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Use of network inference to unravel the mechanisms of action and specificity of aromatase inhibitors

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Abstract:

The vertebrate hypothalamus-pituitary-gonadal (HPG) axis is controlled through various feedback mechanisms in order to maintain a dynamic homeostasis during changing environmental conditions, including exposure to chemical stressors. In this study, three aromatase inhibitors, fadrozole, prochloraz, and ketoconazole, were chosen as model chemicals to assess their effects on the hypothalamus-pituitary-gonadal (HPG) axis in the fathead minnows (*Pimephales promelas*). All three chemicals have been shown to inhibit aromatase activity and decrease estradiol (E2) levels. Fadrozole, a drug used to treat breast cancer, is a potent aromatase inhibitor. Prochloraz, an imidazole fungicide, affects multiple pathways, such as inhibition of aromatase and other CYPs, as well as antagonism of the androgen receptor. Ketoconazole, an anti fungal agent, affects multiple pathways as well, including inhibition of aromatase and other CYPs. We exposed female fathead minnows to two different concentrations of fadrozole (3, 30 ug/L), prochloraz (30, 300 ug/L), and ketoconazole (32, 310 ug/L) during 8 days. We then removed the chemical from the water and sampled for 8 more days. We analyzed plasma hormone levels, as well as gene expression changes in the ovaries using a 15k custom microarray. We used network analysis to try to elucidate the mechanisms of action of the chemicals and their degree of specificity as aromatase inhibitors. These chemicals significantly increased aromatase expression and reduced E2 production. Comparison of the three aromatase inhibitors based on the network inference showed that fadrozole acted as the strongest aromatase inhibitor. Therefore, microarray analysis supported the fact suggested by hormone levels that fadrozole is a more potent aromatase inhibitor than prochloraz and ketoconazole. The inferred network was also able to discern between fadrozole, a more specific aromatase inhibitor, prochloraz, and and ketoconazole, the last two being more general P450 inhibitors. The results also unraveled new connections that have been verified in the literature.