Review Articles

Possible involvement of glucocorticoids in mycotoxin-induced neuroinflammation

Boonrat Chantong[1*] Punnee Nusuetrong[2]

[1]Department of Preclinical Science and Applied Animal Science, Faculty of Veterinary Science, Mahidol University, Phutthamonthon, Nakhonpathom, Thailand

[2]Department of Physiology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

[*]Corresponding author, E-mail address: boonrat.cha@mahidol.ac.th

Abstract

The mycotoxins are commonly encountered in human cereal foods and animal feed throughout the world as a result of infestation of grains in the field and in storage by the fungi including genus *Aspergillus, Penicillum and Fusarium*. Modulation of the inflammatory responses in the central nervous system (CNS) appears particularly critical role of some relevance mycotoxins such as T-2 toxin, fumonisin B1 and ochratoxin A. Specifically, mentioned mycotoxins disturbed mitogen-activated protein kinases (MAPKs) as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which mediate robust induction of pro-inflammatory gene expression in both *in vitro* and *in vivo*. In CNS, glucocorticoids are powerful endogenous and therapeutic modulators of inflammation though both MAPKs and NF-κB signaling. In addition, toxicity of mycotoxins also was altered with glucocorticoid. Taken together, glucocorticoids may possibly involve in the action of mycotoxins on neuroinflammatory responses. Therefore, factors disturbing glucocorticoid regulation in CNS such as stress, infection, and xenobiotics may enhance response to mycotoxin toxicity. It is anticipated that these investigations will be applicable to identify the therapeutic intervention or prevention.

Keywords: Glucocorticoid, Mycotoxin, Neuroinflammation

การมีส่วนร่วมของสารกลุ่มกลูโคคอร์ติคอยด์ต่อกระบวนการอักเสบของระบบประสาทที่เกิดจากการชักนำของสารพิษจากเชื้อรา

บุญรัตน์ จันทร์ทอง[1*] พรรณี หนูซื่อตรง[2]

[1]ภาควิชาปรีคลินิกและสัตวศาสตร์ประยุกต์ คณะสัตวแพทยศาสตร์ มหาวิทยาลัยมหิดล อำเภอพุทธมณฑล จังหวัดนครปฐม 73170
[2]ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ เขตวัฒนา กรุงเทพมหานคร 10110
[*]ผู้รับผิดชอบบทความ E-mail address: boonrat.cha@mahidol.ac.th

บทคัดย่อ

สารพิษจากเชื้อราเป็นสารที่พบได้ทั่วโลกพบได้บ่อยในอาหารประเภทธัญพืชสำหรับมนุษย์และสำหรับเลี้ยงปศุสัตว์ ซึ่งเกิดจากการที่เมล็ดธัญพืชมีการติดเชื้อราในจีนัสต่าง ๆ เช่น *Aspergillus, Penicillum* และ *Fusarium* ในช่วงระหว่างรอการเก็บเกี่ยวและระหว่างการเก็บรักษา สารพิษจากเชื้อราที่มีบทบาทสำคัญ ได้แก่ T-2 toxin, fumonisin B1 และ ochratoxin A มีผลเปลี่ยนแปลงกระบวนการตอบสนองต่อการอักเสบในระบบประสาทส่วนกลาง โดยรบกวนการทำงานของระบบการส่งสัญญาณภายในเซลล์ ได้แก่ mitogen-activated protein kinases (MAPKs) และ nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) ซึ่งมีหน้าที่สำคัญในการกระตุ้นการแสดงออกของยีนที่เกี่ยวข้องกับกระบวนการอักเสบทั้งในสิ่งแวดล้อมที่ทำเทียมขึ้น และในร่างกายของสิ่งมีชีวิต สารกลุ่มกลูโคคอร์ติคอยด์ซึ่งรวมทั้งสารที่มีอยู่แล้วในร่างกายและที่ได้รับจากภายนอกจะทำหน้าที่สำคัญในการควบคุมการส่งสัญญาณผ่านระบบ MAPKs และ NF-κB ในระบบประสาทส่วนกลาง นอกจากนี้พบว่าสารกลุ่มกลูโคคอร์ติคอยด์ยังสามารถปรับเปลี่ยนความรุนแรงที่เกิดจากสารพิษจากเชื้อราดังกล่าวได้ด้วย เมื่อนำหลักฐานการศึกษาดังกล่าวมาเชื่อมโยงกันแสดงให้เห็นว่าสารกลุ่มกลูโคคอร์ติคอยด์อาจมีบทบาทต่อกระบวนการตอบสนองต่อการอักเสบของระบบประสาทที่ถูกกระตุ้นโดยสารพิษจากเชื้อรา ดังนั้น ปัจจัยที่มีผลกระทบต่อการทำงานของกลูโคคอร์ติคอยด์ เช่น ภาวะเครียด การติดเชื้อ และสารแปลกปลอมจึงอาจมีผลเพิ่มการตอบสนองของระบบประสาทส่วนกลางต่อการเกิดพิษของสารพิษจากเชื้อราได้ ข้อมูลการค้นพบเหล่านี้จะนำไปสู่การประยุกต์เพื่อการค้นหาวิธีการรักษาหรือป้องกันการเกิดพิษจากสารพิษจากเชื้อราได้

คำสำคัญ : กลูโคคอร์ติคอยด์ สารพิษจากเชื้อรา การอักเสบของระบบประสาท

Introduction

Mycotoxins are secondary metabolites produced by fungi such as genus *Aspergillus, Penicillum* and *Fusarium*. Toxicity of mycotoxins on human and animals upon ingestion, inhalation, or skin contact has been recognized for decades. The contamination of mycotoxins is widely distributed in environment and food chain and can occur in all agricultural commodities in the field and/or during storage. The Food and Agriculture Organization of the United Nations (FAO) estimated that approximately 25% of the cereals produced in the world are contaminated by mycotoxins (Rice and Ross, 1994; Marin et al., 2013). Regarding animal feed, five mycotoxins, including aflatoxins, deoxynivalenol, zearalenone, fumonisins and ochratoxin A, are covered by European Union legislation (Streit et al., 2012). Fumonisins, nivalenol, zearalenone and aflatoxins were often detected in corn from Southeast Asia including Thailand. In Thailand, increasing evidence suggests that contamination of mycotoxins in food is a critical problem for both animal and human health (Tansakul et al., 2013). For example, a study to assess the levels of fumonisin contamination in swine food composed of corn and other cereals showed that all tested samples were contaminated (Tansakul et al., 2013). Mycotoxins-contaminated favorite foods including fumonisin B2 and ochratoxin A in coffee bean (Noonim et al., 2008; Noonim et al., 2009), aflatoxin M1 in raw milk samples and in pasteurized milk (Ruangwises and Ruangwises 2009; Ruangwises and Ruangwises, 2010), and deoxynivalenol (DON) contamination in wheat products (Poapolathep et al., 2008) alerted most of people in Thailand. Consequently, their contamination in food chain and toxicity need to be concerned.

Furthermore, the relevance of mycotoxins for agricultural, ecological and toxicological reasons has been focused. They can cause economic losses due to contaminated cereals and might be harmful for humans and animals due to their toxicological properties. Mycotoxins could be observed in the food chain because of fungal infection of crops, either by being consumed directly by humans or used as livestock feed. An accumulation of mycotoxins in different tissues is due to ingestion via food chain through meat, milk, or eggs.

Pathogenesis of neurodegenerative disorders associated with mycotoxins have been recognized over the past decade (Doi and Uetsuka 2011). Interestingly, recent findings purposed that mycotoxins may be the underlying cause of neurodegenerative diseases with evidences of neuroinflammatory responses such as multiple sclerosis, Alzheimer's disease, and Parkinson disease (Sava et al., 2006a; Sava et al., 2007; Zhang et al., 2009; Purzycki and Shain 2010; Doi and Uetsuka, 2011). For instance, fumonisin B1 (FB1) disturbs the biosynthesis of sphingolipids which are related to the pathogenesis of multiple sclerosis (Purzycki and Shain, 2010). Additionally, FB1 is well known to cause equine leukoencephalomalacia which is characterized by high mortality (Caloni and Cortinovis, 2010). The neurotoxicity potential of DON has been emphasized due to ability to disturb brain functions via direct action (Bonnet et al., 2012; Maresca 2013). The effect of acute and chronic exposure to ochratoxin A (OTA) on the nervous system has been assessed (Sava et al., 2006a; Mantle and Nolan, 2010). The exposure to OTA has been hypothesized that causes Parkinsonism (Sava et al., 2006b).

For the reasons mentioned above, the impact of mycotoxins on the development and progression of neurodegenerative diseases is extensively elucidated. In the pathogenesis of various neurodegenerative diseases, the important of microglia stimulation and the expression of proinflammation cytokines have been demonstrated (Morales et al., 2010; Collins et al., 2012; Koziorowski et al., 2012; Rubio-Perez and Morillas-Ruiz, 2012; Sorenson et al., 2013).

Molecular mechanisms of neuroinflammation

Inflammatory neurodegeneration contributes to a wide variety of brain pathologies. Although molecular mechanisms of inflammatory neurodegeneration are still unclear, neuroinflammation involving by microglia activation underlies many neurodegenerative diseases (Block et al., 2007). Initial microglial activation was suggested to promote glial neuroimmune responses resulting in persistent increases in innate immune gene expression (Qin et al., 2007). Inflammatory response in the injured brain elicits pro-inflammatory cytokines such as interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Clark et al., 2013; Woodcock and Morganti-Kossmann, 2013).

Under physiological conditions, cellular redox balance is maintained by the equilibrium between the formation and elimination of free radicals such as reactive oxygen species (ROS) and nitric oxide (NO). The CNS appears to be especially vulnerable to oxidative stress due to its high rate of oxygen consumption, low levels of molecular antioxidants and the susceptibility of neurons or oligodendrocytes due to their specific metabolic properties. Accumulating evidence also supports the concept that oxidative imbalance and subsequent oxidative stress play an important role in the patho-physiology of neurodegenerative diseases (Butterfield et al., 2006) due to neuronal cell damage and subsequent cell death from oxidation of cellular components. In addition, ROS have been recognized as an activator to the chronic progression of neurodegenerative diseases (Glass et al., 2010) and plays a key role in microglial response in neurodegeneration (Kettenmann et al., 2011; Beraud et al., 2013; Domercq et al., 2013; Wong, 2013). Therefore, an increase of ROS is a common feature of neurodegenerative diseases (Agostinho et al., 2010; Kovacic and Somanathan, 2012). Microglial intracellular ROS generation facilitates proinflammatory pathways by activating the mitogen-activated protein kinase (MAPKs) and nuclear factor kappa B (NF-κB) signalings (Hu et al., 2011; Ibrahim et al., 2011; Kacimi et al., 2011; Peterson and Flood, 2012).

Upon activation, in addition to cytokines, microglia release NO and produce reactive oxygen ROS that have been associated with demyelination and axonal damage in cerebellar cultures (di Penta et al., 2013). NO, produced by inducible nitric oxide synthase (iNOS), is one of characterized pro-inflammatory factors that induce neuronal death (Brown and Neher, 2010; Li et al., 2012; Khasnavis et al., 2013). iNOS expression plays a prominent role in the mechanism of oxidative stress in various cell types that is also mediated by NF-κB and MAPK signal transduction.

Among the transcription factors that activate the inflammatory genes, NF-κB is one of the most relevant in microglia cells. In quiescent cells, NF-κB which exists primarily as a p50/p65 heterodimer remains inactive in the cytoplasm due to the formation of complexes with the inhibitory protein, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). Upon stimulation by various kinases as well as ROS (Crews et al., 2011), IκBα is degraded, which then allows phosphorylated NF-κB to translocate to the nucleus, bind to cognate DNA binding sites, and initiate the transcription of target pro-inflammatory factors (Barnes and Karin, 1997; Lukiw, 2012) including interleukins, TNF-α and iNOS (Cheng et al., 2009; Lukiw, 2012; Wongchana and Palaga, 2012).

MAPKs are serine and threonine protein kinases that function in multiple pathways and cell types. The MAPK family includes extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 kinase (Waskiewicz and Cooper, 1995; Kolch, 2005), which have been implicated in the release of immune-related cytotoxic factors such as iNOS, cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines (Choi et al., 2009; Lin et al., 2010; Wang et al., 2011). MAPKs have been suggested to be critical regulators of oxidative stress and pro-inflammatory signaling cascades (Wang et al., 2011).

However, the molecular mechanisms underlying mycotoxin-induced neuroinflammatory responses are not fully understood.

The role of mycotoxins on neuroinflammation

T-2 toxin, DON, FB1, and ochratoxin A are well characterized their different types of neurotoxicity in various models (Yamashita et al., 1995). Among the large number of mycotoxins, trichothecenes produced by various species of *Fusarium* are extensively focused due to their high prevalence in food and their high toxicity (Sehata et al., 2004; Rezar et al., 2007; Li et al., 2011; Cortinovis et al., 2013; Ferreras et al., 2013; Mu et al., 2013). The neurotoxicity potential of trichothecenes especially DON and T-2 toxin has been concerned. While the ability of DON-induced proinflammatory gene expression at peripheral tissue was extensively studied (Pestka, 2010), data indicating its effects on the CNS are less abundant. DON can be vastly and rapidly distributed to the brain in the mouse after oral exposure (Pestka et al., 2008). Oral DON administration (12.5 mg/kg) up-regulated IL-1β, TNF-α, and IL-6 mRNAs in the hypothalamus and the dorsal vagal complex of mice (Girardet et al., 2011a). The direct effect of DON on the brain was confirmed by intracerebroventricular

injection (Girardet et al., 2011b). DON modified neuroinflammatory responses of microglia to lipo-polysaccharides (LPS) in primary cortical glial cell cultures. DON significantly potentiated LPS effect for concentrations less than 100 nM. Inversely, DON at concentrations higher than 100 nM decreased in the effect of LPS in concentration dependent manner (Razafimanjato et al., 2011). The recent evidence indicates that DON at the dose related to daily human intake induced pro-inflammatory gene expression in brain structures as well as in systemic inflammation in mouse model. However, the adverse effect of chronically consumed low DON was not detected (Tardivel et al., 2015).

T-2 toxin shows various features of neurotoxicity such as disturbing neurotransmitter signaling in rat brains (Wang et al., 1998a), increasing blood brain barrier (BBB) permeability (Wang et al., 1998b), and inducing apoptosis in the developing mouse embryos (Ishigami et al., 1999). Concerning the neurotoxicity, T-2 toxin has been mainly focused. T-2 toxin triggered apoptotic reactions via caspase-3-activation after short incubation times in primary human astrocytes and was able to cross BBB (Weidner et al., 2013a; Weidner et al., 2013b). Additionally, the permeability of BBB was perturbed by T-2 toxin (Ravindran et al., 2011). The up-regulation of pro-inflammatory cytokines mRNA including IL-1α, IL-1β, IL-6 and TNF-α in brain exposed with T-2 toxin was reported. T-2 toxin induced marked oxidative stress parameters with elevation of lipid peroxidation, ROS levels, and iNOS mRNA expression in brain (Chaudhary and Rao, 2010; Ravindran et al., 2011). For instance, oxidative stress and MAPK pathway have been suggested to be involved in T-2 toxin-induced apoptosis in rat fetal brain (Sehata et al., 2004). The activation of JNK and p38 MAPKs was observed after T-2 toxin exposure in RAW 264.7 murine macrophage (Yang et al., 2000).

Fumonisins produced by *Fusarium verticillioides*, are a worldwide fungal concomitant of various cereals, predominantly corn (Domijan, 2012). Fumonisin B shows neurodegenerative potential in both experimental animals and in cell cultures (Osuchowski et al., 2005; Doi and Uetsuka, 2011; Domijan, 2012; Domijan et al., 2012). FB1 is the most abundant and toxic; it has been associated with a number of diseases in humans and animals. FB1 widely contaminates maize and maize-based food. The potential mechanisms of FB1-induced neurotoxicity are well investigated (Doi and Uetsuka, 2011; Domijan and Abramov, 2011; Domijan, 2012). FB1 inhibited mitochondrial complex I lead to mitochondrial membrane potential depolarization and calcium deregulation in neuronal primary culture (Domijan et al., 2012). The potential of FB1 on neuroinflammatory responses also exhibited by up-regulation of pro-inflammatory related genes including TNF-α, IL-1β, and IL-6 in the murine brain (Osuchowski et al., 2005). Oxidative stress is suggested to be a mechanism of FB1-induced toxicity (Stockmann-Juvala et al., 2004; Doi and Uetsuka, 2011)

OTA is a fungal metabolite produced by *Aspergillus ochraceus* and *Penicillium verrucosum*. OTA is commonly found in a variety of plant food products such as cereals and feedstuffs. Because of its long half-life, it accumulates in the food chain and is frequently detected in human plasma at nanomolar level. A significant oxidative damage in many brain regions including cerebellum, hippocampus, caudate putamen, pons medulla, substantia nigra, and cerebral cortex after OTA exposure was demonstrated (Sava et al., 2006a; Mantle and Nolan, 2010). An impairment of hippocampal neurogenesis *in vivo* contributing to memory loss and depression due to OTA was also postulated (Sava, et al., 2007). OTA reduced dopamine level, loss of mitochondrial membrane potential in neuronal cells (Zhang et al., 2009), and induced neuronal apoptosis in the substantia nigra, striatum and hippocampus (Doi and Uetsuka, 2011). OTA exhibits a wide range of neurotoxic activities such as apoptosis in SH-SY5Y neuronal cells, stimulation of astrocyte reactivity in aggregating rat brain cells, and induction of cytotoxicity in rat embryo midbrain micromass cultures (Zurich et al., 2005; Wilk-Zasadna and Minta, 2009; Zhang et al., 2009). The role of inflammation in OTA-induced neurotoxicity has been proposed. For instance, OTA increased expression of the inducible inflammatory marker, iNOS in aggregating rat brain cultures (Zurich et al., 2005). Microglial activation stimulated by OTA was also observed in the same model (Monnet-Tschudi et al., 1997). Recently, the action of OTA in neuroinflammatory process was

exhibited that neurodegenerative M1 microglial phenotype and up-regulation of pro-inflammatoy cytokines mRNA expression were observed (von Tobel et al., 2014). However, the molecular mechanism underlying mycotoxin-induced neurotoxicity is not well-understood. Especially, the impact of mycotoxins on microglia cells is poorly investigated.

Although the potential of mycotoxin induced-neurotoxicity has been widely reported, a large number of studies focused directly on neuronal cell function. Moreover, increasing evidence suggests that inflammation involving microglia activation through the release of pro-inflammatory mediators underlies many neurodegenerative diseases (Glass et al., 2010; Evans et al., 2013; Niranjan, 2013; Orre et al., 2013). Currently, it is still unclear whether microglia responds to mycotoxins and induces inflammatory cascades.

Effect of glucocorticoid on neuroinflammation

Glucocorticoids, including cortisol in humans and corticosterone in rodents, have profound effects on brain development and adult CNS function. Excess or insufficient glucocorticoids cause abnormalities in neuronal and glial structure and function. In mammals, the mechanisms for responding to stress are regulated by the hypothalamicñpituitary-adrenal (HPA) axis, which results in the release of glucocorticoids. However, the effects of glucocorticoids in neuroinflammation are not fully understood. Glucocorticoids, a double-edged sword, can both enhance neurotoxicity or protect against toxicity (Harvey et al., 1994). Synthetic glucocorticoids have long been used as an anti-inflammatory therapy following injury or suppression of immune response. There is increasing evidence that endogenous glucocorticoids, major hormones released during periods of stress, acts as a priming event resulting in the potentiation of both central and peripheral pro-inflammatory cytokine production following a subsequent systemic immune challenge (Sorrells and Sapolsky, 2007; Sorrells et al., 2009). In contrast, some studies showed that glucocorticoids caused an increase in the number of inflammatory cells, such as granulocytes, monocytes/macrophages and microglia in the hippocampus (Dinkel et al., 2003; Munhoz et al., 2006). Interestingly, glucocorticoids induce the potentiation proinflammatory cytokine production following a subsequent immune challenge (Yeager et al., 2009; Frank et al., 2010). For example, prior exposure to corticosterone potentiated LPS induced spinal neuroinflammation with elevation of IL-1β and IL-6 proteins (Loram et al., 2011). The elevation of corticosterone levels is suggested to be pro-inflammatory to exacerbate LPS on NF-κB, MAPKs, and pro-inflammatory gene expression in frontal cortex (Munhoz et al., 2010).

Stress-induced glucocorticoids function to sensitize the microglial pro-inflammatory response in the hippocampus to immunologic challenges (Frank et al., 2012). Acute and chronic stresses have been found to sensitize the neuroinflammatory response to immunologic challenges (Munhoz et al., 2006; Espinosa-Oliva et al., 2011). Several studies have been documented that stress and glucocorticoids can enhance neuroinflammation. For example, stress-induced priming of subsequent CNS pro-inflammatory cytokine production has been documented to worsen outcomes in a rat model of stroke (Caso et al., 2006). Stress enhances spinal neuro-inflammatory responses leading to cell death (Grau et al., 2004).

For the functions of microglia, several studies demonstrated that corticosterone inhibits microglia cells, reducing inflammatory reactions in the brain (Morale et al., 2004; Sugama et al., 2009). Microglia activation induced by acute stress was reversed by corticosterone administration (Sugama et al., 2012). Triamcinolone inhibited microglia activation and protected neuronal cells from death induced by microglia activation (Hong et al., 2012). Glucocorticoids inhibited proliferation of microglia cells (Ganter et al., 1992). *In vivo* experiments have shown that glucocorticoid injection alters the density and morphology of microglia cells in immature rats (Kaur et al., 1994). Low concentrations of corticosterone decreased the expression of IL-1β and TNF-α in the rat hippocampus following kainic acid stimulus (MacPherson et al., 2005), while chronic administration of corticosterone increased the level of LPS-induced NF-κB activity in the hippocampus of stressed rats (Munhoz et al., 2006).

Corticosteroids such as corticosterone and cortisol mediate their effects by binding to mineralocorticoid

receptors (MR) and glucocorticoid receptors (GR) with different affinity. Both MR and GR differentially regulate the function of MAPKs and NF-κB (Kiyomoto et al., 2008; Nguyen Dinh Cat et al., 2011; Chantong et al., 2012; Queisser et al., 2013). MR expressed on microglia might play a role in the modulation of microglia activity (Frieler et al., 2011). Evidence suggests that spironolactone, an MR antagonist, inhibits production of TNF-α and IL-1β via MR mechanisms and show positive effects in patients with immunoinflammatory diseases (Hansen et al., 2004; Miura et al., 2006; Syngle et al., 2013). It has been reported that spironolactone could reverse the action of corticosterone and aldosterone on microglial activation (Tanaka et al., 1997). However, GR expressing in microglia cells show a suppression effects. The inhibitory of corticosterone on proliferation of microglia cells is mediated by GR, but not MR (Nakatani et al., 2012). After acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment in mice, it was found that microglial GR protected dopaminergic neurons after acute intoxication, meanwhile microglial GR gene inactivation exacerbated both microglial and astroglial reactivities (Ros-Bernal et al., 2011). To date, however, there are no findings on the roles of MR and GR in mycotoxin-induced inflammation in the microglia cells.

Conclusion and outlook

It has been suggested that activation of MAPK and NF-κB pathways have a critical role in mycotoxin-induced inflammation. Glucocorticoids also disturb the function of these two pathways leading to inflammatory impairment in the CNS. Several evidences have demonstrated that the toxicological responses to mycotoxins can be modulated by corticosterone and other natural and synthetic glucocorticosteroids (Harvey et al., 1994; Magnoli et al., 2012). Taken together, endogenous and exogenous glucocorticoids are expected to modulate the sensitivity to mycotoxin neurotoxicity.

In summary, inflammatory and stress responses of microglia cells contribute to neuroinflammation that causes neurodegenerative diseases. Factors that influence on microglia function such as stress, corticosteroids, and mycotoxins may change the susceptibility of microglia activation that may enhance neuroinflammation. Therefore, we propose that deoxynivalenol, T-2 toxin, fumonisin B1, and ochratoxin A on the neuroinflammatory responses may be exacerbated by glucocorticoids via activation of inflammation-related pathways including NF-κB and MAPKs (Figure 1.). Consequently, the roles of glucocorticoids on mycotoxin-induced inflammation need to be highlighted for further research.

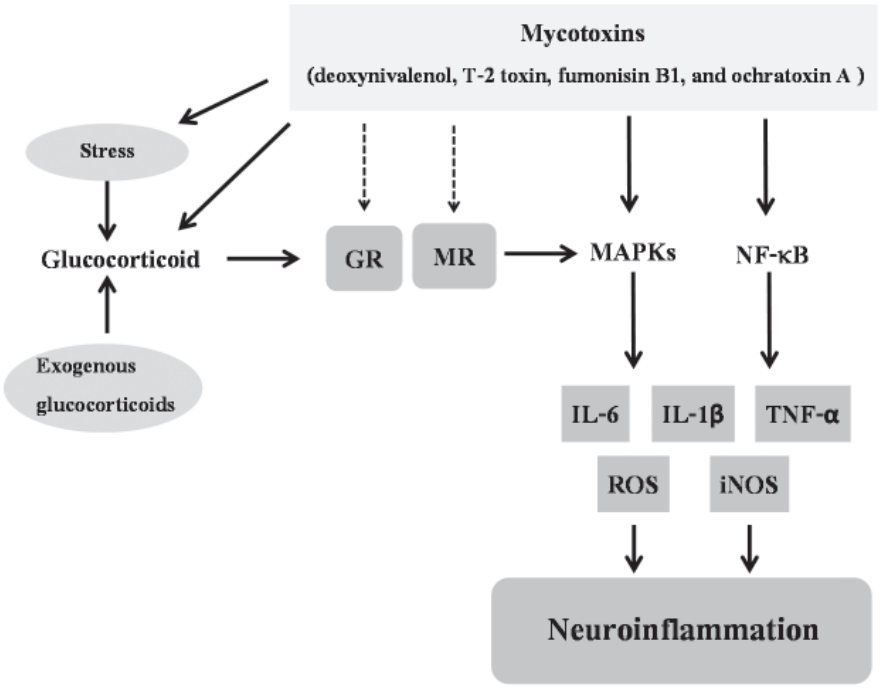

Figure 1 Proposed model for the role of glucocorticoids involving mycotoxin-induced neuroinflammation. This review suggests that glucocorticoids promote a neuroinflammation induced by mycotoxins through disturbing MAPKs and NF-κB which increases cytokine expression. The action of glucocorticoids and mycotoxins on the GR and MR may regulate the inflammatory responses. Factors influencing on glucocorticoid functions such as stress, exogenous glucocorticoids, and mycotoxins may enhance neuroinflammation.

References

Agostinho P, Cunha RA, Oliveira C. Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. Curr Pharm Des 2010; 16(25): 2766-2778.

Barnes PJ, Karin M. Nuclear factor-kappab: A pivotal transcription factor in chronic inflammatory diseases. N Engl J Med 1997; 336(15): 1066-1071.

Beraud D, Hathaway HA, Trecki J, Chasovskikh S, Johnson DA, Johnson JA, et al. Microglial activation and antioxidant responses induced by the Parkinson's disease protein alpha-synuclein. J Neuroimmune Pharmacol 2013; 8(1): 94-117.

Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: Uncovering the molecular mechanisms. Nat Rev Neurosci 2007; 8(1): 57-69.

Bonnet MS, Roux J, Mounien L, Dallaporta M, Troadec JD. Advances in deoxynivalenol toxicity mechanisms: The brain as a target. Toxins (Basel) 2012; 4(11): 1120-1138.

Brown GC, Neher JJ. Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. Mol Neurobiol 2010; 41(2-3): 242-247.

Butterfield DA, Perluigi M, Sultana R. Oxidative stress in Alzheimer's disease brain: New insights from redox proteomics. Eur J Pharmacol 2006; 545(1): 39-50.

Caloni F, Cortinovis C. Effects of fusariotoxins in the equine species. Vet J 2010; 186(2): 157-161.

Caso JR, Lizasoain I, Lorenzo P, Moro MA, Leza JC. The role of tumor necrosis factor-alpha in stress-induced worsening of cerebral ischemia in rats. Neuroscience 2006; 142(1): 59-69.

Chantong B, Kratschmar DV, Nashev LG, Balazs Z, Odermatt A. Mineralocorticoid and glucocorticoid receptors differentially regulate NF-kappaB activity and pro-inflammatory cytokine production in murine BV-2 microglial cells. J Neuroinflammation 2012; 9: 260.

Chaudhary M, Rao PV. Brain oxidative stress after dermal and subcutaneous exposure of T-2 toxin in mice. Food Chem Toxicol 2010; 48(12): 3436-3442.

Cheng YL, Wang CY, Huang WC, Tsai CC, Chen CL, Shen CF, et al. Staphylococcus aureus induces microglial inflammation via a glycogen synthase kinase 3 beta-regulated pathway. Infect Immun 2009; 77(9): 4002-4008.

Choi Y, Lee MK, Lim SY, Sung SH, Kim YC. Inhibition of inducible NO synthase, cyclooxygenase-2 and interleukin-1beta by torilin is mediated by mitogen-activated protein kinases in microglial BV2 cells. Br J Pharmacol 2009; 156(6): 933-940.

Clark KH, Wiley CA, Bradberry CW. Psychostimulant abuse and neuroinflammation: Emerging evidence of their interconnection. Neurotox Res 2013; 23(2): 174-188.

Collins LM, Toulouse A, Connor TJ, Nolan YM. Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. Neuropharmacology 2012; 62(7): 2154-2168.

Cortinovis C, Pizzo F, Spicer LJ, Caloni F. Fusarium mycotoxins: Effects on reproductive function in domestic animals-a review. Theriogenology 2013; 80(6): 557-564.

Crews FT, Zou J, Qin L. Induction of innate immune genes in brain create the neurobiology of addiction. Brain Behav Immun 2011; 25 Suppl 1: S4-S12.

di Penta A, Moreno B, Reix S, Fernandez-Diez B, Villanueva M, Errea O, et al. Oxidative stress and proinflammatory cytokines contribute to demyelination and axonal damage in a cerebellar culture model of neuroinflammation. PLoS One 2013; 8(2): e54722.

Dinkel K, MacPherson A, Sapolsky RM. Novel glucocorticoid effects on acute inflammation in the CNS. J Neurochem 2003; 84(4): 705-716.

Doi K, Uetsuka K. Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways. Int J Mol Sci 2011; 12(8): 5213-5237.

Domercq M, Vazquez-Villoldo N, Matute C. Neurotransmitter signaling in the pathophysiology of microglia. Front Cell Neurosci 2013; 7:49.

Domijan AM, Abramov AY. Fumonisin B1 inhibits mitochondrial respiration and deregulates calcium homeostasis—implication to mechanism of cell toxicity. Int J Biochem Cell Biol 2011; 43(6): 897-904.

Domijan AM, Kovac S, Abramov AY. Impact of fumonisin B1 on glutamate toxicity and low magnesium-induced seizure activity in neuronal primary culture. Neuroscience 2012; 202: 10-16.

Domijan AM. Fumonisin B(1): A neurotoxic mycotoxin. Arh Hig Rada Toksikol 2012; 63(4): 531-544.

Espinosa-Oliva AM, de Pablos RM, Villaran RF, Arguelles S, Venero JL, Machado A, et al. Stress is critical for LPS-induced activation of microglia and damage in the rat hippocampus. Neurobiol Aging 2011; 32(1): 85-102.

Evans MC, Couch Y, Sibson N, Turner MR. Inflammation and neurovascular changes in amyotrophic lateral sclerosis. Mol Cell Neurosci 2013; 53: 34-41.

Ferreras MC, Benavides J, Garcia-Pariente C, Delgado L, Fuertes M, Munoz M, et al. Acute and chronic disease associated with naturally occurring T-2 mycotoxicosis in sheep. J Comp Pathol 2013; 148(2-3): 236-242.

Frank MG, Miguel ZD, Watkins LR, Maier SF. Prior exposure to glucocorticoids sensitizes the neuroinflammatory and peripheral inflammatory responses to E. Coli lipopolysaccharide. Brain Behav Immun 2010; 24(1): 19-30.

Frank MG, Thompson BM, Watkins LR, Maier SF. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav Immun 2012; 26(2): 337-345.

Frieler RA, Meng H, Duan SZ, Berger S, Schutz G, He Y, et al. Myeloid-specific deletion of the mineralocorticoid receptor reduces infarct volume and alters inflammation during cerebral ischemia. Stroke 2011; 42(1): 179-185.

Ganter S, Northoff H, Mannel D, Gebicke-Harter PJ. Growth control of cultured microglia. J Neurosci Res 1992; 33(2): 218-230.

Girardet C, Bonnet MS, Jdir R, Sadoud M, Thirion S, Tardivel C, et al. Central inflammation and sickness-like behavior induced by the food contaminant deoxynivalenol: A PEG2-independent mechanism. Toxicol Sci 2011a; 124(1): 179-191.

Girardet C, Bonnet MS, Jdir R, Sadoud M, Thirion S, Tardivel C, et al. The food-contaminant deoxynivalenol modifies eating by targeting anorexigenic neurocircuitry. PLoS one 2011b; 6(10): e26134.

Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell 2010; 140(6): 918-934.

Grau JW, Washburn SN, Hook MA, Ferguson AR, Crown ED, Garcia G, et al. Uncontrollable stimulation undermines recovery after spinal cord injury. J Neurotrauma 2004; 21(12): 1795-1817.

Hansen PR, Rieneck K, Bendtzen K. Spironolactone inhibits production of proinflammatory cytokines by human mononuclear cells. Immunol Lett 2004; 91(2-3): 87-91.

Harvey PW, Healing G, Rees SJ, Everett DJ, Cockburn A. Glucocorticosteroid interactions with natural toxins: A mini review. Nat Toxins 1994; 2(6): 341-346.

Hong J, Kim BK, Lim H, Lee S, Lee SJ. Identification and characterization of triamcinolone acetonide, a microglial-activation inhibitor. Immunopharmacol Immunotoxicol 2012; 34(6): 912-918.

Hu S, Sheng WS, Schachtele SJ, Lokensgard JR. Reactive oxygen species drive herpes simplex virus (HSV)-1-induced proinflammatory cytokine production by murine microglia. J Neuroinflammation 2011; 8: 123.

Ibrahim AS, El-Remessy AB, Matragoon S, Zhang W, Patel Y, Khan S, et al. Retinal microglial activation and inflammation induced by amadori-glycated albumin in a rat model of diabetes. Diabetes 2011; 60(4): 1122-1133.

Ishigami N, Shinozuka J, Katayama K, Uetsuka K, Nakayama H, Doi K. Apoptosis in the developing mouse embryos from T-2 toxin-inoculated dams. Histol Histopathol 1999; 14(3): 729-733.

Kacimi R, Giffard RG, Yenari MA. Endotoxin-activated microglia injure brain derived endothelial cells via NF-kappaB, JAK-STAT and JNK stress kinase pathways. J Inflamm (Lond) 2011; 8:7.

Kaur C, Wu CH, Wen CY, Ling EA. The effects of subcutaneous injections of glucocorticoids on amoeboid microglia in postnatal rats. Arch Histol Cytol 1994; 57(5): 449-459.

Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiol Rev 2011; 91(2): 461-553.

Khasnavis S, Ghosh A, Roy A, Pahan K. Castration induces parkinson disease pathologies in young male mice via inducible nitric-oxide synthase. J Biol Chem 2013; 288(29): 20843-20855.

Kiyomoto H, Rafiq K, Mostofa M, Nishiyama A. Possible underlying mechanisms responsible for aldosterone and mineralocorticoid receptor-dependent renal injury. J Pharmacol Sci 2008; 108(4): 399-405.

Kolch W. Coordinating ERK/MAPK signalling through scaffolds and inhibitors. Nat Rev Mol Cell Biol 2005; 6(11): 827-837.

Kovacic P, Somanathan R. Redox processes in neurodegenerative disease involving reactive oxygen species. Curr Neuropharmacol 2012; 10(4): 289-302.

Koziorowski D, Tomasiuk R, Szlufik S, Friedman A. Inflammatory cytokines and NT-proCNP in Parkinson's disease patients. Cytokine 2012; 60(3): 762-766.

Li M, Dai FR, Du XP, Yang QD, Chen Y. Neuroprotection by silencing iNOS expression in a 6-OHDA model of Parkinson's disease. J Mol Neurosci 2012; 48(1): 225-233.

Li Y, Wang Z, Beier RC, Shen J, De Smet D, De Saeger S, et al. T-2 toxin, a trichothecene mycotoxin: Review of toxicity, metabolism, and analytical methods. J Agric Food Chem 2011; 59(8): 3441-3453.

Lin LC, Ho FM, Yen SJ, Wu PY, Hung LF, Huang WJ, et al. Carbon monoxide induces cyclooxygenase-2 expression through MAPKs and PKG in phagocytes. Int Immunopharmacol 2010; 10(12): 1520-1525.

Loram LC, Taylor FR, Strand KA, Frank MG, Sholar P, Harrison JA, et al. Prior exposure to glucocorticoids potentiates lipopolysaccharide induced mechanical allodynia and spinal neuroinflammation. Brain Behav Immun 2011; 25(7): 1408-1415.

Lukiw WJ. NF-kappaB-regulated, proinflammatory miRNAs in Alzheimer's disease. Alzheimers Res Ther 2012; 4(6): 47.

MacPherson A, Dinkel K, Sapolsky R. Glucocorticoids worsen excitotoxin-induced expression of pro-inflammatory cytokines in hippocampal cultures. Exp Neurol 2005; 194(2): 376-383.

Magnoli AP, Monge MP, Nazar FN, Magnoli CE, Cavaglieri LR, Bagnis G, et al. Combined effects of aflatoxin B1 and corticosterone treatment on selected performance indices and liver histopathology in Japanese quail. Poult Sci 2012; 91(2): 354-361.

Mantle PG, Nolan CC. Pathological outcomes in kidney and brain in male Fischer rats given dietary ochratoxin A, commencing at one year of age. Toxins (Basel) 2010; 2(5): 1100-1110.

Maresca M. From the gut to the brain: Journey and pathophysiological effects of the food-associated trichothecene mycotoxin deoxynivalenol. Toxins (Basel) 2013; 5(4): 784-820.

Marin S, Ramos AJ, Cano-Sancho G, Sanchis V. Mycotoxins: Occurrence, toxicology, and exposure assessment. Food Chem Toxicol 2013; 60C: 218-237.

Miura R, Nakamura K, Miura D, Miura A, Hisamatsu K, Kajiya M, et al. Anti-inflammatory effect of spironolactone on human peripheral blood mononuclear cells. J Pharmacol Sci 2006; 101(3): 256-259.

Monnet-Tschudi F, Sorg O, Honegger P, Zurich MG, Huggett AC, Schilter B. Effects of the naturally occurring food mycotoxin ochratoxin a on brain cells in culture. Neurotoxicology 1997; 18(3): 831-839.

Morale MC, Serra PA, Delogu MR, Migheli R, Rocchitta G, Tirolo C, et al. Glucocorticoid receptor deficiency increases vulnerability of the nigrostriatal dopaminergic system: Critical role of glial nitric oxide. FASEB J 2004; 18(1): 164-166.

Morales I, Farias G, Maccioni RB. Neuro-immunomodulation in the pathogenesis of Alzheimer's disease. Neuroimmunomodulation 2010;17(3): 202-204.

Mu P, Xu M, Zhang L, Wu K, Wu J, Jiang J, et al. Proteomic changes in chicken primary hepatocytes exposed to T-2 toxin are associated with oxidative stress and mitochondrial enhancement. Proteomics 2013; 13(21): 3175-3188.

Munhoz CD, Lepsch LB, Kawamoto EM, Malta MB, Lima Lde S, Avellar MC, et al. Chronic unpredictable stress exacerbates lipopolysaccharide-induced activation of nuclear factor-kappaB in the frontal cortex and hippocampus via glucocorticoid secretion. J Neurosci 2006; 26(14): 3813-3820.

Munhoz CD, Sorrells SF, Caso JR, Scavone C, Sapolsky RM. Glucocorticoids exacerbate lipopoly saccharide-induced signaling in the frontal cortex and hippocampus in a dose-dependent manner. J Neurosci 2010; 30(41): 13690-13698.

Nakatani Y, Amano T, Tsuji M, Takeda H. Corticosterone suppresses the proliferation of bv2 microglia cells via glucocorticoid, but not mineralocorticoid receptor. Life Sci 2012; 91(15-16): 761-770.

Nguyen Dinh Cat A, Briones AM, Callera GE, Yogi A, He Y, Montezano AC, et al. Adipocyte-derived factors regulate vascular smooth muscle cells through mineralocorticoid and glucocorticoid receptors. Hypertension 2011; 58(3): 479-488.

Niranjan R. The role of inflammatory and oxidative stress mechanisms in the pathogenesis of Parkinson's disease: Focus on astrocytes. Mol Neurobiol 2013.

Noonim P, Mahakarnchanakul W, Nielsen KF, Frisvad JC, Samson RA. Isolation, identification and toxigenic potential of ochratoxin a-producing Aspergillus species from coffee beans grown in two regions of Thailand. Int J Food Microbiol 2008; 128(2): 197-202.

Noonim P, Mahakarnchanakul W, Nielsen KF, Frisvad JC, Samson RA. Fumonisin B2 production by Aspergillus niger in Thai coffee beans. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2009; 26(1): 94-100.

Orre M, Kamphuis W, Dooves S, Kooijman L, Chan ET, Kirk CJ, et al. Reactive glia show increased immunoproteasome activity in Alzheimer's disease. Brain 2013; 136(Pt 5): 1415-1431.

Osuchowski MF, Edwards GL, Sharma RP. Fumonisin B1-induced neurodegeneration in mice after intracerebroventricular infusion is concurrent with disruption of sphingolipid metabolism and activation of proinflammatory signaling. Neurotoxicology 2005; 26(2): 211-221.

Pestka JJ, Islam Z, Amuzie CJ. Immunochemical assessment of deoxynivalenol tissue distribution following oral exposure in the mouse. Toxicol Lett 2008; 178(2): 83-87.

Pestka JJ. Deoxynivalenol-induced proinflammatory gene expression: Mechanisms and pathological sequelae. Toxins (Basel) 2010; 2(6): 1300-1317.

Peterson LJ, Flood PM. Oxidative stress and microglial cells in Parkinson's disease. Mediators Inflamm 2012; 2012: 401264.

Poapolathep A, Poapolathep S, Klangkaew N, Sugita-Konishi Y, Kumagai S. Detection of deoxynivalenol contamination in wheat products in Thailand. J Food Prot 2008; 71(9): 1931-1933.

Purzycki CB, Shain DH. Fungal toxins and multiple sclerosis: A compelling connection. Brain Res Bull 2010; 82(1-2): 4-6.

Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 2007; 55(5): 453-462.

Queisser N, Amann K, Hey V, Habib SL, Schupp N. Blood pressure has only minor influence on aldosterone-induced oxidative stress and DNA damage in vivo. Free Radic Biol Med 2013; 54: 17-25.

Ravindran J, Agrawal M, Gupta N, Rao PV. Alteration of blood brain barrier permeability by T-2 toxin: Role of MMP-9 and inflammatory cytokines. Toxicology 2011; 280(1-2): 44-52.

Razafimanjato H, Benzaria A, Taieb N, Guo XJ, Vidal N, Di Scala C, et al. The ribotoxin deoxynivalenol affects the viability and functions of glial cells. Glia 2011; 59(11): 1672-1683.

Rezar V, Frankic T, Narat M, Levart A, Salobir J. Dose-dependent effects of T-2 toxin on performance, lipid peroxidation, and genotoxicity in broiler chickens. Poult Sci 2007; 86(6): 1155-1160.

Rice LG, Ross PF. Methods for detection and quantitation of fumonisins in corn, cereal products and animal excreta. J Food Prot 1994; 57(6): 536-540.

Ros-Bernal F, Hunot S, Herrero MT, Parnadeau S, Corvol JC, Lu L, et al. Microglial glucocorticoid receptors play a pivotal role in regulating dopaminergic neurodegeneration in parkinsonism. Proc Natl Acad Sci U S A 2011; 108(16): 6632-6637.

Ruangwises N, Ruangwises S. Aflatoxin M(1) contamination in raw milk within the central region of Thailand. Bull Environ Contam Toxicol 2010; 85(2): 195-198.

Ruangwises S, Ruangwises N. Occurrence of aflatoxin m1 in pasteurized milk of the school milk project in Thailand. J Food Prot 2009; 72(8): 1761-1763.

Rubio-Perez JM, Morillas-Ruiz JM. A review: Inflammatory process in Alzheimer's disease, role of cytokines. The Scientific World Journal 2012; 2012: 756357.

Sava V, Reunova O, Velasquez A, Harbison R, Sanchez-Ramos J. Acute neurotoxic effects of the fungal metabolite ochratoxin-A. Neurotoxicology 2006a; 27(1): 82-92.

Sava V, Reunova O, Velasquez A, Sanchez-Ramos J. Can low level exposure to ochratoxin-a cause parkinsonism? J Neurol Sci 2006b; 249(1): 68-75.

Sava V, Velasquez A, Song S, Sanchez-Ramos J. Adult hippocampal neural stem/progenitor cells in vitro are vulnerable to the mycotoxin ochratoxin-A. Toxicol Sci 2007; 98(1): 187-197.

Sehata S, Kiyosawa N, Makino T, Atsumi F, Ito K, Yamoto T, et al. Morphological and microarray analysis of T-2 toxin-induced rat fetal brain lesion. Food Chem Toxicol 2004; 42(11): 1727-1736.

Sorenson M, Janusek L, Mathews H. Psychological stress and cytokine production in multiple sclerosis: Correlation with disease symptomatology. Biol Res Nurs 2013; 15(2): 226-233.

Sorrells SF, Caso JR, Munhoz CD, Sapolsky RM. The stressed CNS: When glucocorticoids aggravate inflammation. Neuron 2009; 64(1): 33-39.

Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun 2007; 21(3): 259-272.

Stockmann-Juvala H, Mikkola J, Naarala J, Loikkanen J, Elovaara E, Savolainen K. Fumonisin B1-induced toxicity and oxidative damage in U-118MG glioblastoma cells. Toxicology 2004; 202(3): 173-183.

Streit E, Schatzmayr G, Tassis P, Tzika E, Marin D, Taranu I, et al. Current situation of mycotoxin contamination and co-occurrence in animal feed—focus on Europe. Toxins (Basel) 2012; 4(10): 788-809.

Sugama S, Takenouchi T, Fujita M, Kitani H, Conti B, Hashimoto M. Corticosteroids limit microglial activation occurring during acute stress. Neuroscience 2012; 232C: 13-20.

Sugama S, Takenouchi T, Kitani H, Fujita M, Hashimoto M. Microglial activation is inhibited by corticosterone in dopaminergic neurodegeneration. J Neuroimmunol 2009; 208(1-2): 104-114.

Syngle A, Vohra K, Khichi D, Garg N, Verma I, Kaur L. Spironolactone improves endothelial dysfunction in ankylosing spondylitis. Clin Rheumatol 2013; 32(7): 1029-1036.

Tanaka J, Fujita H, Matsuda S, Toku K, Sakanaka M, Maeda N. Glucocorticoid- and mineralocorticoid receptors in microglial cells: The two receptors mediate differential effects of corticosteroids. Glia 1997; 20(1): 23-37.

Tansakul N, Jala P, Laopiem S, Tangmunkhong P, Limsuwan S. Co-occurrence of five Fusarium toxins in corn-dried distiller's grains with solubles in Thailand and comparison of ELISA and LC-MS/MS for fumonisin analysis. Mycotoxin Res 2013; 29(4): 255-260.

Tardivel C, Airault C, Djelloul M, Guillebaud F, Barbouche R, Troadec JD, et al. The food born mycotoxin deoxynivalenol induces low-grade inflammation in mice in the absence of observed-adverse effects. Toxicol Lett 2015; 232(3): 601-611.

von Tobel JS, Antinori P, Zurich MG, Rosset R, Aschner M, Gluck F, et al. Repeated exposure to ochratoxin a generates a neuroinflammatory response, characterized by neurodegenerative M1 microglial phenotype. Neurotoxicology 2014; 44: 61-70.

Wang J, Fitzpatrick DW, Wilson JR. Effect of T-2 toxin on blood-brain barrier permeability monoamine oxidase activity and protein synthesis in rats. Food Chem Toxicol 1998b; 36(11): 955-961.

Wang J, Fitzpatrick DW, Wilson JR. Effects of the trichothecene mycotoxin T-2 toxin on neurotransmitters and metabolites in discrete areas of the rat brain. Food Chem Toxicol 1998a; 36(11): 947-953.

Wang YP, Wu Y, Li LY, Zheng J, Liu RG, Zhou JP, et al. Aspirin-triggered lipoxin A4 attenuates LPS-induced pro-inflammatory responses by inhibiting activation of NF-kappaB and MAPKs in BV-2 microglial cells. J Neuroinflammation 2011; 8:95.

Waskiewicz AJ, Cooper JA. Mitogen and stress response pathways: MAP kinase cascades and phosphatase regulation in mammals and yeast. Curr Opin Cell Biol 1995; 7(6): 798-805.

Weidner M, Huwel S, Ebert F, Schwerdtle T, Galla HJ, Humpf HU. Influence of T-2 and HT-2 toxin on the blood-brain barrier in vitro: New experimental hints for neurotoxic effects. PLoS one 2013a; 8(3): e60484.

Weidner M, Lenczyk M, Schwerdt G, Gekle M, Humpf HU. Neurotoxic potential and cellular uptake of T-2 toxin in human astrocytes in primary culture. Chem Res Toxicol 2013b; 26(3): 347-355.

Wilk-Zasadna I, Minta M. Developmental toxicity of ochratoxin a in rat embryo midbrain micromass cultures. Int J Mol Sci 2009; 10(1): 37-49.

Wong WT. Microglial aging in the healthy CNS: Phenotypes, drivers, and rejuvenation. Front Cell Neurosci 2013; 7:22.

Wongchana W, Palaga T. Direct regulation of interleukin-6 expression by Notch signaling in macrophages. Cell Mol Immunol 2012; 9(2): 155-162.

Woodcock T, Morganti-Kossmann MC. The role of markers of inflammation in traumatic brain injury. Front Neurol 2013; 4:18.

Yamashita A, Yoshizawa T, Aiura Y, Sanchez PC, Dizon EI, Arim RH, et al. Fusarium mycotoxins (fumonisins, nivalenol, and zearalenone) and aflatoxins in corn from Southeast Asia. Biosci Biotechnol Biochem 1995; 59(9): 1804-1807.

Yang GH, Jarvis BB, Chung YJ, Pestka JJ. Apoptosis induction by the satratoxins and other trichothecene mycotoxins: Relationship to ERK, p38 MAPK, and SAPK/JNK activation. Toxicol Appl Pharmacol 2000; 164(2): 149-160.

Yeager MP, Rassias AJ, Pioli PA, Beach ML, Wardwell K, Collins JE, et al. Pretreatment with stress cortisol enhances the human systemic inflammatory response to bacterial endotoxin. Crit Care Med 2009; 37(10): 2727-2732.

Zhang X, Boesch-Saadatmandi C, Lou Y, Wolffram S, Huebbe P, Rimbach G. Ochratoxin a induces apoptosis in neuronal cells. Genes Nutr 2009; 4(1): 41-48.

Zurich MG, Lengacher S, Braissant O, Monnet-Tschudi F, Pellerin L, Honegger P. Unusual astrocyte reactivity caused by the food mycotoxin ochratoxin a in aggregating rat brain cell cultures. Neuroscience 2005; 134(3): 771-782.