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Life Sciences 71 (2002) 2015–2023

Life Sciences

www.elsevier.com/locate/lifescie

Fumonisin B_1 alters sphingolipid metabolism and tumor necrosis factor α expression in heart and lung of mice

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Received 23 October 2001; accepted 10 May 2002

Abstract

Fumonisin B_1 (FB_1), produced by *Fusarium verticillioides,* is a common contaminant in foods and feeds. Increase in tissue free sphingoid bases resulting from the inhibition of ceramide synthase is a biomarker of fumonisin exposure. Tumor necrosis factor α (TNFα) is induced in liver in response to FB_1 treatment. This study determined whether fumonisin B_1 caused increases in free sphingoid bases and altered the expression of TNFα in heart and lung, organs that are not targets of FB_1 toxicity, of male and female mice treated with 5-daily subcutaneous injection of 2.25 mg/kg FB_1. A significant increase in free sphingoid bases was observed in both heart and lung of FB_1-exposed mice. The magnitude of increases in free sphingoid bases in both organs of female mice was much higher than that in males. The expression of TNFα was increased by FB_1 treatment in the lung of male mice and in the heart of female mice, whereas the expression of interferon γ was unaltered. Results suggest that both sphingolipid accumulation and TNFα induction are observed in the tissues of mice that are not associated with FB_1 toxicity.

Keywords: Fumonisin; Heart; Lung; Sphingolipid; Tumor necrosis factor α

Introduction

Fumonisins are a group of structurally related mycotoxins produced by *Fusarium verticillioides (*formerly *F. moniliforme)* and *F. proliferatum,* commonly found on corn [1]. Fumonisin B_1 (FB_1) is the

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PII: S0024-3205(02)01988-4

most abundant fumonisin in naturally contaminated foods and feeds. Fumonisins cause equine leukoencephalomalacia and porcine pulmonary edema [2]. It is carcinogenic in rats [3] and mice [4]. Epidemiological surveys reported that there were significantly higher levels of FB_1 in corn samples from high incidence areas of esophageal cancer in Transkei, South Africa than in corresponding samples from low incidence areas [2]; a relationship between fumonisin and primary liver cancer in China has also been suggested [5]. Fumonisin B_1 induces apoptosis and necrosis in many types of cultured cells [6–8] and in liver and kidney in rodents [9,10].

Fumonisin B_1 is structurally similar to sphinganine, and is a potent inhibitor of ceramide synthase (sphinganine and sphingosine-*N*-acyl transferase), a key enzyme responsible for acylation of sphinganine in the *de novo* synthesis of sphingolipid and the reacylation of sphingosine [11,12]. The inhibition of ceramide synthase by FB_1 results in the accumulation of intracellular free sphinganine and sphingosine, and decrease of more complex sphingolipids [8,13]. Studies in pig renal epithelial cells, colonic cells, and human keratinocytes have shown that FB_1-induced apoptosis and necrosis are sphinganine-dependent [8,14,15]. It has been reported that there is a close correlation between FB_1-induced hepatopathy and nephropathy and the disruption of sphingolipid metabolism [13,16].

Previous studies have shown a potential role of tumor necrosis factorα (TNFα) in FB_1 toxicity [9,17–21]. The TNFα activity and expression of TNFα mRNA were increased in FB_1-treated mice [9,17,18,22]. The TNFα pathway was activated in cells treated with FB_1 [19–21]. Other inflammatory cytokines including interferon (IFN) γ were increased in the liver of mice after FB_1 treatment [22].

Lung and heart are the target organs of fumonisins in pigs [23,24]. The National Toxicology Program conducted a 2-year feeding study using rats and mice; the oncogenic and pathologic effects of FB_1 were limited to male rat kidney and female mouse liver [4]. Accumulation of *de novo* synthesized sphinganine is an early biochemical change in liver and kidney in response to FB_1 treatment at doses below those that produce morphological evidence of injury, and these increases in tissue free sphinganine occurs before evident damage can be detected [25]. Moreover, it has been reported that free sphinganine and sphingosine increased in heart and serum of milk-fed calves after FB_1 treatment (intravenous, 1 mg/kg/day for 7 days), but no cardiovascular damage was detected [26], although the degree of increases in free sphingoid bases was greater in these calves than in pigs associated with myocardial dysfunction [23]. It is of interest to investigate whether FB_1 would influence sphingolipid metabolism in heart and lung, which are not principal target organs in either sex of mice. In the current study, exposure of male or female BALB/c mice to 2.25 mg/kg/day FB_1 for 5 consecutive days resulted in accumulation of free sphingoid bases as well as increase in the expression of TNFα mRNA in both heart and lungs. Results suggest that the organ specificity to FB_1 may depend on other intrinsic factors in addition to sphingoid bases accumulation and cytokine modulation.

Materials and method

Animals and treatment

Male and female BALB/c mice, 7–8 weeks old, were obtained from Harlan Laboratories (Indianapolis, IN). The animals were acclimated in the University of Georgia Animal Resources facility for one