BIOMOLECULES & THERAPEUTICS

Original Article
Biomol Ther 29(1), 52-57 (2021)

Fumonisin B1-Induced Toxicity Was Not Exacerbated in Glutathione Peroxidase-1/Catalase Double Knock Out Mice

Taddesse Yayeh[1], Ha Ram Jeong[2], Yoon Soo Park[2], Sohyeon Moon[3], Bongjun Sur[3], Hwan-Soo Yoo[4] and Seikwan Oh[3,*]

[1]Department of Veterinary Science, College of Agriculture and Environmental Sciences, Bahir Dar University, Bahir Dar 5501, Ethiopia
[2]St. Louis College of Pharmacy, St. Louis, MO 63108, USA
[3]Department of Molecular Medicine, School of Medicine, Ewha Womans University, Seoul 07804,
[4]College of Pharmacy, Chungbuk National University, Osong 28160, Republic of Korea

Abstract

Fumonisin B1 (FB1) structurally resembles sphingolipids and interferes with their metabolism leading to sphingolipid dysregulation. We questioned if FB1 could exacerbate liver or kidney toxicities in glutathione peroxidase 1 (Gpx1) and catalase (Cat) knockout mice. While higher serum levels of thiobarbituric acid reactive substances (TBARS) and sphinganine (*Sa*) were measured in Gpx1/Cat knockout mice (Gpx1/Cat KO) than wild type mice after 5 days of FB1 treatment, serum levels of alanine aminotransferase (ALT), sphingosine-1 phosphate (*So-1-P*), and sphinganine-1 phosphate (*Sa-1-P*) were found to be relatively low. Although *Sa* was highly elevated in Gpx1/Cat KO mice and wild mice, lower levels of *So* and *Sa* were found in both the kidney and liver tissues of Gpx/Cat KO mice than wild type mice after FB1 treatment. Paradoxically, FB1-induced cellular apoptosis and necrosis were hastened under oxidative stress in Gpx1/Cat KO mice.

Key Words: Fumonisin B1, Catalase, Glutathione peroxidase1, Sphingosine, Sphinganine

INTRODUCTION

Sphingolipids are composed of sphingosine, sphinganine (dihydrosphingosine), or a phytosphingosine backbone covalently linked to fatty acid molecules (Ebenezer *et al*., 2016). Although mammalian cells are unable to synthesize sphingosine from dihydrosphingosine (Chalfant and Spiegel, 2005), ceramidases act on ceramide to generate sphingosine (*So*), which can be converted into *So-1-P* by sphingosine kinases (Takabe *et al*., 2008). Sphingolipid dysregulation has been tied with obesity, insulin resistance, hyperglycemia, dyslipidemia and hypertension involving various extracellular and intracellular signals (Aburasayn *et al*., 2016; Chen *et al*., 2016; Kuzmenko and Klimentyeva, 2016). However, emerging evidence is unraveling the crucial role of sphingolipid (*Cer* and *So-1-P*) metabolism in regulating liver injury, repair, and regeneration (Nojima *et al*., 2015).

Food containing fusarium mycotoxins poses considerable public health hazard worldwide (Lin and Guo, 2016), particularly in areas where regulatory measures are either lacking or poorly enforced (Alberts *et al*., 2016). Various fusarium mycotoxins (fumonisins) are produced from *Fusarium fujikuroi*, *Fusarium proliferatum*, and *Fusarium verticillioides* (Matic *et al*., 2013). Out of all the fumonisins, FB1 is the most prevalent in both toxicity and incidence (Raiola *et al*., 2015). Chemically, FB1 consists of different stereoisomers with an unsubstituted primary amine group that interferes with sphingolipid metabolism (Escriva *et al*., 2015) and speeds up sphingoid base accumulation which depletes complex sphingolipids (Bouhet and Oswald, 2007). While the liver and kidneys are the primary target organs for FB1 toxicity in mice, further studies unveiled that FB1 toxicity extends to aggravate necrotic enteritis in broiler chickens (Antonissen *et al*., 2015) and facilitate seizures in mice (Poersch *et al*., 2015). The molecular mechanisms behind FB1 toxicity in liver and kidneys are supposed to be linked with early events associated with altering DNA methylation (Demirel *et al*., 2015) and oxidative stress (Wang *et al*., 2016). Catalase (Cat) and glutathione peroxidase 1 (Gpx1) are antioxidant enzymes responsible for controlling intracellular hydrogen peroxide levels. However, their

Open Access **https://doi.org/10.4062/biomolther.2020.062**

Received Apr 14, 2020 **Revised** Jun 4, 2020 **Accepted** Jun 8, 2020
Published Online Jul 7, 2020

***Corresponding Author**
E-mail: skoh@ewha.ac.kr
Tel: +82-2-6986-6271, Fax: +82-2-6986-7014

genetic polymorphism and gene deficiency could hasten liver and kidney injury (Kang and Alexander, 1996; Kim *et al*., 2009; Sousa *et al*., 2016). Therefore, we posed that Cat and Gpx1 gene depletion could exacerbate FB1 intoxication in mice via dysregulated sphingolipid metabolism.

MATERIALS AND METHODS

Animals

C57/BL6 male mice (21 g body weight and 7-8 weeks old) obtained from Daehan Biolink (Eumsung, Korea), and Gpx1/Cat KO mice were generously donated by Dr. Goo Taeg Oh (Ewha Womans University, Seoul, Korea). Gpx1/Cat KO mice and their congenic background strain (C57BL/6) were acclimated for 1 week in the animal facility (22°C, 12 h light/dark cycle). All procedures were conducted according to the guidelines approved by the Animal Care and Use Committee, Ewha Womans University. Mice were housed in groups (n=8) supplied with chow diet and water *ad libitum*. Wild and Gpx1/Cat KO mice were intraperitoneally (i.p.) administered with FB1 (5 mg/kg) for 5 days. Control groups of mice received saline instead of FB1 in a similar manner. After blood collection from mice 7 h following the final injection, serum was separated and used for enzymatic analysis and lipid peroxidation assays. Liver and kidneys were isolated, and the tissues were sectioned and homogenized to determine sphingolipid levels.

Enzymatic and lipid peroxidation assays

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in serum were assayed to assess for liver function using an automated chemistry analyzer as described earlier (Jung *et al*., 2016). The release of thiobarbituric acid reactive substances (TBARS) was assayed for lipid peroxidation via Cayman's TBARS Assay Kit (Cayman, Ann Arbor, MI, USA).

Sphingolipid determination

Levels of sphingolipids such as *So*, *Sa*, *Cer*, sphingomyelin (*SM*), dihydroceramide (*DHCer*), *So-1-P*, and *Sa-1-P* from serum and tissue lysates of liver and kidney were determined by high-performance liquid chromatography (HPLC) as described previously (Min *et al*., 2002; Kim *et al*., 2006). Briefly, liver and kidney tissue homogenates were lysed in 0.2 N NaOH. Next, chloroform/methanol was added to 200 μg protein and 100 μL serum. 5 min incubation was performed for lipid extraction. After centrifugation (15,000×g, 15 min), the alkaline aqueous phase containing *So-1-P* was transferred to fresh tubes whereas the chloroform phase was mixed with 400 μL of 0.15 M methanolic KOH for sphingoid bases analysis.

Histological examination

Mice were anesthetized with ether and perfused with 0.05 M phosphate-buffered saline (PBS) through the heart. Liver and kidneys were isolated and fixed using 4% paraformaldehyde in 0.1 M phosphate buffer. Then, tissues were embedded in paraffin, sectioned at 5 μm, stained with hematoxylin and eosin (H&E), and examined under a LEICA DM750 microscope (Leica Miscrosystems, Seoul, Korea).

Statistical analysis

All values were expressed as mean ± SEM and comparisons between groups were performed using ANOVA followed by Newman-Keuls multiple comparison test. $p<0.05$ was considered as significant.

RESULTS

FB1-treatement in Gpx1/Cat KO mice was associated with elevated level of TBARS in the serum

Acute liver damage is associated with increased levels of ALT and AST in the serum. We determined the levels of these enzymes at the beginning to examine if acute liver damage occurred after administration of FB1. We found that mice treated with FB1 showed an increased level of AST and ALT enzymes in both wild and Gpx1/Cat KO mice. However, both AST and ALT levels were relatively lower in the serum of Gpx1/Cat KO than their wild-type counter parts although significance was shown only in the ALT levels. Similarly, levels of TBARS (indicator of lipid peroxidation) were increased in FB1-treated wild and Gpx1/Cat KO mice compared to saline-treated groups. Unlike ALT/AST, levels of TBARS in the serum were relatively higher in Gpx1/Cat KO groups of mice than wild type mice treated with FB1 (Fig. 1).

FB1 treatment in Gpx1/Cat KO mice was closely linked with excessive accumulation of sphingoid bases in the serum

Inside the body, FB1 intereferes with sphingolipid metabolism at early stage by obliterating the formation of complex sphingolipids while enhancing the accumulation of sphingoid bases such as *So* and *Sa*. To determine if this imbalance was

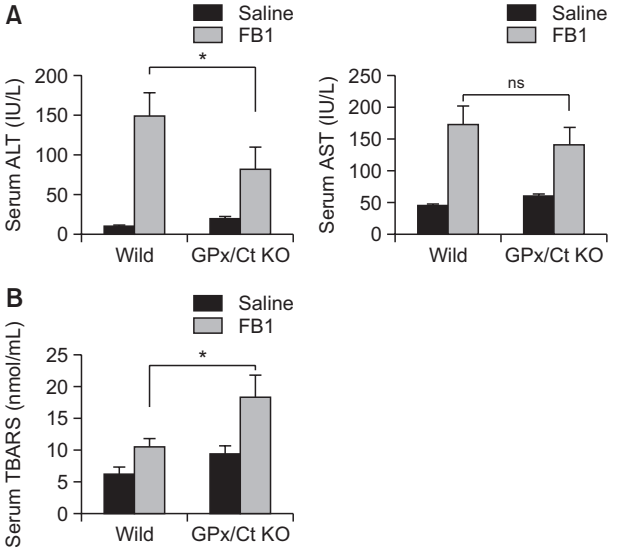

Fig. 1. The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and thiobarbituric acid reactive substances (TBARS) in serum of FB1-treated mice. Mice were treated with FB1 (5 mg/kg, i.p.) daily for 5 days. The levels of ALT and AST (A, B) were assayed from collected serum at 7 h after final injection of FB1 via Automated Chemistry Analyzer. The release of TBARS (C) was assayed via Cayman's TBARS Assay Kit (Cayman, Ann Arbor, MI, USA). *Significant between wild and Gpx/Cat KO groups after treatment with FB1 ($p<0.05$), (n=8).

exacerbated under oxidative stress, we evaluated the concentration of *So*, *Sa*, and their phosphorylation, i.e., *So-1-P* and *Sa-1-P* in the serum. While concentrations of *So* and *Sa* were relatively higher in FB1-teated Gpx1/Cat KO mice than wild-type mice without statistical significance, the levels of *So-1-P* and *Sa-1-P* were lower in Gpx1/Cat KO mice compared to wild-type mice (Fig. 2A, 2B). Like *So* and *Sa* levels, serum *DHCer* level was relatively higher in Gpx1/Cat KO mice than wild-type after treating with FB1. However, serum *Cer* level was lower in Gpx1/Cat KO mice and wild mice (Fig. 2C).

Low levels of *So* and *Sa* were determined in liver and kidney tissues of Gpx1/Cat KO mice with exposure of FB1

The liver and kidneys are the primary organs targeted by FB1 toxicity in mice. Therefore, we determined the concentration of sphingoid bases in these organs. Moreover, histopathological preparations were carried out to examine any damage after FB1 intoxication. When we looked into the histopathological sections in both liver and kidney tissues, leukocyte infiltrations were excess in wild type mice than Gpx1/Cat KO mice (Fig. 3). Lower levels of *So* and *Sa* were found both in liver and kidney tissues after FB1-treatment in Gpx1/Cat KO

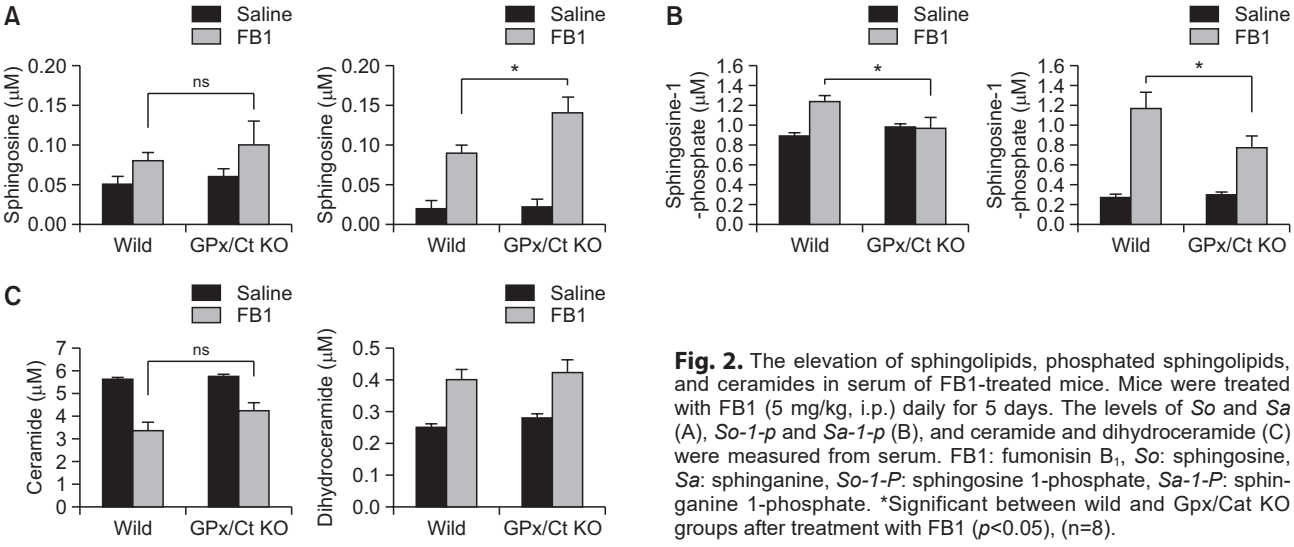

Fig. 2. The elevation of sphingolipids, phosphated sphingolipids, and ceramides in serum of FB1-treated mice. Mice were treated with FB1 (5 mg/kg, i.p.) daily for 5 days. The levels of *So* and *Sa* (A), *So-1-p* and *Sa-1-p* (B), and ceramide and dihydroceramide (C) were measured from serum. FB1: fumonisin B_1, *So*: sphingosine, *Sa*: sphinganine, *So-1-P*: sphingosine 1-phosphate, *Sa-1-P*: sphinganine 1-phosphate. *Significant between wild and Gpx/Cat KO groups after treatment with FB1 (p<0.05), (n=8).

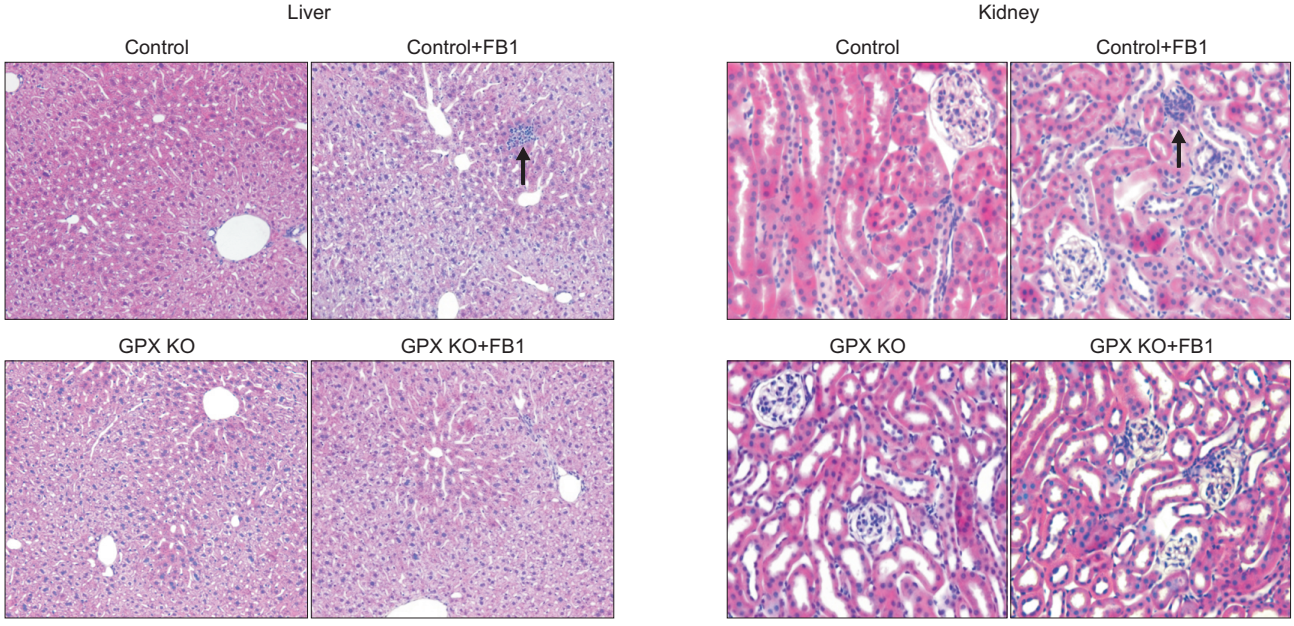

Fig. 3. Histological observation of hepatotoxicity and nephrotoxicity after FB1 treatment. Mice were treated with FB1 (5 mg/kg, i.p.) daily for 5 days. In the FB1-treated liver, sinusoidal/perivenular lymphocytic infiltration and hepatocellular degeneration such as binucleated cells, acidophilic hepatocytes, and apoptotic/necrotic bodies are seen (marked as →) while the control liver shows no inflammatory cell infiltration and hepatocellular change (H&E, ×150). In the FB1-treated kidney, there is interstitial fibrosis, inflammatory infiltration, and tubular dilatation with intraluminal casts (marked as →) while the control kidney shows no interstitial and tubular change (H&E, ×450).

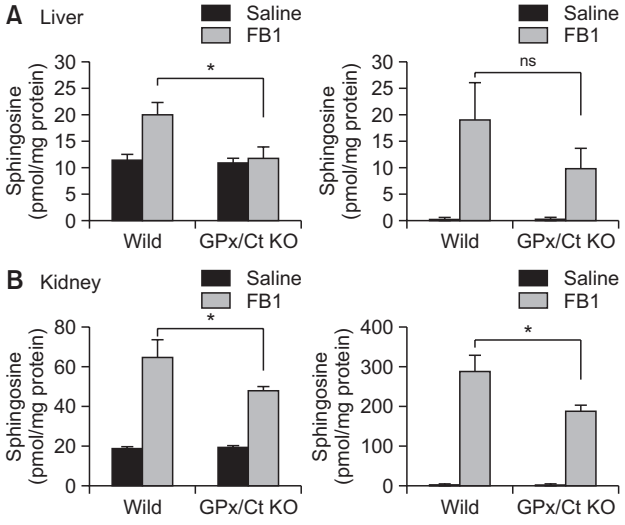

Fig. 4. The elevation of the sphingolipid in tissues of FB1-treated mice. Mice were treated with FB1 (5 mg/kg, i.p.) daily for 5 days. *Significant between wild and Gpx/Cat KO groups after treatment with FB1 (p<0.05), (n=8).

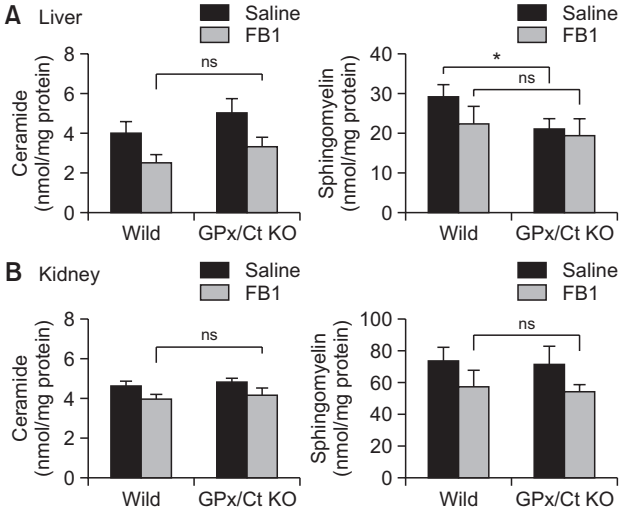

Fig. 5. The levels of ceramide and sphingomyelin in tissues of FB1-treated mice. Mice were treated with FB1 (5 mg/kg, i.p.) daily for 5 days. *Significant between wild and Gpx/Cat KO groups (p<0.05), (n=8).

mice than wild type mice (Fig. 4). Although *Cer* and *SM* levels were found to be decreased or same level in FB1 treated mice compared to saline administered groups in both Gpx1/Cat KO mice and wild mice, concentration differences were not seen between wild type and Gpx1/Cat KO mice after FB1 treatment (Fig. 5).

DISCUSSION

Considering the rampant nature of FB1 toxicities (Lin and Guo, 2016), *in vivo* studies involving sphingolipid metabolism and the anti-oxidant system could have paramount importance. Fusarium species of fungi produce nearly 15 different fumonisins (Escriva *et al*., 2015) with FB1 being predominant. FB1 is highly toxic by inhibiting the enzyme ceramide synthase which metabolizes intracellular sphingosine (*So*) and sphinganine (*Sa*), which produces deleterious effects to cells (Raiola *et al*., 2015). We studied FB1 toxicity in wild type mice and Gpx1/Cat KO) mice. Since the liver is one of the primarily targeted organs in acute FB1 toxicity in mice, we measured the levels of AST and ALT in the serum. We found that serum levels of AST and ALT were increased in FB1 administered mice in a similar manner to acute liver injury during lipopolysaccharide induced inflammation in mice (Tang *et al*., 2016). Serum levels of TBARS were also increased in FB1-treated mice. However, Gpx1/Cat KO mice showed relatively higher level of TBARS than wild type. In contrast, ALT and AST serum levels were relatively lower in knocked down groups of mice than wild type. Increased levels of tissue reactive substances in the serum may be partially explained by oxidative tissue damage either through genetic depletion of major anti-oxidant enzymes or malfunction that could aggravate tissue injury by apoptotic cell death (Dunning *et al*., 2013) thereby increasing serum levels of TBARS as biomarkers of oxidative stress (Tsai and Huang, 2015). In addition, the roles of densely populated peroxisomes in the liver and kidneys may possess unequivocal merit compared to oxidative injury to these tissues (Vasko, 2016). Therefore, it is plausible to speculate that higher serum levels of TBARS in FB1-treated Gpx1/Cat KO mice in this study could be partially explained by sustained cellular apoptosis in the liver and kidney tissues rather than acute tissue necrosis associated with elevation of liver enzymes in the serum. However, further research may be warranted to justify discrepancies between liver enzymes and TBARS levels in the serum during FB1 intoxication.

We found that serum levels of *So* and *Sa* were elevated compared to their phosphorylation types, *So-1-P* and *Sa-1-P*, in mice treated with FB1. The levels of *So* and *Sa* were significantly increased in Gpx1/Cat KO mice treated with FB1 compared to their wild type counter parts whereas *So-1-P* and *Sa-1-P* tend to be decreased. We suggest that elevated levels of *So* and *Sa* might have occurred most likely either due to the dephosphorylation processes of *So-1-P* and *Sa-1-P* by lipid phosphate phosphatases (Tang *et al*., 2015) or created as a metabolite of ceramide during oxidative stress (Hoehn *et al*., 2016). Nevertheless, Gpx1/Cat KO mice serum having depleted *So-1-P* levels may work against its cardio-protective effect (Knapp *et al*., 2013). In addition, ceramide levels were decreased in Gpx1/Cat KO mice and wild type mice after FB1 treatment. However, dihydroceramide level was elevated in both groups. We presumed that higher *Cer* and *DHcer* level in FB1-treated Gpx1/Cat KO mice could be due to the accumulation of reactive oxygen species in the body (Sordillo *et al*., 2015). Due to the fact that the liver and kidneys are primarily targeted organs by FB1 toxicity in mice, we measured the sphingolipid levels from these tissues. Furthermore, we made histological preparations to determine if any pathological conditions were present. When we see the pathway of *de novo* synthesis of sphingolipid and its metabolism, we can understand why the level of *Sa* (*So*) was elevated but the level of *Cer* was decreased after FB1 treatment in mice. FB1 inhibits ceramide synthase and results in the accumulation of *Sa* and *So*. Blockade of ceramide synthase by FB1 resulted in

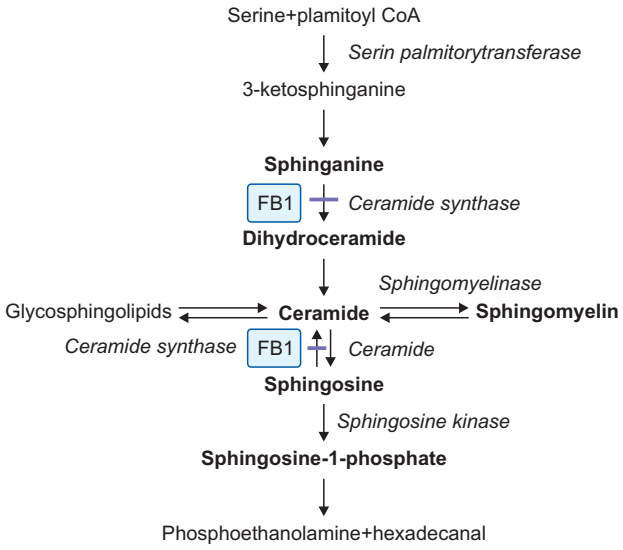

Fig. 6. *De novo* synthesis of sphingolipid and metabolism. Fumonisin B1 (FB1) inhibits ceramide synthase and results in the accumulation of sphinganine and sphingosine. Blockade of ceramide synthase by FB1 results in the decrease of the level of ceramide.

the decreased level of *Cer* (Fig. 6). FB1 toxicity in mice was accompanied by marked elevation of *Sa* levels in liver and kidney tissues. While in Gpx1/Cat KO mice with their wild type counter parts, we found *So* and *Sa* concentrations were less in tissue homogenates obtained from Gpx1/Cat KO mice than wild type mice. We speculated that this could be due to the accumulation of reactive oxygen species in the organs. This notion could be supported by a previous study that showed variations in sphingoid bases in HL-60 cells incubated with H_2O_2 (Son *et al*., 2007), and strengthened by linking the reactive oxygen species with inflammation accompanied by leukocyte infiltration (Voltan *et al*., 2016), as it could be observed from our histological sections infiltrated with leukocytes in liver and kidney tissues.

We conclude that FB1-induced intoxication is associated with escalating levels of *Cer*, *So*, and *Sa* in the serum collected from Gpx1/Cat KO mice compared to their wild counter parts. Although *So* and *Sa* levels were found to be diminished within liver and kidney tissues, concentration of *So-1-P* in the serum was relatively lower in FB1-treated mice of the knocked down group than the wild type. We speculated that FB1 intoxication in Gpx1/Cat KO mice may hasten cellular apoptosis via sphingoid bases during oxidative stress. Considering that FB1-induced tissue injury primarily targets the liver and kidneys, rising serum levels of AST, ALT, and TBARS in Gpx1/Cat KO mice could be an indication for severe necrotic and apoptotic effects of FB1 toxicity in stressed mice. Therefore, enhancing the oxidative system in the body could be an alternative option to reduce the rampant FB1-associated intoxication worldwide.

ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science, ICT, & Future Planning (MRC, 2010-0029355).

REFERENCES

Aburasayn, H., Al Batran, R. and Ussher, J. R. (2016) Targeting ceramide metabolism in obesity. *Am. J. Physiol. Endocrinol. Metab.* **311**, 423-435.

Alberts, J. F., van Zyl, W. H. and Gelderblom, W. C. (2016) Biologically based methods for control of fumonisin-producing fusarium species and reduction of the fumonisins. *Front. Microbiol.* **7**, 548.

Antonissen, G., Croubels, S., Pasmans, F., Ducatelle, R., Eeckhaut, V., Devreese, M., Verlinden, M., Haesebrouck, F., Eeckhout, M., De Saeger, S., Antlinger, B., Novak, B., Martel, A. and Van Immerseel, F. (2015) Fumonisins affect the intestinal microbial homeostasis in broiler chickens, predisposing to necrotic enteritis. *Vet. Res.* **46**, 98.

Bouhet, S. and Oswald, I. P. (2007) The intestine as a possible target for fumonisin toxicity. *Mol. Nutr. Food Res.* **51**, 925-931.

Chalfant, C. E. and Spiegel, S. (2005) Sphingosine 1-phosphate and ceramide 1-phosphate: expanding roles in cell signaling. *J. Cell Sci.* **118**, 4605-4612.

Chen, W., Lu, H., Yang, J., Xiang, H. and Peng, H. (2016) Sphingosine 1-phosphate in metabolic syndrome (review). *Int. J. Mol. Med.* **38**, 1030-1038.

Demirel, G., Alpertunga, B. and Ozden, S. (2015) Role of fumonisin B1 on DNA methylation changes in rat kidney and liver cells. *Pharm. Biol.* **53**, 1302-1310.

Dunning, S., Ur Rehman, A., Tiebosch, M. H., Hannivoort, R. A., Haijer, F. W., Woudenberg, J., van den Heuvel, F. A., Buist-Homan, M., Faber, K. N. and Moshage, H. (2013) Glutathione and antioxidant enzymes serve complementary roles in protecting activated hepatic stellate cells against hydrogen peroxide-induced cell death. *Biochim. Biophys. Acta* **1832**, 2027-2034.

Ebenezer, D. L., Fu, P. and Natarajan, V. (2016) Targeting sphingosine-1-phosphate signaling in lung diseases. *Pharmacol. Ther.* **10**, 30164-30164.

Escriva, L., Font, G. and Manyes, L. (2015) *In vivo* toxicity studies of fusarium mycotoxins in the last decade: a review. *Food Chem. Toxicol.* **78**, 185-206.

Hoehn, R. S., Seitz, A. P., Jernigan, P. L., Gulbins, E. and Edwards, M. J. (2016) Ischemia/reperfusion injury alters sphingolipid metabolism in the gut. *Cell. Physiol. Biochem.* **39**, 1262-1270.

Jung, J. C., Lee, Y. H., Kim, S. H., Kim, K. J., Kim, K. M., Oh, S. and Jung, Y. S. (2016) Hepatoprotective effect of licorice, the root of Glycyrrhiza uralensis Fischer, in alcohol-induced fatty liver disease. *BMC Complement. Altern. Med.* **16**, 19.

Kang, Y. J. and Alexander, J. M. (1996) Alterations of the glutathione redox cycle status in fumonisin B1-treated pig kidney cells. *J. Biochem. Toxicol.* **11**, 121-126.

Kim, D. H., Yoo, H. S., Lee, Y. M., Kie, J. H., Jang, S. and Oh, S. (2006) Elevation of sphinganine 1-phosphate as a predictive biomarker for fumonisin exposure and toxicity in mice. *J. Toxicol. Environ. Health Part A* **69**, 2071-2082.

Kim, S. J., Lee, J. W., Jung, Y. S., Kwon, D. Y., Park, H. K., Ryu, C. S., Kim, S. K., Oh, G. T. and Kim, Y. C. (2009) Ethanol-induced liver injury and changes in sulfur amino acid metabolomics in glutathione peroxidase and catalase double knockout mice. *J. Hepatol.* **50**, 1184-1191.

Knapp, M., Lisowska, A., Zabielski, P., Musial, W. and Baranowski, M. (2013) Sustained decrease in plasma sphingosine-1-phosphate concentration and its accumulation in blood cells in acute myocardial infarction. *Prostaglandins Other Lipid Mediat.* **106**, 53-61.

Kuzmenko, D. I. and Klimentyeva, T. K. (2016) Role of ceramide in apoptosis and development of insulin resistance. *Biochemistry Mosc.* **81**, 913-927.

Lin, X. and Guo, X. (2016) Advances in biosensors, chemosensors and assays for the determination of fusarium mycotoxins. *Toxins (Basel)* **8**, 161.

Matic, S., Spadaro, D., Prelle, A., Gullino, M. L. and Garibaldi, A. (2013) Light affects fumonisin production in strains of Fusarium fu-

jikuroi, Fusarium proliferatum, and Fusarium verticillioides isolated from rice. *Int. J. Food Microbiol.* **166**, 515-523.

Min, J. K., Yoo, H. S., Lee, E. Y., Lee, W. J. and Lee, Y. M. (2002) Simultaneous quantitative analysis of sphingoid base 1-phosphates in biological samples by o-phthalaldehyde precolumn derivatization after dephosphorylation with alkaline phosphatase. *Anal. Biochem.* **303**, 167-175.

Nojima, H., Freeman, C. M., Gulbins, E. and Lentsch, A. B. (2015) Sphingolipids in liver injury, repair and regeneration. *Biol. Chem.* **396**, 633-643.

Poersch, A. B., Trombetta, F., Souto, N. S., de Oliveira Lima, C., Braga, A. C., Dobrachinski, F., Ribeiro, L. R., Soares, F. A., Fighera, M. R., Royes, L. F., Oliveira, M. S. and Furian, A. F. (2015) Fumonisin B1 facilitates seizures induced by pentylenetetrazol in mice. *Neurotoxicol. Teratol.* **51**, 61-67.

Raiola, A., Tenore, G. C., Manyes, L., Meca, G. and Ritieni, A. (2015) Risk analysis of main mycotoxins occurring in food for children: an overview. *Food Chem. Toxicol.* **84**, 169-180.

Son, J. H., Yoo, H. H. and Kim, D. H. (2007) Activation of de novo synthetic pathway of ceramides is responsible for the initiation of hydrogen peroxide-induced apoptosis in HL-60 cells. *J. Toxicol. Environ. Health Part A* **70**, 1310-1318.

Sordillo, P. P., Sordillo, D. C. and Helson, L. (2015) Review: the prolonged QT interval: role of pro-inflammatory cytokines, reactive oxygen species and the ceramide and sphingosine-1 phosphate pathways. *In Vivo* **29**, 619-636.

Sousa, V. C., Carmo, R. F., Vasconcelos, L. R., Aroucha, D. C., Pereira, L. M., Moura, P. and Cavalcanti, M. S. (2016) Association of catalase and glutathione peroxidase 1 polymorphisms with chronic hepatitis C outcome. *Ann. Hum. Genet.* **80**, 145-153.

Takabe, K., Paugh, S. W., Milstien, S. and Spiegel, S. (2008) "Inside-out" signaling of sphingosine-1-phosphate: therapeutic targets. *Pharmacol. Rev.* **60**, 181-195.

Tang, J., Li, C. M., Li, L., Wu, J. and Wang, G. L. (2016) Changes in expression and production of heme oxygenase-1 in rats with acute liver injury induced by lipopolysaccharide. *J. Toxicol. Sci.* **41**, 469-477.

Tang, X., Benesch, M. G. and Brindley, D. N. (2015) Lipid phosphate phosphatases and their roles in mammalian physiology and pathology. *J. Lipid Res.* **56**, 2048-2060.

Tsai, M. C. and Huang, T. L. (2015) Thiobarbituric acid reactive substances (TBARS) is a state biomarker of oxidative stress in bipolar patients in a manic phase. *J. Affect. Disord.* **173**, 22-26.

Vasko, R. (2016) Peroxisomes and kidney injury. *Antioxid. Redox Signal.* **25**, 217-231.

Voltan, R., Secchiero, P., Casciano, F., Milani, D., Zauli, G. and Tisato, V. (2016) Redox signaling and oxidative stress: cross talk with TNF-related apoptosis inducing ligand activity. *Int. J. Biochem. Cell Biol.* **26**, 30281-30283.

Wang, X., Wu, Q., Wan, D., Liu, Q., Chen, D., Liu, Z., Martinez-Larranaga, M. R., Martinez, M. A., Anadon, A. and Yuan, Z. (2016) Fumonisins: oxidative stress-mediated toxicity and metabolism *in vivo* and *in vitro*. *Arch. Toxicol.* **90**, 81-101.