Glutamic Acid: Advances in Biochemistry and Physiology, edited by L. J. Filer, Jr., et al. Raven Press, New York © 1979.

Effects of Glutamate Administration on Pituitary Function

Alan F. Sved and John D. Fernstrom

Laboratory of Brain and Metabolism, Program in Neural and Endocrine Regulation, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

The administration of glutamic acid to neonatal animals in high, repeated doses was originally reported to elicit retinal degeneration (9,16). In 1969, Olney performed experiments to determine whether glutamate injection also caused damage to other portions of the central nervous system (CNS). He anticipated other CNS lesions might be present because of the obesity noted in glutamate animals several months after treatment with the amino acid. Additional lesions were found, particularly in the preoptic area and arcuate nucleus of the hypothalamus (13). Widespread endocrine abnormalities were also suspected, owing to the stunted linear growth of glutamate-treated animals, to their obesity, reduced food intake, and deficient reproductive capacity. It seemed most likely that the hypothalamic lesion modified the normal flow of signals from the brain to the pituitary, thereby producing aberrations in the release of pituitary hormones, and ultimately, in body development and functions. This notion was subsequently explored by Redding et al. (17), who were the first to note abnormalities in pituitary hormone content following glutamate administration. Since 1971, several other investigators have looked for, and found, some abnormalities in pituitary hormone secretion (4,10,11,20). The findings suggest a hypothalamic-pituitary etiology for a few of the peripheral endocrine and metabolic changes associated with glutamate administration. However, the mechanism(s) by which glutamate injection causes the remainder of the abnormalities remains obscure.

This chapter will first review the main alterations in body function found in association with the administration of glutamate to newborn animals. We will then discuss the data currently available on the effects of glutamate administration on the anterior pituitary gland, and on the secretion of its hormones. The likelihood that glutamate administration produces the observed changes in pituitary hormone secretion via the induction of arcuate lesions will also be discussed, along with other possible sites of glutamate action within the CNS that might also elicit such changes in pituitary functions.

In considering these data, it should be borne in mind that, to date, glutamate administration has been shown to produce these gross endocrine abnormalities in adult animals *only* when injected early in postnatal life, in repeated, very large doses. The likelihood that infants of any species might normally be exposed to

levels sufficiently high to induce such alterations seems vanishingly small. In particular, infant animals and humans are unlikely to consume amounts sufficient to induce such lesions, either via prepared diets or breast milk (18,19).

EFFECTS OF MSG ON GROWTH AND ENDOCRINE ORGANS

Growth

The short-term administration of high doses of glutamate to neonatal rodents often produces marked alterations in body growth (11,13,14). When newborn animals are injected with the amino acid at a dose level of 1,000 mg/kg/day on postnatal days 1 to 10, they subsequently gain weight at a faster rate than control animals (14). This effect is more readily apparent in females than males. In mice, the difference in body weight is not manifested until after the animals are 50 days of age or older (14), which may explain the failure of some investigators to confirm this phenomenon in younger animals (17,21). In general, the weight abnormality becomes more exaggerated as the animal becomes older (14).

When such glutamate-treated animals are autopsied, the increased body weight has been noted to result mainly from a large increment in total fat stores (11,13), such that they often exceed twice the amount present in normal animals (5). Although observations such as these have led investigators to suggest that the neonatal glutamate treatment somehow induces a hyperphagia syndrome (13), careful study of food intake has revealed the paradoxical result that treated animals actually consume slightly less food each day than control animals (13,17). The only other alternative was that animals treated with glutamate somehow expended less energy than controls. Some data actually support this view, as well. For example, Djazayery et al. (6) have found O_2 consumption and CO_2 production to be reduced in MSG-treated rats, and Pizzi and Barnhart (14) observed gross locomotor activity to be abnormally low. The mechanism by which glutamate administration causes these effects is presently unknown, but might at least in part follow from the reduced levels of thyroid hormones in the blood reported by one laboratory (11).

Obesity is not the only growth abnormality of glutamate-treated animals. Stunting of skeletal growth is also a significant feature (13). In both rats (11) and mice (13), for example, the neonatal administration of glutamate leads to reductions in nasoanal length of about 10%. This effect is also observable when measurements of the long bones are made: in one study, the adult femur length was found to be 14.5 mm in glutamate-treated rats and 16.3 mm in controls (2). Tibia length was also reduced in treated animals. As will be discussed below, at least one possible mechanism has been suggested to account for stunted bone growth in MSG-treated animals, i.e., reduced secretion of growth hormone (12).

Endocrine and Reproductive Organs

Soon after Olney reported that glutamate administration to newborn mice induced hypothalamic lesions (13), a search was begun to identify endocrine abnormalities

that might be associated with this treatment. Olney (13) himself observed that glutamate treatment decreased the weights of certain reproductive organs and glands in mice, and also impaired reproductive function. Other investigators (17,21) confirmed these findings: ovaries were noted to be abnormally small in glutamate-treated females and to contain numerous atretic follicles (Table 1) (13). In males (17), the testes appeared histologically normal, but were reduced in size. Some (13,15), but not all (1,21), experimenters found these changes to be accompanied by an impairment of reproductive function. For example, the administration of glutamate early in life to female mice reduced their ability to conceive as adults when mated with normal male mice (15). In male mice treated postnatally with glutamate, some investigators noted a reduced ability to impregnate female animals successfully (15), whereas others found the fertility of the male mouse to be unaltered by this treatment (13). Glutamate-treated animals generally have small anterior pituitaries (10,13,17); the intermediate and posterior portions of the pituitary are of normal size. The weight reduction in the adenohypophysis appears to reflect a general diminution in cell number and size. Thyroid size appears to show inconsistent alterations in adult animals injected with glutamate around the time of birth (10,21); similarly, contradictory effects have been obtained on adrenal size (10,21).

EFFECTS OF NEONATAL GLUTAMATE ADMINISTRATION ON ANTERIOR PITUITARY FUNCTION

Alterations in Hormonal Secretions

Only fragmentary data are available on the effects of neonatal MSG treatment on the secretion of individual hormones by the anterior pituitary. Moreover, for the hormones whose secretions do seem to be modified, essentially no *careful* studies have to date been performed to attempt to identify the underlying mechanisms. Hence, the following summaries should be taken as *very* tentative.

Growth Hormone

Serum growth hormone (GH) levels are markedly reduced in animals treated neonatally with MSG (Table 2) (12,20). This probably reflects a decrease in the hormone's secretion, rather than acceleration in its degradation: the normal, pulsatile secretion of growth hormone has been found to be still present in MSG-treated rats, but the pulse heights are reduced (20). Total pituitary growth hormone content is also diminished (Table 3) (17); however, pituitary size is also decreased, and thus smaller differences are noted when hormone levels are expressed per milligram pituitary (10). The observed decrease in growth hormone release does not appear to reflect changes in the hypothalamic content of somatostatin. Somatostatin levels in the hypothalamus, if at all changed, appear to be reduced (Table 4).

Peripheral signs of inadequate growth hormone secretion appear to characterize in part the symptomology of MSG-treated rodents. For example, abnormally small

TABLE 1. *Changes in body weight, food intake, and gland and reproductive organ weights in rats treated with MSG*

Parameter	Control	MSG
Body weight (g)	358	322
Lee index	0.307	0.322[a]
Food intake (g/day)	24.5	20.0
Reproductive organ and gland weights (mg/100 g body weight)		
Thyroid	3.01	2.73[b]
Adrenals	11.58	8.99[a,b]
Testes	930	800[b]
Anterior pituitary	2.02	1.34[a,b]
Ovaries	32	17[a,b]

Groups of rats received MSG every day from day 2 to day 10 of life, in incremental doses between 2.2 and 4.4 g/kg, s.c. They were killed at 110 days of age. All data are for male rats, except for ovary weights, which are from identically treated female rats. The Lee index is an estimate of obesity.

[a] $p < 0.05$ compared with control.

[b] *Absolute* tissue weight is significantly different from control.

Adapted from Redding et al., ref. 17.

adult bone length is a characteristic of GH deficiency during development. In addition, increased fat deposition may well reflect the absence of normal amounts of GH, since GH normally promotes fat mobilization (lipolysis) from adipocytes (22).

It is widely held that GH does not mediate directly its growth-promoting and metabolic effects on the body, but modulates the availability within the body of the somatomedins, a class of peptide compounds whose biologic actions are essentially identical to those of GH (23). No data are available on the effects of MSG-treatment on this class of compounds. Such information might be of interest in explaining

TABLE 2. *Plasma concentrations of pituitary hormones in adult rats treated with MSG as neonates*

	Males		Females	
Hormone	Control	MSG	Control	MSG
Prolactin	40	156[a]	146	108
Thyrotropin	557	889	616	629
GH	52	29[a]	52	12[a]
LH	27	24	42	38

Data expressed in ng/ml. Group size varied between 6 and 15 animals. Holtzman rat pups received i.p. MSG (4 g/kg) on days 1, 3, 5, 7, and 9 postpartum, and were sacrificed at the age of 18 weeks.

[a] Significantly different from control values, $p < 0.05$.

Reproduced from Nemeroff et al., ref. 12.

TABLE 3. *Anterior pituitary hormone contents in rats treated with MSG*

Hormone	Control	MSG
GH (μg/gland)	289	83[a]
LH (μg/gland)	6.6	1.7[a]
TSH (mU/gland)	608	408

Male rats received MSG each day from days 2 to 10 of life, in incremental doses from 2.2 to 4.4 g/kg (s.c.). They were sacrificed at 40 days of age.
[a] Significantly different from controls, $p < 0.001$.
Adapted from Redding et al., ref. 17.

why, for example, when pituitary GH stores are so markedly reduced, only small overall reductions are observed in body length (the large increase in adiposity may not reflect the absence of GH alone, but also of thyroid hormones and gonadal hormones, although no data are available yet on the effects of MSG treatment on circulating gonadal steroid levels).

Gonadotropins

Serum luteinizing hormone (LH) levels are not abnormally low in animals treated with MSG early in life (Table 2) (12). [One abstract, however, does state that both LH and follicle-stimulating hormone (FSH) levels were low in sera obtained from MSG-treated rats (4), but no data were provided.] The pituitary content of LH, however, does not appear to be significantly decreased (Table 3) (17), but hypothalamic luteinizing hormone release hormone (LHRH) levels are reportedly normal (Table 4) (4,8), and the increase in serum LH levels that follows an injection of LHRH is within the normal range (12). The only indication of a possible impairment of LH secretion is found in ovariectomized rats: in these animals, the increase in serum LH induced by estrogen administration was blunted if MSG was administered early in postuterine life (4). It is difficult to reconcile the apparent *lack* of MSG effects on

TABLE 4. *Effect of neonatal administration of MSG on the concentrations of hypothalamic hormones in adult rats*

	Males		Females	
Hormone	Control	MSG	Control	MSG
TRH	5.5	5.9	5.3	5.6
LHRH	4.2	4.2	3.6	4.6
Somatostatin	—	—	32.0	28.0

Data expressed in ng/mg protein; $N = 6$–12. Holtzman rat pups received i.p. injections of MSG (4 g/kg) on days 1, 3, 5, 7, and 9 of life, and were killed at 18 weeks of age. Data are for *ventrobasal* hypothalamus.
Reproduced from Nemeroff et al., ref. 12.

LH in intact animals with the findings of atrophic gonads, disrupted estrous cycle, and possibly impaired reproductive functioning. [Of course, not all investigators obtained such effects (1,21).] Perhaps FSH levels are low, as suggested by Clemens et al. (4). However, no data have been reported on FSH, and this possibility therefore remains speculative. In addition, it is surprising that no measurements of circulating levels of estrogen, progesterone, or testosterone have been made in the 9 years since MSG-induced reproductive abnormalities were first reported (13). Hence, from the available data, it is not possible to state whether MSG exerts its reputed antireproductive actions via indirect action on the hypothalamus, or by a direct effect on the gonads or reproductive organs.

Thyroid hormones

Thyroid-stimulating hormone (TSH) levels in serum and pituitary fall within the normal range in animals receiving MSG (Tables 2 and 3) (12,17). Moreover, hypothalamic thyrotropin-releasing hormone (TRH) levels (Table 4) and TRH-induced TSH release are both normal in MSG-treated rats (8,12). Consistent with this apparently normal function are the observations that thyroid size is not substantially different from normal (Table 1) (10,17) and that the uptake of ^{131}I by the thyroid gland is normal. However, some evidence suggests that MSG-treated animals are hypothyroid, as indicated by reduced serum T_3 and free thyroxine levels (Table 5) (11). Because of these latter observations, it has been suggested that TSH secretion may actually be subnormal since even though serum TSH concentrations are within the normal range, they are too low given the reductions in circulating thyroid hormone levels (12). Thus, MSG might induce the reductions in T_3 and free T_4 via an action on the hypothalamus-pituitary. However, in the absence of convincing data, if the finding that circulating T_3 and free T_4 levels are diminished holds up to the test of time, it seems equally likely that MSG-treatment might exert these effects by direct action on the thyroid gland; the hypothalamo-pituitary control of thyroid function appears quite normal.

Hypothyroidism would be compatible with some of the gross metabolic and behavioral manifestations of MSG-treated animals. As noted above, these animals show decreased O_2 consumption and CO_2 production (6), and appear lethargic [i.e.,

TABLE 5. *Thyroid status of MSG-treated rats*

Hormone	Control	MSG
Serum T_3 (ng %)	~280	~200[a]
Serum free thyroxine index	~4.5	~3.3[a]

Neonatal rats received i.p. MSG (4 g/kg) every other day for the first 10 days of life. They were killed 30 or 47 weeks later.

[a] $p < 0.05$ compared to control values.

Adapted from Fig. 4, Nemeroff et al., ref. 11.

as indicated by reduced locomotor activity (14)]. Hypothyroidism would also tend to promote the accumulation of adipose tissue (24), and neonatal onset hypothyroidism is known to be associated with retarded skeletal growth (25). Clearly, if hypothyroidism is to be invoked as a causative effect of MSG treatment on linear growth and adiposity, many more data are needed; e.g., a careful study of the hypothalamo-pituitary-thyroid axis *during* the growth and development period of prenatal MSG-treated animals.

Prolactin

Serum prolactin concentrations appear to be normal in MSG-treated animals (4,20), although one report does describe increased concentrations in male rats (Table 2) (12). Pituitary prolactin content, however, has been noted by one group to be significantly reduced (10), and some physiologic signs of inadequate prolactin secretion are indicated by retarded mammary gland development in female rats treated with MSG (10).

Prolactin secretion by the pituitary is believed to be controlled by the hypothalamus, which may secrete dopamine as its prolactin release-inhibiting factor (see ref. 7). A reduction in hypothalamic dopamine release would therefore be expected to elicit a rise in serum prolactin levels. Dopamine levels have been measured in the median eminence and the arcuate nucleus, and appear to be diminished in MSG-treated rats (Table 6) (11,12). In contrast, serotonin and norepinephrine concentrations are unaffected (Table 6). The reduction in hypothalamic dopamine could indicate either diminished synthesis and thus release of the amine, or simply enhanced release with no change in synthesis. In the former case, prolactin secretion would be stimulated, and in the latter, inhibited. Retarded mammary gland development (10) suggests too little prolactin, supporting the idea

TABLE 6. *Median eminence and arcuate nucleus levels of monoamines in adult rats injected with MSG soon after birth*

Brain region	Control	MSG
Median eminence		
Serotonin	31 ± 3	24 ± 3
Dopamine	85 ± 3	52 ± 7[a]
Norepinephrine	14 ± 1	14 ± 1
Arcuate nucleus		
Serotonin	12 ± 1	12 ± 1
Dopamine	17 ± 1	8 ± 1[a]
Norepinephrine	17 ± 1	14 ± 1

Data presented as means ± SE in ng/mg protein; $N = 6$. Newborn male and female rats received i.p. MSG (4 g/kg) on postpartum days 1, 3, 5, 7, and 9, and were killed at 18 weeks of age.

[a] Significantly different from control, $p < 0.05$.

Adapted from Nemeroff et al., ref. 12.

of increased release of dopamine; however, reduced pituitary prolactin content (10) and increased plasma prolactin levels (12) could indicate enhanced prolactin secretion, and therefore inhibition of hypothalamic dopamine synthesis and release. Clemens et al. (4) have reported the unusually large increase in plasma prolactin induced by 5-hydroxytryptophan administration to MSG-treated rats, consistent with the notion that inhibition of prolactin secretion by dopamine might be diminished in these animals. However, again, the data are simply too fragmentary, incomplete, and inconsistent to warrant any firm statements or conclusions.

GENERAL COMMENT AND CONCLUSIONS

Based on the above analysis, it would appear somewhat premature to draw conclusions regarding the effects of MSG administration on pituitary function. Available data are often inconsistent among laboratories attempting to reproduce the same experiments; e.g., although some laboratories note reductions in reproductive capacity in MSG animals (13,15), others do not (1,21). Moreover, results obtained within a single laboratory are not always consistent from study to study, e.g., the effect of MSG on plasma prolactin levels in male rats (12,20). The differences in the times after MSG treatment when samples are collected by the various laboratories is often invoked as a possible explanation for such inconsistencies. However, no one has as yet carefully characterized the time course of any of the hypothesized endocrine abnormalities following neonatal glutamate injections (except, of course, for the growth curves). Not only are there inconsistencies in the literature concerning the ability of MSG to change pituitary hormone secretion, but its ability to produce arcuate lesions also is not generally accepted (1,3).

The "glutamate model" (i.e., the production of arcuate lesions in adult animals by the repeated administration of high doses of the amino acid to newborn pups) has been extant for over 10 years, and the *lack* of published data relating to neuroendocrine abnormalities is surprising. This apparent absence of interest on the part of neuroendocrinologists may derive from the conviction that the model is not scientifically useful, or perhaps from the inconsistencies in the literature concerning the production and effects of the MSG lesions. In either case, the data that are available on pituitary function after MSG administration are too fragmentary to allow the development of a useful hypothesis or model to describe possible mechanisms by which extremely high doses of glutamate can occasionally produce abnormalities in growth and reproduction.

REFERENCES

1. Adamo, N. J., and Ratner, A. (1970): Monosodium glutamate: Lack of effects on brain and reproductive function in rats. *Science,* 169:673–674.
2. Araujo, P. E., and Mayer, J. (1973): Activity increase associated with obesity induced by monosodium glutamate in mice. *Am. J. Physiol.,* 225:764–765.
3. Arees, E. A., and Mayer, J. (1970): Monosodium glutamate-induced brain lesions: Electron microscopic examination. *Science,* 170:549–550.
4. Clemens, J. A., Roush, M. E., and Shaar, C. J. (1977): Effect of glutamate lesions of the arcuate nucleus on the neuroendocrine system in rats. *Soc. Neurosci. Abstr.,* 3:341.

5. Djazayery, A., and Miller, D. S. (1973): The use of gold-thioglucose and monosodium glutamate to induce obesity in mice. *Prod. Nutr. Soc.*, 32:30A–31A.
6. Djazayery, A., Miller, D. S., and Stock, M. J. (1973): Energy balances of mice treated with gold-thioglucose and monosodium glutamate. *Proc. Nutr. Soc.*, 32:31A–32A.
7. Fernstrom, J. D., and Wurtman, R. J. (1977): Brain monoamines and reproductive function. In: *Reproductive Physiology*, Vol. 2, edited by R. O. Greep, pp. 23–55. University Park Press, Baltimore.
8. Lechman, R. M., Alpert, L. C., and Jackson, I. M. D. (1976): Synthesis of luteinising hormone releasing factor and thyrotropin-releasing factor in glutamate-lesioned mice. *Nature*, 264:463–465.
9. Lucas, D. R., and Newhouse, J. P. (1957): The toxic effect of sodium L-glutamate on the inner layers of the retina. *AMA Arch. Ophthalmol.*, 58:193–201.
10. Nagasawa, H., Yanai, R., and Kikuyama, S. (1974): Irreversible inhibition of pituitary prolactin and growth hormone secretion and of mammary gland development in mice by monosodium glutamate administered neonatally. *Acta Endocrinol. (Kbh.)*, 75:249–259.
11. Nemeroff, C. B., Grant, L. D., Bissette, G., Ervin, G. N., Harrell, L. E., and Prange, A. J. (1977): Growth, endocrinological and behavioral deficits after monosodium L-glutamate in the neonatal rat: Possible involvement of arcuate dopamine neuron damage. *Psychoneuroendocrinology*, 2:179–196.
12. Nemeroff, C. B., Konkol, R. J., Bissette, G., Youngblood, W., Martin, J. B., Brazeau, P., Rone, M. S., Prange, A. J., Breese, G. R., and Kizer, J. S. (1977): Analysis of the disruption in hypothalamic-pituitary regulation in rats treated neonatally with monosodium L-glutamate (MSG): Evidence for the involvement of tuberoinfundibular cholinergic and dopaminergic systems in neuroendocrine regulation. *Endocrinology*, 101:613–622.
13. Olney, J. W. (1969): Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science*, 164:719–721.
14. Pizzi, W. J., and Barnhart, J. E. (1976): Effects of monosodium glutamate on somatic development, obesity, and activity in the mouse. *Pharmacol. Biochem. Behav.*, 5:551–557.
15. Pizzi, W. J., Barnhart, J. E., and Fanslow, D. J. (1977): Monosodium glutamate administration to the newborn reduces reproductive ability in female and male mice. *Science*, 196:452–453.
16. Potts, A. M., Modrell, R. W., and Kingsbury, C. (1960): Permanent fractionation of the electroretinogram by sodium glutamate. *Am. J. Ophthalmol.*, 50:900–905.
17. Redding, T. W., Schally, A. V., Arimura, A., and Wakabayashi, I. (1971): Effect of monosodium glutamate on some endocrine functions. *Neuroendocrinology*, 8:245–255.
18. Stegink, L. D., Filer, L. J., and Baker, G. L. (1972): Monosodium glutamate: Effect on plasma and breast milk amino acid levels in lactating women. *Proc. Soc. Exp. Biol. Med.*, 140:836–841.
19. Stegink, L. D., Pitkin, R. M., Reynolds, W. A., Filer, L. J., Boaz, D. P., and Brummel, M. C. (1975): Placental transfer of glutamate and its metabolites in the primate. *Am. J. Obstet. Gynecol.*, 122:70–78.
20. Terry, L. C., Epelbaum, J., Brazeau, P., and Martin, J. B. (1977): Monosodium glutamate: Acute and chronic effects on growth hormone (GH), prolactin (PRL) and somatostatin (SRIF) in the rat. *Fed. Proc.*, 36:364.
21. Trentini, G. P., Botticelli, A., and Botticelli, C. S. (1974): Effect of monosodium glutamate on the endocrine glands and on the reproductive function of the rat. *Fertil. Steril.*, 25:478–483.
22. Williams, R. H. (1974): *Textbook of Endocrinology*, p. 51. W. B. Saunders, Philadelphia.
23. Williams, R. H. (1974): *ibid.*, p. 51.
24. Williams, R. H. (1974): *ibid.*, p. 153.
25. Williams, R. H. (1974): *ibid.*, p. 1044.