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A REVIEW

INTRACELLULAR MECHANISMS OF A-TRICHOTHECENES INVOLVED IN THE REGULATION OF CELL SURVIVAL AND APOPTOSIS: A REVIEW

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ABSTRACT

Mycotoxins are secondary metabolites produced by filamentous fungi. Mycotoxins are worldwide contaminats of animal feed, food and food products. T-2 toxin and its metabolit HT-2 toxin are one of the most toxic mycotoxins of type A trichothecenes, which are produced mainly by *Fusarium* species. T-2 and HT-2 toxin cause a different toxic effects in both animal and human. They are inhibitors of DNA and RNA synthesis and synthesis of proteins in several cellular systems, immunosuppressive agents, induce lesions in hematopoetic, lymphoid and digestive tract, impact reproduction functions and cause oxidative stress. T-2 toxin is a strong cytotoxic mycotoxin, which can induce apoptosis of various cells. This review examine the T-2 toxin induce cytotoxicity up to apoptosis on various cells, for instance cells of imunite system, on ovarian granulosa cells as well as induction of maternal and fetal toxicity.

Keywords: mycotoxins, A-trichothecenes, cytotoxicity, apoptosis.

INTRODUCTION

Mycotoxins are secondary metabolites produced by moulds that contaminate a large variety of grains and feedstuffs worldwide **(Schollenberger *et al*., 2007).** Contamination of feeds and feed ingredients with trichothecene mycotoxins is a major problem in livestock production worldwide **(Binder *et al*., 2007).** Some of the well characterized fungal secondary metabolites, such as growth regulators, antibiotics and mycotoxins, are known to affect plant and animal cellular functions **(Yu and Keller 2005).** Despite the fact that they are produced by the same fungal species, the various fusarial toxins might involve different signaling pathways of cytotoxicity and apoptosis. Apoptosis is a tightly regulated cell death program, which plays an essential role during the development and homeostasis of most organisms **(Wyllie, 1997).** Trichothecenes are cytotoxic compounds that have multiple inhibitory effects on eukaryotic cells **(Rocha *et al*., 2005)** like inhibition of protein, DNA and RNA synthesis **(Ji *et al*., 1994).**

Trichothecenes – T-2 toxin

Trichothecenes are mycotoxins produced by many fungi such as *Fusarium, Myrothecium*, *Stachybotrys* and others. They comprise a large group of closely related compounds designated as sesquiterpenoids, which have a tricycled skeleton composed of cyclohexen, cyclopentane, and 6-membered oxyrane rings **(Vidal *et al.,* 1985)**. T-2 toxin is the most toxic trichothecene and deoxynivalenol (DON, vomitoxin) is the most prevalent world wide in crops used for food and feed production **(Hymery *et al*., 2006).** In acute tests with trichothecenes, type A members such as diacetoxyscirpenol (DAS) and T-2 toxin have been found to be more toxic than type B components such as DON and nivalenol (NIV) **(Leeson *et al.,* 1995**). The toxicity of trichothecene mycotoxins varies significantly and is determined by their molecular structures, particularly, toxic functional groups **(Betina, 1989; Nagy *et al*., 2005).** T-2 toxin is the most commonly occurring type-A trichothecene, produced predominantly by *Fusarium sporotrichioides* and *F. langsethiae*, and is often found in cereal grains from Europe **(Gareis *et al*., 2003)**. The main cytotoxic effects of T-2 toxin are an inhibition of eukaryotic protein biosynthesis and apoptosis. Besides this fact, an inhibition of the DNA and RNA synthesis and toxic effects on the cell membrane and cell proliferation could be observed in several cell lines **(Dugyala *et al*., 1994; Lautraite *et al*., 1995; Parent-Massin, 2004).**

Trichothecenes (T-2 toxin) - induced cell stress and apoptosis

Trichothecene toxicity at the cellular level is characterized by inhibited protein synthesis, 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)** and **(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) mitogen-activated protein kinases (MAPKs) *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)**. Studies have shown that oxidative stress is certainly involved in the toxicities of trichothecene mycotoxins including T-2 toxin **(El Golli *et al.,* 2006).** Oxidative stress in the form of reactive oxygen species ROS generation or disruption of the redox balance in the cell not only induces apoptosis but also involved in cell proliferation and signaling **(Martindale and Holbrook, 2002)**. **Chaudhari *et al*., (2009)** showed in their study that oxidative stress is the underlying mechanism by which T-2 toxin causes DNA damage and apoptosis. Similarly, **Rizzo *et al*., (1994)** indicate in their study the involvement of oxidative stress and activation of various signaling pathways such as MAP kinases and caspases have been shown in T-2 toxin induced apoptosis *in vitro.* It is also said that activation of caspase-2 is essential to T-2 toxin-induced apoptosis and that apoptotic signals are mainly transmitted *via* caspase-8 and caspase-3 rather than mitochondrial pathway **(Huang *et al*., 2007).**

Apoptotic effect of T-2 toxin in various cells

Chen *et al.,* (2008) in their study detected increases in Fas, p53 and the pro-apoptotic factor Bax protein and mRNA expressions and a decrease of the anti-apoptotic factor Bcl-xL were observed in a dose-dependent manner after exposures to 1~20 $ng.ml^{-1}$ T-2 toxin, while the expression of the anti-apoptotic factor Bcl-2 was unchanged. Meanwhile, T-2 toxin could

also up-regulate the expressions of both pro-caspase-3 and caspase-3 in a dose-dependent manner. In addition **Ueno et al., (1995)** observed that T-2 toxin caused apoptosis *in vitro* in various cell types such as HL60 cells and Jurkat cells. As well as **Bondy *et al.* (1991)** showed that trichothecenes inhibit both proliferation and Ig production in human lymphocytes in a dose-dependent manner. Another authors reported that T-2 toxin induces apoptosis in lymphoid cell lines by activation of caspases (-9 and -3) **(Nagase *et al.*, 2001**). All in all, **Pestka and Smolinski, (2005)** in their studies examin that high doses of trichothecenes promote rapid onset of leukocyte apoptosis, which is manifested as immunosuppression.

Apoptotic effect of T-2 toxin on cells of ovarian system

The action of hormones and growth factors on ovarian functions is mediated via cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and probably MAPK – dependent intaracellular mechanisms **(Kolesarova *et al.*, 2009; Makarewich *et al*., 2000; Sirotkin and Grossmann, 2003, 2008**) and also by proliferation- and apoptosis related substances **(Kolesarova *et al*., 2008; Sirotkin and Grossmann, 2003, 2008).** However, the mechanism of T-2 toxin-induced apoptosis involved in the regulation of the balance between these pro- and anti-apoptotic proteins is not fully clear **(Chen *et al*., 2008)**. T-2 toxin inhibited the growth of granulosa cells in a concentration-dependent way. The result of Hoechst 33258 staining indicated that T-2 toxin induces granulosa cells apoptosis based on the typical apoptotic morphological changes. Subsequently, T-2 toxin treatment induced ROS accumulation in granulosa cells, resulting in reduction of mitochondrial transmembrane potential. The induction of cell apoptosis was caused by the upregulation of p53, Bax, Bcl-2, Bax/Bcl-2 ration, and the activation of the caspases pathways **(Wu *et al*., 2011)**.

Apoptotic effect of T-2 toxin on in maternal and fetal tissues

Oxidative stress causes lipid peroxidation and induces mitochondrial dysfunction which causes fatty acid β oxidation and induce fatty liver **(Jaeschke *et al.* 2002).** The disturbance of lipid metabolism caused by oxidative stress may occur in the maternal liver, placenta and fetal liver by T-2 toxin **(Sehata *et al*., 2005).** Increased expression of Bax-α as well as p53 was detected in maternal and fetal livers **(Sehata *et al*., 2005).** T-2 toxin readily passes through the placenta and is distributed to embryo/fetal tissues which include many component cells bearing high proliferating activity **(Lafarge-Frayssinet *et al.*, 1990).** In a

study of the mechanism of action of T-2 toxin on the liver, placenta and fetal liver, it was reported that mechanism of T-2 toxin-induced toxicity in pregnant rats is due to oxidative stress followed by the activation of the mitogen-activated protein kinase (MAPK) pathway, finally inducing apoptosis, and that the c-Jun gene was suggested to play an important role in T-2 toxin-induced apoptosis **(Sehata *et al*., 2005)**. **Ishigami *et al.* (1999)** first reported that T-2 toxin (3 $mg.kg^{-1}$) can induce apoptosis, especially in the central nervous and skeletal systems after oral administration to pregnant mice, indicating the direct cytotoxic effect of T-2 toxin on fetal tissues.

CONCLUSSION

The impact of mycotoxins on animal health and production are including incidence of disease, higher susceptibility to secondary diseases, changes in the endocrinne and neuroendocrinne functions, alterations in nutrient content, production loses (milk, meat, eggs) and economic loses, which can be reflected in costs of animal products. Currently, the study of mycotoxins and their impact on animal health is very required issue because of their frequently occurence in various agricultural commodities and feeds.

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