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The Effect of Neonatal Administration of Monosodium Glutamate on the Circadian Control of Food Intake in the Rat

by

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ABSTRACT

Neonatal treatment with monosodium glutamate (MSG) results in a substantial degeneration of the inner layer of the retina and a decreased diameter of the optic nerves. Nevertheless, MSG-treated animals entrain and re-entrain to a light dark cycle. The question arises whether MSG selectively destroys the optic pathways which are involved in vision but not the retinohypothalamic tract that mediates entrainment. In these experiments not only entrainment and re-entrainment of the circadian food intake rhythm of MSG-treated rats was investigated but also the freerunning period under continuous bright and dim light. It appears that MSG-treated rats have shorter freerunning periods under continuous illumination than controls. Therefore, these results suggest that also those pathways involved in entrainment of the circadian food intake rhythm are affected by neonatal treatment with MSG.

INTRODUCTION

Subcutaneous administration of monosodium glutamate (MSG) to newborn mice and rats results in a number of anatomical, physiological and behavioural abnormalities (Nemeroff et al., 1977, 1981; Olney, 1969a). Precocious puberty, sterility and obesity have been reported (Olney, 1969a) and considerable histological changes have been found in the hypothalamic arcuate nuclei (Marani et al., 1982; Schiethart et al., 1983). In addition to this, the neurotoxity of MSG causes a selective degeneration of the inner layer of the retina (Potts et al., 1960) but leaves the outer layers unharmed (Lucas et al., 1957; Cohen, 1967; Olney, 1969b; Hansson, 1970). Moreover, in these animals the visual placing response is absent (Nemeroff et al., 1977), in the electroretinogram only the a-wave is found (Potts et al., 1960) and a reduction of the retinal terminals in the superior colliculi and in the dorsal lateral geniculate nuclei is observed (Pickard et al., 1982). However, Groos (1981) found a normal proportion of dorsal lateral geniculate cells still responding to visual stimulation. Van Rijn et al. (1986) found that retinal ganglion cells surviving MSG treatment are not smaller than those of a control group and that no particular retinal cell group is missing.

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Abstracting keywords: monosodium glutamate, circadian rhythms, retinohypothalamic tract, brightness discrimination, entrainment.

Data on the effect of MSG on the circadian rhythmicity are somewhat controversial. Pickard et al. (1982) claim that both entrainment and re-entrainment of locomotor activity to a shifted light-dark schedule and the freerunning period in constant darkness are similar in MSG-treated hamsters and controls. On the other hand Miyabo et al. (1985) claim a shortening of freerunning period and a rapid decomposition in ultradian components of locomotor activity in blinded MSG-treated rats. The present experiments are aimed to investigate the effect of neonatal administration of MSG on the circadian control of food intake in sighted rats under entrained as well as under freerunning conditions.

MATERIALS AND METHODS

Pregnant Wistar rats were obtained from the animal breeding colony of TNO, Zeist, The Netherlands and were individually housed in a temperature (22°C) and light controlled room (L/D = 12/12, light on at 7.30 a.m., light intensity = ± 100 lux). The average relative humidity was 60%. The pups born in a 24 h period were separated so as to obtain "litters" which consisted of 6 pups of the same sex. Two litters of females and one litter of males received MSG; one litter of males served as a control.

From the second day of life onwards, the experimental pups were subcutaneously injected at about 09.00 a.m. with 0.1 ml of a MSG solution in distilled water for 10 consecutive days. The amount of MSG injected was increased from 2.0 mg/g body weight on the first injection day to 4.2 mg/g on the tenth injection day (Redding et al., 1971).

The control animals received injections with 0.1 ml of 0.9% NaCl solution at the same time and over the same period as the MSG animals. After weaning at 50 days 4 pups from each group were individually housed in perspex cages in a light (L/D = 12/12) and temperature (23°C) controlled room with an average humidity of 60%. The rats had free access to water and food (Muracon pellets; average weight of a pellet 0.124 ± 0.024 g; energy value 9.66 kJ/g). Eating activity was measured according to the method described before in detail (Rietveld et al., 1980). Data were stored in a microcomputer type DEC LSI 11/20. Every 30 min the data were automatically transmitted to a PDP 11/70 system for further analysis.

Primary data analysis was performed by plotting eating activity against time. The presence of rhythmicity was detected by making periodograms (Dörrscheidt and Beck, 1975) for data sets containing at least 20 days. During the first 30 days of recording the animals were synchronized to the L/D cycle. To investigate course of velocity of resynchronisation, a 6-h phase delay shift of the light regimen was introduced twice. The freerunning period of eating activity was determined during a constant light regimen of 7 weeks (light intensity ± 100 lx). Thereafter, one week of L/D was followed by dim red light for another three weeks.

Before weaning the litters were weighed as a whole whereas after weaning the individual rats were weighed each week. In order to estimate the effectiveness of the MSG treatment the Lee obesity index was calculated from body weight and naso-anal length measured at the age of 122 days of both the MSG-treated and control male rats (Bernards and Patterson, 1968). After termination of the experiment the animals were killed, the brains were taken out and the sections of the SCN and the arcuate region were stained according to Klüver-Barrera.

Histological verification of both cell groups was done by gross visual inspection of the number of cells and cell types.

RESULTS

Although rats treated with MSG have significantly lower body weights than rats treated with NaCl (391.0 ± 4.0 v.s. 330.0 g ± 2.0), the Lee obesity index of the first group tends to be higher (299.0 ± 0.9 v.s. 311.5 ± 4.3).

In Figure 1 an actogram for one control rat (left hand side) and one MSG rat is shown.

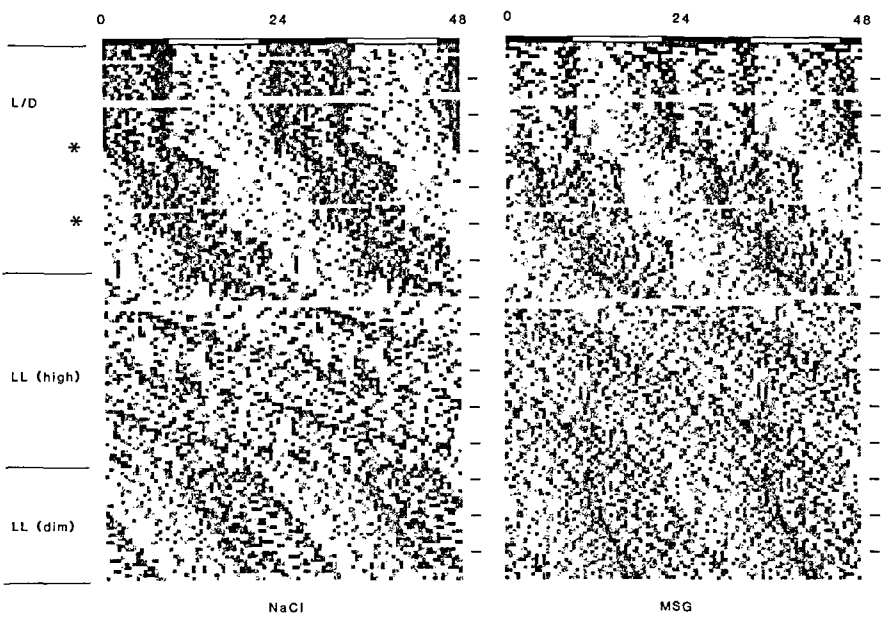
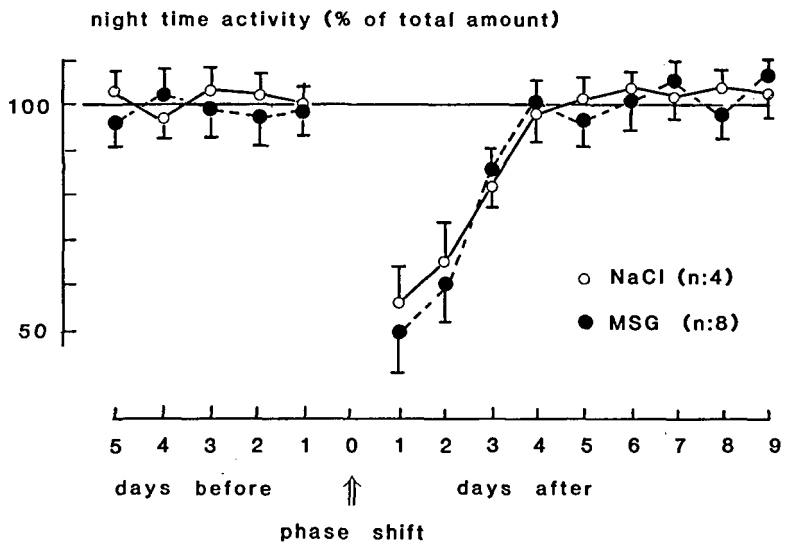


Figure 1: Feeding records of a MSG- and NaCl-treated rat. Both animals entrained well to the initial L/D = 12/12 cycle while re-entrainment to a 6-h delayed cycle (denoted with an asterix) was complete within 5 days. Under LL, a shorter period length was observed in experimental animals as compared to the controls. This difference, although smaller,was still present when the animals were placed under dim red light. The records are double plotted to enable visualization of the rhythms.



Figere 2: The rate of re-entrainment is shown for the NaCl- and the MSG-treated animals. On the vertical axis, the night-time activity is plotted as percentage of the total activity per 24 h (mean ± 1 s.e.m.).
The mean activity during the five days prior to the phase shift is normalized to 100%.

All animals entrained to the initial light dark cycle and, following a phase shift of 6 hours, re-entrainment was complete within 5 days (see Figure 2). Arhythmicity or a decomposition of the circadian rhythm in ultradian components was never observed when the animals were exposed to either continuous bright light or to dim red light.

However, periodogram analysis of the activity data during constant light reveals a statistically significant difference between the experimental and the control group (Student t test: $p<0.001$). The period of the circadian rhythm in food intake of the MSG-treated rats was 25.01 h ± 0.07 (mean ± s.e.m.) and of the control group 25.35 h ± 0.06 h. Within the MSG-treated groups there were no significant differences in pattern between the males and females.

Moreover, the freerunning period during dim red light was significantly shorter in the MSG-treated animals as compared to the saline-treated groups: 24.22 h ± 0.02 and 24.35 h ± 0.03 respectively (Student t test, $p<0.001$). Again there were no differences between the males and females in the MSG-treated group.

Histological examination of the brains after the experiment revealed that the MSG group was clearly different from the NaCl control group. The arcuate region of the MSG-treated males and females showed a paucity of cells. Most of the remnant cells were small non neuronal glial cells. In contrast to this the

SCN of both groups of animals showed no anatomical defects, that is, neither the number of cells nor the cell types were different.

DISCUSSION

Neonatal treatment of rats with MSG results in considerable degeneration of the inner nuclear layer of the retina and a concomitant decrease in the diameter of the optic nerve (Potts et al., 1960). In an extensive study of Pickard et al. (1982) the optic pathways were examined by monocular injections with the anterograde tracer HRP. The results indicate that MSG causes a substantial reduction in the density of retinal terminals in the dorsal lateral geniculate nucleus, in the superior colliculus and in the medial terminal nucleus but not in the retino-hypothalamic pathway which is of major importance for the entrainment of circadian rhythms (Dark et al., 1975; Pickard, 1982; Zucker et al., 1976). Moreover, the projection to the ventral lateral geniculate nucleus appears to be relatively intact. This is interesting since the ventral lateral geniculate nucleus may also be involved in the entrainment of circadian rhythms (Albers et al., 1984; Meijer et al., 1984). Therefore, the results of Pickard et al. indicate that retinal ganglion cells are differentially sensitive to MSG, that is, ganglion cells dealing with vision are affected while ganglion cells involved in information transmission to the circadian pacemaker in the SCN are not. This conclusion is important since it would allow to selectively damage the visual system while sparing the SCN afferents.

Analysis of the axon diameter distribution in the optic nerve of MSG-treated rats by Marani et al. (1984) shows a decrease in the number of axons with a large diameter as well as with a small diameter, mainly leaving the axons with intermediate diameters unharmed. It has been assumed that the bigger the soma size of the ganglion cell, the bigger is the diameter of its extra-retinal axon (Fukuda, 1977). In spite of this structural damage there is no specific loss of one cell size group (van Rijn et al., 1986). Small and large sized ganglion cells are at least present although, in this study, no quantification was undertaken. Furthermore, a normal proportion of dorsal lateral geniculate neurons in MSG-treated rats responds to visual stimulation (Groos, 1981). It is difficult to assess whether or not these results are consistent with the idea that MSG selectively damages the optic pathways which mediate vision.

The observation that MSG-treated animals display normal entrainment to a light-dark schedule as well as normal re-entrainment to a 6-h shifted light dark schedule suggests a functionally intact retinofugal pathway to the SCN (Pickard et al., 1982; Rietveld et al., 1980) and, thus, favours the hypothesis that MSG selectively damages the optic pathways that are involved in vision. The question is whether these behavioural experiments are critial enough to permit this conclusion. Lesions of the VLGN of the hamster for example do affect the afferents of the SCN but do not clearly result in impaired entrainment or

re-entrainment to a 4-h shifted ligt dark schedule (Rusak et al., 1981).

In a new series of experiments we not only investigated the rate of re-entrainment in both control and MSG-treated animals but we also examined the period length under continuous light. As has been shown by Summer et al. (1984) the freerunning period increases in direct proportion to the $\log_{10}$ illuminance of the environment when rats are exposed to continuous light. Possibly, a severed afferent system is reflected in a difference in period length in LL between both groups. Indeed the period in constant light of MSG-treated animals appeared to be smaller than the period of control animals while no difference could be found in the rate of re-entrainment. A decrease of the period can be explained either by a reduced photic input to the pacemaker or by a partial SCN lesion (Rietveld, 1984). Since histological examination of the SCN revealed that the SCN was spared from histological damage following MSG treatment the latter explanation can be excluded. We therefore asumed a reduced photic input to the SCN.

Both the control and the experimental animals were exposed to continuous dim red light for 3 weeks. Red light is often used instead of continuous darkness with the assumption that dim red light cannot be perceived by the circadian system. The observation that the period of MSG-treated animals in continuous red light deviates from the period in controls may interfere with our conclusion because it is not known whether a severed afferent system also affects the freerunning period in continuous darkness. We therefore undertook a new series of experiments to determine whether our red light condition indeed mimicked continuous darkness. Six intact rats were exposed to a dim red light-darkness schedule (L/D = 12/12). All animals entrained to this schedule. Apparently, the dim red light used in our initial experiment is not similar to continuous darkness but resembles continuous dim light. We therefore conclude that a decrease in period length under both light conditions following MSG treatment can be explained by a reduced photic input to the SCN. Thus, MSG not only affects the pathways that are involved in vision but also those optic pathways that mediate entrainment of circadian rhythms.

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