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Inhibition of Pregnancy-Dependent Mammary Tumorigenesis by a Single Treatment of Neonatal GR/A Mice with Monosodium Glutamate (40155)

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Perinatal treatment with monosodium glutamate (MSG) and related substances produces irreversible lesions in the brain, especially in the arcuate nucleus of the hypothalamus of various mammals (1–6). Associated with these lesions, pituitary and ovarian functions are reduced (7, 8) and mammary gland development is also impaired (8).

In this paper, the effects of neonatal administration of MSG on the development of pregnancy-dependent mammary tumors of GR/A mice (9) were studied. Since the development and growth of this type of tumor are largely dependent upon reproductive activity and since reproduction is often affected by neonatal MSG treatment (10), the effects of treatment on reproduction were also recorded.

Materials and methods. Female mice of the highly inbred GR/A strain maintained in our laboratory were used. At 0 day of age (day of birth), half of the females in each litter received a single subcutaneous injection of 4 mg MSG (WAKO Pure Chemicals Inc., Osaka, Japan) dissolved in 0.01 ml physiological saline. The remaining females of each litter received the vehicle only and served as controls. All mice were weaned at 20 days of age, maintained in an air-conditioned (24 ± 0.5° and 65–70% relative humidity) and artificially illuminated (14 hr light from 5:00 AM to 7:00 PM) animal room, and provided with a commercial diet (CA-1: CLEA Japan Inc., Tokyo, Japan) and tap water *ad libitum*.

Mice were weighed on days 20 and 60 (the day of mating) and litter size and number of palpable mammary tumors were counted at parturition. Only the data from mice which were delivered within 33 days after mating were used, since the primiparous age has an influence on the appearance of this type of tumor.

Statistical significance of differences between groups was determined by the Student t test or the χ^2 test.

Results. Extent of mammary tumorigenesis in each group is shown in Table I. The control mice had more than twice the mammary tumor incidence than the MSG-treated mice ($P < 0.001$). Whereas the average number of tumors in the control mice was 1.4 per mouse with tumors, ranging from 1 to 3, all MSG-treated mice had only 1 tumor per mouse with tumor ($P < 0.05$).

Body weight and reproductive ability are illustrated in Table II. Whereas there was no difference in body weight on day 20 between the control and the MSG-treated mice, the weight on day 60 and the percent changes were significantly greater in the MSG-treated mice ($P < 0.01$ and $P < 0.02$, respectively).

No significant difference was found between the control and MSG-treated mice in any feature of reproductivity; interval between mating and parturition, percentage of pregnancy, still birth and still-born pups, and litter size.

Discussion. This study shows that both incidence and number of pregnancy-dependent mammary tumors per mouse of the GR/A strain were significantly suppressed by a single neonatal injection of MSG. On the other hand, reproduction was not influenced by the treatment. It has been reported in mice that

TABLE I. EFFECTS OF NEONATAL TREATMENT WITH MONOSODIUM GLUTAMATE (MSG) ON PREGNANCY-DEPENDENT MAMMARY TUMORIGENESIS IN GR/A FEMALE MICE.

Group and treatment[a]	Mammary tumor incidence (%)	No. of tumors per mouse with tumors
MSG	31.4 (11/35)[b]	1.0 ± 0.0[c]
Control	70.5 (31/44)	1.4 ± 0.1
P	< 0.001[d]	< 0.05[e]

[a] MSG group of mice received single subcutaneous injection of 4 mg MSG dissolved in 0.01 ml physiological saline on the day of birth. The control mice were given vehicle only.

[b] No. of mice with tumors/Total No. of mice examined.

[c] Means ± SEM.

[d] Checked by the χ^2 test.

[e] Checked by the Student t test.

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TABLE II. EFFECT OF NEONATAL TREATMENT WITH MONOSODIUM GLUTAMATE (MSG) ON REPRODUCTION IN GR/A FEMALE MICE.

		Body weight			Reproduction				
Group and treatment[a]	No. of mice	20 days (g)	60 days (g)	% Change	Days between mating and parturition	% Pregnancy	% Still birth	% Still-born pups	Litter size
MSG	35	6.7 ± 0.2[b]	21.2 ± 0.4	232 ± 10	23.5 ± 0.5 (33)[c]	94.3 (33/35)[d]	2.9 (1)[e]	3.0 (6/202)[f]	6.3 ± 0.3 (32)[c]
Control	44	6.9 ± 0.2	19.4 ± 0.2	197 ± 10	22.7 ± 0.4 (43)	97.7 (43/44)	6.8 (3)	1.5 (4/270)	6.8 ± 0.3 (41)
P[g]		NS	<0.01	<0.02	NS	NS	NS	NS	NS

[a] See Table I.
[b] Means ± SEM.
[c] Number of mice examined.
[d] Number of pregnant mice/number of mice mated.
[e] Number of mice which gave birth to still-born pups.
[f] No. of still-born pups/Total No. of pups.
[g] Checked by the Student t test.

reproduction is often impaired by neonatal treatment with MSG (10); however, the doses used were much higher and for longer periods than in the present study. The growth of the pregnancy-dependent mammary tumor is largely determined by progesterone levels (11), and the effects of progesterone are enhanced by placental lactogen (11) and estrogen (12). These hormones are also essential for the maintenance of pregnancy. Thus, the results of the present study suggest that the development of pregnancy-dependent mammary tumors is affected to a greater extent by subtle changes in the hormonal milieu, especially in progesterone, than is the maintenance of pregnancy, although the degree of the alteration by MSG of individual hormone secretion is not precisely understood. In this respect, the amount of progesterone sufficient for maintenance of pregnancy is insufficient to prevent post-ovariectomy regression of pregnancy-dependent mammary tumors (12). This study raises the possibility of prophylaxis of mammary and other hormone-related tumors by alteration in hormonal conditions to minor extent that normal physiological functions are little affected.

Body weight and growth rate on day 60 were significantly greater in MSG-treated mice than in the controls. This may partially reflect early signs of the induction of obesity by MSG (1–6, 8, 13).

Summary. A single subcutaneous injection of 4 mg monosodium glutamate (MSG) on the day of birth resulted in the marked inhibition of appearance of pregnancy-dependent mammary tumors in GR/A mice. MSG treatment also decreased the number of tumors per mouse. On the other hand, reproduction was not affected by the treatment.

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