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Gut satiety hormones cholecystokinin and glucagon-like Peptide-$1_{7\text{-}36}$ amide mediate anorexia induction by trichothecenes T-2 toxin, HT-2 toxin, diacetoxyscirpenol and neosolaniol

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ABSTRACT

The food-borne trichothecene mycotoxins have been documented to cause human and animal food poisoning. Anorexia is a hallmark of the trichothecene mycotoxins-induced adverse effects. Type B trichothecenes have been previously demonstrated to elicit robust anorectic responses, and this response has been directly linked to secretion of the gut satiety hormones cholecystokinin (CCK) and glucagon-like peptide-$1_{7\text{–}36}$ amide (GLP-1). However, less is known about the anorectic effects and underlying mechanisms of the type A trichothecenes, including T-2 toxin (T-2), HT-2 toxin (HT-2), diacetoxyscirpenol (DAS), neosolaniol (NEO). The purpose of this study was to relate type A trichothecenes T-2, HT-2, DAS and NEO-induced anorectic response to changes plasma concentrations of CCK and GLP-1. Following both oral gavage and intraperitoneal (IP) administration of 1 mg/kg bw T-2, HT-2, DAS and NEO evoked robust anorectic response and secretion of CCK and GLP-1. Elevations of plasma CCK markedly corresponded to anorexia induction by T-2, HT-2, DAS and NEO. Following oral exposure, plasma CCK was peaked at 6 h, 6 h, 2 h, 2 h and lasted up to 24 h, 24 h, > 6 h, > 6 h for T-2, HT-2, DAS and NEO, respectively. IP exposed to four toxins all induced elevation of CCK with peak point and duration at 6 h and > 24 h, respectively. In contrast to CCK, GLP-1 was moderately elevated by these toxins. Following both oral and IP exposure, T-2 and HT-2 evoked plasma GLP-1 elevation with peak point and duration at 2 h and 6 h, respectively. Plasma GLP-1 was peaked at 2 h and still increased at 6 h for IP and oral administration with DAS and NEO, respectively. In conclusion, CCK plays a contributory role in anorexia induction but GLP-1 might play a lesser role in this response.

1. Introduction

Produced by diverse groups of fungi, the trichothecene mycotoxins are harmful secondary metabolites and contaminate cereal staples such as wheat, barley and corn (Bennett and Klich, 2003; Schenzel et al., 2012). Trichothecene mycotoxins are generally classified into A, B, C and D categories (Ueno, 1977; Ueno, 1984; Grovey, 2007). Type A and B trichothecenes are of particular public health concern due to their strong toxicity and high contamination rate, respectively (Pestka, 2010a; Jackson and Bullerman, 1999).Type A trichothecene mycotoxins mainly comprise four structurally related congeners including T-2 toxin (T-2), HT-2 toxin (HT-2), diacetoxyscirpenol (DAS) and neosolaniol (NEO) (Fig. 1). Because these toxins are resistant to milling and processing, they can then enter the food chain to cause harmful effects in humans and animals (Sugita-Konishi et al., 2006). In various animals, adverse effects of the trichothecene mycotoxins that have been reported include anorexia, emesis, growth retardation, neuroendocrine changes, and immunotoxicity (Pestka, 2010b; Watson, 2005). Induction of anorexia and resultant growth retardation by trichothecenes is of particular concern from a perspective of human and animal health (Forsell et al., 1986; Iverson et al., 1995; JECFA, 2011).

T-2 is considered one of the most acutely toxic trichothecenes (EFSA, 2011; Sokolović et al., 2008) and has the potency to induce anorectic response in many animal species following several exposure routes including oral, intraperitoneal (IP), sublingual, intravenous (iv) and subcutaneous (sc) (Sato et al., 1975; Lutsky and Mor, 1981; Gentry and Cooper, 1981; Fairhurst et al., 1987; Gaigé et al., 2014). HT-2, a deacetylated form of the T-2, is the main metabolite of T-2 and has comparable toxicity with T-2 including anorexia induction (EFSA, 2011; Wu et al., 2015; Klötzel et al., 2005). Another two members of type A trichothecenes, DAS and NEO display less toxic than T-2 and HT-2 (Thompson and Wannemacher, 1986). DAS is also a metabolite of T-2

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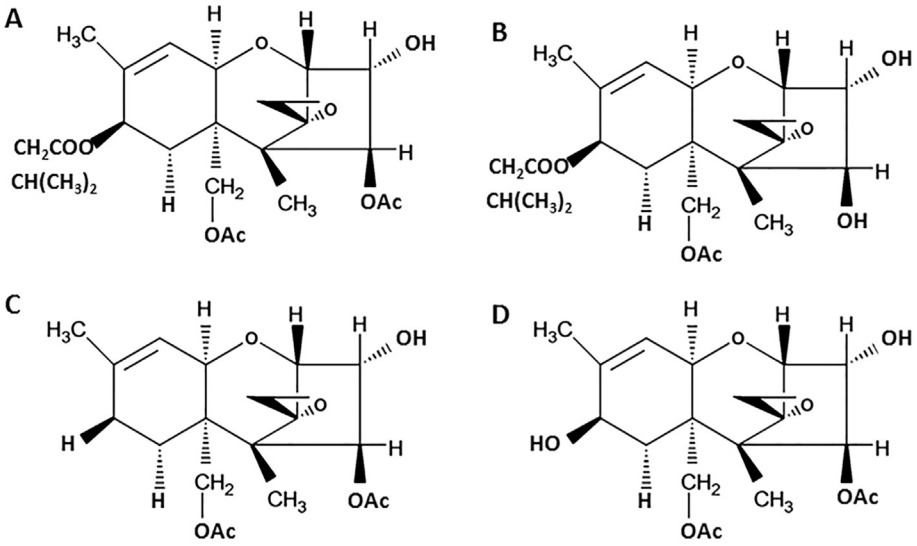

Fig. 1. Structures of Type A trichothecenes. A: T-2 toxin, B: HT-2 toxin, C: Diacetoxyscirpenol, D: Neosolaniol.

and have the potency to induce anorectic response in swine following oral exposure (Bauer et al., 1985). NEO has the similar chemical structure to DAS, with the only difference at the C-8 position being hydroxylated. The anorectic potency of NEO remains unclear up to date. Although anorexia is a common hallmark of trichothecenes-induced toxicity, the underlying mechanisms for this adverse effect are not fully understood.

Anorectic response is a protective reaction to avoid food poisoning. Various factors of both peripheral and central nervous system have the potential to regulate appetite and influence the balance of anorexigenic and orexigenic signaling (Schwartz, 2006). Deoxynivalenol (DON), a common type B trichothecene, has been reported to markedly upregulate the anorexigenic factors including the pro-opiomelanocortin (POMC), melanocortin 4 receptor (MC4R), and cocaine amphetamine-regulated transcript (CART) in mouse hypothalamic neurons (Girardet et al., 2011). Produced by enteroendocrine cells (EECs) in the gastrointestinal (GI) tract, the gut satiety hormone is the possible upstream modulator for elevation of these anorexigenic factors (Moran-Ramos et al., 2012; Steinert et al., 2013). Cholecystokinin (CCK), a satiety hormone released by I cell within the jejunum and ileum, plays an important role in regulation of food intake by up regulating POMC and MC4R expression within the hypothalamic neurons (Strader and Woods, 2005; Kohno et al., 2008). Our previous studies indicated that plasma CCK concentration corresponded to DON and other type B trichothecenes-induced anorexia (Wu et al., 2014a, 2014b). Glucagon-like peptide-$1_{7\text{-}36}$ amide (GLP-1) is another gut satiety hormone secreted by L cell located in the distal ileum and colon (Williams et al., 2009). Both peripheral and central administrations of GLP-1 to animal decrease their consumption of food (Melvin et al., 2016; Sanghee et al., 2008; Turton et al., 1996; Williams et al., 2006). A recent in vitro study indicates that DON dose-dependently elicits GLP-1 release in the murine STC-1 EEC model, suggesting this hormone may also involve in anorexia induction by DON (Zhou and Pestka, 2015). Although the DON and type B trichothecenes-induced anorectic responses are associated with secretion of both the satiety hormone CCK and GLP-1, the anorectic potencies of type A trichothecenes and the possible mechanism are not fully understood.

The purpose of this study was to test the hypothesis that type A trichothecenes-induced anorectic response will correspond to elevated CCK and GLP-1 release. Two methods of exposure, oral gavage and intraperitoneal (IP) administration with a common dose of 1 mg/kg body weight (BW) were used in this study. The results presented herein indicate that (1) Type A trichothecenes T-2, HT-2, DAS and NEO induce robust anorectic response and elevation of plasma CCK and GLP-1 following both oral gavage and IP exposure (2) CCK play a major role in anorexia induction by type A trichothecenes whereas GLP-1 is a minor contributor in this response.

2. Materials and methods

2.1. Chemicals

T-2 (> 98%, TLC) and HT-2 (> 96%, TLC) were obtained from Toronto Research Chemicals (North York, Toronto, Canada). DAS (≥ 98%, HPLC) and NEO (≥ 98%, HPLC) were obtained from Sigma-Aldrich (St. Louis, MO, USA). All four toxins were dissolved in 1% dimethyl sulfoxide (DMSO) with fully vortex blending and were then diluted with filter-sterilized phosphate buffered saline (PBS) to obtain 1 mg/kg BW T-2, HT-2, DAS and NEO.

2.2. Animals

All animal experiments were performed according to the guidelines of the Nanjing Agricultural University Institutional Animal Care and Use Committee (Certification No: SYXK (Su) 2011–0036). Female B6C3F1 mice, 11–12 weeks old, were obtained from the Beijing Vital River Laboratory Animal Technology Co. The mice were individually housed in cages in a specific animal room, which was maintained at 30–70% relative humidity, 19–23 °C temperature, and a 12 h cycle of light (6:00–18:00) and dark (18:00–6:00). All mice were acclimated for at least one week and randomly divided into groups (n = 6/group) based on their body weight one day before the experiment.

2.3. Experimental design

The general experimental design for the anorexia studies (Fig. 2A) was based on protocols developed previously (Flannery et al., 2011; Wu et al., 2012). On the day of experiment, mice were fasted from 10:00 h to 18:00 h and water provided ad lib. At 18:00, mice were administered with 0 or 1 mg/kg BW T-2, HT-2, DAS and NEO in 100 μl 1%DMSO by oral gavage using a sterile 22 G 1.5 in. disposable feeding tube or IP injection using a sterile 27 G 0.5 in. needle. Dose selection was based on our previously study (Wu et al., 2015) as well as preliminary range finding studies. Pre-weighed food pellets was provided immediately following the toxin exposure, and food consumption was measured at 0, 0.5, 2, 6 and 24 h, except for the DAS and NEO gavage exposure groups, which were only monitored at 0, 0.5, 2 and 6 h.

To relate kinetics of toxins-induced anorexia to timing of satiety