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ASSESSMENT OF BENEFICIAL AND TOXIC EFFECTS OF NATURAL SUBSTANCES ON OVARIAN FUNCTIONS

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ABSTRACT

The dynamics of a stress response of the organism towards potential stressors – mycotoxins underlines the need to define limits in which animals develop a state without compromising their health and maintain a stable internal milieu. Tissue and cell cultures are of increasing interest in the evaluation of toxicological risks of toxic compounds and their possible elimination. It is for this reason the solution of the problem in the field of examining effects of the potential protective natural substances in the animal organism and their mechanism of the effect is highly relevant. Ovarian granulosa cells are sensitive to the effects of mycotoxin – trichothecenes but bioactive substances of natural origin may be important in the prevention of reproductive alterations induced by exogenous and endogenous factors.

Keywords: ovary, deoxynivalenol, resveratrol, steroidogenesis, proliferation, apoptosis

INTRODUCTION

The environmental stress is one of the main factors that change the reproductive functions (Kolesarova et., 2010a,b,c; 2011a,b; 2012). Previous reports describe the influence of beneficial (Kolesarova et al., 2011c, 2012) and toxic (Kolesarova et al., 2009; 2010a,b,c; 2011a,b; Medvedova et al., 2011) substances on porcine ovarian (GCs) focused on processes of steroidogenesis, proliferation and apoptosis in these reproductive cells (Kolesarova et al., 2009; 2010a,b,c; 2011a,b; Medvedova et al., 2011). On the other hand the bioactive substances of natural origin may be important in the prevention of reproductive alterations induced by exogenous and endogenous factors (Kolesarova et al., 2012).

Characteristic of Trichothecenes - Deoxynivalenol

Mycotoxins are natural and very stable toxins, with relatively low-molecular weight secondary metabolites of fungal origin, which can contaminate a large variety of feed mixtures (Labuda et al., 2009; Tancinova et al., 2009), grains and foodstuffs worldwide (Schollenberger et al., 2007; Ranzenigo et al., 2008). They are found in a variety of foods and beverages, including both plant-based products and animal products. Among the first ones, its presence in cereal grains (corn, wheat, barley, oats, rye, rice, etc.) and beans (coffee, cocoa, soy, etc.) are harmful to animals and humans (Abouzied et al., 1991). However, not all fungi produce mycotoxins and among the toxigenic species, some only produce one type of mycotoxin, while others are able to produce several. Cereals can be mostly contaminated by Fusarium species, a group of toxin-producing molds (Tiemann et al., 2003a,b; Larsen et al., 2004; Giraud et al., 2010).

Trichothecenes, such as deoxynivalenol (DON), are the major mycotoxins of *Fusarium species* (Larsen et al.,2004; D´Mello et al., 1999). DON ($C_{15}H_{20}O_6$; mol. wt. = 296.32) is also called Dehydronivalenol, 4-Deoxynivalenol, 4-Desoxynivalenol or Vomitoxin. DON can be acutely or

chronically toxic, or both, depending on the kind of toxin and the dose. Also, it could be rapidly absorbed after oral administration passively throughout the gastrointestinal tract and actively in the kidneys (Marquardt and Frohlich, 1992), liver, muscle, adipose tissue (Gareis et al., 2000) and reproductive tissues (Ranzenigo et al., 2008). Major *Fusarium* mycotoxin, DON, negatively influences the establishment of pregnancy in pigs in part because of its ability to inhibit oocyte maturation (Alm et al., 2002; 2006). Thus, mycotoxin exposure that alters granulosa cells and steroid hormone production may also alter oocyte development (Alm et al., 2002), ovulation (Kumagai et al., 1982), reproductive functions and pregnancy outcome (D´Mello et al., 1999; Alm et al., 2002).

Mechanism of the effect of Trichothecenes - Deoxynivalenol

Trichothecene toxicity at the cellular level is characterized by inhibited protein synthesis (Rotter et al., 1994), impairment of membrane functions, altered intercellular communication and deregulation of calcium homeostasis (Pestka and Smolinski 2005). Trichothecenes not only bind eukaryotic ribosomes and interfere with translation (Ueno 1983), but also activate intracellular protein kinases that both mediate selective gene expression and apoptosis, ultimately contributing to downstream pathologic sequelae (Pestka et al., 2004). Moreover, it has been demonstrated that trichothecenes rapidly activate mitogen-activated protein kinase (MAPK) which modulates physiological processes including cell growth, differentiation and apoptosis (Kouadio et al., 2007 , Marzocco et al., 2009; Luongo et al., 2010). In addition to inhibiting translation, trichothecenes can simultaneously activate p38, Jun N-terminal Kinase (JNK) and extracellular signal-regulated kinase (ERK), MAPK *in vitro* and *in vivo* (Chung et al., 2003; Moon and Pestka, 2003; Moon et al., 2003; Yang et al., 2000; Zhou et al., 2003a,b, 2005a,b) via a process referred to as ‘‘ribotoxic stress’’ (Iordanov et al., 1997). Oxidative stress is certainly involved in the toxicities of trichothecene mycotoxins (El Golli et al., 2006). Oxidative stress in the form of *r*eactive oxygen species (ROS) generation or disruption of the redox balance in the cell not only induces apoptosis but also involved in cell proliferation and signalling (Martindale and Holbrook, 2002).) Oxidative stress is the underlying mechanism by which trichotecene causes DNA damage and apoptosis v. At the cellular level, DON induces ribotoxic stress thereby disrupting macromolecule synthesis, cell signaling, differentiation, proliferation, and death (Pestka, 2010).

Trichothecenes affect ovarian functions

Secretory activity: The influence of mycotoxin - DON on secretory activity was detected by Medvedova et al. (2011) and Kolesarova et al. (2012). Dose-response of DON on ovarian granulosa cells was examined in these studies. Isolated ovarian GCs were able to survive in culture and release hormonal substances insulin-like growth factor I (IGF-I) and progesterone after experimental DON addition at the doses 10, 100 and 100 ng/ml. These data confirm previous reports concerning the influence of toxic substances on porcine cellular processes (Ranzenigo et al., 2008; Kolesarova et al., 2009, 2010a,b,c,d; 2011a,b). The effect of DON in relation to IGF-I release by ovarian granulosa cells have been examined previously by Ranzenigo et al. (2008) but the time of cell culture with mycotoxin application lasted 2 days and in the study of Medvedova et al. (2011) it was 24 h. DON had inhibitory effects on IGF-I –induced steroid production and decreased cell numbers at the dose of 1000 ng/ml (Ranzenigo et al., 2008). Medvedova et al. (2011) have shown that the mycotoxin DON decreased IGF-I secretion by cultured GCs at a dose of 1000 ng/ml but it was not affected by the doses of 10 ng/ml and 100 ng/ml. Ranzenigo et al. (2008) have demonstrated inhibited progesterone production induced by FSH plus IGF-I at the doses 100 ng/ml (0.337 μM) and 1000 ng/ml (0.37 μM) of DON. In the study of Medvedova et al. (2011) visible mitosis of GCs after 24 h DON effect at the dose of 10 ng/ml was observed. Progesterone release was stimulated by DON at the dose 1000 ng/ml but not at 10 and 100 ng/ml. (Medvedova et al., 2011). Similarly progesterone release was stimulated by toxic doses of DON (2000, 3000 and 5000 ng/ml) used in the experiment (Kolesarova et al., 2012). The effect of the DON was found to be concentration dependent as it was described in previous study (Ranzenigo et al., 2008; Medvedova et al., 2011; Kolesarova et al., 2012).

Proliferation and apoptosis: Expressions of proliferation (cyclin B1 and PCNA)- associated peptides were stimulated by DON (Medvedova et al., 2011). Analyses of porcine endometrial cells cultivated (for 24h) with different doses of DON were done by Tiemann (2003a). These results point out to significant decrease of proliferation at the concentrations of 1.88 µM and 3.76 µM of DON. These authors also observed expression of PCNA protein, which significantly decreased at the doses of 1.88 µM (for 24h) and 0.94 µM (for 48h) of DON. In the study of Medvedova et al. (2011) expression of cyclin B1 was stimulated by DON (at 1000 ng/ml but not at 10 and 100 ng/ml). Similarly PCNA expression was stimulated by DON (at 100 and 1000 ng/ml but not at 10 ng/ml). On the other hand caspase-3 expression was not influenced by DON treatment (at doses 10, 100 and 1000 ng/ml) (Medvedova et al., 2011).

Conclusion: Porcine ovarian GCs are sensitive to the effects of mycotoxin - trichothecenes. The results indicate, (1) a direct effect of DON on secretion of hormones, (2) expression of markers of proliferation (cyclin B1 and PCNA) but not (3) expression of marker of apoptosis (caspase-3) in porcine ovarian granulosa cells. This in vitro study suggests the dose-dependent association of DON on porcine ovarian functions (Medvedova et al., 2011).

Characteristic of Phytoalexins- Resveratrol

Phytoalexins are antimicrobial substances under natural conditions not found in plants. Their creation occurs in plants attacked by pathogens (Dixon and Paiva, 1995). Resveratrol (RSV, 3,5,4´-trihydroxystilbene) was the first isolated from the roots of white hellebore (Veratrum grandiflorum O. Loes) in 1940 (Takaoka, 2006) and later in 1963, from the roots of (Polygonum cuspidatum) a plant used in traditional Chinese and Japanese medicine (Nonomura et al., 1963). It is a natural polyphenol widely present in plants and in particular in the skin of red grapes and in wine, resveratrol antioxidant properties have been well demonstrated, with a wide range of biological effects (Karuppagounder et al., 2009). It is beneficial against diverse cardiac diseases including ischemic heart disease, hypertrophy, heart failure, atherosclerosis, hypertension, diabetes and obesity (Bertelli and Das, 2009; Mukherjee et al., 2009). Resveratrol is well known for its phytoestrogenic, antioxidant properties, growth-inhibitory and apoptosis-inducing activities (Joe et al., 2002; Jiang et al., 2005; Baur and Sinclair, 2006). It also has protective role in endothelial cells by modulating mitochondrial oxidative stress (Ungvari et al., 2009).

Mechanism of the effect of Phytoalexins- Resveratrol

Resveratrol is able to inhibit PI3K/Akt Protein Kinase/ mammalian target of rapamycin (PI3K/Akt/mTOR) pathway in various types of cells (Jiang et al., 2005). It inhibits proliferation and induces apoptosis in cells at different levels (Ferry-Dumazet et al, 2002, Haider et al, 2003). Resveratrol can alter a variety of genes thereby changing the ‘‘death signal’’ into a ‘‘survival signal’’ (Das and Maulik, 2004). Svechnikov et al. (2009) present investigation has demonstrated that resveratrol and its analogues structure-dependently attenuated steroidogenesis in Leydig cells through suppression of the expression of StAR and cytochrome P450c17.

Phytoalexins affect ovarian functions

Secretory activity: Stimulatory effect of RSV on progesterone release by GCs was recorded after resveratrol treatment at the dose of 50 µg/ml, while doses of 30 and 10 µg/mL did not affect the release of the steroid hormone (Kolesarova et al., 2012). RSV in combination with DON at the highest doses (50 µg/ml of RSV and 5000 ng/ml of DON) stimulated progesterone release by GCs. Stimulatory effect of alone DON on the progesterone release by GCs was lower in comparison with RSV in combination with DON (Kolesarova et al., 2012). The effect of the DON (Medvedova et al., 2011; Ranzenigo et al., 2008) and DON combined with resveratrol (Kolesarova et al., 2012) was found to be concentration dependent.

Conclusion: The results of Kolesarova et al. (2012a) indicate, (1) the dose-depended stimulatory effects of RSV, DON and combination of RSV with DON on release of steroid hormone progesterone and (2) reduction of the stimulatory effect of DON by RSV. The in vitro results suggest that reproductive toxicity of animals induced by mycotoxin - deoxynivalenol can be inhibited by protective natural substance – resveratrol.

Conclusion

In conclusion, it is important to highlight that the impact of fungal toxins upon animals extends beyond their clinical features. Despite the ever-increasing understanding of mycotoxins, they still have a continuous and severe economic impact worldwide (Marquardt, 1996; Hussein and Brasel, 2001). Although acute ingestion of high levels of mycotoxins can be very harmful to the animal, long term consumption of low concentrations of mycotoxins can also be damaging. There are several ways of reducing mycotoxin concentrations both pre and post-harvest, including the addition of feed additives such as, but not limited to, natural clays, yeasts, and enzymes. Since mycotoxins can be so detrimental to swine industry, further determination of sustainable way to combat the global mycotoxin problem is important for maintaining animal health, as well as reducing economic impacts on farmers and producers (Chaytor et al., 2011). Tissue and cell cultures are of increasing interest in the evaluation of toxicological risks of contaminated compounds and their possible elimination. It is for this reason the solution of the problem in the field of examining effects of the potential protective natural substances in the animal organism and their mechanism of the effect is highly relevant.

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