IMPULSIENESS OF HYPOTHYROID RATS SHOWN IN NON-REWARDED TRIALS

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Abstract

Attention-Deficit/Hyperactivity Disorder is characterized by hyperactivity, impulsiveness, and inattention. The present study focused on impulsiveness and examined the relationship between impulsiveness and thyroid hormone systems using two tests: (1) a differential reinforcement of low rate 20 s and (2) extinction. Pregnant rats were treated with methimazole at concentrations of 0, 0.002, or 0.02% from gestational day 15 to postnatal day 21. After weaning, the offspring were tested. Hypothyroid rats displayed higher rates of burst responses (inter-response times <2 s) than control rats. In particular, these animals exhibited greater burst responses after non-reward. This study indicates that prenatal hypothyroidism induces impulsiveness.

Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is a condition characterized by hyperactivity, impulsiveness, and inattention[1]. Although the causes of AD/HD are not clear, incidents in Japan and Taiwan, in which women ingested polychlorinated biphenyls (PCBs) in contaminated rice oil, resulted in delayed developmental milestones, cognitive deficits, and behavioral problems in their offspring. For these reasons, environmental endocrine disrupters such as PCBs and dioxins are considered as possible risk factors. These chlorinated organic compounds disrupt the thyroid hormone systems that are essential for normal development of the central nervous system (CNS) [2]. It is hypothesized that disruptions of thyroid hormone systems cause neurological dysfunctions and thus lead to behavioral alterations observed in AD/HD. It is predicted that hypothyroid rats exhibit poor performance in a differential reinforcement of low rate (DRL) schedule in which animals' behavioral inhibition is required.

The definition of impulsiveness in the DSM Ⅳ is more anthropocentric. It basically means tending to act without patience; e.g. one cannot wait for one's turn, having the tendency to burst out with answers frequently, having the tendency to intrude and interrupt others. According to research on animal behaviors, impulsiveness has been defined as burst responses with short inter-response times (IRTs)[5]. In this study, we measured IRTs (0-2 s) as burst responses and examined the performance of hypothyroid animals. It provided a valuable insight into the relationship between impulsiveness and thyroid hormone systems.

Materials and Methods

Twenty-four pregnant Wistar rats were purchased on gestational day 8, housed in individual cages, and randomly assigned to Control (n=8, C), Low dose (n=8, L), or High dose (n=8, 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 15 to postnatal day 21. After weaning, one male and one female offspring were sampled from each dam and housed in individual cages. Eight male and eight female offspring of each group were tested. These animals were labeled 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.

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 the 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 that is 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 trained 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. In this test, a food pellet would be delivered if the rats press a lever during the period from 20 s to 60 s. No food pellet would be delivered if the rats press a lever before 20 s or after 60 s. The next trial will start soon after a lever is pressed. The DRL test consisted of 150 trials per session per day for 70 sessions.

Following DRL 20 s, the rats performed the extinction. During this phase, all test parameters remained the same except that no reinforces were delivered. Data were collected for three sessions during this phase.

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

In the DRL 20 s, the percentage of rewarded responses reached 30% in CM, 18% in LM and 37% in HM (Fig. 1). Rewarded response percentages for CF, LF and HF groups were 30%, 43% and 45%, respectively. No significant dose-related effect on the percentage of rewarded responses was observed. There was a tendency of dose-related effects on the percentage of burst responses [F (2, 42) = 2.60, p=

0.085] (Fig. 2). In addition, the effects of MMI dose were significant concerning the percentage of burst responses after a non-reward [F (2, 42) = 5.76, p= 0.006]. L and H groups revealed higher percentages of burst responses after a non-reward compared with the C group (Fig. 3).

During the extinction task, the percentage of accuracy (non-reinforced IRT intervals that were 20-60 s in duration) indicated significantly a main effect of sex [F (1, 42) = 5.905, p= 0.0195]. The females exhibited more accuracy than the males. Burst responses indicated a significant dose-related effect [F (2, 42) = 6.451, p= 0.0036]. H group made greater burst responses than did C group.

In a PCB-ingesting test on monkeys in the DRL30 s[4], Rice demonstrates that the monkeys do not develop DRL30 s performance; their IRTs are shorter, and the number of rewarded responses is reduced. PCB-treated animals do not exhibit the inhibition of responding[3], which is consistent with the current results.

In this experiment, no significant effect of MMI on the percentage of rewarded responses was observed, however the hypothyroid rats showed higher rates of burst responses than control rats. In particular, hypothyroid rats exhibited higher burst responses after a non-reward than control rats. These results indicated the possibility that hypothyroid rats resulted in impulsiveness after a non- reward. Taken together, this study supports the hypothesis that disruption of thyroid hormone systems induces impulsiveness.

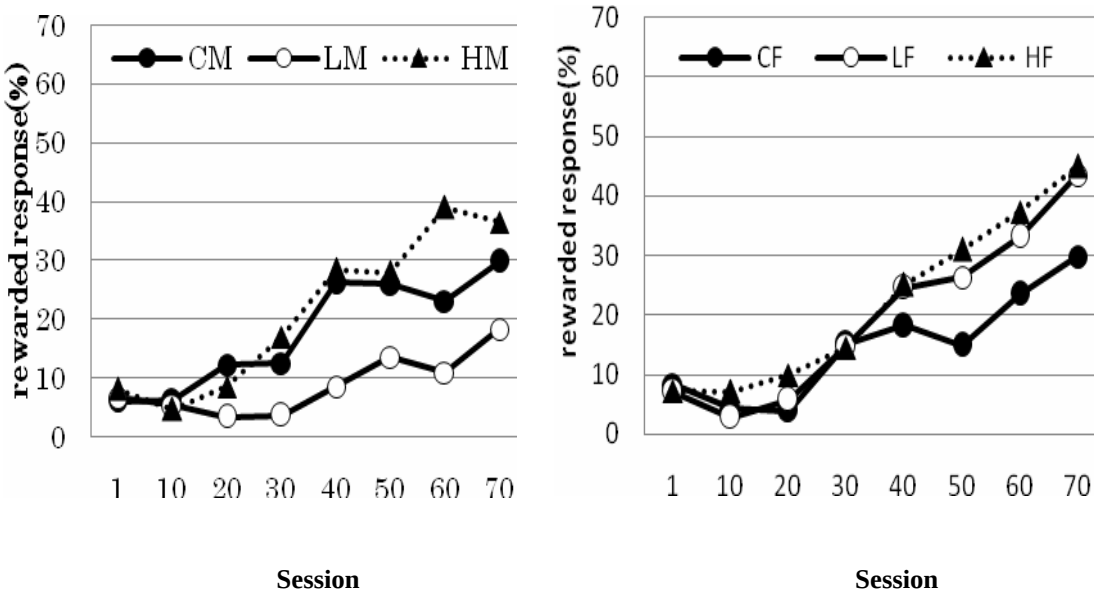

Fig. 1. Effect of methimazole treatments on the percentage of rewarded response.

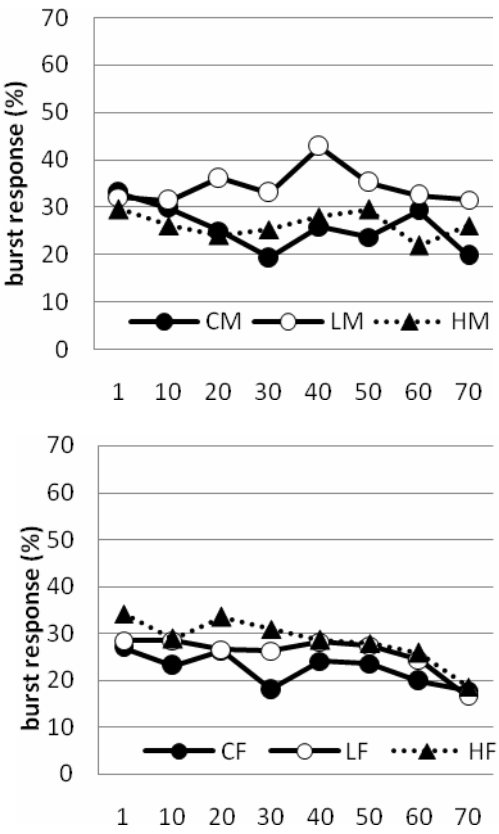

Fig. 2. Effect of MMI treatments on the percentage of burst responses .

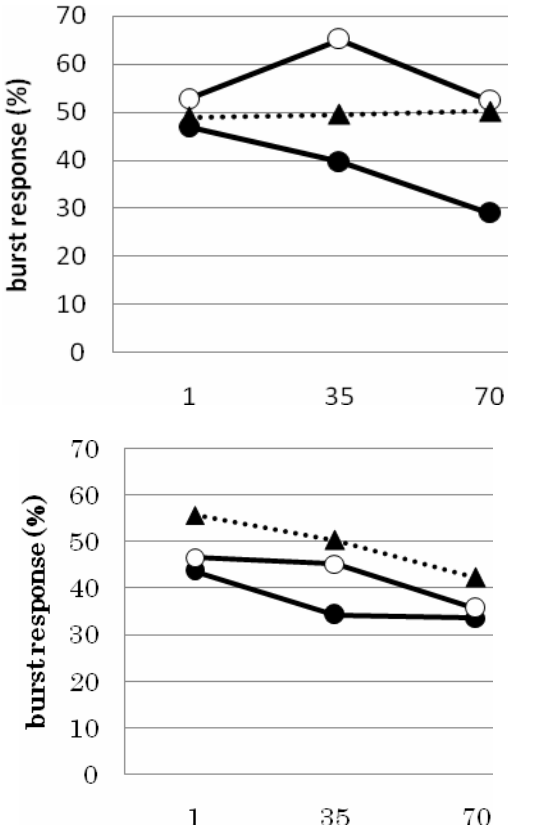

Fig. 3. Effect of MMI treatments on the percentage of burst responses after a non-reward.

Acknowledgments

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