INABILITY OF HYPOTHYROID RATS TO SHIFT ATTENTION QUICKLY IN A TARGET DETECTION TASK

HASEGAWA M WADA H

Division of psychology, Graduate school of Letters, Hokkaido University, Kita10 Nishi7 Kita-ku, Sapporo 060-0810, JAPAN

Abstract

Thyroid hormone is essential for normal development of the central nervous system; disruption of this hormone causes behavioral alterations such as Attention-Deficit/Hyperactivity Disorder (AD/HD). The present study focused on attention deficits, one of the main symptoms of AD/HD, and examined the relationship between attention deficits and hypothyroidism in a target detection task. Hypothyroidism was induced by adding Methimazole to the drinking water of pregnant dams from gestational day 8 to postnatal day 21. Hypothyroid rats showed significantly lower rates of correct response to conditions that required quick changes of attention to a new target. Furthermore, hypothyroid rats exhibited lengthened reaction times at longer limited hold times. These results indicate that hypothyroidism causes attention deficits, particularly in situations requiring quick shifts of attention.

Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is characterized by hyperactivity, impulsiveness, and attention deficits. Although the causes of AD/HD are not clear, environmental endocrine disrupters such as PCBs and dioxins are considered to be among the possible risk factors. These chlorinated organic compounds disrupt the thyroid hormone system that is essential for normal development of the central nervous system (CNS)[4]. It is hypothesized that disruption of the thyroid hormone system causes neurological dysfunction and thus leads to the behavioral alterations observed in AD/HD. Consistent with this, locomotion and exploring behavior is increased in rats treated with anti-thyroid drugs[5]. Furthermore, PCBs cause animals to exhibit impulsive behavior in a fixed interval (FI) and a differential reinforcement of low rate (DRL) schedules[1,6].

It is therefore likely that hypothyroidism induced by environmental endocrine disrupters is a risk factor for AD/HD. However, there is no clear evidence whether hypothyroidism causes attention deficits. In this study, we have examined the relationships between attention deficits and hypothyroidism.

Materials and Methods

Fifteen pregnant rats of the Wistar strain were purchased on gestational day 8. These animals were individually housed and randomly assigned to Control (C), Low concentration (L) and High concentration (H) groups.

Methimazole (MMI) was administered to L and H groups at concentrations (w/v) of 0.002% and 0.02%, respectively. MMI was dissolved in distilled water and given to dams via drinking water from gestational day 8 to postnatal day 21. At the time of weaning, two male and two female offspring were sampled from each dam and housed in individual cages. Ten male and ten female offspring of each group were tested. These animals were abbreviated as CM (Control-Male), LM (Low-Male), HM (High-Male), CF (Control-Female), LF (Low-Female), and HF (High- Female). The animals had free access to food and water until 12 weeks of age. At that time, all animals were placed under restricted food conditions and maintained at 85% and 90% of their free-feeding body weights for the male and the female groups, respectively. The room temperature was maintained at 22±2°C, and the relative humidity was 50±10% under a 12-h light/dark cycle (dark, 07:00-19:00 h). The behavioral experiments were executed in 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. The chambers were arranged as follows: 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 (80 dB) was presented to mask external sounds. The chamber was set in an isolation box designed to attenuate external light and sound. Experiment and data recording were controlled by a personal computer.

After being conditioned to press the lever to obtain a food reward, all animals were trained under a discrete trial-continuous reinforcement (DT-CRF) schedule. A trial started when the signal light (target) was on. If rats pressed the lever during the target presentation, a food pellet was delivered. Then, the target was removed and an inter-trial interval (ITI) began. During ITI, responses did not yield a reward. The ITI was gradually increased from 0s to 10s. DT-CRF training consisted of 50 trials per day and continued for 7 consecutive days. After DT-CRF training, a target detection task started. The target was presented after variable intervals (VIs) consisted of 10, 17.4, 30, and 52.5 s. These intervals were presented pseudo-randomly with equal probability. If the rats responded to the lever within the limited hold (LH), a food pellet was delivered and the target was switched off. This response was considered to be a hit response. If the rats did not respond within the LH, no food pellet was delivered and the target was switched off. Following the VI, the next trial began. The LH was changed with descending series (16, 8, 4, 2, and 1 s). Training for the target detection in each LH consisted of 120 trials per day and continued for 5 consecutive days.

Percentages and reaction times of the hit response were analyzed by a three-way ANOVA (MMI concentration×LH×VI). Since the body weights between male and female groups were significantly different, their data were analyzed separately. The gradual decreases of hunger drive were expected due to smaller body sizes of HM and HF groups in daily training; therefore, we analyzed the data from the first 40 trials in daily training.

Results and Discussion

For male groups, the percentages of hit responses were significantly different in LH 4s, 2s and 1s. The effects of MMI concentrations were significant at VI 10s in LH 4s ($p<0.005$), 2s ($p<0.001$) and 1s ($p<0.005$). The hit percentages of HM were lower than the other groups (Fig.1. A-C). As in the male groups, the hit percentages of female groups were significantly different in LH 4s, 2s and 1s. MMI-treatment was significant at VI 10s in LH 4s ($p<0.005$), 2s ($p<0.001$) and 1s ($p<0.001$) and at VI 17.4s in LH 1s ($p<0.05$). The hit percentages of HF were lower than the other groups (Fig1.D-F). The reaction time of the males was also significantly different between groups; HM animals showed longer reaction times than animals in the other groups for LH 16s ($p<0.01$) and 8s ($p<0.005$). For the females, the effect of MMI-treatment was significant for LH 16s at VI 10s ($p<0.001$), 17.4s ($p<0.01$), 30s ($p<0.01$) and 52.5s ($p<0.05$), and for LH 8s at VI 10s ($p<0.001$). For LH 16s, the reaction time of HF was longer than the other groups at VI 17.4s and 52.5s and longer than LF at VI 10s and 30s. For LH 8s, the reaction time of HF was longer than the other groups at VI 10s.

Attention deficits are one of the behavioral characteristics of AD/HD. However, there is no clear evidence whether hypothyroidism causes attention deficits. Bushnell and Rice[2] did not observe attention deficits in PCB-treated rats. Holene et al.[3] reported attention deficits, but attributed them to hyperactivity; unnecessary behavior is enhanced in PCB-treated animals.

In this experiment, HM and HF groups reduce hit percentages at VI 10 s for LH 4s, 2s and 1s. The shorter VIs require quickness to shift attention to the new target. On the other hand, the longer VIs require sustained attention to the target for a long time. In addition, the shorter LHs require quick responses to the target. Because hypothyroid rats responded appropriately at longer VI (e.g. 52.5s) for the shorter LH, it has been postulated that these rats can respond quickly and sustain their attention for long time. However, the hit percentages of HM and HF were significantly decreased at shorter VI for the shorter LH, suggesting they cannot shift their attention to the next target quickly. Therefore, hypothyroidism specifically affects the ability to shift attention quickly, but has minimal effect on sustained attention.

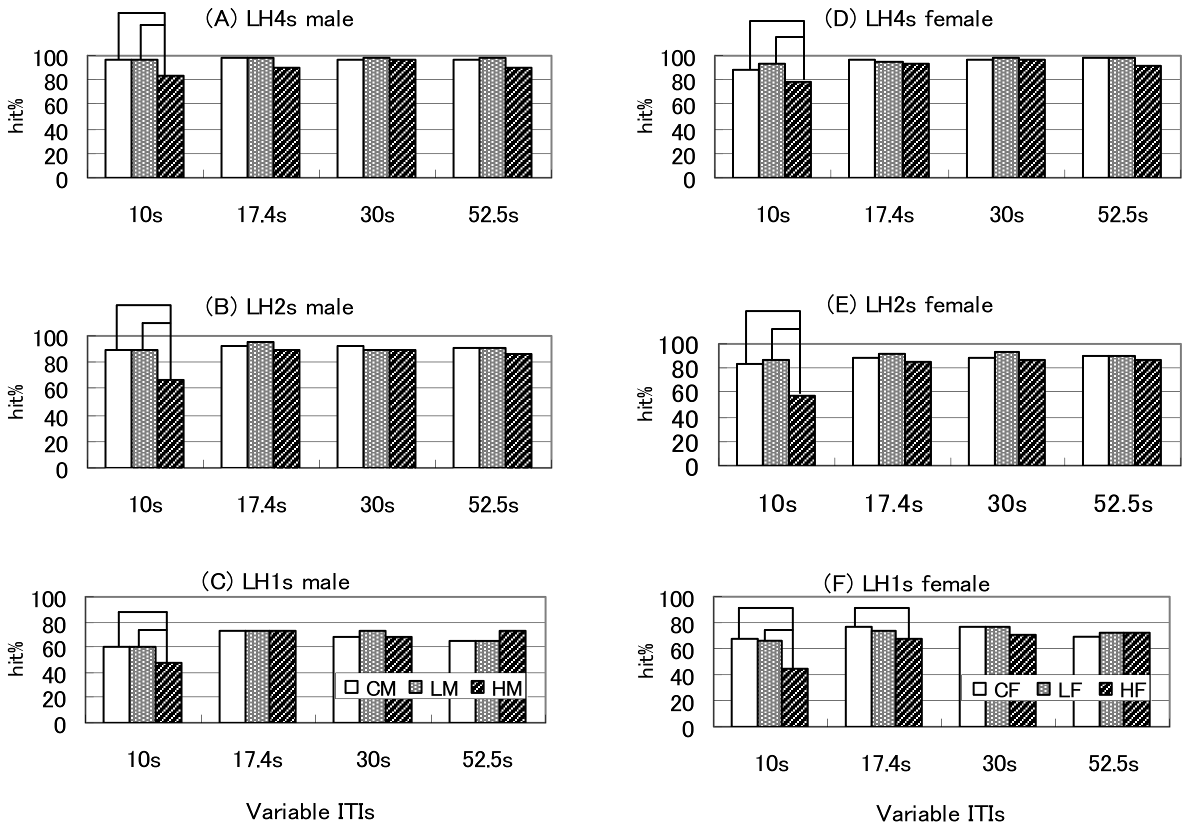

Fig.1. Percentages of hit responses in Limited hold (LH) 4s, 2s and 1s. Male data is on the left side (A-C) and female data is on the right side (D-F). Lines in the graphs mean significant differences between groups ($p<0.05$). These graphs show that the hit percentages of HM and HF are significantly decreased at VI 10s.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research (C) No. 17590531 from Japan Society for the Promotion of Science.

References

1. Berger DF, Lombardo JP, Jeffers PM, Hunt AE, Bush B, Casey A, Quimby F. *Behav Brain Res* 2001;126:1.
2. Bushnell PJ, Rice DC. *Neurotoxicol Teratol* 1999;21:381.
3. Holene E, Nafstad I, Skaare JU, Sagvolden T. *Behav Brain Res* 1998;94:213
4. Porterfield S. *Environ Health Perspect* 2000;108:433
5. Sala-Roca J, Marti-Carbonell MA, Garau A, Darbra S, Balada F. *Physiol Behav* 2002;77:125.
6. Wada H, Kondo T, Kishi R. (under submission).