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Effect of Tricyclic Antidepressants on Taste Responses in Humans and Gerbils

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SCHIFFMAN, S. S., J. ZERVAKIS, M. S. SUGGS, K. C. BUDD AND L. IUGA. *Effect of tricyclic antidepressants on taste responses in humans and gerbils.* PHARMACOL BIOCHEM BEHAV **65**(4) 599–609, 2000.—One of the side effects of antidepressant pharmacotherapy reported clinically is impairment of the sense of taste. In this study, the taste effects of four tricyclic antidepressant compounds (clomipramine HCl, desipramine HCl, doxepin HCl, and imipramine HCl) were evaluated experimentally by topical application of the drugs to the tongue. Taste detection threshold concentrations for all four medications ranged from 0.1 mM to 0.2 mM in young persons but were elevated by as much as 7.71 times that in elderly individuals who were taking no concurrent medications. Each compound had a predominantly bitter taste with other qualities including metallic, sour, and sharp-pungent. In addition, each tricyclic antidepressant at concentrations from 1 mM to 5 mM blocked responses to a wide range of taste stimuli in both humans and gerbils. The differential suppression of other tastes by tricyclic antidepressants at the level of the taste receptors may contribute to the clinical reports of dysgeusia and hypogeusia. © 2000 Elsevier Science Inc.

Tricyclic antidepressants Taste Humans Gerbils

CLINICAL reports suggest that antidepressant drugs can induce altered taste perception including dysgeusia (distortion of taste), hypogeusia (diminished sensitivity of taste), and ageusia (absence of taste) (1,30,37,40–42,54). Both first-generation tricyclic antidepressants and later-developed selective serotonin reuptake inhibitors have been reported clinically to cause chemosensory complaints. While these clinical observations are helpful in determining potential chemosensory side effects of drugs, experimental studies are necessary to quantify potential taste changes. One experimental study (52) assessed the taste effects induced by amitriptyline HCl. Amitriptyline is the most frequently prescribed tricyclic antidepressant drug (6), and is used by at least half a million people aged 65 years or more (55). Amitriptyline HCl was found to have a bitter, unpleasant taste. When amitriptyline HCl was applied topically to the tongue in order to mimic the condition in which the drug is secreted into the saliva, it blocked responses to other taste stimuli in both humans and gerbils.

Tricyclic antidepressant drugs are among the most frequently prescribed medications in the United States (6). Depression occurs throughout the lifespan (4), and more than 18 million people in the United States will suffer from a depressive illness this year (32). The number and proportion of these individuals prescribed antidepressants in outpatient private practices continues to increase. According to statistics based on the National Ambulatory Medical Care Survey, Sclar et al. (53) concluded that the number of office-based visits in the United States resulting in a prescription for or continuation of antidepressant pharmacotherapy escalated from 16,534,268 in 1990 to 28,664,796 in 1995, a 73.4% increase. Olfson et al. (35) also used the survey to conclude that psychiatric patients were approximately 2.3 times more likely to receive an antidepressant from a psychiatrist in 1993–1994 than in 1985, and that the increase was greatest for patients with less severe psychiatric disorders.

The purpose of the present study was to determine the effect of four additional tricyclic antidepressant medications (clomipramine, desipramine, imipramine, and doxepin) on the sense of taste. These drugs were selected for two reasons. First, they are the most frequently prescribed tricyclic antidepressants after amitriptyline HCl (6). Second, all of them are reported clinically to have chemosensory side effects: clomipramine (taste loss), desipramine (peculiar taste), imipramine (peculiar taste), and doxepin (taste disturbance) (37); these

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TABLE 1
CONCENTRATIONS OF TASTANTS USED IN HUMAN SUPRATHRESHOLD STUDIES

Tastant	Concentration			
NaCl	0.1 M	0.2 M	0.4 M	0.8 M
KCl	0.15 M	0.3 M	0.6 M	0.9 M
$CaCl_2$	0.0625 M	0.125 M	0.25 M	0.5 M
Sucrose	0.8 M	1.2 M	1.6 M	2 M
Quinine HCl	0.002 M	0.004 M	0.008 M	0.016 M
Citric Acid	0.01 M	0.02 M	0.04 M	0.06 M
Capsaicin	4 ppm	8 ppm	16 ppm	32 ppm
WS-3	2.5%	5%	10%	30%
$FeSO_4$	80 ppm	120 ppm	160 ppm	200 ppm

taste complaints are terms used in self-reports by patients. Both young and elderly subjects were tested because the sense of taste has been reported to decrease with age (41).

In the studies performed here, the medications were applied topically to the tongue to mimic the situation in which the drug is secreted into the saliva. Most drugs or their breakdown products are secreted into saliva (31) including tricyclic antidepressants (20,29,38). Furthermore, a relationship between salivary and plasma concentrations of several tricyclic antidepressants, including amitriptyline HCl (20,29) and desipramine (38), has been reported. The experiment consisted of three parts: 1) human taste threshold determinations for each tricyclic antidepressant using two application techniques, 2) human suprathreshold studies to examine the effect of lingual exposure to each tricyclic antidepressant on other taste stimuli, and 3) animal dose–response and lingual exposure studies.

METHOD

Human Studies

Subjects. Forty-seven young subjects participated in the study. The young subjects were healthy, nonsmoking volunteers who were taking no regular medications other than female hormones, and ranged in age from 19–33 years (mean age = 24.3 years ± 4.3). Twelve elderly subjects also participated. They were healthy nonsmoking volunteers taking no regular medications, and ranged from 69–82 years of age (mean age = 74 years ± 1.07). Twelve young and 10–12 elderly subjects participated in each threshold determination, and 12 young subjects participated in each suprathreshold experiment. Subjects were asked to refrain from eating, and drinking anything other than water, for 1 h prior to testing.

Materials

Four antidepressant medications were tested: clomipramine HCl, desipramine HCl, doxepin HCl, and imipramine HCl. The drugs were obtained from Sigma Chemical Company (St. Louis, MO).

Threshold studies. For threshold determinations, 10 binary dilutions of the two drugs were prepared in deionized water. Clomipramine HCl was dissolved in deionized water at dilutions ranging from 0.0156–8.0 mM, desipramine HCl from 0.0039–2 mM, doxepin HCl from 0.0078–4.0 mM, and imipramine HCl from 0.0039–2 mM. Thresholds were determined using two application methods. For the liquid drop method, 2 ml of drug solution were dispensed using disposable pipettes. For the filter paper method, grade 1 (0.16 mm thickness) Whatman® filter paper was cut in the shape of half tongues and, saturated with the drug solution.

Suprathreshold studies. The effect of lingual treatment with a drug solution on taste evaluations of nine tastants was tested (see Table 1 for the tastants and concentrations used). The seven water-soluble tastants were presented in deionized water. Capsaicin (burning component of chili peppers) and *N*-ethyl-*p*-menthan-3-carboxamide (WS-3) (a cooling stimulus) were dissolved in ethanol.

The drug and the tastants were applied to the tongue on filter paper. A 1.0-mM solution of each drug was tested. This concentration was chosen because it was at or above the mean and individual detection thresholds for each drug. For the drug application, grade 1 Whatman® filter paper was cut in the shape of half tongues and saturated with the drug solution. For the tastant application, circular discs (1.27 cm) of the same Whatman® filter paper were saturated with the respective tastant solutions. Water-soluble tastants were applied wet (i.e., discs were immersed in aqueous solution and shaken off to remove excess liquid). For the tastants WS-3 and capsaicin, discs were impregnated with 20 μl of solution and dried for at least 1 h to allow the ethanol to evaporate. Other materials for the threshold and suprathreshold studies were paper score sheets with descriptor scales.

Procedure

Threshold studies. Taste detection and recognition thresholds were determined using the triadic forced-choice ascending method (44,52). Two different application techniques were used to present the drug solution to the anterior portion of the tongue. In the first application method, the drug solution and water controls were presented in 2-ml liquid drops. In the second application method, the drug solution and controls were presented in Whatman® filter paper cut in the shape of half tongues and saturated with the solution.

In the forced-choice ascending method using liquid drops, each subject was presented with a set of up to 10 triads. In each triad one 2-ml drop contained a dilution of the drug; the other two 2-ml drops contained deionized water. The experimenter applied 2-ml of the drug solution as well as two 2-ml deionized water controls sequentially on the anterior tongue. The position of the sample containing the drug in each triad was randomized over trials and across subjects. The first triad presented to the subject at a given taste session contained the weakest concentration of the drug, with each successive triad presenting the next higher concentration.

The subject rinsed with deionized water after each triad to reduce any "carryover" effects from the previous sample. After completing a triad, the subject was asked to choose which of the three samples was the strongest, and if possible, to describe the taste quality of the sample. A taste detection threshold was considered to be established when a subject correctly discriminated the stimulus from the water controls on three consecutive trials, i.e., at three consecutive increasing concentrations. The detection threshold for an individual subject was defined as the most dilute of the three correct identifications.

At the third correct identification the subject was asked to describe the taste qualities of the sample chosen as strongest by rating it on either 23 adjective (young control group), or 14 adjective scales (elderly group). The 23 adjective scales were: overall intensity, sweet, sour, salty, bitter, metallic, cooling, hot, spicy, burning, anesthetic, astringent, medicinal, minty/menthol, warming, sharp, alcohol, painful, irritating, stinging, dry, peppery, and paper. The 14 adjective scales used for the elderly were a subset of the 23 scales: overall intensity, sweet, sour, salty, bitter, metallic, cooling, hot, spicy, burning, anesthetic, astringent, medicinal, and minty/menthol. The number of descriptors used for testing the elderly was reduced, because tests with the young subjects revealed that some descriptors were highly significantly correlated (e.g., peppery and spicy). In these cases, one of the two highly correlated descriptors was removed to eliminate redundancy. Participants rated each adjective on a nine-point intensity scale ranging from 0 to 8, where 0 = none at all and 8 = maximal intensity, on provided score sheets.

The procedure for the filter paper method was similar to the liquid drop method with the exception that the experimenter sequentially applied filter paper half tongues saturated with the drug solution or the deionized water controls to the anterior tongue using sterile tweezers. The half tongues were placed on the tongue for 3 s each, approximately the same amount of time used for each liquid application.

Suprathreshold studies. For the suprathreshold studies, subjects rated four concentrations of one of nine tastants, once after the drug treatment, and once after the water (control) treatment. After-drug treatment ratings were compared to after-water treatment ratings.

Each subject was asked to keep his/her tongue extended until further notice. Two pieces of filter paper cut in the shape of half tongues were saturated with deionized water (control) and placed on each half of the tongue using sterilized tweezers. After 2 min the half tongues were removed and two new half tongues soaked in deionized water were placed on the tongue. After the second 2-min application (4 min total), the subject rated the taste of the filter paper on his/her tongue. The lowest concentration of a given tastant was applied using a paper disc placed on the anterior portion of the left half of the tongue. The subject rated the stimulus using the 23 adjective scales, with any additional comments recorded by the experimenter. The next higher concentration was then placed on the right anterior tongue, and rated. The second and first highest concentrations were applied in the same manner as the first two, alternating sides of the tongue, and taste evaluations were again completed by the subject.

During a 5-min intertrial interval, the subject rinsed with deionized water. The procedure described above was then repeated, substituting half tongues soaked in a 1.0-mM drug solution instead of deionized water. A visual shield was placed between the subject and the materials used in each session, and subjects were blinded to the materials/procedure used.

Animal Studies

Animals. Female Mongolian gerbils, *Meriones unguiculatus*, were obtained from Charles River Laboratories (Wilmington, MA). The gerbils were 10–12 weeks old and weighed from 45–65 g (avg. 55 g). Forty-eight gerbils were used in the studies; prior to testing, they were housed in the Duke University Vivarium.

Materials. The drugs clomipramine HCl, desipramine HCl, doxepin HCl, and imipramine HCl were tested for their effects on taste responses in the chorda tympani nerve in the gerbil. Dose–response curves were obtained at the following concentrations: 0.625 mM, 1.25 mM, 2.5 mM, 5 mM, and 10 mM. The effect of lingual treatment with a medication at 5 mM on responses to nineteen aqueous taste solutions with salty, sweet, sour, and bitter tastes was examined. The compounds with salty and/or sour qualities were: NaCl (30 mM and 100 mM), KCl (500 mM), monosodium glutamate-MSG (50 mM and 100 mM), HCl (5 mM and 10 mM), and citric acid (80 mM). The sweet compounds tested were: sucrose (30 mM and 100 mM), glucose (300 mM), fructose (300 mM), maltitol (300 mM), sodium saccharin (10 mM), and dulcin (3.5 mM). The compounds with a bitter component were: quinine HCl (30 mM), $MgCl_2$ (100 mM), $CaCl_2$ (300 mM), and urea (2 M). All concentrations of the drugs were dissolved in deionized water. All solutions were tested at room temperature.

Procedure. Gerbils were anesthetized with an intraperitoneal injection of ketamine HCl (Ketalar 50 mg/ml) at a dose of 330 mg/kg body weight. This dosage was administered in two doses with 15 min separating the two doses. Supplementary injections of sodium pentobarbital (Nembutal at 5 mg/ml) in 0.1-ml doses were delivered to maintain a surgical level of anesthesia. Core temperature was monitored and maintained at 37°C. The method used for exposing and recording from the intact chorda tympani nerve has been used extensively (15–19,43,45–51).

Integrated chorda tympani responses were recorded from four animals for each drug to obtain dose–response curves. Recordings were also obtained from four additional animals for each drug to evaluate the effect of a 4-min lingual exposure to the drug on other taste stimuli. At each of these four trials, 19 taste solutions were first applied to the gerbil tongue with 1-min interstimulus rinses of deionized water. The stimuli were delivered in 2.0-ml samples by a gravity flow system at a rate of 0.20 ml per second (43). Next, the tongue was treated by flowing the drug solution over the apical lingual surface for 4 min at 0.20 ml per second. This treatment was then followed by a reapplication of the 19 taste solutions with 1-min interstimulus rinses of the drug. At the end of the experiment, the gerbil tongue was rinsed with deionized water to measure the recovery of the signal. Full recovery was obtained within 30 min in all experiments performed.

RESULTS

Human Studies

Thresholds. Detection thresholds are listed in Table 2. The mean detection threshold for clomipramine delivered in liquid drops was 0.122 mM for young subjects and 0.451 mM for elderly subjects. Elderly thresholds were significantly different than the young control thresholds, $t(22)$, $p < 0.05$. The mean detection threshold for desipramine delivered in liquid drops was 0.161 mM for young subjects and 0.172 mM for elderly subjects. Young and elderly thresholds were not significantly different (at $p = 0.05$). The mean detection threshold

TABLE 2

MEAN TASTE DETECTION THRESHOLDS (IN mM) WITH STANDARD ERRORS FOR YOUNG AND ELDERLY SUBJECTS AND RATIO OF THRESHOLDS (ELDERLY/YOUNG)

Drug	Liquid (Young)	Paper (Young)	Liquid (Elderly)	Liquid E/Y
Clomipramine HCl	0.122(0.028)	0.132(0.039)	0.451(0.123)	3.70
Desipramine HCl	0.161(0.049)	0.193(0.045)	0.172(0.049)	1.07
Doxepin HCl	0.143(0.021)	0.271(0.045)	1.103(0.496)	7.71
Imipramine HCl	0.125(0.024)	0.285(0.084)	0.369(0.191)	2.95

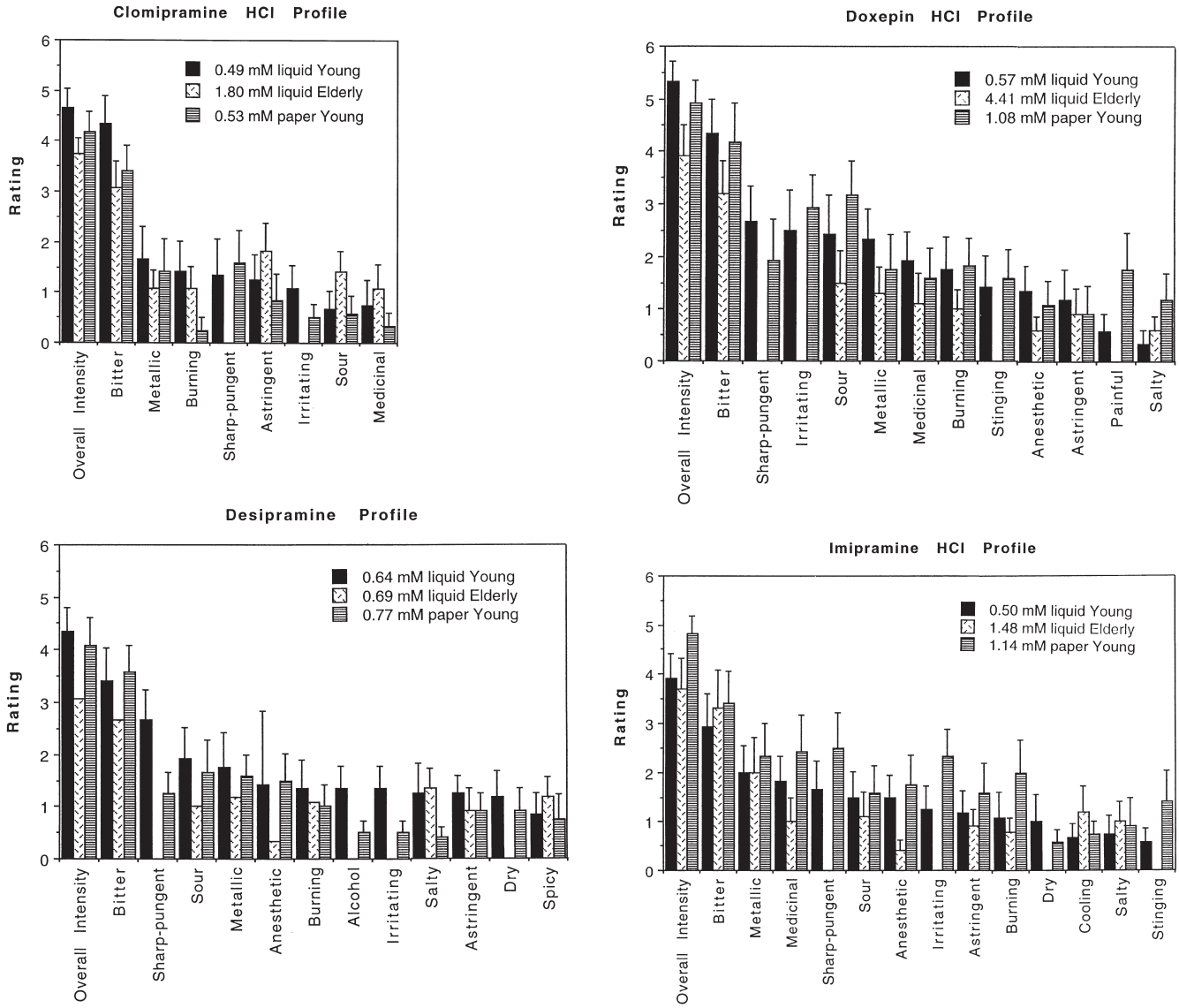

FIG. 1. The taste profile of clomipramine HCl at an average of four times each subject's threshold for the liquid drop method in the young group is shown by the black bars. The taste profile of clomipramine at an average of four times each subject's threshold for the liquid drop method in the elderly group is shown by the light stippled bars. The taste profile of clomipramine at an average of four times each subject's threshold for the paper tongue method in the young group is shown by the dark striped bars. Adjectives are ranked by magnitude, with descriptors rated less than "1" not shown. (b) Same profiles for desipramine HCl. (c) Same profiles for doxepin HCl. (d) Same profiles for imipramine HCl.

TABLE 3

SIGNIFICANT TREATMENT EFFECTS FOR AFTER-DRUG VS. AFTER-WATER (CONTROL) TREATMENT: PERCENT AND DIRECTION OF CHANGE

Tastant	Clomipramine	Desipramine	Doxepin	Imipramine
NaCl	↓ intensity** (−39.8%) ↓ salty** (−42.5%)	↓ intensity* (−16.9%) ↓ bitter* (−84.4%)	↓ intensity*** (−31.3%) ↓ salty** (−35.1%)	↓ intensity*** (−51.6%) ↓salty*** (−53.9%)
KCl	↓ intensity*** (−44.7%) ↓ salty*** (−54.1%)		↓ salty* (−39.0%)	↓ intensity** (−34.5%) ↓ salty** (−35.6%)
$CaCl_2$	↓ intensity** + (−37.8%) ↓ salty*** (−53.6%)		↓ intensity** (−22.4%) ↓salty** (−38.0%) ↑ anesthetic*** (>100%)	↓ intensity*** (−35.2%) ↓ salty*** (−49.6%) ↓bitter* (−37.5%)
Sucrose	↓ intensity*** (−27.4) + ↓ sweet*** (−27.8%) +		↓ intensity** (−20.3%) ↓ sweet*** (−21.8%)	↓ intensity* (−15.6%) ↓ sweet* (−16.7%)
QHCl	↓ intensity* (−22.1%) ↓ bitter* (−21.9%)		↓ intensity*** (−23.4%) ↓ sharp* (−49.1%) ↑ anesthetic** (>100%)	↓ intensity** (−18.9%)
Citric acid		↓ sharpness* (−54.4%)	↓ sweet* (−38.8%) ↑ anesthetic*** (>100%)	↓ intensity* (−20.1%) ↓ sour* (−38.5%)
Capsaicin	↓ intensity* (−19.5%) ↓ hot* (−52.8%) ↓ burning* (−31.2%)	↓ burning* (−29.4%) ↓ stinging* (−42.4%)	↓ intensity** (−18.1%) ↓ burning* (−31.5%) ↓ painful* (−46.1%)	↓ intensity* (−15.8%)
n-Ethyl-*p*-menthan-3-carboxamide (WS-3)		↓ warming* (−27.4%)	↓ intensity** (−17.0%)	↓ intensity* (−21.7%)
$FeSO_4$		↑ metallic* (+62.8%)	↑ intensity* (+84.2%) ↑anesthetic*** (>100%)	

Significant effects for medications, where * indicates significance at the 0.05 level, ** at the 0.01 level, *** at 0.001 or less level. "+" indicates additional treatment by concentration interaction.

for doxepin delivered in liquid drops was 0.143 mM for young subjects and 1.103 mM for elderly subjects. Elderly thresholds were significantly different from young control thresholds, $t(20)$, $p < 0.05$. The mean detection threshold for doxepin on filter paper for young subjects was 0.271 mM. Paper thresholds were also significantly higher than liquid control thresholds, $t(22)$, $p < 0.05$. The mean detection threshold for imipramine delivered in liquid drops was 0.125 mM for young subjects and 0.369 mM for elderly subjects. Elderly thresholds were not significantly different from young thresholds.

Taste profiles. The taste profiles for clomipramine, desipramine, doxepin, and imipramine are shown in Fig. 1 a–d. The taste profile for the drug in liquid at four times the average detection threshold is illustrated with the black bars for the young group and with the stippled bars for the elderly group. The profile for the drug in paper at four times the average detection threshold for the young group is given by the dark striped bars.

Figure 1a shows the taste profile for clomipramine. Young subjects found clomipramine to have a bitter taste with metallic, burning, sharp-pungent, astringent, and irritating components. Elderly subjects rated clomipramine as primarily bitter, with astringent, sour, metallic, burning, and medicinal components.

Figure 1b shows the taste profile for desipramine. Desipramine has a bitter taste, with sharp-pungent, sour, metallic, anesthetic, burning, alcohol, irritating, salty, astringent, and dry components for young subjects. Elderly subjects rated desipramine as primarily bitter with salty, metallic, spicy, burning, and sour components.

TABLE 4
SIGNIFICANT TREATMENT BY CONCENTRATION INTERACTIONS AND CONCENTRATION EFFECTS

Tastant	Effect	Clomipramine	Desipramine	Doxepin	Imipramine
NaCl	Treat. × conc.	—	—	—	—
	Concentration	intensity*** salty***	intensity*** salty***	intensity*** salty**	intensity*** salty***
KCl	Treat. × conc.	—	—	intensity*	—
	Concentration	intensity*** salty***	intensity*** salty*** bitter*** sharp*	intensity*** salty** sour*	intensity*** salty***
$CaCl_2$	Treat. × conc.	intensity*	—	—	—
	Concentration	intensity*** bitter*** salty***	intensity*** stinging*** burning** bitter** salty* spicy* sharp*	intensity*** bitter** salty*	intensity*** salty*** bitter**
Sucrose	Treat. × conc.	intensity* sweet*	—	—	—
	Concentration	intensity*** sweet***	intensity*** sweet***	intensity*** sweet***	intensity*** sweet***
QHCl	Treat. × conc.	—	—	—	—
	Concentration	intensity*** bitter*** sharp*	intensity*** bitter*** medicinal*** sour* sharp*	intensity*** bitter***	intensity***
Citric Acid	Treat. × conc.	—	—	—	—
	Concentration	intensity*** sour***	intensity*** sour***	intensity** sour***	intensity*** sour***
Capsaicin	Treat. × conc.	—	—	—	—
	Concentration	intensity*** burn** hot* spicy* irritating* peppery*	intensity*** burning** peppery* spicy* hot* stinging*	intensity*** irritating*** burning** hot** painful* spicy*	intensity*** spicy** stinging* burning*
WS-3	Treat. × conc.	—	—	—	—
	Concentration	intensity*	—	—	—
$FeSO_4$	Treat. × conc.	intensity*	—	—	—
	Concentration	—	intensity*** metallic*	—	—

Significant effects for medications, where * indicates significance at the 0.05 level, ** at the 0.01 level, *** at 0.001 or less level. Conc. = concentration; Treat. = treatment.

Figure 1c shows the taste profile for doxepin. Doxepin has a bitter taste, with sharp-pungent, irritating, sour, metallic, medicinal, burning, stinging, anesthetic, and astringent components for young subjects. Elderly subjects rated doxepin as bitter, with sour, metallic, medicinal, and burning components.

Figure 1d shows the taste profile for imipramine. Imipramine has a bitter taste to young subjects, with metallic, medicinal, sharp-pungent, sour, anesthetic, irritating, astringent, burning, and dry components. Elderly subjects rated imipramine as primarily bitter and metallic, with cooling, sour, salty, and medicinal components. Suprathreshold studies.

Suprathreshold studies. For each tastant an analysis of variance (ANOVA) was estimated, with tests of effect for treatment (drug vs. water), concentration of tastant (four concentrations), and treatment by concentration effects. Significant effects for descriptors with an average rating below 1 (very weak) are not listed.

Clomipramine HCl. Twelve young subjects participated in the experiment. Regarding treatment effects, application of a 1-mM clomipramine solution decreased the intensity and/or primary taste qualities of NaCl, KCl, $CaCl_2$, sucrose, QHCl, and capsaicin (see Table 3). Treatment by concentration interactions are listed in Table 4. There was a significant treatment by concentration interaction for $CaCl_2$ [intensity, $F(1, 33) = 4.31, p < 0.05$]. Examination of the means indicates that the most effect of treatment occurred at the two lower concentrations. There were treatment by concentration interactions for sucrose [intensity, $F(1, 33) = 3.67, p < 0.05$, and sweet

$F(1, 33) = 3.47, p < 0.05$] in which the most effect of treatment occurred at the two higher concentrations. The significant treatment by concentration interaction for $FeSO_4$, $F(3, 33) = 3.15, p < 0.05$, with no corresponding treatment effect, appears to be due to the drug treatment increasing intensity ratings for two of the four concentrations. Concentration effects are listed in Table 4. All significant concentration effects reported indicate that ratings increased with concentration.

Desipramine. Twelve subjects participated in the experiment. As seen in Table 3, an application of 1 mM desipramine reduced ratings for NaCl (intensity, bitter), citric acid (sharpness), capsaicin (burning, stinging), and WS-3 (warming), and creased ratings for $FESO_4$ (metallic).

Doxepin. Twelve subjects participated in the experiment. As seen in Table 3, significant treatment effects were found for all nine tastants tested. A 1 mM doxepin treatment reduced intensity of the tastants for all but $FESO_4$, for which ratings were increased, compared to the water treatment. There was a treatment by concentration interaction for KCl [intensity $F(3, 33) = 3.13, p < 0.05$, in which intensity was rated lower after drug treatment for two of the four concentrations tested. A doxepin treatment increased anesthetic ratings for $CaCl_2$, QHCl, citric acid, and $FeSO_4$. Although not listed because mean ratings were less than 1, doxepin also demonstrated an anesthetic effect for the tastants KCl, sucrose, capsaicin, and WS-3, so that anesthetic ratings significantly increased after doxepin treatment for eight of the nine tastants tested.

Imipramine. Twelve young subjects participated in the experiment. A treatment of imipramine decreased intensity and/or primary taste qualities for the tastants NaCl, KCl, $CaCl_2$ sucrose, QHCl, citric acid, capsaicin, and WS-3, relative to a water control.

Animal Studies

Dose–response curves. Dose–response curves for clomipramine HCl, desipramine HCl, doxepin HCl, and imipramine HCl expressed relative to the response to 100 mM NaCl are shown in Fig. 2. The threshold response for all of the drugs was slightly greater than 0.625 mM in the gerbil.

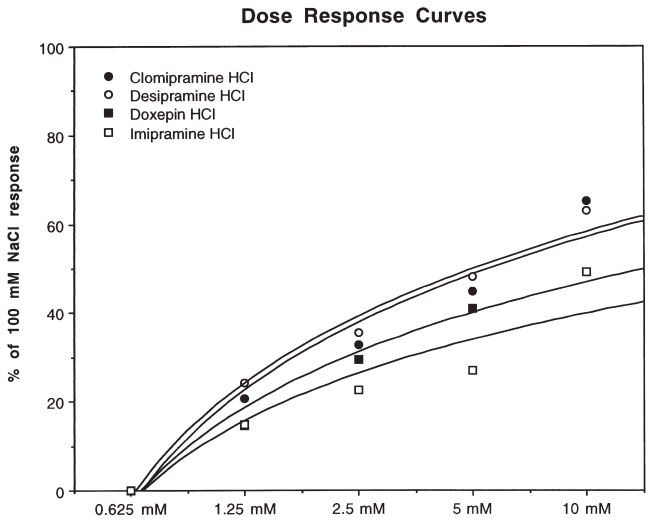

FIG. 2. Dose–response curves for clomipramine HCl, desipramine HCl, doxepin HCl, and imipramine HCl relative to sodium chloride in the gerbil chorda tympani nerve.

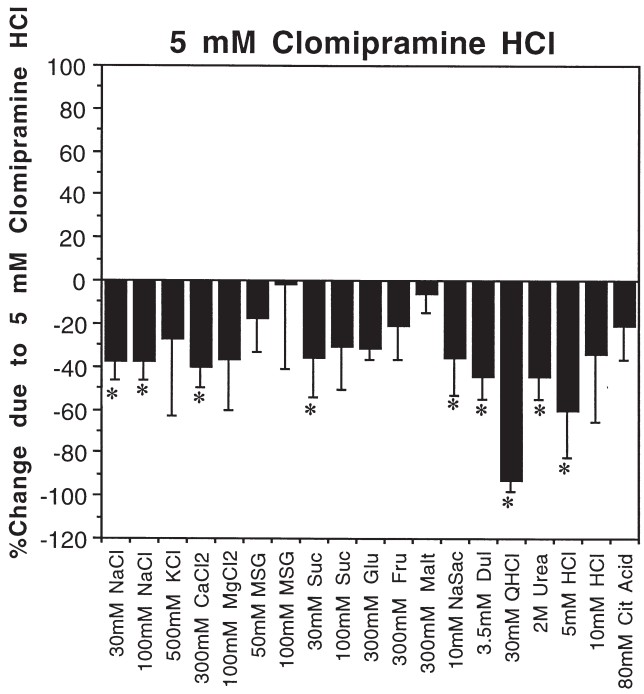

FIG. 3. Percent change in integrated chorda tympani responses after a 4-min application of 5 mM clomipramine HCl. An asterisk (*) indicates a significant suppression as defined as a decrease of 2 standard deviations below the mean response before exposure to the drug. Abbreviations: NaCl, sodium chloride; KCl, potassium chloride; $CaCl_2$, calcium chloride; $MgCl_2$, magnesium chloride; MSG, monosodium glutamate; Suc, sucrose; Glu, glucose; Fru, fructose; Malt, maltitol; NaSac, sodium saccharin; Dul, dulcin; QHCl, quinine hydrochloride; Urea, urea; HCl, hydrochloric acid; Cit Acid, citric acid.

Lingual treatment studies. Clomipramine HCl: a 1 mM clomipramine solution significantly blocked responses to: 300 mM fructose (22%), 3.5 mM dulcin (28%), and 30 mM quinine HCl (51%). Clomipramine HCl (5 mM) demonstrated a greater effect on taste responses by significantly blocking the responses to nine taste solutions. Responses were reduced in a range from 36% to 93% (see Fig. 3 for pattern of suppression at 5 mM clomipramine). Clomipramine HCl (5 mM) blocked the responses to: 30 mM and 100 mM NaCl (37% and 38%, respectively), 300 mM $CaCl_2$ (41%), 30 mM sucrose (36%), 10 mM sodium saccharin (36%), 3.5 mM dulcin (44%), 30 mM QHCl (93%), 2 M urea (44%), and 5 mM HCl (61%).

Desipramine HCl: at 1 mM desipramine HCl significantly blocked responses to: 100 mM NaCl (32%), 300 mM fructose (22%), 3.5 mM dulcin (23%), 300 mM maltitol (34%), 3.5 mM dulcin (40%), 30 mM quinine HCl (50%), 10 mM HCl (36%), and 80 mM citric acid (23%). Desipramine HCl (5 mM) has a greater effect on taste responses by numerically blocking the responses to all taste solutions. Responses that were significantly reduced included: 100 mM NaCl (23%), 100 mM $MgCl_2$ (48%), 50 mM MSG (23%), 30 mM and 100 mM sucrose (41% and 49%, respectively), 300 mM fructose (51%), 10 mM sodium saccharin (39%), 3.5 mM dulcin (60%), 30 mM QHCl (65%), 2 M urea (46%), 5 mM and 10 mM HCl (66%), and 80 mM citric acid (48%) (see Fig 4).

Doxepin HCl: the main findings were that 1 mM doxepin HCl blocked responses to: 30 mM QHCl (53%), 2 M urea (25%), 5 mM HCl (37%), and 80 mM citric acid (32%). Dox-

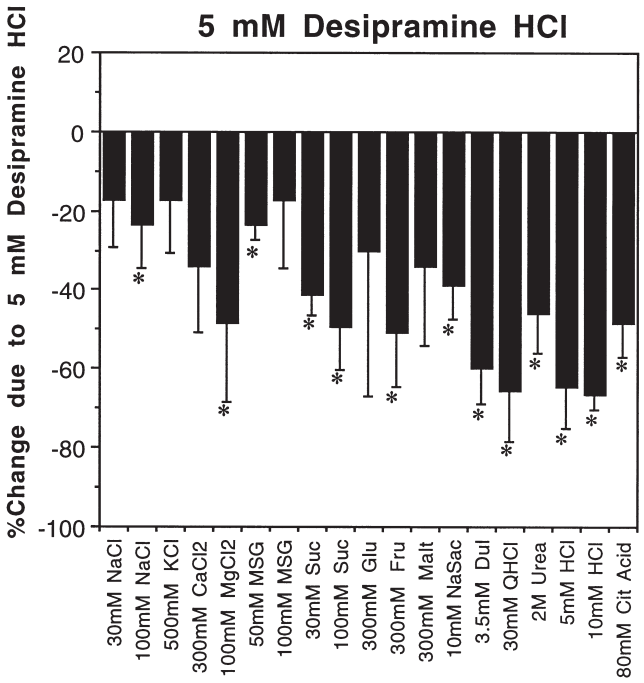

FIG. 4. Percent change in integrated chorda tympani responses after a application of 5 mM desipramine HCl. An asterisk (*) indicates a significant suppression as defined as a decrease of 2 standard deviations below the mean response before exposure to the drug.

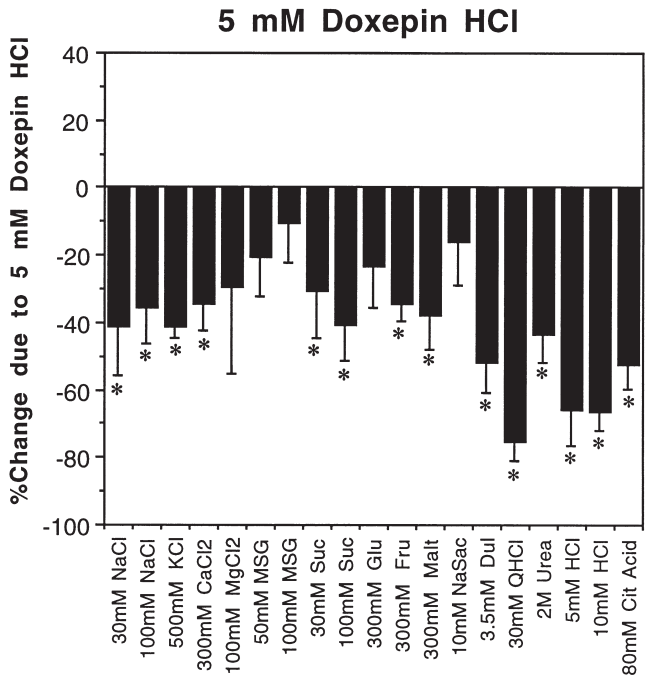

FIG. 5. Percent change in integrated chorda tympani responses after a 4-min application of 5 mM doxepin HCl. An asterisk (*) indicates a significant suppression as defined as a decrease of 2 standard deviations below the mean response before exposure to the drug.

epin HCl (5 mM) blocked responses to all of the taste compounds tested except for 100 mM $MgCl_2$, 50 and 100 mM MSG, 300 mM glucose, and 10 mM sodium saccharin. Doxepin HCl (5 mM) significantly blocked responses to: 30 mM and 100 mM $NaCl_2$ (42% and 36%, respectively), 500 mM KCl (42%), 300 mM $CaCl_2$ (35%), 30 mM and 100 mM sucrose (31% and 41%, respectively), 300 mM fructose (35%), 300 mM maltitol (38%), 3.5 mM dulcin (52%), 30 mM QHCl (76%), 2 M urea (44%), 5 mM and 10 mM HCl (66% and 67%, respectively), and 80 mM citric acid (53%) (see Fig. 5).

Imipramine HCl: a 1 mM imipramine solution blocked responses to some of the compounds tested, while 5 mM imipramine HCl blocked responses to all of the taste compounds tested except for 50 mM and 100 mM MSG. Imipramine HCl (1 mM) significantly blocked responses to: 100 mM NaCl (11%), 300 mM $CaCl_2$ (23%), 100 mM sucrose (22%), 3.5 mM dulcin (19%), 30 mM QHCl (23%), 2 M urea (17%), 10 mM HCl (16%), and 80 mM citric acid (24%). Imipramine HCl (5 mM) significantly blocked responses to all compounds except for 50 mM and 100 mM MSG. Taste responses were blocked in a range from 28% to 72% (see Fig. 6).

DISCUSSION

The four tricyclic antidepressant drugs tested here (clomipramine HCl, desipramine HCl, doxepin HCl, and imipramine HCl) had similar taste detection thresholds and taste qualities. Each tricyclic compound was detected at concentrations of 0.1 mM to 0.2 mM in young persons but at higher concentrations in elderly individuals who were taking no concurrent medications. The detection threshold values for the tricyclic antidepressants used in this study are similar to those previously reported for amitriptyline HCl (52) for which the mean detection threshold in liquid drops was 0.155 mM for young subjects and 0.292 mM for elderly subjects. Elderly individuals in this study had significantly higher thresholds than young subjects for two of the four drugs (doxepin and clomipramine). The greatest mean loss in detection for the elderly subjects was for doxepin HCl, which had a threshold that was 7.71 times higher than that for young subjects. This large difference may be due to two subject's high detection thresholds. Different degrees of age-related loss for bitter taste have been found for compounds that vary in chemical structure (8,44).

Both young and elderly subjects perceived the four compounds tested here as predominantly bitter, with other qualities including metallic, sharp-pungent, and sour. In addition to having a taste of their own, the four tricyclic antidepressants also altered perception of other tastes. A similar finding was reported for amitriptyline (52). These results are consistent with clinical observations that use of tricyclic antidepressants leads to patient complaints of peculiar tastes and hypogeusia.

Of the gerbil and human data, six tastants can be directly compared, and are shown in Table 5. The 5-mM gerbil data are compared to the 1 mM human data because gerbils responded to these tricyclic antidepressants at slightly higher concentrations than humans using the methods employed here (compare the dose response curve for gerbils and the human threshold data). For the gerbil data, if more than one concentration of a tastant was tested, the average response across concentrations is shown. For human data, the difference in after-drug ratings to after-water ratings of a tastant, averaged across the four concentrations, is shown.

Gerbil and human subjects show similar responses after lingual treatment with this group of psychotropic medications; the tricyclic antidepressants reduced the responses to the

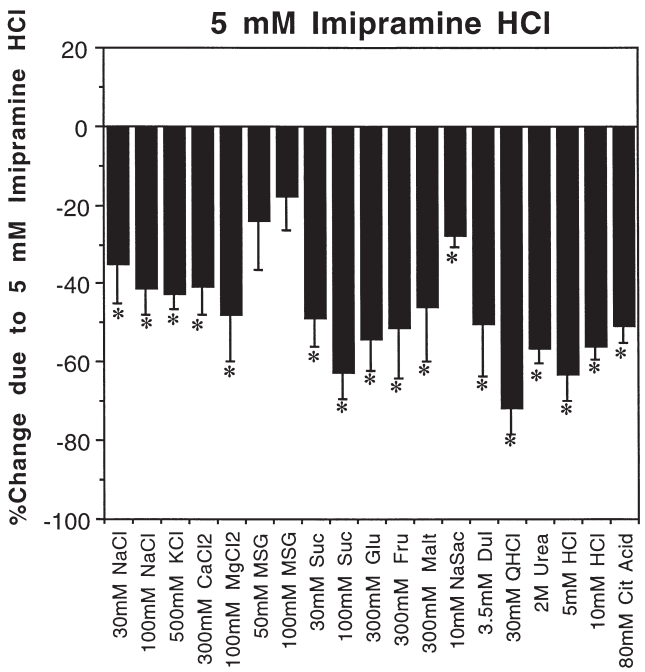

FIG. 6. Percent change in integrated chorda tympani responses after a 4-min application of 5 mM imipramine HCl. An asterisk (*) indicates a significant suppression as defined as a decrease of 2 standard deviations below the mean response before exposure to the drug.

tastants NaCl, KCl, $CaCl_2$, sucrose, quinine HCl, and citric acid. This pattern is similar to the results previously found for amitriptyline HCl, and are included in Table 4. Application of desipramine appeared to have the least extensive effect on taste, for both human and gerbil. Gerbil data did show a systematically stronger suppression of QHCl than do human data.

The sites of action where tricyclic antidepressants induce clinical taste losses are not known, but the present study suggests that one location may be at the level of the peripheral receptors. One possibility is that tricyclic antidepressants exert taste effects of their own by stimulating the taste receptors from the basolateral (blood) side of taste cells or by concentrating in the taste tissues after secretion in saliva. Many drugs and other substances are known to induce taste sensations by a vascular route (5,9,14, 27,28,33,39). Although therapeutic blood levels for desipramine, doxepin, and imipramine are less than the thresholds reported here, antidepressants may concentrate in taste tissues with chronic use, as has been found for amitriptyline in ocular tissue (26); however, this has not yet been tested for taste tissue. Salivary concentrations have shown to be similar to serum concentrations for tricyclic antidepressants such as amitriptyline (29).

Further studies should be performed to quantify systemic effects on taste from these tricyclic antidepressants. Although current study was designed to evaluate acute taste effects at the peripheral level and the impact of the drug in saliva, systemic use of antidepressants may also modify taste centrally by altering the number of receptors or levels of neurotransmitters. When studies are performed on depressive patients, it will be necessary to separate the possible effect of depressive status on taste responses from systemic use of these medications. It is known that depressive symptomology affects scores on cognitive measures, and emotional factors may influence sensory/perceptual responses as well. Specifically, it has been found that subjects may rate stimuli as more bitter if they are placed under stress (11) or score higher on subclinical depression scores (10).

The biochemical mechanisms by which tricyclic antidepressants alter taste responses at the periphery are not yet understood. However, in other tissues, tricyclic antidepressants have been found to alter a variety of transduction mechanisms. Both amitriptyline and imipramine have been shown to block Na^+ K^+, and Ca^{2+} channels (3,7,22,34,36,56). Desipramine was shown to inhibit Ca^{2+}-activated K^+ channels at a stage subsequent to the voltage-gated Ca^{2+} channels (21).

Therapeutic doses of tricyclic antidepressants may also alter signals in chemosensory neural pathways or in the brain. Tricyclic antidepressants have been found to enhance serotonergic or noradrenergic mechanisms or both, but they block histaminic, cholinergic, and α1-adrenergic receptor sites (12,13). Three-week administration of tricyclic antidepressant was found to increase Go α subunits (23).

The taste side effects of tricyclic antidepressants found here may contribute to the discontinuation rates reported in studies of depressed patients. Noncompliance with prescribed medications is associated with the degree of burden from side effects (24). The discontinuation rate due to side effects is higher for tricyclic antidepressants than for selective serotonin reuptake inhibitors (2,25). Further investigations of the chemosensory side effects of selective serotonin reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) must be performed to determine if the taste side effects are less than those of tricyclic antidepressants. Further research is also necessary to understand the effect of ingestion of tricyclic antidepressants on neural coding in chemosensory pathways and in the brain.

TABLE 5

PERCENT CHANGE IN GERBIL OR HUMAN RESPONSE TO TASTANTS AFTER DRUG APPLICATION

	Clomipramine HCl		Desipramine HCl		Doxepin HCl		Imipramine HCl		Amitriptyline HCl	
Tastant	Gerbil	Human	Gerbil	Human	Gerbil	Human	Gerbil	Human	Gerbil	Human
NaCl	**−37.4**	**−39.8**	**−20.3**	**−16.9**	**−36.7**	**−31.3**	**−38.0**	**−51.6**	**−35.6**	**−47.8**
KCl	**−27.5**	**−44.7**	−17.0	+5.25	**−41.5**	**−39.0**	**−42.7**	**−34.5**	**−29.8**	**−46.0**
$CaCl_2$	**−40.7**	**−37.8**	−33.8	−8.9	**−35.0**	**−22.4**	**−40.7**	**−35.2**	**−43.5**	**−63.0**
Sucrose	**−33.4**	**−27.4**	**−45.3**	+2.1	**−36.0**	**−20.3**	**−55.6**	**−15.6**	**−41.1**	**−38.9**
QHCl	**−92.7**	**−22.1**	**−65.4**	−3.9	**−75.6**	**−23.4**	**−71.9**	**−18.9**	**−92.3**	**−35.4**
Citric Acid	−21.4	0.7	**−48.3**	**−54.4**	**−52.4**	**−38.8**	**−50.9**	**−20.1**	**−53.5**	**−26.9**

Significant effects are in bold type.

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