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Review article

The insulin-like growth factor system: A target for endocrine disruptors?

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ABSTRACT

The insulin-like growth factor (IGF) system is a critical regulator of growth, especially during fetal development, while also playing a central role in metabolic homeostasis. Endocrine disruptors (EDs) are ubiquitous compounds able to interfere with hormone action and impact human health. For example, exposure to EDs is associated with decreased birthweight and increased incidence of metabolic disorders. Therefore, the IGF system is a potential target for endocrine disruption. This review summarises the state of the science regarding effects of exposure to major classes of endocrine disruptors (dioxins and dioxin-like compounds, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers, phthalates, perfluoroalkyl substances and bisphenol A) on the IGF system. Evidence from both experimental models (in vitro and in vivo) and epidemiological studies is presented. In addition, possible molecular mechanisms of action and effects on methylation are discussed. There is a large body of evidence supporting the link between dioxins and dioxin-like compounds and IGF disruption, but mixed findings have been reported in human studies. On the other hand, although only a few animal studies have investigated the effects of phthalates on the IGF system, their negative association with IGF levels and methylation status has been more consistently reported in humans. For polybrominated diphenyl ethers, perfluoroalkyl substances and bisphenol A the evidence is still limited. Despite a lack of studies for some ED classes linking ED exposure to changes in IGF levels, and the need for further research to improve reproducibility and determine the degree of risk posed by EDs to the IGF system, this is clearly an area of concern.

1. Introduction

1.1. Insulin-like growth factor system in physiology

The insulin-like growth factor (IGF) system is a highly conserved signalling pathway. The IGF system is involved in the regulation of growth, proliferation and differentiation in most cell types and acts in an endocrine, paracrine and autocrine fashion. The system includes two growth factors, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2), two receptors, IGF-1 receptor (IGF-1R) and IGF-2 receptor (IGF-2R), and IGF binding proteins (IGFBPs) (Fig. 1). IGF-1 and IGF-2 are widely expressed peptides with the liver being the main site of production (Hill, 1990; Rajpathak et al., 2009). The peptides are structurally very similar and they also share substantial sequence homology to proinsulin (50%) (Daughaday et al., 1989). IGFs exert their endocrine functions by binding to two cell surface receptors, which are expressed in almost all cell types, with different levels of affinity (Funk et al., 1992; Kineman et al., 2018). IGF-1R binds IGF-1 with the highest affinity, whereas IGF-2R binds IGF-2 with the highest affinity (Laviola et al., 2007). Furthermore, insulin can also bind IGF-1R and, at the same time, IGFs can interact with the insulin receptor (IR), but with much lower affinity compared to the main ligands (Andersen et al., 2017; Laviola et al., 2007). IGF-2R is considered an inhibitor receptor as IGF-2 binding to this receptor leads to IGF-2 degradation and is not associated with any intracellular signalling (Scott and Weiss, 2000).

Insulin-like growth factor binding proteins (IGFBPs) are a family of carrier proteins acting as major modulators of IGF activity. The affinity of IGFs for IGFBPs is higher than for the IGF-1R, therefore, in the extracellular environment, most IGFs are bound to IGFBPs, with IGFBP-3 being the most prevalent in human serum (Bach, 2018a). By binding IGFs, IGFBPs decrease IGF bioavailability and extend their half-life, also facilitating their transport through body compartments (Ranke and Wit, 2018). IGFBPs are cleaved by specific proteases, including the pregnancy-associated plasma protein A family, and cleavage reduces their affinities for IGFs (Bach, 2018b; Clemmons, 2018).

IGF signalling is involved in a wide variety of fundamental processes,

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with two major domains: growth and metabolic regulation. IGFs mediate growth-promoting actions in several organs, during the different stages of development (Murphy et al., 2006). IGF-1 mediates most of the growth-promoting actions of growth hormone (GH), forming a system which is commonly referred to as the GH-IGF axis (Florini et al., 1996). According to the original somatomedin hypothesis, GH secreted by the pituitary, binds to GH receptor (GHR), this stimulates liver production of IGF-1, which then acts peripherally in an endocrine manner (Daughaday et al., 1989). In turn, circulating IGF-1 is responsible for the negative feedback inhibition on hypothalamic/pituitary regulation of GH secretion (Kineman et al., 2018). The GH/IGF system has been implicated in establishing sexually dimorphic liver functions, at least in rodent models (Adams et al., 2015; Ohlsson et al., 2009). Indeed, liver-specific inactivation of IGF-1 feminises GH-regulated liver functions (Wallenius et al., 2001). Interestingly, sexual dimorphism in IGF-2 action during fetal life has been shown in animal models, with the IGF system in males being more sensitive to exogenous IGF-2 administration (White et al., 2018). The hypothesis has been challenged by subsequent research, as it is now well established that GH actions are not always mediated by IGFs and that, on the other hand, IGFs are not only regulated by GH and also have autocrine and paracrine modes of action (Ohlsson et al., 2009). Although the liver is the major site of production, IGF-1 is also locally produced by the majority of cell types, which also express IGF-1R and IGF-2R (Ferry et al., 1999). For example, both IGF-1 and IGF-2 are also produced by the human placenta, where they act as local growth regulators (Fant et al., 1986; Han et al., 1996). It is difficult to fully differentiate the roles played by circulating IGFs from locally produced IGFs, although great progress has been made using tissue-specific inactivation studies in animal models (Kineman et al., 2018).

In humans, IGF-2 is the major growth factor during fetal life and its concentration is five to six times higher than IGF-1 in the fetus, with levels progressively increasing throughout pregnancy (Fisher, 2016). IGF-1 exerts its role mainly during childhood, with levels peaking around puberty, and subsequently starting to decline (Löfqvist et al., 2001). IGF-1 levels in cord blood are positively associated with birthweight (Geary et al., 2003; Vatten et al., 2002). IGF-2 cord blood levels are only weakly related to birth size, largely because IGF-2 exerts its major growth-stimulating effect during the first part of gestation (Fisher, 2016). The critical role played by IGFs during development is shown by typical phenotypes exhibited by knockout mice models. Mice lacking IGF-1, IGF-2 or IGF-1R show intrauterine growth restriction, whereas IGF-2R knockout fetal mice are overweight, supporting the negative growth-modulating action of this receptor (Baker et al., 1993; DeChiara et al., 1990; Liu et al., 1993). In humans, mutations in IGF-1 and IGF-1R genes are associated with growth retardation (Abuzzahab et al., 2003; Woods et al., 1996). In animal models, IGF-1 stimulates longitudinal bone growth and it is involved in regulating liver, kidney and prostate size (Ohlsson et al., 2009).

IGFs have roles in metabolic regulation and disease and have been recently reviewed (Haywood et al., 2019). Given the large similarities between IGFs and insulin, it is not surprising that their actions are partially overlapping. The IGF-system is directly involved in regulating glucose homeostasis, given its insulin-like effect (Rajpathak et al., 2009). IGF-1 can act independently of insulin or enhance insulin action, as they share part of the same signalling pathway. For instance, once IGF-1 binds IGF-1R, autophosphorylation occurs, providing docking sites for the insulin receptor substrates, activating downstream signalling which results in increased glucose uptake (Haywood et al., 2019). In animals, IGF-1 is of importance for normal carbohydrate metabolism, with IGF-1 acting in concert with insulin to lower glycemia (Sjögren et al., 2001). Similarly, roles in lipid metabolism and fat mass

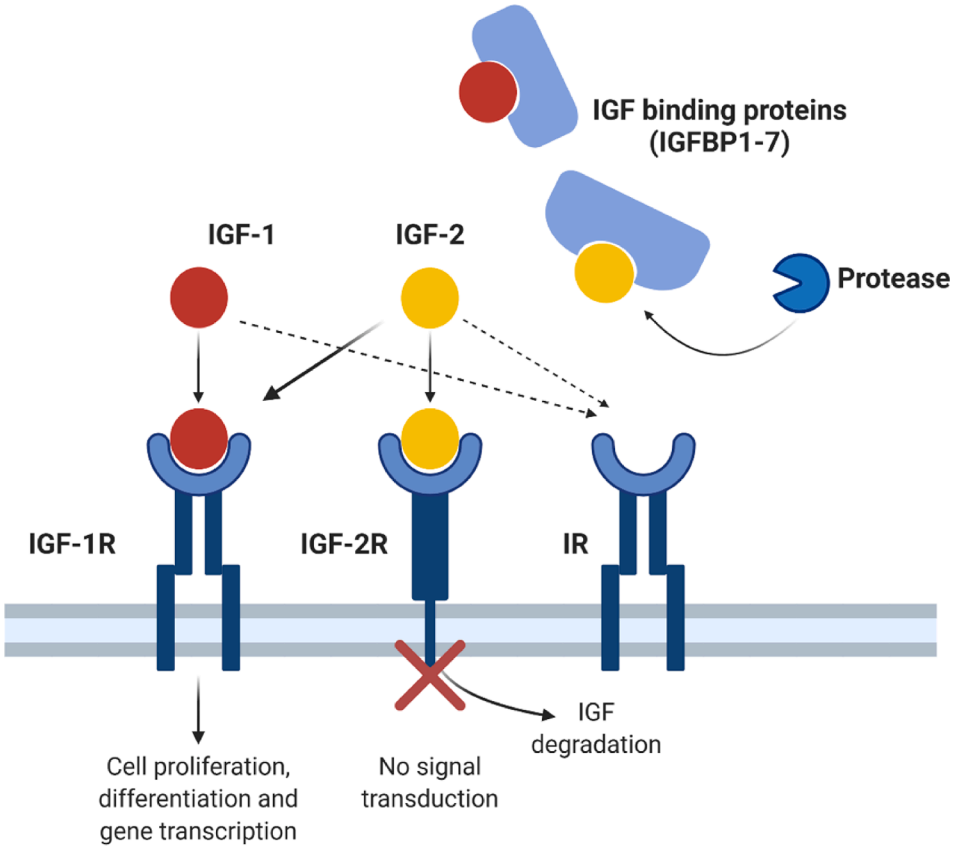

Fig. 1. Components and main functions of the IGF system. Free IGF-1 and IGF-2 can bind to their receptors (IGF-1R, IGF-2R). IGF binding proteins (IGFBP1-7) regulate IGFs bioavailability. IGF-1R is a tyrosine kinase which mediates actions of IGFs. IGF-2R is an inhibitory receptor, as it directs IGF-2 to lysosomes for degradation. IGFs can also bind insulin receptor (IR).

development have also been suggested (Ohlsson et al., 2009). IGF-1 levels are altered in adults with cardiovascular disease (Obradovic et al., 2019; Ren and Anversa, 2015), obesity (Berryman et al., 2013), insulin resistance (Cubbon et al., 2016), and type 2 diabetes (Shi et al., 2018). IGF-1 is also involved in regulating peripheral vascular resistance, sodium retention and insulin sensitivity (Ohlsson et al., 2009). Among the other roles, IGF-1 is involved in regulating ovarian function, particularly in follicular selection. Indeed, targeted disruption of the IGF-1 gene in mice causes infertility due to anovulation in females and a decrease in testosterone in males (Baker et al., 1996). Furthermore, IGF-1 is implicated in brain development, maturation and neuroplasticity (Dyer et al., 2016). IGF-1 and IGF-2 also play a role for cell transformation in several cancer types (Bach, 2018b).

Besides its direct interaction with GH, the IGF system is involved in multiple endocrine pathways. For example, estrogen increases hepatic IGF-1 production (Venken et al., 2005) while locally, estrogen-mediated regulation of IGF-1 is involved in uterine growth (Hewitt et al., 2010). Inactivation of IGF-1R in granulosa cells leads to decreased cell differentiation, proliferation and estrogen production and, hence, to infertility (Baumgarten et al., 2017). Furthermore, combined IGF1R/INSR knockout resulted in decreased glucocorticoid and testosterone production, associated with impaired testicular and adrenal cortical development (Neirijnck et al., 2018).

The main role of IGBFPs is to modulate IGF actions (Rajaram et al., 1997). IGFBP expression is widespread and it has been suggested that they might play a tissue-specific role. The liver is the main site of production of most IGFBPs, but proteins have been found in a number of organs, including uteri, ovaries, smooth muscles and heart (Jones and Clemmons, 1995). Furthermore, in some circumstances, IGFBPs potentiate IGF action and also have IGF-independent actions (Bach, 2018b). IGFBP-1 is the most abundant IGFBP in fetal tissues (Pannier et al., 1994) and is the major regulator of IGF actions during pregnancy (Murphy et al., 2006). Over-expression of IGFBP1, in transgenic mice results in a transient decrease in mid-gestation fetal growth (Crossey et al., 2002). Elevated circulating IGFBP-1 levels have been linked with low birthweight, possibly by reducing IGF bioavailability (Tisi et al., 2005; Vatten et al., 2002; Wang et al., 1991). The main interest in IGFBP-1 is that its production is inversely regulated by insulin (Brismar et al., 1994). On the other hand, IGFBP-3 is the main serum carrier of IGF-1 (Jones and Clemmons, 1995). Although other IGFBPs have been less extensively investigated, a large body of evidence, recently reviewed in (Bach, 2018a; Clemmons, 2018), supports their role in several disease processes, particularly metabolic-related diseases and cancer progression.

1.2. Endocrine disruptors impact on growth and metabolism

Endocrine disruptors (EDs) include a wide variety of compounds able to interfere with hormone action and to negatively impact human and animal health (Gore et al., 2015). For instance, exposure to EDs has been associated with reproductive disorders, cognitive deficits, and various cancers (Gore et al., 2015; Heindel et al., 2015; La Merrill et al., 2020). Furthermore, many of these environmental contaminants can directly impact metabolic organs/tissues, such as the liver, pancreas and adipose tissue and are thus defined metabolism-disrupting chemicals or obesogens (Heindel et al., 2017). Exposure to these EDs has been linked to development of obesity, metabolic syndrome, type-2 diabetes and fatty liver disease (Heindel et al., 2015).

It has been suggested that EDs can also affect growth, therefore many researchers have investigated the relationship between ED exposure and birth weight (Street and Bernasconi, 2020). Exposure to many EDs has been associated with low birthweight, altered anthropometric measures and rapid catch-up growth during childhood (Buck Louis et al., 2018; Fei et al., 2007; Kishi et al., 2017; Zheng et al., 2016). In a large meta-analysis, maternal occupational exposure to at least one ED group (such as polycyclic aromatic hydrocarbons, polychlorinated organic compounds, phthalates and bisphenol A among the others) was linked to an increased risk of having a low-birth weight newborn (Birks et al., 2016). In another study based on 7 different European cohorts, prenatal exposure to polychlorinated biphenyl 153 (PCB-153) and perfluorinated compounds (PFAS) was associated with increased risk of having small for gestational age newborns (Govarts et al., 2018).

The IGF system plays a critical role in ensuring appropriate growth and in regulating metabolic homeostasis. We have, therefore, hypothesised that impact of exposure to EDs on the IGF system might represent a potential mechanism behind well-described adverse outcomes of ED exposure such as growth restriction and metabolic syndrome.

In the present review, we summarize current evidence of the impact of several classes of EDs on the IGF system. We focused on major classes of EDs including dioxins and dioxin-like compounds, polycyclic aromatic hydrocarbons (PAHs), polybrominated biphenyls ethers (PBDEs), phthalates, perfluoroalkyl substances (PFAS) and bisphenol A (BPA) (Fig. 2). In vitro and in vivo studies performed on mammals are presented. Studies performed in fish models are summarised in Supplementary Table 1 but are not included in the body of the review. Epidemiological studies are also reported, and current knowledge gaps discussed.

2. Effects of EDs on the IGF system

2.1. Dioxins and dioxin-like compounds

Dioxins and dioxin-like compounds are highly persistent organic pollutants. They include dioxins, polychlorinated dibenzo-p-dioxins (PCDDs); furans, polychlorinated dibenzofurans (PCDFs); and polychlorinated/polybrominated biphenyls (PCBs/PBBs). PCDDs and PCDFs are by-products of incineration and organic synthesis procedures, whereas PCBs are mostly man-made compounds with many industrial and commercial applications (Giesy and Kannan, 1998; Gore et al., 2015; White and Birnbaum, 2009). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a polychlorinated dibenzo-p-dioxin and is the most potent compound of this class of chemicals. Effects of exposure to TCDD on the IGF pathway have been widely investigated in several cell lines (mainly human breast cancer and hepatocarcinoma lines) and animal models (Tables 1 and 2). In contrast, evidence for other compounds of the group is limited to a few animal studies (Table 3).

In the human breast cancer cell lines, MCF-7 and T47-D, TCDD inhibited IGF-1 and IGF-2 mediated cell proliferation (Liu et al., 1992; Salisbury et al., 2013). TCDD exposure did not change IGF-1R transcript levels, but resulted in a decreased number of IGF-1 induced binding sites in IGF-1R (Liu et al., 1992). The findings were not confirmed in other studies, although similar TCDD dose levels were employed (Tanaka et al., 2007; Tannheimer et al., 1998). In MCF-7 cells, IGF-1R up-regulation following TCDD treatment was reported only in microarray experiments but not confirmed by real-time PCR (Tanaka et al., 2007). In other studies TCDD treatment of MCF-7 cells induced IGFBP-3 and decreased IGFBP-5 expression (Tanaka et al., 2007; Widerak et al., 2006). On the other hand, in an alternative mammary epithelial cell line (MCF-10A), TCDD induced cell proliferation and activated IGF-1 pathways, mimicking signalling through the IGF-1R, but only if cells were cultured under insulin-deficient conditions (Tannheimer et al., 1998). Such differences in cell line and culturing conditions (lack of insulin, which is known to interact with IGF pathway) might explain some of the differences in results reported in these studies.

Given that the liver is one of the main organs of the IGF system, it is not surprising that hepatic in vitro models have been widely used to investigate TCDD effects. Several studies found a positive association between TCDD exposure and IGFBP-1 levels in the human hepatocarcinoma cell line HepG2, at both the transcript and protein level (Adachi et al., 2004; Marchand, 2004; Murray and Perdew, 2007). In this cell line, IGFBP-1 was among the top up-regulated genes following TCDD treatment (Adachi et al., 2004) and regulation of IGFBP-1

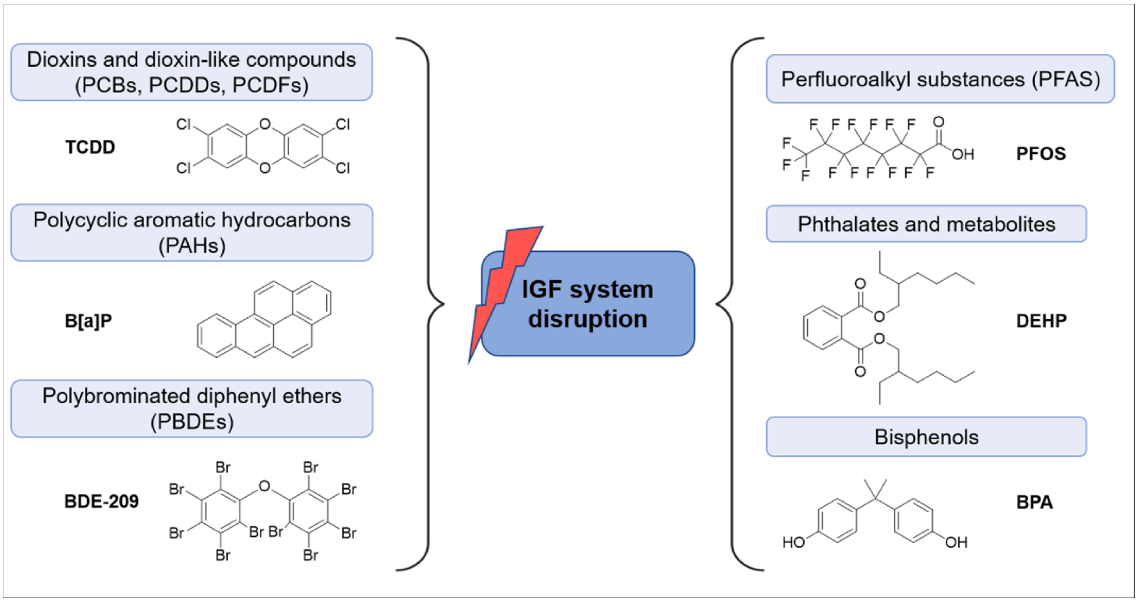

Fig. 2. Schematic representation of chemical classes (and a representative molecule) of endocrine disrupting chemicals impacting IGF system.

transcription by TCDD was dose-responsive (Murray and Perdew, 2007). TCDD-mediated induction of IGFBP-1 was also confirmed in cultured human hepatocytes (Marchand, 2004). Except for IGFBP-1, other elements of the system have been less extensively investigated and are not clearly affected by TCDD. TCDD did not affect IGF-1, IGF-2, IGF-1R, IGFBP-2 and IGFBP-4 expression in human cultured hepatocytes (Marchand, 2004). In another rat hepatoma cell line (5L), TCDD treatment induced IGFBP-4 (IGFBP-1 to IGFBP-7), but the authors argue this is an artefact of the cell line generation process (Brandner et al., 2013). These are amongst the few in vitro studies which evaluated multiple elements of the IGF system. On the other hand, IGF-2 induction by TCDD was reported in the rat hepatoma cell line BRL-3A (Wang et al., 2011), which might indicate differential responses depending on the specific cell line.

Detrimental effects associated with TCDD exposure during development have been investigated in several studies. Most of the studies have focused on the effects on IGF-2/IGF-2R, considering its critical role during the prenatal period. Overall, a negative association between prenatal TCDD exposure and IGF-2 has been found in several organs (Ding et al., 2018; Ma et al., 2015; Wu et al., 2004; Zhang et al., 2019b), although one study reported opposite effects (Wang et al., 2011). In mice prenatally exposed to TCDD during the preimplantation stage only, a trend for a decrease in IGF-2 mRNA was found following whole-body analysis of embryos (Wu et al., 2004). In a transgenerational study, both F1 male mice prenatally exposed to a single dose of TCDD (10 μg/kg body weight) on gestational day 15 (GD15) (direct prenatal TCDD exposure) and F3 male descendants (ancestral exposure) showed decreased placental IGF-2 (Ding et al., 2018). Similarly, prenatal exposure to TCDD from GD8 to GD14 (0.5 μg/kg body weight/day) decreased intra-ovarian transcript levels of IGF-2 in adult female rats (Zhang et al., 2019b). Prenatal exposure to TCDD (0.8 μg/kg body weight/day, GD8-GD14) also decreased IGF-2 expression at both transcript and protein levels in the adult livers of both F1 rats prenatally exposed to TCDD and theirs F3 descendants (Ma et al., 2015). This is in contrast with a previous study (single TCDD exposure on GD10 at 10 μg/kg body weight) in which increased IGF-2 in the fetal liver was found instead (although no changes reported in other organs such as kidney and skeleton) (Wang et al., 2011). The different dose levels and dose timings, as well as differences in life stages when the IGF system was analysed will all contribute to the differences observed, although most reported decreased IGF system expression in some organs following TCDD exposure. The effects of in utero exposure to TCDD on IGF-2R was investigated only in male offspring. TCDD exposure increases IGF-2R transcript levels in sperm, whereas a decreased mRNA was reported in the liver and in the skeletal muscle (Somm et al., 2013). Female pups exposed to TCDD prenatally and during lactation, exhibited a decreased IGF-1 transcript level in the liver (Chaffin et al., 1996). Moreover, an upregulation of IGFBP-1 mRNA has been reported in the kidney of mouse pups exposed to TCDD during lactation (Yoshioka et al., 2014). Prenatal exposure to TCDD up-regulated IGFBP-6 in fetal rat calvaria (Guo et al., 2007), whereas IGFBP-5 was significantly upregulated in fetal brain, but downregulated in fetal liver and in calvaria of female pups (Tanaka et al., 2007).

A few studies evaluated effects of TCDD administered to adult animals. In adult rats exposed to TCDD, both chronically or with a single large dose level, circulating IGF-1 levels significantly decreased (Croutch et al., 2005; Lindén et al., 2014). Moreover, TCDD treatment induced hepatic mRNA expression of IGFBP-1 (Minami et al., 2008). TCDD treatment in mice induced IGFBP-6 in the thymus and bone marrow, at both the transcriptional and protein level, with the finding confirmed in vitro using a thymoma cell line (EL-4) (Park et al., 2001; Park et al., 2003). TCDD is the most widely investigated chemical in terms of interaction with the IGF system. Overall, in cell models, the evidence strongly supports the TCDD effect of inducing IGFBP-1 up-regulation, which is of clear relevance as this protein is produced primarily by hepatocytes in both rodents and humans (Jones and Clemmons, 1995). Moreover, low levels of IGF-1 and IGF-2 have been reported in several organs in animal studies following TCDD exposure, mainly during the prenatal period.

The effects associated with administration of a range of PCBs have been evaluated in a few in vivo studies. Rats prenatally exposed to PCB-126 exhibited reduced circulating levels of both IGF-1 and IGF-2 (Ahmed et al., 2018). PCB-95 administered to early-weaned male rats decreased IGF-1 serum concentration (Ahmed, 2013) and PCB-126 lowered IGF-1 levels in adult rats (Ronis et al., 2020). PCB-126 and PCB-153 increased intestinal IGFBP-3 protein levels in a dose-response manner in a rat model of chronic exposure (Lee et al., 2000). These studies largely support the negative impact of these chemicals on IGF signalling, as shown by studies in which TCDD was administered.

Several epidemiological studies have investigated the association between dioxin-like compounds and IGF-1 and IGFBP-3. The direction of effects varied across studies (Table 3). A cohort of mother-children pairs

Table 1
Summary of ED effects on the IGF axis in vitro.

Chemical	IGF axis	Effect	Cell line	Dose (concentration)	References
TCDD	**IGF-1**	=	Human hepatocarcinona (HepG2) and cultured human hepatocytes	25 nM	(Marchand, 2004)
	IGF-2	↓	Breast cancer (MCF-7)	10 nM	(Salisbury et al., 2013)
		↑	Rat hepatoma (BRL-3A)	10 nM	(Wang et al., 2011)
		=	Human hepatocarcinona (HepG2) and cultured human hepatocytes	25 nM	(Marchand, 2004)
	IGF-1R	↓	Breast cancer (MCF-7)	0.01–10 nM	(Liu et al., 1992)
		↑	Mammary epithelium (MCF-10A)	30 nM	(Tannheimer et al., 1998)
			Breast cancer (MCF-7)	0.1–10 nM	(Tanaka et al., 2007)
		=	Human hepatocarcinona (HepG2) and cultured human hepatocytes	25 nM	(Marchand, 2004)
	IGFBP-1	↑	Human hepatocarcinoma (HepG2)	10 nM 25 nM 0.1–100 nM	(Adachi et al., 2004;Marchand, 2004;Murray and Perdew, 2007)
	IGFBP-2	=	Human hepatocarcinona (HepG2) and cultured human hepatocytes	25 nM	(Marchand, 2004)
	IGFBP-3	↑	Breast cancer (MCF-7)	5 nM	(Widerak et al., 2006)
	IGFBP-4	↑	Rat hepatoma (5L) (possible genetic alteration of cell line)	0.001–1 nM	(Brandner et al., 2013)
		=	Human hepatocarcinona (HepG2) and cultured human hepatocytes	25 nM	(Marchand, 2004)
	IGFBP-5	↓	Breast cancer (MCF-7) and human endometrial carcinoma (RL95-2)	0.1–10 nM	(Tanaka et al., 2007)
	IGFBP-6	↑	Murine thymoma (EL-6)	10 nM	(Park et al., 2001)
B [a] P	**IGF-1**	↓	Human placenta trophoblast (HTR-8)	1–5 μM	(Fadiel et al., 2013)
	IGF1-R	↓	Vascular smooth muscle cell	10 μM	(Karyala et al., 2004)
			Mouse metanephric culture	3 μM	(Nanez et al., 2011)
		↑	Mammary epithelium (MCF-10A)	0.03–3 μM	(Tannheimer et al., 1998)
	IGFBP-7	↓	Vascular smooth muscle cell	10 μM	(Karyala et al., 2004)
PFOS	**IGFBP-1**	↓	Human decidual stromal cells	0.0001–1 μM	(Yang et al., 2016)
BPA	**IGF-1**	↓	hESC-derived embryonic bodies	1 μM	(B. Huang et al., 2017)
			Human ovarian granulosa-like tumor	40–100 μM	(Kwintkiewicz et al., 2010)
		↑	Human uterine leiomyoma	1–20 μM	(Shen et al., 2014)
	IGF-1R	↑	Human ovarian adenocarcinoma (BG-1)	10 μM 10 μM	(Hwang et al., 2013;Kang et al., 2013)
	IGFBP-1	↑↓	Human endometrial stromal cells	5–100 μM 0.1 nM-10 μM 1 pM – 1 μM 10 pM- 10 μM	(Aghajanova and Giudice, 2011;Forte et al., 2016;Mannelli et al., 2015;Xiong et al., 2020)
	IGFBP-4	↑	Ovarian adenocarcinoma	10 μM	(Hwang et al., 2011)

was recruited and followed up to assess the impact of prenatal exposure to dioxins and PCBs on growth and thyroid function in children (Su et al., 2015, 2010; Wang et al., 2005). Pregnant women were recruited and 17 polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/PCDFs) and 12 dioxin-like PCB congeners (PCBs) were measured in their placentas. IGF-1 and IGFBP-3 levels were assessed in blood of their children at birth (n = 118) (Wang et al., 2005), at 2 (n = 70) and 5 years of age (n = 41) (Su et al., 2010) and at 8 years (n = 56) (Su et al., 2015). Children were classified into "high" and "low" exposure groups depending on the PCDD/PCDFs + PCBs levels found in placentas. IGFBP-3 was significantly higher in female newborns with high exposure levels compared with females of the low exposure group (Wang et al., 2005). Furthermore, IGF-1 and IGFBP-3 levels positively associated with placental weight and birth weight. On the other hand, IGFBP-3 was significantly lower in 8-year old girls prenatally exposed to high levels of PCBs (Su et al., 2015). In the high exposure group, 5-year old children, IGF-1 levels were higher compared to the low-exposed group, with a more pronounced effect in males (Su et al., 2010). In this cohort, exposure to PCDD/PCDFs and PCBs was associated with adverse effects on anthropometric parameters (birth length, height and weight) and thyroid hormones. These studies are of considerable interest since children with reported prenatal exposure were followed up at different time points. However, the participant numbers are rather small (<100 individuals), with effects reported only at a specific age, which is likely to contribute to inconsistencies in reported outcomes. Results from Su and colleagues (Su et al., 2010) were partially confirmed in another longitudinal cohort study, in which exposure to dioxin-like compounds (PCBs and PCDD/Fs, measured in the breast milk of 418 women), was associated with increased IGF-1 levels in the blood of infants aged 3 months, along with accelerated height and weight gain (Wohlfahrt-Veje et al., 2014). On the other hand, in a cohort of 456 adults, total circulating dioxin-like PCBs (DL-PCBs), PCB-156 and PCB-167 negatively associated with plasma IGF-1 (Luzardo et al., 2012). However, in this study only DL-PCBs were considered, whereas the previous studies investigated a more complex mixture, including PCDD/Fs. Effects of complex chemical mixtures should be taken into account since they are likely to complicate comparison of findings.

Overall, results of these studies suggest that exposure to dioxins and dioxin-like compounds is associated to increased IGF-1 in children and decreased IGF-1 in adults. It is possible that dysregulation of the IGF system may occur in different ways depending on timing of exposure (prenatal/children vs. adult). As evidence is still limited, these associations need to be confirmed by new studies, in order to clarify the effects of age, sex and chemical mixture evaluated.

Table 2
Summary of ED effects on the IGF axis in vivo.

Chemical	IGF	Effect	Tissue	Exposure (model)	Dose (concentration)	References
TCDD	**IGF-1**	↓	Liver	Prenatal and lactational (rat, female)	1 μg/kg bw (GD15)	(Chaffin et al., 1996)
			Circulating	Adult (rat)	0.0125–3.2 μg/kg bw /day + maintenance (2–128 days) 100 μg/kg	(Croutch et al., 2005;Lindén et al., 2014)
	IGF-2	↓	Liver (F1 and F3)	Prenatal, transgenerational (rat, only males)	0.2/0.8 μg/kg bw/day (GD 8–14)	(Ma et al., 2015)
			Placenta (F1 and F3)	Prenatal, transgenerational (mice, only males)	10 μg/kg bw (GD15)	(Ding et al., 2018)
			Ovary	Prenatal (rat, only female)	0.1/0.5 μg/kg bw/day (GD 8–14)	(Zhang et al., 2019b)
			Total embryo	Prenatal (mouse)	10 nM (blastocyst culture medium)	(Wu et al., 2004)
		↑	Liver	Prenatal (rat)	10 μg/kg bw (GD10)	(Wang et al., 2011)
		=	Kidney, skeleton, skeletal muscle	Prenatal (rat)	10 μg/kg bw (GD10)	(Wang et al., 2011)
	IGF-2R	↓	Muscle, liver	Prenatal (mice, males)	0.002/0.01 μg/kg bw /day (GD9-19)	(Somm et al., 2013)
		↑	Sperm	Prenatal (mice, males)	0.002/0.01 μg/kg bw /day (GD9-19)	(Somm et al., 2013)
	IGFBP-1	↑	Liver	Adult (mice)	40 μg/kg bw (4 days)	(Minami et al., 2008)
			Kidney	Lactational (mice)	20 μg/kg bw (PND1)	(Yoshioka et al., 2014)
	IGFBP-5	↓	Liver, calvaria (female)	Prenatal (mouse)	5 μg/kg bw (GD12)	(Tanaka et al., 2007)
		↑	Brain	Prenatal (mouse)	5 μg/kg bw (GD12)	(Tanaka et al., 2007)
	IGFBP-6	↑	Calvaria	Prenatal (rat)	5/10/15 μg/kg bw (GD10)	(Guo et al., 2007)
			Thymus, bone marrow	Adult (mice)	30 μg/kg bw (3 days)	(Park et al., 2001)
PCBs	**IGF-1**	↓	Circulating	Early-weaned (rat), Prenatal (rat), Adult (rat)	PCB-95: 32 mg/kg bw (PND15-16) PCB-126: 20/40 μg/kg bw (GD1-20) PCB-126: 1.6 mg/kg bw	(Ahmed, 2013;Ahmed et al., 2018; Ronis et al., 2020)
	IGF-2	↓	Circulating	Prenatal (rat)	PCB-126: 20/40 μg/kg bw (GD1-20)	(Ahmed et al., 2018)
	IGFBP-3	↑	Duodenum	Adult (rat)	PCB-126: 0.1–1 μg/kg bw (13 weeks)	(Lee et al., 2000)
B [a] P	**IGFBP-6**	↑	Liver	Adult (mice)	100 mg/kg bw	(Bartosiewicz et al., 2001)
		=	Kidney	Adult (mice)	100 mg/kg bw	(Bartosiewicz et al., 2001)
PBDE	**IGF-1**	↑	Circulating (only males)	Perinatal (rat)	BDE-47:2/200 μg/kg bw (GD15-PND20 every 5 days)	(Suvorov et al., 2009)
			Uterus	Prenatal (rat)	PBDE-99: 1/10 mg/kg bw /day (GD10-18)	(Ceccatelli et al., 2006)
Phthalates	**IGF-1**	↑	Testes	Prenatal (rat)	DEHP: 10/100/750 mg/kg bw /day (GD2-20)	(Lin et al., 2008)
			Wolffian duct	Prenatal (rat)	DBP: 500 mg/kg bw /day (GD12-21)	(Bowman et al., 2005)
			Circulating	Prepubertal (rat)	DEHP: 0.2/1/5 mg/kg bw /day (4 weeks)	(Shao et al., 2019)
			Hypothalamus	Prepubertal (rat)	DEHP: 0.2/1/5 mg/kg bw /day (4 weeks)	(Shao et al., 2019)
		↑↓	Hypothalamus (depending on dose)	Prepubertal (rat)	DEHP: 250/500/1000 mg/kg bw /day (4 weeks)	(Liu et al., 2018)
	IGF-2	↑	Wolffian duct	Prenatal (rat)	DBP: 500 mg/kg bw /day (GD12-21)	(Bowman et al., 2005)
	IGF-1R	↑	Wolffian duct	Prenatal (rat)	DBP: 500 mg/kg bw /day (GD12-21)	(Bowman et al., 2005)
			Hypothalamus	Prepubertal (rat)	DEHP: 0.2/1/5 mg/kg bw /day (4 weeks)	(Shao et al., 2019)
		=	Testes	Prenatal (rat)	DEHP: 10/100/750 mg/kg bw /day (GD2-20)	(Lin et al., 2008)
	IGFBP-1	↑	Liver	Adult (mice)	DEHP: 1100 mg/kg bw	(Bartosiewicz et al., 2001)
		=	Kidney	Adult (mice)	DEHP: 1100 mg/kg bw	(Bartosiewicz et al., 2001)
	IGFBP-5	↑	Wolffian duct	Prenatal (rat)	DBP: 500 mg/kg bw /day (GD12-21)	(Bowman et al., 2005)
PFOS	**IGF-1**	↓	Liver, Testes	Adult (mouse)	PFOS: 1/5/10 mg/kg bw /day (21 days)	(Wan et al., 2011)
	IGF-1R	↓	Testes	Adult (mouse)	PFOS: 1/5/10 mg/kg bw /day (21 days)	(Wan et al., 2011)
BPA	**IGF-1**	↓	Uterus	Perinatal (rat, female)	0.5/50 μg/kg bw /day (GD9-PND21)	(Vigezzi et al., 2015)
		↑	Placentome (trend)	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)
			Circulating	Pubertal (rat)	3 mg/kg bw /day (5 weeks)	(Herath et al., 2004)
			Liver	Neonatal (rat, female)	6.25/62.5 mg/kg bw /day (PND1-10)	(Ramirez et al., 2012)
			Mammary gland	Adult (mouse)	0.5/500 μg/kg bw /day (PND56-112)	(Jenkins et al., 2011)
		=	Circulating	Neonatal (rat, female)	6.25/62.5 mg/kg bw /day (PND1-10)	(Ramirez et al., 2012)
			Ovaries	Adult (rat, female)	Diet supplemented 0.1/1%	(Toda et al., 2002)
		↑	Placentome (trend)	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)
		=	Ovaries	Adult (rat, female)	Diet supplemented 0.1/1%	(Toda et al., 2002)
	IGF-1R	↓	Placentome	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)
			Uterus	Perinatal (rat, female)	0.5/50 μg/kg bw /day (GD9-PND21)	(Vigezzi et al., 2015)
		↑	Mammary gland	Adult (mouse)	0.5/500 μg/kg bw /day (PND56-112)	(Jenkins et al., 2011)
		=	Ovaries	Adult (rat, female)	Diet supplemented 0.1/1%	(Toda et al., 2002)
	IGF-2R	↑	Placentome	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)
	IGFBP-1	↑	Placentome	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)

(*continued on next page*)

Table 2 (*continued*)

Chemical	IGF	Effect	Tissue	Exposure (model)	Dose (concentration)	References
	IGFBP-2	↑	Placentome	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)
	IGFBP-3	↑	Placentome	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)
	IGFBP-4	↑	Placentome	Gestational (sheep)	500 μg/kg bw /day (GD30-90)	(Song et al., 2020)

Bw: body weight

2.2. Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants with known carcinogenic, teratogenic and endocrine disrupting action (Boström et al., 2002; Idowu et al., 2019). They are persistent and highly lipophilic, therefore can easily accumulate in living organisms. PAHs are released as a result of incomplete combustion of organic matter, for example in industrial emissions and tobacco smoke. PAHs are known ligands of the aryl hydrocarbon receptor (AhR) and benzo[a]pyrene (B[a]P) is normally used as the reference compound in toxicological studies. Evidence linking PAH treatment/exposure to changes in the IGF system is summarised in Table 1 and 2.

The interaction between B[a]P and the IGF pathway was first evaluated in a human mammary epithelial cell line. It was found that, under insulin-deficient conditions, B[a]P activated the IGF-1 pathway, mimicking signalling through IGF-1R (Tannheimer et al., 1998). In these experiments, the absence of insulin might have played a significant role and, therefore, the results should be interpreted with caution. Subsequent studies supported a negative effect of B[a]P on IGF signalling. For example, in vascular smooth muscle cells, B[a]P treatment decreased IGF-1R and IGFBP-7 (Karyala et al., 2004). IGF-1R was also found to be decreased upon B[a]P in a mouse metanephric culture (Nanez et al., 2011). In a human placental trophoblast cell line, B[a]P significantly reduced IGF-1 expression in a dose-dependent manner (Fadiel et al., 2013). Furthermore, as B[a]P treatment caused mutations in IGF-1, the authors hypothesised that the predicted altered structure would decrease affinity of the protein for the receptor (Fadiel et al., 2013). These findings are of particular interest since IGF-1 is known to be involved in placenta growth and function (Forbes and Westwood, 2008).

Unfortunately, only one relevant study has been reported in animals. Using DNA microarray, it was reported that mice exposed to B[a]P had an increased level of IGFBP-6 in the liver, whereas no change was reported in the kidney (Bartosiewicz et al., 2001). The principal function of IGFBP-6 is inhibiting IGF-2 actions, but also IGF-independent actions have been described (Bach, 2015). Overall, these studies would indicate that B[a]P exposure negatively impacts the IGF system, however evidence is still limited. In particular, new studies are required to confirm the implications of the dysregulation of the IGF system in the placenta.

The association between PAHs exposure and the IGF system has been investigated in a couple of epidemiological studies (Table 3). In a cohort of pregnant women/newborn pairs living near an electronic waste site in China, 16 PAHs were measured in cord blood and IGF-1 and IGFBP-3 transcript quantified in placental tissue. Exposure to PAHs was associated with increased birthweight. A positive correlation of total 5-ring (Σ5-ring) PAHs with IGF-1 placental mRNA expression was found. On the other hand, total PAHs (Σ_{16}PAHs) and total 4-ring (Σ4-ring) PAHs correlated with IGFBP-3 expression in the placenta (Xu et al., 2013). This is in contrast to results by Fadiel et al., who reported that B[a]P treatment reduced IGF-1 expression in a trophoblast cell line (Fadiel et al., 2013). However, given that the placenta is a very dynamic organ, differences exist between human placental trophoblast cells (HTR-8, which are immortalised human first trimester extravillous trophoblast cells), and placental tissue collected at term. Another element to be considered is the effect of the complex mixture of PAHs, which is likely to have different actions than from B[a]P exposure only. In a recent study on 238 children, a negative association was reported between exposure to atmospheric $PM_{2.5}$-bound PAHs and IGF-1 plasma levels and child height (Zeng et al., 2020). Methodological differences, such as measurement of PAH levels in cord blood compared to the environment (atmospheric PAHs), or IGF-1 measured in the placenta compared with plasma, make findings from these two epidemiological studies difficult to compare.

Taken together, the lack of animal models and the limited evidence provided by in vitro and epidemiological studies, definitive conclusions about the impact of PAHs on the IGF system are not possible.

2.3. Polybrominated diphenyl ethers (PBDEs)

Polybrominated diphenyl ethers (PBDEs) are organobromine compounds widely used as flame retardants with known adverse health effects (Linares et al., 2015).

Effects of exposure to these compounds have been evaluated in only a couple of animal studies (Table 2). In a rat model of perinatal exposure to BDE-47, male pups exhibited increased circulating IGF-1 levels after birth, whereas no effects were reported in females (Suvorov et al., 2009). Also, increased IGF-1 transcript was found in the uteri of rats prenatally exposed to PBDE-99 (Ceccatelli et al., 2006).

In three epidemiological studies, the association between PBDE levels and IGF-1 and IGFBP-3 has been investigated in different cohorts and matrices (Shy et al., 2012; Xu et al., 2014, 2013).

In the first study, 14 PBDEs were measured in breast milk from 149 women and IGF-1 analysed in cord blood of their newborns. Total PBDEs (Σ_{14} PBDEs) did not correlate with IGF-1 and thyroid hormones cord blood levels. However, BDE-196 was positively associated with IGF-1, whereas BDE-85 showed a negative association (Shy et al., 2012). In the other two studies, only 8 PBDE congeners were evaluated (which did not include BDE-196 and BDE-85) (Xu et al., 2014, 2013). In children, circulating IGFBP-3 was positively associated with plasma levels of BDE-209 and negatively associated with BDE-47, but no significant associations were found with IGF-1. Total PBDEs were also negatively associated with free triiodothyronine (Xu et al., 2014). The third study reported that cord blood levels of BDE-154 and BDE-209 positively correlated with placental IGF-1 expression, while total PBDEs were associated with significantly higher placental IGFBP-3 transcript (Xu et al., 2013). These associations were more pronounced in females compared to males, but, surprisingly, PBDE exposure was not associated with changes in birthweight. The high variability of these studies makes the findings difficult to interpret. For example, BDE-209 was positively associated with IGFBP-3 in children (Xu et al., 2014), but not in newborns (Shy et al., 2012) or the placenta (Xu et al., 2013). On the other hand the positive association of BDE-209 with IGF-1 has been found only in the placenta (Xu et al., 2013). Reasons for discrepancies may arise because of different matrices used for the PBDE determination (breast milk vs. blood) and IGF measurements (blood vs. placenta). It is difficult to interpret the positive or negative associations with IGF elements depending on the specific PBDE evaluated, especially because evidence from animal studies is limited and no in vitro investigations have been reported.

Table 3
Summary of epidemiological evidence linking ED exposures to IGF expression levels and methylation.

Chemical class	Cohort	Chemicals	Tissue	IGFs and IGFBPs	Findings	Study
Dioxins and dioxin-like	N = 118 Pregnant women and newborns	17 PCDD/PCDFs, 12 PCBs	Placenta	IGF-1, IGFBP-3 (cord blood)	↑ IGFBP-3 in highly exposed group No effects on IGF-1	(Wang et al., 2005)
	N = 92 Pregnant women and children (2–5 years old)	17 PCDD/PCDFs, 12 PCBs	Placenta	IGF-1, IGFBP-3	↑ IGF-1 in highly exposed group	(Su et al., 2010)
	N = 56 Pregnant women and children (8 years old)	17 PCDD/PCDFs, 12 PCBs	Placenta	IGF-1, IGFBP-3	↓ IGFBP-3 in highly exposed group PCBs	(Su et al., 2015)
	N = 418 Women and children	17 PCDD/PCDFs, 18 PCBs	Breast milk	IGF-1	↑ IGF-1	(Wohlfahrt-Veje et al., 2014)
	N = 465 Adults	12 dioxin-like PCBs	Blood	IGF-1	↓ IGF-1	(Luzardo et al., 2012)
	N = 169 Pregnant women and newborns	58 NDL-PCBs	Blood	IGF-2 methylation (cord blood)	No association	(Kobayashi et al., 2017b)
	N = 116 Pregnant women	32 PCBs	Placenta	IGF-2 methylation (placenta)	No association	(Kappil et al., 2016)
	N = 188 (Case-control, prenatal exposure during war)	TCDD (historical information)	–	IGF-2 methylation (blood)	No association	(Giuliani et al., 2018)
PAHs	N = 154 Newborns	16 PAHs	Cord blood	IGF-1, IGFBP-3 (placenta)	↑ IGF-1 with Σ5-ring PAHs ↑ IGFBP-3 with Σ_{16}PAHs and Σ4-ring PAHs	(Xu et al., 2013)
	N = 238 Children	$PM_{2.5}$-bound PAHs	Blood	IGF-1, IGFBP-3	↓ IGF-1	(Zeng et al., 2020)
	N = 400 Women	Not directly measured but PAHs exposure assumed	Blood	IGF-1, IGFBP-1	↑ IGF-1 and IGFBP-1 in group living in ex-war area and with petrochemical industries	(Tekle et al., 2010)
Phthalates	N = 845 Children (4–9 years)	12 Phthalate metabolites	Urine	IGF-1, IGFBP-3	↓ IGF-1 with ΣDEHP metabolites and MCiOP ↓ IGFBP-3 with ΣDEHP	(Boas et al., 2010)
	N = 216 Children (5–7 years)	8 Phthalate metabolites	Urine	IGF-1, IGFBP-3	↓IGF-1 with MMP and MBP ↓ IGFBP-3 with MMP and MEP	(Wu et al., 2017)
	N = 219 Pregnant women and children (8–14 years)	9 Phthalate metabolites	Maternal and children urine	IGF-1	↑ IGF-1 and maternal ΣDEHP (pubertal girls) ↓ IGF-1 and DBP, MBzP, and MCPP in boys ↑ IGF-1 and ΣDEHP in girls	(Watkins et al., 2016)
	N = 79 < 18 years N = 279 Adults	11 phthalates metabolites	Urine	IGF-1	↓ IGF-1 and ΣDEHP in young ↑IGF-1 and MEHP in adults	(H. Huang et al., 2017)
	N = 88 Children	3 phthalates metabolites (estimated daily DEHP intake)	Urine	IGF-1, IGFBP-3	↓ IGF-1 with estimated levels of daily DEHP intake No effect on IGFBP-3	(Tsai et al., 2016)
	N = 166 Children	9 phthalates metabolites	Urine	IGF-1, IGFBP-3	↓ IGF-1 with MEP ↓ IGFBP-3 with MEP and MMP	(Huang et al., 2020)
	N = 220 Pregnant women	5 phthalates metabolites	Urine	IGF-2 methylation (placenta, maternal side)	↓ IGF-2 methylation with MEHHP, MEOHP and ΣDEHP	(Zhao et al., 2016)
	N = 196 Pregnant women	11 phthalates metabolites	Urine	IGF-2 methylation (placenta)	↓ IGF-2 methylation with MEP, MEOHP, ΣDEHP, Σphthalate, MEHP (females), MEOHP (females), MECCP (female)	(LaRocca et al., 2014)
	N = 109 Pregnant Women	9 phthalates metabolites	Urine	IGF-2 methylation (cord blood)	↓ IGF-2 methylation with MCPP, ΣDEHP, MEP (females)	(Montrose et al., 2018)
PFAS	N = 2292 Children (6–9 years)	PFOA, PFOS, PFNA, PFHxS	Blood	IGF-1	↓IGF-1 with PFOS and PFNA	(Lopez-Espinosa et al., 2016)
	N = 177 Pregnant women and newborns	PFOS, PFOA	Blood	IGF-2 methylation (cord blood)	↓ IGF2 with PFOA	(Kobayashi et al., 2017a)
PBDE	N = 149 Women	14 PBDEs	Breast milk	IGF-1 (cord blood)	↑IGF-1 with BDE-196 ↓IGF-1 with BDE-85	(Shy et al., 2012)
	N = 162 Children (4–6 years)	8 PBDEs	Blood	IGF-1, IGFBP-3	↑IGFBP-3 with BDE-209 ↓IGFBP-3 with BDE-47 No effects on IGF-1	(Xu et al., 2014)
	N = 154 Newborns	8 PBDEs	Cord blood	IGF-1, IGFBP-3 (placenta)	↑ IGF-1 with BDE-154, BDE-209 ↑ IGFBP-3 with total PBDEs	(Xu et al., 2013)
	N = 116 Pregnant women	10 PBDEs	Placenta	IGF-2 methylation (placenta)	No association	(Kappil et al., 2016)
BPA	N = 219 Pregnant women and children (8–14 years)	BPA	Maternal and children urine	IGF-1	No association	(Watkins et al., 2016)
	N = 56 Pregnant women	BPA	Urine	IGF-2 methylation (cord blood)	↓ IGF-2 methylation (females)	(Montrose et al., 2018)

Tissue refers to matrix used for chemical measurements. IGF-1 and IGFBPs were measured in blood unless stated otherwise.

2.4. Phthalates

Phthalates are widely used as liquid plasticisers, therefore can be found in many products, including plastics and cosmetics (Wang et al., 2019). Effects of exposure to these compounds have been evaluated in only a few animal studies (Table 2), which generally indicate an up-regulation of the IGF pathway. Impact of phthalate exposure on reproductive development and puberty has been the main focus, considering that phthalates have an adverse effect on reproductive development and the IGF pathway plays a role in reproductive physiology. Rats prenatally exposed to bis(2-ethylhexyl) phthalate (DEHP) had higher testicular IGF-1 transcript level, whereas no effects were found on IGF-1R expression (Lin et al., 2008). IGF-1, IGF-2, IGF-1R and IGFBP-5 were up-regulated in the Wolffian ducts of rat fetuses prenatally exposed to DBP (Bowman et al., 2005). Furthermore, DEHP exposure increased circulating levels of IGF-1 and up-regulated IGF-1 and IGF-1R in the hypothalamus of prepubertal females (Liu et al., 2018; Shao et al., 2019). The latter studies suggest that phthalate exposure might induce precocious puberty by affecting the hormone levels of GH and IGF-1 in the hypothalamus and serum. The sensitivity of adult animals exposed to DEHP has also been shown by the significant increase in IGFBP-1 in the liver but not in the kidney (Bartosiewicz et al., 2001).

Associations between phthalate levels and IGFs and related proteins have been investigated mostly in children and an inverse association between urinary phthalate metabolites and circulating levels of IGF-1 and IGFBP-3 consistently reported (Boas et al., 2010; H. Huang et al., 2017; Huang et al., 2020; Tsai et al., 2016; Watkins et al., 2016; Wu et al., 2017). In the largest study (845 children) 12 phthalate metabolites were measured and ΣDEHP (sum of all DEHP metabolites) and MCioP were negatively correlated with both IGF-1 and IGFBP-3 (Boas et al., 2010). Moreover, most phthalate metabolites were negatively associated with height, weight and serum levels of free and total triiodothyronine (Boas et al., 2010). In another study, monomethyl phthalate (MMP) and mono-n-butyl phthalate (MBP) were inversely associated with IGF-1, whereas MMP and monoethyl phthalate (MEP) were inversely associated with IGFBP-3 (Wu et al., 2017). The negative association between some phthalate metabolites (MEP and MMP) and IGF-1 and IGFBP-3 was also confirmed in a recent study (Huang et al., 2020). The finding of a negative association between the sum of urinary DEHP metabolites and IGF-1 has been recently confirmed in a cross-sectional study of 79 young individuals (<18 years of age) (H. Huang et al., 2017). Following the major scandal occurring in Taiwan involving the illegal use of phthalates as clouding agents in food products, urinary concentrations of DEHP metabolites were quantified in 88 children and daily DEHP intake calculated. Estimated levels of DEHP intake was found to be negatively associated with IGF-1, height and weight without effect on IGFBP-3 (Tsai et al., 2016). In some studies, sex-specific associations were found. For instance, in the only study evaluating the association between prenatal phthalate exposure and IGF-1 levels in children, a positive association between total maternal DEHP metabolites (measured in urine collected during the third trimester of pregnancy) and serum IGF-1 was found in pubertal girls only, although the size of this group was very small (n = 32) (Watkins et al., 2016). Similarly, in prepubertal girls of the same cohort, total DEHP metabolites measured in their urine were positively associated with IGF-1 (Watkins et al., 2016). Moreover, phthalate metabolites were associated with metabolic biomarkers (leptin, glucose, c-peptide) in patterns that varied by sex, pubertal status, and exposure timing. These findings demonstrate that these variables need to be considered in such studies. In another study, monocarboxyisooctyl phthalate (MCiOP) was negatively associated with IGF-1 in boys and IGFBP-3 in girls (Boas et al., 2010). Among pubertal boys, a negative association between IGF-1 and several phthalate metabolites, including DBP, MBzP, and MCPP was reported (Watkins et al., 2016). Overall, it must be emphasised that IGF-1 levels rise steeply at puberty and are thought to play a role in the timing of puberty onset (Cole et al., 2015; Kanbur et al., 2005), representing a possible explanation for different findings in studies involving peripubertal children. Indeed, in the only study with adults (n = 279), a positive association between IGF-1 and MEHP (H. Huang et al., 2017). We suggest puberty and/or age might contribute to difference in observed effects.

In most of these epidemiological studies, thyroid hormones were also evaluated and positive or negative associations were found depending on the individual phthalate metabolite (Boas et al., 2010; H. Huang et al., 2017; Huang et al., 2020; Wu et al., 2017).

2.5. Perfluoroalkyl substances (PFAS)

Perfluorinated alkylated substances (PFAS) are man-made chemicals with extensive use in industry, for example in fire foams, paints and detergents (Sunderland et al., 2019). The evidence linking PFAS and IGF is very limited (Table 1 and Table 2).

In human endometrial stromal cells, PFOS decreased IGFBP-1 transcript (Yang et al., 2016). PFOS exposure was associated with down-regulation of IGF-1 and IGF-1R transcript in mice testes, furthermore IGF-1 was decreased also in the liver (Wan et al., 2011). Association between IGFs and PFAS has been evaluated in only one epidemiological study. It was found that serum PFAS concentration (PFOS and PFNA) were associated with lower levels of IGF-1 and sex hormones in 2292 children of 6–9 years of age (Lopez-Espinosa et al., 2016). This is currently the largest epidemiological study evaluating the effects of exposure to EDs on the IGF system. Although limited, in vitro and in vivo investigations support the conclusion of a negative effect of PFAS on the IGF system, suggesting that confirmatory studies are needed to confirm the findings.

2.6. Bisphenol A

Bisphenol A (BPA) is a plastic monomer used in the production of polycarbonate plastics, epoxy resins and in consumer products. It is possibly one of the most investigated endocrine disruptors, although many findings are controversial (Vandenberg et al., 2007). BPA exposure reportedly affects several molecules of the IGF system in several cell models (Table 1). BPA decreased IGF-1 during human embryonic body differentiation (B. Huang et al., 2017). In human ovarian granulosa-like tumor cells, BPA reduced FSH-induced IGF-1 expression (Kwintkiewicz et al., 2010). On the other hand, BPA treatment of uterine leiomyoma cells led to an increased transcript expression and protein level of IGF-1 (Shen et al., 2014). Induction of IGF1-R was also demonstrated in human ovarian carcinoma cell lines (Hwang et al., 2013; Kang et al., 2013). BPA treatment significantly induced IGFBP-1 secretion in endometrial stromal cells (Aghajanova and Giudice, 2011), but the finding was not confirmed in subsequent studies (Forte et al., 2016; Mannelli et al., 2015; Xiong et al., 2020). In ovarian carcinoma cells, BPA was able to significantly up-regulate IGFBP-4 transcript (Hwang et al., 2011). In these cell-based studies a great range of BPA dose levels have been used (from 1 pM to 100 μM), which could explain the high variability in the results reported.

Dysregulation of IGF signalling upon BPA treatment has been demonstrated in several animal studies, particularly in prenatal exposure scenarios (Table 2). BPA exposure effects on developmental programming of the placenta has been investigated in a sheep model (Song et al., 2020). Placentomes were collected at 2 different time points, at gestational day 65 (GD65, early gestation) and at GD90 (mid gestation). IGF-2R, IGFBP-1, IGFBP-2, IGFBP-3 and IGFBP-4 transcripts were increased in the BPA-treated group, whereas IGF-1R was down-regulated. IGF-1 and IGF-2 levels tended to be up-regulated, without statistical significance. This represents one of the few studies in which a comprehensive characterisation of the IGF system was provided, although limited to one tissue.

Female rats exposed to BPA during the neonatal period, showed an increased IGF-1 in the liver, with levels approaching those reported in

males, indicating a masculinization of the system. However, levels of the circulating protein was not affected (Ramirez et al., 2012). But male pubertal rats exposed daily to BPA showed increased circulating levels of IGF-1 (Herath et al., 2004). Time of exposure (postnatal vs. pubertal) and treatment (62.5 mg/kg body weight for 10 days vs 3 mg/kg body weight for 5 weeks) might explain difference in the findings. Furthermore, induction of IGF-1 and increased phosphorylation of IGF-1R was reported in mammary glands of adult mice chronically exposed to BPA (Jenkins et al., 2011) and of rats exposed during the early postnatal period (Lamartiniere et al., 2011). On the other hand, female rats exposed to BPA during the prenatal period and lactation showed decreased uterine expression levels of IGF-1 and IGF-1R transcript (Vigezzi et al., 2015). In contrast, BPA exposure did not affect IGF-1, IGF-2 and IGF-1R expression in ovaries of adult mice (Toda et al., 2002).

The association between BPA and IGF-1 has been investigated in only one epidemiological study (Table 3). In a cohort of 250 children, exposure to BPA in utero was not associated with IGF-1 serum levels or other markers of metabolic homeostasis (Watkins et al., 2016).

3. Epigenetics and potential mechanisms

3.1. Methylation studies

It is important to emphasise that IGF-2 is a paternally-expressed imprinted gene and its expression is epigenetically controlled by several differentially methylated regions (DMRs) (Willison, 1991). The methylation pattern is established early in development and it plays a role in regulating fetal growth and development (St-Pierre et al., 2012). Altered IGF-2 methylation is implicated in human growth disorders, like the Silver-Russel syndrome (Binder et al., 2008). On the other hand, the gene encoding for IGF-2R is maternally expressed (Latham et al., 1994). Increasing evidence supports the role of epigenetic changes induced by EDs as one of the mechanisms responsible for long-lasting and transgenerational health effects (Alavian-Ghavanini and Rüegg, 2018). Thus, IGF-2 and IGF-2R represent two potential targets for epigenetic changes associated with EDs exposure. However, the findings related to this mechanism have been mixed.

In male mice exposed prenatally to TCDD, significant changes in the methylation patterns in two of the major control regions of IGF-2 were reported in DNA from liver tissue, with internal control region (ICR) being hypermethylated whereas DMR2 was hypomethylated (Ma et al., 2015). In another transgenerational study evaluating prenatal exposure to TCDD on males, hypomethylation of IGF-2 in sperm in F1 and F3 generation was found (Ding et al., 2018). In females, TCDD did not alter the mean methylation rate of DMR2 and ICR, and hypermethylation was reported for some CpG sites only (Zhang et al., 2019b). In mice prenatally exposed to TCDD only during the preimplantation stage, an increased level of methylation of the IGF2/H19 imprint control region has been found (Wu et al., 2004). The effects of in utero exposure to TCDD on IGF-2R was investigated only in one study of male offspring. An increased level of methylation, at the DMR2, in both liver and muscle was associated to the exposure (Somm et al., 2013). Evidence related to other chemicals is very limited. Prenatal B[a]P exposure did not affect IGF-2 methylation in sperm (Zhang et al., 2019a). Prenatal exposure to BPA decreased methylation in fetal mouse germ cells (Zhang et al., 2012). Also, IGF-2R hypomethylation after BPA treatment in mice oocytes was confirmed also in a model of postnatal exposure (Chao et al., 2012). Mixed effects on methylation have been reported, with differences in tissue and exposure timings will all contribute to the differences observed.

Similarly, findings in humans have been controversial (Table 3). Prenatal exposure to non-dioxin like PCBs (as measured in maternal blood) was not associated with IGF-2 methylation levels in cord blood (Kobayashi et al., 2017b). Similarly, in a study evaluating the placenta, no association between IGF-2 methylation and PCBs and PBDEs levels was found (Kappil et al., 2016). In a case-control study evaluating the Vietnamese population exposed to TCDD during the Vietnam war, many CpGs sites in IGF-2 gene showed significant differences but findings were no longer significant when false discovery rate was applied (Giuliani et al., 2018). Prenatal exposure to PFOA was associated with a decrease in IGF-2 methylation in cord blood, whereas no effect was associated with PFOS in a cohort of 177 mother-children pairs (Kobayashi et al., 2017a). Several phthalate metabolites have been associated with decreased methylation of IGF-2 in the placenta and in cord blood (LaRocca et al., 2014; Montrose et al., 2018; Zhao et al., 2016). Furthermore, maternal urine BPA (measured in the first trimester) was negatively associated with IGF-2 methylation in cord blood of female newborns only (Montrose et al., 2018). Overall, although evidence from animal models is still limited, epidemiological studies support the association between exposure to some EDs and IGF-2 hypomethylation in cord blood.

3.2. Potential mechanisms of ED action on IGF signalling

The evidence presented here largely supports the hypothesis of cross-talk between the IGF system and AhR as one of the possible mechanisms responsible for growth and metabolic disruption associated with dioxins, dioxin-like compounds and PAHs. The effects of these chemicals are mediated by the AhR (Connor and Aylward, 2006). Upon activation by its ligand, AhR is translocated into the nucleus and forms a heterodimer with the AhR receptor nuclear translocator. This heterodimer binds to specific responsive elements defined xenobiotic-responsive elements (XREs), also known as dioxin-responsive elements, and subsequently induces the expression of down-stream genes. Several authors identified XRE sequences in the promoter region of IGFBP-1 (Adachi et al., 2004; Marchand, 2004; Murray and Perdew, 2007). The possible interaction between AhR and IGF signal transduction pathways has also been directly investigated, mainly through studies with functional inactivation of AhR. The regulation of IGFBP-1 transcription impacted by TCDD exposure in HepG2 cells was found to be AhR-dependent (Murray and Perdew, 2007). In a hepatocyte AhR knock-out mouse model, IGFBP-1 was significantly increased in the liver (Girer et al., 2016). The finding was replicated in another study investigating hepatic mRNA expression profile in AhR-null mice. Again IGFBP-1 was identified among the top up-regulated genes (Minami et al., 2008). At the same time, TCDD treatment was able to induce IGFBP-1 in the liver only in wild-type mice and not in the AhR knockout model, supporting the hypothesis that IGFBP-1 induction by TCDD requires a functional AhR, in line with the other studies (Minami et al., 2008). Overall, these findings support the hypothesis of AhR acting as a suppressor of IGF pathway, mainly via up-regulation of IGFBP-1, which in turn would decrease IGFs bioavailability (Fig. 1).

There are indications that other elements of IGF pathway might be also part of a regulatory loop with AhR, although less well supported by findings from studies. For instance, TCDD significantly inhibited IGF-2 mediated proliferation in a breast cancer cell line, and this growth inhibition was dependent on the presence of a functional active AhR (Salisbury et al., 2013). A subsequent study confirmed that IGF-2 promoted cell proliferation of breast cancer cells by inducing AhR (Tomblin and Salisbury, 2014). In vascular smooth cells, B[a]P treatment decreased IGF-1, IGF-1R, IGFBP-2 and IGFBP-7, but in cells with functional inactivation of AhR, the expression levels of IGF-related genes increased (Karyala et al., 2004). B[a]P treatment in the embryonic kidney downregulated IGF-1R, but the effect was no longer present in case of a mutation in AhR allele (Nanez et al., 2011). In a study evaluating AhR expression in breast tumour tissues of 439 patients, a positive correlation has been found between AhR and IGF-2R and IGF-1R, whereas no correlation was found with IGF-2 and IGFBP-5 (Vacher et al., 2018). Overall, these studies suggest that a functionally active AhR is required to regulate expression of IGFBP-1, which has been confirmed as a downstream target of AhR signalling. Other studies suggest that cross-talk between AhR and other elements of the IGF

system occurs, although the molecular mechanisms currently remain unknown.

IGF-AhR crosstalk is likely not the only mechanism involved in mediating the effects of exposure to endocrine disruptors. For example, it has been suggested that the cross-talk between AhR and the estrogen receptor (ER) or the estrogen receptor alone should be considered as a potential mechanisms of action. Indeed, the interactions between estrogen signalling and the IGF system are widely described and the production of several IGFBPs are estrogen-responsive (Clemmons, 2018; Kahlert et al., 2000). PBDEs are mostly known for their thyroid-disrupting properties, however they can interact with both the AhR and ER (Meerts et al., 2001). Phthalates and BPA exert their endocrine-disrupting actions via dysregulation of estrogen signalling, among others (Acconcia et al., 2015; Benjamin et al., 2017; Rochester, 2013).

Both XRE and estrogen responsive elements motifs were found in IGFBP-5 and IGF-1R genes in a study of the effects of developmental exposure to TCDD in the fetal mouse (Tanaka et al., 2007). Prenatal exposure to TCDD up-regulated IGFBP-6 in rat fetal calvaria and an ER genomic binding site was found in the promoter region of the gene, whereas no XREs were found (Guo et al., 2007). Furthermore, TCDD was able to induce IGFBP-6 in EL-4 cells deficient of the AhR, therefore suggesting that TCDD-IGFBP6 crosstalk was AhR-independent (Park et al., 2003).

In order to investigate whether prenatal exposure to PBDE-99 interfered with estrogen responsiveness later in life, female rats were ovariectomised and then challenged with estradiol (E2). It was found that PBDE-99 exposure dose-dependently reduced the magnitude of IGF-1 mRNA induction by E2 in ovariectomized animals (Ceccatelli et al., 2006). Similarly, BPA induces proliferation of ovarian cancer cells via cross-talk between ER and IGF1-R signalling pathways (Hwang et al., 2013; Kang et al., 2013). In another study, Toda et al. showed that BPA exposure in did not affect IGF-1, IGF-2 and IGF-1R in wildtype mice but that IGF-1 expression was elevated and IGF-1R downregulated in ovaries of exposed mice lacking aromatase activity (ArKO) and therefore having little endogenous estrogens (Toda et al., 2002). E2 administration led to recovery of the expression of these genes, confirming that transcription of IGF-1 and its receptor was regulated by E2 (Toda et al., 2002). Furthermore, BPA caused IGF-2R hypomethylation in mouse oocytes but the methylation pattern was recovered when an ER inhibitor (ICI182780) was added (Chao et al., 2012).

Other possibilities have been suggested. For example, TCDD induced IGF-2 transcriptional activation via the CCAAT/enhancer binding protein β (C/EBP β) and a putative C/EBPβ responsive element was identified on the IGF-2 promoter, whereas no XRE was found (Wang et al., 2011). Also, PPARγ might be involved in cross-talk with the IGF system, because it regulates signalling pathways downstream of IGF receptors and is involved in insulin sensitivity (Belfiore et al., 2009). Indeed, in granulosa cells, BPA reduced FSH-induced IGF-1 expression and significantly upregulated PPARγ (Kwintkiewicz et al., 2010). The central role played by PPARγ was confirmed as overexpression of PPARγ mimicked the effects of BPA on IGF-1 (Kwintkiewicz et al., 2010).

Considering the available evidence, dysregulation of the IGF system by endocrine disruptors appears to be mainly mediated by AhR and/or ER. At the moment, only IGFBP-1 has been confirmed as a direct downstream gene in AhR signalling. However, AhR itself interacts with the ER, with AhR able to modulate estrogen signalling depending on the cellular context and type of exposure (Ohtake et al., 2011, 2003). Therefore, a more complex regulation, involving several signalling pathways, could be involved with the IGF system. New functional inactivation studies providing a comprehensive characterisation of IGF system in multiple organs are needed to fully elucidate impact of AhR/ER (and vice versa). It should also be taken into account that cross-talk might be tissue-specific, therefore regulation mechanisms should be evaluated also locally.

4. Discussion

IGFs play a major role in growth and metabolism, thus it is important to consider the adverse impacts of IGF-disruption and its possible implications for human health. The evidence summarised in this review supports the hypothesis that the IGF system should be considered a major target for EDs. Although the direction of specific effects are not always consistent, animal models have revealed the adverse consequences of prenatal exposure to EDs on the IGF system, while many in vitro experiments provided mechanistic insight. Overall, it should be noted that studies presented in this review were highly heterogeneous, in terms of experimental models, dose levels and types/routes of exposure. These aspects render the direct comparison of outcomes difficult and also hamper the translation of the findings of these studies to humans. Also, evidence provided in epidemiological studies is also somewhat inconclusive, with positive or negative association between ED exposure and IGF elements not being consistently reported, the effects, or lack thereof, often depending on specific chemicals and with effects found in one cohort only.

Cell-based studies are rather limited in terms of the number of compounds tested and cell lines used. Some chemical classes have not yet been investigated in vitro (phthalates, PBDE), while for others only a few studies have been performed (B[a]P, PFOS). Perhaps predictably, BPA and TCDD have received more attention. A wide variety of cell lines have been used, and this is justified by the widespread actions of IGF system, which acts virtually in all cell types. However, in most cases only one study has been performed for each cell line. Due to this clear limitation, findings need to be interpreted with caution. Moreover, in the few cases in which the same cell line was used, findings have not been consistently confirmed (see effects of BPA on IGFBP-1 in endometrial stromal cells). Possibly the only exception is the up-regulation of IGFBP-1 induced by TCDD in a hepatocarcinoma cancer cell line, which has been reported by multiple authors. It is clear that more in vitro studies are required to ensure reproducibility and establish clear dose response parameters.

Another limitation of the published in vitro and animal studies is that few of them comprehensively characterised the IGF system, with most assessing only a limited number of IGF system elements. The IGF system is a complex signalling pathway, in which the interactions between IGFs, their receptors and binding proteins are responsible for downstream effects. Therefore, interpretation of findings based on observations related to a small section of the pathway could be misleading. More effort should be made in designing toxicological studies able to provide a more complete characterisation of the system. A major issue is related to great variability in study design between the publications. Although regulation of the IGF system is similar between mice and rats (Ohlsson et al., 2009), differences in timing of exposure and dose levels used make the findings of these studies difficult to compare. Moreover, tissue-specific effects should be taken into account. Besides the endocrine function, the autocrine and paracrine actions are also described for IGFs, which might indicate that the system is likely differentially regulated depending on specific cell type/organ.

A large body of literature supports the negative impact of dioxins, dioxin-like compounds and PAHs on IGFs. Furthermore, the associated increased levels of IGFBPs (particularly IGFBP-1, mainly produced in the liver) would further reduce IGF bioavailability in a “double whammy” effect. Over-expression of IGFBP-1 is associated with growth retardation, impaired fertility and altered glucose homeostasis (Schneider et al., 2000). In humans, high circulating IGFBP-1 levels have been linked with low birthweight (Tisi et al., 2005; Vatten et al., 2002; Wang et al., 1991). Therefore, these effects are likely to have significant health implications. While in vitro studies have provided mechanistic understanding, supporting the role of AhR in IGF-disruption, epidemiological studies have yielded mixed results.

In the case of PBDEs, phthalates and PFAS, the evidence is still limited, with only a few studies in animal models. Based on this limited

evidence, it appears that PBDE exposure stimulates IGF signalling, whereas, for PFAS, a negative association with IGFs has been more commonly reported. Perhaps, the highest level of disagreement between in vivo studies and epidemiology is for phthalate metabolites, for which induction of IGF-1 and IGFBP-1 has been reported in vivo. On the other hand, in most of the epidemiological studies, a negative association between IGF-1 and phthalate metabolites was found. Furthermore, the negative association between maternal phthalate metabolites and IGF-2 methylation in newborns has also been consistently reported, strongly supporting the negative impact of this exposure during prenatal life. While BPA has been more extensively investigated, somewhat mixed findings have been reported. Furthermore, the only epidemiological study assessing BPA in conjunction with the IGF system did not find any association with IGF-1.

Both in vitro and in vivo studies frequently report gene expression and protein changes in IGFBPs, whereas IGFs and their receptors were not affected. While the major function of IGFBPs is to regulate IGF bioavailability IGF-independent actions have also been reported (Clemmons, 2018). However, given, a high degree of functional redundancy and/or genetic compensatory mechanisms suggested by the lack of substantial phenotypes in IGFBP knockout models (Bach, 2018a; Murphy, 1998), it is difficult to predict the implications of increased levels of a subset of binding proteins in specific tissues. Despite overlapping functions, specific roles have recently been described for each IGFBP, depending on cell type and condition (Bach, 2018b). For instance, IGFBP-1 is specifically involved in liver regeneration and in responding to catabolic condition and its levels are negatively associated with biomarkers of cardiovascular disease (Bach, 2018a; Bae et al., 2013; Haywood et al., 2019).

Since 80–90% of IGF-1 is bound to IGFBP-3 (Jones and Clemmons, 1995) epidemiological studies focus mostly on IGFBP-3. Decreased IGFBP-3 has been more consistently associated with phthalate exposure, whereas for the other ED classes only mixed findings have been reported. Given the current evidence, it is therefore impossible to derive definitive conclusions and difficult to predict the clinical implication of IGFBP-3 dysregulation. It should also be highlighted that some authors considered IGFBP-3 as a confounding variable, rather than an outcome (Luzardo et al., 2012), whereas others quantified IGF-1 only (Lopez-Espinosa et al., 2016; Shy et al., 2012; Watkins et al., 2016; Wohlfahrt-Veje et al., 2014). However, as IGFBP-3 is the main serum carrier of IGF-1 and altered levels have now been associated with several diseases, its evaluation is of utmost importance. Furthermore, it is now clear that the other IGFBPs are also involved in many pathological processes, such as metabolic disease and cancer (Bach, 2018a; Baxter, 2014). Therefore, the potential contributions of exposure to EDCs on IGFBP dysregulation represents a considerable gap in our knowledge, given that human epidemiological data are lacking.

Overall, the evidence presented in this review is characterised by high degree of variability. One of the possible explanations is related to the complexity of the IGF system, which acts in an endocrine, paracrine and autocrine manner and is able to respond to a wide set of regulatory mechanisms, which differ based on developmental stage and sex. Transcription and subsequent action of IGF are partially GH-dependent, but their levels in blood are influenced by other hormones (estrogens, thyroid hormones and glucocorticoids), the immune system and also by nutritional status (Blum et al., 1993; Juul, 2003; Ranke and Wit, 2018). Furthermore, it is critically important that IGF-1 levels fluctuate across lifespan, peaking around puberty and then decreasing with age during adulthood (Juul, 2003). This factor might explain the sometimes different direction of findings in epidemiological studies, as well as differences depending on life stage of experimental models used. Sex is also an important variable to consider. Sex-stratified analyses of epidemiological studies reported that effects were more pronounced in females (LaRocca et al., 2014; Montrose et al., 2018; Wang et al., 2005; Watkins et al., 2016; Xu et al., 2013). Unfortunately, in most of the animal studies sex was not considered or studies were performed in one sex only. GH secretion pattern depends on sex, and this in turn differentially regulate sexually dimorphic liver functions, in rodent models (Adams et al., 2015; Ohlsson et al., 2009). For instance, liver-specific inactivation of IGF-1 feminizes GH-regulated liver functions (Wallenius et al., 2001). Finally, in humans there are indications of sexually dimorphic regulation of GH secretion and of interactions between sex steroids and IGF-1 in regulation of GH secretion (Ohlsson et al., 2009). An additional important point is that different classes of EDs might interfere with the IGF system in different ways. Therefore, the effects of complex mixture must be taken into account.

Particular concerns arise from the observed effects associated with prenatal exposure to EDs, which has been reported in animal studies. The hypothesis that epigenetic modifications of the pathway following exposure to EDs has also been confirmed by animal models, while evidence from human studies remains limited. In many human studies, a negative association between EDs (particularly phthalate metabolites) and IGF levels or methylation states have been found. The adverse impact of IGF disruption occurring during these critical windows of susceptibility is therefore probably an important mechanism in endocrine disruption of human development. However, it should be highlighted that most of the epidemiological studies are based on ED quantification in the maternal compartment (e.g. urine or blood), which does not necessarily reflect the actual human fetal exposure.

4.1. Conclusions

The IGF system plays a fundamental role in both growth and metabolism. Although many studies have shown that EDs are able to disrupt IGF signalling, findings have been mixed, especially in human studies. It is evident, therefore, that research is still needed to fill research gaps and increase reproducibility of outcomes, or lack thereof. Additional animal studies are required in order to expand our knowledge about Eds that can disrupt the IGF system, in terms of system-wide changes and investigating the effects of complex mixtures. Furthermore, better designed epidemiological studies are needed to clarify the impacts on human health. Larger studies with simultaneous determination of more classes of EDs would be advantageous. In addition, given the importance of IGF signalling in regulating development, future areas of investigation should focus more sharply on effects of prenatal exposure to EDs, especially in the human.

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