Pharmacology Biochemistry & Behavior, Vol. 32, pp. 391–398. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

A Pharmacological Analysis of Food Intake Regulation in Rats Treated Neonatally With Monosodium L-Glutamate (MSG)[1]

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Received 25 February 1988

DAWSON, R., JR., D. R. WALLACE AND S. M. GABRIEL. *A pharmacological analysis of food intake regulation in rats treated neonatally with monosodium L-glutamate (MSG).* PHARMACOL BIOCHEM BEHAV 32(2) 391–398, 1989.—Studies were conducted to examine deficits in food intake regulation in MSG-treated rats that result from known or suspected damage to neurotransmitter systems involved in feeding. Male rats were injected with either MSG (4 mg/g) or sodium chloride on postnatal days 2 and 4 (MSG-Lo) or postnatal days 2, 4, 6 and 8 (MSG-Hi). As adults, MSG-treated and control rats (n=12/group) were examined for deficits in pharmacologically elicited feeding and other measures of food intake regulation. A second group of MSG-treated (n=9/group) and control rats (n=12) were used to measure basal blood pressure and nociceptive reactivity in adulthood. Organ weights, body weight and neuropeptide Y (NPY) content in brain regions were determined at the end of the study. MSG-Hi rats consumed significantly less food than controls during the dark part of the light cycle. Both MSG-Hi and MSG-Lo groups ate significantly less food than controls after a 48-hour fast. MSG-Hi and MSG-Lo rats consumed significantly less food than controls in response to 1.0 mg/kg morphine. MSG-Hi rats consumed significantly less food than controls during the dark phase and significantly more food than controls during the light phase in response to naloxone (1.0 mg/kg). MSG-Lo ate significantly more than controls in response to 0.1 mg/kg guanfacine. MSG-Hi and MSG-Lo showed a significant attenuation in diazepam-stimulated feeding when compared to controls. Blood pressure was significantly lower in both MSG-Hi and MSG-Lo rats compared to controls. Tail flick latencies were not altered by MSG-treatment. Both doses of MSG produced significant reductions in anterior pituitary, testicular, adrenal and kidney weights relative to the controls. NPY content was significantly reduced in the hypothalamus of MSG-treated (Hi and Lo) rats, but not in other brain regions. The relationship between MSG-induced neurotoxicity and the behavioral and neurochemical deficits of MSG-treated rats was discussed.

Monosodium L-glutamate Neuropharmacology of feeding Arcuate nucleus Neuropeptide Y Opioids and feeding α_2-Adrenoceptor-stimulated feeding

NEONATAL MSG treatment results in a syndrome of obesity, sexual dysfunction, growth stunting and behavioral deficits in rodents (12, 35, 36). The arcuate nucleus of the hypothalamus is severely damaged in MSG-treated rodents as indicated by extensive neuronal loss and concomitant reductions in neurotransmitter markers (10, 14, 15, 35). Despite the comprehensive and detailed studies of the endocrinological (19, 31, 34, 38, 40, 50) and neurochemical (10, 14, 15, 35) consequences of neonatal MSG treatment, the obesity and altered ingestive behaviors of MSG-treated rodents have not been extensively examined.

The obesity of MSG-treated rodents appears to be metabolic in nature since food intake is not increased by MSG treatment (9). MSG-treated rats and mice do however, show altered regulation of day-night feeding and activity patterns (9,28). MSG-treated rats and mice also exhibit altered dietary preferences and respond inappropriately to caloric and glucoprivic challenges (2, 9, 23, 24, 28, 29). Pharmacologi-

[1]These data were presented in a preliminary form at the Society for Neuroscience Meeting in Washington, DC, October 1986.

cal studies of the effects of neonatal MSG treatment have demonstrated no difference in the anorectic potency of amphetamine or fenfluramine (9,11), however, opiate modulation of food intake is disrupted (7,11). The altered pharmacological responsiveness of MSG-treated rodents to opiate drugs that induce changes in food intake (7,11) or endocrine regulation (1,31) are most likely related to the destruction of proopiomelanocortin (POMC) or enkephalinergic neurons in the arcuate nucleus (1, 5, 26).

MSG-induced alteration in adrenergic (22), GABAergic (10,52), opiate (5,26) or dopaminergic (14, 22, 35) systems within the hypothalamus could influence ingestive behavior and metabolic regulatory functions. The endocrine abnormalities of MSG-treated rodents may also contribute to the metabolic efficiency and deficits in food intake regulation that result from MSG-induced neurotoxicity. The present investigation was designed to examine adrenergic, opiate, benzodiazepine and physiological regulation of food intake in MSG-treated rats. Other indices of MSG-induced neurotoxicity such as growth stunting, hypotension, and neuropeptide levels were also examined. Two different dosing regimens for MSG administration were evaluated since dose-response relationships for behavioral parameters of MSG toxicity have not been extensively examined. In summary, drugs known to interact with neurotransmitter systems altered by MSG treatment were evaluated to ascertain the functional integrity of the neural substrates modulating appetite and food intake regulation in MSG-treated rats.

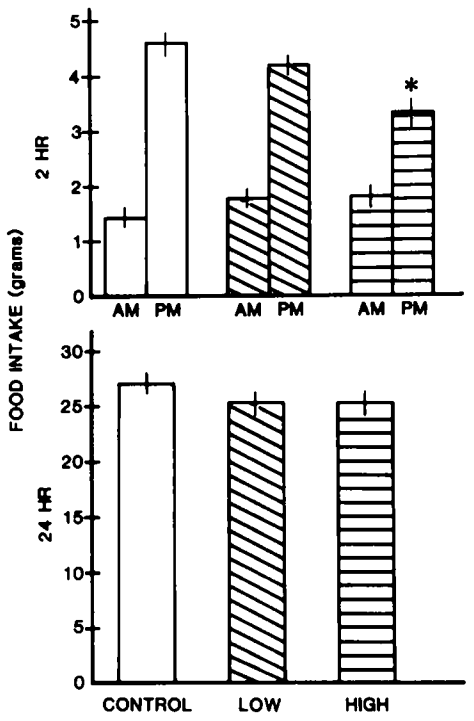

FIG. 1. Baseline food intake after saline injections for the 2-hour test periods and 24-hour food intake (*$p<0.05$ MSG-Hi vs. control).

METHOD

Animals

Timed pregnant Sprague-Dawley rats were obtained from Charles River Breeding Laboratories. Neonatal rats were injected subcutaneously with either 4 mg/g of MSG (Sigma Chemical Co.; concentration=400 mg/ml) or NaCl (1.87% solution). The MSG-treated rats were divided into 2 groups, the MSG-Lo group (n=21) received MSG injections on postnatal days 2 and 4 (postnatal day 1=day of birth) and the MSG-Hi group (n=21) was injected on postnatal days 2, 4, 6 and 8. Rat pups were cross-fostered by randomly assigning MSG-treated or control pups (NaCl injected) (n=24) to dams after the first injection.

Male rats were used in these studies and were weaned on postnatal day 21. The rats were group housed 4–5 rats per cage and maintained ad lib on Purina Rat Chow (5001) and tap water. When the rats were 60 days of age, one group of control (n=12) and MSG-treated rats (MSG-Hi, n=12; MSG-Lo, n=12) were housed singly in hanging wire cages and food intake and behavioral testing was initiated. The second group of control (n=12) and MSG-treated rats (MSG-Hi, n=9; MSG-Lo, n=9) remained in group cages and were used in blood pressure and nociceptive reactivity studies.

Food Intake Studies

Food intake in all experiments was measured by presenting the rats with preweighed quantities of Purina Rat Chow (5001) in glass petri dishes and after the feeding trial was completed, the uneaten food was removed and spillage was collected from underneath the cages and dried if necessary. Food intake was measured to the nearest 0.1 gram. Water was available ad lib throughout the feeding trial.

The rats were acclimated to the food intake measurement procedure prior to any experimental manipulations. Baseline food intake was measured for a 2-hour period from 9:30 a.m.–11:30 a.m. (lights on at 7:00 a.m.). Food intake was then measured after subcutaneous (SC) injection of saline (0.9%) until a stable baseline was obtained. Saline trials were then interspersed between drug trials and drug injections were separated by a minimum of 5 days. The drugs were then tested in the following order and doses: the α_2-adrenergic agonist, guanfacine (0.01, 0.1, 1.0 mg/kg, SC), the α_2-adrenergic antagonists, yohimbine HCl (1.0, 2.5 mg/kg, SC) and idazoxan HCl (2.5 mg/kg, SC), the opiate agonist, morphine sulfate (0.1, 1.0, 2.5, 10.0 mg/kg, SC), the opiate antagonist, naloxone HCl (1.0 mg/kg, SC), and the benzodiazepine agonist, diazepam in a propylene glycol vehicle (1.0, 2.5 mg/kg SC). Propylene glycol vehicle was injected and food intake was monitored to serve as a control for diazepam injections, although food intake after propylene glycol injection did not differ from values obtained after saline injection.

Baseline food intake and food intake after saline injections were measured in the dark phase of the light cycle. All dark phase food intake measures were for 2 hours (7:30 p.m.–9:30 p.m., light out at 7:00 p.m.). The effects of yohimbine HCl (1.0 mg/kg) on food intake were evaluated in the dark phase. Naloxone HCl (1.0 mg/kg) was also tested during the dark phase. Drug injections were performed with the aid of a red safe light.

Twenty-four hour food intake was measured in MSG-treated and control rats as described above. The effects of 48-hour food deprivation was also evaluated. MSG-treated and control rats were deprived of food (but not water) for 48 hours and food intake was measured for the first two hours after the reintroduction of food. Body weight loss and re-

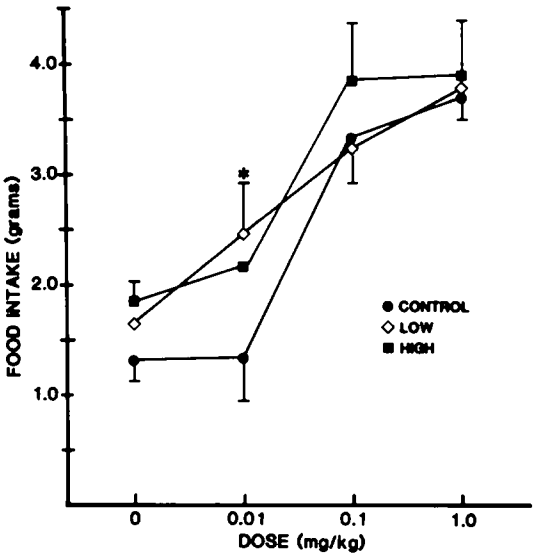

FIG. 2. Dose-response curve for the stimulation of food intake by the α_2-adrenergic agonist, guanfacine. Guanfacine at doses of 0.1 and 1.0 mg/kg significantly ($p<0.05$) increased food intake above baseline levels in all groups tested (*$p<0.01$ MSG-Lo vs. control).

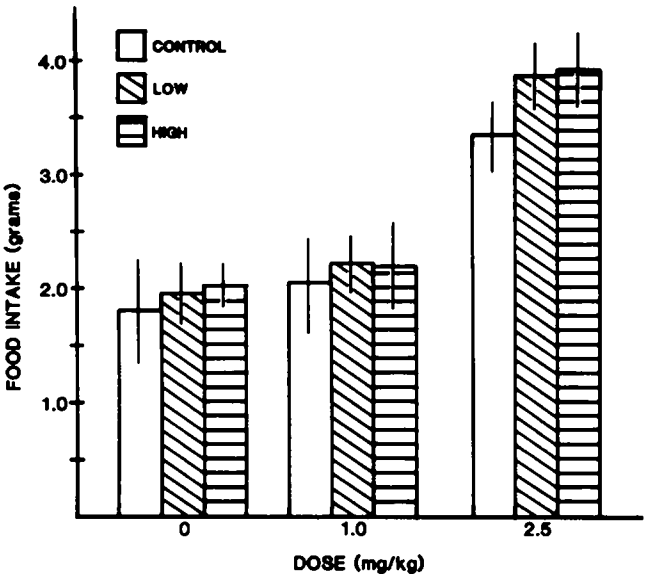

FIG. 3. The effects of yohimbine on food intake in MSG-treated and control rats. Yohimbine at 2.5 mg/kg significantly ($p<0.001$) stimulated 2-hour food intake in all groups.

covery was measured to assess the effects of food deprivation on body weight regulation.

Blood Pressure and Tail Flick Latency Studies

Blood pressure was measured in prewarmed MSG-treated and control rats by the tail cuff method. Blood pressure was measured when the rats were 16 weeks of age and repeated at 18 weeks of age.

Tail flick latency was measured using a Tail Flick Analgesia Meter (Model 33, IITC Inc., Landing, NJ). Tail flick latency was measured at two different beam intensities (75 and 80 at a sensitivity setting of 8). Tail flick testing was conducted when the rats were 70 (beam intensity of 75) and 80 days of age (beam intensity of 80). Three successive trials were run and the average response latency (tail flick) was recorded.

Neuropeptide Assay

The rats used in the feeding studies were killed by decapitation and the brains rapidly weighed prior to placing in boiling 0.5 N acetic acid for 10 min. Brain regions were homogenized using a Brinkman Polytron and centrifuged at 1000×g for 30 min at 4°C. Aliquots of the supernatant were stored at −20°C prior to assay. Neuropeptide Y (NPY) content was determined by radioimmunoassay as previously described (4).

Data Analysis

Two-way analysis of variance (ANOVA) was performed to examine the effects of MSG treatment (control vs. MSG-Lo and MSG-Hi) and the effects of drug doses on food intake measures. Planned comparisons of treatment means were performed using the Newman-Keuls test. One-way ANOVA assessing the effects of MSG-treatment was performed in tail flick, blood pressure studies and other data not involving drug dose-response curves (organ weight, NPY etc.).

RESULTS

Baseline food intake after saline injection was not significantly altered during the light phase by MSG treatment (Fig. 1), although 2 hour baseline food intake during the dark phase was significantly ($p<0.05$) decreased in MSG-Hi rats when compared to controls or MSG-Lo rats. There was no difference in 24 hr food intake in MSG-treated rats when compared to controls (Fig. 1).

The α_2-adrenergic agonist, guanfacine produced significant ($p<0.001$) dose-related increases in food intake in all rats (Fig. 2). MSG-Lo rats consumed 179% ($p<0.01$) more food after 0.01 mg/kg of guanfacine than did the controls (Fig. 2). No other differences in food intake were found between MSG-treated and control rats after guanfacine administration. Yohimbine administered during the light phase had no effect on food intake at 1.0 mg/kg, but significantly ($p<0.001$) increased food intake in all groups at 2.5 mg/kg (Fig. 3). The α_2 antagonist, idazoxan (2.5 mg/kg) did not significantly alter food intake in either control or MSG-treated rats (Fig. 4).

Morphine administration produced a biphasic dose-response curve with 1.0 mg/kg stimulating food intake and 10 mg/kg significantly inhibiting food intake (Fig. 5). MSG-treated rats (MSG-Hi and MSG-Lo) consumed about 20% ($p<0.05$) less food than controls after 1.0 mg/kg of morphine (Fig. 5). The opiate antagonist, naloxone, decreased food intake in all rats, however, both MSG-Lo and MSG-Hi rats consumed 1.5–2 times more food than controls ($p<0.05$) (Fig. 4).

Diazepam administration at either the 1.0 or 2.5 mg/kg dose significantly ($p<0.01$) increased food intake in all the groups of rats (Fig. 6). The diazepam-induced increase in food intake was attenuated relative to the controls in the MSG-Hi group at the 1.0 mg/kg dose and in the MSG-Lo group at the 2.5 mg/kg dose.

Yohimbine at a dose of 1.0 mg/kg did not significantly alter nighttime food intake in any of the groups relative to

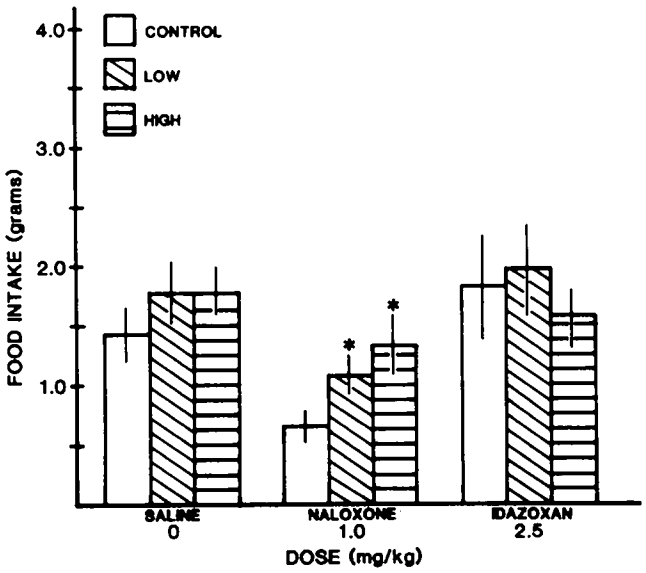

FIG. 4. The effects of the opiate antagonist, naloxone, and α_2-adrenoceptor antagonist, idazoxan, on 2-hour daytime food intake (*$p<0.05$ MSG-Lo and MSG-Hi vs. control at the 1.0 mg/kg dose).

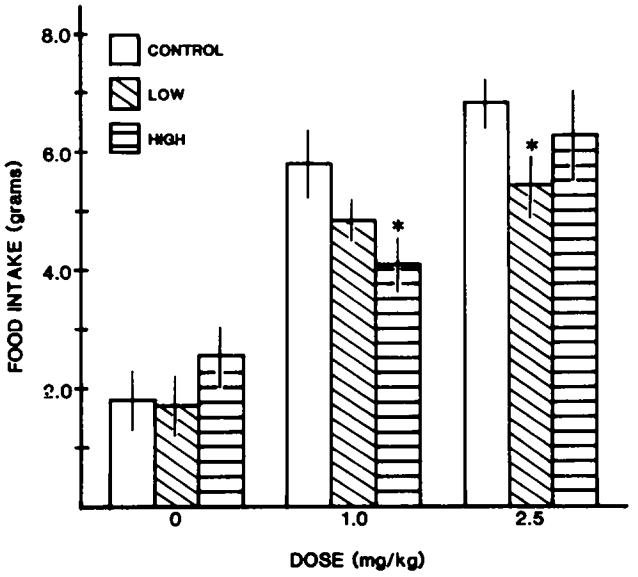

FIG. 6. Diazepam-stimulated food intake in MSG-treated and control rats. Diazepam significantly ($p<0.01$) increased food intake in all groups at both doses tested (*$p<0.05$ MSG-treated vs. control).

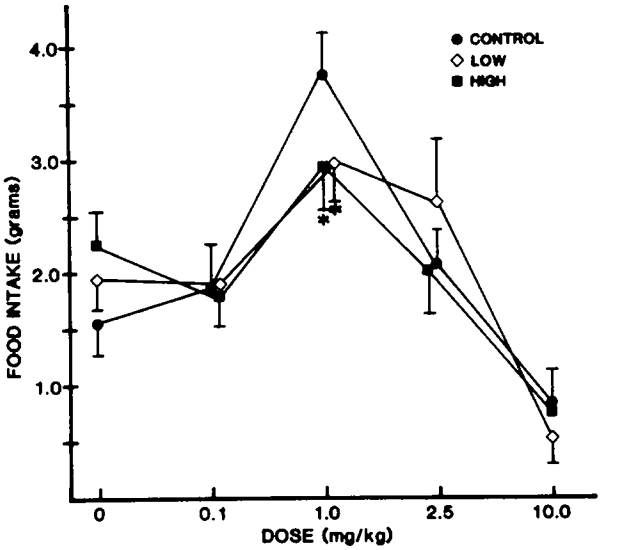

FIG. 5. Dose-response analysis of the effects of morphine on food intake in MSG-treated and control rats. MSG-treated rats (Hi and Lo) ate significantly (*$p<0.05$) less food than controls in response to the administration of 1.0 mg/kg of morphine. The 10 mg/kg dose of morphine significantly ($p<0.05$) suppressed food intake in all the groups.

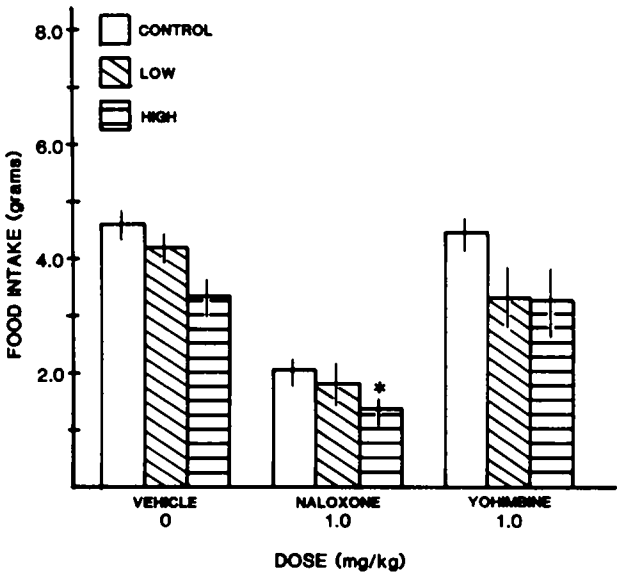

FIG. 7. The effects of naloxone and yohimbine on nighttime food intake. Naloxone significantly ($p<0.01$) decreased nighttime feeding in all groups (*$p<0.05$ MSG-Hi vs. control at the 1.0 mg/kg dose of naloxone).

their baseline measures (Fig. 7). MSG treatment had a significant ($p<0.05$) effect on food intake in rats administered 1.0 mg/kg yohimbine, however, individual comparisons to the control group were not significant ($p<0.1$), due to the fact that the MSG-Hi group did not eat as much food as the controls during the baseline measure. Naloxone did significantly ($p<0.01$) decrease nighttime food intake in all groups relative to their baseline measures (Fig. 7). MSG-Hi rats consumed 33% ($p<0.05$) less food than controls after naloxone which was consistent with their baseline measure.

Although baseline 24-hour food intake did not differ among the groups, food intake for the first 2 hours after a 48-hour fast was altered by MSG treatment (Table 1). MSG-Hi ate significantly ($p<0.05$) less than controls, whereas MSG-Lo did not differ from controls or MSG-Hi (Table 1). MSG-treated rats lost less weight ($p<0.01$) due to the 48-hour deprivation than controls and gained less weight ($p<0.01$) after 5 days of refeeding (Table 1). All groups were able to attain their predeprivation body weight with 5 days of ad lib feeding.

TABLE 1

EFFECTS OF 48 HOURS OF FOOD DEPRIVATION ON FOOD INTAKE AND BODY WEIGHT

Group	2-Hour Food Intake	Wt. Loss	Wt. Gain*
Control	6.83 ± 0.33	54.2 ± 1.6	57.0 ± 2.2
MSG-Lo	6.34 ± 0.40	47.2 ± 1.9‡	47.2 ± 2.1‡
MSG-Hi	5.59 ± 0.43†	46.7 ± 1.50‡	44.2 ± 2.5‡

All values expressed as g ± SE.
*Weight gain after 5 days of free feeding following the 48-hour deprivation period.
†$p<0.05$ control vs. MSG-HI.
‡$p<0.01$ control vs. MSG-treated.

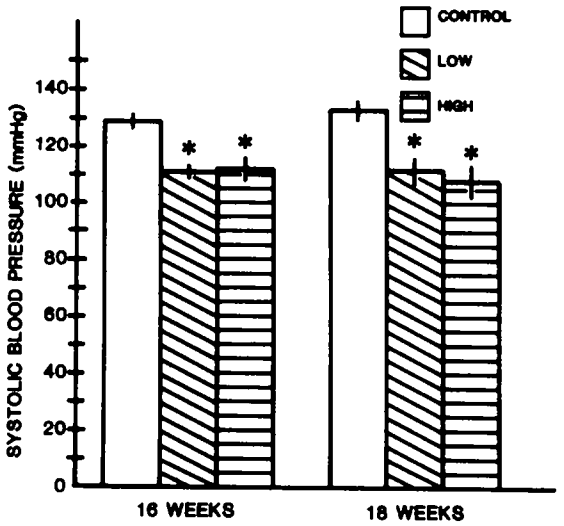

FIG. 8. Blood pressure in MSG-treated and control rats. MSG treatment significantly (*$p<0.05$) decreased basal blood pressure.

TABLE 2

ORGAN AND BODY WEIGHTS IN MSG-TREATED AND CONTROL RATS

Organ	Control	MSG-Lo	MSG-Hi
Body weight (g)	494 ± 8.0	467 ± 16.0	468 ± 14.0
Adrenals (mg)	43.2 ± 2.2	32.6 ± 1.1*	34.2 ± 2.2*
Anterior pituitary (mg)	10.2 ± 0.4	7.1 ± 0.2*	6.2 ± 0.3*†
Kidneys (g)	3.10 ± 0.08	2.64 ± 0.12*	2.48 ± 0.05*
Heart (g)	1.32 ± 0.04	1.16 ± 0.04	1.08 ± 0.03*
Liver (g)	17.18 ± 0.62	16.31 ± 0.69	16.11 ± 0.56
Spleen (mg)	75.8 ± 2.4	67.0 ± 3.7	66.5 ± 2.7
Testes (g)	3.51 ± 0.06	3.12 ± 0.06*	2.85 ± 0.07*†

*$p<0.01$ controls vs. MSG-Lo and MSG-Hi.
†$p<0.05$ MSG-Lo vs. MSG-Hi.
n=12 per group.

TABLE 3

NEUROPEPTIDE Y LEVELS IN BRAIN REGIONS OF MSG-TREATED RATS

Region	Control	MSG-Lo	MSG-Hi
Hypothalamus	179 ± 12	118 ± 5*	119 ± 9*
Hippocampus	75 ± 6	76 ± 8	89 ± 7
Caudate	78 ± 6	77 ± 5	72 ± 8
Forebrain	134 ± 7	140 ± 4	134 ± 10
Pons-medulla	52 ± 3	55 ± 4	58 ± 3

Values expressed as pmol/g ± SE.
*$p<0.05$ vs. control value.
N=10–12 rats per group.

Blood pressure was significantly ($p<0.05$) lower in MSG-treated rats at both 16 and 18 weeks of age when compared to controls (Fig. 8). Both doses of MSG were equally effective in lowering blood pressure. There was no significant effect of MSG treatment on tail flick latency (data not shown) which is in agreement with the findings of Bodnar *et al.* (6).

Body weight at sacrifice was not significantly altered by MSG treatment relative to the controls (Table 2). In contrast, MSG treatment had pronounced effects on organ weights (Table 2). As previously found in female rats (14), male MSG-treated rats had significant ($p<0.01$) reductions in adrenal, anterior pituitary, kidney and heart weights compared to controls. There was also significant ($p<0.01$) testicular atrophy in MSG-treated rats (Table 2). The MSG-Hi dose produced significantly ($p<0.05$) greater reductions in anterior pituitary and testicular weight than did the MSG-Lo dose.

Serum glucose was measured in trunk blood collected from MSG-treated and control rats at the time of sacrifice. There was no difference in serum glucose between the controls (73±5 mg%) and MSG-Lo (77±8 mg%), however the MSG-Hi (91±4 mg%) did have significantly ($p<0.05$) higher glucose levels than the controls.

NPY content in brain regions from MSG-treated and control rats are presented in Table 3. MSG treatment significantly ($p<0.01$) decreased NPY content in the hypothalamus, but not in other brain regions. There was no difference in the degree of NPY depletion produced by the two dosing regimens.

DISCUSSION

MSG treatment had profound effects on numerous physiological and pharmacological indices of integrated hypothalamic function. The behavioral deficits produced by MSG treatment are consistent with the documented alterations in hypothalamic neurochemical and neuroendocrine markers (14, 15, 22, 31, 35). Most studies employing neonatal MSG treatment have used 4 or more injections during the early postnatal period (days 1–10) to produce hypothalamic and circumventricular organ damage. Damage to other CNS structures does occur with high dose MSG treatment and neurochemical alterations are also present in brain regions distant from circumventricular organs (13, 27, 36, 37). Several studies have examined the functional consequences of

using different dosing regimens for MSG administration (23, 28, 35, 44). The results from the use of two different dosing regimens in this study suggest that many of the behavioral and other characteristics of the MSG syndrome are inducible with lower doses of MSG than had previously been utilized. High dose MSG treatment does, however, produce some deficits not seen with the lower dose. As previously suggested (28), feeding disturbances and pituitary atrophy are the most sensitive indicators of MSG-induced neurotoxicity. MSG-Hi rats ate less at night and exhibited a more attenuated response to food deprivation than the MSG-Lo group. Pituitary and testicular atrophy were also more pronounced in MSG-Hi when compared to MSG-Lo. Therefore, damage to neural systems regulating reproductive and ingestive physiology appear especially vulnerable to the dose-dependent neurotoxicity of MSG.

MSG-induced obesity in rodents has been examined as an interesting model of metabolic obesity since significant adiposity occurs in MSG-treated rodents in the absence of hyperphagia or with hypophagia (9, 12, 28). Hypothalamic systems regulating appetite and consummatory behaviors have not been extensively examined in MSG-treated rats, although deficits in caloric regulation are present (9, 23, 24, 29). MSG-treated rats subjected to mild food deprivation fail to show morphine-induced hyperphagia (7). The present study found deficits in morphine-induced hyperphagia in MSG-treated rats, but not in the ability of 10 mg/kg of morphine to suppress food intake. Thus, our study confirms the observations of Bodnar and co-workers (7) on the MSG-induced attenuation of morphine hyperphagia and extends this observation to MSG-treated rats in a nondeprived state. Naloxone was less effective in MSG-treated rats than controls in suppressing food intake during the light phase, which is in marked contrast to the effects of naloxone in MSG-treated mice (11). MSG treatment did not alter the effectiveness of naloxone in suppressing food intake during the dark phase of the light cycle. MSG treatment is known to produce significant depletions in POMC-derived peptides (1, 5, 26). Opiate receptors are also altered by MSG treatment (54), although receptor numbers are increased in some brain regions and decreased (unpublished observations) in others. The exact role of changes in opiate receptor affinity or number is unclear as it relates to MSG-induced alterations in food intake regulation. The mild hypophagia of the MSG-treated rodent may in part be attributable to a loss of "opiate sensitive" neurons in the hypothalamus and/or destruction of POMC synthesizing neurons.

Noradrenergic neurons that project to the paraventricular nucleus of the hypothalamus (PVN) are important in the control of food intake. Stimulation of α_2-adrenergic receptors in the PVN induce feeding (18). Central or systemic administration of the α_2-adrenergic agonist, clonidine, stimulates eating and drinking (18, 30, 43). We administered guanfacine, an α_2-adrenergic agonist, to assess the responsiveness of α_2-adrenergic receptors in MSG-treated rats. Guanfacine stimulated food intake in all rats, although the dose-response curve appeared shifted slightly to the left in MSG-treated rats, especially at the lower doses. During the light phase, neither yohimbine (1.0 mg/kg) nor idazoxan (2.5 mg/kg), α_2-adrenoceptor antagonists, altered food intake in any of the rats. This suggests that α_2-adrenergic receptors do not tonically control feeding. Yohimbine (2.5 mg/kg), in fact, stimulated feeding as had previously been reported (30). The stimulation of food intake by yohimbine, however, most likely represents a nonspecific neurochemical action on dopaminergic or serotonergic neurons (16) since the more selective antagonist, idazoxan, failed to increase food intake. Interestingly, yohimbine (1.0 mg/kg) did appear to produce a modest inhibition of feeding in MSG-treated rats at night, while not altering feeding in control rats.

The MSG-Hi rats ate significantly less during the baseline nighttime measures than controls. The hypothalamic control of diurnal feeding patterns appears to be mediated by noradrenergic neurons (21). The subtle defects in α_2-adrenergic responsiveness demonstrated in this study suggest that previously reported day-night feeding disturbances in MSG-treated rodents (9,28) could be related to MSG-induced alterations in hypothalamic norepinephrine [(22), unpublished findings]. Studies examining the responsiveness of MSG-treated rats α_2-adrenergic agonists need to be conducted to assess feeding during the course of the diurnal cycle and to determine if carbohydrate intake would be selectively altered (24,46). An examination of the relationship between the noradrenergic deficits exhibited by MSG-treated rats and the MSG-induced depletion of PVN NPY (25) would also be of interest.

MSG treatment is associated with significant reductions in hypothalamic markers for GABA (10,52). There are several sites in the hypothalamus that stimulate feeding in response to GABA. Systemic administration of GABA agonists, however, tend to inhibit food intake, although the mechanisms and neural substrates are poorly defined (46). Recent studies point to a GABAergic modulation of benzodiazepine binding (48) and benzodiazepines are potent stimulators of food intake when administered centrally or systemically (46). We examined diazepam-induced feeding in MSG-treated and control rats and found MSG-treated rats to show an attenuated hyperphagia relative to controls. It is evident that at the doses employed in this study MSG-treated rats did not eat as much as controls in response to diazepam. The results suggest that the MSG-induced destruction of GABAergic neurons (10,52) or the loss of neurons with benzodiazepine receptors may account for decreased food intake after diazepam administration. Benzodiazepine binding sites labelled by [^{3}H]flunitrazepam are not significantly altered in the hypothalamus by neonatal MSG treatment (39), indicating that a deficit in GABA would more likely account for the alteration in diazepam-stimulated feeding. The high lipid solubility of diazepam, however, complicates the interpretation of these studies since the greater body fat content of MSG-treated rats may alter the pharmacokinetics of systemically administered diazepam. Studies employing central administration of GABA agonists and benzodiazepines to MSG-treated rats would seem warranted given the limited understanding of the neural substrates of benzodiazepine-induced feeding.

MSG-treated rats exhibited a dose-dependent attenuation in their response to postdeprivation feeding. This is in agreement with previous findings (28,29). Body weight regulation appears normal in MSG-treated rats, although the magnitude of the weight loss after 48 hours of food deprivation was not as great in MSG-treated rats as controls. The actual percentage of total body weight lost due to fasting was not significantly altered since the MSG-treated rats tended to weigh consistently less than the controls. Thus, body weight regulation per se was not altered, despite an impairment in appetite regulation.

MSG administration to adult spontaneously hypertensive rats (SHR) lowers blood pressure (20), but neonatal MSG administration has no effect on SHR or Wistar Kyoto con-

trols (33). Our studies demonstrated that neonatal MSG treatment can lower blood pressure in adult male Sprague-Dawley rats. Takasaki *et al.* (47) also reported reductions in blood pressure in adult male Wistar rat treated neonatally with MSG. MSG treatment damages circumventricular organs that are important in cardiovascular regulation (AV3V, area postrema) and may reduce CNS responsiveness to circulating angiotensin II (41). MSG-treated mice are hypodipsic (11) so alterations in fluid balance and cardiovascular regulation would seem to be a consequence of MSG-induced neurotoxicity.

The arcuate nucleus of the hypothalamus in known to contain NPY-immunoreactive neurons (3,8). Electrolytic destruction of the arcuate nucleus results in a marked decrease in NPY-immunoreactive fibers in the PVN (3), an area where NPY infusion causes increased food intake (45). Kerkerian and Pelletier (25) using immunocytochemistry have demonstrated a loss of NPY neurons in the arcuate nucleus and a loss of NPY fibers projecting to the PVN in MSG-treated rats. The present study has demonstrated a significant depletion of hypothalamic NPY after neonatal MSG administration and a sparing of NPY-immunoreactive neurons in other brain regions. The NPY neurons of the arcuate nucleus do not show the extensive coexistence with somatostatin that cortical neurons exhibit (8) and no alterations in somatostatin content were seen after neonatal MSG treatment (unpublished findings). The NPY depletion seen after neonatal MSG treatment further characterizes that neurochemical lesion that is produced by MSG-induced arcuate nucleus damage. The loss of hypothalamic NPY neurons may contribute to the mild hypophagia and deficits in deprivation-induced feeding since NPY is a potent appetite stimulant.

MSG-treated rats show deficits in β-endorphin, GABA, NPY and norepinephrine, all of which are important endogenous signals for increased food intake. There appear to be extensive neurochemical interactions between β-endorphin, NPY and norepinephrine (17, 32, 49, 51, 53) and the neurotoxic actions of MSG on arcuate nucleus neurons results in an extensive disruption of the interrelationship between these neurotransmitter systems. Food intake and appetite regulation appears to depend on complex interactions involving monoamine and neuropeptide receptors in the hypothalamus (32). The deficits in food intake regulation and other alterations in behavioral and physiological function can be related to the neurotoxic actions of MSG and consequent loss of pre- and postsynaptic elements in the hypothalamus and circumventricular organs. The expression of many aspects of the MSG syndrome can be accomplished using doses much lower than those previously employed. The alterations in ingestive behavior, reproductive function and cardiovascular control produced by neonatal MSG treatment appear to be attributable to the loss of neurons that are particularly susceptible to excitotoxins.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. J. C. Doxey of Reckitt and Colman for the gift of idazoxan and Dr. L. F. Sancilio of A.H. Robins for the gift of guanfacine. The authors also wish to express their thanks to Victoria Redd Patterson and Carol Powell for excellent secretarial assistance.

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