Reproductive BioMedicine Online (2014) **29**, 17–31

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REVIEW

Environmental pollutants and lifestyle factors induce oxidative stress and poor prenatal development

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Dr Kaïs H Al-Gubory is a senior scientist. During his 33-year career at the French National Institute for Agricultural Research, he developed his research in different units: physiology of lactation, animal physiology, endocrinology and embryonic development, developmental biology and reproduction. His research lies in understanding ovarian, luteal, uterine and placental physiology during pregnancy. He is engaged in the development and use of experimental surgery, animal models and live-cell imaging technology. Currently, his major research interest includes maternal environment and peri-implantation development, antioxidants and free radical biology, roles of antioxidants in prenatal developmental outcomes and fertility and peri-conception antioxidants nutritional therapies.

Abstract Developmental toxicity caused by exposure to a mixture of environmental pollutants has become a major health concern. Human-made chemicals, including xenoestrogens, pesticides and heavy metals, as well as unhealthy lifestyle behaviours, mainly tobacco smoking, alcohol consumption and medical drug abuse, are major factors that adversely influence prenatal development and increase susceptibility of offspring to diseases. There is evidence to suggest that the developmental toxicological mechanisms of chemicals and lifestyle factors involve the generation of reactive oxygen species (ROS) and cellular oxidative damage. Overproduction of ROS induces oxidative stress, a state where increased ROS generation overwhelms antioxidant protection and subsequently leads to oxidative damage of cellular macromolecules. Data on the involvement of oxidative stress in the mechanism of developmental toxicity following exposure to environmental pollutants are reviewed in an attempt to provide an updated basis for future studies on the toxic effect of such pollutants, particularly the notion of increased risk for developmental toxicity due to combined and cumulative exposure to various environmental pollutants. The aims of such studies are to better understand the mechanisms by which environmental pollutants adversely affect conceptus development and to elucidate the impact of cumulative exposures to multiple pollutants on post-natal development and health outcomes.

KEYWORDS: environmental pollutants, health outcomes, oxidative stress, prenatal development, reactive oxygen species, unhealthy lifestyle behaviour

http://dx.doi.org/10.1016/j.rbmo.2014.03.002
1472-6483/

Introduction

Humans and wild and domestic animals are exposed to complex mixtures of various organic and inorganic environmental pollutants. Aquatic habitats throughout the world receive a great amount of pollutants due to industrial and agricultural activities as well as human and agricultural livestock waste inputs (Burkholder et al., 2007; Valavanidis et al., 2006). Many hazardous man-made chemicals have been voluntarily and involuntarily released into the environment and thus exposure of humans and wildlife to such pollutants has become inevitable. Industrial discharge, agricultural runoff, human and animal waste, municipal and domestic effluents, spillage of vessels and oil spill are the major sources of river, sea and ocean pollution. Exposure to various environmental pollutants may be difficult to avoid due to their ubiquitous occurrence in air, water, soil, vegetables, food, industrial and domestic products, plastic products, cosmetics and medication.

Epidemiological evidence indicates that prenatal and/or early life exposure to various environmental pollutants adversely affects conceptus (embryo/fetus and associated membranes) development and neonate health (Wigle et al., 2008). In reality, the conceptus, irrespective of maternal exposure pathways, is exposed *in utero* to multiple environmental pollutants during pregnancy that could adversely affect implantation and the developmental trajectory in a cumulative dose-additive manner (Rider et al., 2010). The main recognized disorders and complications linked to such exposure are embryonic mortality, fetal loss, intrauterine growth restriction, preterm birth, birth defects, childhood diseases, neuropsychological deficits, premature or delayed sexual maturation and certain adult cancers (Wigle et al., 2008). Developmental toxicity during pregnancy caused by various environmental pollutants has therefore become a major health concern.

Humans and animals are potentially exposed to a mixture of environmental pollutants that act on one or more organs through different and/or similar mechanisms of action. Endocrine disruptors that act by disparate mechanisms of toxicity to disrupt the dynamic hormone-dependent signalling pathways in differentiating tissues have been shown to produce cumulative dose-additive effects, regardless of the mechanism or mode of action of the individual mixture component (Rider et al., 2012). Multicomponent mixtures of endocrine-disturbing chemicals act as hormone mimics or antagonists, leading to disruption of oestrogen, androgen and other hormonal pathways (Kortenkamp, 2007). The toxicity of the combination of endocrine disruptors results from an antagonist mode of action of these chemicals, due to competitive ligand binding on oestrogen receptors (Li et al., 2012). Furthermore, one of the important mechanisms of action of environmental chemicals may involve reactive oxygen species (ROS)-induced oxidative stress (Luo et al., 2010; Ruder et al., 2008; Wells et al., 2009). Imbalance between ROS production and antioxidant ROS detoxification pathways is considered to be responsible for pregnancy-related disorders, such as embryonic mortality, early spontaneous abortion, intrauterine growth restriction, fetal death, premature delivery and low birthweight (Agarwal et al., 2012; Al-Gubory et al., 2010).

The susceptibility of the conceptus to developmental disturbances induced by environmental pollutants is related to the stage of development, the duration of exposition and the cumulative exposure dose. This might be pivotal in embryonic and fetal vulnerability towards toxicity of environmental contaminants. A weak antioxidant defence system renders the developing conceptus vulnerable to oxidative damage induced by *in utero* exposure to environmental contaminates. Indeed, antioxidant enzymes and detoxification pathways are not fully developed in the conceptus early in pregnancy (Al-Gubory and Garrel, 2012; Davis and Auten, 2010). Therefore, the association between environmental pollutants, oxidative stress and adverse prenatal development constitute a topic of interest in the field of reproductive medicine and fertility. This review focuses on the putative association between oxidative stress and adverse prenatal development caused by man-made chemicals and unhealthy lifestyle behaviours, particularly the notion of increased risk for developmental toxicity due to combined and cumulative exposure to various environmental pollutants.

ROS and oxidative stress

The generation of mitochondrial superoxide radical ($^{\bullet}O_2^-$) is the first step in the formation and propagation of other ROS within cells and tissues. The production of $^{\bullet}O_2^-$ occurs during the passage of electrons through the mitochondrial electron transport system during oxidative phosphorylation. The free radical $^{\bullet}O_2^-$ is catalysed to hydrogen peroxide (H_2O_2) which in turn can be further catalysed to H_2O and O_2 (McCord and Fridovich, 1969). However, unconverted $^{\bullet}O_2^-$ and H_2O_2 interact with each other via the iron-catalysed Haber–Weiss reaction to generate the hydroxyl radical ($^{\bullet}OH$). The free radical nitric oxide ($^{\bullet}NO$), generated from L-arginine in a reaction catalysed by $^{\bullet}NO$ synthases may also react with $^{\bullet}O_2^-$ to produce peroxynitrite ($ONOO^-$). This is a powerful oxidant that can react with amino acids and alter the structure and function of proteins (Alvarez and Radi, 2003). Mitochondria are endowed with $^{\bullet}NO$ synthase and are a source of cellular $^{\bullet}NO$ and $ONOO^-$ production (Valdez and Boveris, 2007). Cellular $ONOO^-$ produced in response to physiological stress and environmental toxicants triggers oxidative DNA damage and apoptosis (Ahmad et al., 2009). ROS are also produced by various enzymic pathways, including membrane-bound NADPH oxidase, xanthine oxidase, the metabolism of arachidonic acid and the mitochondrial cytochrome P450 (Bedard and Krause, 2007; Zangar et al., 2004). In addition, ROS are generated in response to environmental chemicals (Lehnert and Iyer, 2002) and during transformation of xenobiotics and drugs, UV irradiation and inflammation (Jezek and Hlavatá, 2005). The cellular antioxidative mechanism requires therefore a tight control of $^{\bullet}O_2^-$ and H_2O_2 production before their transformation to highly reactive ROS, mainly $ONOO^-$ and $^{\bullet}OH$. Physiological concentrations of $^{\bullet}O_2^-$ and H_2O_2 play important roles in cellular regulation through signal transduction pathways and gene expression involved in cell metabolism, growth, development and differentiation (Dennery, 2007; Valko et al., 2007). In contrast, ROS overproduction induces oxidative stress, a state where increased ROS generation overwhelms