大韓獸醫學會誌(1995) 第35卷 第2號
Korean J Vet Res(1995) 35(2): 405-416

The current status of fumonisin toxicosis in domestic animals: A review

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(Received Feb 13, 1995)

가축의 fumonisin 중독증에 대한 최근 연구 동향 : 종설

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(1995년 2월 13일 접수)

초록 : 말의 뇌화연증(equine leukoencephalomalacia)과 돼지의 폐수종(porcine pulmonary edema)은 *Fusarium*에 오염된 옥수수로 인하여 발생되는 것으로 추정되어 왔다. 1988년에 *F moniliforme*에서 2차 대사산물인 fumonisin B_1(FB_1)이 동정되면서 오염된 옥수수와 순수 분리된 FB_1으로 두질병이 실험적으로 재현되었고, 말과 돼지 이외의 다른 가축에 대해서도 독성 연구가 진행되고 있다. fumonisins(FBs)는 모든 종에서 간에 독성을 나타내나 종에 따라 주요 독성 장기가 각기 다름이 밝혀지고 있다. FB의 독성 기전에 대해서는 잘 알려지지 않았으나 FB가 sphingolipid 생성과정을 차단함으로써 장기 및 혈중에 sphinganine(SA) : sphingosine(SO)를 증가시키는 것으로 알려졌다. 이는 증가된 SA : SO가 FB 독성의 진단기준이 될 수 있음을 시사하는 것이다. 최근 진행 중인 연구에 의하면, 저용량의 FB_1 급식 투여가 돼지에서 혈중 입자(blood-born particle)에 대한 폐혈관 대식 세포(pulmonary intravascular macrophage)의 탐식 능력을 저하시켜, 세균 감염에 대한 감수성이 증가될 수 있음을 시사하고 있다. *Fusarium* 속균은 전세계적으로 생산되는 옥수수에서 발생되고 있으며, 우리나라는 사료에 사용되는 옥수수의 절대량을 수입에 의존하고 있는 점을 고려할 때, 허용기준 및 무해용량 등에 대한 관리가 절실하다. 이 논문에서는 최근 연구된 FB에 의한 가축 독성에 대하여 기술하고자 한다.

Key words : *Fusarium*, fumonisin, equine leukoencephalomalacia, porcine pulmonary edema, sphinganine(SA) : sphingosine(SO)

Introduction

After four decades of extensive research on aflatoxin (AF), the research efforts are shifting substantially from aflatoxins to toxic metabolites from various *Fusarium* species that occur worldwide. The majority of *Fusarium*

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toxins, which include trichothecenes, moniliformin, zearalenone, fusarin C and fumonisin(FB), have been discovered during the last decade, and represent an amazing variety of biosynthetic origins.

Fumonisin B_1, B_2, A_1 and A_2 were isolated in South Africa from culture material of *Fusarium moniliforme* in 1988[1]. Another research group in New Caledonia also independently isolated the most abundant fumonisin, FB1[2]. Since then, FB_3 and FB_4 have been isolated as well[3,4]. Recent surveys have shown that production of FBs in natural substrates and agricultural commodities exists in other strains of *F moniliforme* as well as other *Fusarium* species. They include *F proliferatum, F nygamai, F anthophilum, F dlamini*, and *F napiforme*[5,6]. Among them, however, *F moniliforme* and *F proliferatum* are the only species to date to produce large amounts of FBs.

FB_1, and its presence in animal feeds has been the most widely studied of the FB toxins. During the fall of 1989 and the winter of 1990, the National Veterinary Services Laboratories, Iowa, USA, received numerous field reports and sample submissions related to equine leukoencephalomalacia(ELEM) epizootics and outbreaks of a porcine pulmonary edema(PPE). The 1989 corn crop in many parts of the midwestern and southeastern USA was heavily infected with *F moniliforme* and its consumption by swine and horses led to disease outbreaks[7-9]. FB_1, at concentrations of up to 330ppm, was detected in the contaminated feeds associated with one of the epizootics[9]. After that, many studies focused on reproduction of ELEM in horse and PPE in swine fed naturally FB-contaminated corn or injected purified FBs. Studies on other animals have also been performed. Whereas the role of FBs in human health is not clear, the consumption of FB-contaminated corn has been epidemiologically correlated with increased risk of esophageal cancer in Transkei, South Africa and some provinces of China. Experimentally, FBs have been shown to increase low density lipoprtein cholesterol in serum, and atherogenic effect, in monkeys[10].

FBs contaminated over 60% of corn samples in midwestern USA from 1988-1991 crops, and up to 10% of samples had 10 to 59ppm levels[11]. Corn samples from Linxian, China, a high risk area for human esophageal cancer, were heavily contaminated with FBs and other mycotoxins[12,13]. Of the FB-positive samples at the same area, the mean level was found to be 872ppm for FB_1 and 448pm for FB_2, and *Furarium* species isolated from corn produces FB_1 at levels ranging from 1,280 to 11,300ppm. Fungi isolated in this area also produced various nitramines, which are known carcinogens.

Meanwhile, most feedstuffs of domestic animal would contain a minimum of 50% corn. Corn for feedstuffs in Korea are absolutely depend on import from China and USA. Furthermore, imported corns are undergrade, which is likely to be contaminated with FBs and other mycotoxins. The possibility that there may be several toxic metabolites of *F moniliforme* in imported commodities, should be of concern to the livestock industry. Recently, simultaneous screening for FB_1, AB_1, and zearalenone was developed, which was combined with a line immunoblot assay and image analysis, and termed computer-assisted multianalyte assay system[14].

Toxicosis in Domestic Animals

Equine leukoencephalomalacia(ELEM) : ELEM has being recognized since the late 1800s as a disease caused by ingestion of moldy corn[15-17] and is also known as moldy corn disease, blind staggers, corn stalk disease and forage poisoning[18]. ELEM is non-infectious, sporadic, seasonal, and occurs in epidemic outbreaks that result in a highly fatal disease that affects the central nerve system(CNS).

ELEM occurs as 2 clinical syndromes. The neurotoxic syndrome is reported to be most common while hepatotoxicosis is less frequently described[16]. Clinical signs of the neurotoxic syndrome include ataxia, circling, unilateral blindness, head pressing or shaking, agitation, and terminally, recumbency, seizures and death[16,19]. The hepatotoxic syndrome include facial edema, severe icterus, and abdominal breathing and cyanosis[20]. Histopathologically, CNS lesions are related to vascular endothelial damage and li-

quefaction necrosis of white matter, perivascular hemorrhage, edema with marked satellitosis and neurophagia in the nerotoxic form, while hepatotoxic lesion include centrilobular necrosis and fibrosis accompanied by inflammatory cell infiltration. No other organ seems to be affected, except for a mild swelling of the kidneys[20-24].

In 1973, correlation was first established between corn-feeding infected with *F moniliforme* and ELEM[25]. Although many different toxins are produced by this fungus, which affects varying systems in several mammalian species, only FBs cause ELEM in horses[17]. Consumption of corn infected with *F moliliforme* associated with ELEM has been conclusively demonstrated in experiment with horses by intravenous injection of 7 daily doses of 0.125mg purified FB_1/kg body weight over a 9 day period[26]. Another oral study, with 1-4mg FB_1/kg/day for 29 or 33 days, confirmed that pure FB_1 caused neutotoxic ELEM[22]. Subsequently, experimental ELEM in ponies fed naturally contaminated corn diets with known concentrations was reported by other investigators[24,27].

Previous studies suggested that brain lesions were involved with long-term, low-dose toxin exposure, while higher dosages are required to produce hepatic disease [22-28]. Although liver disease, encephlopathy, and ELEM are caused by consumption of contaminated feed, the length of exposure, level of contaminant, individual animal differences, previous exposure, and possible other conditions may be important factors in the appearance of clinical disease[24]. Within days of giving ponies feed contaminated with 15-44μg FB_1/g, elevation of SA:SO was seen before liver enzymes were noticeably elevated[33]. The ratios returned to control levels after ponies stopped eating the contaminated feed. However, when the ponies resumed consumption of contaminated feed, the ratios once again became elevated.

Efforts to determine the minimum toxic dose of FB in ponies have been reported[27,29]. On FB_1 levels in horse feeds during 1989-1990, 75% of the cases had at least one sample that contained FB_1 above 10ppm. Feeds not associated with problems contained FB levels below 6ppm 94% of the time[30].

Field and laboratory investigation demonstrated the presence of FBs in almost all corn with ELEM outbreaks and FBs were produced mainly by strains of *F moniliforme* and *F proliferatum*[31]. However, the contribution of other FBs has not been taken into consideration. Even culture materials and naturally contaminated feed are prone to contain other FBs. Recently, there was a report that FB_2 produced from *F proliferatum* could be a factor in ELEM[32]. Three horses were fed a dose containing FB_2 75mg/kg, with 3mg/kg FB_1, daily. After 136 days, 2 of 3 horse showed ELEM. However, further study of FB_3 at higher concentrations is needed.

Porcine pulmonary edema(PPE) : Severe pulmonary edema in swine fed *F moniliforme* MRC 826 culture material was first reported in 1981, which contaminated an unknown amount of FB_1[34]. An epidemiological study of PPE associated with the 1989 corn crop showed that mean morbidity rate was 25.9% (1-100%), mean mortality was 70.3%(2-100%), and recovery time for affected animals that survived was 3.6 days. But survivors developed subacute hepatotoxicosis with individual hepatocellular necrosis, hepatomegalocytosis, and increased numbers of mitotic figures. Pregnant sows experienced abortions; in some affected animals within 3 days after onset of acute clinical signs. From the fungal cultures, the predominate isolate was *F moniliforme*, with occasional *F proliferatum*[8]. Harrison at el[7] fed naturally contaminated feed from two farms to two groups of three pigs each. One feed contained 105mg FB_1/kg feed, and the second had 155mg FB_1/kg. Liver disease was produced in all pigs, but only those fed 155mg FB_1/kg developed PPE and pancreatic necrosis. They also injected FB_1 intravenously and saw PPE in a pig given a total dose of 11.3mg, but no disease in pigs given 8.65mg FB_1 or 10mg FB_2. Other investigators have reproduced PPE by feeding pigs with contaminated corn, obtained from field cases of PPE, containing >175ppm total FBs[35,36]. Based on liver histopathology, the no observed adverse effect level (NOAEL) was <23ppm total FBs for the 14 day period, while based on the clinical chemistry, the NOAEL was <12ppm. Thus, liver damage was ob-

served at lower doses, while at higher doses, acute pulmonary edema was superimposed on the hepatic damage.

Grossly, the thoracic cavity contain clear, brown-tinged fluid, and the lung is larger than normal, occupying about two-thirds of the thoracic cavity. The lobular pattern is well demarcated with moderate to marked distension of the pleural and interlobular septa. Histologic changes consisted of edema with distension of the peribronchial, perivascular, and interlobular connective tissue, as well as associated lymphatics, by a nonproteinaceous fluid. Ultrastructual study included loss of sinusoidal hepatocyte microvilli, membranous material hepatic sinsoids, and mutilamellar bodies in kupffer cells, pancreatic cells, and pulmonary intravascular macrophages(PIMs). Thus, the target organs of FB in the pig were the lung, liver, and pancreas[35,37]. But no immunosuppressive effects were observed in sows or piglets fed 100ppm fumonisin for 17 day[38]. In a chroinic study of FB_1, weanling pigs fed a ration with 100mg FB_1/kg for 7 days followed by a diet containing 190mg/kg for 83 days developed nodular hyperplasia of the liver and severe hyperkeratiosis, parakeratiosis, and formation of papillary downgrowths of the stratum basal of the distal esophageal mucosa[39]. Recently, they reported medial hypertrophy of the pulmonary arteries restricted to the muscular layer with no endothelial or adventitial lesions in the 6 months feeding study[40]. The dietary concentrations of 150-190mg FB_1/kg of ration used in their study is compatible with naturally occurring levels in United States corn samples associated with field levels of porcine intoxication[8].

Riley et al[41] studied a dose response relationship between the rations in serum and tissues and the amount of FB-contaminated feed consumed. In pigs fed >23ppm or greater of greater FB, SA:SO elevations were noted in liver, lung, kidney, serum. Statistically significant increases in this ratio were observed after 14 days in pigs consuming feed with FBs as low as 5ppm in feed without any change in liver enzymes or microscopic lesions in the liver, lung, or kidney. *In viro* studies using the lung slices metod, showed uptake of 5-hydroxytryptamine(5-HT) was markedly decrease in slices from FB_1 treated pig lungs *in vivo*, suggesting that FB_1 caues endothelial cell damaged[42]. Based on this discovery, the Haschek group hypothesized that altered sphingolipid metabolism caused hepatocellular damage resulting in release of membranous material into the circulation, This material is phagocytosed by the PIMs thus triggering the release of mediators which ultimately results in pulmonary edema[35]. In cultured lung slices, pig lungs showed that toxicity of FBs was dose and time dependent until day 5, and FB_1 appeared to be most toxic compared FB_2 and FB_3[43].

Recently, there was a report regarding the co-existence of AF and FB on 28 corn samples from 1991 Georgia, USA[44]. 23 samples had detectable levels of both, which consisted of 73 ppb of aflatoxin and 0.87ppm of FB_1, respectively. Although AF and FB apparently induce their biological effects by way of differing mechanisms both are important toxigenic metabolites associated with pig disease. The interaction of AF and FB_1 contaminated diets was studied on clinical performance, serum biochemical, hematologic, and immunologic values. The addictive effect was shown for induction of liver disease in growing barrows fed 2.5mg AF plus 100mg FB_1/kg of feed for 35 day[45].

Toxicity to poultry

In the early 1970s, moldy corn infected with several *Fusarium* species produced severe leg deformities, called "cowboy leg" and paralysis with signs typical of thiamine deficiency[46,47]. Tibial dyscondroplasia was later described in chicken fed *F roseum* contaminaated feed[48,49].

Recently, FB toxicity of broilèr chicks and turkeys has accumulated. Toxicity study in broiler chicks with feed at 300mg FB_1/kg for 2 weeks, showed marked depression of body weight, increase of ralative liver weight, and worsening of feed conversion. Histologically, chicks fed FB had acute multifocal randomly oriented hepatocyte necrosis, biliary hyperplasia, muscle necrosis, and intestinal goblet-cell hyperplasia,

which might due to direct irritating effects of FB on the gut or to FB induced alteraion in the normal intestinal flora. Ricket was characterized with widening of the proliferating and hypertropic cartilage zones of the proximal tibiotasal physes[50]. In day-old chicks fed diets containing 100, 200, 300, or 400mg FB_1/kg for 21 days, liver, proventriculus, and gizzard weights increased. Serum calcium, cholesterol, and aspartate aminotransfease levels increased at higher FB dietary lveels[51]. Other clinical and histological findings were similar to those of the previous study[50]. The effects of feeding FB culture material(FCM) containing from 75, 150, 225, 300, 375, 450 and 525mg FB_1/kg in day-old chicks were done by Weibking et al[52]. Increased kidney weights was observed, which was not seen previously in broilers fed FCM. The hematological changes included an increase in mean cell hemoglobin concentrations in chicks fed FCM that supplied 450 and 525mg FB_1/kg. containing FCM that supplied 225mg/kg. Diets containing FCM that supplied 225mg/kg or higher FB_1, cause hepatic lesions in young broilers. However, diets containing FCM that supplied levels as low as 75mg FB_1/kg affected the physiology of chicks by causing an increased in sphinganine levels and SA:SO ratios. More recently, 2 day old broiler chicks were fed a diet containing 10mg pure FB_1/kg feed for 6 days. In two other experiments, chicks were fed FCM containing 30mg FB_1/kg for 2 weeks, and another received 300mg FB_1/kg for 8 days[53]. Mean spleen relative weight in the highest dose group, was lower than that of control. An increase in cholesterol and a decrease in triglycerides indicate disruption in lipidic metabolism. A uric acid decrease was observed in FB intoxication and may be related to an alteration of protein catabolism due to liver damage. They suggested that pure FB_1 was toxic for young chicks from concentrations of 100mg/kg feed, and FB_1 was also toxic at a concentration of 30mg/kg feed when FB_1 from FCM is used.

Young turkeys fed diets containing 75, 150, 225 or 300mg FB_1/kg prepared from *F moniliforme* cultures showed decreases in feed intake and increases in liver weights and SA : SO, dose dependently. Treatment associated histological lesion were observed in the liver and myocardium[54]. Young turkey poults fed FCM with 0, 100 and 200mg FB_1/kg for 21 days showed increased liver, kidney, and pancreas weights in a linear dose-dependent manner. Biliary hypreplasia with hyperplasia and hypertropy of Kupffer cells in livers and moderate multifocal hematopoiesis in the myocardium were seen in poults fed 100mg/kg FB_1. Tibial lesions were present in poults fed $\geq$100mg/kg. Pathologic mechanisms of its induction have not been determined in either study. Diarrhea in FB-treated poultry may have led to intestinal malabsorption or maldigestion of vitamin D, calcium or phosphorus, resulting in secondary rickets. Both hepatic and bone lesions were not present in broilers until doses reached 200mg FB_1/kg, which suggests increased susceptibility of turkeys for these lesions. Thymic cortical atrophy was only present in poults fed 200mg FB_1/kg, whereas broilers fed 100mg FB_1/kg had this lesion[55].

Feed contaminated with *F moniliforme* was reported to produce deficiencies in the immune system of chickens[56]. In an *in vitro* study, FB_1 induced cytoplasmic blebing or nuclear disintegration, and depression in the phagocytic potential of peritoneal macrophage after 4hr treatment with 20, 40 and 100μg FB_1 in chicken macrophages. This implies that FB_1 exposure may result in increased susceptibility of chickens to bacterial infection[57,58]. Lymphocyte viability from broiler chicks of different ages receiving feed amended with FCM containing mycotoxin, ranging from 61-546ppm FB_1, 14-94ppm FB_2 and 66-367ppm moniliformin was observed. Lymphocyte cytotoxic effects were observed in all treated groups on day 21. Abnormally shaped red cells(Poikilocytes) having a spindle-shape with one or both ends pointed were presented[59]. Turkey lymphocytes that had been exposed *in vitro* to FB_1 and FB_2 at concentration of 0.01-25μg/mL for 48 and 72hr showed inhibition of cell proliferation that was dose-dependent. After 72 hours of exposure to toxin, the 50% inhibitory dose was 1.4μg/mL for FB_1 and 0.4μg/mL for FB_2, indicating that FB_2 was from 3- to 4-fold more cytotoxic than FB_1. Cells exposed to FB_1 or FB_2 exhibited high levels of cytoplasmic vacuolization.

Broiler chicks on feed amended with *F proliferatum*

culture material or with purified FB_1 and/or moniliformin, produced dose- responsive clinical signs, reduced weight gains and mortality in chicks. Additive effects were noted when the toxins were given in combination[60]. They also showed that purified FB_1, FB_2 and/or moniliformin mycotoxins had embryopathic and embryocidal effects by dose- and time-responsiveness[61]. Early embryonic changes in exposed embryos included hydocephalus, enlarged beaks and elongated necks. Gross pathologic changes were most evident in embryos exposed to 1μM FB_1 on day 1, with hemorrhages on the surfaces of feet, legs, breask, neck and skull, because the embryos exposed to the 1μM dose had longer survival times. However, microscopic examination of the tissues from embryos exposed to 10 and 100μM FB revealed that these doses caused, in a dose- dependent manner, more severe pathologic changes in the tissues than the 1μM FB_1 dose. Pathologic changes were noted in liver, kidneys, heart, lungs, musculoskeletal system, intestine, testes and brain toxin-exposed embryos. Studies are still needed to determine the transmissibility of FBs to eggs from hens in an effort to determine the *in ovo* response of the embryo to these toxins.

Toxicity to ruminant : Little is known about FB-toxicity in ruminants. Two sheep fed. *F moniliforme* (isolate MRC826) contaminated culture material for 8 and 10 days developed severe nephrosis and hepatosis[34]. Corn contaminated with *F moniliforme* isolated from a field case caused dramatic feed refused in the cattle, however the FB concentration was not known[62]. Recently an experiment was conducted to determine the effects in cattle of feeding FBs at levels known to be toxic to swine and horse[63]. Diets contained FBs at 15, 31 or 148μg/g were fed for 31 days. There were no differences in clinical appearance of calves including feed intake of weight gain among the three different goups. However, increases occurred in serum liver function tests, including aspatate amino transferase, gamma glutamyl transpeptidase, lactate dehydrogenase, and bilirubin from day 10 through day 31, but were not high enough to indicated severe liver disease. By day 61, all serum values for liver function were within normal ranges in all groups. Serum cholesterol was significantly elevated in animals given the high dose on day 10 and progressively increased on day 17 and 31. Although there was no specific lesion grossly, there was a mild hydropic degeneration and cloudy swelling in a periacinar pattern throught th liver. Lymphocyte blastogenesis was significantly impaired at the end of the feeding period in the group the high dose. Other parameters of immune function were not affected significantly.

Toxicity to rabbit : The effects of FB in rabbits has not been previously reported. Gumprecht et al[64] recently completed their preliminary study of the rabbit. They demostrated that as in other species, pure FB was hepatotoxic. It was also nephrotoxic, as reported in rats. Rabbits were injected with 0.5, 0.3 or 0.15mg FB_1/kg and killed on day 2 or 4. Other rabbits were given a single dose of 1.25mg FB_1/kg and euthanized on days 1, 3 or 5. Rabbits given multiple doses of FB_1 were lethargic, anorectic, and had decreased urine production. Liver- and renal-associated clinical chemistry parmeters were elevated. Renal lesions consisted of severe proximal tubular necrosis. Liver lesions were variable consisting of mild necrosis, vacuolation and bile stasis. The SA:SO ratios were markedly elevated in both target and nontarget tissues, serum, and urine in treated rabbits. Rabbits given a single dose of FB_1 showed similar increases in renal-associated parameters and renal lesions, but no hepatic changes. They concluded that the target organs for FB_1 toxicity in rabbits were kindney and liver, with kidney being the most sensitive regardless of sex, dose, and dosing regimen.

Mechanism of action : The FBs are structurally similar to the long-chain base sphingoid, a component of the long-chain backbone of sphingolipids(Fig 1). Recently, using the chiral gas chromatography and nuclear magnetic resonance, the complete absolute sterochemistry of the FB_1 produced by *F moniliforme* was discovered, which can provide information about the biosynthetic origin of parts of the molecule[65](Fig 2).

Sphingolipids are major components of biological membranes where they have been postulated to play a variety of important roles, including regulation of cell

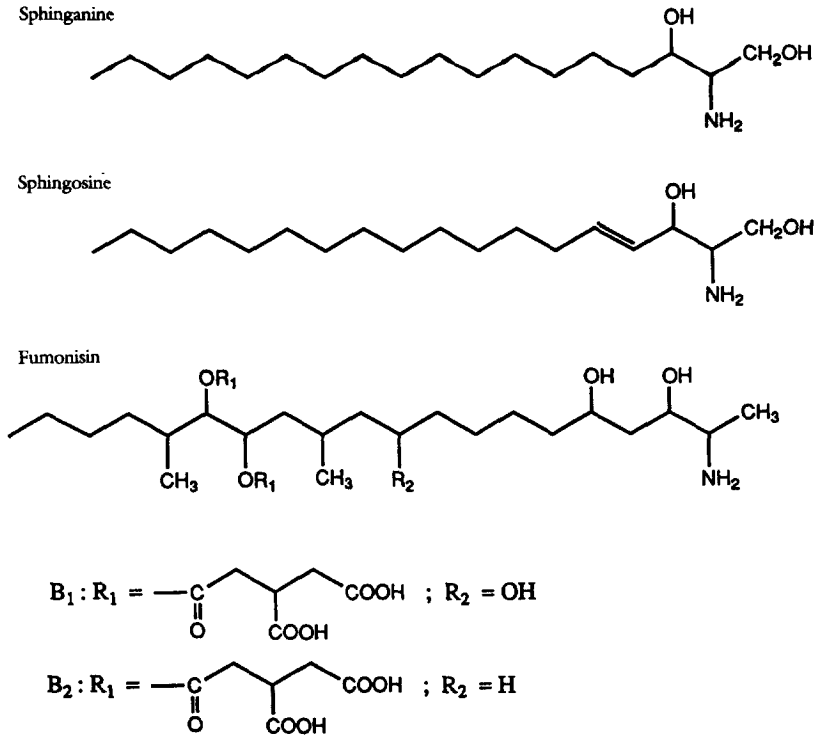

Fig 1. Structural similarity of fumonisins and sphingoid bases.

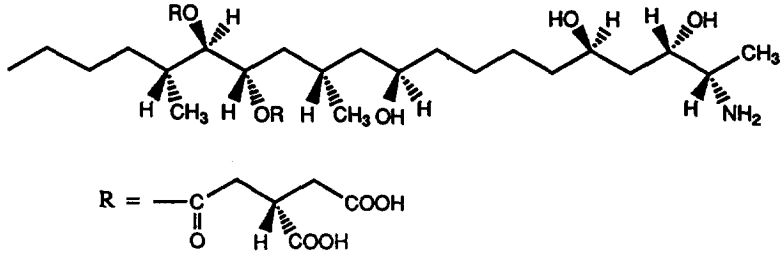

Fig 2. Stereochemistry of fumonisin B_1[65].

proliferation, differentiation, and growth[66,67]. *In vitro* studies with rat hepatocytes and a proliferation cell line of pig kidney cells(LLC-PK1) found that FB_1 and FB_2 block the incorporation of serine into the sphingosine backbone of cellular sphingolipids, causing intracellular accumulation of sphinganine and sphingosine[68,69]. The site of inhibition is ceramide synthase, which catalyzes the conversion of sphinganine to *N*-acyl-sphinganines. The inhibition of *de nove* sphingolipid biosynthesis was found to be reversible after removing FB_1 in cultured neurons[70]. The enzyme sphinganine *N*-acyltranferase normally produces dihydroceramide from sphingosine to ceramide and further on to the sphingolipid. Additionally, FBs have been

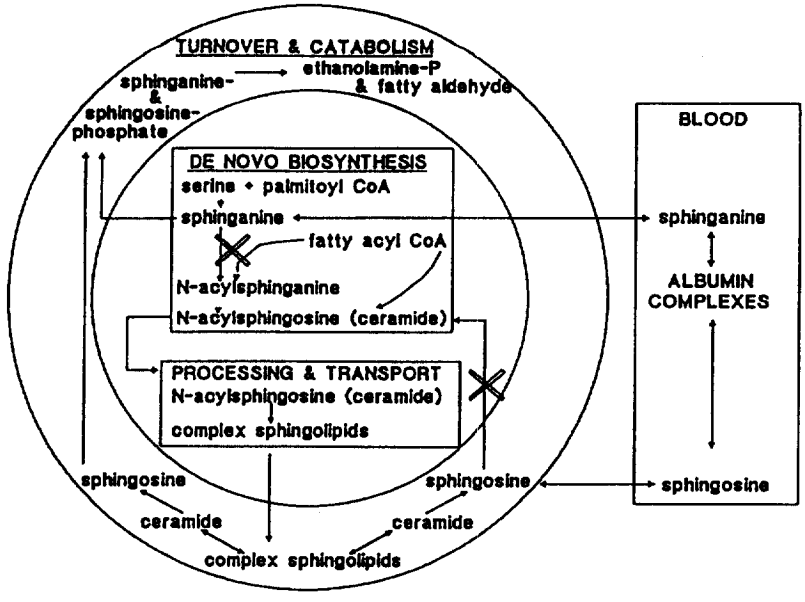

Fig 3. A schematic illustration of the pathway of *de novo* sphingolipid processing(endoplasmic reticulum) and transport(golgi complex and endosomes), and sphingolipid turnover(plasma and nuclear membrane) and catabolism(lysosomes and cytosol) in a mammalian cell. The sites of inhibition("X") by fumonisins and a mechanistic diagram illustration how free sphingoid bases can enter the blood are shown[71].

shown to disrupt sphingolipid metabolism *in vivo* causing elevation of sphingoid bases in serum, urine and tissue. In these cells inhibition of sphingolipid biosynthesis was suggested to cause the animal diseases associated with the consumption of FBs also appeared to inhibit the reacylation of sphingosine within the sphingolipid turnover pathway[71](Fig 3).

The ratio of SA:SO in the sera and tissues of FB-treated animals was increased before detectable lesions of target organs, or before other serum biochemistry changes[41]. This ratio could serve as an early detectable biomarker for diagnosis of FB associated animal disease. However, sphingolipid alterations did not correlate with known target organ damage[64,72]. Another possible mechanism of the toxin is blockage of non-specific carboxylesterases which are observed in the liver, kindney, duodenum and brain at the hightest levels[73]. These enzymes could determine the organ specificity of the toxins in animals.

In an attempt to explain the mechanism that FB acts as a carcinogen, a recent study showed that FB_1 was mitogenic via accumulation of sphingoid bases rather than inhibition of complex sphingolipid biosynthesis *per se.*, providing a plausible molecular mechanism to explain the carcinogenicity of FBs[74]. The mechanism of FB toxicity still remains in a puzzle besides alteration of sphingoid bases.

Summary

FBs, secondary metabolites of several species of *Fusaria*, especially *Fusarium moniliforme* and *F proliferatum*, are commonly contaminated in corn and other food grains throughout the world. Only recently identified, these mycotoxins have been associated field outbreaks of ELEM in horses and PPE in pigs. Currently, naturally or experimentally induced FB toxicosis has been studied in poultry, ruminants and rabbits. Poultry fed FB showed decreased growth rate,

performance, and immune competence, as well as embryopathic, and embryocidal effects, and ricktes. Ruminants seem to be relatively less susceptible to FBs than other doestic animal. FB toxicosis reveals that liver is a target organ in all species, although other organs are affected in a species specific manner. Recently, the main target organs for FB_1 toxicity in rabbits was shown to be the kidney. Even low concentrations of FBs are likely to be a problem for animal health. A current study being conducted showed that feed containing low level of FB_1 reduces the ability of pulmonary intravascular macrophages in pig to clear blood-borne particles which would increase the susceptibility of animals to bacterial disease. The mechanism of FB toxicity remains unknown, but may be related to altered sphingolipid biosynthesis by inhibiting sphinganine *N*-acyltransferase. Elevations of serum and tissue SA:SO ratio have been observed in horse, pig, chicken, turkey, and rabbit, which could could serve as in effective biomarker for consumption of FB-containing feeds. There is limited information detailing dose-effect relationships either from field cases or in the laboratory. More research on the factors, including the prevalence and tolerance levels of FBs in feedstuffs that cause domestic animal disease associated with FBs, is urgently needed.

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