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EDITED BY

Monday Ogaba Ogese,
University of Liverpool, United Kingdom

REVIEWED BY

Jasim Khan,
University of Alabama at Birmingham,
United States

*CORRESPONDENCE

Olivier Sorg,
✉ olivier.sorg@unige.ch

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Development of skin diseases following systemic exposure: example of dioxins

Olivier Sorg* and Jean-Hilaire Saurat

Clinical Pharmacology and Toxicology, University of Geneva, Geneva, Switzerland

Most skin manifestations of exposure to toxic compounds are a consequence of a direct contact with the toxicants. However, some toxicants may reach the skin following systemic exposure, and promote skin diseases. Good examples of such chemicals are dioxin-like compounds. This family of lipophilic molecules comprises polychlorinated (dibenzodioxins, dibenzofurans and biphenyls). The most potent member of this family is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Following oral ingestion of as little as a few mg TCDD, skin lesions appear in a couple of weeks, starting from the face and diffuse then on the trunk and limbs. This syndrome was historically called “chloracne” and the skin lesions have now been shown to be skin hamartoma induced by TCDD. Sebaceous glands release their lipid content on the surface of the skin by a holocrine secretion, and so any lost sebocyte should be transmitted to progenitor cells to differentiate and migrate to the sebaceous gland to replace the lost sebocyte. TCDD acts by inducing a switch in this signal and skin hamartoma develop in place of new sebocytes.

KEYWORDS

dioxin, skin, toxicology, AhR, biomarkers, ingestion

Introduction

Persistent organic pollutants collectively referred to as dioxin-like compounds include polyhalogenated aromatic hydrocarbons such as polychlorinated dibenzodioxins (PCDD), polychlorinated dibenzofurans (PCDF) and polychlorinated biphenyls (PCB) (Figure 1). They were involved in various industrial accidents in the 20th century such as the BASF plant in Ludwigshafen in 1953 (Thiess et al., 1982) and the Icmesa factory in Seveso in 1976 (Assennato et al., 1989). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), the most biologically potent of this family, was shown to be the toxic contaminant of the Agent Orange used by the U.S. Army during the Vietnam War in the 1960s (Steele et al., 1990). During the Ukrainian presidential campaign in 2004, the candidate Victor Yushchenko was poisoned by TCDD at a dinner party organized by the Ukrainian security services (McKee, 2009; Sorg et al., 2009; Saurat et al., 2012). The members of the dioxin-like family are not volatile, and all reported intoxications by these compounds were due to ingestion of contaminated materials. However, the hallmark of clinical manifestations following oral exposure to dioxins is a cutaneous syndrome known as chloracne (Panteleyev and Bickers, 2006; Saurat et al., 2012), which illustrates a mechanism of skin toxicity promoted by chemicals that reached the skin via oral route, and not by direct contact to the skin.

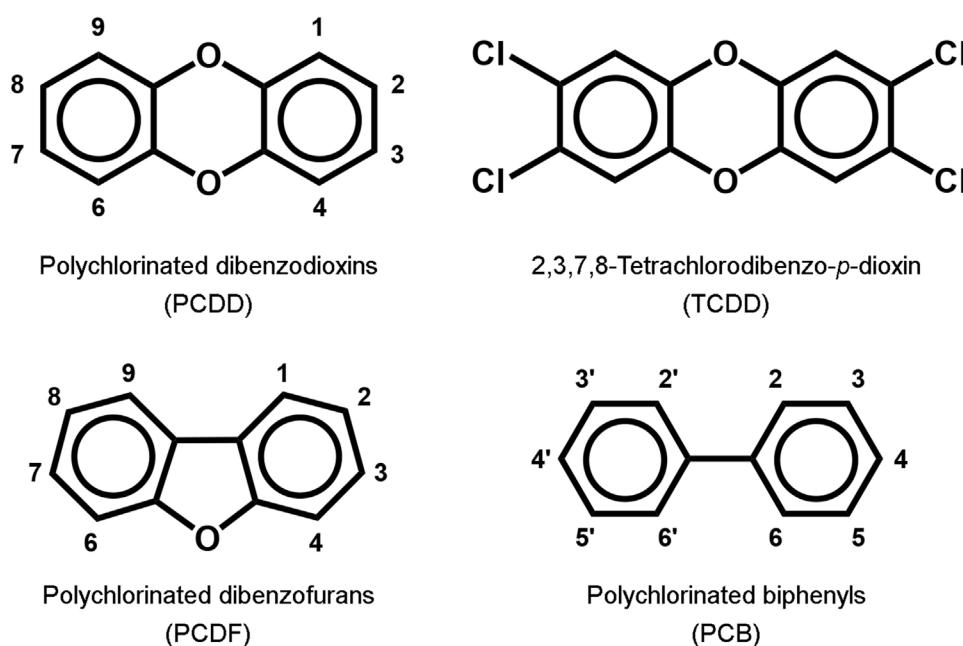


FIGURE 1
Chemical structures of dioxin-like compounds.

Sebaceous gland homeostasis

Sebaceous glands are skin appendages that produce various lipids forming a thin protective film at the skin surface (Schneider and Paus, 2010). Terminally differentiated sebocytes are filled with lipids, undergo nuclear degradation and membrane lysis, and finally release their content by holocrine secretion (the sebum), which flows to the surface of the skin. To maintain a physiological renewal of sebaceous glands, the lost sebocytes must be replaced.

During the terminal differentiation of sebocytes, a signal should be released to induce pluripotent stem cells found in the hair follicle junctional zone to differentiate and migrate to the outermost layer of sebaceous glands. Different proteins, such as SRY-box transcription factor 9 (SOX9), leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1) and (leucine-rich repeat-containing G-protein-coupled receptor 6 (LGR6), are expressed in sebocyte progenitor cells (Clayton et al., 2019; Geueke and Niemann, 2021), and might be involved in the signalling pathway for sebaceous gland renewal.

In cultured sebocytes, a downregulation of LRIG1 by siRNA significantly decreased the CYP1A1 response to TCDD, indicating that LRIG1 contributes to a higher susceptibility of AhR agonists (Fontao et al., 2017). Studies in mice showed that following intraperitoneal injection by TCDD or β -naphthoflavone—another AhR agonist—the first cutaneous targets were sebaceous glands. When these mice were treated by topical application of TCDD, LRIG1-bearing pluripotent cells found in the vicinity of sebaceous glands showed a strong activation of CYP1A1, thus appearing as a main target of TCDD that may be involved in the disturbed turnover of sebaceous gland and hamartoma formation (Fontao et al., 2017).

According to recent studies TCDD, a very lipophilic compound, may accumulate in sebum and leads to deregulation of sebocyte differentiation via i) the activation of the transcriptional repressor B lymphocyte maturation protein 1 (Blimp1), as well as ii) the stimulation of the proliferation of interfollicular epidermis mediated by the Wnt signalling pathway. This may explain the observed atrophy of sebaceous glands and the formation of the mentioned hamartoma (MADISH), the hallmark of TCDD cutaneous toxicity (Ikuta et al., 2010; Bock, 2017a; Bock, 2017b; Feldman et al., 2019).

Biology of dioxins

Dioxin-like compounds are very lipophilic and may cross the plasma membrane of cells via simple diffusion. Once in the cytosol, they bind to an intracellular receptor, the aryl hydrocarbon receptor (AhR). Following AhR binding by an agonist, chaperone proteins maintaining AhR in a quiescent form are released, the (agonist-AhR) complex recruits another protein—the AhR-nuclear-translocator (ARNT)—then the new complex is translocated to the nucleus and binds to xenobiotic response elements (XRE) in the promoters of various genes, leading to the modulation of their expression (Abel and Haarmann-Stemann, 2010; Guyot et al., 2013; Sorg, 2014).

Many genes have XREs on their promoter. Moreover, AhR interacts with different signalling pathways, and may cross-talk with other nuclear receptors. This may explain the pleiotropic actions promoted by the structural diversity of its agonists (Hahn, 2002; Tijet et al., 2006; Borlak and Jenke, 2008; Furness and Whelan, 2009; Hayes et al., 2009; Ma et al., 2009; Puga et al.,



FIGURE 2
Victor Yushchenko several weeks after being exposed to TCDD by ingestion.

2009; Ohtake et al., 2011; Guyot et al., 2013), and makes AhR a promising therapeutic target for chronic inflammatory skin diseases (Kim et al., 2022).

TCDD toxicity is characterised by a very large range of sensitivities among mammals, the LD₅₀ for Syrian hamsters (≈ 10 mg/kg) being 10,000 times higher than that of guinea pigs (≈ 1 μ g/kg) (Geyer et al., 1993). Following oral lethal doses of TCDD animal die mainly from liver failure and gastrointestinal haemorrhage (Nüittynen et al., 2007). The gastrointestinal tract is the first target, followed by the liver and the pancreas, then the peripheral nervous system, and finally the skin, which is also the last organ to recover (Saurat et al., 2012).

Dioxin-like compounds are very lipophilic and are found almost exclusively in body fat; this allows to determine the body burden of dioxin from the blood value of dioxin expressed as [pg/g lipid weight (lw)] and the body fat content (Sorg et al., 2009).

Depending on their reactivity toward the phase I and II enzymes catalysing their metabolic conversion, they stay in subcutaneous fat for various periods of time, where they are delivered to the skin regularly and induce a disruption of cutaneous biology. This is particularly the case for TCDD, which has a very long biological half-life (7–10 years) in spite of a huge activation of cytochromes P450 1A1, 1A2 and 1B1; indeed, in the case of Victor Yushchenko, only trace amounts of two hydroxylated metabolites of TCDD were found several months following TCDD exposure, corresponding to the peak of cutaneous symptoms (Sorg et al., 2009; Saurat et al., 2012). CYP1A1 is highly induced following AhR-dependent signalling pathway, and is a valuable biomarker of exposure to any dioxin-like compound (Chessa et al., 2021).

Various AhR-dependent cutaneous effects were reported in animal or *in vitro* models. *In utero* exposure of mice to TCDD accelerated epidermal barrier formation and promoted a transient chloracne-like

syndrome with sebaceous gland hypoplasia and cyst formation in their offspring (Bhujji et al., 2021). Peripheral blood mononuclear cells and CD4⁺ T cells from patients with psoriasis or atopic dermatitis were more sensitive to the AhR-dependent response to TCDD than these cells from healthy volunteers. These effects were not observed with the AhR agonist N-formylindolo[3,2-b]carbazole (FICZ), which has a much shorter biological half-life than TCDD (Um et al., 2020). Retinoids, in particular isotretinoin, are used to treat acneiform lesions; however, although their metabolism is impaired by dioxins (Esteban et al., 2021), retinoids failed to reverse TCDD-induced cutaneous toxicity, as demonstrated by various *in vitro* and animal models (Rudyak et al., 2018). An aqueous extract of *Deschampsia antarctica* protected cultured human keratinocytes and fibroblasts from TCDD-induced toxicity, which might be interesting to treat chloracne-like syndromes if confirmed in clinical trials (Zamarron et al., 2019).

The case of Victor Yushchenko

In late September 2004, Victor Yushchenko, a candidate for the Ukraine presidency, appeared disfigured in his meetings and on TV channels. His face was swollen and had many skin lesions of greyish colour (Figure 2). A few weeks earlier, coming back from a dinner organised by senior officials of the Ukrainian security services, he became seriously ill. Victor Yushchenko was hospitalised at a private clinic in Vienna for 9 days. He was diagnosed with acute pancreatitis of unknown origin, associated with ulcerations of the intestine and enlargement of the liver.

In December, a sample of his blood sent to a lab in Amsterdam appeared to be contaminated by dioxin-like compounds that activate the AhR signalling pathway, and in January 2005, a chemical analysis performed in Dübendorf (Switzerland) revealed a blood concentration of 110 ng TCDD/g (lw), i.e., more than 5,000 times higher than the global TCDD equivalent of toxicity (TEQ) found in the general population, and corresponding to a body dose of about 2 mg TCDD. It was clear that during his dinner on 5 September 2004, it had been poisoned by TCDD (McKee, 2009; Sorg et al., 2009; Ryan, 2011).

The cutaneous signs appeared 2–3 weeks later, and amplified on a period of 18 months, before decreasing slowly up to 3.5 years after poisoning. The hallmark of the cutaneous signs of dioxin toxicity, known as chloracne, is the development of particular skin lesions showing both “loss of structure” and “gain of structure” features, which we identified as hamartomas and named “metabolising acquired dioxin-induced skin hamartomas” (MADISH) (Saurat et al., 2012). A whole-genome transcriptional analysis of skin samples of V. Yushchenko taken 5 months after TCDD poisoning, compared to matching controls, identified 329 genes with more than four-fold upregulation and 1,533 genes with more than four-fold downregulation. Genes coding for enzymes involved in the metabolism of xenobiotics, as well as genes involved in inflammation and extracellular matrix modulation, were highly induced, whereas many genes of the metabolism of lipids, in particular for the sebogenesis, were highly repressed (Saurat et al., 2012).

Parallel to the development of these hamartomas, there was a disappearance of all sebaceous glands. Since the sebocytes are lost during the holocrine secretion of their content, it seems that TCDD

promoted a disruption of the signalling pathway that normally induces the renewal of sebocytes from progenitor cells. Instead, new structures, the mentioned hamartomas, are produced and sebaceous glands degenerate.

Chloracne-like syndromes

The skin manifestations observed following dioxin exposure seem not specific of these compounds. Besides the herbicides and defoliants 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid, which constituted the Agent Orange used by the US Army during the Vietnam War and contained TCDD as impurity, other chlorinated compounds used in the synthesis of herbicides, such as 3,3',4,4'-tetrachloroazobenzene and 3,3',4,4'-tetrachloroazoxybenzene, were shown to produce chloracne-like skin lesions in chemical workers (Kimbrough, 1980; Scarisbrick and Martin, 1981).

Gawkrodder et al. (2009) reported a case series of seven organic chemists exposed to novel polycyclic halogenated chemicals of the family of triazoloquinoxalines, who developed clinical skin manifestations similar to chloracne, without any other signs of toxicity.

Passarini et al. (2010) reported a case series of nine patients with clinical signs of chloracne. Histological analyses of skin lesions from these patients revealed structures very similar to those observed in the skin samples from Yushchenko. However, the standard chemical analysis of dioxin-like compounds, including 7 PCDD, 10 PCDF and 8 PCB, in the blood of these patients did not show any values outside the normal range of the general population. The cause of these clinical symptoms was not identified.

In a more general manner, many dermatologists encounter patients living near dumping sites and landfills who developed skin lesions similar to MADISH (Megna et al., 2017). These patients were exposed regularly to various mixtures of chemicals, so it is quite difficult to identify the substances involved in the observed skin lesions.

All these examples of chloracne-like skin manifestations raise the question of the biochemical mechanism involved in the development of these particular skin lesions. Most known chloracnogens activate the AhR-dependent signalling pathway. However, various cases of chloracne-like syndromes, such as the case series of Passarini and colleagues mentioned above, are not related to the exposure of AhR agonists. On the other hand, all AhR agonists do not promote chloracne (Forrester et al., 2014). In particular high levels of AhR agonist activity may be reached in the blood following the consumption of various vegetables of the family of brassicaceae, and people who consume these vegetables regularly do not develop skin lesions (Connor et al., 2008).

Other skin diseases following systemic exposure

Besides dioxins other compounds may reach the skin via the blood circulation and exert a toxicity to the skin. Dysregulation of hormone homeostasis by endocrine disruptors may affect the skin too (dioxins are only an example) and promotes various skin

conditions via the binding of cellular targets in keratinocytes, melanocytes, sebocytes and immune skin cells (Ju and Zouboulis, 2016). Ingestion of thallium, a rodenticide no longer in use, induces skin lesions resulting in parakeratotic keratosis, the degeneration of keratinocytes and finally an ulceration of the skin (Bruner, 1991). Toxic epidermal necrolysis is another example of a specific cutaneous toxicity following ingestion of chemically unrelated compounds targeting the death receptor Fas (CD95), and resulting in the detachment of the epidermis from the dermis (Viard et al., 1998; Harr and French, 2010). Systemic contact dermatitis develops in people previously exposed to an allergen by direct contact to the skin when they are exposed again to this allergen via the blood circulation (Park et al., 2021).

Discussion

In the present review we gave an example of a family of compounds that promote a specific disease of the skin following enteral exposure. In the case of dioxins, the main known activated signalling pathway induces the transcription of genes involved in their metabolism and elimination; however, this mechanism does not function for TCDD, the most potent member of this family, because this compound resists to the metabolism by the phase I enzymes it induces, which confers to TCDD a very long biological half-life responsible for its cutaneous toxicity. To better understand the mode of action of TCDD and other chloracnogens we have to find other mechanisms of action besides the activation of xenobiotic response elements found in the promoter regions of many genes. The binding of such compounds to AhR may trigger cross-talks with other signalling pathways, as already mentioned (Hahn, 2002; Tijet et al., 2006; Borlak and Jenke, 2008; Furness and Whelan, 2009; Hayes et al., 2009; Ma et al., 2009; Puga et al., 2009; Ohtake et al.,

2011; Guyot et al., 2013), although it is not clear how this pleiotropic action of AhR may induce the mentioned clinical manifestations.

As a take-home message, it is important to bear in mind that skin chemicals entering the body via systemic exposure may reach the skin and induce a cutaneous toxicity. In general toxicology the skin is often overlooked and not considered as a possible target organ, whatever the mode of exposure. Most often the skin is only seen as a possible route of entry for compounds that may be toxic for internal organs.

Author contributions

OS wrote the manuscript, then the manuscript was discussed with J-HS, who made several changes and clarified some points. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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