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Placental Toxicology of Pesticides

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1. Introduction

The placenta used to be regarded as an organ protecting the fetus from exposure to toxic chemicals. However, we now know that xenobiotics can cross through the placenta and enter the fetal blood stream (Barr et al., 2007). In addition, some toxicants may accumulate in the placenta and potentially affect its development or function. Therefore, understanding how the placenta affects xenobiotics, and conversely, what the latter do to the placenta, should provide a basis for the use of this organ as a tool to investigate and predict some aspects of developmental toxicity (Myllynen et al., 2005). In this sense, the placenta is a key tool for biomonitoring xenobiotic exposure. Furthermore, it provides a large sample for analysis and is the most accessible and readily available component of the triad mother-infant-placenta. The cumulative effects of pregnancy-related events are shown by the placenta, which also reflects the intrauterine environment, and may be examined to a degree that is usually impossible in the infant. A critical issue for placenta toxicological analysis is the availability and appropriate use of biomarkers, as these provide measures of the exposure, toxic effects and individual susceptibility to toxicants. However, as epidemiological studies cannot resolve all the confounding factors, further experiments are also necessary. Thus, *in vitro*, *in vivo* and *ex vivo* models have been used in attempts to elucidate the toxicology of the toxicants occurring in the human placenta. Nevertheless, these approaches have their limitations. Despite having common physiological functions, placentas from different species are not homogeneous in their morphology, transport or metabolism of xenobiotics, thereby making it difficult to obtain a good representative model of the human placenta (Prouillac & Lecoœur, 2010). Moreover, changes in the placental function due to chemical exposure may also depend on the gestational period in which this occurs. Consequently, little research has been carried out into the biochemical and molecular toxicity of xenobiotics in human placenta.

Among the toxicants, pesticides are the only chemicals which have been intentionally introduced into the environment. Experimental approaches have established that exposure to pesticides during embryonic development influences the F1 generation. Furthermore, it has been noted that the epigenetic actions of pesticides may act on a gestating mother to influence subsequent (F1-F4) generations (Anway & Skinner, 2006).

Human environmental exposure to pesticides during the gestational period is associated with adverse reproductive outcomes (Arbuckle et al., 2001; Triche & Hossain, 2007), spontaneous miscarriage (Figa-Talamanca, 2006; Pathak, 2010) low birth weight (Figa-

Talamanca et al., 2006; Lopez-Espinosa et al., 2007; Triche & Hossain, 2007) and intrauterine growth retardation (Levario-Carrillo et al., 2004a). The association of maternal pesticide exposure with an increased risk of urogenital malformations (Fernandez et al., 2007) and impaired reproductive development (Andersen et al., 2008) has also been reported.

Organochlorine pesticides (OC) are persistent and ubiquitous environmental contaminants, with commercial-grade DDT (bis[4-chlorophenyl]-1,1,1-trichloroethane) being one of the most commonly used in history (Cohn et al., 2010). The majority of OC have been restricted or banned in industrialized nations, and their contamination levels have either been reduced or are expected to decline in the future. However, since OC are the most lipophilic pesticides in nature and have long half lives of months, or even years, they tend to accumulate in the adipose tissues and then biomagnify through the food chain, thus creating a persistent exposure risk to humans (Pathak et al., 2010). In fact, nearly all people have measurable levels of DDT-related compounds in their blood or tissue samples. In addition, DDT is still used in developing countries, and many others are currently preparing to reintroduce DDT in vector control to prevent disease (van den Berg, 2009). Therefore, OC exposure may occur not only through the ingestion of residues in the diet but also via inhalation and dermal absorption.

One of the most important classes of chemicals actively applied to the environment is the cholinesterase-inhibiting organophosphates (OP). Almost every person is, or has been, exposed to OP insecticides in their home, work or environment (Casida & Quistad, 2004), with pesticide exposure arising from living next to treated areas or in agricultural regions, as well as from house and yard pesticide treatment. The direct ingestion of residues in the diet or through secondary ingestion of contaminated house dust/soil, or from hand-to-mouth contact, inhalation of vapors or aerosols, or dermal absorption following contact with the skin, may represent other entry vias. Although the dermal and inhalation exposure pathways are likely to dominate in occupational exposure to pesticides, ingestion is likely to be the predominant pathway in the exposure of ordinary people (Eaton et al., 2008).

2. How the placenta affects pesticides

The transfer of molecules between the maternal and fetal circulation occurs across the endothelial-syncytial membrane of the placenta. Moreover, the placenta interferes with chemical delivery to the fetus, by expressing active membrane transporters and xenobiotic metabolism enzymes. The regulation of these enzymes and transporters and the effects of genetic polymorphisms on their functions may have important implications in fetal and placental exposure to xenobiotics and their potential toxicities (Prouillac & Lecoer, 2010).

2.1 Placental incorporation and accumulation of pesticides

OP and OC are non-polar pesticides that can cross the placental microvillus brush border membrane by passive diffusion, with the rate of their incorporation into this compartment being determined by their physicochemical properties, such as lipid solubility and their toxicokinetic characteristics (elimination half-life in the mother, protein binding, lipid sequestration, and metabolism in maternal and placental compartments).

OC are the highest lipophilic but the poorest metabolized pesticides. Therefore, when exposure takes place, they are accumulated preferentially in the adipose tissue. In fact,

dosimetry of *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE, a metabolite of DDT) in the tissue of pregnant rats after oral intoxication, demonstrated that *p,p'*-DDE levels in the placenta were almost four times lower than in the maternal adipose tissue (You et al., 1998). A redistribution of OC storage may occur during late gestation, when there is an enhanced maternal adipose tissue lipolytic activity. Consequently, lipid storage is mobilized and OC enter the maternal blood circulation and reach the placenta. Although no clear and precise model for the bioaccumulation of OC has yet been developed, it is known that some OC metabolites selectively accumulate in the placenta, thereby suggesting a tissue specific metabolic activity. The OC levels in human placenta and paired breast milk samples from Danish and Finnish samples were studied by Shen et al. (2007). As expected by their differential lipid content, the milk samples had higher levels of OC than the placenta. In agreement, when the distribution of the OC levels in the maternal, placental and fetal compartments was analyzed in a Spanish population, the concentration of endosulfan I and II in female adipose tissue was similar to that in breast milk, but higher than that of the placenta or cord blood. In contrast, the polar metabolites endosulfan diol and endosulfan sulfate were more frequently found in the placenta and cord blood (Cerrillo et al., 2005).

Unlike OC pesticides, the OP pesticides are rapidly metabolized and excreted. A study of the toxicokinetics and the placental transfer of a single low dermal dose of labeled [¹⁴C]-methyl parathion administered to pregnant rats, showed that at 96 h the urine contained 91 % of the administered dose. The placenta was demonstrated to be a poor barrier against methyl parathion, resulting in an extensive placental transfer. However, the values of relative residence with respect to the maternal plasma (which reflects OP tissue relative exposure), revealed that among the studied compartments (maternal liver, kidney, brain, placenta and fetus) the placenta exhibited the highest levels, suggesting that this organ functions as a temporary depot (Abu-Qare et al., 2000).

Radiolabeled [¹⁴C]-chlorpyrifos, administered intravenously to pregnant rats in a single injection at various gestational ages, was used to investigate the distribution of chlorpyrifos and the metabolite 3,5,6-trichloropyridinol (TCPy) in the mother and the fetus. Radioactivity and TCPy were identified in all tissues five minutes after dosing. Also, in the matrix studied (maternal blood, liver, brain, and placenta, and fetus), the maximum concentration was found in the maternal liver, with the levels in the fetus and in the placenta only being marginally lower (Abdel-Rahman et al., 2002).

Considering the above information together, it is clear why there exists information about OC residue levels in human placenta whereas there is a lack of information about OP residues. Nevertheless, recognized OP targets, such as acetylcholinesterase (AChE) and carboxylesterase (CaE), may be used as reference biomarkers in order to evaluate OP placenta exposure (see 2.3.1.2).

2.2 Placental extrusion of pesticides

Interest in the ability of the placenta to reduce the passage of drugs has increased since Lankas et al. (1998), reported carrier-mediated transport of xenobiotics in the placenta by the ATP-binding cassette (ABC) transporters in this organ. Depending on their location, some of these proteins can act as efflux pumps, thereby expelling xenobiotics from the placenta to the maternal plasma (Prouillac et al., 2009).

A number of efflux transporters, including multidrug resistance proteins (ABCB1/P-gp), multidrug resistance associated proteins (MRP1-3 and 5) and breast cancer resistance protein (BCRP), are present in the syncytiotrophoblast. Studies using preterm placenta suggest that transporter expression varies with gestation (Sun et al., 2006; Aleksunes et al., 2008). BCRP expression in the placenta peaks at mid-gestation, with P-gp progressively decreasing and MRP2 progressively increasing with gestational age. The differential expression over the course of pregnancy possibly provides a compensatory mechanism for the protection of the fetus at different gestational stages (Mao, 2008), and xenobiotic transporters in fetal membranes may provide an additional route to protect the fetus against chemicals (Aleksunes et al., 2008).

ABCB1/P-gp, located in the microvillous membrane (Atkinson et al., 2003), preferentially transports hydrophobic compounds, such as pesticides, and also weakly basic compounds (Mao, 2008). Consistent with a protective role that limits exposure of the fetus to xenobiotics, Lankas et al. (1998) showed that the absence of P-gp expression increases pesticide avermectine content in the placenta.

ABC transporter polymorphism can produce interindividual variations in the toxicokinetics of foreign compounds in the feto-placental unit. However, it is still unclear whether specific ABCB1 or ABCG2 genotypes are risk factors for teratogenicity/fetotoxicity (Vanderlelie et al., 2008) or placental toxicity.

Several pesticides, including methoxychlor (OC) and fenitrothion (OP) are substrates for human MRP1 (Tribull et al., 2003). MRP2 is expressed in the syncytiotrophoblast, whereas MRP1 and MRP3 are expressed in both the blood vessel endothelia and in the syncytiotrophoblast (St-Pierre et al., 2000), with MRP5 being expressed in the basal membrane of the syncytiotrophoblasts and around fetal vessels (Macias et al., 2009).

In addition, pesticides may affect the ATP-efflux transporters function and expression. The interaction of methoxychlor and fenitrothion, with ABCC1 modulating the transport of physiological substrates has been demonstrated (Sharom, 2008). Also, low exposure to diazinon (OP) increased P-gp expression in the small intestine (Lecoeur et al., 2006). However, there is a lack of information about whether these types of interactions occur in the placenta.

2.3 Placental pesticide metabolism

2.3.1 Detoxifying enzymes

There is little contribution made by placental biotransformation in the conversion of xenobiotics into potential metabolites. Furthermore, compared to the liver, the role of placental metabolism is minor (Pasanen, 1999).

2.3.1.1 Phase I metabolism

Phase I reactions include monooxygenations, oxidations, reductions, hydrolyses and epoxide hydration, with all of these, except reductions, introducing a polar group to the molecule. The vast majority of compounds metabolized in phase I are processed by the microsomal cytochrome P450 monooxygenases (CYPs), which may generate metabolites (such as oxon) that are more neurotoxic than the parent compound (OP). Several CYPs,

including CYP1, CYP2 and CYP3, have been isolated from the placenta. The members and quantity of the CYPs vary as a function of placental development, length of gestation and maternal health status (Hakkola et al., 1996a; 1996b), with the expression of human CYPs declining during gestation from the first to the second and third trimesters (Syme et al., 2004). However, not all CYPs are functional in human placenta, and the full spectrum of phase I enzyme expression, activity and developmental changes remains to be defined. For instance, although expression of CYP3A4 (mRNA and protein) has been demonstrated in the placenta, several marker substrates are not metabolized, suggesting that this enzyme is not functional. CYP1A1 is in fact the only CYP whose function and inducibility have been unquestionably demonstrated in the placenta (Vanderlelie et al., 2008).

Because OPs are esters of phosphoric or phosphotioic acid, they are susceptible to hydrolysis by A-esterases (calcium-dependent hydrolases also called paraoxonases). Their substrates are parent compounds having the P=O group or the oxon metabolites of the parent pesticides, with the hydrolysis being able to destroy the anti-cholinesterase activity of these compounds and being a potentially significant route of detoxification. However, although A-esterases display a low affinity for many compounds, they have high affinity for certain other compounds, such as chlorpyrifos-oxon and diazinon-oxon. In addition, carboxylesterases (CaEs) hydrolyze carboxylic acid esters, which are rarely encountered within the OP pesticides. Nevertheless, CaEs are still important contributors to the stoichiometric detoxication of many oxons, even those that have a low affinity for the A-esterases. Another serine esterase that detoxifies oxons stoichiometrically is the acetylcholinesterase (AChE). However, because this detoxication is stoichiometric and not catalytic, it is saturable and may have a limited efficacy if the OPs are present at high concentrations (Tang et al., 2006).

In summary, due to the variety in the types of atoms and groups present in OP (acids, alcohols, esters and ethers), many phase I reactions are possible, with the most prominent reactions being oxidation and hydrolysis (Tang et al., 2006). Also, by having an active, albeit restricted metabolic capacity, the placenta might convert certain OP to their oxon forms (Gupta, 2007). In fact, we found a significant inhibition (about 40 %) of CaE activity in placentas from women living in agricultural areas exposed to OP (Vera, unpublished results). Related to this, considering that CaE are known to catalyse the biotransformation of pyrethroids (Godin et al., 2006), a decrease in CaE activity in the placenta may have a toxicological significance in women exposed to pesticide mixtures.

With regard to the OC metabolism, it is known that epoxidation/hydroxylation mediated by CYPs are involved in the alicyclic OC metabolism, while DDT dehydrochlorinase (the enzyme transforming DDT to DDE) occurs in the cell soluble fraction (Rose & Hodgson, 2004). However, no information about these biotransformations in the placenta is currently available.

2.3.1.2 Phase II reactions

The phase II metabolism conjugates water-soluble moieties, such as glucuronic acid, sulfate and glutathione (GSH), among other groups, to xenobiotic metabolites. In addition to phase I enzymes, the placenta also expresses phase II conjugating enzymes, for example glutathione-S transferase (GST) isoforms, epoxide hydrolase, N-acetyl transferase, sulfotransferases and UDP-glucuronosyl transferase isoforms. As GST catalyzes the

conjugation of biologically active electrophiles to GSH, it appears that placental GST plays a role in protecting the fetus against electrophiles or oxidative stress (Vanderlelie et al., 2008). Xenobiotic exposure, however, may affect the detoxification pathways. During OP desulfuration, activated sulfur atoms are formed that bind irreversibly to the specific CYP isoforms that catalyze the reaction, resulting in a time-dependent decrease in the enzymatic activity. Also, OP may down-regulate CYP mRNA, as was demonstrated in liver and testis of rats intoxicated with OP profenofos (Moustafa et al., 2008). It has been established that DDE induces CYP2B and CYP3A enzymes and selected conjugation enzymes in liver (You, 2004). Furthermore, enzyme induction by xenobiotics may increase the clearance of endogenous steroids, and hence produce endocrine disruption, which is a matter of great concern. However, there is no information yet available about these potential associations in the placenta.

3. How pesticides affect the placenta

3.1 Endocrine disruption

An endocrine disrupter (ED) is an exogenous chemical substance or a mixture of substances which alters the structure or function (s) of the endocrine system. EDs act by interfering directly with natural hormones, since they are not only able to interact with various hormone receptors, but can also interfere with the synthesis, transport, metabolism and elimination of hormones (Mnif et al., 2011). Many chemicals that have been identified as EDs are pesticides. Nuclear compartmentalization of these compounds, insertion into membranes and chemical stress production may be associated with deleterious consequences on the endocrine system.

3.1.1 Effects on aromatase

The placenta is the main organ responsible for estrogen synthesis in pregnant women. CYP19 aromatase (ArM), the enzyme that catalyzes the conversion of the androgens androstenedione (A-dione) and testosterone to estrogens, has been proposed to be an important molecular target of ED chemicals (Figure 1). ArM, a complex comprised of P450-aromatase and NADH-cytochrome P450 reductase, is an inducible enzyme whose expression is tightly regulated. ArM is located in the microvilli surface, in the the lateral plasma membrane, and in the endoplasmic reticulum in the syncytiotrophoblast of the placenta (Nagamuna et al., 1990).

Several *in vitro* assays have been used for studying ArM as a potential target of pesticides inducing endocrine disruption. Some studies were conducted on human placental JEG-3 cells, which are morphologically similar to their cells of origin (i.e. the trophoblast of the normal first trimester) and provide a cell model to study the placental function (Tremblay et al., 1999). Since regulation of ArM expression in these cells is the same as in the placenta, JEG-3 cells have been proposed to be a valuable tool for the assessment of potential steroidogenesis disruption. ArM activity was found to decrease by incubation with the OCs lindane (γ HCH) and heptachlor (Laville et al., 2006), with a significant association between γ HCH levels in female blood and recurrent miscarriages also being reported (Pathak et al., 2010). These findings could be related to alterations in estradiol levels, since this hormone plays a critical role in the maintenance of primate pregnancy (Albrecht et al., 2000), with its synthesis

depending on ArM activity. In contrast, the OCs aldrin, chlordane, endosulfan and methoxychlor were reported to induce ArM activity in JEG-3 cells (Laville et al., 2006). Considering that an increased level of estradiol in the syncytiotrophoblast may have an impact on testicular descent (Hadžiselimović et al., 2000), and that an association of congenital cryptorchidism with trans-chlordane levels in breast milk has been reported (Damgaard et al., 2006), it now remains to be determined if the increasing incidence of this reproductive abnormality is associated with trans-chlordane induced up regulation of placental ArM.

Exposure of placental explants to two isomers of DDT (*o,p'*-DDT and *p,p'*-DDT) and their metabolites (*o,p'*-DDE and *p,p'*-DDE) caused reductions in estradiol secretion due to a direct action on ArM activity and expression (Wójtowicz et al., 2007a). However, different effects (stimulatory after short-term and inhibitory after long-term exposure) of these compounds were observed on progesterone secretion. In addition, both short- and long-term exposure to these compounds caused decreased hCG (human chorionic gonadotrophin) secretion, a crucial hormone for pregnancy maintenance, suggesting the existence of a local axis between the steroid hormones and hCG in the placenta (Wójtowicz et al., 2007b; 2008).

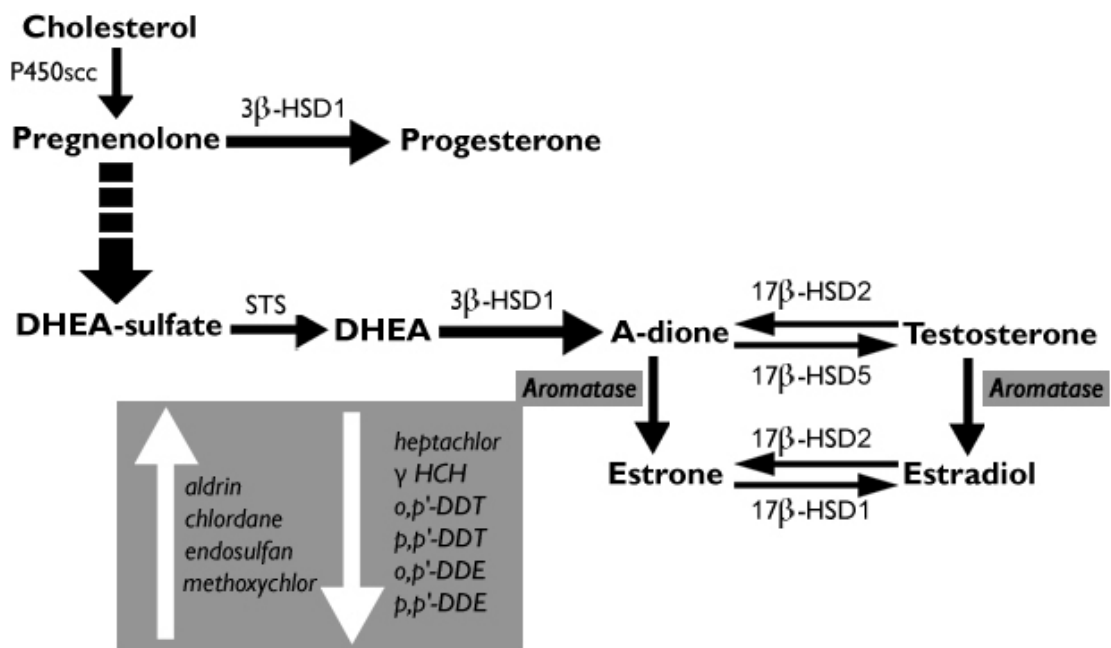


Fig. 1. Estrogen synthesis and OC effects on human placental aromatase

As these authors used concentrations covering the range of OC levels present in the serum of pregnant women, they proposed that these hormonal imbalances could influence the pregnancy outcome. It should be noted that *p,p'*-DDE is currently a dominant pollutant found in the placenta of different populations and *o,p'*-DDT has also been detected in samples of various populations (Lopez-Espinosa et al., 2007; Shen et al., 2005). With respect to OP, there is no available information concerning the OP effect on ArM in the placenta.

3.1.2 Other potential mechanisms involved in endocrine disruption

As shown in Table 1, several authors have studied other possible targets of pesticides affecting the placenta, which could also be associated with endocrine disruption. It has been established that OC may bind hormone receptors, with *o,p'*-DDT being the most estrogenic

component of the DDT complex, and having a relative binding affinity to estrogen receptors (ER) of 2.9×10^{-3} relative to 17- β estradiol. In the case of the *p,p'*-DDE isomer, it is anti-androgenic with an inhibitive binding to the androgen receptor (AR), and has a relative binding affinity of 3.1×10^{-3} relative to dihydrotestosterone (Rogan & Chen, 2005). Considering the persistent exposure of placental tissues to these DDT isomers and that various cellular components of human placenta express ER (in the form of either ER α or ER β) (Bukovsky et al., 2003) as well as AR (Hsu, 2009), then wider implications in terms of their potential role in endocrine disruption may be postulated.

An appropriate intracellular Ca²⁺ concentration is necessary for blastocyst implantation and proper placental development and function, with recent studies having pointed out that alterations in Ca²⁺ homeostasis can lead to placental pathologies such as pre-eclampsia and intrauterine growth restriction (Baczyk et al., 2011). The effects of the exposure of trophoblastic cells to methoxychlor and *p,p'*-DDT in comparison with exposure to estradiol and diethylstilbestrol (DES), were studied to test the hypothesis that cellular Ca²⁺ handling is a target for these EDs. Treatment with DDT, methoxychlor, DES, or estradiol increased the cellular Ca²⁺ uptake, and the expression of trophoblast-specific human Ca²⁺ binding protein (HCaBP) was down-regulated by both methoxychlor and DDT. In addition, treatment with methoxychlor, DDT, and DES inhibited cell proliferation, induced apoptosis, and suppressed the expression of several trophoblast differentiation marker genes. These results strongly suggest that the trophoblast Ca²⁺ handling functions are endocrinally modulated, and that their alteration by EDs, such as methoxychlor and DDT, constitutes a possible pathway for these agents to produce harmful effects on the placental function and fetal development (Derfoul et al., 2003).

| Target | Pesticide | Reported*/potential effect | References |
|---|-----------------------------------|-----------------------------|--------------------------|
| Phosphoinositides metabolism and PI-4 kinase activity | heptachlor <i>o, p'</i> -DDT | Lactogen release disruption | Souza et al. (2005) |
| PKC activity | heptachlor <i>o, p'</i> -DDT | hCG secretion disruption | Magnarelli et al. (2009) |
| PKA activity | <i>o, p'</i> -DDT | hCG secretion disruption | Magnarelli et al. (2009) |
| Ca ²⁺ uptake and expression of trophoblast-specific human Ca ²⁺ binding protein | methoxychlor <i>o, p'</i> -DDT | Estrogen-like effects* | Derfoul et al. (2003) |

Table 1. Other targets associated with pesticide ED in placenta

We have previously reported that a significant increase was produced in protein kinase A (PKA) activity by *in vitro* incubations of human placental villi homogenates with *o-p'* DDT, whereas the protein kinase C (PKC) activity was reduced by heptachlor and *o-p'* DDT (Magnarelli et al., 2009). These differential effects on kinase activities may be associated with the oxidative stress produced by the pesticides. Experimental evidence has demonstrated that the sensitivity of PKA isoforms to oxygen radicals may vary, depending upon the type of oxygen free radicals produced and the antioxidant system present, both of which are

tissue-dependent (Dimon-Gadal et al., 1998). Also, PKC is under a complex redox regulation and shows different responses to oxidative stress depending on the PKC isoform (Poli et al., 2004). Since placental human gonadotropin-releasing hormone (GnRH) transduction signaling couples with both the PKC and PKA pathways (Cheng et al., 2000), the *o,p'*-DDT effects observed may contribute to the impairment of hCG secretion reported by Wójtowicz et al. (2008).

We also studied the placenta phosphoinositide (PI) metabolism as a potential target of pesticide action. PI-mediated signaling plays an essential role in normal morphogenesis and placental function, as was demonstrated in knock out mice by Nakamura et al. (2005). Also, PI- signaling has been associated with lactogen release (Petit et al., 1989) and fibroblast growth factor activation of phospholipase C in the human placenta (Ferriani et al., 1994). *In vitro* incubations of cell-free homogenates showed that different patterns of lipid phosphorylation were produced by OP and OC. However, both types of pesticides affected the post-membrane supernatant of PI 4-kinase, a key enzyme in PI metabolic pathway. A biphasic effect on membrane and nuclear PI4-kinase activity was seen with heptachlor (OC), with the strongest effect being found with *o-p'*-DDT on nuclear PI4-kinase activity, while substantial changes were also observed in membrane fractions (Souza et al., 2004).

3.2 Oxidative stress

Pregnancy is characterized by a strictly regulated physiological increase in the oxidative processes in the mother and the fetus, which is determined by the rise in oxygen consumption and by the use of some reactive oxygen species (ROS) in cellular processes. These ROS include: superoxide radical, hydrogen peroxide and hydroxyl radical, among other molecules. Both a short or a long term lack of anti-oxidant/pro-oxidant balance provokes oxidative stress. ROS excess may cause disorders in protein synthesis and enzyme activity, as well as changes in the synthesis and activity of hormones and cell membrane receptors, and also damage to the DNA. Moreover, these alterations can produce cellular loss of function and apoptosis, thereby affecting the normal course of pregnancy (Corria Osorio & Cruz Manzano, 2009). In fact, oxidative stress in the placental tissues is an essential pathogenic factor of premature delivery miscarriage (Prokopenko et al., 2006) and pre-eclampsia (Vanderlelie et al., 2005).

Placental oxidative stress may directly or indirectly lead to oxidative stress in the maternal circulation. It was reported that the concentration of maternal plasma cell-free fetal DNA was positively correlated with the concentration of urinary 8-OHdG (8-hydroxydeoxyguanosine, an oxidized nucleoside of DNA), and plasma isoprostane (prostaglandin-like compounds formed *in vivo* from the free radical-catalyzed peroxidation of essential fatty acids) at 26 to 30 weeks of gestation. These cell-free fetal DNAs were most likely derived from the placenta, which then entered maternal circulation during the process of deportation of the syncytiotrophoblastic microparticles, with this event possible leading to activation of maternal neutrophils and subsequent production of ROS. Alternatively, both the increase in maternal oxidative stress and the breakdown of the syncytial surface might be caused by a common insult to the placenta, i.e. oxidative damage induced by ischemia-reperfusion (Hung et al., 2010). Interestingly, pesticides are capable of inducing oxidative stress by enzymatic conversion to secondary reactive products and/or ROS, by depletion of antioxidant defenses, as well as by impairment of antioxidant enzyme functions (Franco et

al., 2009). Another way that ROS generation occurs, as described in OP toxicity, is through high energy consumption coupled with oxidative phosphorylation (Lukaszewicz-Hussain, 2010). Preliminary *in vitro* studies in our laboratory with chlorpyrifos treated JEG-3 cells showed that cell viability and the content of GSH (a reducing agent of antioxidant defense) was significantly reduced. However, the pretreatment of JEG-3 cells with the antioxidant N-Acetylcysteine was able to revert these effects, suggesting that oxidative stress was the mechanism of injury (Chiapella et al., unpublished). Also, OC (endrin and γ HCH) were demonstrated to be capable of inducing oxidative stress in fetal and placental tissues in mice after the administration of teratogenic doses of these pesticides (Hassoun & Stohs, 1996).

Oxidative stress is a complex phenomenon to investigate in pesticide exposed populations. Several toxicants, such as metals, carbon monoxide, dioxin, radiations, polychlorinated biphenils, polycyclic aromatic hydrocarbons (Lukaszewicz-Hussain, 2010) and cigarette smoke (Menon et al., 2011) have been identified as producers of pro-oxidant conditions in several tissues and must therefore be considered to be confounding factors when oxidative stress is studied as a probable consequence of pesticide exposure

3.3 Proliferation/death imbalance

Apoptosis is one of the major forms of cell death, in which the cell designs and executes the program of its own death, with this process being important in normal placental development. Trophoblast apoptosis increases in normal placentas as gestation proceeds, and its concurrent appearance with cell proliferation reflects the growth and remodeling of the placenta. These two processes work together to maintain the placental tissue homeostasis. Apoptosis may be initiated by the death receptor pathways or intrinsically by the mitochondria pathway (Straszewski-Chavez et al., 2005). Also, excessive ROS production may lead to cellular dysfunction and culminate in cell death, with the ROS produced during oxidative stress having been shown to initiate signaling cascades and lead to apoptosis (Yuan et al., 2008).

The mechanism of chlorpyrifos (OP) induced cytotoxicity was investigated in the trophoblast JAR cell line, which is less differentiated than the JEG-3 cell line but has a higher proliferation rate. Apoptosis was only partially mediated through activation of caspase system, and surprisingly, the p38 MAPK signaling pathway was involved in protection against chlorpyrifos-induced toxicity. In addition, among the genes known to regulate apoptosis, Bcl-2, DKN2A, MTA2, TEK and TWIST1 were down regulated, while FAS, TNF α , ITGB1 and ITGA4 were up-regulated. These authors concluded that apoptosis was not dependent on FAS/TNF signaling, activation of caspases or the inhibition of AChE (Saulsbury et al., 2008). In agreement, results from our laboratory indicate that incubation of the JEG-3 cell line with chlorpyrifos or phosmet (OP) induces cell death as a consequence of apoptosis induction, and that JEG-3 cells may be more tolerant to chlorpyrifos toxicity than JAR cells (Guiñazú et al, unpublished observations). Differential susceptibility to chlorpyrifos in these two cell lines may be explained, at least in part, by the fact that the transcription factor HNF1 α (hepatic nuclear factor 1 α) is expressed ten times more in JAR than in JEG-3 cells (Serrano et al., 2007), with this transcription factor playing an important role in CYP regulation. Although the involvement of CYPs in OP-induced apoptosis in neuronal cells has been previously reported (Kashyap et al., 2011), it is still not clear whether OP metabolism by CYPs and the induction of oxidative stress are implicated in trophoblast cell death.

OC and ROS generation have been described to interfere with various signaling pathways, including MAPKs. In fact, all MAPK cascades are known to be activated in response to oxidant injury (Martindale & Holbrook, 2002), and they can therefore have an impact on cell survival and death. Wojtowics et al. (2007b) demonstrated that *p,p'*-DDT and *p,p'*-DDE could act as both pro-apoptotic or anti-apoptotic factors, depending on the isomer type and concentration, with a small concentration of all these compounds tending to decrease the caspase-3 activity (Wojtowics et al, 2007b). Derfoul et al. (2003) reported that *p,p'*-DDT inhibited JEG-3 cell proliferation, induced apoptosis and suppressed the expression of several of the marker genes responsible for trophoblast differentiation.

Serine-threonine kinases and transcription factors play important roles in the progression of the cell cycle. Experiments on mouse trophoblast stem cells and the human placental cell line HTR demonstrated that less than half of serine-threonine kinases and transcription factors have a higher level of phosphorylation at the M phase than at the interphase (Liu et al., 2004). Using *in vitro* homogenate villi incubations, we showed that total serine/threonine kinase activity was increased by 10 μ M heptachlor and *o-p'* DDT in a particulate fraction (Magnarelli et al., 2009). Since insufficient trophoblast proliferation is one of the causes for loss of embryos, this result may appear controversial with the reported effects about OC reproductive outcomes. However, the understanding of the mechanisms underlying trophoblast injury by pesticides requires an integrated vision of all the molecular targets involved.

3.4 Impairment of the mitochondrial function

Oxidative phosphorylation, the primary process by which the energy derived from the catabolism of fuels is used to synthesize ATP, occurs in the mitochondria. It has been recognized that the mitochondria has homeostatic functions in metabolic cell signaling, ion homeostasis, regulation of cell morphology, multiplication and apoptosis. The mitochondrias of the human placenta are not only involved in the production of ATP. Mitochondrias of the syncytiotrophoblast are the main source of progesterone, whose synthesis requires the delivery of cholesterol to the inner mitochondrial membrane, in order to convert mitochondrial cholesterol to pregnenolone by CYP_{scc} (Tuckey et al., 2004).

The mitochondrial membranes may be the site of toxic effects of lipophilic pesticides. Because the mitochondria is a ROS source and is an organelle enriched with polyunsaturated fatty acids, the impairment of the mitochondrial function may increase ROS production and lipoperoxides. Some pesticides directly affect the mitochondrial electron transfer chain, which leads to a further increased formation of damaging ROS and nitrogen free radicals (Gomez et al., 2007). The effects of OP (parathion, dichlorvos) and OC (dieldrin and DDE) on the mitochondrial function have been studied in diverse experimental systems, and have identified ROS generation and the inhibition of the electron transport chain complexes, along with ATP-synthase and phosphate transporters, to be the primary mechanisms of action. Depending on the pesticide and concentration used, reduced mitochondrial membrane potential, decreased respiratory control and ADP/O ratio, and initiation of the apoptotic cascade have been observed (Binukumar et al., 2010; Gomez et al., 2007).

We have recently studied the citotrophoblast mitochondria (CM) and the syncytiotrophoblast mitochondria (SM) isolated from term placentas of women living in agricultural areas exposed to OP. On comparing exposed samples to unexposed ones, the complex I and

complex III activities were reduced in both CM and SM. In addition, there was less placental progesterone content (Rivero et al., unpublished results). Alterations in the phospholipid composition were also observed in SM (Vera et al., unpublished results).

3.5 Immune imbalance

The concept that maternal immunity is not in a baseline resting state and is ignorant of the antigens in the invading embryo, is somewhat counterintuitive and requires our reassessment of maternal-fetal immune interactions (Nagamatsu et al., 2010). Immune components play a crucial role during pregnancy by synthesizing and releasing many of the cytokines which contribute to gestation maintenance. Hence, abnormal activation of immune components may be associated with pregnancy complications. Related to this, it has been proposed that cytokines form a self-generating network, a minor increase in key proinflammatory cytokines may eventually invoke terminal events that trigger preterm birth (Bryant-Greenwood et al., 2009). In the early stages of pregnancy, cytokines are involved in embryo implantation, the regulation of trophoblast invasion, as well as immunoregulatory functions (Bowen et al., 2002; McEwan et al., 2009, Naruse et al., 2010, Van Mourik et al., 2009). Then, later on in pregnancy, the cytokines play a role in the initiation of labour (Bowen et al., 2002). Thus, cytokine balance is relevant during pregnancy, in the early stages during blastocyst implantation and also in placental development (Chaouat et al. 2007; Moffett & Loke 2006; Schäfer-Somi, 2003).

Despite it has been demonstrated that OP may alter the cytokine balance (Duramad et al., 2006; Oostingh et al., 2009), few studies have analyzed whether pesticides can produce cytokine imbalance locally at the placenta. Saulsbury et al. (2008) showed that incubation of the JAR trophoblast cell line with chlorpyrifos induces the transcription of the transforming necrosis factor alpha (TNF α). Results from our laboratory also indicate that the incubation of JEG-3 cells with chlorpyrifos or phosmet induces the production of TNF α , mRNA and protein (Guiñazú et al, unpublished observations).

Only limited information is available regarding the production of IL-13 by gestational tissues. Low levels of IL-13 mRNA have been detected in first trimester chorionic villi (Bennett et al., 1999; Dealtry et al., 1998). In addition, IL-13 mRNA has also been identified in placental trophoblasts at all stages of gestation, whereas IL-13 immunoreactivity within the placenta was restricted to between 16 and 27 weeks (Williams et al., 2000). Increased levels of IL-13 have been identified as the dominant effector cytokine of fibrosis in several experimental models of fibrosis (Wynn, 2008). Moreover, results from our laboratory suggest that maternal environmental exposure to OP may regulate cytokine synthesis in the placenta, since the expression of IL-13 mRNA was only found in placentas from women living in rural areas where these pesticides are intensively applied (Bulgaroni et al., unpublished results). Concerning OC exposure, increased placental *p,p'*-DDE was associated with a significant increase in the cord plasma IL-13. Furthermore, both the cord plasma IL-4/ IFN- γ and IL-13/IFN- γ ratios were significantly positively associated with the placental *p,p'*-DDE concentration (Brooks et al, 2007).

3.6 Alterations in the cholinergic system

Although the placenta is a tissue without innervations, it contains all the components of the cholinergic system. Koshakji et al. (1974) demonstrated that placental acetylcholine (ACh)

varies with gestational age, reaching a peak at 20-22 weeks of gestation and declining toward term. This developmental pattern is paralleled by the activity of choline acetyltransferase (ChAT), suggesting that the placental cholinergic system may be involved in regulating the developmental processes relevant to placental growth. Multiple muscarinic receptor (mAChR) subtypes and all subtypes of the nicotinic receptor (nAChR) α subunit are present in the placenta (Bhuiyan et al., 2006; Lips et al., 2005), with ACh appearing to be an important placental signaling molecule that, through the stimulation of nAChR, controls the uptake of nutrients, blood flow and fluid volume in the placental vessels, and also vascularisation during placental development. As placenta ChAT expression overlaps that of eNOS (endothelial nitric oxide synthase), it has been hypothesized that the locally produced ACh may stimulate eNOS via a Ca^{2+} -dependent mechanism. Studies using the trophoblast BeWo cell line have provided evidence that ACh acts via mAChR on the trophoblast cell membrane to modulate NO (nitric oxide) in an estrogen-dependent manner (Bhuiyan et al., 2006). The expression of mAChR receptor in placenta showed a decrease after OP exposure in rats (González-García et al., 2006), suggesting that the related placental cholinergic functions might be affected (Table 2).

| Level of effect | Human OP environmental exposure | Rat OP exposure (sublethal doses) |
|-----------------|---|--|
| Molecular | Up-regulation of the AChE expression | Down regulation of mAChR expression |
| Biochemical | Increased AChE activity | Decrease AChE activity |
| Morphological | Increased placental maturity index and deposition of fibrinoid material Atypical villi | Trophoblast degenerated cells Extensive areas of fibrosis |

Table 2. Molecular and biochemical effects on the cholinergic system and morphological changes in placenta associated with human and experimental OP exposure.

The AChE is active in the syncytiotrophoblast, cytotrophoblast cells, endothelial cells and the media of fetal blood vessels of the human placenta (Hahn et al., 1993). As cited above, AChE inhibition is associated with OP and also with carbamate pesticide exposure (Gil & Pla, 2001). However, differential effects on AChE placental activity have been observed (Table 2). A single cutaneous dose of OP decreased placental AChE activity in rats (Abu-Qare & Abou-Donia, 2001) whereas when the activity of placental AChE in residents of rural communities exposed to OP was studied, the average AChE activity obtained in placentas collected during the pulverization season was significantly higher than in those collected during the non-pulverization period (Souza et al., 2005). This latter result was later confirmed in two biomonitoring assays performed in our laboratory in subsequent years on the same population. We postulate that as a consequence of the transient elevation of ACh levels produced by AChE inhibition, the expression of genes located in the “cholinergic locus” may be stimulated. In fact, an up-regulation of the AChE expression was detected in some of the samples analyzed (Vera et al., unpublished results).

In summary, the above findings demonstrate that the placental cholinergic system is a sensitive target of OP exposure, with potential consequences on the placenta development and function.

3.7 Alterations in placental morphology

Placental morphology was studied in pregnant rats exposed orally to the OP methylparathion (technical formulation) in *ad libitum* fed and restricted diet animals. The main effects of methylparathion treatment were an increase in the vascular congestion at the labyrinth area, a remarkable internalization of material by trophoblast giant cells of the junctional area, an increase in the population of decidual and trophoblast degenerated cells, more extensive areas of fibrosis and haemorrhage in the decidua, and the persistence of nucleated red cells in the fetal circulation. There was also a rise in the number of phagosomic vacuoles per cell in rats exposed to methylparathion, with the authors suggesting that the increased phagocytosis may have been a consequence of the clearance of dead and degenerated cells (Levario-Carrillo et al., 2004). Interestingly, these authors also reported that the placentas of women environmentally exposed to methylparathion showed microinfarctions, microcalcifications and an increased deposition of fibrinoid material, along with a larger proportion of atypical characteristics of villi, such as bullous and balloon-like formations with non-homogeneous surfaces and other areas devoid of microvilli (Levario Carrillo et al., 2001).

Placental maturity is characterized by an increase in the number of terminal villi, a reduction in the thickness of epithelial plates and the development of blood vessels. However, placental maturation involves metabolic and endocrine processes that are still poorly understood. Acosta-Maldonado et al. (2009) performed a morphometric analysis on placentas derived from women living in rural areas exposed to anti-cholinesterasic pesticides. The placenta maturity index (PMI) was calculated by dividing the number of epithelial plates by their thickness in mm² of the placental parenchyma. In the full-term placentas of women not exposed to pesticides, the PMI was similar in both regions, despite the fact that the development of the capillaries and sinusoids was greater in the central area. However, in placentas from women exposed to pesticides, the PMI was greater in the central region than in peripheral areas. These results suggest that exposure to pesticides may affect the homogeneity of the maturity of the placental tissue. Although the mechanisms underlying the effect of pesticides on maturity of placental tissue in a region-dependent manner are not known at present, it has been suggested that the ACh concentration may be related to the development of the terminal villi and/or blood vessels, and in this way plays a role in the maturity of the placenta. Therefore, disruption of the cholinergic system might precede the observed morphological alterations (Table 2).

3.8 Challenges and future directions

Microarray technology and bioinformatics can reveal changes in gene expression profiling simultaneously across thousand of genes. This provides expression profiles that can be used to predict outcomes and thus helps to elucidate the mechanisms of toxicity. The agreement between *in vivo* observations and gene expression findings demonstrates the ability of genomics to accurately categorize chemicals, identify toxic mechanisms of action, and predict subsequent pathological responses (Martin et al., 2007), as well as identifying unexpected molecular targets. Information about gene expression arrays can be complemented by metabolomics (which may reveal target and off-target toxicities) and proteomics (a research field currently undergoing rapid development, involving the analysis of protein level alterations, and post-translational modifications and function). The

main advantage of using these technologies derives from the global approach to understanding the mechanisms involved in toxicology, with these techniques being able to characterize not only novel chemicals but also complex mixtures. However, both are costly and the interpretation and application of the findings requires adequate databases in order to define the range of genes affected by chemicals and those indicative of critical health effects. In this sense, a comparative toxicogenomic data base was recently developed as a tool to investigate the impact of environmental chemicals on human health (Davis et al., 2009). Moreover, novel chemical-protein associations which had not been previously predicted may now be obtained (Audouze et al., 2010).

Because of the central role that the placenta has in fetal and maternal physiology and development, there is the possibility that variations in placental gene expression patterns might be linked to important abnormalities in maternal or fetal health, or even to effects in later life. DNA microarray analyses of gene expression patterns in samples of amnion, chorion, umbilical cord, and sections of villus parenchyma from human placentas of healthy pregnancies have revealed a rich and diverse picture of molecular variation in the placenta, with interindividual differences in the expression patterns of villous parenchyma and systematic differences among the maternal, fetal, and intermediate layers being found (Sood et al., 2006). Although the effects of several environmental toxicants on gene expression have been investigated in human full-term placentas (Huuskonen et al., 2008), there is still a lack of information about pesticide effects on gene expression patterns, metabolites and protein levels.

4. Conclusions

The placenta is a target organ for toxicity originating from persistent and rapidly metabolized and excreted pesticides. The above findings strengthen the view that pesticide-induced damage in the placenta may contribute to the occurrence of reproductive and developmental adverse effects in humans. Endocrine disruption is one of the most established and identified mechanisms, which possibly underlies deleterious OC reproductive effects, whereas the cholinergic system is a sensitive and specific target of OP effects. In addition, oxidative stress is a complex phenomenon that needs to be studied in order to evaluate how pesticides might interfere with human reproduction. As humans are exposed to multiple pesticides, the understanding of the molecular events associated with pesticide exposure is particularly complex. Microarray technology may help to elucidate the mechanisms of mixture toxicity and thus provide the basis for defining new prevention and treatment strategies in order to improve reproductive outcomes.

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This book contains the total of 19 chapters, each of which is written by one or several experts in the corresponding field. The objective of this book is to provide a comprehensive and most updated overview of the human placenta, including current advances and future directions in the early detection, recognition, and management of placental abnormalities as well as the most common placental structure and functions, abnormalities, toxicology, infections, and pathologies. It also includes a highly controversial topic, therapeutic applications of the human placenta. A collection of articles presented by active investigators provides a clear update in the area of placental research for medical students, nurse practitioners, practicing clinicians, and biomedical researchers in the fields of obstetrics, pediatrics, family practice, genetics, and others who may be interested in human placentas.

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