiouracil (PTU), an agent that produces marked hypothyroidism, with similar determinations made for control animals. Despite significant decreases in PTU-treated rats' serum triiodothyronine (T3) and thyroxin (T4), there were no changes in sensitivity or responsivity to the target tastants. However, altered preferences for NaCl, HCl, and quinine sulfate were observed for PTU-treated rats; elevated consumption of HCl and quinine sulfate was present at the end of the study when serum T3 and T4 had returned to near-baseline levels. The data confirm observations that PTU-induced hypothyroidism alters rats' taste preference behavior.

The influence of hypothyroidism on taste sensitivity is controversial. In humans, several studies have reported no effects of this condition on taste threshold sensitivity. For example, Pittman and Beschi (1967) evaluated the threshold sensitivity of normal subjects, hyperthyroid patients, and hypothyroid patients to sodium chloride (NaCl), potassium chloride (KCl), sodium bicarbonate, sucrose, urea, and hydrochloric acid (HCl) and found no differences between these three study groups. Similarly, Lewitt, Laing, Panhuber, Corbett, and Carter (1989) reported finding no differences between hypothyroid and control subjects in the recognition of low concentrations of NaCl, sucrose, citric acid, and caffeine, or in the identification of orange juice and pineapple juice.

In contrast, McConnell, Menendez, Smith, and Henkin (1975) reported significant elevations of both detection and recognition thresholds for NaCl, sucrose, urea, and HCl. Similar threshold elevations for the odorants pyridine and nitrobenzene were also noted. The return of the thresholds to normal levels after thyroid hormone replacement therapy and the absence of dysgeusia and dysosmia before hypothyroidism suggested to McConnell et al. a prominent role for thyroid hormones in the modulation of olfactory and gustatory sensitivity. Indeed, for 1 patient, abnormalities of smell and taste were reported to be completely corrected after 16 days of thyroid hormone replacement therapy, and for most patients in that study, detection and recognition thresholds were lowered after 3 months of replacement therapy.

In a recent study of 750 subjects who had presented with complaints of chemosensory dysfunction (Deems et al., 1991), patients who were taking thyroid medication (e.g., levothyroxine) complained of taste loss more frequently than patients who were not. However, these patients scored higher on a taste identification test and rated low concentrations of caffeine as more intense than did comparison patients. Furthermore, their taste thresholds for citric acid, NaCl, and sucrose were within normal limits, which suggests that subjective reports of taste in such patients are not reflected in detection threshold measures (see also Lewitt et al., 1989).

To date, no animal studies have evaluated the influences of hypothyroidism on taste sensitivity per se, although preferences and ingestive behavior have been examined. For example, rats made hypothyroid by propylthiouracil (PTU) added to drinking water demonstrated increased consumption of and lowered preference thresholds for NaCl (Fregly, 1962; Fregly, Cade, Waters, Straw, & Taylor, 1965; Fregly & Waters, 1965, 1966). These effects, attributed to hypothyroidism, were reversed by administrations of graded dosages of desoxycorticosterone (Fregly & Waters, 1966). Holtzman rats made hypothyroid by administration of radioactive iodide were reported to increase consumption of normally aversive concentrations of sour and bitter tastants, with a return of ingestive behavior to near-baseline levels after 2–3 weeks of thyroid hormone
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replacement (McConnell et al., 1975). Such changes in ingestive behavior are prima facie evidence that hypothyroidism influences the discrimination performance of rats but do not demonstrate that taste sensitivity per se is influenced by this condition.

In our study we examined the effects of PTU-induced hypothyroidism on taste preference and sensitivity measures with sucrose, NaCl, HCl, and quinine sulfate as representatives of the four basic taste qualities. In addition, we examined the influences of such hypothyroidism on the ability of rats to perform a taste-mixture discrimination task. As revealed below, our findings show that although taste preferences are altered by PTU-induced hypothyroidism, neither taste sensitivity nor taste discrimination performance is similarly altered. This is true in spite of the fact that PTU produced marked decreases in free-serum triiodothyronine (T3) and thyroxin (T4).

Method

Subjects

Ten male and 10 female Long-Evans rats, approximately 90 days of age at the beginning of the study, served as subjects. The rats were housed in pairs in 30 x 30 x 60 cm polystyrene cages in a temperature- and humidity-controlled vivarium maintained on a 12:12-hr light-dark cycle. All testing and training occurred within the light phase of the light-dark cycle. Chow was available ad libitum. During pre- and posttreatment all animals were maintained on a 23½-hr water-deprivation schedule. During the treatment period the experimental animals were maintained on ad libitum access to 0.1% PTU dissolved in water; water consumption was measured, and control animals received an equivalent amount of water.

Apparatus

Rats were trained to perform all taste discriminations in a 30 x 30 x 45 cm Plexiglas chamber fitted with a 10-barrel stimulus delivery tube and a single-barrel reinforcement tube mounted on one wall of the chamber (see Brosvic & Slotnick, 1986). The responses of subjects were recorded, and the stimulus deliveries controlled by computer (IBM PC XT; Med Associates interface; MED-PC).

Stimuli and PTU

Reagent-grade aqueous solutions of NaCl and sucrose at molar concentrations from $5 \times 10^{-4}$ to $2 \times 10^{-1}$ were used. Reagent-grade aqueous solutions of quinine sulfate and HCl at molar concentrations from $5 \times 10^{-7}$ to $5 \times 10^{-4}$ were also used. The molar concentrations of the tasteants permitted comparison with results of the detection performance of normal and control animals tested previously (see Brosvic & Hecht, 1989; Brosvic et al., 1991; Brosvic & Hoey, 1990a, 1990b). Triple-deionized water served as the solvent for all solutions, the S- stimulus, and reinforcement.

PTU was added to drinking water at the concentration of 0.1% during the treatment phase. PTU administered at this concentration produces marked hypothyroidism in mice when added to drinking water (Beard & Mackay-Sim, 1986, 1987; Mackay-Sim & Beard, 1987) and rats when added to laboratory chow (Fregly, 1962; Fregly et al., 1965; Fregly & Waters, 1965, 1966).

General Procedure

Animals were weighed daily, placed on a 23½-hr water deprivation schedule for 14 days, and trained and tested on the taste detection, taste-mixture discrimination, and preference tests described later (baseline phase). Two groups of 10 rats (5 male and 5 female) were matched on the signal detection measures of sensitivity and responsibility to each tastant, preference behavior, and serum T3 and T4, all $t$s(18) < 1, all $p$s > .75. One group was randomly designated as the experimental group and received PTU dissolved in drinking water available ad libitum for 9 weeks (treatment phase). PTU was subsequently removed from the experimental rats' water bottles and testing resumed for 9 weeks (posttreatment phase). PTU-treated rats' mean daily water consumption was measured and the same amount of water was made available to the yoked control animals. Blood samples for analysis of free serum T3 and T4 were collected at baseline and at the conclusion of the treatment and posttreatment phases. Signal detection measures of sensitivity and responsibility to NaCl, sucrose, quinine sulfate, and HCl were determined weekly during treatment and posttreatment in 260-trial test sessions. Taste-mixture discrimination performance and preference for NaCl, sucrose, quinine sulfate, and HCl were determined weekly.

Biochemical Verification of Hypothyroidism

After anesthesia with ketamine (0.75 ml ip), approximately 2 ml of blood was taken by orbital puncture with 1.5-mm glass pipettes dipped in heparin. Blood samples were centrifuged at 4,000 revolutions per minute for 7 min, and the serum was stored in separate 1.7-ml conical plastic containers at 8°C until T3 and T4 could be analyzed by radioimmunoassay procedures (see Cullen, Doherty, & Ingbard, 1973; Dozin & De Nayer, 1983; Griessne & Lemarchand-Beraud, 1973; Jacoby, Mueller, & Wurtman, 1975).

Operant Training and Test Procedures

Briefly, animals were trained on a modified discrete trials go-no-go procedure in which a variable (10-30) number of licks at the stimulus delivery tube defined the attending response and produced a 0.01-ml sample of the S+ or S- tastant. On delivery of S+, licking at the reinforcement tube was required to initiate the next trial. If the animal switched to the reinforcement tube before making 10 licks at the stimulus delivery tube, the trial was counted as a correct detection (hit), and the rat received a 0.02-ml water reward. If it perseverated on the stimulus delivery tube (making 10 licks before switching), the trial was counted as a miss, and the subsequent response on the reinforcement tube produced a 0.005-ml water reward. On S− trials the rat was trained to continue responding on the stimulus delivery tube until the next stimulus was delivered. Trials in which it did so were scored as correct rejections. If, on the other hand, it switched to the reinforcement tube before making 10 responses on the stimulus delivery tube, the switching behavior was punished by a 3-s time-out period signaled by operation of a house light, and these trials were counted as false alarms.

Initially, rats were trained in sessions in which only S+ was presented. After the rat attained 90% correct responding in 100 consecutive trials, nonreinforced S− trials were introduced. After a rat achieved 90% correct responding in 100 trials of 50 S+ and 50 S−, descending and ascending series of trials were introduced. A daily test session consisted of 260 trials, the first 20 of which consisted of 10 S+ and 10 S− (triple-deionized water) warm-up trials not used in the signal detection calculations. After these warm-up trials, blocks of 20 trials (10 S+ and 10 S−) were presented according to a 120-trial descending concentration series. In each 20-trial block, the positive
and negative trials were presented in a random order with the restriction that not more than 3 trials of one type, occurred in succession and that there was an equal number of positive and negative trials in successive blocks. A 120-trial ascending concentration series was then initiated for a total of 40 trials for each S+ test stimulus per test session.

**Taste Performance Measures**

The proportion of hits and false alarms were used to calculate nonparametric indexes of sensitivity (SI) and responsivity (RI) described by Frey and Colliver (1973). SI was calculated from the proportion of hits, P(HIT), and false alarms, P(FA), recorded during each test session with the formula:

$$SI = \frac{P(HIT) - P(FA)}{2[P(HIT) + P(FA)] - [P(HIT) + P(FA)]^2}$$

The SI can theoretically range from 0 (no detection) to 1 (error-free detection).

RI represents the general tendency to respond independent of the type of stimulus presented. RI was calculated from the proportion of hits, P(HIT), and false alarms, P(FA), recorded during each test session according to the formula:

$$RI = \frac{P(HIT) + P(FA) - 2}{[P(HIT) - P(FA)]^2}$$

The RI can range from -1 (very conservative response criterion) to +1 (very liberal response criterion).

**Taste-Mixture Discrimination Task**

All rats were tested on a discrimination task in which the standard (S+) stimulus consisted of a mixture of $2.9 \times 10^{-2}$-mol sucrose and $3.4 \times 10^{-2}$-mol NaCl. The comparison S- stimuli were mixtures of sucrose and NaCl with $2.9 \times 10^{-2}$-mol sucrose and NaCl at the molar concentrations of $4 \times 10^{-3}$, $8 \times 10^{-3}$, $1.2 \times 10^{-2}$, $1.6 \times 10^{-2}$, $2.2 \times 10^{-2}$, and $2.5 \times 10^{-2}$. Initially, rats were trained to discriminate between the standard stimulus and the $2.9 \times 10^{-2}$-mol sucrose with $4 \times 10^{-3}$-mol NaCl comparison stimulus. When the criterion of 75% correct responding (15 or fewer errors in 60 consecutive trials) was achieved, the next highest S- stimulus was introduced, and testing continued until the animal failed to achieve criterion in 400 consecutive trials.

**Taste Preference Tests**

Preference for NaCl (3 × $10^{-1}$ mol), sucrose (1.5 × $10^{-1}$ mol), quinine sulfate (1.28 × $10^{-4}$ mol), and HCl (2.5 × $10^{-3}$ mol) was examined in 2-hr tests for each animal during baseline, treatment, and posttreatment. Two 150-ml glass bottles, one with taster dissolved in triple-deionized water and the other with triple-deionized water, were presented, and bottle positions were reversed halfway through each test session. Results of these tests are expressed in terms of the percentage of preference according to the formula:  

$\text{Test Solution Intake} \times 100 + \text{Test Solution} + \text{Water Intake}$. (Intake was measured in milliliters.)

**Statistical Analysis**

To determine whether sensitivity or responsivity to each tastant differed between the two study groups, SI and RI scores were computed, and the data collapsed into 3-week summary scores for baseline, treatment, and posttreatment. Analyses were then performed separately for each group and tastant with Friedman’s test with multiple comparisons (Conover, 1980). Similar analyses were used to examine potential differences in taste-mixture discrimination performance, taste preference behavior, and free serum T3 and T4.

**Control Procedure**

At the conclusion of each day’s testing, all stimulus delivery solenoid reservoirs and solenoid valves were flushed with 500 ml of triple-deionized water (at 22 °C) to remove potential residuals. Tygon tubing and stimulus reservoirs were replaced every 4 weeks, and the solenoid valves used to deliver tastant samples (S+ and S-) were routinely rotated to minimize potential extraneous cues for discriminative responding. In multiple 3,000-trial sessions, two randomly selected channels of the stimulus delivery tube were filled with triple-deionized water, sucrose, KCl, NaCl, or sodium-saccharin. In these tests, equimolar concentrations of the same tastant (or water) served as S+ and S- to examine potential solenoid valve cues for discriminative responding.

**Results**

No significant differences on any dependent measure were observed as a function of sex of subject (Mann-Whitney tests, all ps > .5), so the data were collapsed across sexes for subsequent analyses.

**Sensory Performance Measures**

For each representative of the four taste qualities, there were no significant between-groups differences in SI values at any stimulus concentration (Mann-Whitney tests, all ps > .5). Similarly, there were no between-groups differences when SI values were combined across the stimulus concentrations (Mann-Whitney tests, all ps > .5). SI values combined across concentrations are presented in Figure 1, respectively, for NaCl and sucrose.

**Nonsensory Performance Measures**

For each of the four taste stimuli, there were no significant between-groups differences observed for RI values at any stimulus concentration (Mann-Whitney tests, all ps > .5). Similarly, there were no between-groups differences when RI values were combined across the stimulus concentrations (Mann-Whitney tests, all ps > .5). RI values combined across concentrations for NaCl and sucrose are shown in Figure 2, respectively.

**Taste-Mixture Discrimination Task**

No significant between-groups differences for taste-mixture thresholds were observed (Mann-Whitney and Wilcoxon tests, all ps > .5). All rats could discriminate (75% accuracy or higher) between the S+ ($2.9 \times 10^{-2}$-mol sucrose and $3.4 \times 10^{-2}$-mol NaCl) and the highest S- ($2.9 \times 10^{-2}$-mol sucrose and $2.4 \times 10^{-2}$-mol NaCl) stimuli, but only 7 rats could discriminate between the S+ and the next highest S- stimulus ($2.9 \times 10^{-2}$-mol sucrose and $2.5 \times 10^{-2}$-mol NaCl). In this task, the mean taste mixture
selected pairs of stimulus delivery channels. In these tests all rats discriminated at approximately chance levels ($Mdn = 45.6\%, \text{range}, 37.3\%-56.3\%)$.

**Estimated PTU Consumption**

PTU-treated rats' daily water consumption during treatment averaged 35.4 ml ($SE_m = 3.7$). Because PTU was dissolved in drinking water at the 0.1% concentration, this consumption estimate represents daily PTU consumption per experimental animal.

**Body Weight and Food Intake**

Median body weight (see Figure 4) and food consumption (see Figure 5) did not differ between the groups at baseline, was significantly lower for PTU-treated rats during treatment, and, increased significantly for these same animals during posttreatment, Friedman tests, all $X^2(6) > 38.96$, all $ps < .001$. There were no between-groups differences in food consumption after the 3rd week of posttreatment, and PTU-treated rats weighed significantly less than control subjects at the end of the study.

**Taste Preference Tests**

Pretreatment preferences for each tastant did not differ between the control and PTU-treated groups (Mann-Whitney tests, all $ps > .5$). PTU-treated rats' consumption of NaCl, quinine sulfate, and HCl (see Figure 3) increased significantly during PTU treatment and decreased during posttreatment, Friedman tests, all $X^2(6) > 37.77$, all $ps < .05$. PTU-treated rats' preferences for quinine sulfate and HCl at the conclusion of the study were higher than at baseline. No between- or within-groups differences in preference for sucrose (see Figure 3) and no changes in preference behavior for control subjects were observed at any point during the study.

**Control Procedure**

No solenoid valve cues for discriminative responding were observed when water or tastant was loaded into randomly

**Figure 1.** Median sensitivity index values and interquartile ranges for propylthiouracil-treated and control animals for sodium chloride (NaCl) and for sucrose. (Sensitivity index values were combined over all concentrations. Each test period was 3 weeks in length. (PTU = propylthiouracil.)

**Figure 2.** Median responsivity index values and interquartile ranges for propylthiouracil-treated and control animals for sodium chloride (NaCl) and for sucrose. (Responsivity index values were combined over all concentrations. Each test period was 3 weeks in length. PTU = propylthiouracil.)
Free-Serum Thyroid Hormone Levels

Baseline free-serum T3 and T4 levels did not differ between the PTU-treated and control animals (Mann-Whitney tests, ps > .5). Significant decreases in PTU-treated rats' serum T3 and T4 (see Figure 6) were observed at the end of PTU treatment, Friedman tests, all χ²s(6) > 34.19, all ps < .001, at which point the 95% confidence intervals for the two groups' T3 and T4 distributions were nonoverlapping. Serum T3 and T4 increased significantly in PTU-treated animals by the end of the study (all ps < .05) at which point the distributions of serum T3 and T4 for the two groups were overlapping.

Discussion

In this study, signal detection methodology was used for the detection tests because of its ability to provide separate measures of sensitivity and response bias, as well as its sensitivity to subtle changes in detection performance. No changes in sensitivity and responsivity were observed for the detection of NaCl, sucrose, quinine sulfate, and HCl. Each animal appeared healthy, to maintain stimulus control, and to be well motivated to perform behavioral tasks.

Our results support the efficacy of PTU to induce hypothyroidism in the adult rat, as measured by changes in free serum T3 and T4. The magnitude of the observed thyroid hormone deficiency is similar to prior reports for adult rats (Cullen et al., 1973; Dozin & De Nayer, 1983; Griessne & Lemarchand-...
confirmed in additional testing in which separate groups of rats received thyroidectomy with supplemental thyroxin, thyroidectomy without supplemental thyroxin, or sham operations. No between- or within-groups differences in SIs or RIs or preference for sucrose were observed, and there were no differences in preference behavior between sham-operated rats and thyroidectomized rats that received supplemental thyroxin. Significant increases in preferences for NaCl, HCl, and quinine sulfate were observed for thyroidectomized rats that did not receive supplemental thyroxin.

Also note that PTU, at the concentration used in this and other studies, likely produces a bitter taste. Therefore, we recently completed a study to establish whether exposing rats to bitter solutions (other than PTU) over time would produce similar alterations in their preferences. Accordingly, separate groups of rats were maintained on ad libitum access to PTU (0.1%), caffeine (5 × 10⁻³ mol), urea (2.5 × 10⁻¹ mol), or water and tested on preference and detection tasks. No between- or within-groups differences in SIs or RIs were observed. Taste preferences of rats maintained on caffeine or urea did not differ from those of rats maintained on water, which indicates that exposure to bitter stimuli per se does not produce preference changes analogous to those observed with PTU.

Beraud, 1973; Ito, Valcana, & Timiras, 1977; Jacoby et al., 1975). Similarly, PTU-treated rats’ decreased food consumption and failure to gain weight, in relation to that of control subjects, is similar to prior reports for adult mice (Beard & Mackay-Sim, 1986, 1987; Mackay-Sim & Beard, 1987).

Significant alterations in the ingestion of NaCl (normally preferred) and of quinine sulfate and HCl (normally aversive) were observed for each PTU-treated animal, with preferences for HCl and quinine sulfate influenced more than that for NaCl. This pattern is similar to prior reports for rats made hypothyroid by PTU (Fregly, 1962; Fregly et al., 1965; Fregly & Waters, 1965, 1966) and for humans with either untreated primary hypothyroidism (Mates, Heller, & Rivlin, 1985; Pittman & Beschi, 1967) or pseudohypothyroidism (Henkin, 1968). These changes in ingestive behavior also parallel those observed for zinc-deficient (Jakinovich & Osborn, 1981; McConnell & Henkin, 1974) and selectively desalivated rats (Brosvic & Hoey, 1990b), that is, altered preferences for all tastants except for those that are generally considered sweet. However, preferences for sucrose in this and the prior studies were mitigated by a ceiling effect.

The alterations in preference for NaCl reversed shortly after discontinuation of PTU and within 6 weeks returned to baseline. However, the alterations in preference for HCl and quinine sulfate, although attenuated after discontinuation of PTU, remained significantly higher than baseline. In follow-up tests conducted in our laboratory, we found that considerably longer recovery periods (range, 2–6 months) are required for PTU-treated rats’ preferences for sour and bitter tastants to return to baseline, and this range is consistent with the 3 months of thyroxin replacement therapy reported to return human hypothyroid patients’ thresholds to more normal levels (McConnell et al., 1975). Alterations in preference behavior appear to be closely related to thyroid-hormone deficiency, as

**Figure 5.** Median food consumption and interquartile ranges for propylthiouracil-treated and control animals. (The baseline period was 3 weeks; all other test periods were 1 week each. PTU = propylthiouracil.)

**Figure 6.** Median free-serum triiodothyronine (T3) and thyroxin (T4) and interquartile ranges for propylthiouracil-treated and control animals. (PTU = propylthiouracil.)
The addition of PTU to the rat’s drinking water reduced free-serum T₃ and T₄ and altered preferences for NaCl, HCl, and quinine sulfate. However, preference tests are not sufficient measures of sensory capacity, and when measured with a signal detection procedure, changes in neither sensitivity nor responsivity to representatives of the four taste qualities were observed. The reversibility of altered NaCl intake during the posttreatment phases, the gradual return of preferences for bitter and sour tastants to baseline levels in follow-up studies, and the changes in preference behavior in thyroidectomized animals that did not receive supplemental thyroxin indicate that thyroid hormones play a role in altering ingestive behavior, presumably by somehow influencing chemosensory input; however, no specific mechanisms have been identified. The changes observed in this study may be similar to alterations in synaptic delay and specific changes in peripheral, sensory, and motor function reported in humans (Rivlin, 1971, 1975) or may parallel decreased auditory and visual evoked potentials observed in animals and humans with untreated hypothyroidism (Bradley, Eayrs, Glass, & Heath, 1961; Bradley, Eayrs, & Schmalbach, 1960; Harris, Della Rovere, & Prior, 1965).

References


American Journal of Medicine, 59, 354–364.