TCDD Blocks the Weight Increasing Effect of Paraventricular Lesion

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1. Introduction

The regulation of body weight is a complex system, where several inter- and independent factors increase and reduce food intake and energy consumption. A balance that is achieved and defended against dietary manipulations such as over- and underfeeding is descriptively called a body weight set-point[1)2)]. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) reduces the body weight set-point permanently after a single non-lethal dose, because the body weight decreases, and the new, lower level is defended[1)2)].

Paraventricular nucleus (PVN) is a hypothalamic structure that regulates food intake and the circadian rhythms of macronutrient intake[3)4)]. Lesioning of this brain area causes increase in food intake and body weight, especially with palatable diet. However, it has little effect in the energy consumption, or metabolism[5)]. In this study, we followed the effects of TCDD in PVN-lesioned rats after a non-lethal dose.

2. Methods

Forty 11-week-old female TCDD-resistant Han/Wistar (Kuopio) rats were housed singly in wire mesh cages with feeding tunnels. Thus, it was possible to strictly measure feed intake and spillage. The rats were offered regular feed (R36, Ewos, Södertälje, Sweden) and tap water *ad libitum*. In addition, two weeks after PVN-lesioning, chocolate (Iso vaalea kilosuklaa, Oy Panda Ab, Vaajakoski, Finland) was offered *ad libitum* to increase palatability and energy content of the diet. The feed contained energy 12.6 kJ/g (13 % of total energy from fat, 25 % from protein and 62 % from carbohydrate). The chocolate contained energy 23.4 kJ/g (53 % of total energy from fat, 6 % from protein and 41 % from carbohydrate). The animal room had 12/12 hour lighting rhythm, the temperature was 21.5±1 °C and the relative humidity was 55±10 %.

The PVN lesions were performed under ketamine (60 mg/kg i.p.) and medetomidine (0.5 mg/kg s.c.) anaesthesia. The rats were placed on a stereotaxic device with the incisor bar 3.5 mm lower than interaural line; thus, the bregma and the lambda were at the same horizontal level. The coordinates for paraventricular nucleus were 1.6 mm posterior, ±0.4 mm lateral, and 8.1 mm ventral to bregma. The bilateral lesion was made by lowering an insulated stainless steel electrode (diameter 0.4 mm) into the brain and passing through 1 mA anodal current for 15 s. The sham rats were operated similarly except that the electrode was lowered 1 mm less and no current was passed through. The rats were awakened with atipamezole (0.25 mg/rat i.m.).

The groups were statistically compared with the analysis of variance (ANOVA; with repeated measures when appropriate) and then Duncan's multiple range test if the analysis showed a statistically significant difference.

3. Results

PVN lesion did not change food intake or body weight, until two weeks later chocolate was added to the diet. Then energy intake increased from 216±64 kJ/day to 387±73 kJ/day in lesioned rats and 310±55 kJ/day in sham operated rats (two week average). Chocolate reduced the amount of feed consumed to less than a half of original and thus replaced it as the main energy source. Weight gain was faster in the lesioned groups (18±7 % in two weeks) than in control ones (9±3 %) after chocolate diet.

After TCDD, the rats reduced energy intake and started to lose weight. The effect was slightly stronger in lesioned rats than in control rats. Within three weeks, the weight difference between the TCDD groups (caused by PVN lesion and palatable diet) had disappeared. The effects of TCDD and PVN lesion on energy intake and body weight appeared to be interactive (repeated measures ANOVA, $P<0.05$). Thus, wasting syndrome was slightly enhanced in the PVN lesioned rats, which started at a higher body weight level than sham-operated rats.

Macronutrient intakes of each TCDD group were compared to the values of the respective control group at the same time. During the first two weeks after TCDD, relative fat intake decreased by 56-74 % and carbohydrate by 25-45 %, while protein did not change significantly. Fat and carbohydrate intakes remained lower until the end of the experiment.

4. Discussion

We have studied TCDD wasting syndrome with different brain lesions that affect body weight regulation. In this study, the effect of PVN lesion on body weight seemed to be blocked by TCDD. The effects were interactive, and the weight loss rate was greater in obese, PVN-lesioned rats. However, the final body weight level was similar in both lesioned and sham-operated rats. Previously, ventromedial hypothalamic lesion was shown to aggravate the wasting syndrome, as the body weight of the obese, lesioned rats decreased below that of sham-operated rats[6]. Thus, the interactions between TCDD and the two lesions seem to be different. The lesions are dissimilar in the respect that PVN lesion causes obesity by hyperphagia only, while ventromedial hypothalamic lesion alters also metabolism and can cause obesity even if food intake is restricted to control level[5].

TCDD-exposed rats clearly decreased energy intake and changed diet composition by reducing chocolate intake. This caused reduction in carbohydrate and especially in fat intakes, while protein intake did not change. The interpretation of this finding is not straightforward. Rats could prefer different macronutrients after TCDD exposure, but taste and especially sweetness could also be important factors in the change of diet selection. The rats had only two choices, namely regular feed and chocolate. Both are rich in carbohydrate, and therefore the rats could not choose to avoid it without changes in other macronutrients.

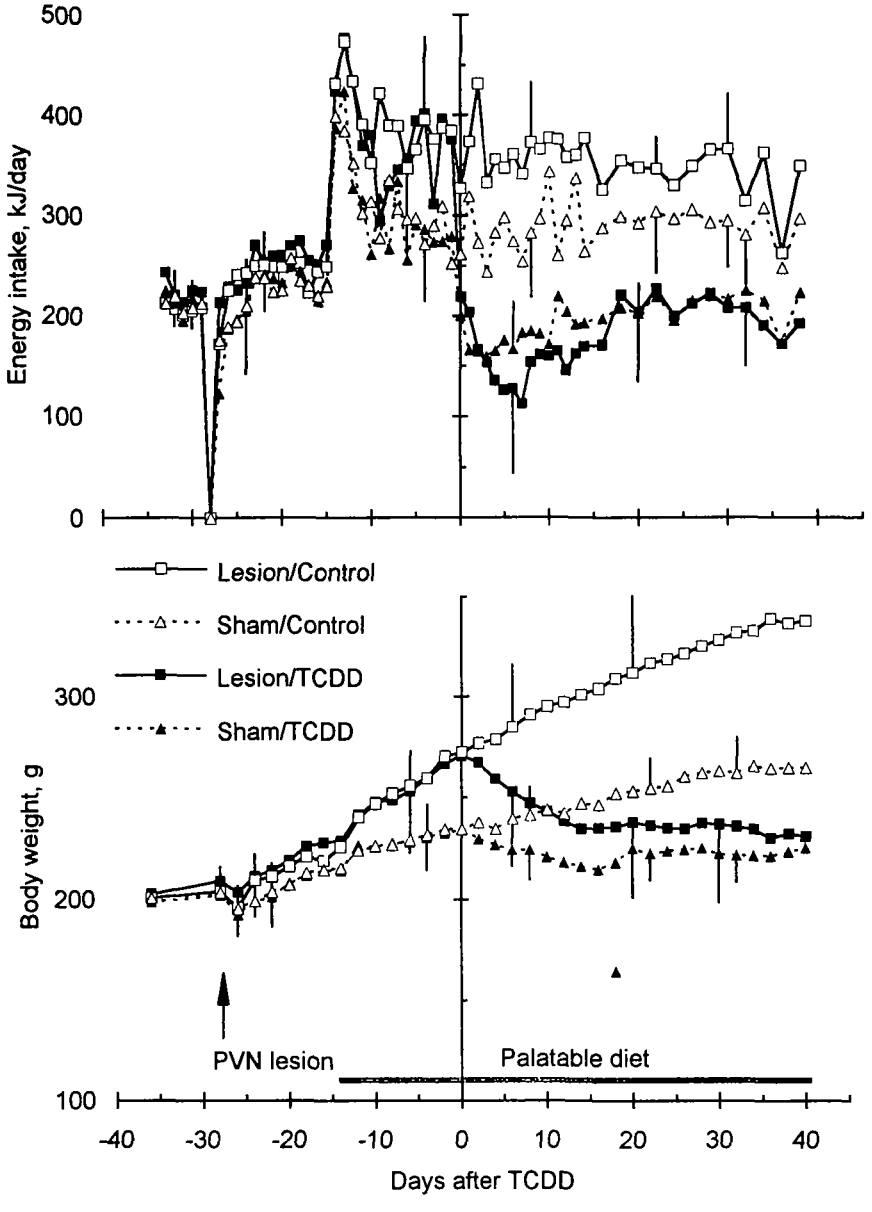

Figure 1. Energy intake and body weight (mean±S.D.) in PVN-lesioned H/W rats after a sublethal dose of TCDD (1000 μg/kg i.p.). The rats were operated on day -28 and exposed on day 0. On days -14 - 40 the rats were offered feed and chocolate, otherwise feed only. One rat in sham/TCDD group died and its weight and time of death is shown with a single symbol. *n*=7-8.

5. References

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