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Placebo-Controlled Studies of Human Reaction to Oral Monosodium L-Glutamate

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In 1972 Kenney and Tidball (3) reported an investigation of human susceptibility to monosodium L-glutamate (MSG) administered orally. This study used two samples of tomato juice: one as the vehicle for administering the MSG and the other as a "placebo" in which an equivalent degree of saltiness was obtained by the addition of NaCl. They reported that 32% of the 77 subjects tested at the level of 5 g MSG dissolved in 150 ml of juice reported one or more of the following sensations: warmth or burning, stiffness or tightness, weakness in the limbs, pressure, tingling, headache, light-headedness, or heartburn or gastric discomfort. These subjects were then studied in greater depth. This study led the authors to conclusions summarized as follows:

1. When MSG was administered as a 1.32% solution in 150 ml of tomato juice, reports of symptoms were no more common than after ingesting a seasoned juice containing no MSG.
2. When administered in heavy concentration (3.33%), symptoms were provoked in 32% of the test population.
3. Symptom experience bore no apparent relation to the level of plasma glutamic acid before the ingestion of MSG or to the extent of its rise after the ingestion.
4. With increasing dosage of MSG there was an increasing frequency of reports of sensations of warmth or burning, stiffness or tightness, weakness in the limbs, and tingling.
5. In a limited number of cases tested, no objective correlate of the reported symptom could be discerned.

This present chapter reports two further placebo-controlled trials designed to examine this problem further.

TRIAL A

Fifty-one volunteers were recruited within the Medical Center by the local publication of a notice containing a description of the project objective and procedure used in the form of informed consent.

A schedule of administration of unique sets of three juices from a total of seven samples was prepared in which each set was identified by number. The juices were designated A–G. Of these, C, F, and G were placebo juices consisting of tomato juice with 0.8 g common salt added to each 150 ml. Samples A, B, D, and E contained in 150 ml of tomato juice with 5 g MSG, purchased in the form of Accent. Each set of three juices consisted of one placebo juice and two juices containing MSG. The administration sequences were selected so that placebo juice appeared an equal number of times in each of the three positions. The technician in charge was given the only available copy of the list of juice administrations. On enrolling in the experiment, the procedure was explained to each volunteer and each subject was given three packets of Granola bars (either "Cinnamon" or "Honey and Oats") and three 6-oz cans of either grapefruit or orange juice with the instructions that on each of the test days one packet of bars and one can of juice was to be taken as breakfast as near to 7:00 a.m. as possible. At this time the subjects also signed their consent forms and drew a number assigning their sequence of juices. The technicians kept sole charge of the subject identifications and was unaware of the composition of the juices.

The subjects reported to the laboratory at 10:00 a.m. on their assigned days and were issued the appropriate glass of juice and given a copy of a standard questionnaire. Completed questionnaires were returned at noon. The questionnaires were collected and were read and classified at the completion of the series. The classification system used was as follows:

A questionnaire specifying no unusual sensation was classified as 0.

A questionnaire reporting only headache, thirst, light-headedness, or gastric discomfort was classified as type A.

A questionnaire reporting one or more of the sensations of warmth or burning, stiffness or tightness, weakness in the limbs, or tingling was classified as type B.

A box was provided on the form for the specification of sensations other than those listed. This was seldom used and when used was essentially a paraphrase of one of the listed items, in other words no "new" sensations were reported, save for two reports of tremor and four of difficulty in reading fine print. The questionnaires were then identified with the juice administered on a particular day.

TABLE 1. *Response pattern to test and placebo tomato juice*

	Reaction to placebo		
	0	A	B
Reaction to test juice			
0/0	8	3	1
0/A	3	2	
A/A	2		
0/B	6		1
A/B	3	1	1
B/B	5	6	5

TABLE 2. *Average symptom scores (symptoms/day/subject)*

	Juice sample								
	A	B	C	D	E	F	G	H	I
MSG content	1 g	0	2 g	0	3 g	0	4 g	0	5 g
Reactors (N = 7)	0.36	0.28	0.59	0.43	1.59	0.28	1.71	0.36	2.17
Nonreactors (N = 9)	0.22	0.33	0	0.44	0	0	0.22	0.11	0.34

Although 51 subjects began the study, only 47 completed the series. The reasons for this dropout included a major fracture of a wrist requiring high levels of analgesics, intercurrent illness, and, one suspects, boredom.

Of the 47 subjects completing the series, 24 were men and 23 were women. In Table 1 are recorded the numbers of subjects showing various patterns of reaction classified by reaction types O, A, or B.

Accepting an A-type reaction to placebo juice as a nonspecific observation, two groups can be clearly identified, the 11 subjects (5 males and 6 females) in the upper pair of cells who may be regarded as confirmed *nonreactors* and the 11 subjects (5 males and 6 females) in the lower pair of cells who may be regarded as *confirmed reactors*. These individuals were invited to participate in further studies. Nine nonreactors and 7 reactors completed these studies.

As before, subjects ate the standard breakfast at 7:00 a.m. and reported to the laboratory at 10:00 a.m. The study involved nine attendances, and on each occasion the subject was given 150 ml of either placebo or juice containing MSG in the range of 1 to 5 g. The nine juices administered were designated A through I; their contents were as follows:

A = 1 g MSG
B = 0.8 g NaCl
C = 2 g MSG
D = 0.8 g NaCl
E = 3 g MSG
F = 0.8 g NaCl
G = 4 g MSG
H = 0.8 g NaCl
I = 5 g MSG

On the first attendance of the subject, a number from 1 to 10 was drawn by lot, this number serving to identify the sequence of juices for that subject for the 9 days. Only the technician was aware of which juice a subject received on a particular day. After drinking the juice under supervision, the subject was given a questionnaire to be completed over the course of the following 2 hr.

Before drinking the juice on 2 of the 9 days, each subject was tested for fine tremor of the hand and visual acuity was measured. These tests were repeated on subjects reporting symptoms at the time of symptom experience. The results were negative with respect to both tremor and visual acuity.

The questionnaires were classified on the same basis as in the earlier trial, save that a numerical value of 0.5 was assigned to the type A responses. Type B responses were quantitated in terms of the number of significant symptoms reported. When all questionnaires had been graded, the juice code was broken and mean symptom scores calculated for each juice for the reactor and nonreactor groups (Table 2).

These results essentially confirm the reliability of the two groups and confirm the earlier observation of the relationship in the reactor group between the number of symptoms reported and the quantity of MSG administered.

As a part of this phase of the study, seven reactor subjects in the reactor group and nine subjects in the nonreactor group volunteered to provide blood samples for analysis by Dr. Karl Folkers (University of Texas) for erythrocyte GOT estimation. The subjects reported to the laboratory at or about 10:00 a.m. on each of 3 days. On each occasion 10 to 15 ml blood were drawn by venipuncture and stored in ice prior to shipment to Dr. Folkers. In addition, on 1 of the 3 days a further blood sample was taken and submitted for a standard SMA 12/60 analysis by the Division of Laboratory Medicine. There was excellent coincidence between the groups of the mean values for the basal level of EGOT, SGOT, and all of the standard blood chemistry items save for glucose and LDH. The blood glucose in the reactor subjects was 71 ± 10 mg/dl compared with 81 ± 6 in the nonreactor subjects. The reactors showed a mean LDH value of 188 ± 18 U/liter; the nonreactors, a mean value of 166 ± 10 U/liter. Neither of these differences is statistically significant. This trial appeared to have accomplished the following:

1. Confirmed the existence in a random population of subjects of a group who react reliably and predictably to a heavy dose of MSG and of a group who are reliably symptom free after such a dose.
2. Confirmed previous observations that at the dosage level used 33% of the men and 50% of the women will report symptoms following MSG administration and, further, that reaction to placebo juice will occur in one out of six trials.
3. Confirmed that in the reactor subjects, reports of symptoms appear to be related to the quantity of MSG administered.
4. Failed to demonstrate any tremor or visual change accompanying the reaction.
5. Failed to demonstrate any significant difference in blood chemistry between the two groups.

TRIAL B

At this point, it was felt that elucidation of the action of MSG in producing symptoms called for a closer pursuit of the objective correlates of symptom experience. The series up to this point had been clouded in its analysis by the significant rate of placebo response. It was apparent that the subjects received symptom suggestion by the information provided when their consent to experimentation was obtained and further suggestion was provided by the questionnaire that the subjects had completed. In addition, tomato juice was perhaps not the ideal vehicle of administration. There being no ethical or legal way in which symptom suggestion at the time of informed consent could be avoided, it was decided to avoid reinforcement of the suggestion by questioning each subject after an administration either personally or over the telephone rather than by employing a check-list-type ques-

TABLE 3. *Results of triangle tests*

Test material	Subjective response				
	All different	All the same	Wrongly paired	Correctly paired	Total
Tomato juice	1	4	9	4	18
Soft drink	5	3	12	7	27

tionnaire. Pairs of samples of a soft-drink mix in powder form were made available for use in place of the tomato juice samples. The compositions of each pair are as given below:

Placebo (sample S)	Sample with MSG (sample G)
Sucrose	Sucrose
Citric acid (monohydrate)	Citric acid (monohydrate)
Trisodium-Citrate (2-hydrate)	MSG
Lemon flavor (natural)	Lemon flavor (natural)
Caramel color	Caramel color
Naringin[1]	Naringin[1]

Each pair of samples thus consisted of a placebo sample and a mixture containing 6 g MSG. The materials as supplied to the investigator were identified in a coded fashion so that the trial could be conducted in a double-blind format. The material was prepared for administration by dissolving the powder in precisely 200 ml of cool (15° C) distilled water.

Triangle tests of the soft-drink materials were made by a taste panel. The same panel was used to triangle test the tomato juice samples used in the earlier studies. The outcome of these tests is given in Table 3.

It would appear, therefore, that both vehicles are effective for concealment of MSG, but in the case of tomato juice, one is dealing with a substance the flavor of which is well known to most subjects and any addition, whether it be of salt or of MSG, produces a "spoiled tomato juice" flavor. The soft drink, on the other hand, provides a flavor never previously experienced, and since there exists no expectation of basic flavor, no clue is provided as to the presence of an additive. This material has therefore been used in the latest trial.

Since some months had elapsed from the earlier series of trials, the majority of the previous subject population was dispersed and the study had to be reinitiated. The protocol was further modified from that of the earlier studies by administering the trial solutions to the subjects in a fasting state.

Fifty-seven volunteer subjects were recruited from among Medical Center personnel. Of these, 9 subjects were black, 4 oriental, and 44 white. The age range was

[1] Naringenin-7-rhamnosidio-glycoside: grapefruit bitter principle (natural).

20 to 56 years; 22 were male and 35 female. The subjects read a statement of the purpose and protocol of the trial and, after asking any questions and receiving answers, signed the statement to acknowledge their informed consent to serve as a subject.

At this time each subject was registered with a number and assigned two pairs of samples selected at random from the supply. On each of the first 2 test days, one member of the assigned pair was administered; on the second 2 test days, the remaining assigned pair was used. The subjects reported to the laboratory kitchen in a fasting state within a few minutes of 8:00 a.m. on each test day. They were given their assigned juice and asked to drink it at a leisurely pace and to follow it with a small drink of cool water. This the subjects did in the presence of the investigator and then returned to their normal workplace with the instruction that they were not to eat or drink with the exception that if they experienced a severe thirst they might assuage this with water from the cooler.

An hour (± 10 min) after drinking the juice the subjects whose workplace was within the laboratory building were visited and questioned. Those situated in other buildings were questioned by telephone. The questioning was stereotyped and followed the following plan:

1. What did you think of your juice this morning? Did you find it pleasant or unpleasant?
2. What made it pleasant/unpleasant?
3. Could you describe the taste?
4. What was the aftertaste?
5. How long did the aftertaste last? (At this point check on drinking of water relative to aftertaste.)
6. Did you experience any other sensations? (If the answer here is positive, details of nature, location, and time of onset and offset are sought.)
7. Are you still experiencing any of these sensations? (If the answer is positive, a second contact is made later.)

Answers to the questions were recorded as obtained. When the administration of the trial samples was completed, the decoding document was obtained and the sheets recording the subject's daily responses sorted and classified in terms of referring to an S (placebo) or G (MSG) juice.

Of the 57 subjects in the study, 48 received two pairs of samples and 9, for any one of several reasons, received one pair of samples. S and G juices were each therefore administered on a total of 105 occasions.

The sensations reported are recorded in Table 4. In only a few cases has it been necessary to paraphrase a subject's own terminology, probably because the statement of informed consent had in effect provided a vocabulary of description. Where a subject reported more than one sensation, these have been included in the two or more categories. These sensations clearly fall into two groups. One group of sensations common to exposure to both S and G samples and the other group almost exclusively related to exposure to G samples. The first group coincides with what in the

TABLE 4. *Sensations reported for soft drink*

Description	Frequency of report	
	S sample	G sample
Nausea or heartburn	4	3
Thirst or dryness	8	3
Light-headedness or headache	6	10
Tightness	1	9
Pressure	0	7
Tingling	0	5
Weakness	0	3
Warmth	0	1
Burning	0	2

Omitted from this record are 6 reports of tingling of the tongue that occurred as a regular response to either S or G samples in two subjects.

earlier trial was termed a type A response; the second with the type B response. Experience of type B sensations was confined to 16 of the 57 subjects, a frequency that agrees well with earlier experience. Of these 16 subjects, 15 were female and 1 male. The 15 women include 1 black subject and 1 oriental subject. The response pattern is given in Table 5.

TABLE 5. *Response pattern to soft drink*

	Reaction to S					
	0/0	0/A	0/B	A/A	A/B	B/B
Reaction to G						
0/0	19 (7)	3	(1)			
0/A	4	1		1		
0/B	4	2				
A/A	2			1		
A/B	4					
B/B	6 (2)					

Figures in parentheses refer to individuals who received only one pair of samples.

The loci of the type B sensations are confined to a very sharply defined and restricted part of the body surface, i.e., the face or head, in the shoulders, on the upper arms, or on the upper part of the chest (Fig. 1). The frequency of location of sensation to the various body areas is as given below; where more than one locus was mentioned, all the areas were included in the accounting:

Face or head	19 reports of tightness or pressure
Shoulders	8 reports of warmth, tingling, or tightness

Upper arms	4 reports of tingling or fatigue
Upper chest	4 reports of burning or pressure
Neck	1 report of warmth

Review of the reports in the earlier series confirmed this restricted location of B-type sensation.

The 16 subjects identified in this screening procedure formed the population for further studies. To better define the sensitivity of these individuals, trials were made with pairs of samples, with one sample containing MSG at either the 3- or 1.5-g level. Four subjects were lost to the study at this point, 2 being reluctant to experience further sensations and 2 whose duties made them unavailable. A double-blind trial with the remaining 12 subjects was made at the 3-g level, and 3 subjects, 2 female and 1 male, reported type B sensations. In each case the modality of the sensation and its locus was the same as that experienced at the 6-g level but at a lower perceived intensity in all cases. These 3 subjects were then further tested using the samples containing 1.5 g MSG. Two of these subjects reported mild, brief, transient type B sensations, and the third experienced nothing. It was apparent that these sensations would have gone without notice had not attention been directed to them by prior experience. One of the sensitive subjects reported the following:

6-g level: First experience—"Burning sensation in upper chest and arms—began 15 min after drinking juice—lasted 15 min."

Second experience—"Burning sensation began in chest and upper arms about 15 min after drinking juice—lasted 20 min."

3-g level: "Slight burning sensation in left shoulder off and on for 5 min—started 15 min after juice."

1.5-g level: "Little tingling in shoulders 20 min after drinking juice—lasted 2 min."

Three members of the reactor group who had consistent and well-defined symptoms were studied in some detail during symptom experience. These subjects

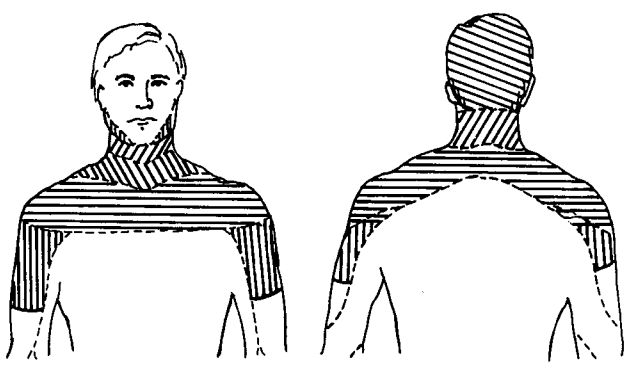

FIG. 1. The hatched areas, together with the face, define the body area in which type B sensations are experienced.

reported to the laboratory on each of 2 days in a fasted state. They were fitted with chest electrodes to record the electrocardiogram, with adhesive surface electrodes to record the electrical activity of muscles or muscle groups where these subjects had previously reported tightness or weakness. Temperature sensors were taped to the body surface in areas where sensations of warmth or burning had been reported. The subjects were seated comfortably in a room with background music, and the transducers were connected via appropriate signal-conditioning devices to a photographic recording galvanometer. The outputs were monitored continuously on a cathode ray tube and photographic hard-copy records taken from time to time. When the subjects were at ease, they were given 200 ml of one or other of a pair of the soft-drink solutions. This administration was double blind. The subjects were asked to volunteer statements about the sensations they experienced. All three reported sensations on the day the G solution (at the 6-g level) was administered. No sensations were experienced in response to an S solution. The sensations reported were warmth, weakness, tightness, and palpitation. In no case were the sensations accompanied by an appropriate objective sign. Blood pressure, monitored frequently throughout, remained stable.

These observations, taken in conjunction with earlier failures to demonstrate objective correlates of symptoms (3), are interpreted as indicative of sensations referred to the body surface from a viscus, rather than peripheral, area. When one compares the areas of the body where type B sensations occur (Fig. 1) to those where esophageal pain is referred (5), one finds a remarkable degree of coincidence. The area for referred esophageal pain "corresponds, as a rule, fairly well with the portion of the esophagus involved." Thus, heartburn, believed to arise by spasm or irritation of the gastroesophageal junction, is felt at the lower end of the sternum. A preferred site for the experience of upper esophageal pain is the midline at the upper sternal border. From here the sensation spreads to involve the face, the head and neck, the upper chest and back, the shoulders, and the upper arms. Those areas outside of the face correspond to the dermatomal distribution of the nerves of the 2nd, 3rd, 4th, and 5th cervical segments. Clinical experience indicates that pain arising in the esophagus is of two varieties: burning and pressure. Major causes of pain arising from the esophagus are spasm of the muscle coats and chemical stimulation of free nerve endings of the mucous surface by the backwashing of the strongly acid gastric juice from the stomach, giving rise to the sensation of heartburn.

If one accepts that tingling or warmth are lesser intensities of burning sensation and that tightness or stiffness may be varieties of pressure sensation, one is driven to the conclusion that the type B response observed on exposure to MSG solutions might be described accurately as a transient esophagalgia.

In order to test this hypothesis, some further experiments were undertaken. Four members of the reactor group who had experienced symptoms at the 6-g (3%) level but had no response at the 3-g (1.5%) level were selected. They were subjected to a double-blind administration of 100 ml solutions, one containing 3 g MSG. These subjects were thus exposed to a total dose of MSG that had previously failed to

provoke symptoms, although the concentration of the material had been effective. Three of the four subjects experienced typical type B sensations.

The two females and one male who reacted at the level of 3 g MSG in the 200 ml of soft drink were given a 3-g dose of MSG in gelatin capsules with the objective of avoiding contact with nerve endings of the oropharynx and esophagus. A placebo control was provided by an equal number of capsules containing lactose. One of the three subjects experienced a typical reaction of burning in the upper chest and shoulders, whereas the two other subjects experienced nothing. The reacting subject was differentiated from the other two in that she reported regular heartburn "after eating her own cooking"; the others denied any experience of this sensation.

In an attempt to further localize the source of the type B sensations, a group of nine subjects, five nonreactors and four reactors used the soft-drink mixtures with or without MSG at the 3% concentration as a mouthwash and gargle, avoiding swallowing the solution. Each was given 100 ml of solution and instructed to spend 3 to 5 min using it. This procedure gave one report of a type B reaction: a reactor subject using a G solution. All other reports were of taste, aftertaste, salivation, or dryness. The possibility that the one reaction arose from the inadvertent swallowing of the solution cannot be excluded.

The experiments of Shaumberg et al. (6) leave no doubt that typical symptoms can be produced by MSG administered intravenously. Furthermore his studies demonstrate the ability of MSG to produce a rather general irritation of free nerve endings. These experiments, however, should not lead one to conclude that the customary production of symptoms relies on an elevated concentration of MSG in the blood since we have demonstrated no relationship between blood levels of glutamic acid and the occurrence of symptoms (3). Comparison may be made with the use of the bitter substance Decholin (dehydrochloric acid) to measure the arm-to-tongue circulation time where injection of Decholin into an arm vein is followed about 15 sec later by the perception of a bitter taste. The latency of the first appearance of sensation after MSG injection (17 to 20 sec) accords well with an arm-to-esophagus transit.

The nerve endings of the esophagus are accessible to an irritant substance in three ways: (a) by direct exposure following swallowing, (b) by reflux of the material back into the esophagus from the stomach, and (c) from the circulation. The latency (usually about 20 min) of the appearance of symptoms following ingestion of MSG has often been tacitly equated with the time needed for absorption. However, such a latency would be quite compatible with gastroesophageal reflux. Furthermore, tests of esophageal irritability undertaken to differentiate esophageal pain from angina pectoris (1) demonstrate that the development of sensation is dependent on two factors: (a) the concentration of the irritant material and (b) the length of time that the material is present at the esophageal mucosa. A lapse of 15 to 30 min from the start of superfusion of the esophagus with 0.1 N HCl and the appearance of pain is not uncommon (1).

From the perspective, therefore, of dietary exposure to MSG, the following conditions would predispose to the appearance of symptoms:

1. Ingestion of a solution with a high concentration of MSG. (Experience indicates that for the vast majority of individuals the threshold concentration is in excess of 1.5%.)
2. A lack of a good flow of saliva to dilute and wash away the agent.
3. A tendency to experience gastroesphageal reflux.

CONCLUSIONS

These three studies, the one cited (3) and the two reported here, are consistent in demonstrating that large doses, or high concentrations, of MSG will provoke a variety of sensations in approximately 33% of a test population. However, the new soft-drink vehicle has provided a better definition to the problem by sharply defining the MSG-attributable symptoms. It is now possible to say with confidence that with concentrations of MSG of the order of 0.75%, it is extremely unlikely that any of the symptoms will be experienced by even a demonstrably sensitive individual. Furthermore, at a level of 1.5%, only a few individuals will be affected.

Type A sensations, evoked by G and S samples with equal frequency, are of common experience (4) and indeed might be expected when a fasting subject drinks a solution of high carbohydrate and significant sodium content.

Type B sensations arise from the upper part of the esophagus where high concentrations of MSG appear to be a specific or nonspecific irritant.

It is interesting that although the anecdotal literature of the Chinese restaurant syndrome contains reports of individuals who believed themselves to be suffering cardiac pain (2) and sought attention for this condition, no mention is to be found of the differential diagnosis (1) of esophagalgia being considered.

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