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Changes in Food Intake and Food Selection in Rats After 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure

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TUOMISTO, J. T., M. VILUKSELA, R. POHJANVIRTA AND J. TUOMISTO. *Changes in food intake and food selection in rats after 2,3,7,8-tetrachlorodibenzo*-p-*dioxin (TCDD) exoposure.* PHARMACOL BIOCHEM BEHAV **65**(3) 381–387, 2000.—Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on food selection were studied in TCDD-resistant Han/Wistar and TCDD-sensitive Long–Evans rats and their crosses. The rats were offered a selection diet consisting of chocolate, cheese, and chow, and TCDD was given at the same time or 4 or 16 days later. TCDD persistently reduced the chocolate intake. When the selection diet was started at the time of or less than 11 h after TCDD exposure, TCDD almost completely prevented the intake of chocolate and also cheese in all strains already on the first day, while controls started to consume large amounts of both foods. This may be due to conditioned taste aversion. The effect on food selection with familiar foods seemed to reduce fat intake, while protein and carbohydrate intakes were more variable. There were no major strain differences in the chocolate intake inhibition despite a 1000-fold sensitivity difference in TCDD lethality. © 2000 Elsevier Science Inc.

TCDD; 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Appetite Food intake Macronutrient intake Feeding behavior Rat

2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) is a highly toxic man-made chemical found ubiquitously in the environment. After low doses to experimental animals, it is known to cause, for example, enzyme induction, immune suppression, reproductive defects, and hormonal alterations; after higher doses, it causes cancer, porphyria, and a specific wasting syndrome characterized by reduced food intake and weight loss [for a review, see (9)]. In humans, a skin disease called chloracne is the only symptom reported with certainty after very high exposures.

Many effects of TCDD are mediated by the aryl hydrocarbon (AH) receptor. It is a cytosolic receptor regulating gene expression of a number of genes (6,17). The physiological functions or the endogenous ligand of the AH receptor are not known.

A typical toxic effect in the rat is the wasting syndrome with feed refusal and permanent body weight loss of about 10–20% during a few weeks after exposure. After a lethal dose, an animal loses weight up to 40% and dies only after 2–3 weeks. Because the body weight stays subnormal after a single sublethal dose for at least several months, and the level is defended against dietary challenges, the phenomenon may be descriptively regarded as decreased body weight set point (5,9,16). A palatable, high-energy diet causes a parallel weight gain in both control and TCDD-exposed rats; TCDD-treated rats are also fully capable of increasing their feed intake in response to repeated 24-h fasts (19–21). Thus, the effects of TCDD and dietary manipulations on body weight seem to be additive rather than interactive (20).

Although TCDD clearly affects total food intake, the effects on macronutrient selection or preferences of other food properties are unclear. There are some data showing changes in diet selection after TCDD. TCDD (dosed IP several weeks previously) enhanced responsiveness to a satiating effect of sucrose when it was offered or given enterally (PO or IG), but not when it was given parenterally (IP) (12). Sucrose intake decreased after TCDD, while the opposite was true of saccharin, a sweetener without energy (10). In addition, there were

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slight tendencies towards high-protein food and away from high-fat food in a diet selection study, although the changes were small (10).

Previously, we found that the ventromedial hypothalamus was involved in the wasting syndrome, as lesioning of this nucleus aggravated the syndrome (24). To study the effects of lesioning on obesity, a control experiment was performed with dietary-obese rats. The obesity was an additive, not an aggravating factor (23). However, TCDD was found to have effects on food selection when a palatable selection diet was offered (23). Therefore, we decided to study the phenomenon more closely.

The sensitivity to lethality varies at least 1000-fold between two rat strains—highly resistant Han/Wistar (Kuopio) (H/W), and sensitive Long–Evans (Turku AB) (L-E). The resistance is determined by at least two separate genes (7,25). The main difference between these strains is a deviant AH receptor in the resistant H/W rat (15). We have developed three new rat lines from H/W and L-E: line A has the deviant AH receptor, and is highly resistant to TCDD lethality, while B and C have normal AH receptors, and are moderately resistant or sensitive, respectively (25). The deviant AH receptor seems to mediate some effects normally (e.g., induction of CYP1A1 enzyme) but fail to mediate others after typical doses (e.g., lethality) (25). A moderate wasting syndrome occurs after similar doses in all strains, but the syndrome does not lead to death in H/W or Line A rats even after a very high dose (9,25). As some aspects of the wasting syndrome show strain differences and some do not, it would be important to find out, if the possible differences in food selection are strain dependent or not.

We studied the effects of TCDD on diet selection for four reasons. First, to find out if TCDD affects food selection when choices are freely available; second, to study the onset of this possible effect; third, to explore if there are changes that could be explained by differences in macronutrient contents of the foods; fourth, to compare the effects among rat lines that differ in sensitivity to TCDD lethality.

METHOD

Animal Husbandry

Outbred H/W, inbred L-E rats , and their crosses (Lines A, B, and C) were obtained from the breeding colony of the National Public Health Institute, Kuopio, Finland (8,25). Line A has the mutant AH receptor from H/W strain, which makes it almost as resistant to TCDD as the H/W strain (LD_{50} >10,000 μg/kg TCDD) (25). Line B has the wild-type AH receptor, but is homozygous to an unknown gene that greatly increases its resistance to TCDD lethality (LD_{50} value 400–800 μg/kg), while Line C has neither of the resistance alleles, and it is approximately as sensitive as the L-E strain (LD_{50} <40 μg/kg TCDD) (25). LD_{50} values for H/W and L-E rats are >10,000 μg/kg TCDD and 10–20 μg/kg TCDD, respectively (9,25).

The rats were 11–12 weeks old at the onset of the experiments. Female and male H/W and L-E rats were used, and male A, B, and C rats were used. The rats were housed singly in wire-mesh cages with a feeding tunnel to measure feed intake and feed spillage. The room temperature in the animal rooms was 21 ± 1°C and relative humidity 50 ± 10%. The lighting rhythm was 12 h on, 12 h off, with lights off at 1900 h.

The experimental protocols were approved by the Research Animal Committee of the University of Kuopio and the Provincial State Office. (Institute permission 36-712-93, Experiment permissions 68Zd/6.10.1993, STO89/5.2.1998). The procedures are in compliance with the Finnish Law of Animal Protection (Eläinsuojelulaki 247/96, Eläinsuojeluasetus 396/96).

The TCDD administered was >99% pure as determined by gas chromatography-mass spectrometry. It was dissolved in corn oil as described previously (11), and the rats were dosed 5 ml/kg IP (4 ml/kg IG in Experiment 4).

Nutrients

The rats had free access to tap water and standard laboratory animal chow (R3 or R36, Ewos, Södertälje, Sweden). The chow was powdered.

Some rats were offered a palatable selection diet. This comprised a self-selection of the regular rat chow (energy content 12.6 kJ/g; of this 13% from fat, 25% from protein, and 62% from carbohydrate), chocolate (Iso vaalea kilosuklaa, Oy Panda Ab, Vaajakoski, Finland: 23.4 kJ/g; 53, 6, and 41%, respectively), and cheese (Edam 40, Ingman Foods Oy, Finland: 13 kJ/g; 66, 34, and 0%, respectively) ad lib. In Experiment 3, low-fat cheese was used (Minora, Valio, Lapinlahti, Finland: 9.5 kJ/g; 39, 56, and 5%, respectively). In addition, 10% sucrose solution (1.7 kJ/ml) was offered in Experiment 1.

Statistics

Group food intakes as a function of time were usually compared by calculating individual averages from day −3 to 0, from day 1 to 5, and from day 6 to 10. The values were compared by the analysis of variance (ANOVA), with repeated measures if applicable. Duncan's multiple range test was used as a post hoc test, if the ANOVA showed a statistically significant difference. Logarithmic transformation was used when the first-night chocolate intakes were analyzed in Experiment 4. In the case of nonhomogenous variances (tested by Bartlett-Box or Levene test), Kruskal–Wallis and Mann–Whitney *U*-tests were used. Two-group comparisons were performed by two-tailed Student's *t*-test. The level of significance was set at 0.05.

Experimental Design

Three experiments were performed to study the effects of TCDD on food selection in TCDD-sensitive (L-E) and resistant (H/W) rat strains. Both genders and different times from food selection to TCDD exposure were used. First, female H/W rats were offered a palatable food selection for 16 days before TCDD exposure (1000 g/kg IP, a nonlethal dose). Second, the food selection was offered to female rats immediately after TCDD exposure (a lethal dose of 50 μg/kg for L-E; 1000 μg/kg for H/W rats). The results on body weight and clinical chemistry of the first two experiments are reported elsewhere (23). Third, the food selection was offered for 4 days before TCDD exposure (50 μg/kg) to male L-E and H/W rats.

One experiment was performed to study the time course of the altered food selection after TCDD. Chocolate was offered for one dark period and the intake was measured. The rats had been exposed to TCDD 11, 4, or 1 h before this period. This experiment was done with the new Lines A, B, and C. It was also tested if the effects occur similarly with enteral administration.

RESULTS

Experiment 1: 16-Day Selection Before TCDD

Effects of TCDD on food selection were studied with a series of experiments with several foods available ad lib. First,

the effects of TCDD on the intakes of a selection of foods were studied after 16 days on the selection diet in female H/W rats. The diet consisted of rat chow, chocolate, cheese, and sucrose solution (see Nutrients).

The selection diet resulted in an increased total energy intake due to chocolate and also cheese intake (Fig. 1), and, consequently, body weight gain. Chow intake was remarkably decreased, as it was displaced by other food items. Sucrose intake was larger during the first days (ca. 100 kJ/day), but then diminished.

TCDD (1000 μg/kg IP) reduced total energy intake (10-day average) to 64 ± 13% in the selection-diet group and 60 ± 21% in the regular-diet group when compared with the respective control groups (Fig. 1). The effect of TCDD with time was statistically significant, $F(2, 32) = 34.34$, $p < 0.001$, repeated-measures ANOVA. The body weights followed the changes in energy intake in all experiments (data not shown). Chocolate intake decreased progressively (after 2 days of slight increase), the effect of TCDD with time being statistically significant, $F(2, 16) = 8.44$, $p = 0.003$, repeated-measures ANOVA, (Fig. 1). Sucrose intake decreased slightly, but showed large interindividual variation and did not reach statistical significance. There were no differences in cheese consumption between the two groups. Total energy intake increased after about 2 weeks postexposure but stayed at a subnormal level in both the regular-diet and selection-diet groups (data not shown). Chocolate intake remained at a low level in TCDD-exposed rats until the end of the experiment, i.e., 5 weeks (data not shown).

Experiment 2: Selection After TCDD

After the first result implying differences in chocolate intake, the phenomenon was studied further in both TCDD-resistant and TCDD-sensitive rat strains. A possible interference by diet-induced obesity was eliminated by offering the palatable foods only after TCDD exposure. Female L-E and H/W rats were exposed to 50 and 1000 μg/kg TCDD IP, respectively, and offered chow, chocolate, and cheese ad lib immediately after exposure.

In control groups, the selection diet increased energy intake compared with regular diet in H/W rats, but not significantly in L-E rats. However, both strains showed a rapid and permanent shift from the rat feed to cheese and chocolate with a compensatory decrease in chow intake, as seen in the first experiment.

TCDD effectively prevented chocolate and also cheese intake after exposure (Fig. 2) ($p = 0.004$, Mann–Whitney U). This effect was evident already on the first day postexposure. Unlike chocolate and cheese, chow intake was significantly higher in the selection-diet/TCDD group than in the respective control group, implying that this food was not disliked. The total energy intakes in the selection-diet/TCDD groups were similar to, or occasionally slightly higher than, the regular diet/TCDD groups in both strains.

The doses used were lethal to L-E but not to H/W rats. TCDD caused little effect on total energy intake in H/W rats, while L-E rats showed a progressive and severe reduction in total energy intake and body weight. No deaths occurred during the experiment.

Experiment 3: 4-Day Selection Before TCDD

The third experiment was aimed at solving a few unanswered questions. First, do the observed changes in food se-

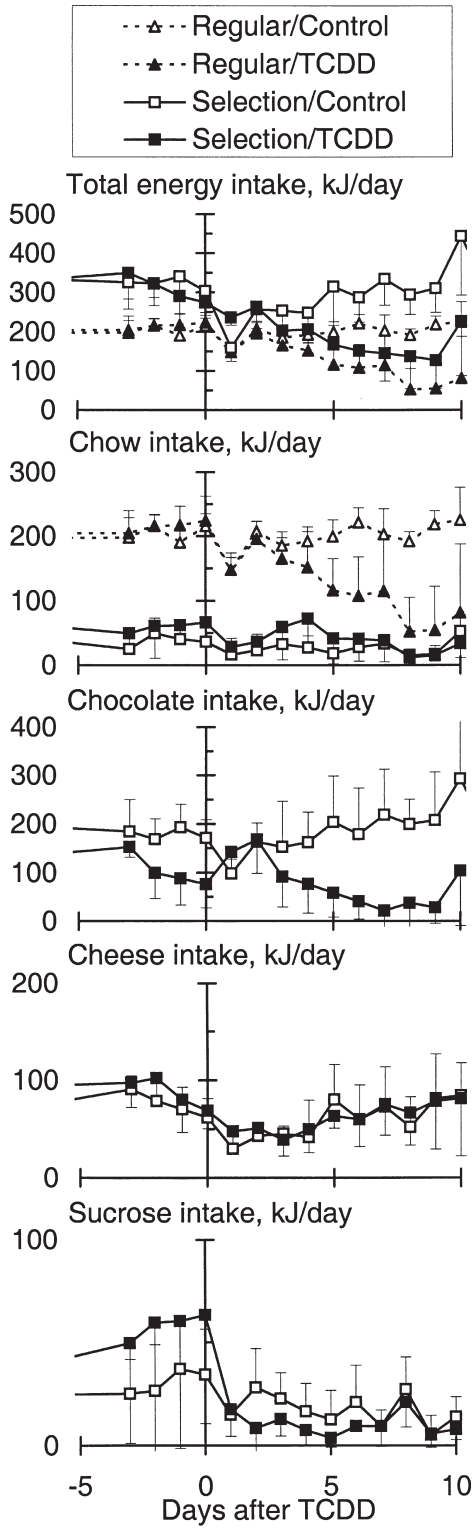

FIG. 1. Effect of TCDD on the intake of different food items (mean ± SD) in female H/W rats on the selection or regular diets ($n = 5$). The selection diet was started 16 days before TCDD exposure (day 0), and consisted of rat chow, chocolate, cheese, and sucrose solution ad lib.

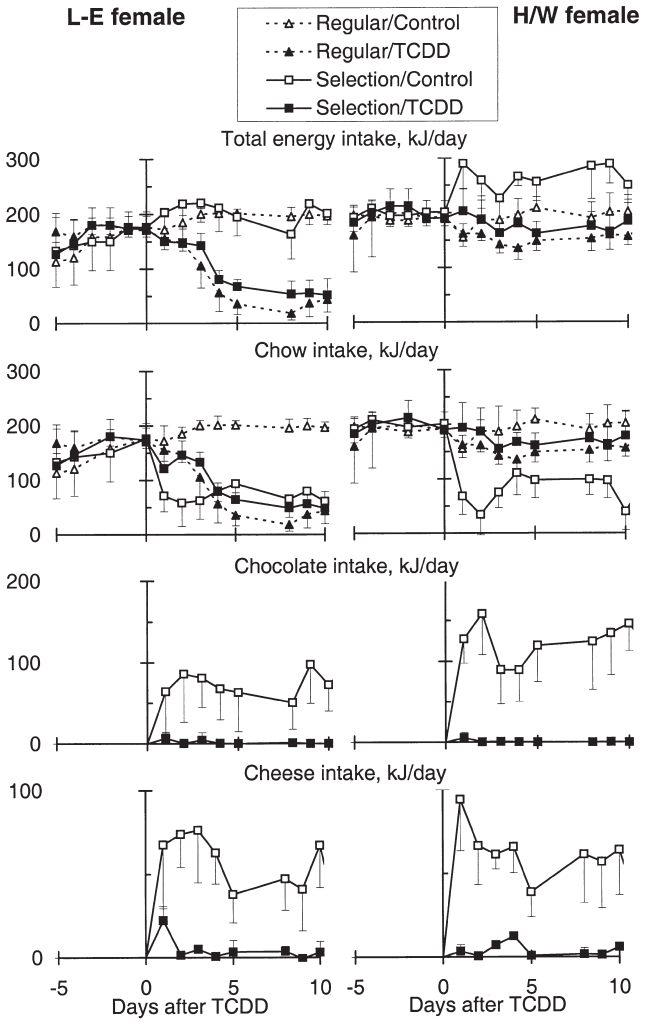

FIG. 2. Effect of TCDD on the intake of different food items (mean ± SD) in female L-E and H/W rats on the selection or regular diets (n = 6). The selection diet was started immediately after TCDD exposure (day 0) and consisted of rat chow, chocolate, and cheese ad lib.

lection occur in both genders? Second, what is the role of novelty of the food item, i.e., can the dramatic inhibition of chocolate and cheese intake in the second experiment be explained by avoidance of all new foods? Third, is the selecting of the foods specific to their macronutrient content?

Male L-E and H/W rats were offered chow, chocolate, and low-fat cheese ad lib for 4 days before TCDD exposure (50 μg/kg IP). This was considered a time period long enough to familiarize the rats to the new foods but short enough not to induce obesity or major changes in nutrient metabolism.

The pre-TCDD changes were similar to those in other experiments: increased total energy intake, remarkable chocolate and cheese intake, and decreased chow intake in selection-diet groups (Fig. 3).

TCDD rapidly reduced chocolate intake in both strains (Fig. 3) ($p < 0.01$, t-test). Cheese intake decreased only in L-E rats and only after 6 days postexposure, implying that this was related to progressively decreasing energy intake rather than cheese in specific. In addition, TCDD increased chow intake significantly in selection-diet rats, which seemed to compensate the reduction in chocolate intake. The availability of several foods maintained the total energy intake at a higher level than in rats offered only chow.

The food items consumed were also calculated as macronutrients, and related to the respective values in the selection diet/control group (Fig. 4). Protein intake level did not change during the experiment in H/W rats. In L-E rats, total energy intake decreased progressively, but protein intake stayed above this level (p = 0.004, Mann–Whitney U), although it also decreased.

In contrast, fat intake decreased more than total energy intake in both strains, the difference being largest between days 1 to 5 postexposure ($p < 0.05$, Mann–Whitney U). Carbohydrate intake followed total energy intake in this experiment.

Similar analyses were performed with the data from the other experiments. After 16 days with selection diet (Experiment 1), TCDD reduced carbohydrate and fat intake simi-

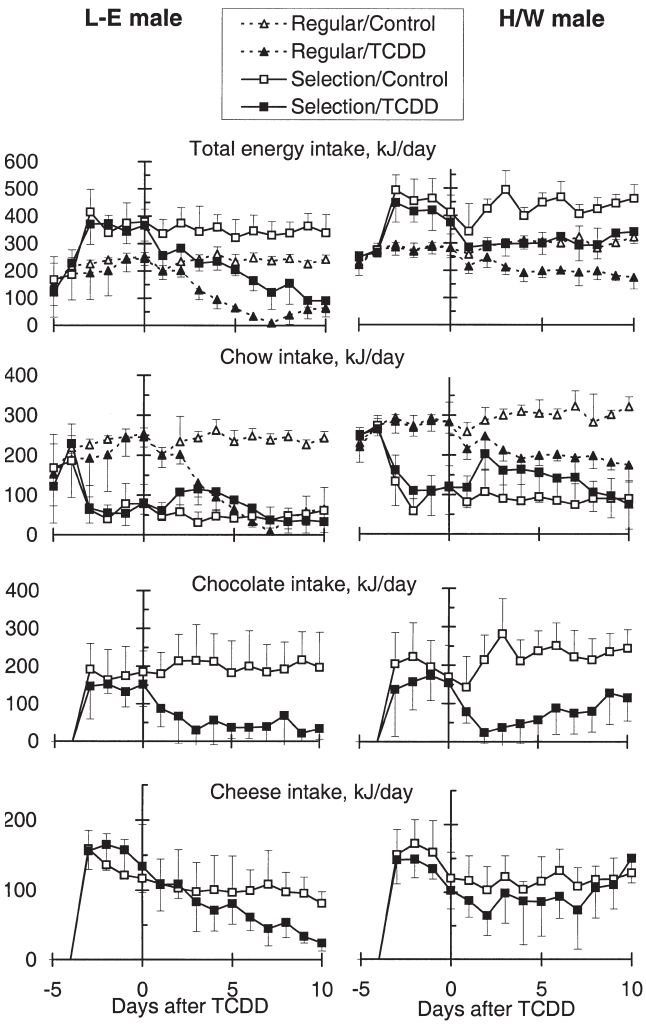

FIG. 3. Effect of TCDD on the intake of different food items (mean ± SD) in male L-E and H/W rats on the selection or regular diets (n = 6). The selection diet was started 4 days before TCDD exposure (day 0), and consisted of rat chow, chocolate, and cheese ad lib.

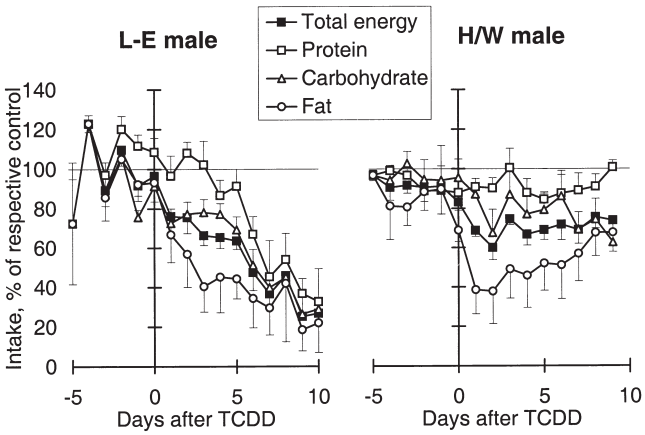

FIG. 4. Total energy and macronutrient intakes of the selection diet/TCDD group in male L-E and H/W rats ($n = 6$). The selection diet was started 4 days before TCDD exposure (day 0). The amount of each macronutrient was calculated as the sum of its content in each food consumed by the rat. The values were then related to the values of the respective control group at the same time (mean ± SE).

larly to energy intake, but protein intake remained significantly higher ($p < 0.05$, Duncan). When selection diet was offered only postexposure (Experiment 2), TCDD reduced fat intake more than energy intake, protein intake similarly to energy, and carbohydrate intake remained higher than energy intake (data not shown).

Experiment 4: 11-Hour Time Course

TCDD prevented the shift to palatable foods if they were offered after the exposure. The time response of this phenomenon was studied in the fourth experiment. Male rats from Lines A, B, and C were exposed at 0800, 1500 and 1800 h. Chocolate was given immediately before the beginning of dark period (1900–0700 h), which is the active period for rats. In addition, rat chow, but no cheese, was offered ad lib. Chow and chocolate intakes were measured next morning at 0800 h, and chocolate was removed from the diet. The doses were well below lethal doses (Lines A and B: 100; Line C: 10 μg/kg TCDD IG).

TCDD prevented chocolate intake almost completely in all strains (Fig. 5; median consumption only 0.05 g; quartiles 0.02 and 0.21 g), while control animals consumed more (median 2.78 g; quartiles 0.74 and 4.27 g). In contrast, TCDD did not affect chow intake after the nonlethal doses used (Fig. 5). The TCDD effect on chocolate was fully developed already in the group that was exposed only 1 h before darkness.

However, there were three rats in Line B that consumed more chocolate (range 1.32–8.96 g) than any other TCDD-exposed rat (range 0–0.45 g). Surprisingly, the three rats were from the same litter. There was a fourth rat from the same litter in the experiment. It was also TCDD exposed, and its chocolate consumption was more than the median value (0.30 g). It is unlikely that the deviant response would appear only in this litter by coincidence ($p = 0.002$, Fisher's exact test). The four rats are shown separately in Fig. 5., but they were included in statistical analyses. In contrast to chocolate intake, TCDD-induced body weight loss during consecutive days was similar in the deviant litter and other rats in Line B.

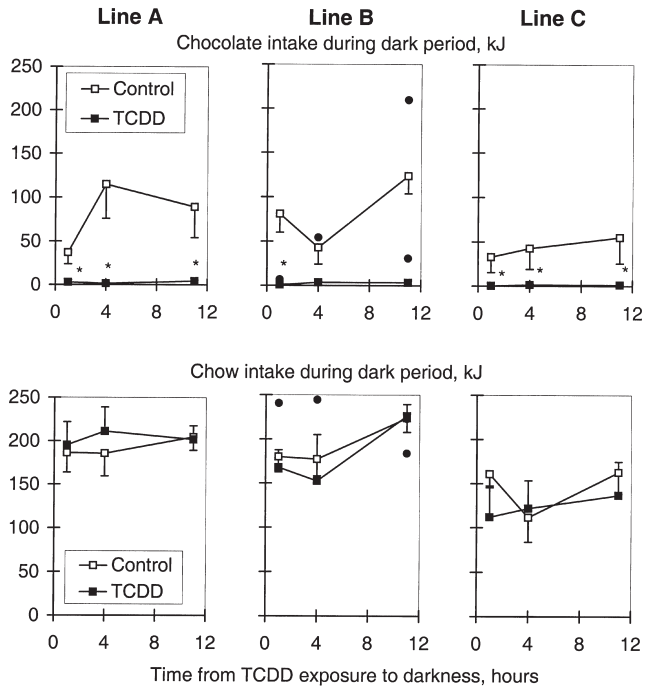

FIG. 5. Effect of exposure time on food intake (mean ± SE) during the first dark period in male rats from Lines A, B, and C (see introduction). Time 0 denotes the start of dark period (1900 h). In line B, the four rats from a deviant litter are shown individually (black circles, all TCDD-exposed; see Results). *Statistically significant difference compared with control group ($p < 0.05$, Duncan).

To study the persistence and specificity of the TCDD effect, the rats were offered cheese ad lib during one dark period 13 days postexposure. The rats had not been offered cheese before. There were no differences between TCDD and control groups (Fig. 6), or groups exposed to TCDD at different times of day (data not shown).

Chocolate intake was studied again during one dark period 19 days postexposure. The exposed rats consumed more chocolate than they did immediately after exposure (median 2.65 g, quartiles 0.03 and 7.48 g), but also control rats ate more chocolate than before (median 9.87 g, quartiles 8.70 and 10.38 g). Chocolate intake was still clearly smaller in the TCDD groups, $F(1, 25) = 73.8$, $p < 0.001$, ANOVA).

DISCUSSION

TCDD clearly affected food selection in rats. It reduced chocolate intake and also cheese intake in certain experiments, but did not reduce chow intake. This was seen in all strains tested and both genders. The two main questions are, which food properties were involved, and which mechanisms lead to the outcome. The answers may be of importance in two ways, as a means to understanding diet-selective antiobesity mechanisms, and as a means to understanding the mechanisms of dioxin toxicity. Several doses were used in the study, and the effect was evident already after 10 μg/kg TCDD in Line C. The smallest doses tested had clear effects in H/W rats (50 μg/kg) and Line A (100 μg/kg). Thus, the deviant H/W-type AH receptor does not cause major differences in the responsiveness of the rats.

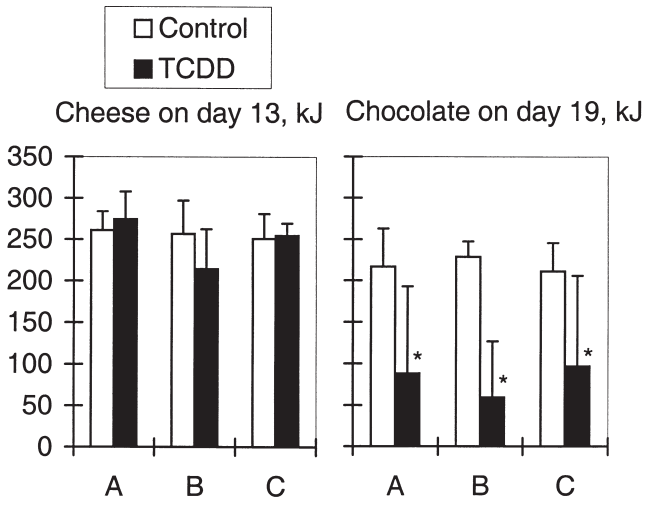

FIG. 6. Cheese and chocolate intakes (mean ± SD) during one dark period 13 and 19 days after TCDD exposure, respectively, in male rats from Lines A, B, and C. *Statistically significant difference compared with control group ($p < 0.05$, Mann–Whitney U).

The palatability of food may affect the amount and proportion of foods the TCDD-treated rats consume. Highly palatable choices were offered in this study to enhance voluntary food intake, and this should be kept in mind when the results are interpreted.

The timing of the start of the selection diet seems to be critical. If the food items were novel, their intakes were much smaller after TCDD than if they were familiar to the rats. Thus, it is likely that the novelty of a food is an important factor in food selection in TCDD-exposed rats.

Immediate Effects With Novel Foods

TCDD reduced chocolate and cheese intakes similarly in all strains and after all doses when they were novel foods. The effect was rapid and appeared within a few hours, as the reduction was seen within one dark period. Although food intake was not measured during the night, rats eat a considerable amount of food during the early dark phase, and even this had to be inhibited to explain the results. TCDD-induced neophobia of new food items could be one explanation. However, this seems unlikely for several reasons. First, the effect remained for 10 days, which should be enough to get used to the new foods. Second, most rats ate some food already during the first night and supposedly familiarized with it, but for some reason did not start to consume it. Third, given the slow elimination and, therefore, long-lasting effect of TCDD (14), neophobia should be seen also on day 13 when cheese was offered as a new food to Lines A, B, and C. This was not the case, but on day 19, the rats still showed aversion to chocolate, the food they were offered at the day of dosing.

Another explanation is conditioned taste aversion (3). If TCDD induces malaise, this could be conditioned to a novel food offered at the time of dosing. The association to a familiar food would be weaker, as was indeed seen in this study. However, it is somewhat surprising that the effect was seen also when chocolate was offered after the putative malaise must have developed (i.e., 11 h after dosing). Previously, some, although not consistent, evidence of nausea was seen in conditioned taste aversion and kaolin intake tests (13).

Progressive Effects With Familiar Food

Results were different if the foods were familiar. There was a clear decrease of chocolate intake after TCDD, but the effect was smaller or missing with cheese. This was a consistent finding in L-E and H/W rats in both genders. Chocolate intake decreased progressively for a few days and stayed below control values up to 5 weeks.

This outcome cannot be explained by neophobia, as the foods were familiar. Also, it would be difficult to understand how conditioned taste aversion could develop to only one of the three food items that rats have been eating for several days, and why it would take several days to develop the aversion in full.

It is unlikely that the change would be secondary to the wasting syndrome because 1) the change started to appear before any major alterations in body weight or energy stores were observed; 2) the change was seen similarly in both strains, although H/W rats show only a moderate wasting syndrome even after high doses; and 3) the change remained for 5 weeks in H/W rats, although their food intake and weight gain recovered after 2 weeks. It seems more plausible that some kind of sensory feedback due to certain food properties would result in chocolate aversion.

TCDD may change taste or smell perception, and as a result, some properties of chocolate, but not cheese or chow, would be disliked. TCDD is not known to affect senses, but it is interesting that the AH receptor density is high in the olfactory bulb (4). Food texture may also be an important factor affecting these processes. TCDD increases food spillage dose dependently (19).

Altered intestinal or postingestive feedback is a plausible explanation for changes in food selection. TCDD increased responsiveness to nutrient energy, if the nutrient was ingested or intubated IG, but not if the nutrient was injected IP (12). This implies that the intestinal feedback of ingested food is altered. Different foods produce different feedback signals depending on their energy, macronutrient, or nutrient content.

Macronutrients

There appear to be distinct and strict regulation systems for both protein and carbohydrate intakes, and the protein regulation seems to be separate from that of energy (1,2). However, it is questionable if any of the three macronutrients has an inherent sensed quality, and therefore, an animal must learn to associate certain foods with certain ingestive feedback signals (22).

Carbohydrate (and also protein) intakes were at the same level as, or higher than, total energy, depending on experimental setting. If carbohydrates are avoided, the rats must differentiate sucrose (main carbohydrate in chocolate) and starch (main energy source in chow, which was not avoided). Indeed, rats seem to have a sense of taste for polysaccharides, and it is different from that for sweet sugars (18). There was a nonsignificant tendency of avoidance of sucrose solution after TCDD. In a previous study, intake of sugar solution was decreased in TCDD-exposed H/W rats, while intake of saccharin solution tended to increase, suggesting that it was the amount or type of energy rather than sweet taste that was disliked (10).

Fat intake was always below or at the level of total energy intake, which makes it a promising candidate for the avoided property. But if chocolate fat is avoided, it remains to be explained why there were no changes in cheese intake in experiments where cheese was a familiar food. Cheese contains

66% of its energy as fat (the value even for the low-fat cheese used in experiment 3 is 39%). Again, different fatty acids may have different effects. Large protein content could also increase acceptability of this food.

Protein seems not to be avoided after TCDD. On the contrary, protein intake was similar to or often higher than total energy intake. In H/W rats, it was at the same level as in control rats, if they were familiar with the selection food items before TCDD exposure.

Previous studies have shown only a slight TCDD-induced avoidance of fat-rich diet in male H/W rats (10), and slight preferences for protein-rich diet in male L-E (10,13) and H/W (13) rats, while female L-E rats preferred regular feed (13). More detailed studies with new food items should be performed to be able to distinguish macronutrient-specific effects from food-dependent effects.

CONCLUSIONS

Taken together, there are clear changes in food selection after TCDD exposure. The changes occur rapidly, within a few hours after TCDD exposure. Conditioned taste aversion may play a role in experiments with novel foods. However, also other mechanisms seem to be involved in experiments with familiar foods. TCDD-exposed rats seem to reduce fat intake but show variable results with carbohydrate. Protein intake seems to be less affected. On the other hand, results depend on experimental setting and may be explained by other factors such as taste, texture, and energy content of food. No major differences in food selection were found between rat lines with different TCDD susceptibilities. The results in susceptible rats were affected by a severe wasting syndrome after lethal doses.

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