Pharmacology Biochemistry & Behavior, Vol 24, pp 975–981, 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

Impaired Selective Attention in Methylazoxymethanol-Induced Microencephalic Rats

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Received 20 August 1985

MOHAMMED, A K, G JONSSON, U SODERBERG AND T. ARCHER *Impaired selective attention in methylazoxymethanol-induced microencephalic rats* PHARMACOL BIOCHEM BEHAV 24(4) 975–981, 1986 —Prenatal treatment of rats on gestation day 15 with methylazoxymethanol (MAM) caused forebrain microencephaly. Several behavioral tests were performed when the rats had reached an adult age MAM treated rats were hyperactive, and were severely impaired in the acquisition of successive position reversal in a T-maze The microencephalic rats failed also to demonstrate contextual control of latent inhibition (the stimulus preexposure effect) in taste-aversion conditioning. These results indicate that MAM treatment disrupts attentional processes and that this may account for the learning impairment.

Methylazoxymethanol Microencephaly Hyperactivity Successive position reversal Taste-aversion Latent inhibition Selective attention

PREGNANT rats treated with the antimitotic agent methylazoxymethanol (MAM) on gestation day 15, produce offspring with a marked forebrain microencephaly, while the brainstem remains essentially unchanged [6, 7, 22]. The atrophy in forebrain structures (e g., cerebral cortex and hippocampus) is associated with a relative hyperinnervation of monoamine and acetylcholine nerve terminals [11,12]. A number of studies have recently been undertaken with a view to delineating the functional consequences of MAM induced microencephaly. Accumulating evidence indicates that prenatal MAM treatment causes hyperactivity (e g., [4,23]) and acquisition deficits in a variety of maze tasks such as the Hebb Williams [7], Lashley III [21] and water maze [3,9]. One possible explanation emerging from these observations is that the acquisition deficits may be due to disrupted attentional processes More specifically it is suggested that the acquisition deficits may stem from the microencephalic rats incapacity to attend adequately to different features of environmental stimuli.

The present study was therefore undertaken to examine the effect of MAM treatment on selective attention in the rat Animals were tested in an appetitively motivated task and in an aversively motivated test. In the former case animals were exposed to a T-maze discrimination task designed to reveal cognitive deficits (see [20]), and in the latter animals were tested for contextual control of latent inhibition (stimulus preexposure effect) using the taste aversion procedure described previously [1]. Latent inhibition refers to the well established observation that the nonreinforced preexposure of a stimulus retards acquisition when that stimulus is later paired with a reinforcement [16,17]. This procedure has been used often as a means of testing selective attention, the hypothesised process by which organisms differentiate relevant from irrelevant stimuli (e.g., [1,18]).

METHOD

Animals and Drug Treatment

Four pregnant Sprague Dawley rats were injected (IV) with 25 mg/kg MAM acetate under light ether anaesthesia on gestation day 15 MAM was diluted in 0.9% NaCl and injected in a concentration of 10 mg/ml of the solvent. Controls received an equal IV injection of the solvent alone Offspring were weaned at 3 weeks of age. The animals were housed in an air-conditioned room with controlled temperature and kept on a standardised light dark schedule (14/10 hr, light on 06.00 hr and off 20 00 hr). Animals were maintained on ad lib food (Lab Chow R3, Ewos, Sodertälje, Sweden) and water except where indicated.

Spontaneous Motor Activity

Apparatus. An automated device consisting of rat cages (40×25×15 cm) placed within two series of infrared beams

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TABLE 1

THE ORDER OF PRESENTATION OF SACCHARIN AND WATER, NOISY BOTTLES, AND SILENT BOTTLES DURING THE DIFFERENT PHASES OF THE LATENT INHIBITION EXPERIMENT

Groups	Acclimatization and deprivation schedule	Preexposure	Conditioning	Testing*
CONT-NS	WATER + SILENT	SACC + NOISY	SACC + NOISY	SACC + NOISY
CONT-SS	WATER + SILENT	SACC + SILENT	SACC + NOISY	SACC + NOISY
MAM-NS	WATER + SILENT	SACC + NOISY	SACC + NOISY	SACC + NOISY
MAM-SS	WATER + SILENT	SACC + SILENT	SACC + NOISY	SACC + NOISY

SACC=saccharin, NOISY=noisy bottle, SILENT=silent bottle For the acclimatization and deprivation schedules, preexposure phase and conditioning phase 30-min SACC/WATER presentations were maintained

*For the testing phase, the first two tests (T_1 and T_2) were 30-min presentations of SACC in the noisy bottles, and the third test (T_3) was an 8-hr presentation of one NOISY bottle with saccharin and one NOISY bottle with water to each rat

See also text for further details

(low level and high level), was used to measure spontaneous activity (Rat-o-matic, ADEA elektronik AB, Uppsala, Sweden)

Locomotion was registered when rats moved horizontally breaking the invisible infrared beams.

Rearing was registered when rats raised their front legs and/or rested on their haunches, with the upper part of the body breaking the high level infrared beams

Activity was registered by a pickup (mounted on a lever with a counterweight) with which the test cage was in contact.

Procedure At 100–106 days of age each rat was placed individually in the activity cage and locomotion, rearing and general activity recorded for two 30 min periods These measurements were taken over 4 consecutive days.

Maze Learning

Apparatus T-maze successive position reversal. The cognitive function of the animals was investigated in a T-maze where they were trained to discriminate between two goal arms for food reinforcement, and to alternate between these goal arms in order to obtain maximal reinforcement [20] The apparatus used was a modified T-maze, described previously [2]

Procedure Two weeks before the start of the maze learning task rats were food deprived and food intake was measured during 2-hr per day over a 7-day period On the day after the final measurement, rats were maintained at 80% of their original body weight At the start of the deprivation schedule the animals were 100–106 days of age with the experimental animals weighing about 257 g and controls weighing 360 g The procedure described by Olton [20] was employed Before the first testing day animals were habituated to the apparatus Testing started when the animals were aged 108–114 days The animal was placed at the start box at the beginning of each trial Each trial consisted of two runs (1) *forced run* in which one goal arm of the T-maze was blocked so that the animal was forced to go to the opposite arm for food reward, (2) *choice run* where both goal arms were available for the rat. However, only the arm not visited during the forced run contained a good pellet Thus the rat was required to alternate between the two goal arms for reinforcement Eight trials were run daily on each of 8 consecutive days (Day 1 to Day 8) with a 5 minute intertrial interval, the inter-run interval was 10 seconds Errors were recorded. The latency from startbox to either of the 2 goal boxes for each run was measured from Day 4 onwards

Latent Inhibition

Apparatus Two types of drinking bottles were used. (1) "silent" bottles consisting of 2 mm stainless steel nozzles which did not have any ball bearings in them and made no noise when the rats licked the tips of the nozzles, (2) "noisy." Plexiglas bottles (Techniplast, Italy) had 6 mm diameter stainless steel nozzles that contained two stainless steel ball bearings (diameter 5 mm) These bottles created a considerable amount of noise each time a rat licked the tip of the nozzle, causing the ball bearings to bounce up and down, during a particular burst of drinking

Procedure The animals were 120–126 days of age with the MAM-treated animals weighing 340 g and controls weighing 427 g. Ad lib food (Lab Chow, R3) was available throughout. Water was freely available in the silent glass bottles up to the period when the experiment began and rationed during the drinking training period (30 min), which was initiated one week prior to the preexposure trials

The experiment consisted of 3 phases preexposure, conditioning and testing phases. Table 1 presents an outline of the experimental design for the saccharin, water, and silent and noisy bottle presentations over all the experimental phases

Thirty min water intake (baseline water intake) was measured on the 3 days (W_1–W_3) prior to presentation of preexposure trials (P_1–P_5) On the first preexposure trial half the experimental (MAM-treated) animals and half the control animals were offered saccharin in the noisy bottles while the other half were offered saccharin in the silent bottles for 30 min Saccharin intake was recorded This procedure was repeated during the next four alternate days Thus there were five preexposure trials Water was offered for 30 min in silent bottles on the days interpolating the preexposure trials During the conditioning trials all the animals were given saccharin in the noisy bottles for 30 min Shortly after the saccharin presentation all the rats received a 10 mg/kg injection of lithium chloride (0 15 M solution)

Two such conditioning trials (C1 and C2) were presented with an interval of 48 hr between them, and with a 30 min water presentation in the silent bottles 24 hr after C1

Two days following the last lithium chloride presentation,

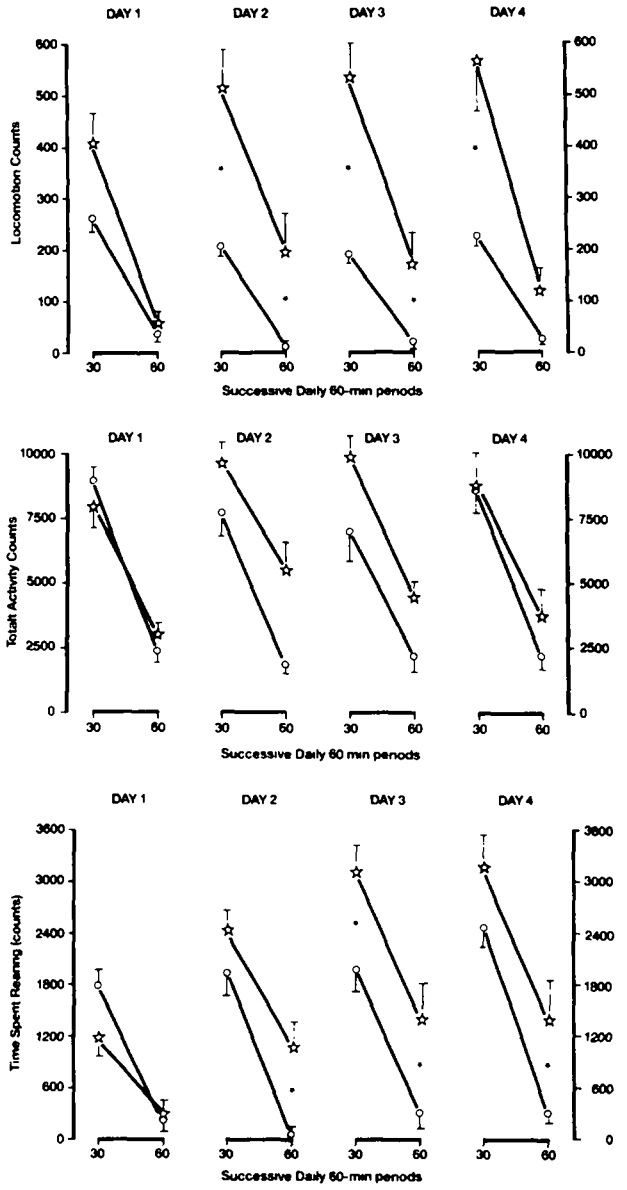

FIG 1 Locomotion, rearing and activity counts of MAM-treated rats (stars) (n=12) and controls (circles) (n=12) during two 30 min periods over 4 successive days

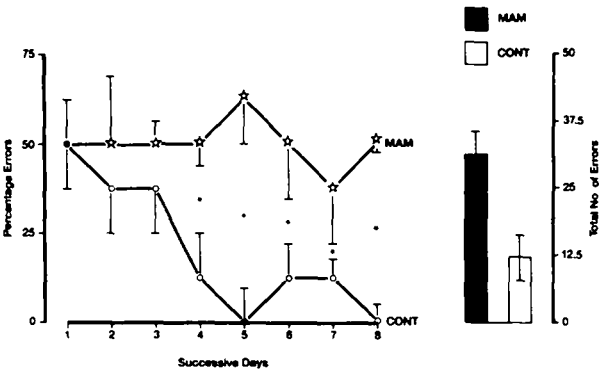

FIG 2 Performance of MAM-treated rats (stars) (n=8) and controls (circles) (n=8) on the T-maze successive position reversal, expressed as percentage errors Total number of errors for all 8 days of testing of MAM animals (shaded bar) and controls (open bar)

the first test (T_1), consisting of a 30 min saccharin presentation in the noisy bottles, was performed. This procedure was repeated for the second test (T_2) 48 hr later with a normal 30-min water presentation in the silent bottles occurring 24 hr after T_1. The third saccharin preference test (T_3) was offered 24 hr later, whereby rats were given two noisy bottles, one containing saccharin and the other water, during an 8 hr period. Throughout, fluid intake was recorded by weighing the bottles to the nearest 1.0 g. The preference for saccharin in relation to total fluid intale

Catecholamine and catecholamine metabolite assay. At the end of behavioral tests animals were sacrificed by decapitation. The brains were rapidly removed and dissected, as described by Jonsson and Sachs [13]. The brain tissues were homogenized by sonication in 310 μ 0 1 M perchloric acid containing 10–50 pmol 3,4-dihydroxybenzylamine (internal standard) using a Branson B 30 sonifier. After a cleanup step of the extracts using an Al_2-0_3-adsorption, desorption procedure [14], noradrenaline (NA), dopamine (DA), 3,4-dihydroxyphenylglycol (Dopeg), 3,4-dihydroxyphenyl acetic acid (Dopac) and dihydroxyphenylalanine (Dopa) were assayed by liquid chromatography with electrochemical detection (LCEC) according to Durkin *et al* [5]. The values are expressed as ng/g wet weight of the tissue based on measurement using 3,4-dihydroxybenzylamine as internal standard. Aliquots of the extracts were, after filtration through a membrane filter (pore size 0.2 μ) injected into the chromatography The values obtained are expressed as ng/g wet weight of the tissue

Results

Motor activity Three different parameters of motor activity were measured: Locomotion, rearing and total activity. The MAM-treated rats displayed a notable increase in all three measures of activity. Figure 1 presents the locomotion, rearing and total activity by the MAM-treated and control rats over four consecutive daily sessions, each consisting of two 30-min periods. Two-way ANOVA indicated a significant Groups × Periods interaction for the locomotion data, $F(7,167)=2\,4$, $p<0.01$.

Pairwise testing between groups using the Tukey HSD test indicated significantly more locomotion counts by the MAM-treated rats during both periods on Days 2 and 3 and during the first 30 min on Day 4. The Groups × Periods interaction was significant for the Rearing data, $F(7,165)=2\,3$, $p<0.01$, as a result of more rearing counts during both periods on Day 3, and the second 30 min period on Day 2 and Day 4. There was a significant Groups effect, $F(1,165)=10.2$, $p<0.01$, for the total activity data

Pairwise testing between groups over all the eight test periods indicated significantly more total activity counts by the MAM-treated animals. It should be noted that in neither locomotion, rearing nor total activity did MAM-treated rats demonstrate a greater activity from the outset, i.e , the first 30 min period on Day 1.

Successive position reversal. MAM-treated rats showed a severe deficit on the successive position reversal task. Figure 2 presents the percentage errors by the MAM-treated rats and the control rats over all eight days of testing as well

TABLE 2

TWO HR FOOD INTAKE MEASUREMENT, OVER A 7-DAY PERIOD, CARRIED OUT TWO-WEEKS PRIOR TO THE START OF THE SUCCESSIVE POSITION REVERSAL TASK

	2 hr Food Intake (g)						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
MAM-treated*	6 9 ±0 4	8 3 ±0 5	8 3 ±0 4	5 9 ±0 6	8 7 ±0 4	9 0 ±0 6	9 6 ±0 5
Controls	7 5 ±0 4	9 1 ±0 4	10 5 ±0 3	6 7 ±0 7	9 2 ±0 5	9 8 ±0 4	11 4 ±0 9

	Run Latency (sec)				
	Day 4	Day 5	Day 6	Day 7	Day 8
MAM-treated	3 6† ±0 3	3 2† ±0 3	2 8† ±0 2	3 0† ±0 2	3 4† ±0 5
Controls	16 0 ±1 1	6 1 ±1 2	5 1 ±0 8	5 0 ±0 6	4 3 ±0 5

Mean average latency (from 16 runs per rat) from the start box to either of the 2 goal boxes from Day 4 to Day 8 of the successive position reversal task

*Groups effect, $F(1,147)=15\ 2$, $p<0\ 01$ †Student's t-test, $p<0\ 01$

Values are expressed as mean ± s e m

The mean run latencies were derived from the average latency of 16 runs from each rat on each of the test days when the latencies were measured

as the total number of errors Mann-Whitney U-tests indicated significantly more errors by the MAM-treated rats during sessions 4, 5, 6, 7, and 8 ($p<0.01$), and a significantly greater number of total errors ($p<0.01$). It should be noted again that the MAM-treated rats and the control rats made the same number of errors during the first session Table 1 presents the 2-hr food intake measurements and the mean average latency for the MAM-treated and the control rats MAM-treated rats consumed significantly less food than controls, $F(1,147)=15\ 2$, $p<0.01$, and their mean average running latencies were significantly shorter than the controls during Days 4, 5, 6, and 7

Latent inhibition MAM-treated rats showed a lower baseline water intake level. Table 3 presents the baseline water intake and preexposure saccharin intake for the MAM-treated and control rats. MAM-treated rats drank significantly less saccharin than the control rats during the preexposure phase Note however that MAM and control rats did not differ at the first saccharin exposure (P_1). The lower saccharin intake was probably the result of a lowered fluid baseline intake (see Table 3) During conditioning (in the noisy bottles), the CONT-NS group drank significantly more saccharin than the CONT-SS group whereas the MAM-NS group in fact drank *less* saccharin than the MAM-SS groups. Since during the preexposure phase the -NS groups received saccharin in the noisy bottles whereas the -SS groups received saccharin in the silent bottles, it was expected that the -NS group would show more latent inhibition, i e., drink more saccharin, the contextual conditions being identical from preexposure to conditioning (cf. [1]) During testing (again presented in the noisy bottles), the same result as for the conditioning phase was obtained The CONT-NS group drank more Saccharin (T1 and T2) and showed a greater saccharin preference (T3) than the CONT-SS groups whereas the MAM-NS group drank *less* saccharin than the MAM-SS group (Mann-Whitney U-tests, $p<0.01$). Figure 3 presents the saccharin intake and preference test data from the conditioning and testing phases The results of the latent inhibition in taste-aversion conditioning experiment indicate that MAM-treated rats do not attend to both the taste (saccharin) and the contextual (noisy drinking bottle) cue during the preexposure and conditioning of saccharin aversions

Catecholamine and metabolites assay In agreement with previous studies [10,11] it was found that prenatal MAM treatment caused a marked increase in NA and DA concentrations in the cerebral cortex and hippocampus Analysis of catecholamine metabolites indicated that there was a general increase of DOPEG, DOPA and DOPAC in the cerebral cortex and hippocampus of MAM treated rats (see Table 4)

DISCUSSION

Prenatal administration of MAM on gestation day 15 was found to cause a marked forebrain microencephaly with considerable weight reduction of cerebral cortex, hippocampus and striatum This is in agreement with earlier findings (e.g., [8, 10, 22]). The brainstem which is formed around gestation day 13 [19] and containing the monoamine cell bodies was essentially unchanged. The volume reduction of the forebrain structures was associated with a relative hyperinnervation of catecholamine terminals These obser-

TABLE 3

BASELINE WATER INTAKE (W_1–W_3) AND SACCHARIN INTAKE DURING THE PREEXPOSURE TRIALS (P_1–P_5)

Groups		Water			Saccharin				
	(N)	W_1	W_2	W_3	P_1	P_2	P_3	P_4	P_5
MAM-NS	(5)	17	16	18	10	18	17 5	19	23 5
MAM-SS	(6)	17	17	21	14	25	22	23	27
CONT-NS	(5)	24	22	25 5	10 5	26	27 5	30 5	33
CONT-SS	(6)	23	21	25	12	25	28	29	32 5

-NS groups received saccharin in the noisy bottles and -SS groups received saccharin in the silent bottles during the preexposure trials Water and saccharin were as offered for 30 minutes The MAM groups drank significantly less water during W_1 to W_3 and less saccharin during P_1 to P_5, Mann-Whitney U-tests, $p<0$ 02

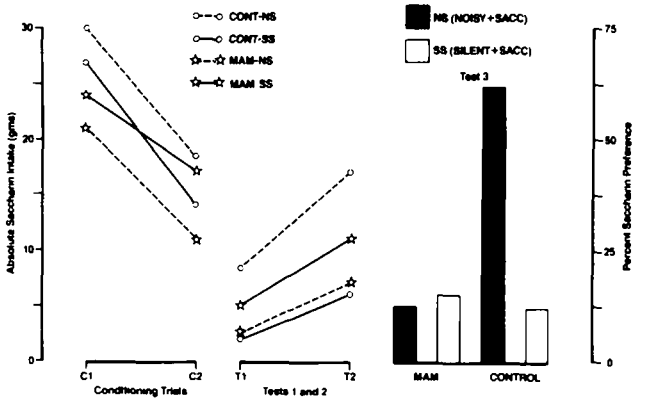

FIG 3. Mean saccharin intake in noisy bottles by MAM-treated and control rats during the conditioning trials (left-hand panel), and during the saccharin intake tests, T1 and T2 (middle panel). Percentage saccharin preference during the preference test, T3 (right-hand panel)

TABLE 4

EFFECT OF PRENATAL MAM TREATMENT ON CATECHOLAMINE AND METABOLITE LEVELS IN CEREBRAL CORTEX AND HIPPOCAMPUS

Region		n	NA	DA	DOPEG	DOPAC	DOPA
Cerebral Coretx	MAM	14	614 ± 32	329 ± 50*	56 ± 7*	154 ± 17*	9 ± 2*
	(%)		(188)	(206)	(193)	(226)	(225)
	Control	14	327 ± 15	160 ± 21	29 ± 3	68 ± 8	4 ± 0 7
Hippocampus	MAM	14	718 ± 54*	33 ± 5*	51 ± 4*	34 ± 3*	26 ± 4*
	(%)		(161)	(183)	(159)	(189)	(217)
	Control	14	445 ± 46	18 ± 2	32 ± 1	18 ± 1	12 ± 2

n=Number of rats
(%)=Percent of control values
Values are expressed as means ± S E M , *$p<0$ 01, Mann Whitney U-test

vations suggest that the catecholamine neurons are programmed to produce a certain quantity of nerve terminal arborizations in regions they innervate during development. The results of the present study are in agreement with earlier findings in showing that MAM treated animals are hyperactive [4, 9, 15] and show habituation [23]. One line of reasoning has implicated the forebrain catecholaminergic hyperinnervation in the MAM induced hyperactivity [4]. This interpretation, however, must be tempered with the consideration that the MAM preparation encompasses a broad spectrum of abnormal neural events, rendering it difficult to ascribe the observed behavioural changes to a specific neurochemical substrate. For example, cholinergic, GABAergic and glutamatergic neurones are all affected by MAM treatment [3, 10, 11] However, as has been recently suggested [23], it may eventually be possible to relate the behavioural changes following MAM treatment with some of the neurochemical alterations documented.

The result of the T-maze task showed that MAM treated animals were severely impaired in acquiring a successive position reversal for food reward; since the task requirement for the *choice run* was that the rat recognised to which goal arm (right or left) reinforcement had been presented during the *forced run*, before making its choice, a cognitive deficit may be suggested. The MAM-treated animals may or may not have failed to discriminate between the two goal arms, but they certainly exhibited perseverative tendencies by persistently running to the arm that had previously contained the food pellet, thus failing to alternate between the two arms for reinforcement. As shown in Fig. 2 the performance of MAM-treated rats remained at about the same level (chance) throughout the testing period (8 days), whereas the controls rapidly acquired the alternation response. MAM-treated rats also ran to a particular goal arm faster than controls. Their food intake did differ significantly from the controls but since they showed shorter latencies to reach the goal arm no motivational defects appear to be indicated. The lower food intake may explain the lower body weight. The findings from the successive position reversal task suggest that the microencephalic rats have a narrowed span of attention and that this may be a contributory factor in the deficits these animals show in the variety of maze tasks. It has been reported that MAM-treated animals are comparable to controls in some operant conditioning tasks [21], T-maze learning [21] and conditioned flavour aversion [25]. It appears that these tasks which do not place too much of an attentional load are more easily handled by the MAM-treated rats. On the other hand, tasks that require the division of attention to more than one

environmental stimuli and the extraction of information with regard to relevant and irrelevant stimuli appear to overload the attentional capacity of MAM-treated rats In this regard it should be noted that MAM-treated rats entered the goal arm of their choice *four times as quickly* as the control rats, the MAM-treated rats did not decrease latencies from Day 4 to Day 8 although the control rats did so to a most notable extent However, it must be noted that the MAM-treated rats showed significantly greater spontaneous activity as measured by the locomotion and total activity parameters, and so one must be cautious in using the latency data to discount a motivational hypothesis. Notwithstanding this consideration, the slightly lower food intake of the MAM rats in comparison with the controls is offset by the smaller size of the MAM animals (the ratio of food intake to body weight was slightly higher for the MAM-treated rats in comparison with the control rats) and this argument does not support any motivation hypothesis Thus, the latency data may suggest considerable discrepancies between the MAM-treated and control rats in the amount of attention paid to the stimulus situation

The results of the latent inhibition experiment offer further support for the view that MAM treatment results in severe attentional disruptions During the preexposure phase, MAM-treated and control rats received saccharin in either *familiar* silent bottles (-SS groups) or *novel* noisy bottles (-NS groups). At conditioning, saccharin was presented in noisy bottles for all the rats. Thus, for the -SS groups the saccharin was presented in *novel* bottles while for the -NS groups the saccharin was presented in *familiar* bottles during conditioning It was found previously that taste-aversion conditioning was retarded considerably more under conditions in which both the taste (saccharin) and the particular drinking bottles were familiar than when only the saccharin was familiar [1] The present data confirm these results with regard to the control groups, i e , the CONT-SS group showed more saccharin aversion than the CONT-NS group. However, in the case of the MAM-treated rats the novelty/familiarity of drinking bottles failed completely to influence the strength of the saccharin aversion, i e , the MAM-NS group showed at least as much, possibly even more, saccharin aversion than the MAM-SS group This result suggests that MAM-treated rats clearly fail to attend to both the taste stimulus and the particular contextual cue (drinking bottle) within which it was presented during the preexposure and conditioning phases of the experiment However, there is an alternative hypothesis that ought to be considered During the preference test the control animals showed strong latent inhibition or not, depending upon their prior experience with presentation of saccharin in the noisy or silent bottles It may be argued that if the contextual cue (noisy/silent bottle) was indeed ignored by the MAM rats then one would expect both the MAM-SS and MAM-NS groups' intake of saccharin in relation to water to resemble that of the CONT-NS group, i e , they would drink saccharin as though they had not had any prior experience to inhibit them In the event, the MAM-SS group behaved more or less as the CONT-SS group whereas the MAM-NS group failed to show latent inhibition under the conditions designed to produce it Can it be that MAM rats simply fail to show latent inhibition? The problem with this argument is the data from T_1 and T_2 Here, the CONT-NS group showed considerably *more* latent inhibition than the CONT-SS group, indicating the contextual control of latent inhibition, whereas the MAM-NS group showed notably *less* latent inhibition than the MAM-SS, which appears to be a clear indication of absence of contextual control of latent inhibition It should be noted that the contextual control of latent inhibition has been postulated in a retrieval-based model [1], for example Wagner's Priming model [24] The possibility of some memory retrieval deficit in the MAM animals is presently under consideration

In summary, the results of both the successive position reversal in the T-maze and the context-dependent latent inhibition taste-aversion experiment provide evidence suggesting a cognitive deficit in the MAM-treated rats possibly due to some alteration of the functioning of selective attention processes

ACKNOWLEDGEMENTS

The skillful technical assistance of Bodil Kaller, Eva Lindqvist and Birgitta Wiehager is gratefully acknowledged

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