2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Lesion of Dorsomedial Hypothalamic Nucleus Have Additive Effects on Body Weight Loss

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Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is the most potent congener of dioxins, environmental contaminants that are found ubiquitously in the environment. It has been shown to cause several effects in laboratory animals varying from teratogenicity and cancer to immunosuppression and enzyme induction in liver. One poorly understood effect is severe and permanent reduction of body weight even after a single dose. After a non-lethal dose, the new, lower weight level is defended against dietary challenges (1).This hypophagia followed by body weight loss is called wasting syndrome. In previous studies, we have shown that ventromedial hypothalamic lesion, which normally causes hyperphagia and weight gain, paradoxically aggravates the TCDD wasting syndrome (2). In addition, palatable diet had additive effect on body weight both in TCDD-treated and control rats. This implies that ventromedial hypothalamus might be involved in the mechanism on TCDD wasting syndrome, while palatable diet may have only a nonspecific modulating effect. It would be interesting to study effects of other hypothalamic nuclei that are involved in body weight and food intake regulation.

Lesioning of dorsomedial hypothalamic nucleus (DMN) cause acute decrease in food and water intake followed by decreased weight gain and even weight loss. However, DMN lesion decreases body size with little effect on the proportion of adipose tissue (3), while TCDD causes dramatic loss of body fat stores. After the acute phase with body weight loss, the food intake of both TCDD-exposed and DMN-lesioned rats returns to normal level determined by their metabolic body weight (body weight in $kg^{0.75}$).

Materials and methods

38 adult male TCDD-resistant Han/Wistar (Kuopio) rats were used. The rats were housed singly in wire mesh cages and offered powdered food (R36, Ewos, Sweden) and tap water *ad libitum*. Food intake was measured daily and strictly corrected for spillage. Body weight was measured every second day.

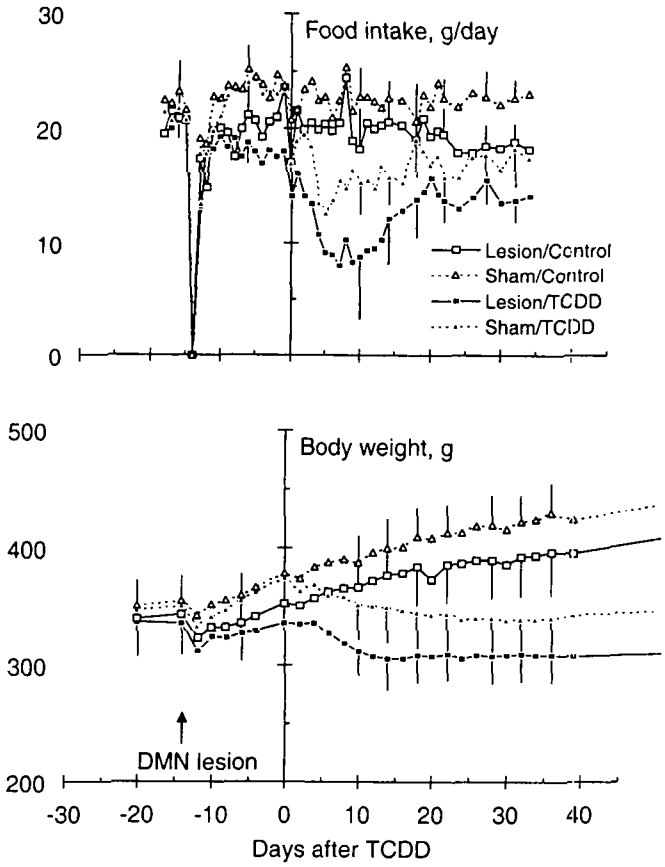

Figure 1 Food intake and body weight (mean±S.D.) after dorsomedial hypothalamic nucleus lesion (day -14) and TCDD (1000 μg/kg i.p.; day 0).

The rats were operated under ketamine-medetomidine anaesthesia. Lesions were done in stereotaxic control with an electrode (diameter 0.4 mm) that was lowered 2.6 mm posterior, 0.6 mm lateral and 8.5 mm ventral to bregma. 1 mA anodal current was passed for 15 s. Sham operation was performed similarly except that the electrode was lowered 1 mm less and no current was passed. No food was given to the rats for 24 h after the operation.

The rats were exposed to TCDD (1000 μg/kg intraperitoneally; this is a non-lethal dose to these rats) two weeks after the operation. Control rats were given vehicle only (corn oil 5 ml/kg).

Results and discussion

DMN lesion reduced food intake. The average difference between lesioned and sham operated

rats was 32 g after two weeks. Three lesioned rats died within a few days after the operation. After TCDD, both lesioned and sham operated rats lost weight at about the same rate (*ca.* 30 g in three weeks). Decrease in food intake seemed to be somewhat greater in lesioned rats. There was no interaction between the effects of TCDD and dorsomedial lesion in food intake or in body weight (repeated measures analysis of variance).

One hypothesis was that TCDD might (partially) act by inhibiting DMN activation and thus have similar effects to DMN lesion. However, this seems not to be the case, as the effect of TCDD is not inhibited by DMN lesion. There might even be a slight trend of enhancement (although this small difference was not statistically significant). It could also be due to ventromedial hypothalamic nucleus (which aggravates TCDD wasting syndrome), since structures in hypothalamus are located very closely, and DMN lesion can always cause some damage in adjacent nuclei, like ventromedial hypothalamic nucleus.

Another hypothesis was that TCDD and DMN lesion cause weight loss by affecting the same mechanistic pathway at different steps. Thus, these factors could have synergistic effects on body weight loss. However, there was little, if any, synergism. It is therefore more likely that they do not share the same mechanism.

In conclusion, TCDD wasting syndrome is not mediated via DMN, and probably the effects of TCDD and DMN lesion are mediated with different mechanisms.

References

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