Correspondence

Bitter taste induces nausea

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Nausea is the most characteristic negative experience that typically accompanies toxin-induced illness. Because most plant-derived toxins taste bitter, there is a rational link between bitter tasting compounds in the mouth and nausea that often results from their ingestion. It is surprising then that there are no experimental data demonstrating this connection. There are, however, data consistent with this notion. For example, people who are the most sensitive to bitter stimuli are more prone to motion sickness [1], and bitter taste sensitivity and pregnancy associated nausea are positively related, a response postulated to protect the fetus from poisoning [2]. Moreover, we know that bitter taste slows gastric emptying, a correlate of nausea [3]. Bitter taste is strongly sensed by the glossopharyngeal and vagus nerves [4], which innervate the posterior oral cavity and the gastrointestinal tract, respectively. The two projection fields of these sensory nerves are immediately adjacent within the nucleus of the solitary tract as well as in other brain relays [5], thus establishing a neuro-anatomical substrate for taste inputs to influence gastrointestinal states. Here, we report the first direct demonstration that bitter taste stimulation, but not sweet, salty, or umami taste, induces nausea, showing that the body not only detects potential toxins but anticipates their ingestion by inducing a prophylactic aversive state.

The induction of perceived nausea was measured on a modified Muth Nausea Profile (MNP) [6] and by the physiological measure of gastric myoelectrical activity (GMA) by recording electrogastrograms (EGGs), which have long been used, both experimentally and clinically, to assess gastric correlates of nausea sensations [7]. The MNP questionnaire asks for ratings of nausea, as well as 14 other feelings such as queasiness, weakness and gastric churning (see the Supplemental Information for details). GMA is modulated by activity from pacemaker areas of the stomach. Normal GMA oscillates at 3 cycles per minute (cpm). During either physical illness or sensations of nausea, the pattern shifts and dysrhythmias (bradygastria, 1–2.5 cpm, and tachygastria, 3.75–10 cpm) increase. Fast Fourier transform of the EGG signal enables the experimenter to determine the onset of nausea via shifts in the frequencies of GMA (see Figure 1E for power analyses) [8].

We asked 63 healthy subjects (fasted for four hours) to sample an intensely bitter, but non-toxic, solution (0.8 mM sucrose octa-acetate, SOA). The SOA solution was held in the mouth for three minutes and then expectorated. Overall, 20% of the subjects reported being strongly nauseated (MNP score > 45) by oral exposure to the bitter stimulus, 45% were mild to moderately nauseated (MNP score 45 to 15), and 35% did not experience any nausea or discomfort (MNP score < 15) (Figure 1A). MNP scores provided by the subjects were not correlated with their perceived bitterness intensity ($r^2 = 0.06$; Figure 1B), nor to their unpleasantness ratings of the solution (also $r^2 = 0.06$; data not shown). Almost all the subjects rated the SOA solution as being very bitter and very unpleasant. Why some people report nausea and others do not to the same nauseogenic stimulus is unknown, but such diversity of nausea responses is ubiquitous. Studies demonstrate there is a genetic component to nausea susceptibility. In addition, anxiety, conditioning, adaptation and tendency to report bodily changes also may underlie individual differences in nausea susceptibility (see [9] for review).

To determine whether the induced nausea was specific to SOA, we tested a different group of subjects (n = 12) with both SOA and a second bitter intensity-matched solution of quinine hydrochloride (also 0.8 mM), a natural alkaloid that is commonly employed as a bitter tasting stimulus. The same proportions of subjects as in the previous study reported being nauseated by SOA and quinine solutions (Figure 1C). Moreover, the nausea ratings in response to SOA and quinine were highly correlated ($r^2 = 0.93$). We also asked a subset of subjects from the first experiment, those who were strongly SOA-nauseated (n = 12) and half of those who were not (n = 11), to perform the same sensory test with a sweet sucrose solution (2.0 M sucrose) that had been intensity matched to SOA (see Supplemental Information). In this case, none of the subjects reported being strongly nauseated by the exposure to the sweet stimulus and 70% reported no discomfort (data not shown). To test further the specificity of bitter taste for nausea induction, we employed another aversive taste stimulus, 1.0 M monosodium glutamate (MSG), which tastes strongly umami and moderately salty and is considered the most unpleasant taste stimulus after bitterness at this high concentration. In contrast to the two bitter stimuli, the nausea ratings of SOA and 1.0 M MSG were uncorrelated ($r^2 = 0.002$; n = 7). Five of seven subjects reported no nausea from MSG and two reported mild to moderate nausea, ratings considerably lower than their responses to SOA (data not shown).

During the sessions, subjects were connected to EGG electrodes. The first 13 minutes of recording established baseline GMA. Afterwards, subjects rinsed, gargled and expectorated either the bitter SOA or the sweet stimulus for three minutes followed by 15 minutes of EGG recording. As a reference for shifts in GMA occurring during the onset of nausea, 13 subjects were exposed to an opto-kinetic drum, painted inside with alternating white and black vertical stripes, that rotated around their head and upper body at 10 rpm while nothing was held in the mouth. The opto-kinetic drum provides a kinetic visual stimulus for the subject and is commonly used in motion sickness research to induce nausea through apparent motion. Among the 13 subjects tested, all except one reported on the MNP being strongly nauseated by the rotating drum. Figure 1D shows the analysis of EGG data obtained during these sessions for all the subjects (mean ± SEM). The values on the graph represent the amount of normal (3 cpm) and dysrhythmic (1–2.5 cpm and 4–9 cpm) gastric activity recorded during the rotation period divided by the amount of gastric activity recorded during the baseline

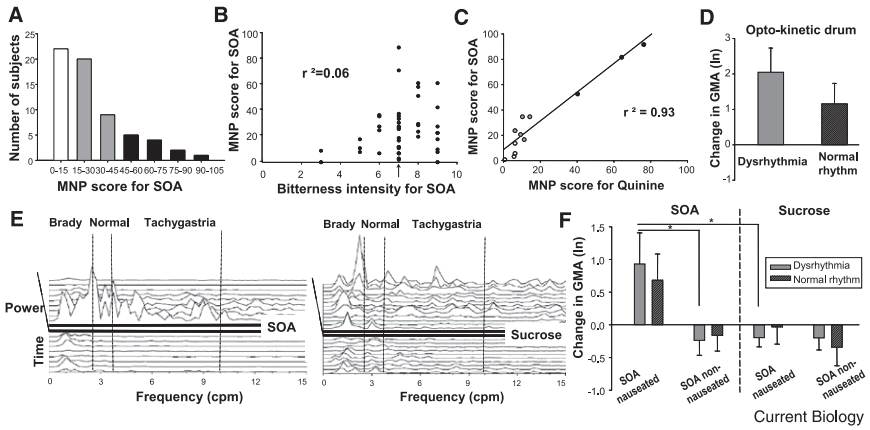

Figure 1. Bitter taste selectively induces nausea and dysrhythmia of gastric myoelectrical activity.
(A) Muth Nausea Profile (MNP) scores of 63 subjects after tasting the bitter stimulus sucrose octa-acetate (SOA). (B) Bitterness intensity ratings (10 point scale) *vs* MNP scores after tasting SOA. Arrow indicates mean bitterness. (C) MNP scores to equi-bitter SOA *vs* quinine-HCl, tested randomly on different days (n = 12). 25% were strongly nauseated by SOA and quinine (black circles), 42% were mildly nauseated (grey circles), and 33% were not nauseated (open circles). (D) The shifts in gastric myoelectrical activity (GMA) are depicted at the onset of nausea, provoked by the potent nauseogenic rotating opto-kinetic drum (n = 13). Change in GMA is shown between the pre-stimulus period (drum not rotating) and the post-stimulus period (drum rotating) in dysrhythmia and normal frequency ranges (mean ± SEM). Values were natural log transformed (zero represents no change). Compare this to the shift observed with bitter taste-induced nausea (Panel F, far left). (E) Representative spectral analyses of EGG signal Fast Fourier transforms, recorded during bitter taste (SOA) exposure in a strongly nauseated subject (MNP > 45) (left) and sweet taste exposure (right). X-axis represents GMA frequency (cycle per minute, cpm), Y-axis represents time (one minute intervals between the lines); bold lines indicate taste exposures), and the Z-axis represents GMA power. The first five minutes of EGG recording after stimulus exposure were analyzed. (F) Shifts in GMA activity, plot as in Panel D, when tasting SOA (left) and sucrose (right) [mean ± SEM]. 23 subjects were tested (12 nauseated by SOA; 11 non-nauseated by SOA). Asterisk: $p < 0.05$.

period (when drum is not rotating). As expected, GMA increased at all frequencies during nausea onset (drum rotation), but most notably in the dysrhythmic range. This establishes the pattern of activity for a potent, stereotypical nauseogenic stimulus against which the pattern of nausea-related activity to SOA should be compared (Figure 1F, lower left).

The EGG data from the taste sessions (see Figure 1E for representative traces) were analyzed similarly. Taste-related EGG data in Figure 1F were segregated into two categories, an SOA nauseated group (n = 12; far left) and an SOA non-nauseated group (n = 11; near left) based on the individual's post-stimulus MNP scores (Figure 1A). The changes in GMA occurring immediately after oral exposure to SOA are similar to the ones induced by the opto-kinetic drum: a marked and significant increase in dysrhythmia occurred, but only in the SOA nauseated group. No changes occurred in the SOA non-nauseated group ($p < 0.05$; Figure 1F, near left panel). If any change to SOA can be observed in this group, there was a slight decrease in the overall level of gastric activity, which also represents the response to oral sucrose exposure in both groups (Figure 1F, right panel).

Hence, exposure to a bitter stimulus in the SOA nauseated group significantly increased their gastric dysrhythmia ($p < 0.05$), whereas a sweet stimulus had no such effect. Therefore, GMA correlates with a subject's nausea self-assessment and confirms that oral exposure to a bitter tasting stimulus can induce nausea in healthy participants. Such a direct link between oral exposure to bitter stimuli and nausea elicitation has not been established previously. We believe this work, complementary to and extending Wicks *et al*. [3], demonstrates that there are, in addition to appetitive anticipatory responses to nutrients preparing the body to digest food and reward its ingestion [10], aversive anticipatory responses that prepare the body to contain, repel, and punish our ingestion of anti-nutrients or toxins.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.cub.2011.02.028.

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References

1. Sharma, K., Sharma, P., Sharma, A., and Singh, G. (2008). Phenylthiocarbamide taste perception and susceptibility to motion sickness: linking higher susceptibility with higher phenylthiocarbamide taste acuity. J. Laryngol. Otol. *122*, 1064–1073.
2. Sipiora, M.L., Murtaugh, M.A., Gregoire, M.B., and Duffy, V.B. (2000). Bitter taste perception and severe vomiting in pregnancy. Physiol. Behav. *69*, 259–267.
3. Wicks, D., Wright, J., Rayment, P., and Spiller, R. (2005). Impact of bitter taste on gastric motility. Eur. J. Gastroenterol. Hepatol. *17*, 961–965.
4. Hao, S., Sternini, C., and Raybould, H.E. (2008). Role of CCK1 and Y2 receptors in activation of hindbrain neurons induced by intragastric administration of bitter taste receptor ligands. Am. J. Physiol. Regul. Integr. Comp. Physiol. *294*, R33–R38.
5. Contreras, R.J., Beckstead, R.M., and Norgren, R. (1982). The central projections of the trigeminal, facial, glossopharyngeal and vagus nerves: an autoradiographic study in the rat. J. Auton. Nerv. Syst. *6*, 303–322.
6. Muth, E.R., Stern, R.M., Thayer, J.F., and Koch, K.L. (1996). Assessment of the multiple dimensions of nausea: the Nausea Profile (NP). J. Psychosom. Res. *40*, 511–520.
7. Koch, K.L., Stern, R.M., Stewart, W.R., and Vasey, M.W. (1989). Gastric emptying and gastric myoelectrical activity in patients with diabetic gastroparesis: effect of long-term domperidone treatment. Am. J. Gastroenterol. *84*, 1069–1075.
8. Stern, R.M., Koch, K.L., Stewart, W.R., and Lindblad, I.M. (1987). Spectral analysis of tachygastria recorded during motion sickness. Gastroenterology *92*, 92–97.
9. Stern, R.M., Koch, K.L.and Andrews, P.L.R. (2011). Nausea as a protective control mechanism with a dynamic threshold. In Nausea: Mechanisms and Management. (New York: Oxford University Press), pp. 29–38.
10. Pavlov, I. (1902). The work of the digestive glands. (London: Charles Griffin), pp. 76–92.

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