Nonsynonymous single nucleotide polymorphisms in human \textit{tas1r1}, \textit{tas1r3}, and mGluR1 and individual taste sensitivity to glutamate\textsuperscript{1–4}

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\textbf{ABSTRACT}

Several studies indicate an essential role of the heterodimer Tas1R1-Tas1R3 for monosodium \textit{l}-glutamate (MSG) detection, although others suggest alternative receptors. Human subjects show different taste sensitivities to MSG, some of whom are being unable to detect the presence of glutamate. Our objective was to study possible relations between phenotype (sensitivity to glutamate) and genotype (polymorphisms in candidate glutamate taste receptors \textit{tas1r1}, \textit{tas1r3}, mGluR4, and mGluR1) at the individual level. The sensitivity was measured with a battery of tests to distinguish the effect of sodium ions from the effect of glutamate ions in MSG. A total of 142 genetically unrelated white French subjects were categorized into 27 nontasters (specific ageusia), 21 hypotasters, and 94 tasters. Reverse transcriptase polymerase chain reaction and immunohistochemistry showed expression of \textit{tas1r1}, \textit{tas1r3}, and \textit{z}-gustducin in fungiform papillae in all 12 subjects tested, including subjects who presented specific ageusia for glutamate. Amplification and sequencing of cDNA and genomic DNA allowed the identification of 10 nonsynonymous single nucleotide polymorphisms (nsSNPs) in \textit{tas1r1} (n = 3), \textit{tas1r3} (n = 3), and mGluR1 (n = 4). In our sample of subjects, the frequencies of 2 nsSNPs, C329T in \textit{tas1r1} and C2269T in \textit{tas1r3}, were significantly higher in nontasters than expected, whereas G1114A in \textit{tas1r1} was more frequent in tasters. These nsSNPs along with minor variants and other nsSNPs in mGluR1, including T2977C, account only for part of the interindividual variance, which indicates that other factors, possibly including additional receptors, contribute to glutamate sensitivity. \textit{Am J Clin Nutr} 2009;90(suppl):1S–11S.

\textbf{INTRODUCTION}

We have described subjects perceiving only the saltiness of monosodium \textit{l}-glutamate (MSG) but not its specific taste nor its persistence (1), a specific ageusia independent of the ageusia to phenylthiocarbamide (2). The detection of glutamate in taste papillae is considered to involve Tas1R1 (taste receptor type 1, member 1) and Tas1R3 (taste receptor type 1, member 3) receptors (3–8) linked to phospholipase C (\textit{Cf2} and TRPM5 (transient receptor potential M5) activation and release of ATP to activate nerve fibers (9).

Knockout mice that lack a functional Tas1R3 receptor still exhibit behavioral and residual neural responses to MSG (10–12). Furthermore, taste nerves still respond to MSG in mice with nonfunctional TRPM5 channels (13). Moreover, some taste cells respond to MSG by a decrease of intracellular cAMP (14) independently of the phospholipase C transduction pathway.

The expression of several metabotropic glutamate receptors (mGluRs), including truncated forms, has been reported in rodent taste papillae: mGluR4, mGluR1, and mGluR2/3 (15–20). NMDA (N-methyl \textit{d}-aspartate) and non-NMDA ionotropic glutamate receptors (iGluRs) are also expressed in taste cells (21–24), whereas MSG and glutamate receptor agonists NMDA and 2-amino-4-phosphonobutylate induce complex membrane conductance changes in some taste cells (25–27) as well as an increase or a decrease in intracellular calcium concentration on stimulation with MSG (28).

Glutamate exhibits specific taster properties as assessed with electrophysiologic and human psychophysical data (29, 30). Hamster chorda tympani responses to various agonists of brain glutamate receptors, including ionotropic \textit{z}-amino-3-hydroxy-5-methylisoxazole-4-propionic acid–kainate iGluRs, suggest distinct receptor mechanisms (31). Glutamate elicits the “umami” taste (32) and enhances the palatability of various foods (33, 34). Ribonucleotides such as 5’-inosine monophosphate or 5’-guanosine-monophosphate (5’GMP), which reinforce the perceived intensity of MSG (35), also elicit an umami sensation but are discriminated from MSG by humans and by rats (36). The umami taste in humans is elicited by various agonists of iGluRs and mGluRs (31, 37). Gustatory neural responses in different strains of mice discriminating between compounds eliciting an umami taste suggest that these compounds involve distinct sensory pathways (38). Rats easily distinguish MSG from 5’GMP (36), MSG from 2-amino-4-phosphonobutylate, and

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\textsuperscript{2} Presented at the “100th Anniversary Symposium of Umami Discovery: The Roles of Glutamate in Taste, Gastrointestinal Function, Metabolism, and Physiology,” held in Tokyo, Japan, September 10–13, 2008.
\textsuperscript{3} Supported by ACI INSERM-INRA, ANR (PNRA 1.5), COFAG-ECU, Région Ile de France, and the International Glutamate Technical Committee, a nongovernmental organization funded by industrial producers and users of glutamate in food.
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MSG from NMDA (39). Altogether this body of literature suggests that responses to MSG in the taste system may involve other receptors than Tas1R1-Tas1R3 (11).

Our aim was to examine a possible link between the glutamate taste sensitivity of subjects (phenotype) and their genotype. Taste sensitivity was measured with a battery of tests to distinguish the stimulatory effects of glutamate and the sodium cation in MSG. We looked for the expression of Tas1R1-Tas1R3 in taste buds and further explored for the presence of single nucleotide polymorphisms (SNPs) in tas1r1, tas1r3 (40, 41), as well as in mGluR1 and mGluR4 (41). We then established statistical relations between modifications in the coding sequences of candidate receptors for umami and the observed phenotypes.

SUBJECTS AND METHODS

Stimuli

For tests at constant concentration, MSG (29 mmol/L; Ajinomoto Eurolysine, Paris, France) and disodium GMP (14.5 mmol/L; Sigma-Aldrich, St Louis MO) were compared with isomolar sodium chloride (29 mmol/L; Merck Chimie SAS, Fontenay ss Bois, France) prepared in low mineral tap water. For some sodium-low sensitive subjects, test concentrations were increased to 43 mmol/L for MSG and sodium chloride and to 21.5 mmol/L for GMP. For tests sent by mail with instructions, the substances were weighted in disposable tubes, and subjects were told to add a specified amount of water. For evaluation of iso-intensity concentrations, the reference for sodium chloride was 29 mmol/L; the maximal concentrations of solutions of MSG, GMP, and sucrose were 60, 90, and 175 mmol/L, respectively.

Subjects’ phenotype

Screening

A total of 3084 subjects were screened for their sensitivity to MSG in laboratories, Research Centers of Jouy and Dijon, Faculty of Odontology, Museums (La Villette, Palais de la Découverte). The test was designed to preferentially select subjects whose sensitivity to MSG was doubtful and included 2 paired presentations namely: water compared with 29 mmol NaCl/L and 29 mmol NaCl/L compared with 29 mmol MSG/L, each one associated with the question: "Do you perceive a difference?" If the subject could not perceive a difference between salt and water, the test was repeated with water and 43 mmol NaCl/L. If the subject clearly expressed a difference of perception between sodium chloride and MSG, he or she was supposed to be a glutamate taster. Otherwise, the subject was supposed to be a potential glutamate non or hypotaster and submitted to 10–30 triangular tests. If the criterion of \( P = 5\% \) (\( \alpha \) risk) for discrimination was reached, the test was stopped, and the subject was categorized as “glutamate taster.” If not, the subject was categorized as a potential “glutamate hypotaster.” Borderline subjects were categorized as potential hypotasters. All available potential non- and hypotasters as well as 94 tasters selected at random were included in the study. The final study group consisted of 142 white, French, genetically unrelated subjects (55 men and 87 women). All were submitted to further psychophysics evaluation and provided oral cells on swabs; 20 provided fungiform taste papillae. They were paid 10 euros/h for participating in further phenotype characterization by psychophysical testing in the laboratory.

Available relatives (parents, grandparents, children, siblings, aunts, uncles, nephews, and nieces when available) of 11 tasters (n = 70; 28 men and 42 women) and of 17 nontaster or hypotaster subjects (n = 62; 28 men and 34 women) were selected to document the inheritance of both the phenotype and the genotype (total n = 274).

Psychophysics

All 142 subjects participated in tests addressing intensity, quality, and preference to document their individual capacity to discriminate between MSG and sodium chloride (study approved by Hôpital Saint Louis-Fernand Vidal, Paris; CCPRPB no. P0040805).

Evaluation of iso-intense concentrations (MSG, GMP, and sucrose compared with 29 mmol NaCl/L)

This test measures the stimulus concentration perceived as intense as the 29 mmol NaCl/L reference. Iso-intense concentrations (C-ISOs) were measured with the staircase Up & Down method (Up&D) of Dixon and Massey (42). Single tests were forced-choice paired comparisons; subjects answered the question: “which is stronger?” The concentration of stimulus varied according to subject’s responses. One Up&D test represented an average of 7–8 paired presentations (≈15 min), and one session included 3–4 Up&D tests per stimulus. The experiment was computer assisted as described in Lugaz et al (1). Fifty-six subjects, including all putative nontasters and all hypotasters of the 142 independent subjects, participated in ≥6 sessions at intervals of several days.

Questionnaire based on paired comparisons

Four successive pairs, including 1) water compared with 29 mmol NaCl/L, 2) 29 mmol NaCl/L compared with 29 mmol MSG/L, 3) 29 mmol NaCl/L compared with 14.5 mmol GMP/L, and 4) 29 mmol MSG/L compared with 14.5 mol GMP/L, were presented, and the same series of 10 questions were asked for each pair: “Do you perceive a difference of taste? Do you perceive a difference in the nature of the taste? Do you perceive a difference of intensity? Which tube has the stronger taste: A? or B?” The hedonic value was assessed for each tube on a −10 to 10 scale. A description of the perception was required twice for each solution. A total of 252 subjects had this test. Some subjects not perceiving 29 mmol NaCl/L repeated this test with 43 mmol NaCl/L.

Ranking test

Three tubes that contained 29 mmol NaCl/L, 43 mmol NaCl/L, and 29 mmol MSG/L were ranked by 47 subjects according to perceived intensity. They also had to state whether the taste quality varied and whether they perceived persistence, the hallmark of MSG, in any solution.

Electrogustometric threshold

Electrogustometric test was used to detect and exclude subjects with general taste impairment. Electrogustometric threshold
was measured at 9 loci in 51 subjects; medication, smoker status, and the number of dental deafferentations were noted (43–45).

The family subjects received the questionnaire or the ranking tests or both by mail. If they did not obviously perceive glutamate different from isomolar sodium chloride, they were submitted to the discrimination triangular test, and eventually to the C-ISO evaluation test (the latter 2 in the laboratory). In case no quantitative measurement was possible on these relatives, putative nontasters were named hypotasters.

**Subject genotype**

**mRNA**

Twenty subjects gave 4 fungiform papillae (study approved by Hôpital Saint Louis-Fernand Vidal, Paris; CCPRB no. P0040805). The inclusion criteria were nonsmokers or subjects smoking <6 cigarettes/d, no medication besides contraceptive pills or patches, <7 dental deafferentations, and not pregnant.

A small part of the anterior tongue was anesthetized by lidocaine (5%) and disinfected by chlorhexidine digluconate (0.2%). Fungiform papillae were gently pulled up with fine Brussels, and the upper part carefully sectioned with ophthalmological scissors by the study surgeons under sterile conditions. Papillae were instantaneously frozen (−80°C) so as to extract total mRNA. For histologic analysis, papillae were fixed (4% paraformaldehyde in phosphate-buffered saline).

**Genomic DNA**

All 142 subjects collected their own oral swabs before or long after eating, gum chewing, or teeth brushing; the samples were kept at −20°C for extraction of genomic DNA (BuccalAmp DNA Extraction, tebu-bio; Epicentre Biotechnologies, Madison, WI). Polymorphisms were identified by amplification and sequencing of the entire coding regions of tas1r1, tas1r3, mGluR1, and mGluR4 receptor genes from the genomic DNA of 20 subjects. Then, the presence of each SNP was further analyzed in the genomic DNA of 142 subjects. Polymerase chain reactions (PCRs) were performed with the Turbo Hotstart Pfu DNA proofreading polymerase (Stratagene, La Jolla, CA). Oral swabs of relatives were treated similarly.

**Statistics**

Factor analysis of correspondences (SPAD, version 5.5, 2002; Decisia, Pantin, France) was used to analyze the multidimensional space built from the individual phenotype and genotype characteristics (columns) of all subjects (lines). The analysis gives the dimension and structure of the subjects’ sensitivity space and the proximity relations between SNPs and subjects.

Chi-square statistics (XLSTAT, version 2007; Addinsoft, Paris, France) evaluated the significance of the prevalence of polymorphisms in each group of subjects compared with expectation if these polymorphisms were distributed independently from the observed phenotype. The table of contingency tested the independence of 2 characteristics: having or not having a given phenotype trait, and having or not having a given nucleotide polymorphism.

**RESULTS**

**Phenotype**

On the basis of the complete set of test results, 142 genetically independent subjects were classified as 94 tasters, 27 nontasters, and 21 hypotasters (Table 1). It should be emphasized that these figures do not represent the natural frequency in the population (1): the proportion of nontasters was artificially overrepresented for the sake of the phenotype-genotype correlation study.

Tasters clearly perceived a peculiar taste for MSG and its persistence in the mouth; tasters type T (n = 70) disliked the taste of MSG and tasters type TL (n = 24) liked it. Nontasters (NT; n = 27) did not perceive glutamate: type NT subjects (n = 9) perceived sodium in MSG and in isomolar sodium chloride equally well, whereas type NTI subjects (n = 14) needed stronger MSG solutions to match the intensity of 29 mmol NaCl/L and evaluated sodium chloride stronger than MSG in isomolar solutions; their sensitivity to sodium was decreased (inhibited) in the presence of the glutamate ion. In type NTR (n = 2) conversely, the saltiness of MSG (the only taste perceived) was higher (reinforced) in MSG than in isomolar sodium chloride, and the iso-intense MSG concentration <29 mmol NaCl/L, demonstrating an enhanced sensitivity to sodium by glutamate. Both NTI and NTR subjects may be missed at screening because they discriminate MSG from sodium chloride on an intensity criterion, as opposed to NT subjects. It was remarkable that in this group of 142 subjects, 2 of them acquired the sensitivity to glutamate on repeated exposure during the 6 sessions of iso-intense concentration evaluation to which every nontaster and hypotaster was submitted together with some tasters (Figure 1). This shows the pressing necessity of familiarization and repeated tests before categorizing subjects. Potential nontasters and hypotasters and some tasters measured their concentration of MSG and of sucrose iso-intense to sodium chloride during ≥6 sessions covering a minimum of 3 wk which ensures reproducibility. One subject who was measured at a 6-y interval, for example, gave the same iso-intense concentration [mean ± SD: 56.1 ± 7.8 (n = 26) and 53.6 ± 12.1 (n = 51)], and similarly for several subjects who were repeatedly measured during ≤19 sessions and retested semiquantitatively after several years.

Finally, hypotasters (n = 21) could discriminate MSG from sodium chloride at the limit of statistical criterion. Two types were distinguished: type H subjects (n = 11) perceived MSG as strong as or slightly stronger than isomolar sodium chloride; type HI subjects (n = 10) perceived glutamate less strong than isomolar sodium chloride.

**Genotype**

Expression of tas1r1, tas1r3, and gustducin

Reverse transcriptase–PCR on cDNA from taste papillae tissue showed the expression of the mRNA coding the candidate receptors Tas1R1, Tas1R3, and the G protein α-gustducin in tasters, hypotasters, and nontasters (Figure 2). Immunohistochemistry also showed that Tas1R1, Tas1R3, and α-gustducin were present in all subjects (41).

**Single nucleotide polymorphisms**

The 142 genetically independent subjects showed 20 SNPs, among which 10 nonsynonymous SNPs (nsSNPs) change the
<table>
<thead>
<tr>
<th>Subject status</th>
<th>Perceived taste for 29 mmol MSG/L</th>
<th>Persistence</th>
<th>Hedonic evaluation of MSG</th>
<th>Discrimination test (triangles), NaCl-MSG</th>
<th>MSG isoaintense concentration (vs 29 mmol NaCl/L)</th>
<th>Intensity ranking</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasters disliking MSG (n = 70)</td>
<td>Strong taste, qualitatively different from NaCl</td>
<td>++</td>
<td>Unpleasant</td>
<td>Significant</td>
<td>&lt; Na29 &lt; Na43 &lt; MSG29</td>
<td>Na29 &lt; Na43 &lt; MSG29</td>
<td>Perceive the glutamate anion stronger than the sodium cation</td>
</tr>
<tr>
<td>Tasters liking MSG (n = 24)</td>
<td>Strong taste, qualitatively different from NaCl</td>
<td>++</td>
<td>Pleasant</td>
<td>Significant</td>
<td>&lt; Na29 &lt; Na43 &lt; MSG29</td>
<td>Na29 &lt; Na43 &lt; MSG29</td>
<td>Perceive glutamate stronger and like it</td>
</tr>
<tr>
<td>Nontasters (n = 9)</td>
<td>Salty</td>
<td>0</td>
<td>Depending on judgment on salt</td>
<td>Nonsignificant</td>
<td>= Na29 = MSG29 &lt; Na43</td>
<td>Na29 &lt; MSG29 &lt; Na43</td>
<td>Do not perceive the glutamate anion, only the sodium cation</td>
</tr>
<tr>
<td>Nontasters who perceive sodium less intense in MSG than in isomolar NaCl (n = 14)</td>
<td>Water or slightly salty</td>
<td>0</td>
<td>Depending on judgment on salt</td>
<td>Significant</td>
<td>&gt; MSG29 &lt; Na29 &lt; Na43</td>
<td>Na29 &lt; MSG29 &lt; Na43</td>
<td>Do not perceive the glutamate anion; moreover, the perception of the sodium cation is reduced in presence of glutamate anion</td>
</tr>
<tr>
<td>Nontasters who perceive sodium stronger in MSG than in isomolar NaCl (n = 2)</td>
<td>Salty</td>
<td>0</td>
<td>Depending on judgment on salt</td>
<td>Significant</td>
<td>&lt; Na29 &lt; MSG29 ≤ Na43</td>
<td>Na29 &lt; MSG29 ≤ Na43</td>
<td>Do not perceive the glutamate anion, but the perception of the sodium cation is reinforced in presence of glutamate anion</td>
</tr>
<tr>
<td>Subjects becoming tasters with exposure (n = 2)</td>
<td>Nothing or salty; but, after several tests, a specific taste appears and becomes obvious</td>
<td>0 → ++</td>
<td>Nonsignificant, then significant</td>
<td>≥ then &lt; MSG29 ≤ Na29 &lt; Na43 at screening then like tasters</td>
<td>MSG29 &lt; Na29 &lt; Na43 ≤ Na29 ≥ then &lt; MSG29 ≤ Na29 &lt; Na43</td>
<td>MSG29 &lt; Na29 &lt; Na43</td>
<td>Nontasters becoming tasters by repeated exposure to MSG (at least four to five 1-h repeated quantitative testing sessions)</td>
</tr>
<tr>
<td>Hypotasters (n = 11)</td>
<td>Slight taste, different or maybe different from salt</td>
<td>Slightly</td>
<td>Not very unpleasant</td>
<td>Just significant or significant</td>
<td>≤ Na29 ≤ MSG29 &lt; Na43</td>
<td>Na29 ≤ MSG29 &lt; Na43</td>
<td>Perceive the glutamate anion stronger or slightly stronger than the sodium cation</td>
</tr>
<tr>
<td>Hypotasters who perceive sodium less intense in MSG than in isomolar NaCl (n = 10)</td>
<td>Slight taste, different from salt</td>
<td>Slightly</td>
<td>Not very unpleasant</td>
<td>Significant</td>
<td>&gt; MSG29 &lt; Na29 &lt; Na43</td>
<td>MSG29 &lt; Na29 &lt; Na43</td>
<td>Perceive the taste of glutamate anion, but the intensity perceived for MSG is reduced compared with the perception elicited by isomolar NaCl</td>
</tr>
</tbody>
</table>

\[ Na29, 29 \text{ mmol NaCl/L}; \ Na43, 43 \text{ mmol NaCl/L}; \ MSG29, 29 \text{ mmol MSG/L}. \]
Subjects were categorized as nontasters or hypotasters only after repeated exposure to the stimulus. Subjects were tested during six 1-h sessions comparing variable concentrations of MSG to 29 mmol NaCl/L; the horizontal line shows the reference of 29 mmol NaCl/L. The taster subject T first evaluates 9 mmol MSG/L elicits a sensation isointense to 29 mmol NaCl/L, then, from the third session on, the isointense concentration (C-ISO) is stable at 4.8 ± 1.2 mmol NaCl/L. NT represents the nontaster subject who had difficulty in evaluating the concentration of MSG isointense to 29 mmol NaCl/L (reference) as 60 mmol/L, the maximum available concentration is not sufficient. C-ISO often nears 60 mmol/L with a ceiling effect; this subject (nontaster inhibited) shows inhibition of his perception of sodium in the presence of the glutamate (MSG) concentration isointense to 29 mmol NaCl/L with a ceiling effect; this subject (nontaster inhibited) shows inhibition of his perception of sodium in the presence of the glutamate (MSG) concentration isointense to 29 mmol NaCl/L, even with 60 mmol MSG/L, but, by the fifth session, he tended to be more frequent in nontasters than expected in tasters ($P = 0.008$). The mutation G1520A (Table 2), found in 7 subjects, only tended to be more frequent than expected in nontasters and hypotasters without inhibition of salt taste in the presence of the glutamate anion ($P = 0.04$). Conversely, the mutation G1114A found in 44 subjects (40 heterozygous and 4 homozygous subjects) was more frequent than expected in tasters ($P = 0.008$). The mutation G1520A (Table 2), found in 7 subjects, only tended to be more frequent than expected in nontasters ($P < 0.1$; not shown in Table 3).

Phenotype-genotype relations: occurrence of nsSNPs in the different groups of subjects
tas1r1

The mutation C329T, found in 10 subjects, was more frequent in nontasters (5 of 27) than expected if this polymorphism was distributed independently from the observed phenotype ($P = 0.007$, chi-square test) and similarly in hypotasters (2 of 21; $P = 0.01$). It was less frequent (3 of 94) than expected in tasters ($P = 0.005$; Table 3, top). This mutation was also associated with the inhibition of salt taste in the presence of the glutamate anion ($P = 0.04$). Conversely, the mutation G1114A found in 44 subjects (40 heterozygous and 4 homozygous subjects) was more frequent than expected in tasters ($P = 0.008$). The mutation G1520A (Table 2), found in 7 subjects, only tended to be more frequent in nontasters ($P < 0.1$; not shown in Table 3).

tas1r3

The mutation C2269T, found in 7 subjects, was less frequent than expected in tasters ($P = 0.04$) and tended to be more frequent in nontasters ($P = 0.08$). The mutation G13A, found in 14 subjects, was associated with nontasters and hypotasters without inhibition of sodium taste by glutamate ($P = 0.04$).

mGluR1

The mutation T2977C in the exon 8 (P993S rs6923492), among them 39 were homozygous. Other mutations corresponded to A1670C (Q557P) in the exon 6 (1 subject), G2651A (G884E rs362936) in the exon 7 (5 subjects), and C3206T (P1069L) in exon 8 (3 subjects). All these nsSNPs are located in the C-terminal tail of the protein. No nsSNPs, but only 3 silent SNPs, were identified in mGluR4. Allergic frequencies of the nsSNPs are very low (1–2%) except for G1114A and T2977C (41).
 Subjects with the mutation C329T in *tas1r1* (n = 9) were more often unable to propose words to describe the taste of MSG than expected if the perception were independent of the genotype (P = 0.01). Subjects with the mutation G1114A in the same gene (n = 37) could discriminate MSG from sodium chloride more often than expected, from the nature of the taste (P = 0.05); they could discriminate MSG from GMP, from the perceived intensity (P = 0.01). Subjects with the mutation G1520A in *tas1r1* (n = 6) tended to be unable to perceive the difference between water and 29 mmol NaCl/L at first testing (P = 0.06) and could not describe MSG (P = 0.03; not shown in Table 3). Subjects with the mutation C2269T in *tas1r3* (n = 5) did not perceive a difference (P = 0.0001), neither in terms of a qualitative difference of taste nor of intensity, between sodium chloride and MSG as often as would be expected if the perception were independent of the SNP. They also did not perceive the difference between sodium chloride and 5’GMP (P = 0.009) and were not able to propose words for the taste of umami solutions (P = 0.04). Subjects with the mutations G13A in *tas1r3* (n = 14) did not reach any significant statistical criterion for any tentative relation in these data.

Subjects with one allele mutated in T2977C in mGluR1 (59 heterozygous of 124 subjects, not shown in Table 3) tended not to discriminate MSG from sodium chloride (P = 0.07) and did not describe a taste for MSG as often as expected (P = 0.04). Adding both the homozygous and heterozygous together led to a group of 96 of 124 subjects who did not discriminate, as often as expected, MSG from sodium chloride (P = 0.01) or GMP from sodium chloride and did not discriminate MSG from sodium chloride.

### Table 3

#### Statistical evaluation of phenotype-genotype relations

<table>
<thead>
<tr>
<th></th>
<th>C329T</th>
<th>G1114A</th>
<th>G13A</th>
<th>C2269T</th>
<th>T2977C</th>
<th>mGluR1</th>
</tr>
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<tr>
<td><strong>Categorization</strong></td>
<td></td>
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<tr>
<td>NT (n = 27)</td>
<td>0.007</td>
<td>—</td>
<td>—</td>
<td>0.008</td>
<td>—</td>
<td>—</td>
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<tr>
<td>H (n = 21)</td>
<td>0.01</td>
<td>—</td>
<td>—</td>
<td>0.03</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>T (n = 94)</td>
<td>—</td>
<td>0.005</td>
<td>0.008</td>
<td>—</td>
<td>—</td>
<td>0.04</td>
</tr>
<tr>
<td>NT and H with sodium</td>
<td>0.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.08</td>
<td>—</td>
</tr>
<tr>
<td>presence of glutamate (n = 25)</td>
<td></td>
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<tr>
<td>NT and H without</td>
<td>0.03</td>
<td>—</td>
<td>—</td>
<td>0.003</td>
<td>0.04</td>
<td>—</td>
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<td>inhibition to sodium (n = 23)</td>
<td>—</td>
<td>0.01</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.08</td>
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<tr>
<td><strong>Questionnaire</strong></td>
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<tr>
<td>Discriminate water NaCl</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discriminate NaCl MSG</td>
<td>—</td>
<td>—</td>
<td>0.05</td>
<td>—</td>
<td>—</td>
<td>0.0001</td>
</tr>
<tr>
<td>Discriminate NaCl GMP</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.009</td>
<td>—</td>
</tr>
<tr>
<td>Discriminate intensity of MSG GMP</td>
<td>—</td>
<td>—</td>
<td>0.01</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Identify water</td>
<td>—</td>
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1. Cov, covariance between the genotype and the phenotype tested; Anti-cov, anticovariance between genotype and phenotype; NT, nontasters; H, hypotasters; T, tasters; MSG, monosodium L-glutamate; TL, tasters who like MSG; GMP, guanosine-monophosphate.
2. Subjects (n = 142) were grouped according to all sensory tests. P values (chi-square test) that resulted from a test of independence between the presence of nonsynonymous single nucleotide polymorphisms (nsSNPs; columns of the contingency table) and the phenotype characteristics of subjects (lines of the contingency table) are shown. n = 10 for C329T; n = 44 for G1114A; n = 14 for G13A; n = 7 for C2269T; n = 110 for T2977C.
3. P values (chi-square test) that resulted from the test of independence between the presence of nsSNPs and some of the questions of the questionnaire on MSG-NaCl discrimination and MSG identification ability of 124 subjects are shown. n = 9 for C329T; n = 37 for G1114A; n = 14 for G13A; n = 5 for C2269T; n = 96 for T2977C.
sodium chloride ($P = 0.03$). The high prevalence of the mutation in all subjects is responsible for low levels of significance of the differences between nontasters and tasters; however, this gene seems to contribute to signaling MSG.

Relation between C-ISOs and nsSNPs

The concentration of MSG found to be isointense to the sodium chloride reference varied across subjects, from 1.8 mmol/L to values above mother solutions (60 mmol/L for MSG and 90 mmol/L for 5’GMP) hence, >29 mmol NaCl/L. Results were very consistent at least in the last 2 d of a 6-d protocol, the learning phase being visible in the first 2–4 d. These data showed that paired GMP and MSG C-ISOs were correlated at $r = 0.75$ (Pearson $r$; df = 19), whereas the correlation between MSG and sucrose or GMP and sucrose were very low ($r = 0.36$; Pearson $r$; df = 42; $r = 0.23$; Pearson $r$; df = 19), showing that mechanisms signaling sucrose are clearly discriminated from mechanisms discriminating either MSG or GMP.

Chi-square calculations on 53 subjects showed a trend to associate C329T with high C-ISO (meaning low sensitivity: $P < 0.10$), a trend for G1114A not to be associated with elevated C-ISO ($P < 0.10$), and a trend for the mutation G1520A to be associated with elevated C-ISO ($P = 0.06$). These data are reflected in factor analysis of correspondences (Figure 3).

Inheritance of phenotype and genotype: a family study

The group of 62 relatives of nontasters or hypotasters as defined in Subjects and Methods contained 11 nontasters or hypotasters, whereas the group of 70 relatives of tasters did not contain any nontaster or hypotaster. This statistically significant difference ($P < 0.001$, chi-square test) points at glutamate ageusia being an inherited trait.

The proportion of mutations compared with wild alleles was compared across the 4 groups (17 nontasters and hypotasters, their 62 relatives; 11 tasters and their 70 relatives) for nsSNPs C329T in tas1r1, C2269T in tas1r3, and T2977C in mGluR1. The 17 nontasters or hypotasters presented 20% of mutated alleles, their 62 relatives presented 11.4%, the 11 tasters presented 10% and their 70 relatives presented 5.2%. These figures are significantly different from a random distribution ($P < 0.001$, chi-square test; df = 3). The difference of the prevalence of nsSNPs in nontasters and hypotasters compared with the group of their relatives was significant ($P = 0.04$, chi-square test; df = 1); this group, genetically related to nontasters and hypotasters, showed a lower prevalence of nsSNPs. The difference of the proportion of polymorphisms between tasters and their relatives was not significant. The group of tasters’ relatives and the group of nontasters’ or hypotasters’ relatives, on the contrary, had significantly different prevalence of nsSNPs ($P = 0.005$). Hence, the significant difference of the prevalence of nsSNPs shown in tasters compared with nontasters and hypotasters in genetically unrelated subjects is also found between relatives of nontasters or hypotasters and relatives of tasters.

Looking at minor variants specifically, without nsSNPs C329T and G1114A in tas1r1, C2269T in tas1r3, and T2977C in mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$). The same calculation across 4 groups taking in account the 9 nsSNPs in tas1r1, tas1r3, and mGluR1, showed significantly more of these minor nsSNPs in the families of nontasters or hypotasters (3.9%) than in the families of tasters (1.4%; $P = 0.02$).

FIGURE 3. Factor analysis of correspondences. Factor analysis of data (SPAD, version 5.5; Decisia, Pantin, France) included both subjects’ phenotypes classified into categories and genotypes noted as occurrence or no occurrence of each nonsynonymous single nucleotide polymorphism (nsSNP) in each subject ($n = 142$). T, tasters; TL, tasters liking monosodium glutamate (MSG); NT, nontasters; NTI, nontasters who perceive sodium less strong in the presence of the glutamate anion (so-called inhibited); H, hypotasters; HI, hypotasters with sodium taste inhibited in presence of glutamate. This figure shows particularly well the discrimination of tasters compared with nontasters and hypotasters on the first axis and nontasters compared with nontasters whose sensitivity for sodium is inhibited in the presence of glutamate on the third axis. The nsSNPs C329T in tas1r1 and C2269T in tas1r3 are associated with nontasters and hypotasters, whereas the nsSNP G1114A in tas1r1 is associated with tasters. Other nsSNPs, including T2977C in mGluR1 in homozygous subjects (ho), are tentatively associated with nontasters and hypotasters.
(P = 0.009, chi-square test; ddl = 3). Again, the prevalence of nsSNPs in the relatives of nontasters and hypotasters was significantly different from the prevalence of nsSNPs in the relatives of tasters (P = 0.003, chi-square test; ddl = 1).

Hence, the phenotype seems to be transmitted to relatives together with the prevalence of nsSNPs studied here. The observation of mutations in 28 families showed that nsSNPs are transmitted from generation to generation.

**DISCUSSION**

MSG concentrations that were found to be isointense to 29 mmol NaCl/L varied among subjects continuously from ≈1 to >60 mmol/L. This study could categorize subjects into 3 classes. Tasters, who easily discriminated between MSG and isomolar sodium chloride, perceived a typical persistence and a typical taste for MSG; 2 subclasses were observed according to hedonic valence, most subjects considering it as unpleasant, fewer liking it. Nontasters were not able to perceive either the taste or the persistence of glutamate itself and described only a salty sensation. Three subclasses of nontasters could be distinguished according to the intensity of the salty perception elicited by MSG compared with isomolar sodium chloride. Apparently, in some nontasters, the presence of glutamate interfered with the detection of sodium ions either by decreasing it (56% of NT) or by increasing it (8%). It should be emphasized that nontasters with sodium taste modified by glutamate may easily be confused with tasters, eg, inhibited nontasters or NTI, who discriminate MSG from sodium chloride because they perceive MSG less intensely than an isomolar solution of sodium chloride. Clearly, various complementary tests are needed to properly establish individual phenotypes; in this study, the evaluation of the concentration of MSG eliciting the same intensity as the reference was a key tool to identify NTI and discriminate them from tasters. In addition, in some cases, tasters perceiving isointensity at isomolarity can be identified because their hedonic valence for MSG is reproducibly highly different from their hedonic valence for sodium chloride. Finally, subjects classified as hypotasters were subjects who were at the statistical limit for discrimination and who were tremendously less sensitive to glutamate than tasters, even after the six 1-h repeated familiarization testing sessions ensuring sufficient repeated exposure to the stimulus (46). Moreover, these subjects were doubtful about the nature of their perception and some referred only to textural semantics (viscous, thick, fat, or “a sensation”). Two subclasses of hypotasters could be distinguished; as for nontasters, 50% of hypotasters showed an inhibition of the sodium sensitivity in the presence of glutamate. In tasters, the sensitivity to the stimulus increased on repeated exposure and C-ISOs were modified in a factor by 2–3 as already shown (46). This is reminiscent of data obtained when recording from hamster chorda tympani (47). But most remarkably, 2 subjects, apparently nontasters after discrimination tests, became tasters through repeated exposure to MSG in quantitative evaluations (the six 1-h testing sessions). In these cases, the decrease of the MSG concentration isointense to the reference after exposure was about 20-fold. For this reason, in this study, all nontasters and hypotasters together with some control tasters were submitted to the C-ISO evaluation test. Furthermore, most subjects were tested 1 y (and ≤8 y) after to confirm their phenotype, before classification.

Only C329T, G1520A, and G1114A in *tas1r1*; G13A and C2269T in *tas1r3*; and T2977C in mGluR1 were submitted to individual statistical analysis, the other nsSNPs being too rare to be treated individually. C329T in *tas1r1*, C2269T in *tas1r3*, and T2977C in mGluR1, taken individually, were significantly associated with the nontaster trait. Conversely, G1114A in *tas1r1* was associated with tasters. G1520A in *tas1r1* and G13A in *tas1r3* showed only a trend in their association with the NT phenotype. Taste spaces obtained from factor analysis of correspondences on subjects and phenotype categories (Figure 3) or on single responses in the questionnaire or on C-ISOs (not shown) all exemplified the association of C329T and C2269T to nontasters or hypotasters and G1114A to tasters.

C329T and G1114A are both localized on the external domain of Tas1R1, which suggests that they may modify the binding of glutamate. Interestingly, all subjects with both C329T and G1114A were tasters, which suggests that G1114A might be compensating the possible deficit because of C329T. Interestingly, G1114A exhibits a much higher allelic frequency (20%) than does C329T or C2269T (1–1.5%) (41). C2269T is localized at the border between the transmembrane domain and the C terminal tail and therefore could affect signal transduction.

This study shows that a part of the interindividual variability of sensitivity to MSG and 5’GMP is likely controlled by nsSNPs in *tas1r1* and *tas1r3*, thus emphasizing the role of Tas1R1-Tas1R3 in MSG detection. This work adds to a long list of genetic polymorphisms affecting taste receptor function (48–51).

The fact that not all nontasters exhibited either C329T or C2269T, which, conversely were possibly found in some taster subjects, suggests that none of these nsSNPs is either necessary or sufficient to explain the taster or nontaster phenotypes. Extending the analysis to mGluR4 coding for another candidate glutamate taste receptor did not show nonsynonymous polymorphisms. In contrast, 4 nsSNPs were found in mGluR1, including T2977C, which was frequent enough (50% heterozygous and 28% homozygous subjects) to allow statistical evaluation to show a higher prevalence than expected in subjects who did not discriminate either MSG from sodium chloride or 5’GMP from sodium chloride. Although P values were moderately low, several criteria in the data converged to correlate the occurrence of this T2977C nsSNP and the non taster or hypotaster phenotype. Factor analyses indicated a low weight, hence a discrete contribution of T2977C to the discrimination of tasters from nontasters.

The prevalence of C329T or C2269T is significantly different between nontasters or hypotasters (n = 11 of 48) and tasters (n = 6 of 94; P = 0.005, chi-square test; df = 1), but 37 of the former group do not display these nsSNPs. Including minor variants, 18 of 48 nontasters or hypotasters presented 1 or 2 of the 5 nsSNPs found in *tas1r1* and *tas1r3* (except G1114A which is associated with tasters) compared with 17 of the 94 taster subjects. The difference is statistically significant despite that 30 of 48 nontasters or hypotasters did not show any nsSNPs in *tas1r1* and *tas1r3*. When considering 4 nsSNPs found in mGluR1 together with 5 nsSNPs in *tas1r1* and *tas1r3* (excluding G1114A), 98% of nontasters and hypotasters compared with 75% of tasters have 1–3 of the 10 possible nsSNPs found in these 3 genes (P < 0.001, chi-square test; df = 1). Moreover, comparison of the
The phenotype of family members disclosed the apparent inheritance of the phenotype together with a significantly higher prevalence of C329T, C2269T, and T2977C in the relatives of nontasters and hypotasters compared with the relatives of tasters.

Focusing on all possible combinations of the 10 nsSNPs found in the 48 nontasters and hypotasters, we observe 20 combinations. Looking at nontasters specifically and excluding G1114A, 5 of the 13 different combinations observed in the 27 nontasters were also represented in tasters. This constitutes a further argument adding to our finding that the interindividual variance is not entirely explained by the 10 nsSNPs we found in tas1r1, tas1r3, and mGluR1.

Taken together these results indicate that nsSNPs found in tas1r1, tas1r3, and mGluR1 account for part of the interindividual variance to MSG. Still, all combinations of nsSNPs in the 3 genes are not sufficient to explain all the phenotypic data.

Regulation factors might justify the increase of sensitivity during repeated exposure to the stimulus but could not explain specific ageusia to glutamate because Tas1R1 and Tas1R3 receptors were present in nontasters. Hence, the present results strongly suggest that other factors than Tas1R1-Tas1R3 need to be taken into account to fully explain the sensitivity to MSG, as suggested by other studies (10–13, 52, 53). Indeed, there are strong arguments in favor of the involvement of several receptors for umami taste (10, 11, 29, 39). MSG and 5’-GMP are discriminated, several compounds, including ionotrophic non-NMDA agonists (31, 37), mGluR type I (18, 19), mGluR type III (15–17), and mGluR type II (20) agonists, taste umami (37). Moreover, some antagonists of these receptors, namely methylserine-O-phosphate for mGluR type III, 6-cyano-7-nitroquinoxaline-2,3-dione for ionotropic receptors can inhibit chorda tympani responses in the rodent (Vandenbeuch and Faüron, unpublished data, 2009).

CONCLUSIONS

We attempted to find a relation between the phenotype and the genotype of individual subjects who perceive or do not perceive the specific taste of glutamate. With a battery of psychophysical tests, we clearly have shown the existence of various phenotypes of taster and nontaster subjects for MSG, including complex effects of glutamate on sodium taste perceived intensity, the mechanisms of which remain to be explained. Absence of Tas1R1-Tas1R3 receptor expression in glutamate nontasters was ruled out, but nsSNPs C329T, G1114A in tas1r1 and C2269T in tas1r3 were significantly more prevalent in nontasters and in hypotasters than in tasters and also significantly more prevalent in the family members of nontasters or hypotasters than in the family members of tasters. Moreover, it seems that, when considered together, minor variants were also more prevalent in nontasters or hypotasters than in tasters. The relation between the higher prevalence of nsSNPs and the nontaster or hypotaster status may explain a part of the interindividual variance and confirms that Tas1R1 and Tas1R3 contribute to oral glutamate detection in humans.

Nevertheless, none of the nsSNPs found in tas1r1, tas1r3, and mGluR1 was either necessary or sufficient to explain the ageusia to MSG. Moreover, no combination of nsSNPs across the 3 genes could provide an exhaustive explanation for the different phenotypes and tastes elicited by glutamate. Therefore, the possibility remains that, besides nsSNPs in these 3 genes, other independently coded receptor mechanisms functionally cooperate to perceive glutamate. (Other articles in this supplement to the Journal include references 54–82.)

The PCR conditions, primer sequences, and sequences containing the polymorphisms have been deposited in GenBank under accession numbers BV725433–BV725462.

We thank Patrick MacLeod (Prof E.P.H.E. Paris) and Victoria Barham (University of Ottawa) for reading the manuscript; Jean Claude Pernollet and Loïc Briand for comments throughout the study; Valérie Bézirard and Sylvie Grall for technical assistance; and Camille Legrand and Béatrice Trottier for on-site psychophysical testing.

The authors’ responsibilities were as follows—MR, AW, and J-PM: carried out immunohistochemistry, genotyping, and RT-PCR; A-MP and AP: collected psychophysical data and designed and constructed the mobile prototypes; CE and YB: collected taste papillae; DT and AF: wrote the manuscript; and AF: designed the study. The presenting author’s (AF) expenses associated with participation in the symposium were paid by the conference sponsor, the International Glutamate Technical Committee, a non-governmental organization funded by industrial producers and users of glutamate in food. None of the authors had a conflict of interest.

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