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Review

Mechanism of deoxynivalenol effects on the reproductive system and fetus malformation: Current status and future challenges

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ABSTRACT

Deoxynivalenol (DON) is a toxic fungal secondary metabolite produced by molds of the *Fusarium* genus, and it is known to cause a spectrum of diseases both in humans and animals, such as emesis, diarrhea, anorexia, immunotoxicity, hematological disorders, impairment of maternal reproduction, and fetal development. The recently revealed teratogenic potential of DON has received much attention. In various animal models, it has been shown that DON led to skeletal deformities of the fetus. However, the underlying mechanisms are not yet fully understood, and toxicological data are also scarce. Several animal research studies highlight the potential link between morphological abnormalities and changes of autophagy in the reproductive system. Because autophagy is involved in fetal development, maintenance of placental function, and bone remodeling, this mechanism has become a high priority for future research. The general aim of the present review is to deliver a comprehensive overview of the current state of knowledge of DON-induced reproductive toxicity in different animal models and to provide some prospective ideas for further research. The focus of the current review is to summarize toxic and negative effects of DON exposure on the reproductive system and the potential underlying molecular mechanisms in various animal models.

Contents

Abbreviations: 3β-HSD, 3β-hydroxysteroid dehydrogenase/isomer; 4E-BP1, 4E binding protein, eIF4E repressor protein; Col9A2, alpha 2 (IX) collagen; COCs, cumulus oocyte complexes; DHEA, dehydroepiandrosterone; DON (DNV), Deoxynivalenol; eIF-4E, eukaryotic initiation factor 4E; FBN1, fibrillin-1; IGF, insulin-like growth factor; IPEC-J2, porcine intestinal epithelial cells; IUGR, intrauterine growth retardation; JECFA, Joint FAO/WHO Expert Committee on Food Additives; MAPKs, Mitogen-activated protein kinases; MDA, Malondialdehyde; MFS, Marfan syndrome; OAT, organic anion transporter; OB, osteoblasts; OC, osteoclast; OCT, and organic cation transporter; PAPSS2, 3′-phosphoadenosine 5′-phosphosulfate synthase 2; Pax1, paired box1; PCNA, proliferating cell nuclear antigen; PDB, Paget Disease of Bone; PMTDI, provisional maximum tolerable daily intake; PTHLH, parathyroid hormone-like hormone; P450SCC, P450 cholesterol side-chain cleavage enzyme; RANKL, receptor activator of nuclear factor *k*B ligand; RUNX2, Runt-related transcription factor 2; UBA, ubiquitin associated.

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1. Introduction

Food contamination caused by natural toxins, especially mycotoxins, is a significant problem for agricultural and food industries worldwide. Deoxynivalenol (DON) belongs to the type B trichothecenes, which are the most common mycotoxins in cereal commodities (Fig. 1). This mycotoxin is mainly produced by *Fusarium graminearum*, *Fusarium culmorum*, and *Fusarium crookwellense*.

DON mainly affects animals and humans by causing vomiting, digestive disorders, oxidative damage, and reproductive toxicity (Berthiller et al., 2011). At the molecular level, DON is observed to inhibit DNA, RNA, and protein synthesis (Bony et al., 2006; Hassan et al., 2015; Payros et al., 2016). Numerous studies demonstrate that ribosomes in cytosol and autophagy are major targets (Bae et al., 2010; Berthiller et al., 2011; Di and Tumer, 2005; Pestka, 2008). To reduce the risk of DON-induced toxicity, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) set a limit of provisional maximum tolerable daily intake (PMTDI) of DON at 1 μg/kg body weight/day (JECFA, 2010).

The mycotoxin DON is implicated in reduced reproductive performance in different animal models by both impairing oocyte maturation and embryo development and by reducing feed intake. An example of this was shown by Côté et al., who systematically observed DON-induced reproductive problems and reduced growth performance of pigs fed by DON-contaminated rations (DON concentration ranging from 0.1 to 41.6 ppm, mean: 3.1 ppm) in Illinois and neighboring states (Cote et al., 1984). Díaz-Llano et al. also demonstrated that DON caused longer estrus intervals and increased the incidence of stillbirth in pigs fed contaminated diets (Diaz-Llano and Smith, 2006, 2007). The no-observed-effect level for fetal toxicity in the rat is 1 mg/kg compared with the general reduction in fetal development at 2.5 and 5 mg/kg (Collins et al., 2006), and DON is considered a teratogen at 5 mg/kg/day in Sprague-Dawley rats due to the anomalous development of the sternebrae (Collins et al., 2006). In other studies, including male animals, IL-6-KO (B6129-IL6 [tmlKopf, IL-6 gene deficient]) and B6C3F1 DON-treated mice revealed significantly reduced cauda epididymal weights and an increased germ cell degeneration as well as high sperm retention rates; in addition, abnormal nuclear morphology was observed in Sprague-Dawley rats (Sprando et al., 2005; Sprando et al., 1999). However, there were no observations of treatment-related histologic abnormalities in testes or ovaries from male and female Sprague-Dawley rats fed with purified DON (20 ppm) for 15 and 60 days (Morrissey and Vesonder, 1985). At the same time, low levels of DON (0–5 ppm) had no obvious adverse effects on the incidence of gross, skeletal, or visceral abnormalities in Fischer 344 rats (aged 15 weeks) (Morrissey, 1984).

Autophagy as the major catabolic process of eukaryotic cells degrades and recycles damaged macromolecules and organelles. Furthermore, autophagy has been shown to regulate functions and numbers of ova and spermatozoa as well as pre-implantation and post-implantation embryo development (Nollet et al., 2014; Sisti et al., 2015). Mutations in autophagic genes can cause the Yunis-Varón syndrome affecting bone remodeling, osteoclast differentiation, and mineralization of bone matrix (Campeau et al., 2013). Han et al. found that DON exposure reduced the capability of porcine oocytes to mature through affecting cytoskeletal dynamics, cell cycle, autophagy/apoptosis, and epigenetic modifications (Han et al., 2016). The regulatory axis of HIF1α-miRNA20a-Atg16L1 might play a crucial role as a mechanism for osteoclast differentiation (Sun et al., 2015). In the same line of evidence, Chung et al. also found that Beclin-1 and receptor activator of nuclear factor κB ligand (RANKL) could induce osteoclast differentiation in mouse bone marrow (Chung et al., 2014). Gong et al. also summarized potential risk factors that are linked to a dysregulation of autophagy, for example, regarding fetal growth and development during pregnancy. Autophagy is reported to be increased in placenta-related obstetrical diseases, such as preeclampsia and intrauterine growth retardation (IUGR) (Gong and Kim, 2014). To sum up the work described, autophagy and its relative signaling pathways have been shown to be involved in DON-induced miscarriage, fetal growth restrictions, and fetal malformation. More research is needed to understand the exact processes and to find possible treatment.

The aim of the following review is to summarize and discuss DON-induced problems in the reproductive system based on past and recent prominent publications. We believe that this review will provide important information for understanding the mechanism of DON-induced reproductive toxicity.

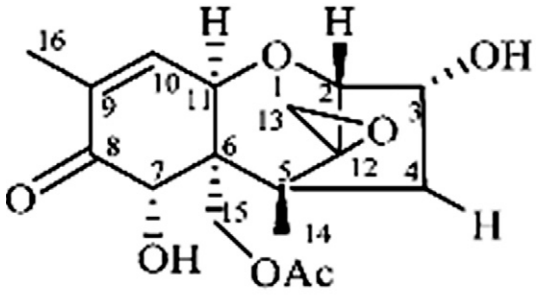
2. DON-induced toxic effects on the genital system of male and female animals

The potential for DON to act as an endocrine disruptor has been the subject of much recent and on-going research. DON has been implicated in the reproductive performance in animals of both genders because of its ability to impair oocyte maturation and embryo development (summarized in Table 1).

2.1. Effects on female and male genital systems

2.1.1. Male rodents

Sprando et al. carried out DON-induced pathological observations in male mice, and the potential effect of DON on testicular morphology and on testicular and epididymal sperm counts was assessed in 3 strains of



Deoxynivalenol (DON)

Fig. 1. The chemical structure of deoxynivalenol (DON).