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STEFFENS, AB; LEUVENINK, H; SCHEURINK, AJW

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Effects of Monosodium Glutamate (Umami Taste) With and Without Guanosine 5′-Monophosphate on Rat Autonomic Responses to Meals

ANTON B. STEFFENS, HENRI LEUVENINK AND ANTON J. W. SCHEURINK

Department of Animal Physiology, University of Groningen, PO Box 14, 9750 AA Haren, The Netherlands

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STEFFENS, A. B., H. LEUVENINK AND A. J. W. SCHEURINK. Effects of monosodium glutamate (umami taste) with and without guanosine 5′-monophosphate on rat autonomic responses to meals. PHYSIOL BEHAV 56(1) 59–63, 1994.—Monosodium glutamate (MSG) is used as a food additive to improve the taste of food. The effect of MSG on sweet taste is enhanced by guanosine 5′-monophosphate (GMP). Because increased palatability is known to increase the vagally mediated preabsorptive insulin response (PIR), we hypothesized that MSG and GMP will enhance the PIR. To study this, male Wistar rats were provided with permanent cannulas for venous blood sampling and intragastric drug administration. The MSG and GMP were either added to a test meal or infused into the stomach during a test meal. Blood samples were taken to measure concentrations of glucose, insulin, epinephrine (E), and norepinephrine (NE). Addition of 56 mg MSG to a control meal markedly reduced both phases of the meal-induced increase in plasma insulin and had no effects on blood glucose and plasma E and NE responses. Infusion of 56 mg MSG into the stomach at the onset of food intake reduced the PIR with no effect on glucose, E, NE, or the second phase insulin release. Addition of 2 mg MSG in combination with GMP to the test meal or gastric administration of these drugs did not affect the changes in any of the blood components measured. It is concluded that addition of a high dose of MSG to a test meal leads to a reduction in the vagal response to food.

MONOSODIUM glutamate (MSG) Guanosine 5′-monophosphate Autonomic nervous system Glucose Norepinephrine Epinephrine Preabsorptive insulin response

MONOSODIUM glutamate (MSG) is widely used as a food additive to improve the taste of food (umami in Japanese). It potentiates the activity of gustatory nerves (10,11), in particular those nerves that mediate sweet taste (7,19). The effect of MSG is attributed to the presence of the sodium ion, although the glutamate ion by itself can also intensify the activity of gustatory nerves (19). The effect of MSG on sweet taste is enhanced by guanosine 5′-monophosphate (GMP), a compound that is generally present in food (7).

The taste of food evokes the so-called preabsorptive insulin response (PIR). The PIR is defined as the increase in insulin release that occurs in the first minute after the start of a meal before any increase in blood nutrient level can be observed (1,3,18). Increased palatability (a better taste) leads to an increased PIR (4). The PIR is considered a vagally mediated oropharyngeal reflex because it is completely absent when food is infused directly into the stomach (17), or when vagal input into the pancreas is destroyed (16,18).

It is tenable that gustatory neurons, and particularly those mediating sweet taste, contribute to the afferent pathway of this vagally mediated oropharyngeal reflex. This idea is supported by the following evidence. First, electrophysiological data show that glucose applied to the tongue of anesthetized rats increases the activity in the vagal nerves innervating the pancreas (6). Secondly, administration of MSG on the tongue of anesthetized rats leads to increased activity in pancreatic vagal nerves (6). Finally, application of 1 ml of a 0.15 M MSG solution on the tongue of a freely moving rat elicited an increase in plasma insulin levels (6).

From the above-mentioned data, it may be hypothesized that food additives that improve the taste of food, such as MSG and GMP, will also enhance the vagal reflexes that are normally seen during a meal. The aim of the present study was to investigate this phenomenon by studying the effects of MSG and GMP on the size of the PIR during a meal. The food additives were either added to the test meal or infused into the stomach during a test meal to establish the contribution of gustatory neurons in the mouth to the hypothesized effect of MSG and GMP. Because we recently observed that food intake is also accompanied by enhanced activity of the sympathetic nervous system (15), we also measured the effect of MSG and GMP on sympathoadrenal responses (reflected by plasma levels of norepi-
nephrine and epinephrine) to the test meal in all the experiments.

METHOD

Animals and Housing

Male Wistar rats weighing 300–320 g at the beginning of the experiments were used. They were housed individually in Plexiglas cages (25 × 25 × 30 cm) at room temperature (20 ± 2°C) and had continuous access to food (Hope Farms rat chow) and water, unless otherwise stated. The rats were maintained on a 12:12 h light:dark cycle (0700–1900 h) and they were handled and weighed every day at 0900 h.

Surgery

Surgery was performed under halothane anesthesia. All animals were provided with a silicon catheter for blood sampling inserted into the heart through the jugular vein and externalized on the top of the skull according to the techniques described earlier (13). The animals were also provided with a permanent intragastric catheter (i.d. 0.8 mm, o.d. 1.4 mm) inserted into the antrum wall of the stomach for stress-free intragastric administration of drugs (17). One week of recovery was allowed between subsequent surgeries. The experiments started as soon as the rat returned to preoperative body weight.

Blood Sampling Procedure and Chemical Determination

Forty minutes before the start of an experiment the rats were connected with two polyethylene tubings (in mm: 400 length, 1.25 o.d., 0.75 i.d.). One tubing was connected to the stomach cannula for intragastric administration of MSG, GMP, or saline, and the other was connected to the heart cannula from which blood was sampled as described previously (12). During the whole experiment, nine blood samples of 0.4 ml were withdrawn for determination of blood glucose, plasma norepinephrine (NE), epinephrine (E), and insulin concentrations. After each sample, a transfusion of 0.4 ml of heparinized donor blood was given to avoid diminution of the blood volume with related changes in hemodynamics. Donor blood was obtained from undisturbed rats with permanent heart catheters.

Blood samples were immediately transferred to chilled (0°C) centrifuge tubes containing 0.01% EDTA as an antioxidant and 10 μl heparin solution (500 U/ml) as an anticoagulant. Blood glucose was measured by the ferricyanide method of Hoffman (Technical autoanalyzer TMII) with 0.05 ml blood taken from the 0.4-ml sample. The remaining 0.35 ml blood was centrifuged for 15 min at 5000 revolutions/min and 4°C. A part (100 μl) of the supernatant was immediately stored at −80°C for the catecholamine measurements. The remaining part (about 75 μl) was immediately stored at −30°C for the insulin assay. Rat-specific plasma immunoreactive insulin was determined by means of a radioimmunoassay kit (NOVO, Denmark). Guinea pig serum M8309 served as antiserum. Duplicate assays were performed in 25-μl samples. The bound and free 125I-labeled insulin were separated by means of a polyethylene glycol solution (23.75% w/w) as suggested by Henquin et al. (2).

Determination of plasma catecholamine concentrations was performed by high pressure liquid chromatography in combination with electrochemical detection (HPLC-ECD) as previously described (9), with minor modifications. The HPLC-ECD system included an LKB 2150 pump (LKB Instruments, Bromma, Sweden), a Rheodyne injection valve with a 50-μl loop, two reversed-phase chromosphere C18 cartridge columns in connections (Chrompack, The Netherlands), held at 30°C by a column stove (LKB), an ESA 5100 A electrochemical detector with a 5011 high-sensitive analytical cell and a 5020 guard cell (ESA, Kipp, The Netherlands), and a BD 41 two-channel flat recorder (Kipp). Guard cell potential in front of the injection valve was +450 mV, and the potentials of the working electrodes were -50 and +350 mV, respectively. The mobile phase contained 0.05 M sodium acetate, 0.08% 1-heptanesulfonic acid, 0.01% EDTA, 0.01% NaCl, and 5% methanol−95% H2O (pH 4.75). Absolute detection levels for E and NE in plasma were 0.010 and 0.005 ng/ml, respectively.

Experimental Procedure

The animals were trained to ingest (within 2 min) a test meal consisting of 1 g of ground chow and 1 ml of water. During the training sessions food was removed at 0900 h. At 1030 h a dish with the test meal was offered. After a few sessions, most animals consumed the test meal within 2 min. Those animals participated in the experiments. The rats were also accustomed to be connected to the blood sampling and stomach infusion tubes, and they were accustomed to blood sampling during a test meal. On an experimental day, food was removed at 0900 h and the animals were connected to the blood sampling and stomach infusion tubings. All experiments were performed between 1030 and 1130 h. The experimental animals were subjected in random order to the following experiments:

1. test meal without additives (control meal),

<table>
<thead>
<tr>
<th>Meal additives</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (μU/ml)</th>
<th>NE (pg/ml)</th>
<th>E (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Exp. 1)</td>
<td>99 ± 1.8</td>
<td>33 ± 2.9</td>
<td>267 ± 33</td>
<td>36 ± 10</td>
</tr>
<tr>
<td>MSG (Exp. 2)</td>
<td>96 ± 3.7</td>
<td>30 ± 3.5</td>
<td>326 ± 33</td>
<td>23 ± 11</td>
</tr>
<tr>
<td>MSG + GMP (Exp. 3)</td>
<td>98 ± 2.7</td>
<td>30 ± 3.2</td>
<td>236 ± 31</td>
<td>12 ± 5</td>
</tr>
</tbody>
</table>

Stomach infusion

<table>
<thead>
<tr>
<th>Stomach infusion</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (μU/ml)</th>
<th>NE (pg/ml)</th>
<th>E (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Exp. 4)</td>
<td>103 ± 2.1</td>
<td>30 ± 1.9</td>
<td>217 ± 17</td>
<td>21 ± 9</td>
</tr>
<tr>
<td>MSG (Exp. 5)</td>
<td>98 ± 3.8</td>
<td>29 ± 4.2</td>
<td>247 ± 35</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>MSG + GMP (Exp. 6)</td>
<td>103 ± 3.7</td>
<td>35 ± 5.4</td>
<td>232 ± 25</td>
<td>30 ± 8</td>
</tr>
</tbody>
</table>

Values are mean ± SE; n = 8 rats for all groups.

![Table 1](image-url)
treatments and the control experiment were determined by applying multivariate analysis of variance (MANOVA of SPSSPC+) and a post hoc t-test. Significance was set at \( p < 0.05 \).

RESULTS

Baseline levels for blood glucose, plasma insulin, NE, and E as measured at \( t = -1 \) min are presented in Table 1. No differences in baseline levels could be observed for any of the blood components measured.

Figure 1 presents the data from the control experiment (Exp. 1) vs. the effects of the addition of 56 mg MSG to the test meal (Exp. 2) on the changes in blood glucose, plasma insulin, E, and NE levels during and after the ingestion of the test meal. In the control experiment, blood glucose gradually increased after the test meal from baseline levels of 102.6 ± 2.1 to a maximum of 108.4 ± 2.8 at \( t = 17 \) min. The increase of blood glucose was significant at \( t = 17 \) min. Plasma insulin increased immediately after the onset of eating from a baseline value of 33 ± 8 μU/ml to a first peak value of 49 ± 6 μU/ml at \( t = 3 \) min. Thereafter, a relative decline occurred to a level of 40 ± 7 μU/ml at \( t = 7 \) min, after which plasma levels of insulin gradually increased to-

FIG. 1. Blood glucose and plasma insulin, epinephrine, and norepinephrine levels ± SE (in mg/dl, μU/ml, and pg/ml, respectively) in rats (n = 8) eating either a test meal without additives (○) or a test meal containing 56 mg monosodium glutamate (●). Start of meal is at time point 0.

2. test meal including 56 mg MSG,
3. test meal including 2 mg MSG and 5 mg GMP,
4. control meal combined with simultaneous intragastric injection of saline (1 ml),
5. control meal combined with simultaneous intragastric injection of 56 mg MSG in 1 ml saline,
6. control meal combined with simultaneous intragastric injection 2 mg MSG and 5 mg GMP in 1 ml saline.

Eight animals participated in all the experiments. The amounts of MSG and GMP were chosen to obtain the right umami flavor as suggested by Mori et al. (5). The start of food ingestion was designated time point \( t = 0 \) min. Tepid (38°C) intragastric injections of MSG, GMP, or saline were given at \( t = 0 \) min and lasted no longer than 50 s. Before, during, and after the test meal, blood samples of 0.4 ml were taken at \( t = -10, -1, 1, 3, 5, 7, 12, 17, \) and 25 min.

Data Analysis and Statistics

Data were expressed as averages ± SE. The paired t-test was used to compare the levels of the blood components relative to the baseline level at \( t = -1 \) min. Differences between the various

FIG. 2. Blood glucose and plasma insulin, epinephrine, and norepinephrine levels ± SE (in mg/dl, μU/ml, and pg/ml, respectively) in rats (n = 8) eating either a test meal without additives (○) or a test meal containing 2 mg monosodium glutamate and 5 mg guanosine 5'-monophosphate (●). Start of meal is at time point 0.
Meal ingestion, or more specifically, the taste of food, leads to a rapid increase in plasma insulin concentrations before any change in blood nutrient levels can be observed (1,3,18). This increase in insulin is called the PIR. In the present experiments, a PIR could be observed in all control experiments as well as in the experiments in which GMP and a low dose of MSG were added to the food or infused into the stomach at the onset of a meal. Infusion of the high dose of MSG into the stomach completely prevented the occurrence of the PIR, with no changes in second phase insulin levels. The addition of the high dose of MSG to the test meal markedly reduced the total insulin response to the meal (both PIR and second phase insulin release).

The observed effects of MSG are somewhat surprising. Monosodium glutamate is widely used as a food additive to improve the taste of food. Increased palatability (a better taste) is supposed to lead to an increased PIR (4). Recently, Niijima et al. (6) showed that MSG by itself also has a stimulatory effect on the PIR. Therefore, we hypothesized that addition of MSG to the test meal would lead to an enhanced PIR in the present study. In
the present study, the opposite effect, that is, a decreased insulin response, could be observed after administration of MSG. This suggests that the vagal response to the meal was reduced by the dose of MSG used. The slightly enhanced plasma NE levels seem to confirm this inhibitory action of MSG on vagal activity (vagal activation inhibits norepinephrine outflow presynaptically). The MSG-induced reduction of insulin release is not accompanied by an increased release of blood glucose concentrations. Taken together, these data suggest that the addition of the high dose of MSG to the food leads to a general reduction in vagal activity, resulting in a decreased insulin response, increased sympathetic activity (reflected by the somewhat enhanced NE levels), and reduced gastric motility (leading to a delayed uptake of glucose into the blood, which might explain the normal glucose levels despite a reduced insulin response). This effect of MSG seems to be mediated mainly by oropharyngeally afferents because gastric administration of MSG was much less effective than addition of MSG to the food. However, the reduction of the PIR after gastric administration of MSG reveals that a possible role of gastric afferents cannot be excluded completely.

In conclusion, the data of the present study reveal that addition of a high dose of MSG to a test meal leads to a reduction in the vagal response to food. This finding is in contradiction to the expected potentiation of the PIR that is normally seen when palatability of food is enhanced. A lower dose of MSG combined with GMP (which is supposed to potentiate the action of MSG on gustatory afferents) did not affect any of the meal-induced changes of the blood components measured.

ACKNOWLEDGEMENT

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REFERENCES