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Review

Dysregulation of energy balance by trichothecene mycotoxins: Mechanisms and prospects

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ABSTRACT

Trichothecenes are toxic metabolites produced by fungi that constitute a worldwide hazard for agricultural production and both animal and human health. More than 40 countries have introduced regulations or guidelines for food and feed contamination levels of the most prevalent trichothecene, deoxynivalenol (DON), on the basis of its ability to cause growth suppression. With the development of analytical tools, evaluation of food contamination and exposure revealed that a significant proportion of the human population is chronically exposed to DON doses exceeding the provisional maximum tolerable daily dose. Accordingly, a better understanding of trichothecene impact on health is needed. Upon exposure to low or moderate doses, DON and other trichothecenes induce anorexia, vomiting and reduced weight gain. Several recent studies have addressed the mechanisms by which trichothecenes induce these symptoms and revealed a multifaceted action targeting gut, liver and brain and causing dysregulation in neuroendocrine signaling, immune responses, growth hormone axis, and central neurocircuitries involved in energy homeostasis. Newly identified trichothecene toxicosis biomarkers are just beginning to be exploited and already open up new questions on the potential harmful effects of chronic exposure to DON at apparently asymptomatic very low levels. This review summarizes our current understanding of the effects of DON and other trichothecenes on food intake and weight growth.

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1. Introduction

Trichothecenes are toxic metabolites produced by fungi belonging to the *Fusarium* genus that commonly colonize various cereals. They constitute a broad family of over 200 esters of sesquiterpenoid alcohols containing the trichothecene tricyclic ring and possess a double bound at C9–C10 and an epoxide at C12–C13. Trichothecenes have been subdivided into four groups (types A–D). Type A includes the T-2 toxin and its metabolite HT-2 toxin considered as the most toxic thrichothecene (Joint FAO/WHO expert Committee on Food Additives (JECFA) 2001). Type B includes deoxynivalenol (DON) and its two acetylated precursors, 3-acetyldeoxynivalenol (3-ADON), and 15-acetyldeoxynivalenol (15-ADON), as well as nivalenol (NIV) and its acetylated precursor 4-acetylnivalenol called Fusarenon X (FUS-X). Although less toxic than type A, type B trichothecenes are found at greater concentrations in cereals grains and foods, DON being by far the most prevalent and best studied one to date. At the cellular level, trichothecenes bind to ribosomes, inhibit protein synthesis, and activate several signaling kinases associated to the ribosome (Pestka, 2010b). In immune cells, these effects result in the production of inflammatory cytokines or apoptosis depending on the dose and duration of exposure. Upon ingestion of food contaminated with type B trichothecenes, humans and animals display an array of effects including anorexia, abdominal pain, diarrhea, vomiting, reduced weight gain, as well as neuroendocrine and immunological changes, leukocytosis, hemorrhage, circulatory shock, and can eventually lead to death. The occurrence and the severity of part or all of these effects depend on the dose and duration of exposure, and on the exposed species (Ueno, 1987; Yoshizawa, 1983; Pestka and Smolinski, 2005; Pestka, 2010a). The type A trichothecene T-2 similarly induces food refusal and vomiting, but also induces lethargy, ataxia, hemorrhages, sepsis, and cardiopulmonary failure in experimental animals and has been related to historical food poisoning outbreaks in humans (Hsu et al., 1972; Ueno et al., 1972; Wyatt et al., 1972; Joffe, 1983; JECFA, 2002). Although T-2 proved to be more acutely toxic than DON, these two trichothecenes are equipotent in inducing anorexia and weight gain reduction (Rotter et al., 1996). The main overt effects observed in animal studies at low dietary DON concentrations appear to be reductions in food intake and weight gain, while higher doses induce vomiting (Rotter et al., 1996). On the basis of studies on growth impairment, the JECFA (2001) proposed a tolerable human daily intake (TDI) for DON of 1 μg/kg body weight (bw), i.e. 100 times less than the non-observed adverse effect level (NOAEL) for growth impairment in mice (100 μg/kg bw/day, Iverson et al., 1995–1996).

In the last few years, considerable research efforts have addressed the mechanisms by which trichothecenes reduce food intake and weight growth, with highlighted target organs including the brain, gut, liver, and spleen. This review summarizes our current understanding of the multifaceted action exerted by trichothecenes on the central neurocircuiteries involved in energy homeostasis, as well as on the growth hormone axis. Opening perspectives are also presented, including a highlight on the potential harmful effect inflammatory mediators might have upon chronic exposure to trichothecenes at apparently asymptomatic very low levels.

2. Molecular targets of trichothecenes

2.1. Ribosomes: Inhibition of translation and complex ribotoxic stress response

The 60S ribosomal subunit is the main identified molecular target for trichothecenes (Pestka and Smolinski, 2005). Trichothecenes bind to ribosomes, inhibit translation and induce activation of several ribosome-associated mitogen activated protein kinases (MAPKs), including p38, c-Jun N-terminal Kinase (JUNK), and extracellular signal-regulated kinase 1 and 2 (ERK1/2), an effect called ribotoxic stress response (RSR), in several animal and human immune and epithelial cell lines (Pestka et al., 2004; Pestka, 2010b). Leucocytes, notably those of mononuclear lineage, are particularly sensitive to trichothecenes. Activation of p38 and ERK1/2 triggers two competing signaling pathways, one downstream of p38 favoring apoptosis and one downstream of ERK1/2 favoring survival and cytokine expression, the net effect on cell fate depending on the dose and duration of exposure. Upon exposure to DON at low or moderate concentrations, MAPK activation drives an expression surge in proinflammatory cytokines through rapid (1–2 h) and strong (10–1000-fold) transcriptional activation and stabilization of mRNAs (Pestka, 2010b). Two upstream kinases have been identified as mediating DON-induced MAPK activation: the double-stranded RNA (dsRNA)-activated protein kinase (PKR) (Zhou et al., 2003) and the hematopoietic cell kinase (Hck) (Zhou et al., 2005). While Hck is specifically expressed in myelomonocytic cell lineages, PKR is widely distributed and constitutively expressed. Both PKR and Hck are associated with ribosomes and could sense trichothecene-induced changes in ribosome structure. When RAW 264.7 macrophages are exposed to DON, PKR, and Hck are activated prior to the MAPK and pharmacological inhibition of PKR or Hck prevents DON-induced MAPK activation (Zhou et al., 2005). Recently, Zhou et al. (2014) have demonstrated that multiple PKRs are basally associated with ribosome subunits and that DON-induced PKR activation can be obtained in a cell-free system. These authors proposed an elegant model where PKR monomers are positioned to sense rRNA structure perturbations induced by DON or other ribotoxins. These rRNA structural changes could promote PKR dimerization and autophosphorylation. Phosphoproteomic analyses were performed to delineate the effects of DON-induced RSR *in vivo* on the mouse spleen (Pan et al., 2013a) and *in vitro* on immune cell lines (Pan et al., 2013b). These studies exploited doses of DON (5 mg/kg bw *in vivo* and 250 ng/mL *in vitro*) known to partially inhibit translation and causing a robust RSR, and short time exposure (0–30 min), corresponding to the initiation and peak of RSR in terms of MAPK activation, before the induction of proinflammatory cytokine expression. The results revealed rapid and extensive DON-induced changes, encompassing around 17% of the phosphoproteome, involving several intracellular signaling pathways, and potentially affecting an array of cellular functions, such as translation, regulation of transcription, protein folding, biosynthesis of glucose, ATP and nucleotides, and cytoskeleton, and chromatin organization.

2.2. Non-ribosomal targets: Induction of oxidative stress

Trichothecenes have also been shown to cause oxidative stress in numerous cell lines, resulting in oxidative damage to lipids, proteins, and DNA (for review see Mishra et al., 2014). Of note, DON-induced reactive oxygen species (ROS) generation proved to