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► To cite this version:

Chloé Terciolo, Marc Maresca, Philippe Pinton, Isabelle P. Oswald. Review article: Role of satiety hormones in anorexia induction by Trichothecene mycotoxins. *Food and Chemical Toxicology*, 2018, 121, pp.701-714. 10.1016/j.fct.2018.09.034 . hal-03331270

HAL Id: hal-03331270

<https://ut3-toulouseinp.hal.science/hal-03331270v1>

Submitted on 1 Sep 2021

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Review article: Role of satiety hormones in anorexia induction by Trichothecene mycotoxins

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Abstract:

The trichothecenes, produced by *Fusarium*, contaminate animal feed and human food in all stages of production and lead to a large spectrum of adverse effects for animal and human health. An hallmark of trichothecenes toxicity is the onset of emesis followed by anorexia and food intake reduction in different animal species (mink, mice and pig). The modulation of emesis and anorexia can result from a direct action of trichothecenes in the brain or from an indirect action in the gastrointestinal tract. The direct action of trichothecenes involved specific brain areas such as nucleate tractus solitarius in the brainstem and the arcuate nuclei in the hypothalamus. Activation of these areas in the brain leads to the activation of specific neuronal populations containing anorexigenic factors (POMC and CART). The indirect action of trichothecenes in the gastrointestinal tract involved, by enteroendocrine cells, the secretion of several gut hormones such as cholecystokinin (CCK) and peptide YY (PYY) but also glucagon-like peptide 1 (GLP-1), gastric inhibitory peptide (GIP) and 5-hydroxytryptamine (5-HT), which transmitted signals to the brain via the gut-brain axis. This review summarizes current knowledge on the effects of trichothecenes, especially deoxynivalenol, on emesis and anorexia and discusses the mechanisms underlying trichothecenes-induced food reduction.

Keywords: trichothecenes, deoxynivalenol, emesis, anorexia, gut hormones.

Abbreviations:

3-ADON	3-AcetylDeoxynivalenol	EEC	EnteroEndocrine Cells
3-epi-DON	3-epi-Dexynivalenol	FX	Fusarenon X
5-HT	5-HydroxyTryptamine	GIP	Gastric Inhibitory Peptide
15-ADON	15-AcetylDeoxynivalenol	GLP-1	Glucagon-Like Peptide 1
α -MSH	α -Melanocyte-Stimulating Hormone	MCR	MelanoCortin Receptor
ARC	ARcuate Nuclei	NEO	NEOsonaniol
AgRP	Agouti-Related Peptide	NIV	Nivalenol
bw	Body Weight	NPY	NeuroPeptide Y
CART	Cocaine and Amphetamine-Regulated Transcript	NTS	Nucleus Tractus Solitarius
CaSR	Calcium-Sensing Receptor	PKR	Protein Kinase R
CCK	CholeCystoKinin	POMC	Pro-OpioMelanoCortin
D3G	DON-3- β -Glucoside	PYY	Peptide YY
DAS	DiAcetoxyScirpenol	ROS	Radical Oxygen Species
DOM-1	De-epoxy-deoxynivalenol	TRPA1	Transient Receptor Potential Ankyrin-1
DON	Deoxynivalenol		

1 Introduction

Mycotoxins are natural products produced as secondary metabolites by filamentous fungi. Among mycotoxins, the trichothecenes family is a vast group mainly produced by several *Fusarium* species and to a lesser extent by other genera such as *Trichothecium*, *Myrothecium* (Hussein and Brasel, 2001).

Trichothecenes, especially the ones originating from the A and B groups can contaminate cereals including wheat, corn and barley. Changes in climate conditions in Europe favor an increased level of contamination by such toxins (Yazar and Omurtag, 2008). In addition, trichothecenes are very stable during milling and other processes and are consequently difficult to eliminate from final products (Pestka, 2010, Karlovsky et al., 2016). Their presence in cereal-based foods can harm humans and animals (Wu et al., 2016). Type D trichothecenes are found in a variety of commodities and are a significant indoor environmental contaminant that has been correlated with damp building-related illnesses (McCormick et al., 2011, Aleksic et al., 2016, Aleksic et al., 2017).

Trichothecenes have a spectrum of adverse effects including emesis, anorexia, growth retardation, neuroendocrine changes and immunotoxicity (Ueno, 1985, Escrivá et al., 2015). Since trichothecenes induce emesis and growth retardation, mycotoxin contamination is becoming a major issue for child and young animal health (Hussein and Brasel, 2001) (Wu et al., 2012). Trichothecenes, especially deoxynivalenol (DON) also called “vomitoxin” or “food refusal factor”, are known to induce vomiting and anorectic responses in several animal models and in humans (Pestka, 2007). The balance between anorexigenic and orexigenic signals that modulate food intake behavior is mediated by several factors of the peripheral and the central nervous systems (Strader and Woods, 2005); both systems are thus potential targets of trichothecenes.

The central nervous system receives information from peripheral organs, regulates energy intake, and sends signals to the peripheral organs to maintain energy homeostasis (Hussain and Bloom, 2013). Signals received by the brain are mediated by appetite modulators or gut hormones released from enteroendocrine cells along the gastrointestinal tract. The short- term regulation of food intake is under the control of the stomach and the intestine while the liver and the adipose tissue are involved in long- term regulation and energy storage (Yu and Kim, 2012). Gut hormones including ghrelin, the only orexigenic hormone, and anorexigenic mediators such as cholecystikinin, peptide YY, glucagon-like peptide and 5-hydroxytryptamine play a fundamental role in maintaining the energy balance (Perry and Wang, 2012).

This review summarizes current knowledge on the effects of trichothecenes, especially DON, on emesis and anorexia and discusses the mechanisms underlying trichothecenes-induced food reduction.

2 Structure and classification of trichothecenes

More than 200 molecules are classified as trichothecenes (Grove, 2007) (McCormick et al., 2011). They are cyclic terpenoids with a common tricyclic 12,13-epoxytrichothec-9-ene core structure characterized by the presence of a double bond between carbons 9 and 10 and an epoxide group between carbons 12 and 13 (figure 1), both being essential for their activity (Bennett and Klich, 2003). Although all trichothecenes share this common core structure, they also possess unique substitution groups at carbons 3, 4, 7, 8 and 15, allowing their classification as type A, B, C or D. Types A, B and C differ in the substitution present at carbon 8 (figure 1):

- In type A trichothecenes (e.g. T-2 toxin, Neosolaniol or Trichodermin) substitution groups of carbon 8 are either hydroxyl group, ester group or no substitution (figure 1).
- In type B trichothecenes, a substituent group corresponds to carbonyl function (figure 1). This subtype of trichothecenes includes five structurally related congeners: DON, 3-acetyldeoxynivalenol (3-ADON), 15-acetyldeoxynivalenol (15-ADON), fusarenon X (FX) and nivalenol (NIV). Some transformations produce mycotoxin derivatives, also called “masked/modified mycotoxins” that are undetectable by conventional analytical techniques.

These derivatives result from changes in the “native mycotoxin” structure after transformation by process, bacteria or plants (Berthiller et al., 2013, Payros et al., 2016, Rychlik et al., 2014). In the case of DON, derivatives can be generated by bacterial transformation, for example de-epoxy-deoxynivalenol (DOM-1) and 3-epi-deoxynivalenol (3-epi-DON). DOM-1 is produced after a reduction of the 12, 13-epoxy group while 3-epi-DON is an epimerization of the C3 carbon hydroxyl group (Pierron et al., 2016b, Carere et al., 2017). Some plants also have the ability to transform mycotoxins. For example, DON-3- β -glucoside (D3G) results from enzymatic conjugation of glucose to DON by plant (Berthiller et al., 2013). Generally, this biotransformation results in a decrease in toxicity (Berthiller et al., 2013, Pierron et al., 2016a, Pierron et al., 2016b). DON has also been derivatized in pharmacological form (EN139544 and EN139528) (Wu et al., 2014c, Wu et al., 2014b). EN139544 has a large benzoyloxy group that replaces C-15 hydroxyl of DON and EN139528 has an hydroxyl group that replaces the 8-keto group and an acetyl group that replaces the C-3-hydroxyl group in DON.

- Type C trichothecenes (including Crotocin) are characterized by the presence of a second epoxide group between carbon 7 and 8 (figure 1).
- Finally, type D trichothecenes (e.g. Roridins, Verrucarins and Satratoxins) possess an additional ring between carbon 4 and carbon 15 (figure 1), which is why they are also called “macrocyclic” trichothecenes, whereas types A, B and C trichothecenes are called “simple” trichothecenes.

3 Mechanisms of action of trichothecenes

3.1 Inhibition of protein synthesis

The main mechanism of action of trichothecenes in eukaryotes is inhibition of protein synthesis through their interaction with ribosomes, especially the 60S ribosomal sub-unit (Garreau de Loubresse et al., 2014). This inhibitory action requires the double bond between carbons 9 and 10 and more importantly the epoxide group between carbons 12 and 13, explaining why metabolic derivatives lacking the epoxide motive are not toxic (Ueno et al., 1973, Cundliffe et al., 1974, Pierron et al., 2016b). This observation initially led to the belief that the epoxide group present in all trichothecenes allows them to covalently bind to ribosomal RNA as observed with epoxide derivatives of aflatoxins that bind to DNA and RNA (Bedard and Massey, 2006). However, the presence of the epoxide group in a non-toxic form of DON, 3-epi-DON, suggests that other molecular groups are implicated in trichothecenes toxicity (Pierron et al., 2016b). What is more, the absence of covalent binding of trichothecenes to nucleic acids (either DNA or RNA) or to other molecules challenges this hypothesis and suggests that the epoxide group of trichothecenes is not reactive, does not participate directly in the binding of trichothecenes to ribosomes but plays important role in the correct spatial conformation required for the interaction with the ribosome (Maresca, 2013, Dellafiora et al., 2017, Payros et al., 2017).

The interaction of trichothecenes with 60S ribosomal sub-unit through non-covalent hydrogen bonds leads to the so-called *ribotoxic stress effect* resulting in:

- inhibition of protein synthesis,
- rRNA cleavage
- activation of different cellular signaling pathways, leading to modulation of gene expression and to post-translational protein modifications (Maresca, 2013).

Trichothecenes activate the same signaling pathways as other ribotoxins (e.g. ricin) or ribotoxic stress activators (such as viral infection or UV exposure), including:

- Two rRNA associated protein kinases, i.e., double-stranded RNA (dsRNA)-activated protein kinase (PKR) and Hematopoietic cell kinase (Hck) (Pestka, 2008).
- MAP kinases (p38, ERK1/2, JNK), both of which are able to modulate the expression of proteins involved in the inflammation (through NF κ B activation) and apoptosis (through p53) (Pinton et al., 2012, Maresca, 2013, Lucoli et al., 2013).

3.2 Effect on oxydative stress

In parallel to the ribotoxic stress effect, trichothecenes are known to target mitochondria and to cause mitochondrial stress leading to the generation of Radical Oxygen Species (ROS), lipid peroxidation, and oxidative stress that can also cause apoptosis (Wu et al., 2014a, da Silva et al., 2018).

3.3 Modulation of gene expression and post-translational protein modification

Other regulatory proteins can be activated / modulated by trichothecenes including the Resistin-Like Molecule β (RELM-beta), HuR/Elav-like RNA binding protein 1, the CCAAT/enhancer-binding protein (CHOP) homologous protein, the peroxisome proliferator-activated receptor γ (PPAR γ), the Early Growth Response Gene 1 (EGR-1), the activating transcription factor 3 (ATF3), histone methylase, and GRP78/BiP (Maresca, 2013, Pinton and Oswald, 2014). This list is not exhaustive and a proteomic approach has revealed that cell exposure to DON leads to the phosphorylation of 188 proteins involved in transcription, epigenetic modulation, the cell cycle, RNA processing, translation, ribosome biogenesis, cell differentiation and cytoskeleton organization (Pan et al., 2013). Other post-translational modifications of protein are also altered by trichothecenes, including the ubiquitinylation of iNOS (Graziani et al., 2015).

4 Toxicological effects of trichothecenes

Modulation of gene expression, post-translational protein modification, protein synthesis inhibition and/or oxidative stress caused by trichothecenes eventually lead to cellular and tissue alterations. Exposure to trichothecenes triggers a spectrum of adverse effects including growth retardation, neuroendocrinal changes, immunocytotoxicity, emesis and anorexia (Pestka, 2010). The tissues affected by the trichothecenes and the severity of the observed alterations greatly depend on:

- The exposure route, i.e. inhalation of toxins and/or the ingestion of contaminated food, the second route being the most frequent one,
- The ability of the trichothecenes to cross the respiratory and/or intestinal epithelium and to diffuse to other organs. Thus, the more a trichothecene is able to cross the epithelium and to diffuse into the body, the more organs it will affect, including the brain in the case of the toxins able to cross the blood-brain barrier. Once in the brain, these toxins disrupt the regulation of food behavior through anorexigenic and emetic effects.

4.1 Toxicological effects of type A and type B trichothecenes

Type A and type B trichothecenes (including T-2 toxin or DON) can cross physiological barriers (the epithelial wall and the blood-brain barrier), and target almost all organs, but the intestine, the immune system and the brain are particularly affected (Meissonnier et al., 2008, Maresca, 2013, Pinton and Oswald, 2014). The intestine is the first and the most exposed organ after ingestion of contaminated food (Pinton and Oswald, 2014). Accordingly, numerous studies have reported intestinal alterations caused by types A or B trichothecenes, including:

- a decrease in nutrient absorption (Maresca et al., 2002),
- a decrease in intestinal barrier function (impaired tight junctions and decreased production of mucus) (Maresca et al., 2002, Maresca et al., 2008, Pinton and Oswald, 2014, Pinton et al., 2015).
- alteration of the microbiota (i.e. dysbiosis) (Waché et al., 2009, Payros et al., 2017)
- an increase in the expression/secretion of pro-inflammatory cytokines (Maresca et al., 2008, Alassane-Kpembi et al., 2017b, Alassane-Kpembi et al., 2017a).

These intestinal alterations are associated with reduced weight gain and altered feeding behavior (Table 1). Different mechanisms may be involved in the modification of feed intake observed after exposure to type A and B trichothecenes. For example, gut dysbiosis is

associated with brain dysfunction and behavioral changes (Peng et al., 2017). Secretion of pro-inflammatory cytokines may also reduce feed intake, since IL-1 or IL-6 are known to cause anorexia (Clark et al., 2015a, Clark et al., 2015b). In addition, types A and B trichothecenes modulate the secretion of various intestinal hormones, affect different physiological functions, including the energy balance and feed intake (Table 2) (Flannery et al., 2012, Zhou and Pestka, 2015, Chen et al., 2017). In addition to their peripheral action and linked to their ability to cross blood-brain barrier, types A and B trichothecenes can act centrally on the brain (Razafimanjato et al., 2011, Behrens et al., 2015, Guo et al., 2018).

4.2 Toxicological effects of type C trichothecenes

Little is known about the mechanism of action and the effects of type C trichothecenes such as crotocin on the cell and/or organs, only three papers on the topic are referenced in PubMed (Glaz et al., 1966, Liao et al., 1976, Chi and Mirocha, 1978). Like other trichothecenes, crotocin inhibits protein synthesis through ribotoxic action in HeLa cells, but no information is available regarding the possible involvement of oxidative stress in the effect of this toxin on cells. When tested in animals, ingested crotocin did not cause necrotic oral lesions whereas T-2 toxin did (Chi and Mirocha, 1978), suggesting that type C trichothecenes are less active *in vivo* than type A trichothecenes. However, only one dose of crotocin was tested in that study. No study has been conducted to investigate the impact of type C trichothecenes on organs and on feeding behavior (Table 1).

4.3 Toxicological effects of type D trichothecenes

Data have confirmed the ability of type D trichothecenes to inhibit protein synthesis through ribotoxic effects (Cundliffe et al., 1974, Thompson and Wannemacher, 1986, He et al., 2012, Palanivel et al., 2013), causing the activation of MAP kinases, inflammation and cell toxicity / apoptosis. Exposure to type D trichothecenes occurs mostly through inhalation and is associated with the so-called damp building-related illnesses that produce respiratory, immunological, and neurological symptoms (Pestka et al., 2008b, Polizzi et al., 2009). Although part of the inhaled type D trichothecenes is able to reach the blood flow and activate circulating immune cells such as macrophages and trigger the production of anorectic cytokines (Chung et al., 2003a, Chung et al., 2003b, Kankkunen et al., 2009, Kankkunen et al., 2014), these toxins are rapidly cleared from the systemic circulation, suggesting rather a local effect on nasal / airway tissues (Amuzie and Pestka, 2010). Type D trichothecenes cause neurotoxic, inflammatory and local mucosecretory responses in the airways of animals exposed to these toxins (Islam et al., 2009, Corps et al., 2010). Satratoxins have also been suggested to cause inflammatory and apoptotic pathways at low levels of exposure in human brain capillary endothelial cells, astrocytes, and neural progenitor cells, leading to damages to cells in the neurological system (Karunasena et al., 2010). Regarding feeding behavior, only satratoxins have been reported to be anorectic (Table 1), and their effect may be the result of the local inflammation (peripheral effect) and of a direct effect on brain neurons (central effect) (Wu et al., 2015).

5 Physiological impact of trichothecenes in relation to emesis and food intake

As described above, exposure to trichothecenes has toxic effects on molecules and cells that impact human and animal health (Pinton et al., 2012, Payros et al., 2016). In particular, exposure to trichothecenes can lead to nausea, emesis and reduced food intake (Friend et al., 1982, Pestka et al., 1987, Chen et al., 2017). The pig is particularly useful to investigate the emetic response induced by trichothecenes for several reasons: its cereal rich diet, its agricultural importance and its gastrointestinal system resembles that of humans (Szelenyi et al., 1994, Helke and Swindle, 2013). Contrary to other species, rodents lack an emetic reflex and are preferentially used to study its anorexic effects (Bonnet et al., 2012).

5.1 Effects on emesis

Emetic reflex is a natural protective mechanism against food poisoning and is a hallmark of food poisoning by trichothecenes (Chen et al., 2017). Despite contaminating grain less frequently and at lower concentrations, type A are considered to be more toxic than type B, especially for emesis and anorexia. Among type A trichothecenes, T-2 and HT-2 toxins are the most potent inducers of emesis (Bennett and Klich, 2003, Male et al., 2016). In swine, intraperitoneal injection of 0.005 mg T-2 toxin /kg bw induced emesis in 25% of the animals while 0.25 mg toxin/kg bw provoked vomiting in all animals. The effect of HT-2 toxin resembled that of T-2 toxin within 30 min (Wu et al., 2016) (Table 3).

Regarding type B trichothecenes, DON was originally called “vomitoxin” because of its strong emetic effects in several animal models and humans (Tominaga et al., 2016). The first study to investigate DON-induced emesis in swine was conducted in 1977 by Forsyth and colleagues (Table 3). Intraperitoneal administration of DON at doses of 0.05; 0.075; 0.1 and 0.2 mg/kg bw induced emetic response after respectively 29, 42, 39 and 27 minutes in 75% animals and oral doses from 0.1 to 0.4 mg/kg bw provoked vomiting after respectively 82, 68 and 59 minutes (Forsyth et al., 1977, Bonnet et al., 2012). In human, 32 outbreaks after ingestion of scabby wheat, scabby barley and moldy corn have been observed. The authors of the study reported that 64% of 9382 persons were affected by nausea, vomiting and diarrhea after ingestion of cereals contaminated by DON (range of 0.34-92.8 mg/kg) (Li et al., 2002, Knutsen Helle et al., 2017). Other 8-ketotrichothecenes (3-ADON, 15-ADON, NIV, FX and DON) also induced emesis as demonstrated in mink. Intraperitoneal administration at different doses ranging from 0.05 to 0.4 mg/kg bw indicated that NIV and FX have a higher emetic potency than DON, 3-ADON and 15-ADON (Wu et al., 2013b).

5.2 Effects on food intake

Trichothecenes, especially DON, directly enter the brain and modify appetite (Berni Canani et al., 2011, Pestka et al., 2008a). Many studies and several meta-analysis have demonstrated the effects of trichothecenes on food intake (Knutsen Helle et al., 2017). A meta-analysis of pig experiments (Andretta et al., 2012) showed that DON (average concentration of 3.63 mg/kg bw) reduced food consumption by 26% (average of 17 animals/group) and reduced weight gain by 26% (Andretta et al., 2012). Another meta-analysis showed that in 20 pigs experiments exposed to DON, feed consumption decreased linearly upon increasing concentration of DON (0.02 – 2.5 mg/kg bw) (Hee Mok et al., 2013). DON induced vomiting in a dose dependent manner but the mechanisms underlying emesis by DON remain unknown.

While swine is the most sensitive species to DON-induced anorexia, numerous *in vivo* studies have been conducted on rodents, especially mice. Flannery and colleagues reported that the food intake level was reduced 2 h after DON exposure in response to intra-peritoneal (1 and 2.5 mg/kg bw) or oral administration (0.5 to 5 mg/kg bw) and increased 16 h after exposure (Table 1). Food reduction was dose- dependent and anorexia was transient (Flannery et al., 2011). In another study, anorexia was observed 3 h after DON exposure *per os* (12.5 and 25 mg/kg bw) and at 6 h (6.25 mg/kg bw). All studies in rodents have shown that DON-induced anorexia has a dose-dependent effect (Table 1) (Girardet et al., 2011a, Girardet et al., 2011b). Besides DON, other trichothecenes also modulate food intake regulation (Table 1) and this is associated with regulation of gut hormone release (see below 7.2).

In recent years, researches has focused on the mechanisms responsible for the reduced food intake induced by trichothecenes (Chen et al., 2017). Regulation of food intake is a complex process that involves two major structures, the gastrointestinal tract, responsible for intake and absorption of food and the central nervous system.

6 Central regulation of emesis and food intake

Studies from the 1940s and 1960s led to a concept of “a dual center model” in which the satiety center located in ventromedial hypothalamus inhibits food intake whereas the feeding

center, located in lateral hypothalamus, promotes food intake (Stellar, 1994). Since then, many studies have shown that other parts of the brain are also involved in food regulation, forming a network of neuronal pathways (Austin and Marks, 2009). Specific regions, in the hypothalamus (the Arcuate Nuclei or ARC) and in the brainstem (the Nucleus Tractus Solitarius or NTS and the ventral tegmental area) play important roles in food regulation. The hypothalamus receives metabolic or hormonal afferent signals via the vagus nerve or the blood flow; and thus plays a pivotal role in the short and long-term regulation of food intake (Hussain and Bloom, 2013). Indeed, peripheral signals from the gut, pancreas, liver or adipose tissue converge directly or indirectly on the hypothalamus.

It was originally proposed that DON modifies serotonergic and catecholaminergic activities in the central nervous system based on an increase in serotonin or its metabolites in DON-treated swine and the ability of serotonin receptor antagonist to prevent DON-induced emesis (Prelusky et al., 1992, Prelusky and Trenholm, 1993, Morton et al., 2006). However, using c-Fos expression to identify the neuronal groups activated, Girardet and colleagues observed that the serotonergic system did not express c-Fos after DON ingestion (Girardet et al., 2011a). In addition, an increase in neuron activity in NTS, in the postrema area and in the ventrolateral medulla was observed in mice treated with DON (Girardet et al., 2011b). These results were confirmed in a pig model. *Per os* administration of DON (1 mg/kg bw), activated specific brain areas in the brainstem, such as NTS and ventrolateral medulla, as well as specific hypothalamic areas (arcuate nuclei and paraventricular nucleus of the hypothalamus) (Gaigé et al., 2013). Besides, DON activates catecholaminergic group neurons in the brainstem. However, these data need to be confirmed in other *in vivo* species. Neurons of the NTS are the first relay for visceral afferent information and project neurons into feeding behavior centers including the hypothalamus (Travagli, 2007). Among hypothalamic centers involved in food regulation, Arcuate Nuclei (ARC) plays a critical role because it is responsible for the passage of signals through the blood-brain barrier and because it expresses neurons that control appetite (Minor et al., 2009).

Thus, in contrast to what was originally thought, recent advances suggest that the reduction in food intake induced by DON is independent of the serotonergic system and is rather due to activation of other neuron networks involved in food behavior regulation such as NTS and ARC (Girardet et al., 2011b). Two types of neurons that control the anorexigenic and orexigenic responses in the hypothalamus, regulate the homeostasis of food intake. They are the first targets of peripheral signals.

6.1 Modulation of the anorexigenic pathway by DON

Pro-opiomelanocortin (POMC) is a pre pro hormone converted into ACTH by pro hormone convertase 1. The activation of neurons secreting POMC promotes the production of two anorexigenic molecules, Cocaine and Amphetamine-Regulated Transcript (CART) and α -MSH (α -Melanocyte-Stimulating Hormone). CART activates the melanocortin receptor family (MCR-3 and-4) which in turn bind to α -MSH, leading to a reduction of food intake and an increase in energy expenditure (Austin and Marks, 2009). POMC and CART belong to the neuronal network neurons that also contain Neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP), responsible for orexigenic effects (figure 2A) (Austin and Marks, 2009). It has been shown, in a POMC-GFP transgenic mice model, that acute exposure to DON induces the expression of POMC and nesfatin-1, leading to a subsequent increase in the expression of CART and MC4R mRNA expression (Table 2). This DON-induced activation of POMC expressing neurons was shown to be correlated with a reduction in meal frequency (28 %) and in meal size (68%) (Girardet et al., 2011b). Acute exposure to DON also increased POMC and CART downstream targets including MC4R (figure 2A), thereby inhibiting food intake and stimulating energy expenditure (Girardet et al., 2011b) (Table 2). DON exposure also increased the mRNA level of pro-inflammatory cytokines such as IL-1 α , IL-6 and TNF- α in the hypothalamus, leading to the activation of nuclear factor kappa B (NF κ B). Because NF κ B is known to be an upstream factor of POMC, this suggests that pro-inflammatory cytokines induced by DON are also involved in inhibition of food intake (Tominaga et al., 2016).

6.2 Modulation of the orexigenic pathway by DON

Neuropeptide Y (NPY) is a 36 amino acid peptide that belongs to the pancreatic polypeptide family. Hormonal factors regulate its synthesis and secretion: insulin and leptin act as inhibitors, whereas ghrelin and glucocorticoids act as stimulators. Once stimulated, neurons release NPY onto lateral hypothalamic neurons. The release of NPY increases the production of orexins A, B and Melanin Concentrating Hormone (MCH) resulting in stimulation of food intake. NPY is the most potent orexigenic peptide in the brain. The orexigenic effect of NPY/AgRP neurons is also mediated by the antagonist effect of Agouti-Related Peptide (AgRP) on melanocortin receptor-4 which in turn inhibits POMC/CART neurons (Pénicaud et al., 2012). Chronic exposure to DON (10 mg/kg bw for 147 days) increased the hypothalamic mRNA expression of AgRP without changing the POMC level, suggesting an effect of DON on the orexigenic pathway. These data raised the possibility that acute exposure of DON induces toxic effects like emesis, nausea and that, compensatory mechanisms then restore the balance between orexigenic and anorexigenic pathways. This also suggests that DON-induced anorexia is reversible (Kobayashi-Hattori et al., 2011, Flannery et al., 2013). In addition, mice exposed to 12.5 mg/kg bw of DON for a short period (3 h) had increased hypothalamic mRNA of POMC and CART but NPY and AgRP were not affected indicating that DON modulates the anorexigenic pathway without affecting the orexigenic pathway. However, these mechanisms were only described in mice and need to be confirmed in other animal species.

In conclusion, acute doses of DON act on the central nervous system activate the anorexigenic pathway leading to a reduction in food intake whereas chronic DON doses seems to activate orexigenic pathway. However, this hypothesis needs to be confirmed.

7 Gastrointestinal regulation of emesis and food intake

The gastrointestinal tract plays a pivotal role in the regulation of food intake. The perception of appetite and satiety involves not only gut mobility but also hormone secretion by enteroendocrine cells (EEC) located in the gastrointestinal tract (Posovszky and Wabitsch, 2015). The presence of finger-like extensions in the lumen enables these cells to play the role of sensors to detect the luminal content. The detection of luminal nutrients leads to the secretion of intestinal peptides, which play the role of appetite modulators (Strader and Woods, 2005). Once secreted, these gut hormones bind to their receptors located in the gastrointestinal tract or in the brain. The binding of the gut hormones with their receptors in the gastrointestinal tract lead to the integration of signals in the brain *via* the vagus nerve and to the regulation of food intake (figure 2B) (Strader and Woods, 2005).

7.1 Gut hormones in food intake regulation

EECs are very important in the sensing of luminal contents and the gut hormones secreted by these cells not only influence gastric emptying or intestinal motility but also regulate appetite and satiety. They represent the primary factors of satiety signaling from the gut to the central nervous system and are thus, an important target in the modulation of food intake by trichothecenes. EECs secrete more than 30 gut hormones, among which peptide YY (PYY) and cholecystokinin (CCK) play pivotal roles in satiety regulation in the gastrointestinal tract and are major DON-induced anorexia mediators (Flannery et al., 2012). Several other gut hormones secreted by EECs, including glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), are also involved in the anorexic effects of trichothecenes.

Cholecystokinin (CCK) discovered in 1928, is synthesized and secreted in the gastrointestinal tract mainly in the duodenum and the jejunum by I cells. CCK secretion is stimulated in response to fat- and protein- containing meals (Posovszky and Wabitsch, 2015). Two types of receptors belonging to the family of seven transmembrane domain receptors mediate the CCK effects: CCK-1 receptor (CCK-1R) and CCK-2-receptor (CCK-2R) (Morisset, 2005). These receptors are located throughout the gastrointestinal tract and the central nervous system. Despite their similar locations, they are involved in different

responses. For example, CCK-1R plays a major role in satiety response whereas CCK-2R is implicated in central nervous system functions such as pain, anxiety and memory signaling (Woodruff et al., 1991).

Peptide YY (PYY) belongs to the pancreatic polypeptide family and contains tyrosine at N- and C-termini. This peptide is synthesized and secreted by L cells in the distal ileum and colon as a 36 amino acid peptide. Dipeptidyl peptidase-4 degrades the secreted form of PYY into its circulating form (PYY₃₋₃₆) (Strader and Woods, 2005). The presence of nutrients, especially lipids, in the intestinal lumen, stimulates PYY secretion (Perry and Wang, 2012). In response to food intake, PYY mediates anorexigenic actions. This hormone slows down gastric emptying, reduces pancreatic and gastric acid secretions, inhibits gall bladder contraction and increases electrolyte absorption in the ileum (Austin and Marks, 2009). PYY influences food intake by interacting with specific receptors that belong to the neuropeptide Y family of protein-G coupled receptors. In neuropeptide Y2 receptor-deficient mice, Batterham and colleagues showed that PYY binds with high affinity to this receptor, which is located in the ARC in the brain and on the vagus nerve (Batterham and Bloom, 2003). The location of NPY2 receptor in the brain suggests that PYY crosses the blood-brain barrier and targets the central signalization implicated in food behavior.

5-hydroxytryptamine (5-HT) is synthesized and released by enterochromaffin cells located in the stomach and in the small and the large intestine. 5-HT is mainly released after neural stimulation but also after chemical stimulation by short-chain fatty acid or glucose intake. Secretion of 5-HT mediates functions involved in appetite regulation including gastric and pancreatic secretion, intestinal motility or insulin release (Mawe and Hoffman, 2013).

Glucagon-Like Peptide-1 (GLP-1) is derived from posttranslational modification of glucagon and is produced by L-cells in the small intestinal and colon. Release of GLP-1 is stimulated in response to nutrient and neurohumoral stimulation. GLP-1 inhibits gastrointestinal motility, reduces gastrointestinal secretions and attenuates gastric emptying. GLP-1 reduces food intake by binding to its receptor GLP-1R, located in the periphery (gut and pancreas) and in the central nervous system (Strader and Woods, 2005).

Gastric Inhibitory Peptide (GIP) is a 42-amino acid produced by K cells in the duodenum and jejunum and belongs to the incretin hormone family. GIP potentiates glucose-induced insulin secretion, and regulates postprandial glucose homeostasis. The GIP receptor is a G protein-coupled receptor, which are located throughout the body including the brain and gastrointestinal tract (Irwin and Flatt, 2013).

7.2 Impact of trichothecenes on gut hormones

Trichothecenes, especially DON, modulate the central anorexigenic pathway and influence the balance of food intake. They also modulate feeding behavior in the periphery via the gut hormones that serve as early mediators of trichothecenes-induced anorexia (figure 2B) (Table 2).

7.2.1 Impact of DON on gut satiety hormones

In recent years, research has focused on the impact of DON on gut satiety hormones, especially CCK and PYY, as well as on pro-inflammatory cytokines in the mouse, pig and mink models.

In mice, ingestion of DON (2.5 and 10 mg/kg bw) increased plasma levels of PYY and CCK respectively 15 and 60 min, after exposure to the toxin (table 3). The increased levels of these gut peptides were associated with a decrease in food intake (86 % decrease 60 min after exposure) (Flannery et al., 2012). An NPY2 receptor antagonist interfered with approximately 40% PYY and DON-induced food refusal. In that study, the use of CCK receptor antagonist had no effect on DON-induced anorexia suggesting that PYY play a more important role than CCK in DON-induced anorexia (Flannery et al., 2012, Flannery et al., 2013).

Piglets exposed to feed naturally contaminated with DON (1 to 3 mg/kg feed) for 21 days showed a slightly different response. In this species, an increase in CCK and pro-inflammatory cytokines (including IL-1 α , IL-6 and TNF- α) with no changes in PYY were

observed (Table 2)(Li et al., 2018) . Thus, in contrast to what has been observed in rodents, exposure of pig to feed naturally contaminated with plausible concentrations of DON is associated with secretion of pro-inflammatory cytokines and only moderately affects the secretion of anorexigenic peptides.

The implication of PYY in the emetic response of DON was also evaluated in the mink model (Table 2). Consumption of DON (0.25 mg/kg bw) induced emesis within 15-30 min and emetic events were associated with increased plasmatic levels of PYY and 5-HT. Granisetron, a pharmacological antagonist of the NPY2 receptor partially blocked PYY and 5-HT secretion and reduced emetic events to 50% (Wu et al., 2013a).

These studies show that in different animal models, DON increases the secretion of CCK, PYY, 5-HT and pro-inflammatory cytokines. However, experiments with pharmacological antagonists reveal that the implication of these appetite modulators is not fully understood.

Other gut hormones such as GLP-1 and GIP are thought to play an important role in food intake and satiety. The role of these hormones has also been investigated in DON-induced anorexia in the mouse model. Exposure to DON by oral gavage at two doses (1 and 2.5 mg/kg bw) increased the plasma level of glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) (Table 2). There was an approximately 2-fold increase in GLP-1 plasma level after 30 min and which then returned to the control level after 2 h with the lower dose but was still high after 6 h with the higher dose. With the two doses of DON, there was an approximately 3-fold increase in the GIP plasma level within 1 h and returned to control level after 2 h. Antagonist receptors of GLP-1 (exendin₉₋₃₉) and GIP (pro3GIP) were used to delineate the roles of these two gut hormones in DON anorectic effects. Pretreatment with antagonist receptors before intraperitoneal injection of DON increased the food consumption. These results confirm that the secretion of GLP-1 and GIP and the activation of their receptors play a major role in DON-induced anorexia (Jia et al., 2017).

In conclusion, several studies shown that DON caused emesis and anorexia by stimulating the secretion of various gut hormone including PYY, CCK, 5-HT, GLP-1 and GIP. Gut hormones receptors also play a role in DON anorexia. However, emesis and anorexia are also induced by others trichothecenes members such as NIV, FX, DON derivatives, T-2 toxin (Table 2).

7.2.2 Impact of DON derivatives and other type B trichothecenes on gut satiety hormones

Pestka's research group investigated the effects of type B trichothecenes, other than DON, on gut satiety hormones. They analyzed the plasma level of CCK and PYY, after oral gavage of a standard anorexigenic dose of 2.5 mg/kg bw (Table 2). CCK was induced upon oral administration of all toxins (DON, 3-ADON, 15-ADON, FX and NIV) within 30-120 min after exposure to the toxin whereas PYY was only induced after exposure to DON and NIV (Wu et al., 2014d). More specifically, an increase in PYY plasma level was observed 30 min after exposure to DON and 2 to 6 h after exposure to NIV. These results indicate differential release of gut satiety hormones by the different type B trichothecenes (Wu et al., 2014d). One possible explanation is the intestinal absorption of these toxins. PYY and CCK are secreted in the upper and lower parts of the gastrointestinal tract, respectively. The authors speculated that all type B trichothecenes are able to stimulate the production of CCK in the upper part of the intestine, whereas some toxins such as FX, 3-ADON or 15-ADON, are absorbed rapidly, and consequently do not reach the lower part of the intestine and do not stimulate the production of PYY (Wu et al., 2012, Wu et al., 2013b, Wu et al., 2014d).

This group also investigated the effects of different DON derivatives (Table 2). In particular, they analyzed the effects of the masked/modified form of DON (D3G) and two synthetic forms (EN139544 and EN139528) (Pierron et al., 2016a). Acute oral exposure to DON and derivatives (2.5 mg/kg bw) increased the plasma level of CCK. More specifically, CCK plasma level increased 30 min after exposure to DON but only 2 h after exposure to D3G and synthetic derivatives. These authors also showed that the plasma levels of PYY increased 30 min after exposure to DON and 6 h after exposure to D3G. The two synthetic

forms did not affect the PYY plasma level. The increased level of the gut hormone in the plasma was associated with a reduction in cumulative food intake that was greater for DON than D3G, EN139544 and EN139528 (Wu et al., 2014c).

These data demonstrate that the modification of the DON structure affect the regulation of food behavior. More investigations are needed to characterize the mechanisms involved in the secretion of satiety hormones by DON derivatives.

7.2.3 Mechanisms involved in the secretion of DON-dependent gut hormones

The murine EEC line STC-1 was used to understand the mechanisms underlying the release of DON-dependent hormones in the gut. G protein-coupled receptors are chemosensors of lumen content and are located in the EEC. In STC-1 cells, DON induced the secretion of CCK and GLP-1 via calcium-sensing receptor (CaSR) and transient receptor potential ankyrin-1 (TRPA1)-mediated Ca^{2+} signaling pathway (Zhou and Pestka, 2015). DON first triggered CaSR activation and then activation of the inositol triphosphate receptor and mobilization of intracellular Ca^{2+} in storage vesicles. Activation of the inositol triphosphate receptor induced TRPM5 activation, a Ca^{2+} cation channel, which caused Ca^{2+} to enter the cell. Amplification of Ca^{2+} entry activates TRPA1 and this pathway leads to exocytosis of CCK and GLP-1 (Zhou and Pestka, 2015, Tominaga et al., 2016).

These downstream mechanisms of DON-induced food refusal were also evaluated in mice and mink. *In vivo* data confirmed that DON induced the release of gut hormones by a CaSR- and TRPA1-dependent signaling pathway (Wu et al., 2016, Wu et al., 2017a, Wu et al., 2017b).

7.2.4 Impact of type A trichothecenes on gut satiety hormones

The implication of PYY and 5-HT in the emetic effect induced by type A trichothecenes was investigated in the mink model (Table 2). Oral exposure to 0.5 mg/kg bw of T-2 and HT-2 toxin significantly increased plasma PYY throughout the 2 h post exposure period and the trend elevated the 5-HT plasmatic level after 2 h. The increase in gut satiety hormones was linked to emetic events (Table 2). Thus, as already described for type B trichothecenes, these results indicate that 5-HT and PYY also contribute to type A-induced emesis and anorexia (Wu et al., 2016).

Substance P is a neuropeptide secreted by EEC in the gastrointestinal tract and the central nervous system, causing anorexia, emesis, and inhibiting gastric emptying. In the central nervous system, substance P was shown to increase POMC mRNA expression (Karagiannides et al., 2008). Implication of substance P as well as 5-HT was also evaluated by feeding different type A toxins including T-2, HT-2, DAS and NEO by oral gavage and intraperitoneal injection to mice at a standard dose of 1 mg/kg bw (Table 2). Oral or intraperitoneal exposure to the type A trichothecenes resulted in a reduction in food consumption and in elevation of plasma level of 5-HT and substance P. The only differences observed between the toxins was the duration of the transient and the persistence of the response, which ranged from 6 h for DAS and NEO to 24 h for T-2 and HT-2 toxins (Zhang et al., 2018). Thus, despite differences in time response, 5-HT and substance P mediate type A trichothecenes-induced anorexia in mice. The authors then analyzed the role of GLP-1 and CCK in mice treated with 1 mg/kg bw of T-2, HT-2, DAS and NEO. DAS had less toxic effects than T-2 but also induced anorexia in mice following oral exposure (Zhang et al., 2017). T-2 toxin has the most anorectic effect of type A trichothecenes and on different animal models. This anorectic effect involved several gut hormones but mechanisms underlying anorexia mediated by T-2 toxin are still unknown.

A study focuses on the role of GLP-1 and CCK in T-2-induced anorexia. Mice orally treated with 0.1, 0.5 and 1 mg/kg bw of T-2 toxin had a food consumption decrease by 50, 61 and 68% respectively, after 2 h (Wu et al., 2018). This reduction in food consumption was associated with an increase of plasma level of GLP-1 and CCK and the use of GLP-1R and CCK receptors antagonists indicates that T-2 mediated anorexia through receptors of these two hormones (Wu et al., 2018). These authors were then interesting by the role of others gut hormones, GIP and PYY, in T-2 anorectic effects. Mice orally treated with 0.1, 0.5 and 1

mg/kg bw of T-2 toxin reduced their food consumption by 53, 62 and 64 % respectively. This reduction in food intake was associated with an increase in plasma GIP and PYY after 2h and pretreatment with receptors antagonists revealed that GIP and PYY are involved in T-2 mechanisms-dependent (Sheng et al., 2018).

7.2.5 *Impact of Type C and D trichothecenes on gut satiety hormones*

As mentioned earlier, the effects of type C trichothecenes on food intake and on the release of gut peptides have not yet been assessed. Concerning type D, only one study describes the anorectic potency of satratoxin but did not investigate the effects on the secretion of gut peptides (Wu et al., 2015).

8 Conclusion and perspectives

Mycotoxins may contaminate animal feed and human food at all stages of production. National and international food safety authorities recognize that contamination by mycotoxins and especially by trichothecenes represent a major risk affecting animal and human health (Knutsen Helle et al., 2017). Trichothecenes are responsible of several deleterious effects including emesis and anorexia. Within this class of mycotoxin, DON is the most documented both in term of occurrence, toxicity and mode of action.

Emetic and anorexic effects produced by trichothecenes can result from a direct action of the mycotoxin on the brain. Trichothecenes cross the blood-brain barrier and activate the anorexigenic pathway in different areas including ARC in hypothalamus and associated neuronal network in the brainstem (NTS, tegmental ventral area). Activation of the neuronal network leads to stimulation of neurons containing POMC and CART, responsible for anorexigenic regulation of feeding behavior. DON targets specific areas in the brain such as the hypothalamus. Researches are needed to determine how DON targets these regions and whether or not this toxin diffuses throughout the brain. It will also be interesting to understand the mechanisms involved in the specific activation of brain areas by DON. We can speculate that the entry of DON into the ARC throughout the blood-brain barrier explain the specific activation of brain areas.

Trichothecenes also acts indirectly through the secretion of gut hormones. By sending afferent signals in the hypothalamus via the gut-brain axis, the gut hormones secreted in the intestine represent important mediators in the regulation of food intake. Then the hypothalamus integrates the signals and regulate the appetite (Zhang et al., 2018). More than 30 hormones are secreted throughout the gastrointestinal tract but CCK and PYY are the most important in the regulation of food intake by trichothecenes and especially by DON (Flannery et al., 2012, Wu et al., 2013a, Zhou and Pestka, 2015) but new studies indicate that other hormones such as GLP-1, GIP or 5-HT are also implicated in DON-induced anorexia (Wu et al., 2013a, Jia et al., 2017). Mechanisms underlying DON-induced food reduction are not fully understood but data suggest that CaSR play an essential role in the exocytosis of hormones in the blood flow (Wu et al., 2017a, Wu et al., 2017b). Future researches should focus on specific mechanisms by which DON activates CaSR in EECs. CaSR-mediated activation of phospholipase C and activates a signaling cascade leading to the activation of TRPA1 and to the hormone exocytosis (Wu et al., 2017a). *In vivo* results reported that the use of antagonists of CaSR and TRPA1 inhibited emesis induction by DON. However, TRPA1 belongs to a family of TRP channel and others TRP channels might be involved in DON emetic effects. (Wu et al., 2017a, Wu et al., 2017b).

Trichothecenes subtypes induce a differential hormone response. Within type B trichothecenes, NIV but not FX is able to induce the secretion of CCK. One possible explanation is that FX is more rapidly absorbed than NIV in mice leading to a lesser activation of EECs than NIV (Poapolathep et al., 2003). The differential secretion induced by DON and other type B trichothecenes can also be explained by difference in bioavailability and metabolism distribution. These hypothesis need to be investigated.

Type A trichothecenes, especially T-2 toxin, impact the same gut hormones than DON i.e. GLP-1, CCK, PYY, GIP and 5-HT. It is thus tempting to speculate that T-2 toxin have the same mechanisms of action but this need to be demonstrated. Data concerning the

damages caused by other types of trichothecenes, especially type C and D and by masked/modified forms of all trichothecenes are scares. More studies are needed, especially concerning the signaling pathway and molecular mechanisms involved in the toxicity of these toxins.

Another challenge is to address the toxicity of mycotoxin mixtures (Alassane-Kpembé et al., 2017c). Indeed co-contamination by several trichothecenes is confirmed on one hand by the co-occurrence of these toxins in food and on the other hand by co-exposure monitoring surveys. Simultaneous exposure to several mycotoxins may lead to additive, synergistic or antagonist toxic effect, which have been poorly documented.

Through their action on food intake at the brain and at the intestinal level, trichothecenes induce a reduction of body weight and growth retardation. All the issues raised here indicated the need to better understand the mechanism underlying the emetic and anorectic effects of trichothecenes in order to develop strategies for preventing these effects in animals and humans.

Acknowledgments:

The authors are grateful to Nicolas Loiseau (INRA, Toxalim) for this help with the figures.

The English in this manuscript has been edited by an independent scientific language editing service (Daphne Goodfellow).

This study was supported in part by the French National Research Agency ANR (projects Newmyco ANR-15-CE21-0010 and CaDON ANR-15-CE21-0001).

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Table 1: Modulation of food intake by trichothecenes

trichothecenes	toxin	animal model	toxin administration	LOAEL (mg/kg bw)	delay of action	references
Type A	T-2	Mice	IP	0.1	30 min	(Wu et al., 2015)
			Oral/Gavage	0.1	30 min	
	HT-2	Mice	IP	0.1	30 min	
			Oral/Gavage	0.5	30 min	
	T-2	Mice	IP	1	30 min	(Zhang et al., 2018)
			Oral/Gavage	1	30 min	
	HT-2	Mice	IP	1	30 min	
			Oral/Gavage	1	30 min	
	DAS	Mice	IP	1	30 min	
			Oral/Gavage	1	30 min	
NEO	Mice	IP	1	30 min		
		Oral/Gavage	1	30 min		
T-2	Mice	Oral/Gavage	0.1	2h	(Sheng et al., 2018)	
T-2	Mice	Oral/Gavage	0.1	2h	(Wu et al., 2018)	
Type B	DON	Mice	Diet	0.30	ND	(Forsell et al., 1986)
	DON	Mice	Diet	0.36	ND	(Robbana-Barnat et al., 1987)
	DON	Pig	Diet	2.5	ND	(Friend et al., 1992)
	T-2	Pig	Diet	3.2	ND	
	DON + T-2	Pig	Diet	2.5 and 0.8	ND	
	DON	Mice	Diet	0.6	ND	(Rotter et al., 1992)
	DON	Pig	Diet	1.7	ND	(Bergsjö et al., 1993)
	DON	Pig	Diet	3	ND	(Prelusky et al., 1994)
	DON	Pig	Diet	3.4	ND	(Trenholm et al., 1994)
	DON + FB1	Pig	Diet	5 and 100	ND	(Harvey et al., 1994)
	DON	Pig	Diet	4	ND	(Rotter et al., 1995)
	DON	Mice	Diet (high fat Diet)		ND	(Kobayashi-Hattori et al., 2011)
	DON	Mice	IP	1.5	2 h	(Flannery et al., 2011)
			Oral/Gavage	2.5	2 h	(Flannery et al., 2012)
	3ADON	Mice	IP	1	2 h	(Wu et al., 2012)
			Oral/Gavage	2.5	2 h	
	15ADON	Mice	IP	1	2 h	
			Oral/Gavage	2.5	2 h	
	NIV	Mice	IP	0.5	2 h	
			Oral/Gavage	1	2 h	
	FX	Mice	IP	0.25	2 h	
			Oral/Gavage	0.25	2 h	
	DON	Mice (diet-induced obese)	Diet	10	ND	(Flannery et al., 2013)
	DON	Mice	Oral/Gavage	25	30 min	(Wu et al., 2014b)
	3-ADON	Mice	Oral/Gavage	25	30 min	
	15-ADON	Mice	Oral/Gavage	25	30 min	
NIV	Mice	Oral/Gavage	25	30 min		

	FX	Mice	Oral/Gavage	25	30 min	
	DON	Mice	Oral/Gavage	2.5	2 h	(Wu et al., 2014a)
	D3G	Mice	Oral/Gavage	2.5	2 h	
	DON	Mice	Oral/Gavage	125	24 h	(Tominaga et al., 2016)
	DON	Mice	IP	1	30 min	(Jia et al., 2017)
	DON	Mice	Oral/Gavage	25	30 min	(Wu et al., 2017)
	DON	Pig	Diet (naturally contaminated)	3	ND	(Li et al., 2018)
Type C	No data					
Type D	SG	Mice	IP	0.25	30 min	(Wu et al., 2015)
			Intranasal	0.5	30 min	

DAS: Diacetoxyscirpenol; NEO: Neosolaniol; D3G: DON-3- β -glucoside; 3-ADON: 3-acetyldeoxynivalenol; 15-ADON: 15-acetyldeoxynivalenol; NIV: Nivalenol; FX: Fusarenon X; SG: Satratoxin; IP: intraperitoneal. ND: not described.

Table 2: Modulation of feeding behavior by trichothecenes in the central nervous system and in the periphery

Gastrointestinal effects							
trichothecenes	toxin	animal model	toxin administration	LOAEL (mg/kg bw)	toxin effects	delay of action	references
Type A	T-2	Mink	Oral/Gavage	0.5	PYY 5-HT	2h	(Wu et al., 2016)
	HT-2	Mink	Oral/Gavage	0.5	PYY 5-HT	30min 2h	
	T-2	Mice	Oral/Gavage	1	CCK GLP-1	2h 30min	(Zhang et al., 2017)
			IP	1	CCK GLP-1	2h	
	HT-2	Mice	Oral/Gavage	1	CCK GLP-1	2h 30min	
			IP	1	CCK GLP-1	2h	
	DAS	Mice	Oral/Gavage	1	CCK GLP-1	2h	
			IP	1	CCK GLP-1	30min 2h	
	NEO	Mice	Oral/Gavage	1	CCK GLP-1	2h 30min	
			IP	1	CCK GLP-1	2h 2h	
T-2	Mice	Oral/Gavage	0.1	GIP PYY	2h	(Sheng et al., 2018)	
T-2	Mice	Oral/Gavage	0.1 0.5	GLP-1 CCK	2h 2h	(Wu et al., 2018)	
Type B	DON	Mice	IP	1	CCK PYY	15min	(Flannery et al., 2012)
			Oral/Gavage	2.5	CCK PYY	30min	
	DON	Mink	IP	0.25	PYY 5-HT	30min 60min	(Wu et al., 2013)
	DON	Mice	Oral/Gavage	2.5	CCK PYY	30min	(Wu et al., 2014a)
	D3G	Mice	Oral/Gavage	2.5	CCK PYY	2h 6h	
	EN139528 EN139544	Mice	Oral/Gavage	2.5	CCK CCK	30min	
DON	Mice	Oral/Gavage	2.5	CCK PYY	30min 30min	(Wu et al., 2014b)	

	3-ADON	Mice	Oral/Gavage	2.5	CCK PYY	30min no effect	
	15-ADON	Mice	Oral/Gavage	2.5	CCK PYY	30min no effect	
	NIV	Mice	Oral/Gavage	2.5	CCK PYY	2h	
	FX	Mice	Oral/Gavage	2.5	CCK PYY	30min no effect	
	DON	STC-1 cells		0.5mM	CCK		(Zhou and Pestka, 2015)
	DON	Mink	Oral/Gavage	0.5	PYY 5HT	30min	(Male et al., 2016)
	DON	Mice	IP	1	GLP-1 GIP	30min	(Jia et al., 2017)
	DON	Mice	Oral/Gavage	2.5	CCK PYY	30min	(Wu et al., 2017)
	DON	Pig	Diet (naturally contaminated)	3	CCK PYY	d7	(Li et al., 2018)

Central Nervous System effects							
type B	DON	Mice	Oral/Gavage	12.5	POMC nesfatin-1	3h	(Girardet et al., 2011)
	DON	Pig	Oral/Gavage	1	PVN ARC NTS	3h	(Gaigé et al., 2013)
	DON	Mice	Oral/Gavage	12.5	POMC MC4R	3h	(Tominaga et al., 2016)

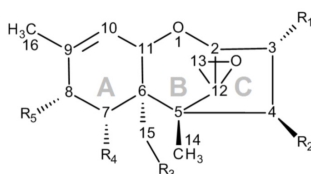
DAS: Diacetoxyscirpenol; NEO: Neosolaniol; D3G: DON-3- β -glucoside; 3-ADON: 3-acetyldeoxynivalenol; 15-ADON: 15-acetyldeoxynivalenol; NIV: Nivalenol; FX: Fusarenon X
IP: Intraperitoneal; CCK: Cholecystokinin; PYY: Peptide Tyrosine Tyrosine; GLP-1: Glucagon-Like Peptide-1; GIP: Gastric Inhibitory Peptide; POMC: Pro-opiomelanocortin; MC4R: Melanocortin Receptor family 4; PVN: Paraventricular Nuclei; ARC: Arcuate Nuclei; NTS: Nucleus Tractus Solitarius

Table 3: Modulation of emesis by trichothecenes

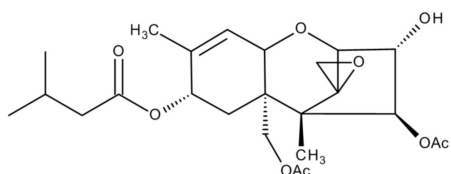
trichothecenes	toxin	animal model	toxin administration	LOAEL (mg/kg bw)	delay of action	references
Type A	T-2	Mink	IP	0.05	30 min	(Wu et al., 2016)
			Oral/Gavage	0.05	22.5 min	
	HT-2	Mink	IP	0.05	27 min	
			Oral/Gavage	0.05	27 min	
Type B	DON	Pig	IP	0.05	29 min	(Forsyth et al., 1977)
			Oral/Gavage	0.1	82 min	
	DON	Pig	Oral/Gavage	0.1	24 min	(Pestka et al., 1987)
			IP		27 min	
	15-ADON	Pig	Oral/Gavage	0.1	19 min	
			IP		19 min	
	DON	Pig	diet	0.15	ND	(Young et al., 1983)
	DON	Pig	IG	0.3	ND	(Prelusky and Trenholm, 1993)
			IV	0.08	ND	
	DON	Mink	IP	0.1	15 min	(Wu et al., 2013a)
	DON	Mink	IP	0.1	14 min	(Wu et al., 2013b)
			Oral/Gavage	0.05	15 min	
	3-ADON	Mink	IP	0.25	36 min	
			Oral/Gavage	0.25	62 min	
	15-ADON	Mink	IP	0.25	12 min	
			Oral/Gavage	0.1	20 min	
	NIV	Mink	IP	0.1	83 min	
			Oral/Gavage	0.25	31 min	
	FX	Mink	IP	0.1	63 min	
			Oral/Gavage	0.05	23 min	
D3G	Mink	Oral/Gavage	2	21 min	(Wu et al., 2014)	
DON	Mink	Oral/Gavage	0.5	10 min		
DON	Mink	Oral/Gavage	0.05	15 min	(Male et al., 2016)	
Type C	No data					
Type D	No data					

3-ADON: 3-acetyldeoxynivalenol; 15-ADON: 15-acetyldeoxynivalenol; D3G: DON-3- β -glucoside; NIV: Nivalenol; FX: Fusarenon X; IP: intraperitoneal; IV: Intravenous; ND: not described

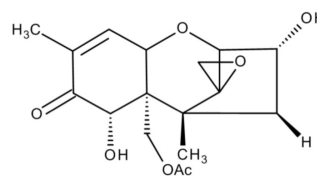
Figure 1: Chemical structures of trichothecenes
 General structure of trichothecenes and for each subtype of trichothecenes examples of toxin with its specific substitution groups.



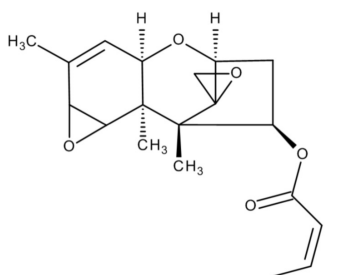
General structure of trichothecenes



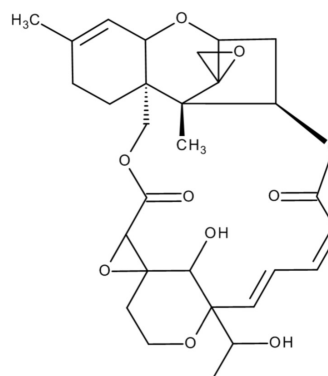
Type A example: T2-toxin



Type B example: Deoxynivalenol

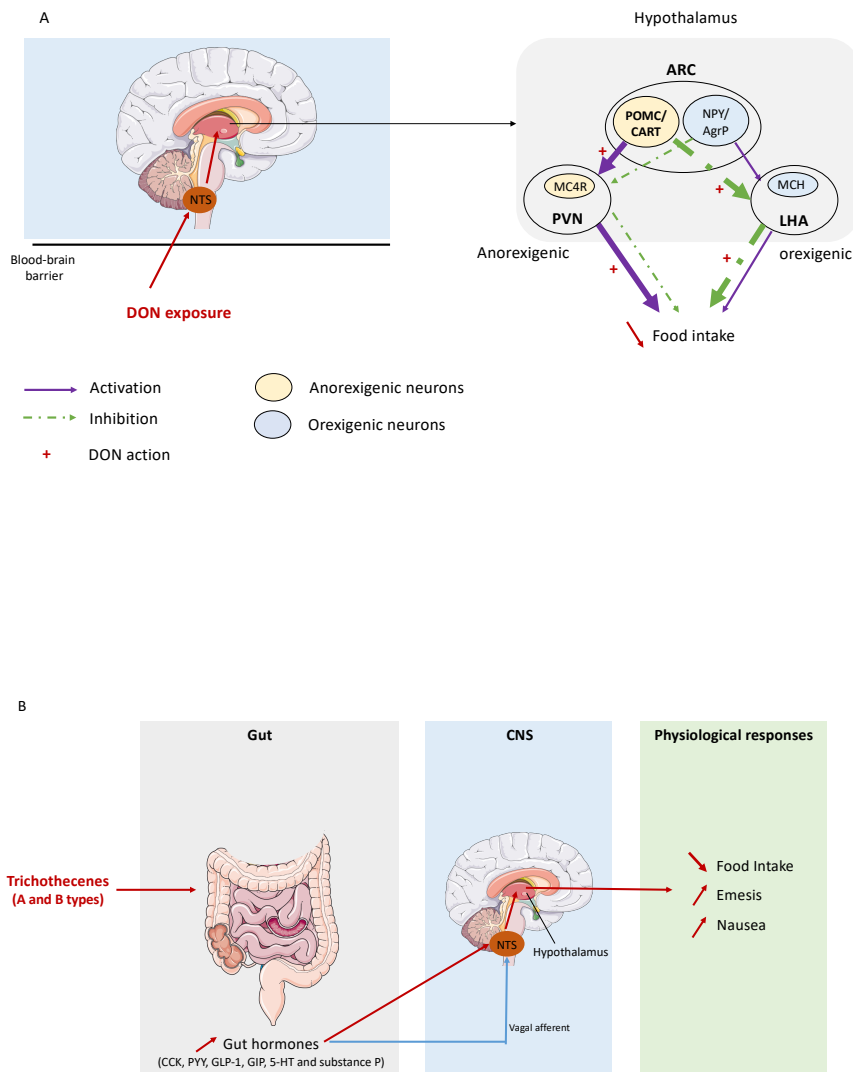


Type C example: Crotoxin



Type D example: Satratoxin G

Figure 2: Food intake regulation by trichothecenes



Exposure to trichothecenes, including DON, can have a direct action on the brain (panel A) or an indirect action through the secretion of gut hormones (panel B).

Panel A: In the brain, DON activates neurons in the nucleus tractus solitarus (NTS) which in turn activates neuronal network on the hypothalamus. DON activates the anorexigenic pathway in the hypothalamus by activation of POMC/CART producing neurons and inhibition of NPY/AgRP producing neurons in the arcuate nuclei (ARC). Activation of anorexigenic neurons leads to the activation of downstream factors such as MC4R in the paraventricular neurons (PVN) and to a reduction in food intake.

Panel B: Following ingestion of feed contaminated with type A or B trichothecenes, in the gastrointestinal tract, satiety signals are released from EECs. They modulate feeding behavior directly *via* the bloodstream or indirectly by interacting with receptors located on vagal afferent axons.

CNS: Central Nervous System.