Good effects of ergot alkaloids on cyp450 enzyme activity research proposal examp...

Environment, Animals

Introduction

Studies have shown that fescue toxicosis is caused by low levels of ergot alkaloids which are highly toxic in endophyte-infected tall fescue grass. It is believed that a number of the ergot alkaloids are involved in the modulation of physiological mechanisms in animals and man. One of the best approaches that can be used to solve the problem of fescue toxicosis from the body system is by adopting the process used by animals to remove the ergot alkaloids toxins from circulation. This can be achieved through understanding of the role played by the cytochrome P450 (CYP3A4) in the elimination of ergot alkaloids through extensive hepatic biotransformation as suggested by Moubarak, Rosenkrans & Johnson (2002). A number of tissues such as kidneys, intestines and lungs have the cytochrome P540 enzyme but it mainly exists in the liver. The main objective of the research is the investigation towards finding preliminary information on the relationship between CYP3A4 and the metabolism of an ergot alkaloid representative known as ergotamine in the liver.

Objective

The aim of this study was to find out whether the presence of ergot alkaloids toxins induces cytochrome P450 (CYP3A4) enzyme activities or inhibits them.

Also, another aim was to find out the action of the cytochrome P450 (CYP3A4) enzyme activity in the metabolism of aflatoxins.

Justification

It is indicated that endophyte infected tall fescue grass which are commonly found in the Southern United States is the major consumption feed of all beef cattle in the area. Consumption of this grass by beef cattle causes the fescue toxicosis syndrome due to presence of ergot alkaloids toxins. According to Moubarak, Rosenkrans & Johnson (2012), cytochrome P450 (CYP) enzyme activities in an animal's body is vital in biotransformation of a number of exogenous and endogenous compounds with the inclusion of both toxins and drugs. There are a large number of proteins in the CYP enzyme family with varied substrate specificities and catalytic characteristics which are membrane-bound. These membrane-bound catalytic properties of CYP enzyme family are localized to mitochondrial inner membranes and the endoplasmic reticulum.

Ergot alkaloids that are mainly present in tall fescue constitute of two major subfamilies of compounds. One of them is the tetracyclic ergoline nucleus subfamily such as lysergic acid, lysergic acid ethylamide, ergopeptide alkaloids and ergonovine group. This group is said to share the tetracyclic ergoline nucleus. There is also another group of tricyclic amino acids such as bromocriptine, ergotamine and ergocriptine. Moubarak, Rosenkrans & Johnson (2012) point out that metabolism of dihydroergotamine and bbromocriptine which is a group of ergot alkaloids and other structurally alike ergot products is mediated by CYP3A4. Additionally, it has been shown that bromocryptine inhibits the P450-dependent oxidative metabolism process of xenobiotics. It was also established that cytochrome P450 3A displays a particularly high attraction for ergopeptides. It can therefore be

pointed out that the induction or inhibition of cytochrome P450 enzyme activity may result in severe consequences of the metabolism of the ergot alkaloids.

In an experiment conducted by Moubarak, Rosenkrans & Johnson (2012), there is a variation of the cytochrome P450 enzyme activity subjected to different conditions. The experiment involved a seed extract of endophyte infected tall fescue. The aim of the experiment was to investigate the effects of toxins present in seed extract of endophyte infected tall fescue. It was found out that endophyte infected tall fescue inhibited the activity of CYP3A4 enzyme. However, the inhibition of CYP3A4 enzyme activity is dependent on dosage applications. Hence it was established that the higher the extract concentration, the higher the inhibition percentage for the CYP3A4 enzyme activity. Therefore, the toxins found in these extracts influenced CYP3A4 enzyme systems activities in a similar inhibition as that of the commercially obtainable ergot alkaloids.

In retrospect, Settivari et al (2008) has indicated that an experiment conducted on rats treated with DHET, 100 nM DXM, or EN showed that there was no significant activity improvement of CYP3A4 to convert ET to its metabolites. This is an indication that the enzyme system responsible in the metabolism of ergot alkaloids that are present in endophyte-infected tall fescue, according to Settivari et al (2008), has not yet been fully categorized in beef animals. However, bromocriptine and dihydroergotamine which are structurally related ergot alkaloids have been found to be metabolized by the CYP3A4 enzyme systems. In the experiments conducted, it was clear that beef steer liver microsomes found in both man and animals have the

enzymatic capability to metabolize ergotamine.

Aflatoxins are also another group of toxins known as secondary fungal metabolites that easily contaminate foods like maize and groundnuts. Increased exposure to aflatoxins has been associated with risks of hepatocellular carcinoma (HCC) in combination with the hepatitis B virus (HBV) human beings. It is also observed that its interaction with HBV induces liver cancer in animals. Therefore, the understanding ofhe action of cytochrome P450 (CYP3A4) enzyme activity on aflatoxin metabolism will aid formation of chemopreventive trials and biomarkers to modulate on the undesirable effects of nutritional exposure to aflatoxins (Wild & Turner, 2002).

Rationale Summary

It is apparent that the presence of ergot alkaloids inhibits the enzymatic activity of cytochrome P450 enzyme. The degree with which the inhibition occurs is dependent on a number of variables. It is also evident that many ergot alkaloids are involved in the modulation of physiological mechanisms in animals and man. Since the CYP3A4 enzyme has been found to be responsible in the metabolism of ergot alkaloids toxins in the liver and other tissues such as the kidney and the intestines, experiments have indicated that the increase of the concentrations of these toxins also increases the enzyme inhibition activity. Also, the metabolism of bromocriptine and hydroergatomine substances that are structurally similar to the ergot alkaloids toxins is influenced by the CYP3A4 enzyme. These compounds exist in tricyclic amino acid groups which is one of the two major subfamilies of

the ergot alkaloids. The analysis of the influence of ergot alkaloids in the activity of cytochrome P450 enzyme is a major step forward towards establishing a way of metabolizing these toxins in human beings and animals in order to avoid occurrence of toxicosis syndrome. However, more research and experimental analysis is required in the area fore mentioned so as to establish a pharmacological approach in solving the problem of toxicosis syndrome. In order to come up with markers that can effectively be utilized to choose animals that are resilient to fescue toxins, the knowledge and understanding of the way ergot alkaloids are metabolized is important. The cytochrome P450 system is one of the mechanisms that can easily be used. Additionally, it is recorded that AFB1 is metabolized by CYP3A4 to form G1, B2 and G2 substrates in humans that are less carcinogenic, toxic and mutagenic. The CYP3A4 is said to be the major enzyme involved in aflatoxin metabolism in humans. However, the general contribution of the enzyme in aflatoxin metabolism such as AFB1 is dependent on expression levels in human liver as well as theaffinity (Wild & Turner, 2002).

Conclusion

The consumption of endophyte infected fescue grass by cattle in America is a major concern to the health of the population involved. This is mainly because of the presence of ergot alkaloids toxins in these grasses. These toxins cause toxicosis syndrome that is a major health challenge. However, in the study of effects of ergot alkaloids on the activity of cytochrome P450 enzyme, it was found out that the activity of this enzyme is vital in the biotransformation of endogenous and exogenous organic toxins and drugs. It

is therefore established that the presence of ergot alkaloids influences the activity of CYP3A4 enzyme in the metabolism of compounds that are toxic and are likely to cause toxicosis syndrome. In addition, the CYP3A4 enzyme is also vital in aflatoxin metabolism which helps in the reduction of their toxicity levels in humans and animals.

References:

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