Physiological Impact of Ergot Alkaloid Consumption in Ruminant Livestock

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Abstract
Ergot alkaloids in feeds and forages are a worldwide concern. Consumption of ergot alkaloids by ruminant livestock can range from extreme cases that threaten the life of the animal to more frequent and chronic outcomes where livestock productivity is decreased. Consumption of ergot alkaloids alters ruminant physiology such that it outwardly manifests in lower animal intake and gain, decreased reproductive efficiency, and a compromised circulatory system. This talk will cover current research that is improving our understanding of how ergot alkaloids alter cell and tissue physiology that results in the compromised growth and reproduction observed at the whole animal level.

Introduction
Livestock feed contaminated with ergot alkaloids is a global problem that can range from cereal grains *Claviceps spp.* in Canada (Menzies and Turkington, 2014) and Australia (Blaney et al., 2011) to endophyte-infected forages in the United States (Kallenbach, 2015), Ireland (Canty et al., 2014), and New Zealand (Klotz and Nicol, 2016; Nicol and Klotz, 2016). Whether ergot alkaloids are consumed on pasture or at the bunk, the effects consistently result in a loss of animal productivity. Symptoms can range from gangrene and loss of extremities, elevated respiration, salivation, and body temperature decreased intake, weight gain, serum prolactin, pregnancy rates, birth weights, milk production, and persistent vasoconstriction (Strickland et al., 2011; Klotz, 2015). The most notable effects of these symptoms other than extreme cases that result in the loss of the extremities are those that result in declines in feed intake (Koontz et al., 2015) and fetal growth rates (Duckett et al., 2014). Understanding how consumption of ergot alkaloids culminates in anorexia and decreased reproductive success is critical to developing solutions. The objective of this talk is to review the current research on ergot alkaloid-induced decreases in feed intake, intra-uterine growth restriction, and vasoconstriction associated with these problems.

Ergot Alkaloids and Feed Intake
Ergot alkaloids found in the living plant serve as antiherbivory compounds and are very effective at protecting the plant from over or complete consumption with the crown of the plant having the highest concentrations and the leaf having the lowest (Lane et al., 1997). Herbivores that consume sufficient quantities of ergot alkaloids can demonstrate lower intakes that are exacerbated by elevated environmental temperatures (Koontz et al., 2012). It is not fully understood how this occurs and impacts on intake can range from 10 to 50% reductions (Hoveland et al., 1983; Bond et al., 1984). Research studying the negative effects of ergot alkaloids on weight gain is challenged by the fact that ergot alkaloids often confound research because they decrease feed intake as well as produce the negative effects of the ergot alkaloid treatment. Is the decrease in feed intake solely responsible for the decrease in weight gain or are there other contributing factors? Do ergot alkaloids have a direct negative effect on fermentation? Do ergot alkaloids affect gut smooth muscle, decrease motility, and decrease passage rate? Is there an effect on appetite regulating hormones and an increased sense of satiety?

Studies have been conducted that separate ergot alkaloid intake from feed intake by using ruminally cannulated cattle (Koontz et al., 2012). Studies that pair-fed cattle with feed intake fixed at the level of the animal receiving ergot alkaloids and administration of ergot alkaloids through the cannula demonstrated that ruminal DM content was greater in cattle receiving the ergot alkaloid treatment (Foote et al., 2013; Koontz et al., 2013; Koontz et al., 2015). Matthews et al. (2005) reported the lower dry matter and crude protein digestibilities in steers receiving an ergot alkaloid treatment. Further, Koontz et al. (2015) reported increased liquid passage associated with the presence of ergot alkaloid treatment which could further contribute to the observed increase in rumen dry matter contents. Ergot alkaloid interference with gut motility was an obvious culprit when

attempting to interpret the effects on gut fill. Studies evaluating the direct effect of ergot alkaloids have shown some disruption in digestion (McLeay and Smith, 2006; Poole et al., 2009). However, when using the rumen-cannulated pair-fed steer model, no effects of ergot alkaloids on gut motility were observed that could explain the differences in dry matter content (Egert et al., 2014b). However, when motility was evaluated with eating behavior, Ahn et al. (2020) were able to demonstrate a decrease in frequency and amplitude in ruminal contractions associated with ergot alkaloids as well as a slower eating pattern. A key regulator of gastrointestinal smooth muscle contractility is serotonin. Recent reports have shown that circulating levels of serotonin are decreased in cattle exposed to ergot alkaloids (Valente et al., 2020) and may be a potential solution in the efforts to mitigate the negative effects of ergot alkaloids.

Blood flow to the absorptive surface of the digestive tract is critical for nutrient absorption and decreases in blood flow can result in decreased nutrient absorption (Dobson, 1984). Ergot alkaloids have been shown to decrease blood flow to tissues in the digestive tract (Rhodes et al., 1991). More specifically, ergot alkaloids can cause substantial and prolonged vasoconstriction in exposed livestock (Oliver, 1997) and blood vessels directly exposed or collected from animals that were exposed to ergot alkaloids have much lower vasoactivity (Foote et al., 2011; Egert et al., 2014a; Jia et al., 2015). Concurrently using a similar rumen cannulated and pair-fed animal model, Foote et al. (2013) showed a decrease in flux of volatile fatty acids in cattle exposed to ergot alkaloids that occurred with a corresponding decrease in blood flow to the rumen epithelium. In a subsequent study evaluating the barrier function of rumen epithelium exposed to ergot alkaloids, Foote et al. (2014) concluded that reductions in VFA absorption due to ergot alkaloid exposure are a result of decreased blood flow to the absorptive surface.

Ultimately, the decreases in weight gain are a result of decreases in feed intake. Substantial progress has been made in understanding the decreases in feed intake associated with ergot alkaloids. The decreases in intake appear to be a consequence of altered eating behavior, gut fill, and motility; however, the relationship of this conclusion with gut vasoconstriction and nutrient absorption is not fully understood. Is this a direct effect of ergot alkaloids or an indirect effect caused by decreased motility and slower eating frequency? How does this affect hormones related to satiety? Preliminary work has suggested that ergot alkaloids decrease feed intake through shifts in hormones associated with intake such as ghrelin (King et al., 2022). There is much to learn regarding how ergot alkaloids decrease feed intake in grazing livestock.

Ergot Alkaloids and Fetal Growth and Development

In addition to decreases in feed intake and corresponding decreases in weight gain associated with ergot alkaloid exposure, there is also an associated effect on fetal growth and development. In nutrient restriction models, the dam has been shown to protect the growth and development of the fetus at the expense of her body condition (Vasquez-Hidalgo et al., 2022). This is not the case with ergot alkaloid-induced nutrient restriction. Duckett et al. (2014) demonstrated asymmetric growth and intra-uterine growth restriction (IUGR) in sheep exposed to ergot alkaloids during gestation. Further work went on to demonstrate that exposure to ergot alkaloids in the second half of gestation caused asymmetrical growth and altered fetal muscle development (Greene et al., 2019). In the same experiment the maternal side demonstrated reduced uterine and placentome weights (Britt et al., 2019). Studies that have evaluated the effects of gestational exposure to ergot alkaloids on the performance of offspring have shown that in addition to lower birth weights, postnatal growth rates and weaning weights are lower (Britt et al., 2020a). Further investigation into the postnatal effects of gestational exposure to ergot alkaloids has shown a delayed onset of puberty and changes in body composition associated with fat deposition and tenderness (Greene et al., 2020). How does exposure of the dam to ergot alkaloids result in such far-reaching effects on the offspring?

There are attempts made by the maternal side to protect the fetus from ergot alkaloids during gestation. Britt et al. (2020b) demonstrated that there is remodeling of the cotyledon transcriptome to increase nutrient supply to the fetus. Further evaluation at two different time points in pregnancy demonstrated changes in placental insufficiency at d110 that continued to d133 that occurred in conjunction with asymmetric fetal growth with an evident brain-sparing effect (Britt et al., 2022). There has even been evidence to suggest that the maternal side attempts to offset ergot alkaloid-induced vasoconstriction at the placentome with larger vascular lumens in ewes exposed to ergot alkaloids (Britt et al., 2021). If the dam is designed to mitigate the negative effects caused by ergot alkaloids, then how are the toxins causing the negative effects on the fetus?

If ergot alkaloids or their metabolites cross over to the fetal side of the placentome, then there may be little that can be done from the maternal perspective. There are no published reports that describe the permeability

of the placentome to ergot alkaloids in sheep; however, there is work in other species that demonstrates the ability of ergot alkaloids to cross the placental barrier. Indänpään-Heikkilä and Schoolar (1969) demonstrated the transplacental passage of [^{14}C]LSD that was given intravenously to mice during the final week of pregnancy. Five minutes following infusion, the label was detected in the fetus. Leist and Grauwiler (1973) looked at the intravenous infusion of the structurally more complex ergopeptide alkaloid [^{3}H]ergotamine in rats. Female rats received infusions of ergotamine 14 d following breeding and radioactivity levels were three-fold higher in the uterus and placenta than in blood suggesting that ergot alkaloids accumulated at this barrier. Further, radioactivity was detected in amniotic fluid and fetal tissues indicating that the ergot alkaloids or a metabolite were capable of crossing the placental barrier over to the fetal side (Leist and Grauwiler, 1973).

Further work has shown that umbilical and uterine arteries collected from ewes that received ergot alkaloids in the second half of gestation had reduced contractile response to increasing concentrations of serotonin (Klotz et al., 2019) in addition to IUGR and abnormally developed fetuses (Greene et al., 2019). In a similar study, ewes were dosed with ergot alkaloids in the second half of gestation and umbilical arteries and veins were collected and assessed for vasoactivity via stimulation with selective agonists for 5-HT$_{1B/1D}$ and 5-HT$_{2A}$. Umbilical artery smooth muscle contractions were mediated by 5-HT$_{2A}$ receptor and 5HT$_{2A}$ receptor vasoactivity was negatively affected by ergot alkaloids in the umbilical artery, but not the umbilical vein (Klotz et al., 2022). This agrees with the earlier observations that ergot alkaloids are making it to the fetus and disrupting the biological processes. This disruption of serotonin regulation and function could extend beyond vasoconstriction and contribute to other negative effects ergot alkaloids have on the fetus. The role of ergot alkaloids influencing serotonin and its receptors needs further clarification in understanding the associated IUGR.

Conclusions and/or Implications

Ergot alkaloids cause profound effects on the physiology of the animal consuming them whether it is a growing or pregnant animal. Much has been delineated in the past 10 years in understanding how ergot alkaloids accomplish such a broad array of effects from the transcriptome up to the whole animal perspectives; however, there remains much to learn.

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