DEFICIENCY OF BEHAVIORAL INHIBITION IN HYPOTHYROID RATS: A PILOT STUDY

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Abstract

We examined the relationships between behavioral inhibition and thyroid hormone systems. Pregnant rats were treated with methimazole at a dose of 0.02% from gestational day 15 to postnatal day 21. Offspring were subjected to a differential reinforcement of low rate 20 s. Animals were required to wait to press a lever for greater than or equal to 20 s after the previous response to be rewarded with a food pellet. Treated rats were unable to shift the distribution of inter-response times toward 20 s, instead displaying a tendency to respond prematurely. This study supports the hypothesis that disruption of thyroid hormone systems induces a deficiency of behavioral inhibition.

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by poor behavioral inhibition[1]. The causes of ADHD, however, are unclear; the influences of environmental endocrine disrupters, such as PCBs and dioxins, are cited as risk factors for ADHD. These chemicals disrupt thyroid hormone systems and affect the normal development of the CNS[3]. Hypothyroid animals are predicted to exhibit poor performance in a differential reinforcement of low rate (DRL) schedule in which animals' behavioral inhibition is required.

In this study, examination of the performance of hypothyroid animals provided valuable insight into the relationships between behavioral inhibition and thyroid hormone systems.

Materials and Methods

Four pregnant Wistar rats, housed in individual cages, were randomly assigned to either a control group (n=2) or a methimazole group (n=2). Methimazole was dissolved in distilled water and administered to pregnant rats in their drinking water at a dose of 0.02% (w/v) from gestational day 15 to postnatal day 21. After weaning, the offspring were divided into male control (n=3, MC), male methimazole (n=3, MM), female control (n=5, FC), and female methimazole (n=5, FM). Animals were individually housed under free-feeding conditions until 12 weeks of age. At that time, the intake of all animals was restricted to maintain the male and female rats at 85% and 90% of their free-feeding body weights, respectively. Additional food was supplied daily to maintain body

weights after experimentation.

Five standard operant chambers were employed. A room light, a food cup, and a response lever were installed on the front panel of the chamber. The room light was mounted 11 cm above the floor on the center of the panel. Dim light was provided throughout experimentation. The food cup was placed 10 cm below the room light. A food pellet (50 mg) was delivered as a reward from a pellet dispenser. The response lever protruded from the panel 3 cm above the floor and 8 cm to the right of the food cup. White noise (70 dB) was present throughout the experiments to mask external sounds. The chamber was placed in an isolation box.

After being training to press the lever, the rats underwent the DRL20 s. In this test, animals were required to press a lever greater than or equal to 20 s after the previous response. If the animals pressed the lever before 20 s had elapsed or did not press the lever for 60 s, no food pellet was delivered, and the next trial was started. The DRL test consisted of 100 trials per session per day for 60 sessions.

This research was performed with the approval of the Center for Advanced Science and Technology (Hokkaido University). Environmental conditions complied with the Guide for the Care and Use of Laboratory Animals (Hokkaido University).

Results and Discussion

The dams ingested a mean level of methimazole of 0.609 mg/day. No malformations or signs of overt toxicity were detected in the dams. There was, however, a significant difference in the body weights between MC and MM animals on the last day of free-feeding conditions [$F(1,4)=19.60$, $p<0.05$]. Body weights averaged 243.3 g and 220.0 g for MC and MM animals, respectively. The female animals averaged 146.0 g and 137.0 g in body weight for FC and FM animals. No significant differences were observed between the female groups. These results are consistent with previous studies[2,6] in which methimazole treatments caused several developmental delays, such as inability to achieve the normal weight gain and the maturation of physiological landmarks.

The percentage of rewarded responses reached 22% in MC and 3% in MM animals (Fig. 1). Rewarded response percentages for FC and FM animals were 35% and 18%, respectively. MM animals did not learn to wait on the DRL20 s test and the ability of FM animals to achieve on the DRL20 s was slower than that of FC animals. After 60 sessions of training, we measured the peak of inter-response time (IRT) distributions (Fig. 2). This value was typically located at 20 s, because the DRL20 s requires a 20 s response inhibition. The control groups exhibited a peak of IRT at 20-22 s. The methimazole-treated groups, however, did not display a clear peak at 20-22 s. For example, MM animals displayed a high frequency of IRT at 0-2 s.

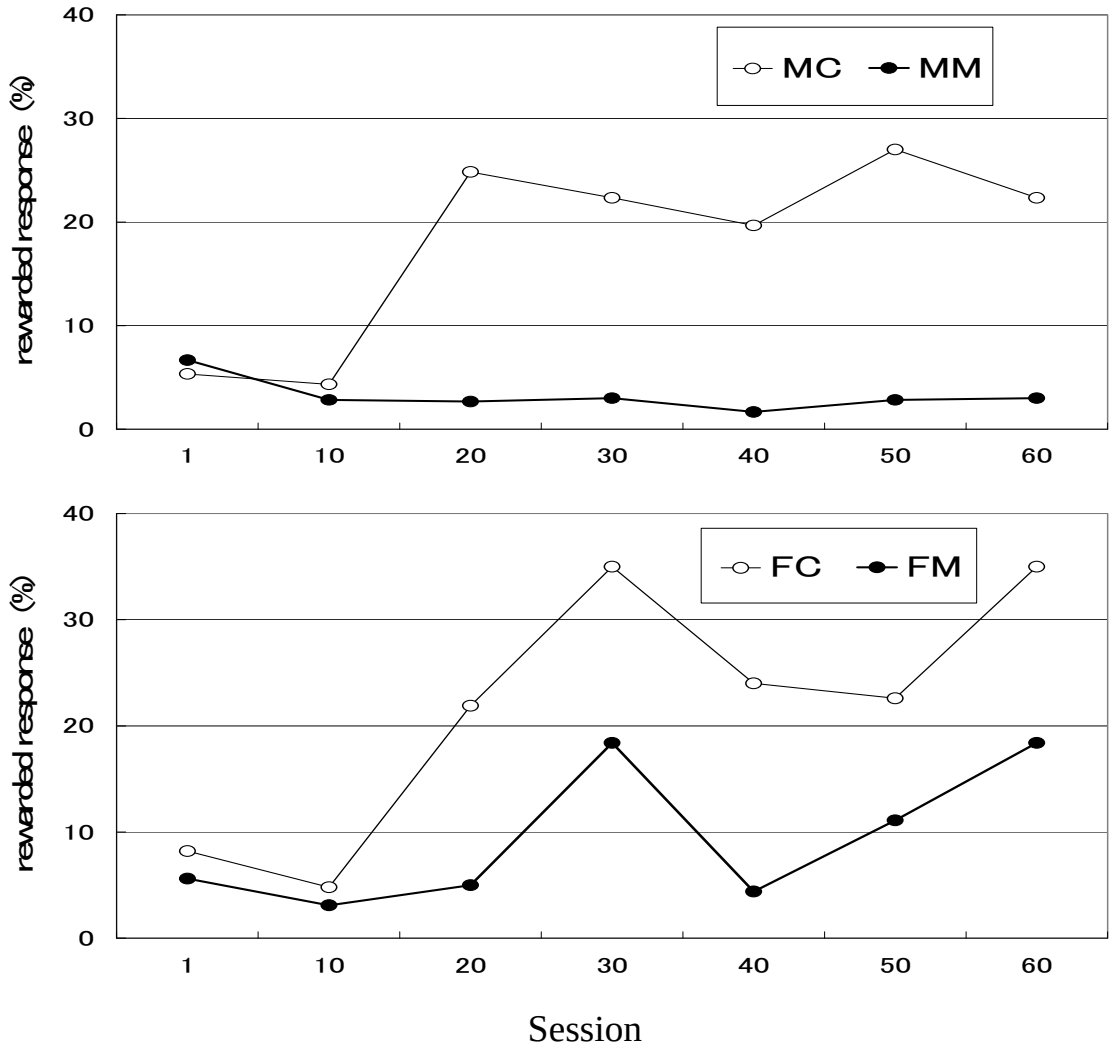

Fig. 1. Effect of methimazole treatments on the percentage of rewarded response.

Rice[5] tests PCB-ingesting monkeys in the DRL30 s. This result demonstrates that the monkeys do not develop DRL30 s performance; their IRT is shorter, and the number of rewarded responses is reduced. PCB-treated animals do not exhibit the inhibition of responding[4], which is consistent with the current results.

In this work, no significant effect of methimazole on the percentage of rewarded responses was observed; neither the mean, mode, nor median of the IRT distributions were significantly different between groups, likely because of the small numbers of animals enrolled. The methimazole groups, however, did not increase the numbers of rewarded responses with time. Neither of the methimazole-treated group shifted the peak of IRT distributions toward 20 s. Taken together; the methimazole groups displayed a tendency to be unable to wait for 20s, suggesting a deficiency of behavioral inhibition. Now we are challenging this point with a larger sample size.

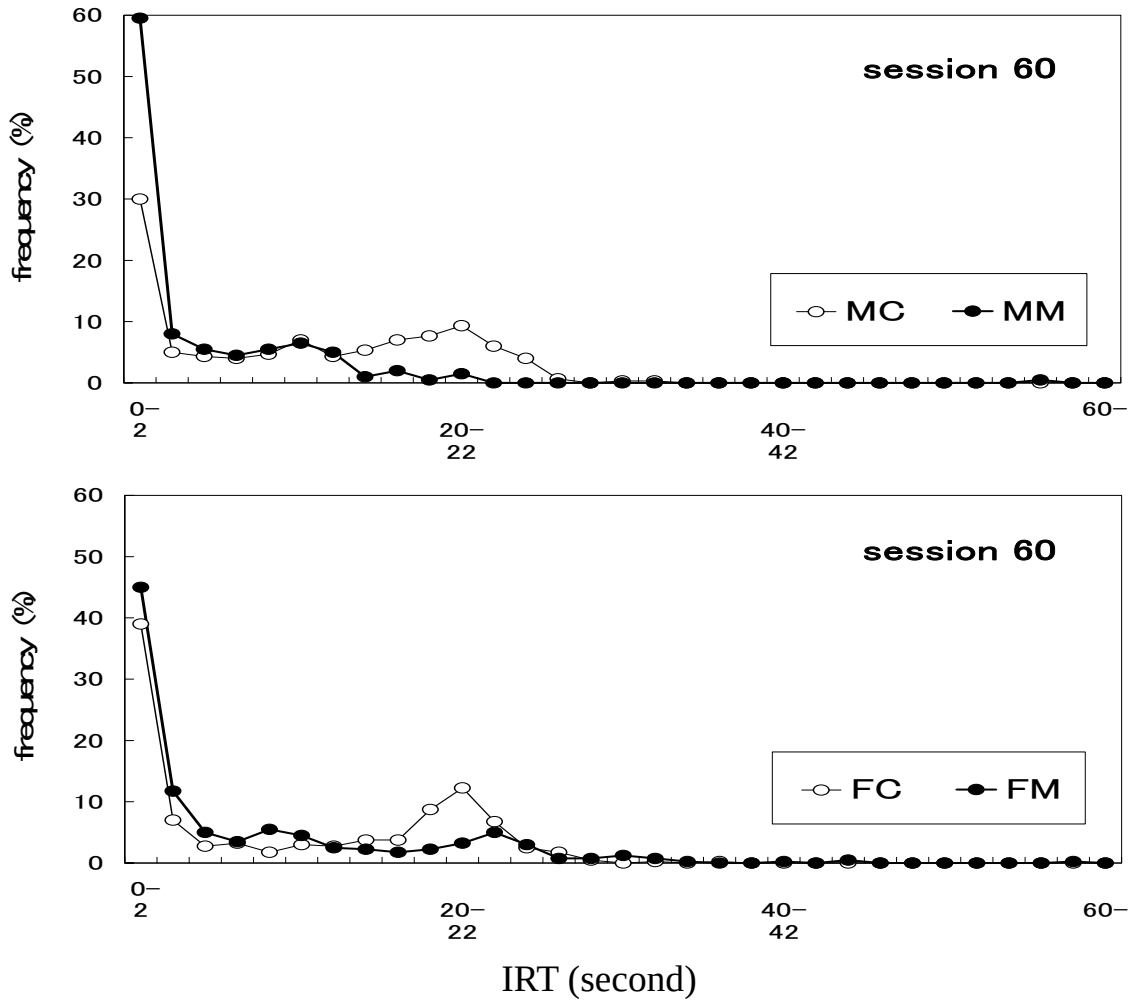

Fig. 2. Effect of methimazole treatments on the distributions of inter-response time (IRT).

Acknowledgments

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References

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