Toxicology 390 (2017) 43–52

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Chronic exposure of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induces an obesogenic effect in C57BL/6J mice fed a high fat diet

Axelle Brulport[a,b,c], Ludovic Le Corre[a,b,c,*], Marie-Christine Chagnon[a,b,c]

[a] Université de Bourgogne Franche-Comté, LNC UMR1231, F-21000 Dijon, France
[b] AgroSup, LNC UMR1231, F-21000 Dijon, France
[c] Nutrition Physiology and Toxicology Team (NUTox), INSERM, LNC UMR1231, F-21000 Dijon, France

ARTICLE INFO

Keywords:
TCDD
Chronic exposure
Obesogen

ABSTRACT

Contaminant involvement in the pathophysiology of obesity is widely recognized. It has been shown that low dose and chronic exposure to endocrine disruptor compounds (EDCs) potentiated diet- induced obesity. High and acute exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a persistent organic pollutant (POP) and an EDC with anti-estrogenic property, causes wasting syndrome . However at lower doses, the TCDD metabolic effects remain poorly understood. We investigated the obesogenic effect during chronic exposure of TCDD at 1 µg/kg body weight (bw)/week in adult C57BL/6J mice fed with a high fat diet (HFD) and exposed from 10 to 42 weeks old to TCDD or equal volume of vehicle by intragastric gavage. Under these conditions, TCDD was obesogenic in adult mice (7% in males and 8% in females), which was linked to fat mass. A sex effect was observed in the fat mass distribution in adipose tissue and in the hepatic triglyceride content evolution. In visceral fat pad weight, we observed a decrease (11%) in males and an increase (14%) in females. The hepatic triglyceride content increase (41%) in females only. TCDD failed to induce any change in plasma parameters regarding glucose and lipid homeostasis. Messenger ribonucleic acid (mRNA) levels involved in adipose tissue and hepatic metabolism, inflammation, xenobiotic metabolism and endocrine disruption were differently regulated between males and females. In conclusion, these results provide new evidence that dioxin, a POP and EDC can be obesogenic for adult mice with multi-organ effects.

1. Introduction

Dioxins are a family of compounds including 210 congeners. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) exhibits the greatest toxicity of the class. The toxicity of TCDD relates to high concentration acute exposure which was notably demonstrated after the Seveso industrial accident which occurred in Italy (1976). However, TCDD is currently ubiquitous at low concentrations in industrialized countries, mainly due to anthropogenic activities (Conesa et al., 2008; Roeder et al., 1998; Umbreit et al., 1986; Wilson et al., 2008). Since the reduction of industrial processes that use chlorination, open combustion (waste, fires, and volcanic eruptions) has been the major dioxin emitter. Since the signing of the Stockholm convention in 2001 and the introduction of dioxin emission reduction policy in Europe, sediment analysis shown the efficiency of these measures on dioxin level, but local disparities remain present (Van Metre et al., 2015).

The half-life of TCDD is about 8.3 days in air, 0.5 years in water, and 100 years in soil and sediments (Sinkkonen and Paasivirta, 2000). This leads to food-chain bioaccumulation; wildlife constituting a TCDD reservoir. Currently, over 90% of human dioxin exposure comes from diet via contaminated fat sources (dairy products, meat and fish notably) due to the lipophilic nature of dioxins (Roeder et al., 1998). In a recent study, TCDD levels in food ranged from 1 pg/kg for vegetables/fruits/pulses and cereals to 21 pg/kg for fish and seafood with intermediate values for meat (4 pg/kg) and dairy products (6 pg/kg) (Perello et al., 2012). Population are now faced with low dose and chronic exposure to TCDD.

Bioavailability of TCDD may depend on the macronutrient composition as well as methods used to prepare food (Shen et al., 2016; Zhang et al., 2013). In 1998, the World Health Organization (WHO) established a tolerable daily intake (TDI) of 1–4 pg/kg body weight (bw)/day. In 2001, the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA) defined the Provisional Tolerable Monthly Intake (PTMI) at 70 pg/kg bw/month. Recently, in 2012, the U.S Environmental Protection Agency (EPA) proposes a reference dose for chronic oral exposure of 0.7 pg/kg bw/day. Recent studies suggest that dietary exposure largely exceeds the current recommendations for dioxin exposure with an estimation of

* Corresponding author at: NUTox laboratory, UMR1231 INSERM, AgroSup Dijon, 1 Esplanade Erasme, 21000 Dijon, France.
E-mail address: ludovic.le-corre@u-bourgogne.fr (L. Le Corre).

http://dx.doi.org/10.1016/j.tox.2017.07.017
Received 12 May 2017; Received in revised form 24 July 2017; Accepted 31 July 2017
Available online 01 August 2017
0300-483X/

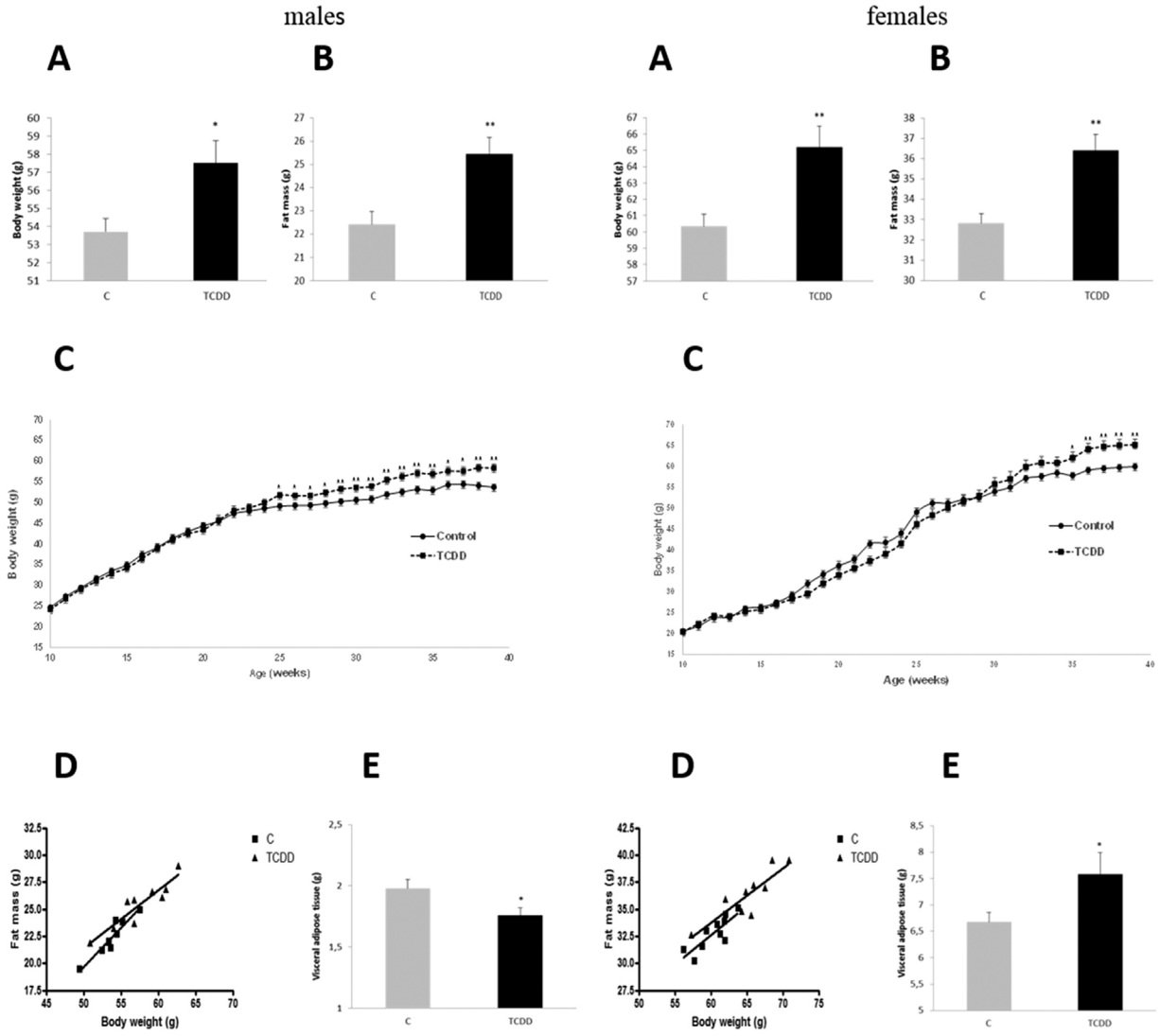

Fig. 1. TCDD effect on body weight, fat and VAT masses in males (left) and females (right). (A) Body weight, (B) fat mass, (C) body weight gain kinetic, (D) correlation between body weight and fat mass and (E) visceral adipose tissue mass in C57Bl/6J mice fed with a high fat diet and after a TCDD exposure or not from 10 to 42 weeks old at 1 µg/kg body weight/week. Except for the weight gain kinetic that was assessed weekly, all other parameters were measured at 42 week of age. Values represent means ± SEM. Paired student *t* test were performed; *p < 0.05, **p < 0.01 (compared to the control group (c)). Pearson correlation between body weight and fat mass in control (r^2 = 0.89; p = 0.0002) and TCDD treated (r^2 = 0.84; p = 0.0005) males, and in control (r^2 = 0.69; p = 0.003) and TCDD treated (r^2 = 0.75; p = 0.003) females. n = 10 per group.

1.3 ± 0.4 pg/kg bw/day in French women with similar levels in U.S children and adolescents (Charnley and Doull, 2005; Danjou et al., 2015).

TCDD exhibits biological adverse effects as it disrupts homeostasis via its actions on the immune and nervous system, reproductive function, as well as altering functions of many organs including skin, liver, pancreas and adipose tissue. Furthermore, TCDD has been classified as carcinogenic for humans by the International Agency for Research on Cancer (IARC). Concerning energy metabolism, environmental substances such as endocrine disruptors (EDCs) have been implicated in obesity development. Indeed, they are obesogenic substances that inappropriately regulate lipid metabolism and adipogenesis to potentiate obesity (Baillie-Hamilton, 2002; Grun and Blumberg, 2006). TCDD has been shown to be an EDC with anti-estrogenic effect *in vivo* (Franczak et al., 2006; Mocarelli et al., 2008; Safe and Wormke, 2003; Shi et al., 2007) and *in vitro* (Göttel et al., 2014; Matthews and Gustafsson, 2006; Swedenborg and Pongratz, 2010).

TCDD is also an energy metabolism disruptor. High and acute TCDD exposure causes a « wasting syndrome » characterized by a loss of body weight accompanied by a decrease in adipose tissue mass in rodents (Brewster and Matsumura, 1988; Chapman and Schiller, 1985; Gasiewicz and Neal, 1979). However little data are available regarding the effects of low dose chronic exposure on metabolism. Only in the French E3N cohort, it has been shown that the body mass index (BMI) is associated with dioxin exposure (Danjou et al., 2015). Notably the proportion of women with a BMI < 25 kg/m^2 was greater in the upper quartile of dietary dioxin exposure (> 1.52 pg/kg body weight (bw)/day) than those in the lower quartile (< 0.98 pg/kg bw/day) wherein there were more women with a BMI ≥ 25 kg/m^2 (Danjou et al., 2015). At low doses, most of the already known obesogenic EDCs do not directly induce obesity but rather act to potentiate obesity, as observed in rodents when they are fed with an high fat diet (HFD) (Ivry Del Moral et al., 2016; Mackay et al., 2013).

So, the aim of this present study was to check if TCDD could induce an obesogenic effect after chronic exposure at 1 µg/kg bw/d in adult mice fed with a HFD. C57BL/6 strain is an established model for diet-induced obesity. C57BL/6 mice will develop severe obesity, hyperglycemia, and insulin resistance if weaned onto a high-fat diet (Surwit et al., 1995; Rossmeisl et al., 2003).