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EC PHARMACOLOGY AND TOXICOLOGY
Comprehensive Review

Fumonisins: Effects on Human and Animal Health and Mechanisms of Toxicity

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Received: January 27, 2018; **Published:** March 06, 2018

Abstract

Fumonisins, a group of closely related mycotoxins produced by a number of *Fusarium* and *Aspergillus* species, have been associated with a number of diseases in humans and animals. Fumonisin B_1 (FB_1) is the most prevalent of all of the naturally occurring fumonisins. They are structurally related to cellular sphingolipids and have been shown to inhibit sphingolipid biosynthesis via the ceramide synthase pathway. Cellular mechanisms involved in fumonisin-induced toxicity include the induction of oxidative stress, apoptosis, and cytotoxicity, as well as alterations in cytokine expression. Fumonisin production by *Aspergillus niger*, which is a widely occurring food contaminant and an important organism in the biotechnological industry, raises concerns about the widespread presence of fumonisins in food and feed and is expected to have important implications for biotechnology and food safety. Larger quantitative surveys of the occurrence of fumonisins in *Aspergillus* and *Fusarium*-infected food and feed products, as well as in biotechnology products produced by *Aspergillus* species, are warranted. This article presents an overview of the mechanisms of action of the fumonisins and their toxic effects in humans and animals.

Keywords: *Fumonisins; Fusarium verticillioides; Aspergillus niger; Mycotoxins; Mycotoxicoses; Food Safety; Mechanisms*

Introduction

Fumonisins are mycotoxins produced by *Fusarium verticillioides* and other Fusaria and are among the most important toxins in food and feed safety [1,2]. They are suspected to cause human and animal toxicoses by the consumption of contaminated corn-based food and feed products. Studies indicate that the fumonisins may be involved in esophageal cancer in South Africa and have been shown to cause leukoencephalomalacia in horses and pulmonary edema in pigs [3-5]. To avoid human toxicity, the United States Food and Drug Administration recommends that corn products should not be used for human consumption when contaminated with more than 2 - 4 mg/kg total fumonisins, whereas the European Union has a regulatory limit of 0.2 - 2 mg/kg [6-8]. In addition to corn, fumonisins have also been detected in rice, sorghum, wheat bran, soybean meal, and poultry feed. In recent years, fumonisins were detected for the first time in the industrially important fungal pathogen *Aspergillus niger*, suggesting severe implications for both the biotechnological uses of the fungus and potential fumonisin contamination of the many foods and feeds in which *A. niger* has been reported to grow [9,10]. *A. niger* is often used for the production of citric acid and extracellular enzymes and as a biocatalyst for the expression of heterologous proteins in the biotechnological industry. *A. niger* is also one of the most common contaminants of food, particularly fruits and certain vegetables [11,12]. It is a very important opportunistic pathogen of grapes and has been reported to grow and damage a large number of crops, including green coffee beans, corn and other cereals, peanuts, onions, mango, dried fruits, and apples. Following the discovery of fumonisin production by *A. niger*, analytical studies revealed widespread occurrence of these mycotoxins in coffee, grapes, raisins, and wine [13,14], raising the possibility of the presence of fumonisins in many other *Aspergillus*-infected food and feed products. Larger studies are underway in our laboratory to examine the occurrence of fumonisins in other *Aspergillus* and *Fusarium*-infected food and feed products as well as in biotechnology products that are produced/expressed by *Aspergillus* species.

Structurally, fumonisins are a group of related polyketide-derived, non-fluorescent mycotoxins [3,15]. At least 53 different fumonisins and fumonisin-like compounds have been reported so far in the literature. These polar mycotoxins are chemically similar to cellular sphingolipids (Figure 1) and have been shown to inhibit sphingolipid biosynthesis via the ceramide synthase pathway. They can be divided into four main series (A, B, C, and P), with the B series, mainly FB_1, FB_2, and FB_3 as the most abundant naturally occurring fumonisins. Although all three fumonisin B compounds (FB_1, FB_2 and FB_3) are toxic, most studies published to date have focused on the most prevalent fumonisin B compound FB_1 (Figure 1). Chemical structures of fumonisin B compounds consist of a long hydroxylated hydrocarbon chain (pentahydroxyeicosane) to which tricarballylic acid, methyl, and amino groups are added [15,16]. FB_1 differs from FB_2 and FB_3 only in the hydroxylation pattern. Structure-activity relationship studies revealed that the primary amino and tricarballylic acid groups in fumonisins and fumonisin-like compounds are necessary for biological activity [17]. Acetylation of FB_1 to FA_1 blocks the cytotoxicity and the ability to inhibit ceramide synthase. On the other hand, hydrolysis of the tricarballylic side chains in FB_1 causes a 60 - 70% decrease in its biological activity. Three-dimensional conformational analyses also showed that the primary amino and carboxylic acid groups in fumonisin B compounds are spatially related, suggesting that they have chelating properties and may cause membrane ion leakage [18]. Moreover, extending the 'hydrocarbon chain' in these compounds resulted in increased toxicity in cell cultures [19]. The mammalian metabolism of FB_1 was studied in rats, primates, and cultured rat hepatocytes [20-22]. In rats and primates, radiolabeled FB_1 is almost entirely eliminated unchanged in the bile regardless of whether it is administered orally or by injection. Studies in cultured rat hepatocytes also showed no detectable metabolites of FB_1. In this review, we focus on providing an overview of the current state of knowledge regarding the mechanisms of action of the fumonisins and their harmful effects on human and animal health.

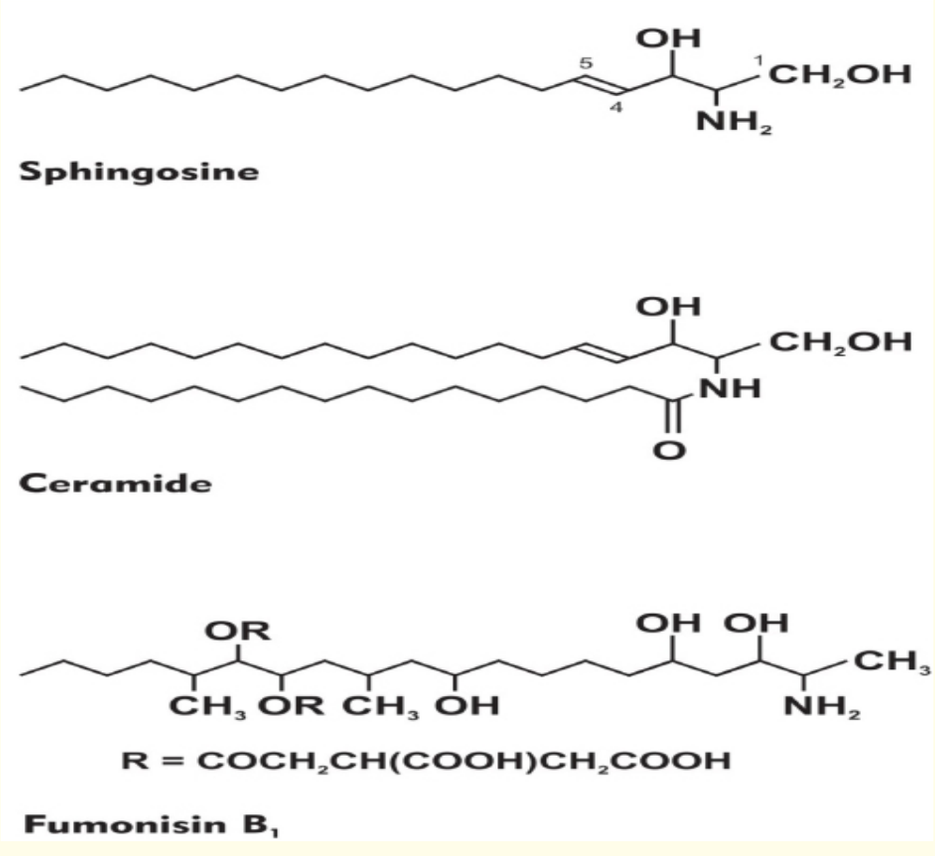

Figure 1: *Chemical structures of the most relevant sphingolipids and the mycotoxin Fumonisin B_1. Note that sphinganine has the double bond between C4 and C5 saturated and sphingosine-1-phosphate has a phosphate group attached to C1.*

Effects of fumonisins on human and animal health

Studies have shown that fumonisin consumption may negatively affect both human and animal health. In humans, fumonisin consumption has been associated with neural tube defects and cancer, notably esophageal and hepatocellular cancer. In animals, fumonisin exposure has been most commonly associated with leukoencephalomalacia, pulmonary edema, hepatotoxicity, hepatocarcinogenesis, nephrotoxicity and renal carcinogenesis.

Fumonisins and human toxicity

Neural tube defects: Neural tube defects (NTDs) are embryonic defects of the spinal cord and brain resulting from failure of the neural tube to close during the first few weeks of development. The most common types of NTDs are spina bifida and anencephaly and normally affect less than 3 per 10,000 live births in the United States [23]. Spina bifida is characterized by protrusion of the spinal cord and its membranes while anencephaly is absence of major portions of the brain, skull, and scalp. The association between maternal fumonisin consumption and NTDs was first recognized in the early 1980s and several times since then in human populations in areas of high corn consumption such as Guatemala, China, South Africa, as well as in areas of the United States along the Mexico border [23-30]. For example, in northern China and areas of Guatemala and South Africa the rate of NTDs is approximately 60 per 10,000 live births [23]. Along the Texas-Mexico border, the average yearly rate of NTDs is 15 per 10,000 live births, approximately five times higher than the average rate in the United States [29]. A population-based case-control study examined the risk of NTDs in offspring of mothers exposed to fumonisins [30]. Fumonisin consumption was estimated from recall of periconceptional corn tortilla intake as well as postpartum serum sphinganine:sphingosine (Sa:So) ratio, a commonly used biomarker of fumonisin exposure. It was shown that maternal fumonisin exposure increased the risk of NTDs in a dose-dependent manner, up to a threshold at which NTD risk declined. It was suggested that the decline in occurrence of NTDs at the highest exposures may be due to increased fetal death. Results of animal and *in vitro* studies have supported a causal relationship between fumonisin exposure and NTDs [23,31-34]. Using an *in vivo* mouse model, the administration of fumonisin increased the number of NTDs in offspring in a dose-dependent manner [31]. Pregnant LM/Bc dams were administered fumonisin B_1 via intraperitoneal injection on gestational day 7.5 and 8.5. Dams receiving the lowest dose, 5 mg/kg body weight, gave birth to 1 fetus with an NTD in 4 of the 10 litters. Dams receiving the highest dose, 20 mg/kg body weight, gave birth to at least 2 or more fetuses with an NTD in all 10 litters. Control dams did not give birth to any pups with NTDs. Collectively, these studies support a causal role of fumonisin exposure and toxicity to NTDs.

Cancer: Fumonisin B_1 has been classified as a Group 2B carcinogen by the International Agency for Research on Cancer [35]. Group 2B agents are those that may be carcinogenic to humans but have limited evidence in humans and less than sufficient evidence in experimental animals. In humans, fumonisin exposure has been most notably associated with esophageal and liver cancer. Several ecological studies have shown that in areas of high prevalence of esophageal and/or liver cancer, such as in certain areas of China and South Africa, there is also elevated levels of fumonisin exposure, predominantly through maize consumption [36-41]. Several case-control studies have shown a positive relationship between maize consumption and esophageal cancer [42,43], however, only one prospective case-control study has been published examining the association specifically between fumonisin consumption and esophageal cancer [44]. This was a nested study within a larger trial called the General Population Trial which followed healthy participants from Linxian, People's Republic of China for 5.25 years of vitamin and mineral supplementation [45]. Cancer-free individuals were interviewed to assess lifestyle, dietary patterns, and medical history, and given a physical exam. Participants were then started on a vitamin and mineral supplementation for 5.25 years. This nested study examined the relationship between baseline serum Sa:So ratio and the incidence of esophageal squamous cell carcinoma during the 5.25 years of vitamin and mineral supplementation [44]. No association was found. Limitations to this study include no follow-up serum Sa:So. The baseline Sa:So ratio may not be representative of the long-term exposure over the 5.25 years. Furthermore, studies have shown that serum Sa:So ratio may not be an accurate biomarker of dietary exposure in humans [46]. Current studies have shown that urine fumonisin B_1 levels appear to be a more accurate biomarker of fumonisin dietary exposure in humans compared to the serum Sa:So ratio [46,47]. Collectively, these human studies suggest that esophageal and/or liver cancer is associated with maize consumption but it is not clear if fumonisin is the carcinogenic mycotoxin. The carcinogenicity associated with maize consumption may be due to the presence of other mycotoxins found in maize or another factor independent of mycotoxins. However, numerous animal studies have shown that fumonisin B_1 can be carcinogenic and has been shown to induce liver and/or renal cancer, but not esophageal cancer [48-52]. Therefore, future case-controlled studies using a more accurate biomarker for fumonisin exposure, such as urinary fumonisin B_1 concentrations, may clarify the role of fumonisin in causing cancer in humans.

Fumonisins and animal toxicity

Leukoencephalomalacia: Fumonisin exposure has been shown to cause leukoencephalomalacia in horses. The primary pathological feature is liquefactive necrosis of the white matter of the cerebral hemispheres [53]. Central nervous system inflammation and edema are also characteristic. Acute symptoms include frenzy, aimless circling, head pressing, paresis, ataxia, blindness, depression, and hyperexcitability [54]. There have been several cases of equine leukoencephalomalacia outbreaks around the world. Upon feed analysis it was shown that the feed was contaminated with mold and higher than normal concentrations of fumonisin [54-58]. Further, leukoencephalomalacia has been induced experimentally via ration feeding to ponies with known concentrations of fumonisin B_1 [59,60]. For example, Ross., *et al.* fed four ponies a ration that was naturally contaminated with fumonisin B_1 in a three phase design [60]. For the first 98 days ponies were fed a diet containing a fumonisin B_1 concentration of 44 ppm followed by 120 days of feeding a diet with a very low concentration (less than 1 ppm) of fumonisin B_1. The last phase consisted of 75 days at a fumonisin concentration of 88 ppm. Control ponies were fed a diet of less than 1 ppm fumonisin B_1 for 280 days. All four ponies in the experimental group died or were euthanized due to signs of distress by the end of phase 3; two as early as phase 1. Upon postmortem examination all ponies experienced leukoencephalomalacia as well as hepatic necrotic lesions. Hence, it appears that fumonisin B_1 exposure is capable of causing leukoencephalomalacia in equine.

Pulmonary edema: It has been documented that fumonisin consumption causes pulmonary edema in swine. In 1989, the Iowa State University Veterinary Diagnostic Laboratory received reports of an outbreak of acute fatal porcine pulmonary edema syndrome with clinical signs of lethargy, dyspnea, cyanosis, and death [61]. Corn screenings from the swine outbreak revealed the presence of fumonisin B_1. The fumonisin B_1 concentration in most corn samples was found to be between 20 - 330 μg/g [61]. Experimental exposure of fumonisin B_1 supports its causal effect on porcine pulmonary edema [61-64]. Fumonisin B_1 exposure via contaminated corn feeding or IV administration was shown to cause pulmonary edema often within 3 - 6 days, along with hepatic injury [62-64]. The hepatic injury was found to precede the appearance of pulmonary edema and, therefore, has been hypothesized that liver membrane fragments are released into the bloodstream causing a macrophage response in the lung and increased pulmonary capillary permeability [63,64]. However, others have found no increase in pulmonary capillary permeability upon fumonisin exposure [65]. Rather, pulmonary edema was found to be due to fumonisin-induced left ventricular failure via altered cardiac myocyte calcium handling [65,66]. Thus, fumonisin B_1 is a causative agent inducing pulmonary edema in swine, possibly as a consequence of hepatic injury and/or myocardial failure.

Hepatotoxicity and carcinogenesis: Unlike leukoencephalomalacia and pulmonary edema, fumonisin-induced hepatotoxicity is not species specific. Fumonisin exposure has been shown to cause hepatic injury and/or carcinogenesis in horses, pigs, rats, mice, and others [49,60,61,63,64,67]. Routine early findings of fumonisin-induced hepatic toxicity include the presence of apoptotic and necrotic hepatocytes [68]. Consistent with early hepatic injury are elevated serum liver enzymes such as alanine transaminase, aspartate transaminase, alkaline phosphatase, and lactate dehydrogenase as well as elevated cholesterol and triglyceride concentrations [68,69]. Progression of injury involves continuation of apoptosis and necrosis, enhanced mitosis and hepatocellular hyperplasia, cytoplasmic vacuolation, cytomegaly with variation in nuclear size, bile duct and oval cell proliferation, cholangiomatous lesions, and fibrosis [67,68]. Serum gamma-glutamyltransferase (GGT) activity and bilirubin concentrations begin to rise as hepatic injury worsens [68]. Some have also found increased hepatic lipid peroxidation and altered antioxidant status [49,67,70]. It has been suggested that enhanced oxidative stress and lipid peroxidation may be a causative initiating factor in hepatic carcinogenesis [70,71]. Enhanced cell proliferation in response to injury may be a supporting factor in the cancer initiation by fumonisins [70,71]. In summary, much data supports the role of fumonisins in causing hepatic toxicity and carcinogenesis in a variety of animals.

Nephrotoxicity and carcinogenesis: Fumonisins have been shown to cause nephrotoxicity in mainly rats and rabbits. Similar to fumonisin-induced hepatotoxicity, increased apoptosis is an initial finding [68]. As injury progresses the number of apoptotic cells increases as mitotic figures start to appear, indicating a cycle of cell loss and regeneration [72]. However, the inability of regeneration to keep pace with cell loss is evidence by tubular atrophy and loss in kidney weight [68,69]. Fumonisin-treated rats experience signs of functional damage, such as proteinuria and increased serum creatinine and urea nitrogen. Further, signs of functional decline of the renal tubules include increased urinary enzyme levels, such as N-acetyl-B-glucosaminidase, GGT, and lactate dehydrogenase, presence of casts, and production of hypoosmotic urine [68]. As with hepatic carcinogenesis, it is thought that the stimulated regeneration in response to injury and apoptosis plays a role in the fumonisin-induced renal carcinogenesis [72]. In conclusion, fumonisin exposure has been shown to cause renal toxicity with functional decline and carcinogenesis.

Mechanisms of fumonisin toxicity

Currently the only clearly defined target of the fumonisins (FBs) in animals is the inhibition of the enzyme ceramide synthase [73] (CerS: also known as sphingosine N-acyltransferase) which is involved in sphingolipid metabolism (Figure 2). Sphingolipids are an important family of lipids in the emerging field of lipodomics. Sphingolipids are vital in regulating important cellular processes such as cell growth, apoptosis, inflammation and migration [74]. Sphingolipids are further modified to become complex sphingolipids which are important functional membrane components [75-81]. Fumonisin toxicity is therefore thought to be due to the disruption of sphingolipid metabolism. This disruption which typically includes elevations in both sphinganine and sphinganine-1-phosphate have repeatedly correlated with FB toxicity in animals [82]. Fumonisins have been linked to neural tube defects (NTDs) in humans, brain lesions in equine, lung edema in swine and cancer in several different animal species [83]. In order to understand the various effects produced by FBs the physiology of the sphingolipids must first be considered.

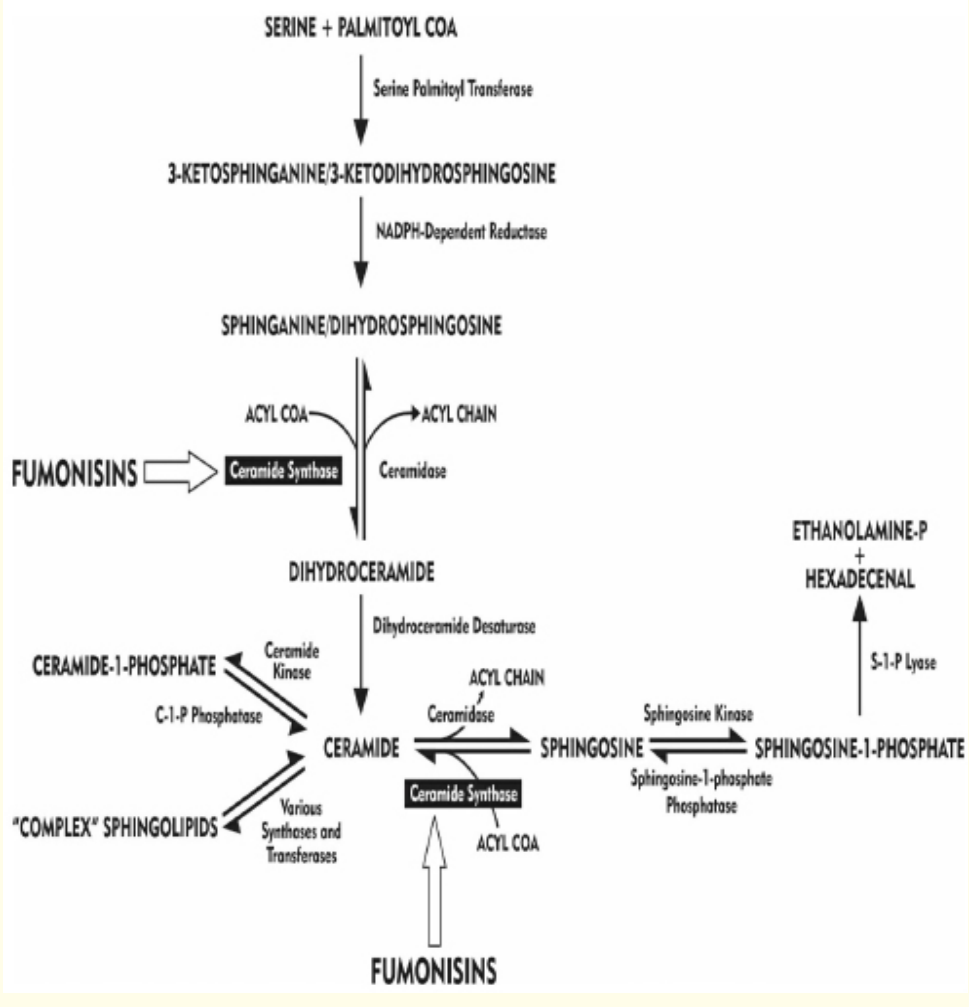

Figure 2: *Summary of the metabolic pathways of the most important sphingolipids showing their interrelationships. The target of the fumonisins, ceramide synthase, can be seen to affect both de novo sphingolipid synthesis from serine and palmitoyl CoA and the recycling of "complex" sphingolipids. Single arrows denote an irreversible step while dual arrows indicate a reversible step.*

Sphingolipids

Sphingolipids are a large family of metabolically-linked signaling molecules, some of which can cause opposite effects on the same cellular process such as apoptosis. Metabolic linking means disruption of one part of the pathway can produce a "rippling effect," affecting the levels of several of these molecules in turn [74]. Sphingolipids are defined by a sphingoid base backbone (1,3-dihydroxy, 2-aminoalkane) typified by sphingosine (Figure 1). Sphingosine is D-erythro-1,3-dihydroxy, 2-aminooctadec-4-ene (also known as trans-4-sphingenine). Physically some sphingolipids are quite hydrophobic so limiting them to a particular organelle, usually where synthesized, or even a specific membrane face while others are more amphipathic and can enter the cytoplasm. A brain sphingolipid ("sphingosin") was first described in the 19th century [84] but it was not until 1947 that the collective term sphingolipid was applied [85] and by 1983 many individual sphingolipids had been described [86]. Sphingolipids can vary in chain length, position and number of double bonds and other additional functional groups such as methyl or hydroxyl (for an extremely detailed and comprehensive review of the structure of sphingolipids the reader is recommended to access the Merrill laboratory web site) [87]. A detailed review of sphingolipid metabolism is beyond the scope of this review but is covered in-depth in the book "Sphingolipids as Signaling and Regulatory Molecules" [88]. However, to summarize, *de novo* sphingolipid synthesis starts with the joining of serine with palmitoyl-CoA to form 3-keto-dihydrosphingosine (also known as 3-ketosphinganine) catalyzed by the enzyme serine palmitoyl transferase in the endoplasmic reticulum [89] (Figure 2). An abnormal subunit in this enzyme is responsible for hereditary sensory neuropathy type 1 which was the first human genetic disease associated with sphingolipid metabolism [90,91]. The 3-keto-dihydrosphingosine is then reduced to form dihydrosphingosine (also known as sphinganine; see Figure 1) by an NADPH-dependent reductase [92] followed by the addition of an acyl chain of variable length via amide formation by CerS (see later) [93,94]. This reaction can be reversed by one of several ceramidases which exhibit organelle-specific expression and various pH optimums [95,96]. The resulting molecule is known as dihydroceramide and is normally converted by the addition of a double bond in the 4-5 position by dihydroceramide desaturase [97] to form ceramide [74]. Ceramide can then be phosphorylated via ceramide kinase after transportation to the Golgi apparatus [98] to form ceramide-1-phosphate and this reaction can also be reversed by ceramide-1-phosphate phosphatase [99]. Ceramide is the main entry point to complex sphingolipid production which also occurs principally in the endoplasmic reticulum or Golgi apparatus. Ceramide is very hydrophobic and needs to be transported to the Golgi apparatus either via vesicular transport or by binding to the ceramide transfer protein [100] (CERT). Once in the Golgi apparatus various "headgroups" such as glucose, galactose or phosphocholine can be added to the C1 position via the action of glucosylceramide synthase, ceramide galactosyltransferase or sphingomyelin synthase respectively before subsequent modification to become important functional membrane components which will be discussed later [101,102]. Complex sphingolipids are degraded via various hydrolases to release ceramide back into the sphingolipid pool [103,104]. Sphingomyelin for example is broken down first to ceramide via the action of one of several sphingomyelinases each with a different optimum pH and location on the plasma membrane (outer vs. inner faces) [105] and then to sphingosine via ceramidase. Although both ceramide and sphingosine can "flip-flop" across the plasma membrane their hydrophobicity means they can only be recycled back into the cell by endocytosis. After internalization and fusing with lysosomes, sphingomyelinases and ceramidases undertake the breakdown and recycling of complex sphingolipids [74]. Therefore there are two entry points into sphingolipid metabolic pathways: *de novo* synthesis and the recycling of complex sphingolipids (Figure 2). Ceramide can be converted directly to sphingosine by several ceramidases and in the reverse direction by CerS with the dihydroderivatives. Sphingosine can also be phosphorylated, via either of 2 sphingosine kinases [106], (SphK1 and 2: reversed by sphingosine phosphate phosphatase) [107] to produce sphingosine-1-phosphate which is also an important messenger molecule [108]. Sphingosine-1-phosphate is also the so-called "exit" from sphingolipid metabolism as the action of sphingosine-1-phosphate lyase irreversibly degrades it into ethanolamine phosphate and hexadecenal [109,110]. Sphingosine-1-phosphate is also released from cells to act extracellularly in an auto- and paracrine fashion via G-protein coupled receptors [111]. It is thought that sphingosine-1-phosphate can exit a cell via the ABC transporter ABCC1 [112]: it's more amphipathic nature making this possible. It also is found in serum at levels significantly higher than intracellularly (high vs. low nanomolar respectively) where it is associated with lipoproteins and albumen [113] and can also enter cells via the cystic fibrosis transmembrane regulator [114].

The application of high-performance liquid chromatography-tandem mass spectrometry has revealed the cellular levels of many of these sphingolipids [115]. A concentration gradient from sphingomyelins (high levels in membranes) to sphingosine-1-phosphate (low nanomolar concentrations) via ceramide and sphingosine is observed: the level of each family member decreasing by roughly an order of magnitude from the previous one [113]. Thus it can be appreciated that small changes in ceramide levels may cause a significant change in sphingosine-1-phosphate levels [74]. This had given rise to the concept of a sphingolipid "rheostat" balancing pro- and anti-apoptotic signals. However, this model may be a little simplistic as has been indicated by initial results to some sphingomimetic drugs being developed for clinical use [116].

Sphingolipid function

The first identified sphingolipid target was protein kinase C (PKC) that is inhibited by sphingosine which competes with activators (diacetlyglycerol and phorbol esters) in human platelets [117]. A sphingosine-dependent proteolytic component of PKC that phosphorylates 14-3-3 protein has been identified [118]. Other important targets include 3-phosphoinositide-dependent kinase 1 [119], protein kinase A type II [120], casein kinase 2 [121], the cannabinoid receptor CB1 [122] and several ion channels. These include a member of the melastatin-like transient receptor potential channel family (TRPM3) [123], the cardiac ryanodine receptor channel (intracellular calcium stores) [124] and L-type voltage-activated calcium channels [125]. Sphingolipids are strongly implicated in apoptosis. It is thought that ceramide, released from lysosomes by the action of acid sphingomyelinase [126], can form channels in the outer mitochondrial membrane to allow the release of pro-apoptotic proteins. Cytochrome c, procaspases, apoptosis inducing factor, heat shock proteins, Smac/Diablo and endonuclease G have all been implicated [127]. Sphingosine can also form channels in mitochondrial membranes but these are apparently of smaller diameter and not capable of allowing the release of these pro-apoptotic proteins [128]. Acid sphingomyelinase-catalyzed release of ceramide is stimulated by TNFα, CD95 and certain chemotherapeutic agents [129]. Sphingolipids, especially ceramide, have also been implicated in the process of inflammation including the activation of the transcription factor NF-κB which affects many genes including those encoding for cytokines and chemokines [130,131]. It has been shown that ceramide may be involved in lung inflammation in cystic fibrosis [132]. When large amounts of ceramide are generated they can actually change the biophysical properties of a membrane such as its phase behavior and alter its cholesterol content [133]. Although outside the scope of this review this is an important consideration as such changes can affect the function of vital membrane proteins. The reader is recommended to the review by Meer., *et al*. [134]: some aspects of this will be considered later when discussing the function of complex sphingolipids. Ceramide can also activate cathepsin D to induce apoptosis via BID [126]. Ceramide's other targets include protein phosphatases 1 and 2A which are involved in regulating apoptosis and cell growth [135], a kinase suppressor of ras which can regulate TNFα-mediated activation of ERK1 and 2 in intestinal epithelial cells [136,137], activation of c-Raf and the MAPK pathway in kidney glomerular mesangial cells [138], and many members of the PKC family [139-141]. Ceramide can apparently bind to and activate SAPK/JNK and cause kidney glomerular epithelial cells to undergo apoptosis distinct from the effect in mesangial cells via MAPK [142]. Ceramide is implicated in metabolic syndrome and the development of type 2 diabetes. High saturated fatty acid levels and inflammatory cytokines such as TNFα cause an increase in ceramide which, via protein phosphatase-2A, activates PKB/Akt and decreases insulin sensitivity [143]. Finally ceramide can cause autophagy; the anti-estrogen drug tamoxifen, which can induce autophagy, acts via sphingolipids [144,145]. Recently FB_1-mediated disruption of sphingolipid metabolism was shown to cause autophagy in monkey kidney MARC-145 cells [146]. The phosphorylation by ceramide kinase of ceramide to ceramide-1-phosphate results in the production of another bioactive sphingolipid. Ceramide-1-phosphate however has mitogenic functions and is an inhibitor of apoptosis, depending on cell type, and is therefore antagonistic with respect to ceramide [147]. In macrophages ceramide-1-phosphate blocks apoptosis by inhibiting acid sphingomyelinase, therefore reducing ceramide levels [148], and by activating phosphatidylinositol 3-kinase which can cause the expression of anti-apoptotic genes [149]. Ceramide-1-phosphate affects phagocytosis by neutrophils and is also involved in inflammation and is thought to mediate these effects via acid sphingomyelinase and phospholipase A_2 [150]. Ceramide-1-phosphate has also been implicated in mast cell degranulation which is another component of the inflammatory response [151]. Unlike sphingosine and ceramide, ceramide-1-phosphate is amphipathic and cannot "flip-flop" across the

membrane; it can therefor only accumulate on one face of the membrane so possibly affecting membrane curvature [152]. Finally we must consider sphingosine-1-phosphate which is typically found at very low concentrations within cells but higher in plasma. It acts extracellularly on G-protein coupled receptors (GPCR's); this is possible due to its amphipathic nature [111]. In plasma, sphingosine-1-phosphate is mainly associated with high-density lipoproteins and is thought to contribute to their protective properties [153]. It is also found in high levels in platelets where it is released rapidly upon platelet activation [154]. The 5 sphingosine-1-phosphate GPCR's (S1PR1-5) display varying tissue expression and affect typical heterotrimeric G-proteins [155,156] including G_i, G_q and G_{12} [157]. The S1PR1 receptor also activates MAPK [158] and in knockout mice the deletion of S1PR1 is embryonic lethal as it is required for angiogenesis (deletion of S1PR2 or 3 is not) [159]. Sphingosine-1-phosphate may have intracellular targets but these are not well characterized as yet. Unlike sphingosine and ceramide, sphingosine-1-phosphate inhibits apoptosis and promotes cell proliferation and therefore can be tumorigenic which has stimulated much research into sphingosine kinase inhibitors [160,161]. Recently such an inhibitor was developed that significantly reduced sphingosine-1-phosphate levels while increasing ceramide in leukemia cells; tumor growth was reduced while apoptosis was increased [162]. Sphingosine kinase is affected by many factors including growth factors (PDGF, IGF and VEGF) and cytokines (TNFα and IL-1) [74,163]. Obviously there is much interest in being able to manipulate sphingosine-1-phosphate levels. Sphingosine-1-phosphate has also been implicated in inflammation, endothelial barrier homeostasis and viral infection [161]. Similarly to ceramide-1-phosphate, sphingosine-1-phosphate can affect mast cell function [164].

Complex sphingolipid function

Complex sphingolipids can be divided into 3 categories depending on which headgroup is initially added to the C1 position of ceramide; this results in the production of glucosphingolipids, galactosphingolipids (collectively known as glycosphingolipids) and sphingomyelin respectively. These are synthesized either in the endoplasmic reticulum or Golgi apparatus and can exhibit great diversity. Which headgroup is added depends on which of three enzymes are utilized for the synthesis of these complex sphingolipids; these include glucosylceramide synthase, ceramide galactosyltransferase and sphingomyelin synthase adding glucose, galactose or phosphocholine respectively [88]. Glucosylceramide is essential to life in mammals; mice lacking this synthase are embryonic lethal but the condition can be rescued by addition of exogenous glucosylceramide. It is thought that these sphingolipids are essential for correct cell-cell recognition [165]. Mouse knockouts of glucosylceramide synthase confined to the skin or nervous system lead to either a breakdown of the hydrophobicity of the skin allowing excessive water loss and death or death 11-24 days after birth presumably due to lack of proper brain development [166,167]. Ceramide galactosyltransferase appears to have limited tissue expression principally in kidneys, testes and intestines. It is found in myelinating glial cells both in the CNS and peripheral nervous system (oligodendrocytes and Schwann cells respectively). CNS myelin has a significant galactosylceramide content and knockout mice for ceramide galactosyltransferase display severe motor weakness among other problems such as male infertility [168,169]. Sphingomyelin is the commonest complex sphingolipid found in mammalian cells and is essential for survival [88,170]. The synthesis of sphingomyelin from ceramide and phosphatidylcholine also produces DAG which has opposite effects to ceramide on proliferation and cell survival [171]. Vitamin D_3 stimulates sphingomyelinase activity and results in an increase in ceramide levels due to sphingomyelin breakdown [172]. Complex sphingolipids are necessary for maintaining membrane structure and certain functional microdomains (caveolae) [75,76] and are binding sites for various proteins as well as certain bacterial and viral pathogens and toxins [77,78]. This is observed most clearly with the sphingomyelins but is also seen to a lesser extent with glycosphingolipids. This will obviously affect membrane function such as endocytosis and signal transduction in particular and much research is still needed on this subject [79-81]. It has been shown that depletion of complex sphingolipids from plasma membranes due to fumonisin-mediated disruption of sphingolipid metabolism affects endocytosis of folate. Folate is required for the correct development of the CNS and a deficiency in animals and humans causes an increase in NTDs. Fumonisins cause this in animal models and are strongly implicated in increased incidences of NTDs in humans where fumonisin-contaminated foods have been consumed [173]. Sousa., *et al.* recently demonstrated that fumonisins (B_1 and B_2) impaired the development of myenteric neurons in rats [174].

Ceramide synthase and fumonisins

CerS is currently the only known target of the fumonisins. After initial characterization of CerS in yeast, 6 mammalian isoforms have now been identified (originally named Lass genes for Longevity Assurance) [93,175]. CerS1 is found in brain and skeletal muscle and prefers to acylate (dihydro-)sphingosine with C18 acylCoA. CerS2 is found in kidney and liver and prefers C20-26 (even numbers only: double bond preferences are not considered here). CerS3 is found in testes and prefers C26 and longer. CerS4 is found in heart, leucocytes, liver and skin and prefers C18 and C20 while CerS5 and 6 both prefer C14-18 (even numbers only) and are found in all tissues (CerS5) and intestines and kidney (CerS6) [176]. CerS1 may be regulated by sphingosine availability [177]. Although not specifically identified a partially purified CerS from bovine liver was shown to have an optimal pH of 7.5, an apparent k_m of 146 μM and V_{max} of 11.1 nmol/min/mg protein for stearoyl-CoA (18 carbons). For the other principal substrate sphingosine, the K_m and V_{max} were 171 μM and 11.3 nmol/min/mg protein respectively. Sphinganine (minus sphingosine's 4-5 double bond) is also a good substrate with a K_m and V_{max} of 144 μM and 8.5 nmol/min/mg protein respectively [178]. Although there are many members of the fumonisin family, fumonisin B_1 (FB_1) is the predominant form found in infected corn [179] and accordingly virtually all published data concerns FB_1: where other forms have been tested it will be noted specifically. Wang., *et al*. noted the structural similarity of fumonisins with several sphingolipids and proposed that these mycotoxins might act by disrupting sphingolipid metabolism (Figure 1) [73]. Using rat liver microsomes they found that FB_1 inhibited the incorporation of ^{14}C-labeled serine into sphingolipids with an IC_{50} of 0.1 μM; similar results were seen with FB_2, FB_3, FB_4 and FC_4. Hydrolyzed fumonisins FB_1, FB_2 and FB_3 lacking the tricarballylic side chains were only ~30 - 40% as effective [179]. Wang., *et al*. also observed an increase in the intermediate sphinganine indicating that FB_1 was inhibiting CerS and the formation of ceramide (Figure 2) [73]. Complete inhibition of *de novo* synthesis was obtained with 10 μM FB_1 while 25μM failed to affect serine palmitoyl transferase (first enzyme in the *de novo* pathway). They observed no accumulation of 3-ketosphinganine (indicating that the second enzyme in this pathway, the NADPH-dependent reductase, is not affected either) so confirming CerS as the target. Merrill., *et al*. proposed a model whereby FB_1 interacts competitively with the binding sites of both sphinganine and acyl-CoA: the sphingolipid-like region of FB_1 blocking sphinganine binding while the negatively charged tricarballylic side chains mimic the phosphate groups of CoA [180-182]. In addition N-acetylated FB_1 (FA_1) had no effect on CerS so indicating that the amino group is essential [179]. The removal of the tricarballylic side chains to give aminopentol (AP_1) produces a less potent blocker of CerS but is now, unlike FB_1, a substrate of CerS. Acylation by CerS produces N-palmitoyl-aminopentol (PAP_1) which appears to be a more potent inhibitor of CerS than FB_1. The process of nixtamalization of maize, common in Central and South America and used to release niacin and avoid malnutrition, produces AP_1 from FB_1 [183]. Nixtamalization utilizes lime (alkali) to cause hydrolysis of FB_1 to AP_1 [184]; this is puzzling as nixtamalization is also used to reduce mycotoxins in infected maize including those producing FB_1 such as *Fusarium moniliforme*. Fumonisin inhibition of CerS is reversible both *in vitro* and *in vivo* [185,186]. In South Africa in the 1980's a causative link was noticed between the occurrence of human esophageal cancer and maize infected with *Fusarium moniliforme*: at that time the actual causative agents were unknown [187]. Fumonisins were suspected and several animal studies using isolates from *Fusarium verticillioides* affected rats and primates, (causing cardiovascular problems and possibly hepatic cirrhosis depending on dose), horses, (leukoencephalomalacia), pigs, (pulmonary edema), and sheep, (nephrosis and hepatosis). These animals were estimated to have possible overall body concentrations of FB_1 well above the IC_{50} for CerS inhibition (> 10μM) [188]. Subsequent research using reasonably purified FB_1 (~90%) confirmed that FB_1 alone was responsible for virtually all the toxic effects to the liver in rats [189]. Wang., *et al*. also demonstrated in rats fed FB_1 for 2 days (5 mg/200g body weight) produced a decrease of between 10 - 35% in free sphingosine. This resulted in a decrease in the ratio of free sphingosine to sphinganine from ~2.6 to 0.5 as might be expected from inhibition of the *de novo* pathway (Figure 2) [73]. Many studies use an increase in the sphinganine to sphingosine ratio as an indicator of fumonisin exposure. But, as Merrill., *et al*. point out, there are certain situations where free sphingosine is elevated also as when there is significant cell death and sphingolipid recycling. They recommend measuring actual amounts as well as considering the ratio [183]. Merrill., *et al*. also looked at the disruption of complex sphingolipid synthesis in cultured mouse cerebellar neurons by FB_1. They reported decreased incorporation of labeled serine into glucosylceramide, lactosylceramide, sphingomyelin and various gangliosides plus decreased incorporation of labeled galactose and sphinganine into complex sphingolipids [181].

Recent findings

Recently the effects of fumonisins on sphingolipid metabolism have focused on oxidative stress and effects on the immune system with its obvious implications in healthcare. Studies have shown FB_1 can increase the generation of reactive oxygen species (ROS) causing oxidative stress and immunotoxic effects [190-192]. Increased ROS production is known to cause peroxidation of membrane lipids and damage to DNA [193,194]. Mary., *et al.* exposed spleen mononuclear cells (lymphocytes and monocytes) from rats to FB_1 and saw an increase in ROS; mitochondrial complex I, CYP450, arachidonic acid metabolism and NADPH oxidase were all implicated [191]. Cultured rat primary astrocytes, human neuroblastoma and glioblastoma cells treated with FB_1 produced similar effects [195,196]. A CerS2 null mouse produced by Zigdon., *et al.* could not synthesize long acyl-chain ceramides and displayed severe hepatopathy. It had increased lipid peroxidation, protein nitrosylation and elevated levels of many antioxidant enzymes (response to increased oxidative stress) along with increased ROS due to impaired mitochondrial complex IV function [197]. Previous research had shown the effects of sphingolipids on ROS generation and regulation of mitochondrial function [178,198-204] but Zigdon., *et al*. suggested the ROS source were the mitochondria and that the now predominating shorter chain sphingolipids directly inhibited complex IV. Additionally a fluorescent sphinganine analog accumulated in heart mitochondria. Fumonisin B_1 may cause hyperexcitability in the mouse cerebral cortex by disrupting mitochondrial function [205]. The lipid composition of the plasma membrane is vital in regulating clathrin-mediated endocytosis; sphingolipids play an important role in this and affect membrane fluidity [206-208]. The CerS2 mutant displayed various phenotypes thought due to the disruption of ligand and receptor internalization via endocytosis [209-213]. Previous research has shown specific effects by FB_1 on the immune systems of poultry, swine, mice and cattle [214,215]. A recent paper by Li., *et al.* shows bone marrow-derived dendritic cells having altered maturation and function as antigen-presenting cells by FB_1-induced disruption of sphingolipid metabolism [216]. Effects appeared to include reduced antigen uptake, processing and presentation plus a decreased number of dendrites required for antigen endocytosis. The levels of various cytokines were also affected. Fumonisins can significantly increase lipid peroxidation and damage certain proteins although the observed effects varied with tissue type [191]. DNA damage has also been seen after FB_1 treatment in human lymphocytes and spleen mononuclear cells [191,217]. DNA synthesis can be inhibited and DNA fragmentation occurred in U-118MG, C6 glioma and MEF cells after FB_1 treatment [67,196,218]. Demirel., *et al.* have shown that FB_1 can even affect DNA methylation and chromatin modification and therefore epigenetics in rat kidney cells [219]. Finally Mary., *et al.* also suggested that CYP450-induced ROS production might be caused by FB_1 which also appeared to induce the NADPH oxidase system [191,195]. In a recent study, she indeed showed that FB_1, together with the mycotoxin aflatoxin B_1, could induce CYP450 and arachidonic acid metabolism in rat hepatocytes [220].

Conclusion

Fumonisins are important mycotoxins produced by *Aspergillus* and *Fusarium* species. They are known to cause human and animal toxicoses by the consumption of contaminated foods and feeds. The widespread presence of fumonisins in many *Aspergillus*-infected food and feed products, including coffee, grapes, wine, and raisins, is a real cause for concern in both health and economic terms. Although the detected fumonisin levels in some of these products (e.g. 1 - 25 µg/L in wine samples and 1 - 14 µg/kg in retail raisins) [13,14] were below the regulatory limits set by the European Union and the United States Food and Drug Administration for similar commodities such as maize, the high frequency of fumonisin occurrence clearly calls for larger surveys that would establish whether different climatic and/or production conditions/procedures can lead to fumonisin concentrations that are above the set regulatory limits. Larger quantitative surveys, which we are actively pursuing in our laboratory using liquid chromatography-tandem mass spectrometry methods, will also be able to determine how widespread fumonisins are in other *Aspergillus* and *Fusarium*-infected food and feed products as well as in biotechnology products that are produced by *Aspergillus* species. In addition, high frequency of fumonisin occurrence in foods and feeds calls for the need to conduct exposure assessment studies, especially concerning populations with a high intake of one particular fumonisin-contaminated product or a combination of several fumonisin-contaminated products.

Acknowledgment

We would like to thank Vanessa C. Wright for her help with Figures 1 and 2. This review is dedicated to the memory of Professor Sidney D Nelson.

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