Taste responses to naringin, a flavonoid, and the acceptance of grapefruit juice are related to genetic sensitivity to 6-n-propylthiouracil1-3

Adam Drewnowski, Susan Ahlstrom Henderson, and Amy B Shore

ABSTRACT Increased consumption of vegetables and fruit has long been the focus of dietary strategies for disease prevention. Some vegetables and fruit have bitter tastes, which can be aversive to consumers, particularly children. The present study tested the hypothesis that acceptance of grapefruit juice is influenced, in part, by sensitivity to the bitter taste of 6-n-propylthiouracil (Prop), a heritable trait. A sample of 123 women, mean age 28 y, was divided into nontasters (n = 39), tasters (n = 49), and supertasters (n = 35) of Prop by using procedures validated previously based on Prop detection thresholds and on intensity scaling of five suprathreshold solutions of Prop and sodium chloride. The subjects tasted and rated five solutions of the bioflavonoid naringin in 4% sucrose. Naringin, the principal bitter ingredient of grapefruit juice, has been implicated in the regulation of cytochrome P-450 enzymes. Increased taste acuity for both Prop and naringin was associated with greater dislike for each bitter compound. Prop supertasters disliked bitter naringin solutions significantly more than did either tasters or nontasters. Prop sensitivity was also associated with reduced acceptability of grapefruit juice. Acceptability of orange juice, which does not contain naringin, was unrelated to Prop taster status. Is the acceptability of other bitter vegetables and fruit also limited by inherited taste factors? If so, then genetic taste markers might limit dietary exposure to valuable dietary constituents and pose a barrier to current strategies for dietary change. Am J Clin Nutr 1997;66:391-7.

KEY WORDS 6-n-Propylthiouracil, genetic taste markers, nontasters, tasters, supertasters, naringin, grapefruit juice, cytochrome P-450, dietary change

INTRODUCTION

Increased consumption of vegetables and fruit has been the goal of multiple nutrition education and intervention programs (1-3). Such programs are often based on the social marketing theory (4) and other strategies for behavioral change (5). Whereas the social and behavioral factors that may prevent the adoption of healthy eating patterns have been addressed in many previous studies (4, 6), the role of taste responsiveness as a potential barrier to dietary change has received less research attention (7, 8).

Most consumers state that taste is the main determinant in food selection (9). Although food preferences are subject to multiple influences, including taste, bitterness can be the key reason for food dislikes or food rejection (10, 11). The bitter taste of many vegetables and fruit is aversive to some consumers, particularly children. Low acceptance of bitter cruciferous vegetables and bitter citrus fruit (12, 13) may prevent some consumers from adopting diets consistent with dietary guidelines, including the 5-A-Day for Better Health Program (5).

We hypothesized that low acceptability of some bitter vegetables and fruit is not only taste based, but has a significant inherited component. Sensitivity to the bitter taste of 6-n-propylthiouracil (Prop) has long been known to be a heritable trait (14, 15). It has been associated with increased acuity for other bitter and some sweet substances that are found in ordinary foods (16-18). Past studies have also explored the potential connection between Prop sensitivity and low consumption of cruciferous vegetables and other sharp- and bitter-tasting foods, though with inconsistent results (19-22). The potential influence of genetic taste markers on food habits is of interest to cancer research because many phytochemicals associated with cancer prevention are either bitter-tasting or are found in bitter vegetables and fruit (10).

To our knowledge, no study has explored the relation between genetic sensitivity to Prop and the taste response to the bitter flavonoid, naringin, that accounts for the characteristic bitter flavor of grapefruit juice (23, 24). By far the most prevalent flavonoid in grapefruit juice, naringin is present in concentrations of up to 0.4-0.7 g/L as a mixture of isomers whose proportions can vary depending on the maturity of the fruit and the method of purification (25). Naringin is not present in oranges or orange juice.

Consumption of grapefruit juice as opposed to orange juice has implications for clinical nutrition. Although both serve as sources of vitamin C (26), pharmacokinetic studies have shown that consumption of a single glass of grapefruit juice resulted in a four- to fivefold increase in peak plasma concentrations of dihydropyridine calcium channel blockers (27-29). This effect, thought to involve inhibition of cytochrome P-450 3A4 (27).

1 From the Program in Human Nutrition, School of Public Health, The University of Michigan, Ann Arbor.
2 Supported by NIH grant CA-61680.
3 Address reprint requests to A Drewnowski, Human Nutrition Program, M-5170 SPH II, 1420 Washington Heights, Ann Arbor, MI 48109-2029.
E-mail: adamdrew@umich.edu.
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was not produced by orange juice (29). Grapefruit juice also inhibited the metabolism of caffeine (30), possibly through the inhibition of cytochrome P-450 isozymes by naringenin, the aglycone of naringin (31). Although the mechanisms of action of the components of grapefruit juice remain unclear (32), grapefruit juice is thought to have potential therapeutic value in protecting against environmental toxins or the side effects of chemotherapeutic drugs (33).

Sensory factors that influence the habitual consumption of grapefruit juice are therefore of equal interest for clinical nutrition and public health. One potential factor, the genetic sensitivity to the bitter taste of Prop solutions, appears to be more than a behavioral trait. Studies of tongue anatomy suggest that supertasters of Prop, most of whom are women, had more fungiform papillae, more taste buds, and a higher density of taste buds per papilla than did either tasters or nontasters of Prop (34). Enhanced acuity for bitter taste might then be associated with increased likes or dislikes for bitter-tasting foods (10). Our hypothesis was that greater Prop sensitivity and greater dislike for Prop would be associated with a progressively greater dislike of aqueous naringin solutions and with diminished acceptance of grapefruit and grapefruit juice.

SUBJECTS AND METHODS

Subjects

Subjects were 123 white women, mean age 28 y (range: 20–60 y), recruited by advertising in the university community. All were nonsmokers in good physical health. The subjects were weighed and measured and mean body mass index (BMI; kg/m²) values were calculated. Subjects also completed the Eating Attitudes Test (EAT; 35) and Restraint Scale (36). Women who lived in student dormitories and ate meals in university cafeterias were not eligible for the study. All research protocols had been approved by the Institutional Review Board of the University of Michigan School of Public Health. Subjects were compensated for completing the two experimental sessions.

Stimuli

Taste thresholds were determined by a series of 15 Prop solutions that ranged in concentration from $1.0 \times 10^{-6}$ to $3.2 \times 10^{-3}$ mol/L, and increased in quarter-log steps (16). The highest concentration, solution 15, contained 0.5446 g Prop/L; the next concentration contained 0.3064 g/L, and so on (14, 37). The less concentrated solutions were prepared by diluting the four stock solutions.

Suprathreshold taste stimuli included solutions of Prop (Pfaltz & Bauer, Waterbury, CT) and reagent grade sodium chloride (Fisher, Pittsburgh) in deionized water. Concentrations of Prop were 0.032, 0.1, 0.32, 1.0, and 3.2 mmol/L (solutions 7, 9, 11, 13, and 15). Concentrations of sodium chloride were 0.01, 0.032, 0.1, 0.32, and 1.0 mol/L. Naringin concentrations were 0.034, 0.069, 0.14, 0.28, and 0.55 mmol/L in 4% sucrose solution to resemble more closely the composition of grapefruit juice. All solutions were prepared ≥ 1 d before testing and were stored at 4 °C.

Prop taste thresholds

The determination of Prop taste thresholds followed two phases. First, each subject was presented with the least concentrated solution of Prop (solution 1), and then with increasingly higher solutions, until she reported detecting a taste distinct from that of water. Next, the subject was presented with two identical cups, one containing the detected concentration of Prop and the other containing deionized water. The water was kept at the same temperature and was stored in the same location as the Prop solution. The subject was asked to judge which of the two samples had the bitter taste (16, 38). Wrong answers led to the presentation of more concentrated Prop solutions, again paired with deionized water, whereas correct answers led to a second presentation of the same solution. Two consecutive correct answers at the same concentration led to presentation of less-concentrated Prop solutions. Reversal points were defined as the concentration at which a series of correct responses turned to an incorrect response or vice versa. After discarding the first reversal, the calculated Prop threshold was the arithmetic mean of the subsequent five reversal points.

Subjects rinsed thoroughly with deionized water after each stimulus. All stimuli were presented in plastic medicine cups (10 mL) at room temperature. On average, each threshold determination took 25 min.

Suprathreshold scaling

Suprathreshold aqueous solutions of Prop, sodium chloride, and naringin were presented in 10-mL plastic cups at room temperature. Stimuli within each series were randomized. Solutions of sodium chloride and naringin were presented in counterbalanced order, with the Prop series presented last.

The subjects rated the saltiness or bitterness intensity of each stimulus using 9-point category scales, where 1 = “not at all ______” and 9 = “extremely ______.” They also rated the sensory acceptability of each stimulus, using the standard 9-point hedonic preference scale (39). This fully anchored 9-point category scale ranges from 1 = “dislike extremely” to 9 = “like extremely,” with a neutral point at 5 (“neither like nor dislike”). The subjects tasted the solutions using whole mouth tasting and the standard sip-and-spit technique (40), rinsing with deionized water between samples. Successive tests were separated by a minimum of 45 s.

Food-preference checklists

All subjects completed a food-preference checklist, also based on a 9-point category scale (39). The list included grapefruit, grapefruit juice, lemons, oranges, and orange juice, as well as a variety of other vegetables and fruit.

Statistics

All data were analyzed by using SPSS for Windows (SPSS Inc, Chicago). Differences in subject characteristics were tested by using one-way analyses of variance (ANOVA) followed by post hoc Scheffé tests. Taste data, including both intensity and hedonic ratings, were analyzed by using 3 × 5 ANOVAs for repeated measures with taster status (nontaster, taster, or supertaster) as the grouping factor and stimulus intensity (five solution concentrations) as the within-subject variable. In this way, the main effect of taster status tested differences between the mean level of response averaged across five solution concentrations. Additional cross-tab analyses of acceptance ratings by taster status were followed by chi-square statistics.
RESULTS

Subjects

Subject characteristics are summarized in Table 1. Mean weight was 63.6 kg and mean BMI was 23.3. The three subject groups did not differ in body weight, BMI value, or in restraint or EAT scores. Nontasters were older than the other two groups ($P < 0.05$).

Nontasters, tasters, and supertasters of Prop

The distribution of Prop detection thresholds was bimodal, consistent with previous studies (10). The antimode that separated tasters from nontasters fell at solution 9. Similar to previous studies (41, 42), tasters were defined as having thresholds $< 1.0 \times 10^{-4}$ mol/L (equivalent to solution 9) and nontasters as having thresholds $> 2.0 \times 10^{-4}$ mol/L (equivalent to solution 10).

Separation of tasters into regular tasters and supertasters was based on detection thresholds and on the mean ratio of intensity ratings of Prop solutions relative to sodium chloride solutions. The current procedure, adapted from that of Bartoshuk (42), defined supertasters as having thresholds below solution 7 ($3.2 \times 10^{-5}$ mol/L). Whereas Bartoshuk segregated supertasters and regular tasters on the basis of their intensity ratings of the two most concentrated Prop solutions relative to the two most concentrated sodium chloride solutions (42), the current procedure was based on the full range of five solutions of Prop and sodium chloride. The mean ratio measure, based on five Prop and five sodium chloride solutions, was given by $(p_1/n_1 + p_2/n_2 + p_3/n_3 + p_4/n_4 + p_5/n_5)/5$, where $p_1, p_2$ stood for Prop solutions and $n_1, n_2$ stood for sodium chloride solutions. To qualify as supertasters, subjects had to have Prop detection thresholds $< 3.2 \times 10^{-5}$ mol/L (solution 7) and mean Prop-sodium chloride ratios $> 1.6$. These procedures allowed us to identify 39 nontasters, 49 regular tasters, and 35 supertasters of Prop. These data are summarized in Figure 1.

Taste perceptions and preferences

Nontasters, tasters, and supertasters of Prop showed dramatic differences in their bitterness intensity ratings and in the rated dislike for Prop solutions. Bitterness intensity and hedonic ratings for Prop solutions are shown in Figure 2 separately for each subject group. ANOVA of intensity ratings showed a significant main effect of Prop concentration ($F_{14, 180} = 186.4, P < 0.01$), reflecting greater perceived intensity of the more bitter solutions. A significant main effect of taster status ($F_{12, 120} = 72.3, P < 0.01$), and a taster by concentration interaction ($F_{14, 180} = 11.03, P < 0.01$) reflected major differences in bitterness perception by nontasters, tasters, and supertasters of Prop. Similarly, analysis of hedonic ratings showed main effects of Prop concentration ($F_{14, 180} = 144.5, P < 0.01$) and Prop taster status ($F_{12, 120} = 46.0, P < 0.01$), and a taster by concentration interaction ($F_{14, 180} = 6.66, P < 0.01$). Supertasters of Prop were more likely to dislike the bitter taste of Prop solutions.

Mean bitterness intensity and mean hedonic ratings, averaged over the five Prop solutions, were strongly and inversely linked ($r = -0.83, P < 0.01$). Increased dislike of bitter Prop solutions was wholly accounted for by differences in perceived bitterness intensity across the three subject groups. Tasters and supertasters disliked the bitter taste of Prop more than did nontasters.

Consistent with previous studies, nontasters, tasters, and supertasters of Prop did not differ in their taste responses to sodium chloride solutions. Only the main effect of sodium chloride concentration was significant ($P < 0.01$), and no effects of Prop taster status were observed.

Prop sensitivity and response to naringin

Bitterness intensity ratings for naringin solutions relative to sodium chloride solutions are shown in Figure 3. Although tasters and supertasters of Prop rated naringin solutions as more bitter than did nontasters, this effect was not significant. He-

![FIGURE 1. Distribution of 6α-propylthiouracil (Prop) detection thresholds by Prop taster status.](image)

<table>
<thead>
<tr>
<th>Table 1 Subject characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontasters ($n = 39$)</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
</tr>
<tr>
<td>Restraint score</td>
</tr>
<tr>
<td>EAT score$^*$</td>
</tr>
</tbody>
</table>

$^*$ SEM.
$^*$ Significantly different from nontasters, $P < 0.05$.
$^*$ The Eating Attitudes Test (35).
FIGURE 2. Bitterness intensity and hedonic ratings for 6- n-propylthiouracil (Prop) solutions, shown separately for nontasters, tasters, and supertasters of Prop.

donic ratings for naringin relative to sodium chloride solutions are shown in Figure 4. ANOVA for repeated measures with Prop taster status as grouping variable showed a significant interaction between taster status and naringin concentration \( F_{(5, 213)} = 1.96, P = 0.050 \). An additional ANOVA showed that Prop supertasters gave significantly lower hedonic ratings to naringin solutions than did the pooled group of tasters and nontasters \( F_{(1, 121)} = 4.06, P < 0.05 \). As was the case with Prop solutions, increased bitterness of naringin solutions was associated with lower acceptability ratings. Mean bitterness and mean hedonic ratings for naringin solutions were inversely linked \( r = -0.49; P < 0.01 \).

FIGURE 3. Bitterness intensity ratings for naringin solutions in 4% sucrose relative to sodium chloride solutions, shown separately for nontasters, tasters, and supertasters of 6- n-propylthiouracil (Prop).
Prop sensitivity and acceptance of grapefruit juice

Preference ratings for selected fruit and juices as a function of Prop taster status are shown in Table 2. The only significant difference between nontasters and supertasters was obtained for grapefruit juice (P < 0.05). No significant differences were observed for apples, oranges, or lemons. Higher SEMs and greater CVs for grapefruit as opposed to orange juice suggest that the distribution of preference ratings for grapefruit juice may be bimodal.

As shown in Figure 5, the distribution of mean preferences for grapefruit and grapefruit juice was indeed bimodal, allowing us to separate a small subgroup of dislikers characterized by low mean acceptance scores (score < 3.0). A cross-tab analysis of mean preferences by taster-nontaster status revealed that 19 of 84 Prop tasters had acceptance scores <3 on a 9-point scale. In contrast, only a few Prop nontasters (3 of 37) disliked grapefruit or grapefruit juice to that degree (chi square <0.05). The distribution of preferences for oranges, orange juice, and apples was unimodal and no effect of Prop taster status was observed.

Further correlations between Prop thresholds, selected measures of taste responsiveness, and the rated acceptance of grapefruit and orange juices are shown in Table 3. Taster status (nontaster, taster, or supertaster) was negatively linked to the log of Prop detection threshold (r = −0.77), mean hedonic ratings for both Prop (r = −0.66) and naringin solutions (r = −0.18), and the acceptance of grapefruit juice (r = −0.20). Dislike for Prop and dislike for naringin solutions were also

### Table 2
Mean preference ratings (9-point scale) for selected fruit and fruit juices by 6-n-propylthiouracil taster status

<table>
<thead>
<tr>
<th></th>
<th>Nontasters (n = 39)</th>
<th>Tasters (n = 45)</th>
<th>Supertasters (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grapefruit</td>
<td>6.7 ± 0.4</td>
<td>5.9 ± 0.4</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>5.9 ± 0.4</td>
<td>5.4 ± 0.4</td>
<td>5.5 ± 0.5</td>
</tr>
<tr>
<td>Lemons</td>
<td>6.5 ± 0.3</td>
<td>6.2 ± 0.3</td>
<td>5.9 ± 0.4</td>
</tr>
<tr>
<td>Oranges</td>
<td>7.7 ± 0.3</td>
<td>7.5 ± 0.3</td>
<td>7.5 ± 0.2</td>
</tr>
<tr>
<td>Orange juice</td>
<td>7.6 ± 0.2</td>
<td>7.2 ± 0.2</td>
<td>7.5 ± 0.3</td>
</tr>
<tr>
<td>Apples</td>
<td>7.6 ± 0.2</td>
<td>7.3 ± 0.3</td>
<td>7.1 ± 0.3</td>
</tr>
</tbody>
</table>

1 SEM.
2 Significantly different from nontasters, P < 0.05.

![Figure 4](https://academic.oup.com/ajcn/article-abstract/66/2/391/4655721)

**FIGURE 4.** Hedonic ratings for naringin solutions in 4% sucrose relative to sodium chloride solutions, shown separately for nontasters, tasters, and supertasters of 6-n-propylthiouracil (Prop).

![Figure 5](https://academic.oup.com/ajcn/article-abstract/66/2/391/4655721)

**FIGURE 5.** Distribution of mean preference ratings for grapefruit and grapefruit juice and oranges and orange juice.
TABLE 3
Correlations between selected measures of taste responsiveness and acceptability of grapefruit and orange juices

<table>
<thead>
<tr>
<th></th>
<th>Prop threshold</th>
<th>Prop hedonic</th>
<th>Naringin hedonic</th>
<th>Grapefruit juice</th>
<th>Orange juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taster status</td>
<td>−0.77</td>
<td>−0.66</td>
<td>−0.18</td>
<td>−0.20</td>
<td>−0.03</td>
</tr>
<tr>
<td>PROP threshold</td>
<td>0.61</td>
<td>0.12</td>
<td>0.15</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>PROP hedonic</td>
<td>0.23</td>
<td>0.10</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naringin hedonic</td>
<td>0.14</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>−0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Measure are log of 6-n-propylthiouacil (Prop) detection threshold, mean hedonic ratings for Prop and naringin solutions (9-point scale), and mean acceptability ratings for grapefruit and orange juice (9-point scale). n = 123.

DISCUSSION

Hedonic responses to naringin solutions and the acceptability of grapefruit juice were related to genetic sensitivity to Prop. Supertasters of Prop disliked naringin solutions, and naringin grapefruitjuice lower than did nontasters. In contrast, dislike for aqueous sodium chloride solutions was unrelated to Prop sensitivity. Acceptability ratings for orange juice, which contains no naringin, were unaffected by Prop taster status.

The association between genetic taste markers and the acceptability of grapefruit juice may have considerable implications for clinical nutrition. In past studies, daily consumption of grapefruit juice led to increased plasma cyclosporine concentrations in patients who received kidney transplants (32, 43). Grapefruit juice may potentiate the bioavailability of the calcium channel blockers nifedipine, felodipine, and nisoldipine (28, 29), and has been reported to alter caffeine clearance by inhibiting metabolism of the human cytochrome P-450 isofom CYP1A2 (30). The reported inhibitory effects of naringin or other constituents of grapefruit juice on P-450 reactions in vivo may influence the metabolism of drugs and other xenobiotics (27, 28).

Naringin and other bitter-tasting flavonoids derived from vegetables and fruit appear to have a role in cancer chemoprevention (27, 44). As a result, any study that explores reasons for low acceptability of such foods by segments of the population may have implications for the design of dietary change strategies in public health. Numerous studies have attempted to link Prop sensitivity with the rejection of sharp and bitter-tasting foods (10). That line of research was spurred by the argument that Prop tasting genes in humans owed their continued existence to the evolutionary advantage conferred by the ability to reject and avoid bitter toxins (45). However, most early studies separated respondents into groups of tasters and nontasters only, often with the help of phenylthiocarbamide crystals or Prop-impregnated filter paper (22). Food preferences were typically established by using checklists of food names (20, 41). Although the acceptability of grapefruit juice was addressed in some of the studies (13, 20, 21), it was as part of composite measures (19). Very few studies examined actual taste rejection profiles, a necessary intermediate step (21, 46).

Not surprisingly, direct association between Prop sensitivity and food preferences has proved elusive. Food preferences are influenced by age, sex, and a variety of demographic, cultural, and socioeconomic variables, as well as by prior learning (9, 11, 47). Sensitivity to bitter taste is more likely to predict dislike of marginally acceptable foods (10). The present study established a link between genetic sensitivity to Prop, sensory rejection of naringin solutions (an intermediate variable), and lower acceptability of grapefruit juice. Several methodologic problems were also resolved.

First, the subjects were 123 white women who, for the most part, were young, normal-weight nondieters. The women were separated into nontasters, tasters, and supertasters of Prop by using recently developed procedures that included both Prop detection thresholds and the scaling of suprathreshold solutions of both Prop and sodium chloride (48).

Second, the study established that greater dislike for bitter Prop solutions by supertasters as opposed to tasters and nontasters was wholly explained by the supertasters’ enhanced perception of bitterness. Although this relation was stronger for Prop (r = −0.83), it was also significant for naringin (r = −0.49). Further, the study showed that dislike of naringin solutions was related to dislike of Prop solutions and to Prop taster status.

Third, preference ratings for grapefruit juice and grapefruit, but not oranges or orange juice, were weakly related to Prop thresholds and significantly related to Prop taster status. The bimodal distribution of preferences for grapefruit and grapefruit juice was again linked to Prop taster status. These data confirm our hypothesis that the acceptability of naringin solutions and grapefruit juice is related to genetic taste markers.

However, some limitations of the study should also be stressed. First, the observed effects of Prop sensitivity on the hedonic response to naringin were small, accounting in some cases for no more than 4% of the variance. However, given that the prevalence of supertasters among white women has been estimated at 25% (34), even small effects observed in the laboratory can have a major effect on consumer behavior in real life. Second, estimated habitual consumption of grapefruit and grapefruit juice by nontasters compared with supertasters would be the ideal endpoint for this and similar studies. This issue is under investigation. However, such data must be obtained by using food diaries because most food-frequency questionnaires combine oranges and grapefruit as well as orange and grapefruit juices as single items (49–51).

Previous researchers have argued that genetic differences may place individuals in separate worlds of taste (52). The present observation that the acceptance of grapefruit juice is related to inherited taste factors adds a new twist to the design of behavioral strategies for dietary change. It is unclear to what extent the effect of neuroanatomy and inherited taste traits on food selection can be modified by positive social-affective context (6), systematic exposure to adult and peer modeling (6), or other models of behavioral change (53). Our hypothesis is that genetic taste markers may in some cases limit the success of nutrition education programs and prove a barrier to existing dietary intervention strategies.

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