HYPOTHYROID RATS EXHIBIT ATTENTION DEFICITS IN A TARGET DETECTION TASK

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterized by hyperactivity, impulsiveness, and attention deficits. Although the number of children diagnosed with ADHD has increased, the causes of ADHD are unclear. One of the risk factors for ADHD is exposure to environmental endocrine disrupters such as polychlorinated biphenyls (PCBs) and dioxins. These chemicals disrupt thyroid hormone function and affect normal development of the central nervous system. In fact, PCBs and the anti-thyroid drug Methimazole (MMI) increase locomotion and exploration in rats.[4,8] Furthermore, these chemicals cause the animals to exhibit impulsive behavior. PCB-treated animals display response acceleration with a fixed interval and a differential reinforcement of low rate schedules.[2,7] MMI-treated rats exhibit greater reactions to the rapid reduction or cessation of rewards.[9]

It is therefore likely that hypothyroidism is one of the risk factors for ADHD. There, however, is no clear evidence that hypothyroidism induces attention deficits. Bushnell and Rice[3] did not detect attention deficits in PCB-treated rats, whereas Holene et al.[6] suggested some attention problems were present in these animals. In this study, we have examined the relationship between attention deficits and hypothyroidism.

Materials and Methods

Nine pregnant rats of the Wistar strain were purchased on gestational day 8. These animals were housed in individual cages and were randomly assigned to a Control group (n = 3), a Low concentration group (n = 3), or a High concentration group (n = 3). MMI was dissolved in distilled water and administered to the pregnant rats via drinking water from gestational day 15 to postnatal day 21. The concentrations of MMI (w/v) were 0% (Control; C), 0.002% (Low concentration; L), and 0.02% (High concentration; H). After weaning, two male and two female offspring were sampled from each dam. Six male and six female offspring from each group were tested. These animals are abbreviated as MC (Male-Control), ML (Male-Low concentration), MH (Male-High concentration), FC (Female-Control), FL (Female-Low concentration), and FH (Female-High concentration). The animals were individually housed under *ad libitum* feeding conditions until 12 weeks of age. Then, all animals were placed under restricted food conditions and maintained at 85% and 90% of their free-feeding body weights for the male groups and female groups, respectively. Supplementary food to maintain their body weights was supplied daily after the experiment. Tap water was always available in the home cages. The room temperature was maintained at 22 ± 2°C and the relative humidity was 50 ± 10% under a 12-h light/dark cycle (light, 19:00-07:00 h; dark, 07:00-19:00 h). Behavioral experiments were executed during the dark period. This research was carried out with the approval of The Center for Advanced Science and Technology (Hokkaido University). The environmental conditions complied with The Guide for the Care and Use of Laboratory Animals (Hokkaido University).

Five standard operant chambers were used. A room light, a food cup, and a response lever were installed on the front panel of the chamber. The room light was mounted on the center of the panel, 11 cm above the floor. Dim light was provided throughout the experiments. The food cup was 10 cm below the room light and a food pellet (50 mg) was delivered as a reward from a pellet dispenser. The response lever protruded from the panel at a position 3 cm above the floor and 8 cm to the right of the food cup. A signal light was fixed on the ceiling. The presentation of the signal light served as the target to be detected. A speaker with a diameter of 17 cm was placed outside of the chamber and white noise (70 dB) was presented to mask external sounds. The chamber was set in an isolation box designed to attenuate external light and sound. Experiments and data recording were controlled by a personal computer.

After training to press the lever, all of the rats were trained under a discrete trial with a continuous reinforcement (DT-CRF) schedule. A trial began when the signal light (target) was presented. A response while the target was on resulted in a food pellet being delivered. Then, the target was removed and an inter-trial interval (ITI) began. Any response during the ITI did not yield a food pellet. The ITI gradually extended from 0 s to 10 s. DT-CRF training consisted of 50 trials per day and continued for 7 days. After DT-CRF training, a target detection task started. A target was presented 0, 7.4, 20, or 42.5 s after a trial began. These intervals were ordered pseudo-randomly with an equal probability. If the rat responded within a time limit after the target presentation, a food pellet was provided and the target was removed. This response was considered to be a hit response. The reaction time from the target presentation to the hit response was recorded. If the rats did not respond within the time limit, the target was removed and no food pellet was provided. The next trial was started following a 10-s ITI. Any response during the ITI did not result in food pellet delivery. The time limit started at 16 s before it was reduced to 8 s and then to 4 s. The target detection task for each time limit consisted of 120 trials per day and continued for 5 days.

Results and Discussion

The mean levels of MMI that the dams ingested were 0.69 mg/day and 5.23 mg/day for the Low concentration and High concentration groups, respectively.

The body weights on the last day of the *ad libitum* feeding conditions were 293.3, 295.0, and 256.7g for MC, ML, and MH rats, respectively. The effect of MMI treatment was significant for the male groups ($F(2,15) = 8.96$, $p < 0.01$) . The body weights of the MH rats were lower than those of both the MC and ML rats ($p < 0.05$ for both groups). The body weights of the female groups were 170.0, 165.8, and 160.8g for FC, FL, and FH rats, respectively. No significant differences were obtained for the female groups. These results are consistent with previous studies of hypothyroid animals. MMI treatment induces developmental delays that are evident in the body weight of the animal and the maturation of physiological landmarks,[5,10] and normal body weight gain is prominently delayed in male animals.[9]

The percentage of hit responses for the male groups was more than 90% for the time limits of 16 s and 8 s, and the effect of MMI treatment was not significant. For the time limit of 4 s, the hit percentage of MH rats decreased and the effect of MMI was significant ($F(2,15) = 8.53$, $p < 0.01$). The hit percentage of MH rats was significantly reduced for the targets presented 0 s and 7.4 s after the start of the trial (Fig. 1, upper panel) compared to those of MC and ML rats for the same target presentations ($p < 0.05$ for both groups). For the female groups, the hit percentages were significantly different between the groups for the time limits of 16 s, 8 s, and 4 s ($F(2,15) = 9.41$, $p < 0.01$; $F(2,15) = 5.14$, $p < 0.05$; $F(2,15) = 8.53$, $p < 0.01$, respectively). The hit percentages of FH rats were significantly lower than those of FC and FL rats for the time limits of 16 s and 8 s. Fig. 1 (lower panel) displays the hit percentages for the female groups for the time limit of 4 s. The hit percentages of the FH rats decreased when the target was presented 0 s, 7.4 s, or 20 s after the trial

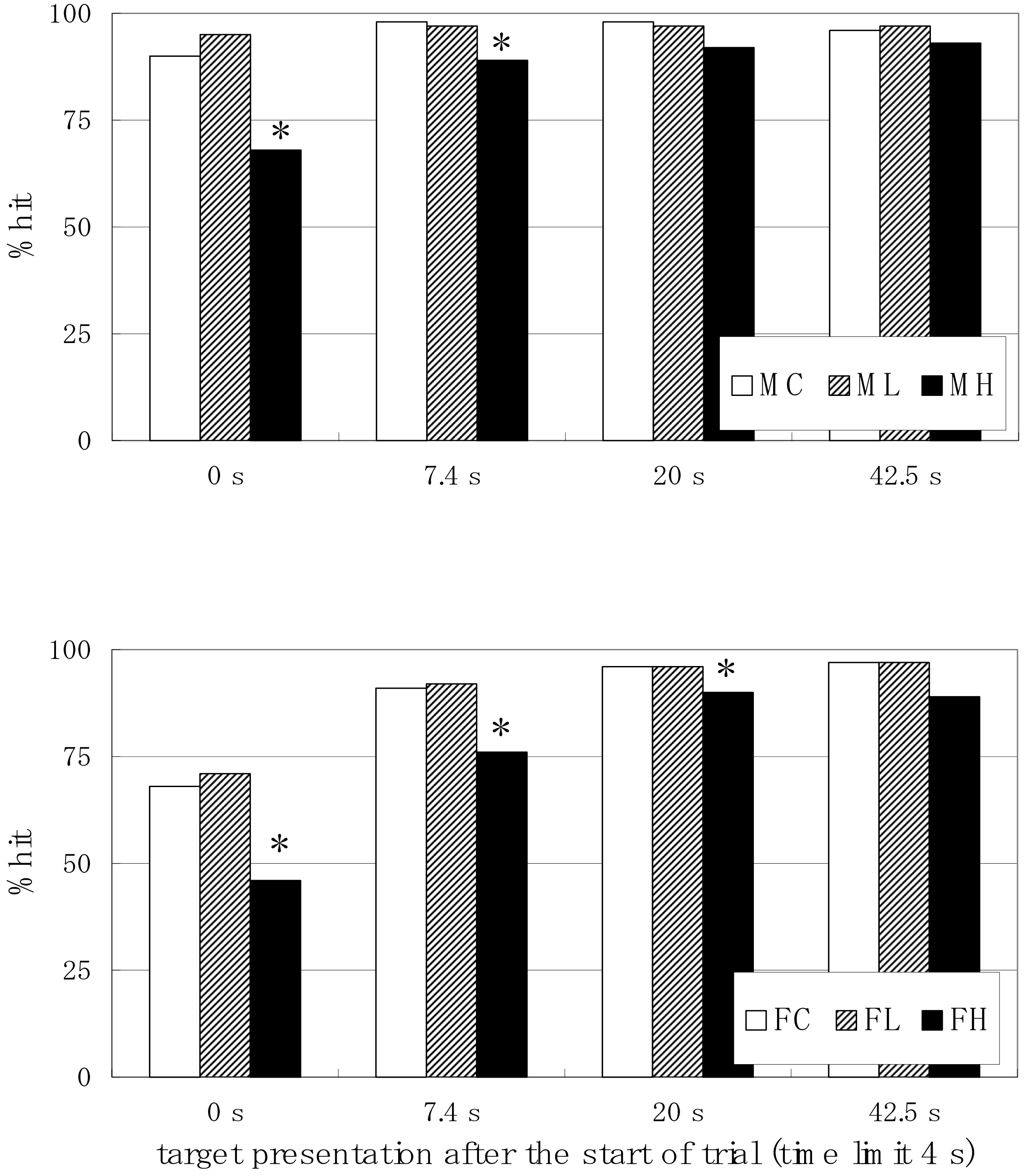

Fig. 1. Effects of MMI treatment on the percentage of responses that were hits. The graphs display the hit percentage of the male groups (upper panel) and the female groups (lower panel) for the time limit of 4 s. * indicates $p < 0.05$ compared to MC or ML rats for the male groups and compared to FC or FL rats for the female groups analyzed by LSD tests.

began. These percentages were significantly lower than those of both the FC and FL rats ($p < 0.05$ for both groups).

The reaction times for the time limits of 16 s and 8 s were not significantly different between the male groups. Significant changes in the reaction time were obtained for the time limit of 4 s ($F(2,15) = 5.17$, $p < 0.05$). MH rats had a shorter reaction time for the targets presented 7.4 s, 20 s, or 42.5 s after the trial began. MH rats responded more quickly than MC and ML rats ($p < 0.05$ for both groups). For the female groups, FH rats showed longer reaction times when the target was presented 0 s after the start of the trial. The effect of MMI was significant for the time limit of 16 s ($F(2,15) = 6.27$, $p < 0.05$). FH rats responded slower than FC and FL rats to target presentations that coincided with the start of the trial ($p < 0.05$ for both groups).

Attention deficits are one of the behavioral characteristics of ADHD; there, however, is no clear agreement that hypothyroidism causes attention deficits. Holene et al.[6] reported that unnecessary behavior was enhanced in PCB-exposed animals. This was interpreted as attention deficits partially caused by hyperactivity. Bushnell and Rice[3], however, did not observe attention deficits in PCB-treated rats. These animals were trained to choose a lever near the target cue. In addition, the animals were required to choose one lever when the signal was presented and a second lever when the signal was not presented. These animals did not exhibit attention deficits.

In this work MH and FH rats displayed reduced hit percentages for the targets presented 0 s, 7.4 s, or 20 s after the start of the trial. The decrease in the hit percentages was significant when the time limit was shorter. The rats need to react quickly to the target presentation in the condition where the target was presented soon after the start of trial (e.g. at 0 s and 7.4 s) and the time limit was short (e.g. 4 s). The decrease in the hit percentages can be interpreted as deficits of attention toward the new target. These animals, however, were able to respond to the target when the target was presented 42.5 s after the trial began. In addition, the reaction times of these animals were not different or were shorter compared to that of the Control or Low concentration groups. This indicates that MH and FH rats were able to sustain attention toward the new target for more than 40 s and were able to respond quickly to the target. It has been postulated that hyperactivity and impulsiveness constitute a single impairment, whereas attention deficits constitute a second, independent impairment.[1] Hypothyroidism may therefore affect hyperactivity and impulsiveness, but not attention deficits.

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