Pharmacology Biochemistry and Behavior, Vol. 43, pp. 881–886, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Central Effects of Monosodium Glutamate on Feeding Behavior in Adult Long-Evans Rats

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Received 10 February 1992

STRICKER-KRONGRAD, A., B. BECK, J. P. NICOLAS AND C. BURLET. *Central effects of monosodium glutamate on feeding behavior in adult Long-Evans rats.* PHARMACOL BIOCHEM BEHAV 43(3) 881–886, 1992.—Monosodium glutamate (MSG) is known as a neurotoxic molecule when injected neonatally in rats, where it produces a marked decrease in food intake and an increase in adipose tissue mass. But, in adult rats subcutaneous injections of MSG produce a small, dose-dependent increase in food intake. It is not known if this action is centrally or systemically mediated. Therefore, the feeding pattern of adult rats injected intracerebroventricularly with MSG was measured. Seven days after installation of a cannula in the right lateral ventricle, rats were injected either with artificial cerebrospinal fluid or twice with 3 mg/brain MSG within a 3-day interval. The feeding pattern was recorded via a complete computerized system during 24 h. Feeding behavior was significantly modified by MSG treatments. These effects were observed immediately after drug injections, that is, upon the first meal, as well as during the 24 h that followed. For the first meal, modifications in meal size (+285%; p = 0.0001), meal duration (×10; p = 0.0005), postmeal interval (×4; p = 0.0005), and the satiety ratio (−50%; p = 0.01) were observed. During the 24-h postinjection period, modifications in meal number (−3; p = 0.0007), total amount of food eaten (+21%,; p = 0.007), time spent eating (+40%; p = 0.007), meal duration (+53%; p = 0.005), and meal size (+44%; p = 0.01) were noted. When the two MSG injections were compared, differences were also noted. For the first meal, postmeal interval (−50%; $p < 0.005$) and satiety ratio (−50%; $p < 0.005$) were decreased after the second injection. During the 24-h postinjection period, meal duration (−50%; $p < 0.05$) and time spent to eat (−25%; $p < 0.05$) were also decreased. This study showed that MSG must be considered a potent stimulant of food intake when administered through a central route. This effect was more powerful than that observed with systemic MSG injection, even at several thousand-fold smaller doses. This stimulation of food intake might be mediated by the stimulatory effect of MSG on release of neuromodulators present in the circumventricular nuclei such as the arcuate nucleus. A small neurotoxic action of MSG is possible when the injections are repeated.

Monosodium glutamate Brain Feeding behavior Hyperphagia Neurotoxicity Adult rat

MONOSODIUM glutamate (MSG), a well-known food additive, promotes neural and behavioral disturbances after ingestion in mice (24,28). In humans, it produces the well-known "Chinese restaurant syndrome."

Neonatal subcutaneous treatment with MSG results in profound disturbances in endocrinology (2,17,25,36,42), neuroanatomy (2,24,39), neurochemistry (10–12, 28), and metabolism (6,20,26) of rodents. Endocrinologic disturbances are characterized by depletion in growth hormone and prolactin (2,16,29,42), inducing growth stunting and sexual dysfunction. Neuroanatomic disturbances are characterized by neuronal loss localized in the circumventricular organs (9,24, 27,28,30,32), such as the area postrema (32), arcuate nucleus, and median eminence (39). These anatomic modifications have important effects on the neuropeptides and neurotransmitters present in these areas. A general loss of these neuromodulators is observed in the mediobasal hypothalamus (12,13,25,28,40). Growth hormone-releasing factor and neuropeptide Y completely disappears in the hypothalamus (13,28). A loss of neuropeptide Y fibers originating from the arcuate nucleus is noted in the paraventricular nucleus (21). Tyrosine hydroxylase and glutamic acid decarboxylase are decreased in the arcuate nucleus (28). Finally, dopamine but not serotonin levels are reduced (25). These modifications are associated in adulthood with metabolic and behavioral disturbances. Plasma corticosterone levels (25) are high, and glucose sensibility is modified (26). Adult rats are also obese and hyperactive and their feeding behavior is disturbed. The modifications of the latter include a decrease of food intake (11) and a preference for carbohydrates (19), but the regulation of day-night feeding patterns is not altered (11).

Subcutaneous treatment with MSG in adults rats results in less significant damage to the circumventricular organs (27, 31). It shares common features with neonatal treatment such as degeneration of tyrosine hydroxylase-immunoreactive neurons in the area postrema (33). But, contrary to the latter it

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induces a dose-dependent increase in food intake (35,37). Lesion of the area postrema, a region implicated in emetic and dietary controls (7), blocks intraperitoneal MSG stimulation of food intake (38).

MSG does not cross the blood-brain barrier (31). Differences of MSG action between the neonate and adult rat might be related to the immaturity of the neonate blood-brain barrier and therefore to its neurotoxic effects. In the adult rat, the mechanism is unknown but we supposed that it may only act at circumventricular levels (34). So, we investigated the central effects of MSG injections on feeding behavior in the normal adult rat. If MSG is really implicated in feeding behavior via central sites of action, we hypothesized that a central route of drug administration might reproduce the effects of systemic drug injection at a higher level of efficacy.

METHOD

Experimental Animals

Ten male Long-Evans rats (Ets Janvier, Le Genest-Saint-Isle, France) weighing 280.0 ± 3.4 g were housed in single wire cages with food and water ad lib in an air-conditioned room with a 12 L : 12 D cycle. They were fed a well-balanced diet supplying 54% of energy from carbohydrate and 30% from fat (2). The diet was mixed with water [40/50 (w/w)] to obtain a paste usable in our automatic feeding system.

Surgery and Pharmacological Treatments

After 1 week of habituation, all rats were anesthetized with 130 mg/kg IP chlorhydrate ketamine (Ketalar, Parke-Davis, Detroit, MI) and implanted with a 27-g stainless steel needle (10 mm length) aimed in the right lateral ventricle. The needle was secured on the skull surface with jeweler's screws and dental cement. A stainless steel stylet was used to occlude the cannula during surgical recovery and between injections. One week after surgery, rats were injected with the control solution (artificial cerebrospinal fluid corrected for osmolality with NaCl 0.9%) with a 33-g stainless steel needle (11 mm length) connected to a Harvard syringe pump (Harvard Apparatus, South Natick, MA) via 20 cm of catheter tubing. Injections were made under a controlled light ether anesthesia that did not exceed 5 min. After injections, animals were replaced in the feeding apparatus for behavioral measurement. Three days later, rats were injected intracerebroventricularly with 3 mg/brain MSG (Sigma Chemical Co., La Verpillière, France) diluted in artificial cerebrospinal fluid with the same method. A second identical injection of MSG was performed 3 days later. Volume of intracerebroventricular injections were fixed to 5 μl/brain.

Behavioral Record

Each cage included a complete automatic feeding system with food delivery under the animal's control. Each feeding system was coupled to an Apple IIe computer. The computer system was adapted to hardware described earlier (14). Briefly, a plastic syringe including the pastry diet is connected to infrared light diodes that control its delivery with a step-to-step motor. Data from the feeding system are registered in the computer for treatment and analysis in a second step. Behavioral recording was performed during a period of 24 h following the three injections. Before the first injection, an intraanimal reliability calculation was performed a minimum of three times 24 h to ensure that animals were well adapted to the feeding system.

Design and Analysis

A meal was defined as the ingestion of a minimum of 1.2 g of the pastry diet followed by at least 10 min during which no feeding occurred. The following dependent variables and derived measures were evaluated for short- and long-term analysis. The short-term analysis consisted of the study of the first meal that occurred after drug or control injections. In this case, meal size (g), meal duration (seconds), local eating rate (g consumed during the meal/duration of that meal), postmeal interval (min), and satiety ratio (postmeal interval/meal size) were calculated for each animal. The long-term analysis was performed on the values registered during the entire 24-h period. In this case, meal number, meal size, total amount of food eaten (g), meal duration, eating rate, meal intervals (min), and time spent eating (min) were calculated as the mean of each variable for each animal.

Statistical Analyses

All analyses were conducted following dependent- or repeated-measures experimental design. Gaussian-distributed variables were analyzed with Fischer's two-way analysis of variance (ANOVA) for repeated measures and compared with Student's paired *t*-test. In the case of non-Gaussian variables (i.e., discrete values) or unequal variances, they were analyzed with Friedman's two-way ANOVA for dependent variables and compared with paired Wilcoxon's *t*-test. Only probability values less than 0.05 (two tailed) were taken into account. Drug × order interaction variance was avoided by the use of the same dose in the two injections, allowing direct comparisons between the two MSG treatments. This was done to examine possible toxic properties of the first injection. Nondiscrete variables are presented as mean corrected by SEM. Discrete variables are presented as median.

RESULTS

Profiles of food intake for one individual for the three injections are shown in Fig. 1. From this figure, it is obvious that MSG has strong effects on food intake. This was confirmed by the integration and analysis of these data for the entire group.

Effects on First Meal

Short-term effects of monosodium glutamate on feeding behavior are shown in Table 1. The two MSG injections produced profound modifications in meal size, $F(2, 27) = 26.33$, $p = 0.0001$, meal duration, $\chi^2(2, 27) = 15.2$, $p = 0.0005$, postmeal interval, $\chi^2(2, 27) = 15.2$, $p = 0.0005$, and satiety ratio, $F(2, 27) = 6.07$, $p = 0.01$, when compared to the control injection. No modifications were found for the local eating rate, $F(2, 27) = 1.2$, $p = 0.30$. When compared to the control injection, the first MSG injection produced a large increase in meal size (+285%; $p < 0.005$). This increase was associated with an important augmentation in meal duration, which was 10 times larger than after control injection ($p < 0.005$). On the other hand, the local eating rate was not modified by the treatment. Consequently to the supranormal duration of the meal, the postmeal interval was four times longer ($p < 0.005$). According to the augmentation of the postmeal interval, the satiety ratio was not modified for this injection.

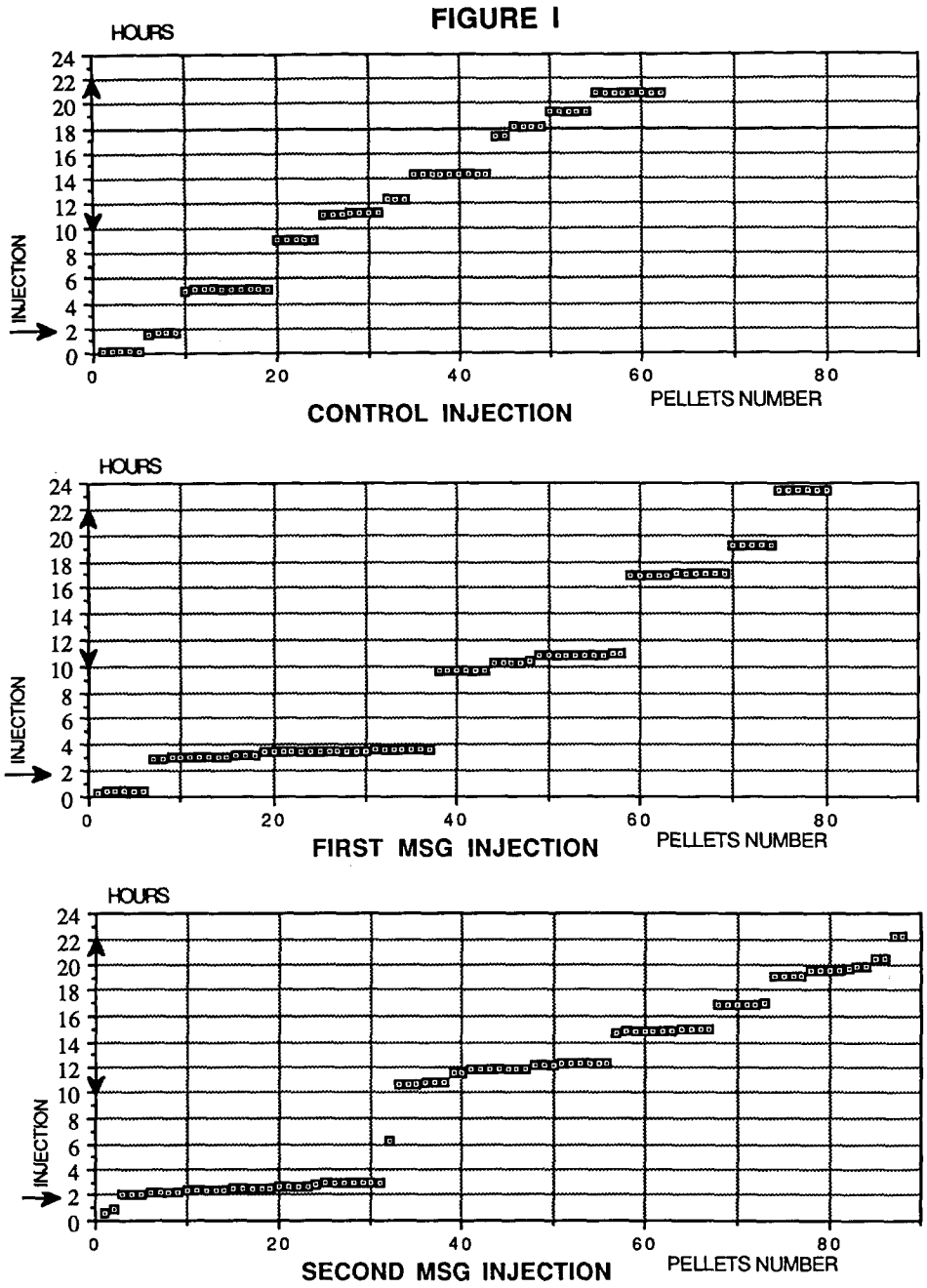

FIG. 1. Individual records for the same rat of feeding behavior following cerebrospinal fluid or MSG injections. Top: control injection. Middle: first MSG injection. Bottom: Second MSG injection. Time scale between arrows indicates the dark period. Each plot represents the intake of a pellet at a given time of the 24-h period. Groups of plots represent a meal in its duration and size.

When compared to the control injection, the second MSG injection produced approximately the same effects on feeding behavior. An 224% increase in meal size was noted ($p < 0.005$), as well as an eightfold increase in meal duration ($p < 0.005$). Local eating rate and postmeal interval were not modified. Surprisingly, a marked diminution was observed for the satiety ratio (-50%; $p < 0.05$). When the second MSG injection was compared to the first, a diminution of the postmeal interval was noted (-50%; $p < 0.005$). No effect was observed for meal size and consequently a diminution of the satiety ratio was observed (-50%; $p < 0.005$).

Twenty-Four-Hour Effects

Long-term effects of MSG on feeding behavior are shown in Table 2. The two MSG injections produced modifications

TABLE 1

EFFECTS OF ICV MSG INJECTIONS (3 mg/BRAIN) ON THE FIRST MEAL

Variables	CSF	MSG	
		First Injection	Second Injection
Meal size (g)	2.7 ± 0.3	10.4 ± 1.0*	8.76 ± 1.0*
Meal duration (min)	3.32 ± 0.25	28.93 ± 5.48*	26.67 ± 5.63*
Local eating rate (g/min)	0.81 ± 0.06	0.54 ± 0.13	0.70 ± 0.17
Postmeal interval (min)	83 ± 11	313 ± 40*	158 ± 37†
Satiety ratio (min/g)* 100	2.2 ± 0.2	2.0 ± 0.1	1.2 ± 0.2†‡

Values represent mean ± SEM. CSF, cerebrospinal fluid.
*$p < 0.005$ vs. corresponding CSF control injection.
†$p < 0.005$ vs. first MSG injection.
‡$p < 0.05$ vs. corresponding CSF control injection.

in meal number, $\chi^2(2, 27) = 14.6$, $p = 0.0007$, total amount of food eaten, $F(2, 27) = 6.52$, $p = 0.007$, time spent eating, $F(2, 27) = 6.69$, $p = 0.007$, meal duration, $\chi^2(2, 27) = 10.4$, $p = 0.005$, and meal size, $F(2, 27) = 5.54$, $p = 0.01$, when compared to the control injection. No modifications were found for meal intervals, $F(2, 27) = 2.24$, $p = 0.13$, and local eating rate, $F(2, 27) = 1.07$, $p = 0.58$. When compared to the control injection, the first MSG injection produced a diminution in the number of meals (three meals less; $p < 0.01$). Meal size was augmented by 44% ($p < 0.01$). Consequently, the total amount of food eaten was 30% greater ($p < 0.005$). Meal duration was multiplied by two ($p < 0.005$) and time spent eating by 1.5 ($p < 0.005$). No modifications were found for meal intervals and local eating rate. When compared to the control injection, the second MSG injection produced a diminution in the number of meals (one meal less; $p < 0.05$). No modifications were found for meal size, meal duration, total amount of food eaten, meal interval, time spent eating, and local eating rate. When the second MSG injection was compared to the first, an augmentation in the number of meal was observed (two meals more; $p < 0.05$). Diminutions in meal duration (−50%; $p < 0.05$) and time spent eating (−25%; $p < 0.05$) were noted. No modifications in meal intervals, meal size, and local eating rate were found. Diminution of the total amount of food eaten was not significant ($p = 0.07$).

DISCUSSION

In this experiment, we have shown that after central injection MSG produced a drastic increase in food intake that lasted 24 h. This effect on food intake was quite similar to that observed after systemic injections at doses of 6 g/kg, but in our study we used a several thousand-fold smaller dose than those used for systemic route of injection (35,37,38). Intrahypothalamic injections of large doses of glutamic acid have also induced a mild increase in food intake in the satiated sheep (41).

The effects of MSG injection were rapid and appeared upon the first meal that occurred after drug injection as increasing meal size and meal duration. Meal regulation was conserved after drug treatment as postmeal interval was increased in relation with meal size, as shown by the absence of effect on satiety ratio. Interinjection comparisons showed that the second MSG injection, made at the same dose, produced a different pattern of response. All values are intermediate between the control and first MSG injection values. At the same time, postmeal interval was not different from the control value and the satiety ratio was decreased.

TABLE 2

EFFECTS OF ICV MSG INJECTIONS (3 mg/BRAIN) ON 24-h FEEDING BEHAVIOR

Variables	CSF	MSG	
		First Injection	Second Injection
Meal intervals (min)	110 ± 7	148 ± 26	116 ± 9
Meal number (discrete values)	9	6*	8†‡
Meal size (g)	2.9 ± 0.2	4.2 ± 0.3*	3.2 ± 0.2
Total amount of food eaten (g)	23.6 ± 1.8	30.0 ± 1.8§	24.8 ± 2.3
Meal duration (seconds)	267 ± 27	579 ± 50§	380 ± 50‡
Time spent eating (min)	40 ± 3	66 ± 5§	52 ± 7‡
Local eating rate (g/min)	0.80 ± 0.11	0.99 ± 0.10	1.04 ± 0.08

Values represent mean ± SEM or median (discrete values). CSF, cerebrospinal fluid.
*$p < 0.01$ vs. corresponding CSF control injection.
†$p < 0.05$ vs. corresponding CSF control injection.
‡$p < 0.05$ vs. first MSG injection.
§$p < 0.005$ vs. corresponding CSF control injection.

During the 24 h that followed the injection, the increase in total amount of food eaten was associated with a decrease in meal number. During this period, meal size and meal duration were always greater, as shown by the total time spent eating. Interinjection comparisons showed that all values for the second MSG injection were intermediate between control and first MSG injections and reached statistical significance for time spent eating, meal number, and meal duration.

The intracerebroventricular action of MSG showed that it might act in areas close to cerebral ventricles. As neonatal treatment with MSG is characterized by neuronal loss localized in the circumventricular organs (9,24,27,30,39), central MSG actions on feeding behavior might go through one of these organs. As postulated by some authors (9,32,37,38), the area postrema or the arcuate nucleus might be one of them. It can be speculated that MSG stimulates food intake by an excitatory action on glutamate-sensitive neurons in these organs, as it has been postulated that these neurons might be implicated in the glucoprivic control of feeding (37). In addition, neonatal systemic treatment with MSG is associated with modifications of glucose sensitivity (26) and elevated plasma glucose levels (25) and paired with hypophagia (11). In our experiment, the diminutions of the satiety ratio and postmeal interval that occurred after the first meal for the second MSG injection might reflect a dysregulation possibly induced by a modification of cerebral glucose utilization.

Our results showed that the second injection of MSG did not produce the same effects as the first. These results can be compared to the absence of effect of systemic injection of MSG on food intake in the adult rat after neonatal treatment with MSG (37). We showed that a period of only 3 days is sufficient to reveal a possible toxic effect of central MSG on neurons implicated in the regulation of feeding behavior. This confirms some previous information because in the adult rat a single systemic injection of MSG produced a degeneration of tyrosine hydroxylase-immunoreactive neurons after a 24-h period in the area postrema (33). This showed that catecholamine-synthesizing neurons of this area are sensitive to the neuroexcitotoxic effect of MSG. Diencephalic noradrenergic neurons that project to the paraventricular nucleus are important in the control of food intake. But, systemic administration of guanfacine, an α_2-adrenergic agonist, or yohimbine, an α_2-adrenergic antagonist, failed to produce differences between neonatal MSG-treated and control rats for their effects on food intake (13). In the neonate, MSG treatment produces a diminution of neuropeptide Y content only in the hypothalamus (13). This diminution must be related to the decrease of neuropeptide Y immunoreactivity in the arcuate nucleus (28), known to be the major site of neuropeptide Y synthesis (8,18). It projects to the paraventricular nucleus (3,8), where neuropeptide Y exerts a tonic and phasic regulation on food intake (23). This arcuate-paraventricular nuclei axis (APA) is involved in nutritional events such as fasting and refeeding (4,5). Therefore, hypophagia of the neonatally MSG-treated rat might be related to the loss of neuropeptide Y synthesis (1). As these neurons are sensitive to MSG treatment, and as it mediates fast synaptic transmission in the hypothalamus (15,22), central MSG in the adult rat might possibly act on food intake via neuropeptide Y-synthesizing neurons by exerting a stimulatory effect.

In conclusion, central MSG induced a stimulatory effect on food intake in the adult rat by increasing meal size and meal duration and this effect remains positive for 24 h. This effect was obtained at doses that were several thousand-fold smaller than those used for systemic injections. This action might go through nervous organs situated close to the cerebral ventricles. On the other hand, we showed that the neurotoxic effect of MSG might appear already after a period of 3 days, as the second MSG injection failed to reproduce exactly the same effects than did the first. If so, MSG cannot be used as a normal stimulant of food intake in behavioral experiments as proposed by some authors (35). Further studies will be necessary to confirm the involvement of glucose-sensitive and/or neuropeptide Y-synthesizing neurons in this action and the long-term effects of MSG on feeding behavior in adult rats.

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