Chapter

Aflatoxin and Disruption of Energy Metabolism

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Abstract

Aflatoxins constitute a cluster of mycotoxins that are derived from fungal metabolites and are produced from diverse fungi species, especially *Aspergillus.* They are a collection of closely linked heterocyclic compounds produced predominantly by two filamentous fungi, *Aspergillus flavus* and *Aspergillus parasiticus.* They are also known to cause severe health threats to humans and animals, thereby resulting to several complications like immunotoxicity, teratogenicity hepatotoxicity. Aflatoxins interfere with normal metabolic processes. This interference encompasses the regulatory processes that occur throughout the progression of energy metabolism. Thus, the effects of aflatoxins are seen in the inhibition of ATP generation, carbohydrate and lipid metabolism, mitochondrial structure and proteins synthesis. This chapter will focus on the mechanisms of aflatoxin-induced disruption of lipids, carbohydrates, and proteins metabolism, and how they affect the bioenergetic systems.

Keywords: aflatoxin, mitochondria, lipids, carbohydrates, proteins, energy

1. Introduction

Aflatoxins constitute a cluster of mycotoxins that are derived from fungal metabolites and are produced from diverse fungi species, especially *Aspergillus* [1]. They are a collection of closely linked heterocyclic compounds produced predominantly by two filamentous fungi, *Aspergillus flavus* and *Aspergillus parasiticus* [2]. These fungi are generally infectious to cereal produces like wheat, walnut, rice, cotton, peanuts, tree nuts and corn [3]. Aflatoxins are members of the difuranocoumarins with two significant chemical structure series. These series include – (a) difurocoumarocyclopentenone series (b) difurocoumarolactone series [4]. They are also known to cause severe health threats to humans and animals, thereby resulting to several complications like immunotoxicity, teratogenicity hepatotoxicity [5]. The key aflatoxins are B1, B2, G1, and G2. They are noted for their ability to induce huge amplification of inflammatory responses during the body's, cutaneous and mucous respiratory cycles [6].

Food contamination by aflatoxin is a global concern particularly in the tropical and subtropical areas of the biosphere whereby warm temperatures and moisture enhance the growth of the Aspergillus fungi. Aflatoxins are well recognized carcinogens specifically aflatoxin B1 (AFB1) to man and animals [4]. Currently, there are over 18 identified aflatoxins of which have been inadequately researched for their

occurrence, health-risk, and mechanisms of toxicity [7]. Owing to their extensive distribution in foods and feeds, Aflatoxins are the mycotoxins of utmost concern to food security. As a result of the public health fears that these toxicants add and their relationship with energy metabolism disruption, intensive findings have been carried out since their discovery to elucidate their interference with energy metabolism and related concerns. The elucidation of these toxic features is a criterion to the design of therapeutic or protective means, and to sufficiently regulate their existence in foods and feeds [8].

Aflatoxins are extremely lipo-soluble compounds; hence they are readily absorbed via the gastrointestinal tract and respiratory tract which is usually their site of exposure into blood stream [9, 10]. Aflatoxins are found in human and animals based on two significant routes. They are either directly ingested as aflatoxin-contaminated foods or inhaled from dust particles containing aflatoxin, usually expelled from industries and factories [9, 11]. In the body, aflatoxins are absorbed across the cell membranes where they enter the blood stream. From the blood stream, they are distributed in blood to various tissues, especially the liver which is the primary organ for metabolism of xenobiotic [11]. Aflatoxins are predominantly metabolized by the liver to yield a reactive epoxide intermediate, to be converted to a less harmful aflatoxin [12, 13]. In humans and predisposed animal species, aflatoxins, particularly Aflatoxin B1 (AFB1) are metabolized by cytochrome P450 (CYP450) microsomal enzymes to yield aflatoxin-8, 9-epoxide. This metabolite is a responsive form that binds to DNA and to albumin usually in the blood serum, giving rise to adducts and thus triggering DNA impairment [12, 13].

2. Aflatoxin-induced disruption of energy metabolism

Aflatoxins interfere with normal metabolic processes. This interference encompasses the regulatory processes that occur throughout the progression of energy metabolism. Thus, the effects of aflatoxins are seen in the inhibition of ATP generation, carbohydrate and lipid metabolism, mitochondrial structure and proteins synthesis [14].

2.1 Inhibition of ATP generation

Aflatoxin B1 (AFB1), a member of the mycotoxins inhibits the electron transport chain (ETC) in the mitochondria which is a major tissue in energy metabolism. This inhibition occurs at both ADP-coupled and dDNDP-uncoupled stages [15]. At the cytochrome oxidase level and also between cytochrome b and c, AFB1 inhibits the electron transport chain. This however, can be reversed by the electron acceptor N′-tetramethylphenylenediamine (TMPD) [4]. AFB1 gives rise to reduction in cellular ATP synthesis. Consequently, an enlargement of the mitochondria develops and then sodium, potassium gradient is distressed within the cell [16].

2.2 Effect of aflatoxins on mitochondrial DNA

In the mitochondria, AFB causes radical structural changes [17–19]. Similarly, it causes mitochondrial directed apoptosis, consequently reducing their function [17, 18, 20]. The presence of aflatoxins may also disturb the telomere length and the different check points in the cell cycle, thereby initiating further harm to the regulatory processes of the cell cycle [20]. Furthermore, the degree of aflatoxin binding to DNA and its injured state, the stages of various protein modifications ranging from cell cycle and apoptotic pathways like protein kinase C (PKC), protein

kinase A (PKA), c-Myc, pRb, Ras, Bcl-2, p53, NF-kB, CKI, cyclins and CDK have significant implications to the life processes that may lead to the deregulation of cell proliferation resulting in the development of cancer [17, 18].

During hepatocarcinogenesis, the reactive aflatoxin-8,9-epoxide binds to mitochondrial DNA (mitDNA) when compared to nuclear DNA which prevents the production of ATP and FAD/NAD-linked enzymatic roles [19]. This results in the disturbance of mitochondrial functions in different body parts that require energy production in form of ATP [19]. Mitochondrial damage as a result of aflatoxin influence can give rise to mitochondrial illnesses and may account for aging mechanisms [19]. Reports have stated that specific mitochondrial diseases occur as a result of the nucleus being able to detect energy deficits in its region. The nucleus then tries to recompense the ATP shortages by initiating the replication of any neighboring mitochondria; however, the feedback enhances replication of the original mitochondria that causes the energy deficit, thus, causing further complications [15]. Gene mutations are also seen when AFBI binds to DNA. This is such that structural alterations are formed, which results in length changes of the telomeres and the cell cycle check points [17, 18]. Also, the binding of Aflatoxin B1 to DNA at the guanine base in hepatic cells corrupts the genomic code that controls cell growth, thereby resulting in the formation of tumors [17–19]. The injury to mitochondrial DNA is initiated by mutations of mitochondrial membranes resulting in heightened apoptosis as well as a disruption in the production of energy [18, 21, 22].

2.3 Carbohydrate and lipid metabolism

Metabolites of aflatoxin react with various cells, which in turn cause the inhibition of carbohydrate and lipid metabolism, as well as reduced liver function [23, 24]. The gluconeogenesis process is inhibited by AFB1. This is done by a reduction in the activity of glycogen synthase and transglycolase. This accounts for the rearrangement and elongation of glycogen molecules [15]. Furthermore, AFB1 lowers the enzymatic function of phosphorglucomutase, which reversibly converts glucose –6-phosphate to glucose –1-phosphate. It also lowers the amount of glycogen present in the liver via the oxidation of glucose –6- phosphate [4]. A major interference caused by aflatoxins, especially AFB1, is the process of lipid deposition in the hepatic tissue. This can be attributed to impaired lipid transport in contrast with a prediction of increased lipid biosynthesis [15]. This lipid deposition in the hepatic tissue can be ascribed to a decreased oxidation of fat as the mitochondria are being compromised [15]. Also increased fat contents have been reported in plasma, liver, and adipose tissues in several studies [25–27] and linked to reduced oxidation of lipids and increased fatty acid synthesis, owing to altered expression of genes involved in lipid and lipoprotein metabolism, following AFB1 exposure [26].

2.4 Inhibition of proteins synthesis

Metabolites of Aflatoxins exhibit negative effects with diverse cells, which inhibit the synthesis of protein [28]. AFB1 directly inhibits the production of protein via the inactivation of enzymes involved in protein synthesis; that is initiation, transcription and translation processes of protein synthesis. Indirectly, AFBI inhibits protein production by changing the activity of DNA template. They obstruct pyrimidine and purines nucleosides subsequently leading to the inhibition of protein synthesis via the development of DNA, RNA and protein adducts [4].

Furthermore, the decrease in protein content of body tissues such as the kidney, heart, skeletal muscle and liver could be due to increased liver and kidney necrosis [29].

AFB1 is known to be mutagenic, immunosuppressive and teratogenic. These features may interfere with regular processes of protein production as well as inhibition of several metabolic systems; consequently, initiating harms to several organs particularly the kidney, heart and liver [15, 30]. The precise reversible non-covalent and nonspecific-irreversible covalent binding with aflatoxins can alter the activities and structure of proteins [21].

3. Conclusion

Aflatoxins, a cluster of mycotoxins produced by *Aspergillus* and other fungal species, are known to interfere with normal metabolic processes, thereby posing severe health threats to humans and animals. This chapter focused on mechanisms underlying aflatoxin-induced inhibition of energy metabolism, which involve disruption of lipids, carbohydrates, and proteins metabolism, as well as mitochondrial function, culminating in depletion of ATP pools.

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