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Fumonisin B_1 and the kidney: Modes of action for renal tumor formation by fumonisin B_1 in rodents

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ABSTRACT

The mycotoxin fumonisin B_1 (FB_1) is an important contaminant of maize and maize-based products. In rodent toxicity studies, FB_1 was shown to be hepato- and nephrotoxic, and to induce renal tumors in rats when administered via the diet. Of particular note are the aggressive growth characteristics of FB_1-induced tumors with a high potential to metastasize. While genotoxicity does not appear to contribute to FB_1 carcinogenicity, it is well established that FB_1-mediated disruption of sphingolipid metabolism plays a key role in FB_1 toxicity. This review provides an overview on human dietary exposure to FB_1, FB_1 toxicity and carcinogenicity, and potential mechanisms involved in FB_1-mediated tumor formation, with a particular focus on cellular functions of sphingolipids and biological consequences of FB_1-mediated perturbation of sphingolipid metabolism.

1. Introduction

Exposure to mycotoxins – secondary metabolites produced by molds – *via* contaminated food may present a serious risk to human health. While acute adverse health effects in humans are generally not expected to occur at levels of contamination normally found in food, irreversible effects such as reproductive toxicity and carcinogenicity resulting from chronic exposure are a matter of great concern. In rodent bioassays conducted by the National Toxicology Program – U.S. Department of Health (NTP, 1989, 2001), nephrotoxicity and renal carcinogenicity were identified as the most sensitive endpoints of toxicity for both ochratoxin A and fumonisin B_1 (FB_1), two widespread mycotoxins and food contaminants produced by *Aspergillus*/*Penicillium* and *Fusarium* species, respectively. A remarkable feature of the carcinomas induced by either of these structurally unrelated compounds was their exceptionally aggressive growth and potential to metastasize (NTP, 1989, 2001; Boorman et al., 1992; Hard et al., 2001), which is otherwise a rare event in chemically induced renal carcinogenesis in rats. Although numerous studies aimed at elucidating the mechanisms of ochratoxin A and FB_1 carcinogenicity as a basis for risk assessment have been conducted, a detailed understanding of the molecular events leading to renal tumor formation and malignant progression of tumors following exposure to ochratoxin A and FB_1 is still lacking. In a previous article, we critically reviewed proposed modes of action for ochratoxin A carcinogenicity (Mally and Dekant, 2009). In analogy, the scope of the present article is to provide a comprehensive overview on the current knowledge base of the biochemical, cellular and molecular events associated with FB_1-induced renal tumor formation and the highly aggressive nature of the carcinomas in rats, with a particular focus on cellular functions of sphingolipids and biological consequences of FB_1-mediated perturbation of sphingolipid metabolism.

2. Human exposure to fumonisin B_1

Fumonisins are a group of structurally related mycotoxins produced by Fusarium *verticillioides* and several other *Fusarium* species (Gelderblom et al., 1988; Marasas, 1996) that grow on crops, particularly maize, worldwide. FB_1 (Fig. 1), the most abundant homologue among these secondary fungal metabolites, is a com-

Abbreviations: AP, aminopentol; aSMase, acid sphingomyelinase; FB_1, fumonisin B_1; JNK, c-Jun N-terminal kinase; CYP, cytochrome P450 superfamiliy; ERK, extracellular regulated kinase; GCS, glucosylceramide synthase; GSH, glutathione; HFB_1, hydrolyzed FB_1; MAPK, mitogen-activated protein kinase; NfκB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; MMP, matrix metalloproteinase; NOEL, no observed effect level; OSOM, outer stripe of the outer medulla; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; PAI-1, plasminogen activator 1; PAP, phosphatidic acid phosphatase; PKC, protein kinase C; PLC, phospholipase C; PMTDI, provisional maximum tolerable daily intake; RAS, rat sarcoma; ROS, reactive oxygen species; Sa1P, sphinganine 1-phosphate; Sphk1, sphingosine kinase 1; So1P, sphingosine 1-phosphate; TNF-alpha, tumor necrosis factor alpha; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen receptor.

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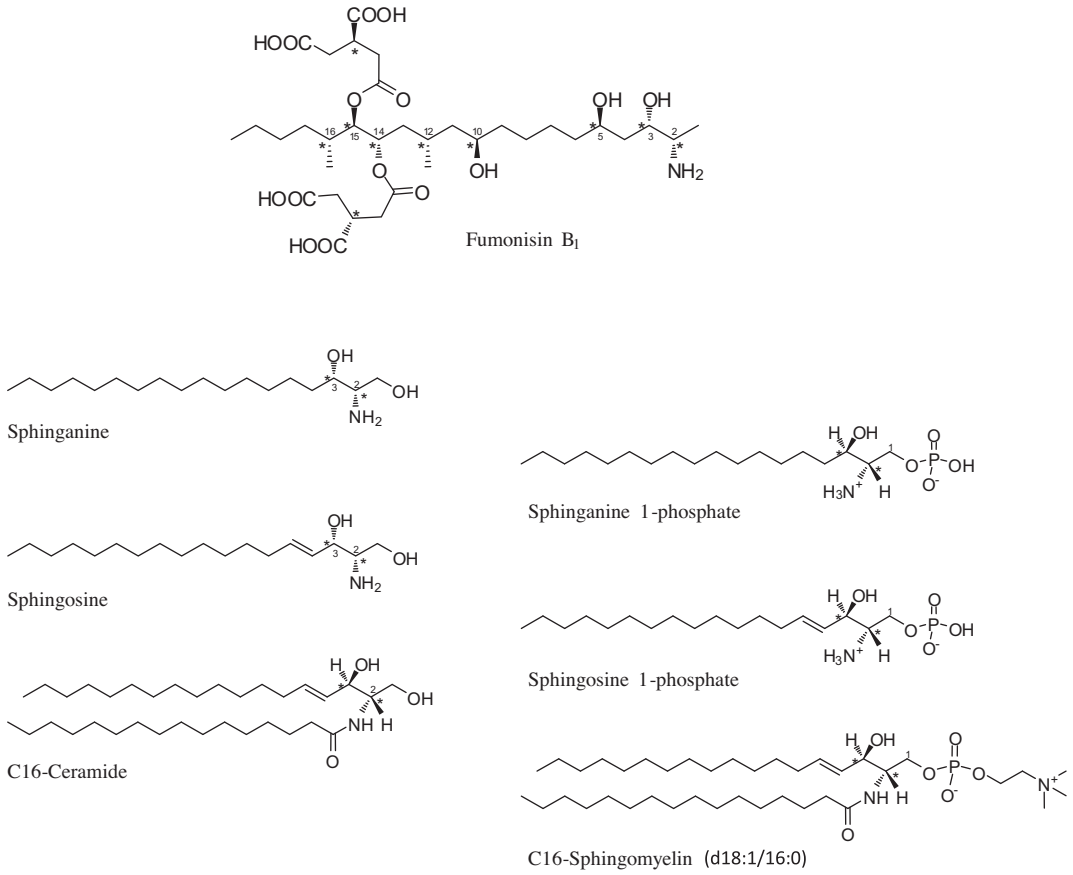

Fig. 1. Chemical structures of fumonisin B_1 and sphingolipids.

Table 1
Estimated human exposure to FB_1 or total fumonisins (FB) in different areas of the world from maize-based food.

Continent/Country region	Mean FB concentration in food [mg/kg] (or mean range)	Mean food consumption [g/d] (or mean range)	Mean FB intake [μg/kg bw per day] (or mean range)	Ref.
Europe				
Germany	0.013	6	0.01[a]	Zimmer et al. (2008)
North America				
United States[b]	n.s.	n.s.	0.08	Humphreys et al. (2001)
South America				
Guatemala				
Rural	3.55	454	15.6	Torres et al. (2007)
Urban	3.55	102	3.5	
Asia				
China home-grown cor[b]	0.08–41	100–750	0.4–740	Qiu and Liu (2001)
Africa				
South Africa				
Rural (moldy corn)[b]	54.0	460	354.9	Marasas (2001)
Rural (healthy corn)[b]	7.1	460	46.6	
Urban[b]	0.3	276	1.2	

n.s. = not specified.
[a] Calculated based on body weight of 70 kg for adults.
[b] FB_1 only.

mon and thus economically important contaminant of maize and maize-based food stuffs. Fungal infestation of crops and subsequent contamination with FB_1 can occur during different stages of cultivation including crop growth, harvesting or storage, and is influenced by temperature and humidity. Accordingly, human exposure to FB_1 varies widely around the world depending on