Available online at www.sciencedirect.com
ScienceDirect
Toxicology 242 (2007) 31–38
TOXICOLOGY
www.elsevier.com/locate/toxicol

Mycotoxin fumonisin B_1 alters cellular redox balance and signalling pathways in rat liver and kidney

Lada Rumora[a], Ana-Marija Domijan[b,*], Tihana Žanić Grubišić[a], Maja Peraica[b]

[a] *Faculty of Pharmacy and Biochemistry, Department of Medical Biochemistry and Haematology, Domagojeva 2, 10000 Zagreb , Croatia*
[b] *Institute for Medical Research and Occupational Health, Unit of Toxicology, Ksaverska cesta 2, 10000 Zagreb , Croatia*

Received 12 July 2007; received in revised form 3 September 2007; accepted 4 September 2007
Available online 12 September 2007

Abstract

Mycotoxin fumonisin B_1 (FB_1) is a frequent contaminant of grain, particularly maize, but the mechanism of its toxicity in the kidney and liver is not fully understood. FB_1-stimulated oxidative stress might disturb cellular redox state and signal transduction pathways of the target cells. In this study we measured total intracellular glutathione (GSH), and assessed mitogen-activated protein kinases (MAPKs) activation and the expression of heat shock proteins (Hsps) Hsp25 and Hsp70 in the liver and kidney of male Wistar rats given 0.5 mg FB_1/kg b.w. intraperitoneally for 2 or 7 days. The effect of FB_1 on GSH levels, MAPK activation and Hsp expression was found to be related to the type of tissue affected and the length of treatment. In rat liver, cellular GSH content increased, Hsp expression was up-regulated, and ERK and p38 were activated after the 7-day treatment, while even the 2-day treatment sufficed to produce phospho-JNK signal. In rat kidney, GSH levels decreased after the 2- and 7-day treatment with FB_1, while after the 7-day treatment all three MAPKs were activated, Hsp25 expression increased and Hsp70 expression decreased. In conclusion, FB_1 alters cellular redox balance, which leads to tissue-specific activation and expression of redox-sensitive signalling molecules. It seems that kidney cells are more sensitive to adverse effects of FB_1.
© 2007 Elsevier Ireland Ltd. All rights reserved.

Keywords: Fumonisin B_1; Glutathione; Mitogen-activated protein kinases; Heat shock proteins; Liver; Kidney

1. Introduction

Mycotoxin fumonisin B_1 (FB_1) is a natural contaminant of grain, particularly maize, all round the world. It is involved in domestic animal diseases such as equine leukoencephalomalacia and porcine pulmonary oedema. In laboratory animals FB_1 is hepatotoxic and nephrotoxic, hepatocarcinogenic in male rats and female mice, and nephrocarcinogenic in male rats. Although exposure to FB_1 in humans is believed to be associated with high incidence of oesophageal cancer in South Africa and primary liver cancer in China, due to the lack of epidemiological evidence, International Agency for Research on Cancer (IARC) has classified FB_1 as a possible carcinogen for humans (Group 2B) (IARC, 2002).

It has been shown that FB_1 either stimulates or suppresses cell proliferation, and might affect cell viability by inducing apoptosis and/or necrosis (Rumora et al., 2002; Stockmann-Juvala et al., 2004). The molecular mechanism of FB_1 toxicity is poorly understood, but

Abbreviations: FB_1, fumonisin B_1; ROS, reactive oxygen species; GSH, glutathione; GSSG, glutathione disulphide; γ-GCS, γ-glutamylcysteine synthetase; MAPKs, mitogen-activated protein kinases; Hsps, heat shock proteins; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; HSFs, heat shock transcription factors; HSEs, heat shock elements; ASK1, apoptosis signal-regulating kinase 1; GST, glutathione-S-transferase; AP-1, activator protein-1.

* Corresponding author. Tel.: +385 1 4673188; fax: +385 1 4673303.
E-mail address: adomijan@imi.hr (A.-M. Domijan).

0300-483X/$ – see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.tox.2007.09.006

it appears to be related to the deregulation of sphingolipid metabolism. FB_1 is structurally similar to the sphingoid bases sphinganine and sphingosine and, as such, can bind to and inhibit ceramide synthase, a key enzyme in *de novo* sphingolipid biosynthesis and sphingolipid turnover (Wang et al., 1990; Merrill et al., 2001). As sphingoid bases regulate cell growth, differentiation, transformation and cell death, it is reasonable to assume that FB_1 can also affect these processes.

Oxidative stress might play a role in FB_1-induced toxicity as suggested by increased production of reactive oxygen species (ROS) and lipid peroxidation after FB_1 treatment in Stockmann-Juvala et al. (2004) and Šegvić Klarić et al. (2007). Among different antioxidant systems operative in the cell, glutathione (GSH) is the most important low-molecular weight antioxidant. It is present in reduced form, GSH, and in two oxidized species: glutathione disulphide (GSSG) and glutathione disulphide mixed with protein thiols. Two enzymes synthesize GSH: γ-glutamylcysteine synthetase (γ-GCS) and glutathione synthetase. The former is catalysing the rate-limiting step in the process and is a point of feedback regulation. Overall maintenance of cellular GSH and cellular redox status is a dynamic process achieved by a balance between the rate of GSH synthesis, GSH/GSSG efflux, and GSH utilization. The ability of the cell to regenerate GSH (either by reduction of GSSG or new synthesis of GSH) is an important factor in efficient managing of oxidative stress within the cell (Curtin et al., 2002; Filomeni et al., 2002; Han et al., 2006).

The generation of ROS or the perturbations of the cellular redox state stimulate redox-sensitive signalling molecules, such as mitogen-activated protein kinases (MAPKs) and heat shock proteins (Hsps).

The MAPK superfamily of serine/threonine kinases is activated by a number of extracellular stimuli, and is involved in signal transduction cascades that play an important regulatory role in cell growth, differentiation and apoptosis. Three major mammalian MAPKs have been described: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK. While ERK is most commonly associated with the regulation of cell proliferation, JNK and p38 are primarily activated by various environmental stresses, such as oxidative stress, UV irradiation, heat and osmotic shock, and proinflammatory cytokines. Therefore, JNK and p38 MAPK are often jointly referred to as stress kinases. A common trigger activating all MAPK isoforms is the phosphorylation of both the threonine and the neighbouring tyrosine regulatory site by a specific upstream protein kinase. Once activated, MAPKs phosphorylate other cytoplasmic proteins and translocate from the cytoplasm to the nucleus to regulate the activity of transcription factors, thus modulating expression of different genes (Chang and Karin, 2001; Matsuzawa and Ichijo, 2005).

Hsps are ubiquitous and highly conserved proteins whose expression is induced in response to a wide variety of physiological and stress insults. These proteins act as molecular chaperones by assisting in the refolding of the misfolded proteins and aiding their elimination when they become irreversibly damaged. Hsp synthesis is tightly regulated at the transcriptional level by heat shock transcription factors (HSFs), especially by HSF-1. In resting cells, HSF-1 is a monomer; however, active HSF-1 exists as a trimer and binds to the heat shock elements (HSEs) present in the promoters of the heat shock-inducible genes. It is well documented that the expression of Hsp25/27 and Hsp70 might affect cell survival by interfering with apoptotic machinery. These proteins inhibit apoptosis both upstream and downstream of the caspase cascade in caspase-independent manner. They could also protect cells from oxidative damage by decreasing ROS production, neutralizing the toxic effects of oxidized proteins, and by affecting cellular GSH levels (Ferns et al., 2006; Schmitt et al., 2007; Mahlen et al., 1996).

The aim of this study was to explore the underlying mechanisms of FB_1-induced hepatotoxicity and nephrotoxicity. Oxidative stress stimulated by FB_1 might affect cellular redox balance and signal transduction pathways of the target cells. Therefore, we measured intracellular GSH levels, valuable in determining the overall redox state of the cell, as well as MAPK activation and expression of Hsp25 and Hsp70 in the liver and the kidney of male Wistar rats treated with FB_1 (0.5 mg/kg b.w.) for 2 or 7 days.

2. Materials and methods

2.1. Animal study

Adult male Wistar rats (∼230 g of weight) exposed to a 12 h light/dark cycle and constant temperature of 24 °C were kept in macrolone cages. The animals were fed on a standard diet for laboratory rodents (Mucedola, Settimo Milanese, Italy) and had free access to water.

The rats were randomised in four groups of five animals each. The animals were intraperitoneally (i.p.) given either FB_1 dissolved in sterile saline (0.9% NaCl) (0.5 mg/kg b.w.) or solvent only (control animals) for 2 or 7 days. The i.p. injection was chosen because it is considered to be a valuable tool for clarifying mechanism of action of mycotoxins (Bondy et al., 1995). FB_1 (98% purity) was purchased from Sigma Chemicals (St. Louis, MO, USA).

Download English Version:

https://daneshyari.com/en/article/2597132

Download Persian Version:

https://daneshyari.com/article/2597132

Daneshyari.com