EFFECTS OF FESCUE TOXICOSIS AND CHRONIC HEAT STRESS ON MURINE HEPATIC GENE EXPRESSION

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ABSTRACT

Fescue toxicosis affects domestic animals grazing fescue pasture infected with the endophytic fungus, *Neotyphodium coenophialum*. Signs of fescue toxicosis include increased body temperature and respiration rate and decreased milk yield and reproductive performance. Laboratory mice also exhibit symptoms of fescue toxicosis as indicated by reduced growth rate and reproductive performance. Mice were used to study effects of fescue toxicosis on hepatic gene expression. Twenty-seven mice were randomly allocated to a diet containing either 50% endophyte-infected (E+) or endophyte-free (E-) fescue seed for two wks under thermoneutral conditions. A two-stage ANOVA of microarray data identified thirty-six genes differentially expressed between mice fed E+ and E- diets. The E+ diet resulted in down-regulation of genes involved in sex-steroid pathway and in cholesterol and lipid metabolism. Genes coding for ribosomes and protein synthesis were up-regulated by the E+ diet.

Mice were also used to study the effects of chronic heat stress on hepatic gene expression. Twenty-five mice were randomly allocated to either chronic heat stress (cHS; 34 ± 1°C) or thermoneutral (TN; 24 ± 1°C) conditions for a period of two wks from 47 to 60 d of age. A two-stage ANOVA of 1353 gene oligoarray data identified thirty genes as differentially expressed due to cHS. Genes involved in the anti-oxidant pathway were up-regulated due to cHS. Genes involved in generation of reactive oxygen radicals and a number

of mitochondrial expressed genes were down-regulated by cHS. However, cHS did not produce an increase in oxidative stress induced mitochondrial DNA damage.

Furthermore, effects of heat stress on changes in gene expression due to fescue toxicosis in mice liver were studied using DNA microarrays. Our goal was to characterize the differences in liver gene expression of mice exposed to chronic heat stress (cHS) and E+ when compared to mice fed E+ at TN. Mice were fed E+ diet under cHS (34 ± 1°C; n = 13; E+cHS) or TN conditions (24 ± 1°C; n = 14; E+TN) for a period of two wks between 47 to 60 d of age. Forty-one genes were differentially expressed between treatment groups. Genes coding for phase I detoxification and anti-oxidant pathway were up-regulated in E+cHS mouse liver. Key genes involved in *de novo* lipogenesis and lipid transport were also up-regulated. Finally, genes involved in DNA damage control and unfolded protein responses were down-regulated.

In summary, mice fed an E+ diet at TN resulted in change in expression of genes involved in sex-steroid pathway while this pathway was not perturbed in mice exposed to cHS or to E+cHS treatments. Changes in expression of genes involved in lipid and cholesterol metabolism pathway occurred in mice exposed to E+ and to E+cHS treatment. Anti-oxidant gene expression changes occurred in mice exposed to cHS and to E+cHS, but not in E+ treated mice. Interestingly, gene expression changes involved in the detoxification pathway were seen only in mice exposed to combination of E+ and cHS. Biological pathways and gene expression changes identified in mouse liver due to E+, cHS, and E+cHS will help to understand molecular mechanisms by which fescue toxicosis and heat stress affects animals.