DISSERTATION ABSTRACT

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Contamination by various pollutions is an environmental concern. Many fish populations are continuously exposed to xenobiotics, including endocrine disrupting chemicals. Cytochrome P450 (CYP) enzymes metabolize lipophilic compounds facilitating their excreation, which prevents bioaccumulation. The aim of this thesis was to study effects of estrogenic compounds on CYP, redox status and endocrine responses in fish. Furthermore, to identify possible sites of interaction between two classes of environmental pollutants, 1) estrogenic compounds, *i.e.* alkylphenols, ethynylestradiol (EE_2) and 2) antifungal azoles, *i.e.* ketoconazole. We hypothesize that estrogenic compounds and azoles share common routes of excretion in fish through CYP1A and CYP3A.

Atlantic cod (*Gadus morhua*) and rainbow trout (*Oncorhynchus mykiss*) were exposed orally or by i.p. injections. Effects on hepatic CYP1A and CYP3A protein expression and activities were investigated as well as glutathione, glutathione-related enzymes, vitellogenesis and sex steroid hormone levels.

Alkylphenols induced CYP1A and CYP3A protein expressions in male Atlantic cod, but not in females. Alkylphenols had no effect on CYP1A activities in either males or females. *In vitro* inhibition studies showed that the alkylphenols efficiently inhibited CYP1A activity. In addition, ketoconazole induced CYP1A and CYP3A protein expression, whereas CYP1A and CYP3A activities were inhibited. These results indicate that CYP1A and CYP3A represent sites of interactions between these classes of xenobiotics. Combined exposure of ketoconazole with EE_2 increased the responsiveness to EE_2 measured as vitellogenesis. Thus, co-exposure to ketoconazole appears to make juvenile rainbow trout more sensitive to EE_2 exposure. Combined exposure to ketoconazole and EE_2 also decreased circulating androgens. This study shows interactions between ketoconazole and EE_2, which affect the endocrine system and that CYP1A and CYP3A may play an important role in this interaction.

Keywords: Cytochrome P450, CYP1A, CYP3A, glutathione, alkylphenols, ethynylestradiol, ketoconazole, vitellogenin, Atlantic cod, rainbow trout, fish
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