Neurotoxicity mechanism of Ochratoxin A

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REVIEW ARTICLE

Abstract

Mycotoxins, such as Ochratoxins, are widely distributed in nature and are common contaminants of human foodstuffs. Ochratoxins are a group of mycotoxins produced by a wide range of molds. Ochratoxin A (OTA), the most prominent member of this toxin family, is produced by various *Aspergillus* and *Penicillium* species. OTA is frequently found in foods such as cereals, oleaginous seeds, coffee, and meat products. This mycotoxin has been described as teratogenic, genotoxic, carcinogenic, and immunotoxic, and has been proven to be a potent neurotoxin. In the present study, the neurotoxicological perspective of OTA was reviewed and discussed. The main possible mechanisms of neurotoxicity are oxidative DNA, protein and lipid damage, and apoptosis. However, further studies are needed to conclude the exact neurotoxicity mechanism of OTA and find the approaches that reduce the neurotoxicity induced by OTA.

Keywords: brain; mycotoxins; neurotoxicity; Ochratoxin A

Introduction

Mycotoxins are a group of secondary metabolites that are often produced by fungi such as *Penicillium* and *Aspergillus* (Frisvad *et al.*, 2018; Magan and Aldred, 2007). The greatest threats to these toxins are related to food, especially cereals. The various diseases threatening these mycotoxins range from simple allergic responses to immune suppression and cancer (Pitt, 2000). Mycotoxins are the most important fungal metabolites that, due to their high prevalence, can damage human and animal health. Ochratoxin A (OTA) is one of the most important mycotoxins that have an interactive effect on cells and widely affect human and animal health. Produced by *A. ochraceus* and *P. verrucosum* OTA (Lund and Frisvad, 2003), it is able to enter the human food chain through the introduction of livestock products (Magan and Aldred, 2005), the animal feeding of contaminated grains, as well as the consumption of food products (Otteneder and Majerus, 2000). OTA has little solubility in water and is highly soluble in organic solvents. Thus, the uptake of OTA from biological membranes is easily accomplished. This toxin is structurally solid and white in color and is also heat-resistant. Analysis of OTA's structure reveals a polyketide-derived secondary metabolite that contains a dihydrocoumarin moiety coupled to l-β-phenylalanine (Phe), derived from the shikimic acid pathway, by an amide bond (Huffman *et al.*, 2010).

Reportedly, OTA is detectable in most blood samples even at very low levels in most people. OTA is known as a cause of Balkan Endemic Nephropathy (Agarwal *et al.*, 2020). For example, OTA was detected in 58% of human milk (as high as 6.6 μg/l). OTA also was detected in the urine of pregnant women and 100% of human blood samples (maximum 0.04 μg/L). According to these studies, infants are likely exposed to the level of 1 ng/kg body weight, which is above the recommended dose per day (Skaug *et al.*, 2001). This mycotoxin, in particular, is a succinate inhibitor in the electron transport chain and

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is capable of causing neurogenic disorders, especially Parkinson's disease, through a mechanism similar to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and rotenone. The International Agency for Cancer Research has classified OTA as a type 2B carcinogen, and it has been shown to be capable of causing DNA damage as well (Sueck *et al.*, 2019). This toxin affects organs, such as the kidney and the liver, bypassing the placenta, causing inappropriate effects of mutagenesis and suppression of the immune system, especially in monocytes and lymphocyte function (Köhler *et al.*, 2002). As noted, ochratoxins consist of an isocoumarin moiety and a phenylalanine moiety linked by an amide bond (Figure 1). According to research, OTA is chlorinated, Ochratoxin B is not chlorinated, and Ochratoxin C is the ethyl ester of OTA, OTB, and OTC, which is less toxic and less common. The most important focus group is the OTA. OTA is introduced with the following specifications (C20H18ClNO6; with melting point: 168–173°C and molecular weight: 403.8) (Petzinger and Ziegler, 2000).

Therefore, the most important mycotoxins are effective in neurotoxicity mentioned in Table 1. Given the importance and scope of mycotoxins, we investigate the mechanism of neurotoxicity induced by OTA as one of the most important mycotoxins. In terms of temperature tolerance, OTA is resistance for 3 hours of high temperature (121°C) and pressure steam sterilization (Blanc *et al.*, 1998; van der Stegen *et al.*, 2001). Ochratoxin is classified as a Class 2B substance by the International Agency for Research on Cancer (IARC) and World Health Organization (WHO) (Pfohl-Leszkowicz and Manderville, 2007; Rindi *et al.*, 2018). Various studies,

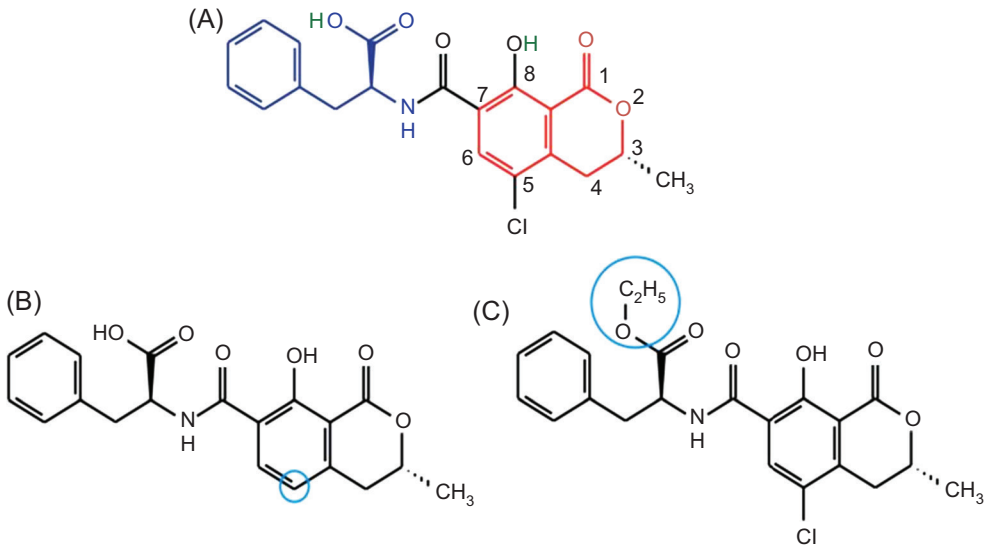

Figure 1. Chemical structures of (A) Ochratoxin A, (B) Ochratoxin B and (C) Ochratoxin C. Red color related to dihydroisocoumarin ring and dark blue related to phenylalanine part.

Table 1. Important mycotoxins-induced neurotoxicity.

Mycotoxins	Species producer	Chemical Formula	Metabolism	Exposure	Neurotoxicity Mechanism
T-2 Toxin	*Fusarium. sporotichioides*	$C_{24}H_{34}O_9$	Ester hydrolysis Hydroxylation	Corn, Wheat Barley, Rice	Mitogen-activated protein kinases (MAPKs)
Macrocyclic Trichothecenes	*Stachybotrys chartarum*	$C_{27}H_{29}O_{10}$	Peptidyl Transferase Inhibition	Food stuffs or in livestock feeds	DNA damage MAPKs Inflammation Sesquiterpenoid compound
Fumonisin B1	*Fusarium verticillioides*	$C_{34}H_{59}NO_{15}$	Changes in Lipid Metabolism	Orally via food	Inflammation Apoptosis Isoflavonoid compound
Ochratoxin A	*Aspergillus ochraceus*	$C_{20}H_{18}ClNO_6$	Phenylalanine t-RNA inhibition	Coffee, Wheat Barley, Rice	Inflammation Apoptosis MAPKs

including in vivo studies and in vitro studies, have investigated the toxic effects of ochratoxin. Nowadays, ochratoxin is very prominent among other toxins and despite its toxicity to organs such as kidney and liver, it also causes extensive toxicity to nerve tissues (Fuchs *et al.*, 2001). Different toxicity mechanisms have been suggested for OTA, such as cell death and oxidative stress. Extensive studies have been carried out on the development of digestive, urinary, immune, and reproductive toxicity by Ochratoxin. Hence, in the present study, we tried to review all possible articles from the neurotoxicological perspective of OTA.

Regulation of Ochratoxins in Foods

The fungi responsible for OTA contamination vary from crop to crop and from place to place.

The general rule, succinctly stated by authors, is "Ochratoxin A is produced by *Penicillium verrucosum* in cereal grains in cold climates, by *A. carbonarius* in grapes, wines, and vine fruits, and by *A. ochraceus* sometimes in coffee beans" (Seabra *et al.*, 2020). However, *P. verrucosum* has recently been found in cereals in warmer climates: Italy, Spain, France, and Portugal (Czerwiecki, 2001). In general, the average concentration of OTA is reported to range from 0.1 to 100 ng per gram of foodstuffs of plant origin (Dhanshetty and Banerjee, 2019). Due to the proliferation of mycotoxin infections, such as aflatoxins and Ochratoxin, here are some cases of contamination with Ochratoxin. According to European Union (EU) reports and surveillance, the restrictions on Ochratoxin include 5 μg/kg in raw cereal grains, 10 μg/kg in dried vine fruits (raisins), and 3 μ/kg in processed cereal foods (FAO). The EU also announced restrictions on the amount of Ochratoxins in wine (2.0 μg/kg), grape juice (2.0 μg/kg), and coffee (10.0 μg/kg for instant coffee, 5.0 μg/kg for roasted coffee) since April of 2005 (FAO, 2005). The cases reviewed in 2005 were reevaluated in 2006. Other European countries have also introduced restrictions on the amount of Ochratoxin in coffee beans. In Italy, for example, this number was reported at 8 μg/kg (FAO, 2005). The sensitivities shown to control pollution in coffee are due to its high economic value and the importance of its export to developing countries (Iriondo-DeHond *et al.*, 2019). Because coffee beans are stored in inappropriate places, it is not possible to accurately detect contamination. According to the opinions and forecasts of the European Coffee Federation, the maximum permitted level of Ochratoxin in green coffee is 5 μ/kg, which could reject 18% of transactions in South Africa (Romani *et al.*, 2000). After the Joint Food and Agricultural Organization (FAO)/WHO Expert Committee on Food Additives (JECFA), an expert body which provides scientific advice to the CAC, repeatedly dealt with OTA in 1991, 1995, 2001, and 2007, a maximum limit of 5 μg/kg with respect to wheat, barley, and rye has been recently established under the Codex General Standard for Contaminants and Toxins in Food and Feed (Ropejko and Twarużek, 2019). In contrast, the United States has not individually reported dietary restrictions for Ochratoxin levels (Yu *et al.*, 2019). However, the absence of these restrictions has a significant impact on the economy of each country (Lee *et al.*, 2019). Numerous exposures to diets with Ochratoxin contamination remains a significant source of OTA exposure in humans (Huong *et al.*, 2019). Background studies on average levels of OTA in humans eating a typical diet have, however, only shown modest elevations in urinary OTA levels, well under the 2.0 ppb limit of detection level used by the commercial lab to test these patients (Czerwiecki, 2001; Duarte *et al.*, 2010; Fazekas *et al.*, 2002).

Toxicokinetics of OTA

Absorption

Studies show that OTA can affect plasma membrane micro domains as one of the important factors in intestinal transport and thereby alter the uptake through the intestinal epithelium (Maresca *et al.*, 2001). The amount of uptake varies by species, for example, up to 60% uptake in pigs, which is much more than in rodents (Studer-Rohr *et al.*, 2000). Studies have reported lower plasma levels of Ochratoxin B protein than OTA, which indicates less toxicity of Ochratoxin B (Coronel *et al.*, 2010; Galtier *et al.*, 1981; Heussner and Bingle, 2015). According to studies, the bioavailability of oral OTA in humans was the highest at 93%. Nonionic and mono-ionic forms of OTA have high reabsorption capacity through the stomach and proximal jejunum (Ricci *et al.*, 2021). As regards of OTA uptake in intestinal lumen, MRP2 (multidrug resistance-associated protein) can decrease OTA absorption (Berger *et al.*, 2003). In addition to the above, studies show that OTA inhibits intestinal absorption and reduces the rate of reabsorption of the intestinal epithelium and intestinal transport activity (Maresca *et al.*, 2001; Ranaldi *et al.*, 2009).

Distribution

One of the distribution systems of OTA is through binding to plasma proteins (Studer-Rohr *et al.*, 2000). OTA has a high potential for binding to plasma albumin. But, studies have reported a small amount of OTA in blood erythrocytes located on the subdomain (Perry *et al.*, 2004). Some proteins with molecular masses (more than 20 kDa) bind to albumin. These proteins were lower in concentration than albumin. Several studies have been

performed on the distribution of OTA in tissues (Biró *et al.*, 2002). Studies of traceability have reported that 0.04 µg/l (100%) OTA was detected in blood samples. It was indicated that OTA is detected at 0.9 µg/l (58%) in Norwegian human milk samples, which is lower than reported in plasma samples in different studies (Skaug *et al.*, 2001). Similar studies in Sweden reported blood plasma levels of OTA from 0.09 to 0.9 µg/l and also 21% (1.8 µg/l) in breast milk samples of nephropathy patients. In a Tunisian study, both blood and food samples from nephropathy patients had significantly higher OTA levels than healthy controls (Commission, 1998). In a Taiwanese study, excretion of OTA in urine of diabetes mellitus patients was significantly higher than in control patients, and patients with other types of nephropathy (Hsieh *et al.*, 2004). These show correlation rather than causality, but taken together they suggest that exposure to high OTA levels is associated with damage to various organs (Chen and Wu, 2017; Skaug *et al.*, 2001).

Excretion

Excretion of OTA is often by secretion through the renal tubes and partly due to glomerular filtration due to the ability of OTA to bind to albumin (Il'ichev *et al.*, 2002; Perry *et al.*, 2003). Studies show that OAT1 is one of the most important receptors in the kidney and OAT3 in the liver and brain, which plays a major role in the reabsorption of toxins from the blood into the tissue (Jung *et al.*, 2001). Studies of the reabsorption of this toxin in renal nephrons have reported both active and inactive pathways (Berger *et al.*, 2003; Leier *et al.*, 2000). Enterohepatic circulation is another fecal excretion of OTA, which enhances the slow elimination of toxicants from the body (Schrickx *et al.*, 2006). BCRP (Breast cancer resistance protein) transporters were known as important for intestinal excretion of OTA (Skaug *et al.*, 2001). In animals, especially in rodents, the role of entero-hepatic circulation of OTA has been demonstrated. In addition, the conjugated form of the toxin is excreted tthrough bile in the studied rat specimens. Moreover, studies have described different concentrations of toxin in milk, besides that breast milk may have been at the highest level in the first few days after delivery (Boudra *et al.*, 2007).

Mechanisms of Toxicity

Oxidative stress

Oxidative stress means an imbalance between free radicals and antioxidants. Free radicals contain oxygen and can react with other molecules (Gautier *et al.*, 2001). Free radicals have the potential to produce large chemical reactions in the body called oxidation reactions. These reactions are often harmful and may interfere with cellular communication. Oxidative stress is recognized as one of the most important factors associated with diseases (Schaaf *et al.*, 2002). The most important cellular damage they cause is damage to DNA, proteins, lipid, and even lipid peroxidation (using Fe^{3+} as cofactor). According to recent reports by researchers, oxidative stress is one of the modes of actions in various toxicities of Ochratoxin (Zhu *et al.*, 2017).

Ochratoxin is able to increase the expression of metallothionein and induce oxidative stress in the cell by decreasing the amount of superoxide dismutase (Poor *et al.*, 2014). On the other hand, it has been suggested that reactive oxygen species (ROS) production is not only the main mechanism of OTA toxicity but also that OTA decreases the cellular antioxidant agents and increases the toxic effects of it. The following can affect and decrease activator protein 1 (AP-1) and nuclear factor erythroid 2–related factor 2 (Nrf2) activation (Marin-Kuan *et al.*, 2005). Cavin *et al*. showed that OTA can also inhibit the expression of Nrf2 protein, its translocation into the cell nucleus, as well as its binding to DNA in rat liver and kidney cells (Cavin *et al.*, 2006).

Based on the results of the abovementioned studies, it is important that the levels of reactive nitrogen species are also increased in the samples affected by Ochratoxin. High levels of nitric oxide (NO) because of the reaction with O_2^- may cause nitrosative stress. However, studies in the field of carcinogenicity of Ochratoxin show that the mechanism of creation of carcinogenic effects is independent of the mechanism of oxidative stress. One of the important neurotoxicity mechanisms of Ochratoxin is the inhibition of Nrf2 transcription, which subsequently increases neurotoxicity (Limonciel and Jennings, 2014). Activation of the oxidative esterification mechanism causes lipid peroxidation, DNA oxidative damage, and phototoxic stress (Boesch-Saadatmandi *et al.*, 2008).

In 2001, a study showed that there was a significant decrease in SOD, GSH, CAT, and GSPx levels in the groups treated with Ochratoxin. Based on these studies, we conclude that ROS plays an important role in the occurrence of OTA-induced neurotoxicity and that GSH levels play an important role in limiting neurotoxicity of this mycotoxin (Uetsuka, 2011; Zhang *et al.*, 2009).

OTA has also been reported to inhibit succinate-dependent electron transfer in the electron transport chain, but at higher concentrations will also inhibit electron transport at complex I, suggesting mitochondrial toxicity (Babayan *et al.*, 2019). The developing brain appears to be very susceptible to the deleterious effects of OTA. The calculation in this research suggested that OTA

significantly affects the striatal DA metabolism enzymes involved in the metabolism of DNA and regional brain oxidative stress. Initial studies were conducted in year 2 on the teratogenicity of Ochratoxin and brain injury. In this research, it was indicated that exposure to OTA in pregnant mice (5 mg/kg) on gestation day 9 leads to the exencephalic in offspring (Lagace *et al.*, 2006). Such differences between cell lines might be due in part to the complex nature of protein expression and functional regulation required during the intracellular signaling of apoptosis. Because inhibition of the expression of propyl 4-hydoxylase is known to attenuate upregulation of neuronal cells associated with ROS, it leads to apoptosis and loss of mitochondria membrane potential (Zhang *et al.*, 2009).

Cell apoptosis

OTA can directly cause cell death through apoptosis and necrosis (Lioi *et al.*, 2004). However, nanomolar level of Ochratoxin can also induce cell changes in the expression of different genes and can be one of the most likely causes of apoptosis in the cells (Gekle *et al.*, 2000; Sorrenti *et al.*, 2013). Changes in the transcriptional level of many genes, such as GADD153, GADD45, p53, and clusterin, are involved in causing DNA damage and also contribute to cell death. (Lühe *et al.*, 2003; Qi *et al.*, 2014).

Studies on rat liver and kidney cells identified Ochratoxin as one of the most important tumor promoters and also showed activation and expression of proteins involved in apoptosis such as MAPK, ERK, p38, and JNK (Horvath *et al.*, 2002). Another study suggested apoptotic cell death in mouse hippocampal HT22 cells (Yoon *et al.*, 2009). It is clear that OTA-induced cytotoxicity and proteome response can be indicative of neurodegeneration. OTA-induced neurotoxicity seems to be, at least party, mediated by apoptosis, and OTA may contribute to the pathogenesis of neurodegenerative diseases (e.g., Alzheimer's and Parkinson's disease) in which apoptotic processes are centrally involved (Zhang *et al.*, 2009). It can be said that Ochratoxin can induce necrosis, cell damage, apoptosis, and ultimately brain cell death (Weidenbach *et al.*, 2000; Zhang *et al.*, 2009). Neurotoxicity in human astrocytes through apoptosis and intracellular calcium overload was also reported in recent researches (Park *et al.*, 2019).

Protein synthesis inhibition

Another very important mechanism of OTA toxicity is the inhibition of protein synthesis in cells (Weidenbach *et al.*, 2000). The mechanism of inhibition in cellular protein synthesis may also be associated with an effect on normal cells (Al-Anati and Petzinger, 2006). By this mechanism, OTA inhibits as well as decreases cell growth and proliferation. It has been shown that phenylalanine t-RNA inhibition is one of the main mechanisms of OTA. Although it has been shown that phenylalanine moiety of OTA has a major role as a competitor between phenylalanine and the toxin, isocoumarin structure is more important in this interaction than the phenylalanine moiety because modification of the isocoumarin structure has a significant impact on this action (Xiong *et al.*, 2020). Studies, of course, have provided some evidence to support the importance of OTA isocoumarin structures. It is important to note that studies by researchers have shown that the effects of OTA on phenylalanine hydroxylase and phenylalanine t-RNA synthase occur after high doses of Ochratoxin. Although nonspecific methods of inhibiting protein synthesis have been proposed, OTA is particularly effective in the transcription of many proteins (Hong *et al.*, 2002).

Calcium homeostasis

It's clear that impaired calcium homeostasis can effects on cell cytotoxicity. Various studies of the effect of intrathecal and in vivo OTA toxin on calcium homeostasis were investigated (Benesic *et al.*, 2000). Some studies have shown that cells treated with Ochratoxin after lipid peroxidation is highly prone to calcium permeability. Some authors indicated that impairment of the endoplasmic reticulum membrane is directly related to calcium homeostasis of cells. This in turn leads to abnormal cell proliferation. According to the results of some studies in 1989, OTA can inhibit ATP-dependent calcium uptake by up to 45%.

In addition, studies show that impairment of calcium homeostasis induced by toxicity with OTA is related to impairment of endoplasmic reticulum membranes and also through increased lipid peroxidation. It was indicated that OTA effects affects renal endoplasmic reticulum calcium pump activity and also decreases renal mitochondrial state-3 respiration and calcium uptake (Pagliassotti *et al.*, 2016). In line with previous studies, authors indicated that OTA can affect the modulation of intracellular calcium levels in syrian embryonic fibroblast (SHE), and ultimately, by disrupting extracellular calcium, may produce a long-lasting signal of calcium channel damage (Park *et al.*, 2019).

Cell autophagy

Autophagy is a response to adaptation under conditions of cellular damage. In fact, autophagy and mitophagy

adapt and control a variety of diseases and damage to the cell (Aleo *et al.*, 1991; Xing *et al.*, 2019). Studies show that one of the most important functions of OTA is cellular destruction through autophagy (Shen *et al.*, 2014). As noted, mitophagy is one of the most important and complex mechanisms of mitochondrial elimination (Ariafar *et al.*, 2020). A study in 2014 noted activation of autophagy and mitophagy pathways by ochratoxin. This study refers to the Nix role as selective and central autophagy receptor. It was indicated that Nix-deficient HEK293 cells occur after the presence of OTA. Moreover, OTA is able to upregulated bad and AIF proteins as proapoptotic factors that all leads to an increase in cell death (Novak, 2012; Zhu *et al.*, 2017).

Influence on mitosis

Although various studies have described the toxicity of OTA as a carcinogenic agent, the direct effect of the toxin on DNA has not been discussed. Studies in human renal cells suggest that OTA may be a promoter for tumor formation and an apoptotic inducer by impairing cell division regulation. It was indicated that OTA plays an important role as an inhibitor of histone acetyl transferase (HAT) tumble microtubular system and asymmetric cell division (Adler *et al.*, 2009). In addition, OTA inhibits HATs with an epigenetic mechanism which conducted to kidney tumors inductions and genetic mutability (Adler *et al.*, 2009; Mally, 2012). OTA apoptosis mechanisms and cell signaling pathways shows in Figure 2.

Neurotoxicity due to OTA, Which Interferes with the Development of Diseases

Motor disorder and Parkinson's disease

Various studies have shown neurotoxicity effects of OTA; for example, the study of Belmadani and co-authors show the cytotoxicity of OTA (403 ng/10 µl) in various parts of the brain tissue, "Due to the increased rate of lactate dehydrogenase (LDH)," especially in cerebellum (34.4%) as the main OTA-target (Crago *et al.*, 2003). In addition, necrotic cells were increased in the ventral mesencephalon (VM) and cerebellum due to the regional

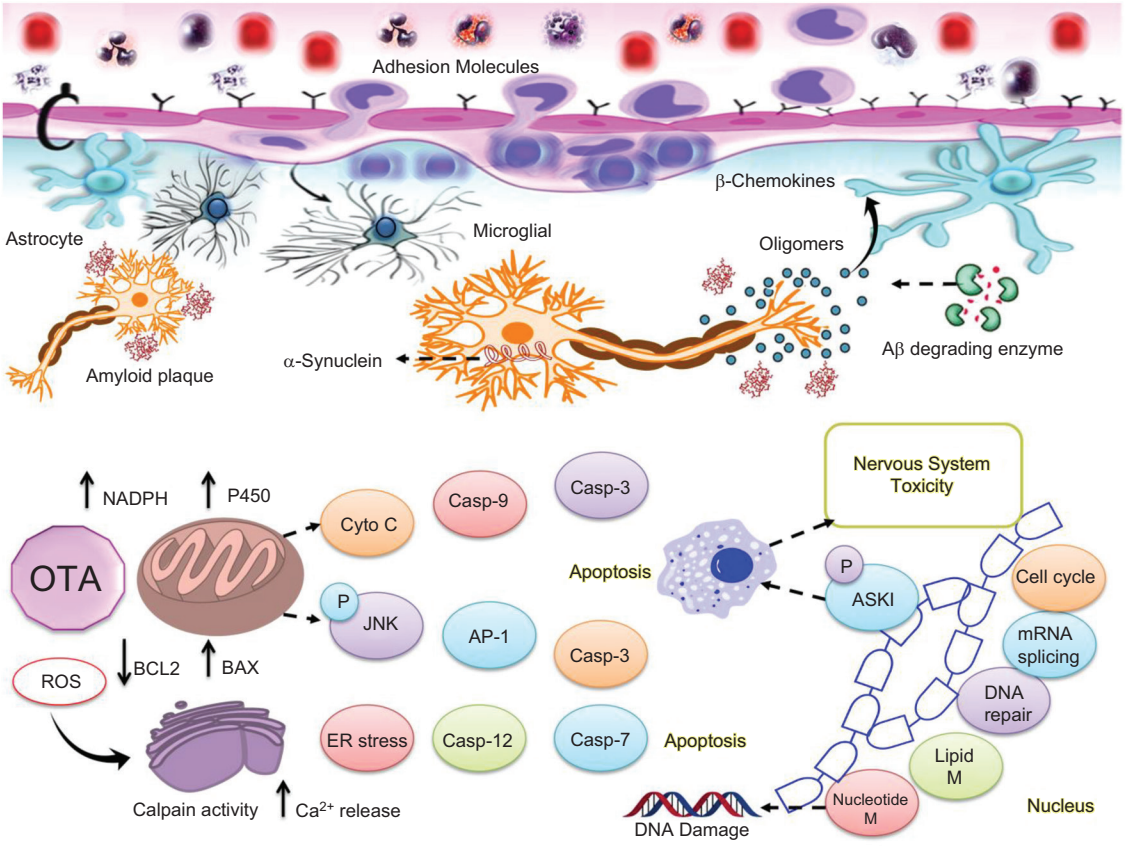

Figure 2. OTA-induced apoptosis and cell signaling. OTA induced the increase of NADPH and P450 enzyme, which activates the caspase signaling pathway and induces apoptosis. The increase of ROS caused mitochondria and endoplasmic reticulum oxidative stress, inducing calcium release and inhibiting the cell cycle, mRNA splicing, DNA replication, lipid and nucleotide metabolism. All of these could lead to cell apoptosis.

selectivity of OTA (Sava *et al.*, 2006). This concept is in line with another research of Sava *et al*. that shows low level of OTA to induce Parkinsonism in male mice. It was revealed that OTA induced neurodegenerative diseases and brain dysfunction; low-level administration of OTA leads to depletion of striatal dopamine, increased oxidative stress, and decreased intensity of tyrosine hydroxylase immunoreactivity (TH+) (Sava *et al.*, 2006). Proliferating NSC exhibited a greater vulnerability to the toxin than differentiated neurons despite robust DNA repair and antioxidant responses. Such a result is unexpected since DNA repair systems are typically more active and efficient in proliferating cells than in post-mitotic differentiated cells (Hameed *et al.*, 2017).

In line with these studies, Masao Tamaru and co-authors showed that OTA affects cerebral hemispheres, cortex and subjacent white matter, hippocampus, and amygdale of pregnant mice on day 11 of gestation. It was indicated that total content of noradrenaline (NA), dopamine (DA) 5-hydroxytryptamine (5-HT) were directly affected by OTA (Sava *et al.*, 2007). It has also been proved that sub-chronic treatment of OTA affects the young adult rat brain**.** Furthermore (289 mg/kg/48 h dose), injection of OTA also affects free amino-acid concentrations**;** in particular, it plays a role in increasing the amount of phenylalanine and necrotic cells with pyknotic nucleus (Aimone *et al.*, 2006).

DNA damage, lipid peroxidation, and superoxide dismutase (SOD) increase cellular toxicity in various parts of the brain (Sava *et al.*, 2006). It was demonstrated that low dose of OTA (10% of the LD_{50}) leads to DNA repairmen and up-regulation of anti-oxidant systems. The study also examined the distribution of toxins in different parts of the brain; based on the results, cerebellum has the highest absorption of OTA, half-life of elimination (T1/2) in midbrain was lower than other regions of the brain, and OGG1 activities increased in all parts of the brain (Yoon *et al.*, 2009). Inhibition of protein synthesis, competition with phenylalanine in the amino acylation reaction of phenylalanine-tRNA conducted to disruption in produce of dopamine and catecholamine. An increase in the ratio of acetylcholine to dopamine in the basal glands of the brain causes symptoms of tremor, muscle stiffness, and slowness of movement (Sueck *et al.*, 2019).

Hippocampal Toxicity and Memory Impairment

The clinical significance of the impact of OTA on hippocampal neurogenesis in adult brain relates to its potential effect on cognitive function, provided that effects on neurogenesis observed in vitro can be reproduced in vivo. It has been suggested that generation of new neurons throughout life is related to the formation of temporal associations in memory (Aimone *et al.*, 2006). These findings confirm the previous researches demonstrate the partial protective effect of melatonin in OTA toxicity (Delibas *et al.*, 2003). Overall, these results lead to speculation that OTA exposure may contribute to impaired hippocampal neurogenesis in vivo, resulting in depression and memory deficits, conditions reported to be linked to mycotoxin exposure in humans (Sava *et al.*, 2007). In addition to cognitive deficits, a significant association between psychological disorders such as melancholic depression with mycotoxin exposure has been reported (Crago *et al.*, 2003). Interestingly, impaired hippocampal neurogenesis may underlie depression, as suggested by the observation that certain antidepressants (selective serotonin uptake inhibitors) stimulate hippocampal neurogenesis. In light of the critical role played by HP in cognitive function, and the importance of neurogenesis in this structure throughout life, the impact of mycotoxins on hippocampal neural stem/progenitor cells (NSC) is highly relevant from both molecular pathogenesis and clinical perspectives (Sava *et al.*, 2006).

As mentioned, 0.01–100 mg/mL of OTA decreases the both proliferating and neurogenesis of hippocampal neural cell (Sava *et al.*, 2007). Ongoing studies are investigating the impact of sub acute and chronic OTA administration on hippocampal-dependent learning paradigms and correlating these cognitive deficits with impaired hippocampal neurogenesis in vivo. All reports can be based on studies of mycotoxins-induced brain toxicity, resulting in depression and cognitive deficits (Gordon and Cantor, 2004). The potential harm caused by environmental exposure to OTA in terms of its effects on neuronal cell viability and proteome profiles using mouse hippocampal HT22 and human neuroblastoma SH-SY5Y cells has been investigated. Generation of ROS was detected in OTA-treated SH-SY5Y and HT22 cells; however, caspase activation and an increase in p53 phosphorylation were only detected in HT22 cells, even though OTA treatment caused oxidative stress in both cell lines (Otteneder and Majerus, 2000). Upregulation of propyl 4-hydroxylase was reported in HT22 cells after treatment with OTA (Agarwal *et al.*, 2020). All this shows that OTA would contribute to the pathogenesis of neurodegenerative diseases (e.g., Alzheimer's and Parkinson's disease). Due to the toxic effects of OTA in brain cells, it has been shown that there is relationship between OTA toxicity and glial reactivity. Changes in astrocyte integrity and the cell cytoskeletal were also seen in OTA-treated mice (Fuchs *et al.*, 2001). A peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist blocked OTA-induced neurotoxicity by inhibiting AP and NF-κB activation in cultured rat embryonic midbrain cells (Hong *et al.*, 2002).

Changes in Brain Tissue

Studies have shown that OTA has immunological, genotoxic, teratogenic, especially nephrotoxic, as well as carcinogenic and neurogenic effects. Due to teratogenic effects of OTA, it can have several histopathological changes in the brain tissue (Delibas *et al.*, 2003). A similar study was conducted to investigate the rate of uptake of OTA into brain tissue in 1998. Increasing the duration of exposure of animals increased the amount of OTA absorbed in the brain tissue. The study also showed that OTA had a significant effect on tyrosine and phenylalanine content. Various necrotic cells with pyknotic nucleus were reported by these researchers (Sava *et al.*, 2007). Similar studies in encephalic embryos showed extensive destruction of the brain tissue due to exposure to OTA and also 0.50 mg/kg treatments resulted in degeneration of lenticular fibers, adhesion of anterior epithelial cell of the lens with the cornea, narrowing of the anterior chamber, degeneration, detachment of upper retinal layers, and extension of damaged retinal layers over optic nerve fibers (Delibas *et al.*, 2003). All studied brain regions shows that apoptosis in the substantia nigra (SN), striatum and hippocampus and other brain regions, significantly decreased oxyguanosine glyosylase (OGG1) (Sava *et al.*, 2006). In contrast to OGG1, other indices of oxidative stress (lipid peroxidation and SOD activity) exhibited a monophasic increase over time throughout the brain (Sava *et al.*, 2006). Due to the widespread toxicity of OTA and the tissue damage noted, several studies have been reported on the antioxidant effects of the substances. Aantioxidant substances for the treatment OTA toxicity are listed in Table 2. Given the importance of OTA and the mechanisms of brain toxicity and neurodegenerative diseases through different mechanisms, further studies are recommended.

Conclusion

OTA has been described as a teratogenic, genotoxic, carcinogenic, immunotoxic, and also neurotoxic mycotoxin.

Table 2. The effect of antioxidant substances and food components in Ochratoxin toxicity.

Substances	Antioxidant mechanism	Organs	Results/conclusion
Vitamins E (α-tocopherol) **Vitamins C (ascorbic acid)**	↓ Peroxyl radical scavenger DNA adduct ↓ Cytochrome P450 isoenzymes	BME-UV1 MDCK Human cell line Mice kidney HepG2 cells Neuronal cells	Function as a peroxyl radical scavenger that terminates chain reactions is well documented. Retinol (A), ascorbic acid (C) act as superoxide anion scavengers.
Phenolic Compounds **(EGCG)** **(ECG)** **(C3G)**	↓ ROS production ↓ DNA fragmentation and Tumor angiogenesis	LLC-PK1 HepG2 cells Rat Liver, Kidney, and Brain	Cytoprotective effects of catechins. C3G is the most effective compound that counteracts the effects of OTA. LPE exerts a potent antioxidant capacity such as flavonoids.
Vitis vinifera	↓ DNA adduct ↓ ROS production	Rat Liver and Kidney	Berry and leaf juice of *Vitis vinifera* Hepatic and Renal damage.
Lycopene	↓ Damage of lipids, ↓ Proteins, and DNA	Rat Kidney Brain cortex	Glutathione peroxidase (GPx) activity and GSH levels
Glutathione	↓ Genotoxicity ↓ DNA adduct	Rabbit Kidney OK Proximal tubular epithelial cells	Oxidative stress by increasing free thiols in kidney, BSO, ACIVICIN
Zinc **Mg** **Selenium**	↓ SOD ↓ ROS production ↓ DNA adduct ↓ Apoptosis	HepG2 cells	Zinc is an essential component of Cu/Zn SOD1 to increase OTA toxicity and it can be used in the diet
Antioxidant Mixture **(CoQ10)** **(Mel)** **(L-carnitine)** **(N-acetyl cysteine)**	↓ ROS production ↓ Apoptosis	Mice Liver Rat Liver, Kidney, and Brain	Affected Malondialdehyde (MDA) levels in the plasma and GSH levels. Involved in mitochondrial oxidative phosphorylation system and ameliorates OTA toxicity

BME-UV1: Bovine Mammary Epithelial Cells, **MDCK**: Madin Darby Canine Kidney Cells, **HepG2**: liver (HepG2) cells, **EGCG**: Epigallocatechin Gallate, **C3G**: Cyanidin 3-O-β-D-glucoside, **LLC-PK1**: LLC-PK1, **LPE**: Liquorice Plant Extract, **OK**: Opossum Kidney Cells, **BSO**: Buthionine Sulfoximine, **ACIVICIN**: alpha amino-3-chloro-4, 5-dihydro-5-isoxazole acetic acid, **SOD1**: Superoxide Dismutase, **CoQ10**: Coenzyme Q10.

Various studies have shown regional selectivity of OTA neurotoxicity, especially by LDH or increased mitochondrial SOD activity. Therefore, noradrenaline (NA), dopamine (DA) 5-hydroxytryptamine (5-HT) can directly affected by OTA, which can be conducted to brain toxicity motor disorder and memory impairment.

The underlying mechanisms of neurotoxicity of the OTA still need to be elucidated. Recent advances mainly support oxidative DNA, protein, lipid damage and loss of cell membrane integrity induced by ROS production of OTA.

Given the potential chronic human exposure to the mycotoxins, a better understanding of the toxicokinetics and the mechanisms of neurotoxicity of the OTA is necessary to provide adequate human risk assessments.

Conflict of interest

The authors declare that there are no conflicts of interest.

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