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Endocrine disruptors and early development

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Background and hypothesis: Atrazine is a potent endocrine disruptor that increases aromatase expression and estrogen production in some human cancer cell lines. The mechanism involves the inhibition of phosphodiesterase and subsequent elevation of cAMP. We hypothesized that the transcription factor (SF-1) is important for atrazine's activity.

Methodology: We compared SF-1 expression in atrazine responsive and non-responsive cell lines and transfected SF-1 into non-responsive cell lines to assess SF-1's role in atrazine-induced aromatase. We used a luciferase reporter driven by the SF-1 dependent aromatase promoter (ArPII) to examine activation of this promoter by atrazine. We mutated the SF-1 binding site to confirm the role of SF-1. Finally, we examined atrazine and simazine's ability to bind to SF-1 and enhance SF-1 binding to ArPII.

Results: Atrazine-responsive adrenal carcinoma cells (H295R) expressed 54 times more SF-1 than non-responsive ovarian granulosa KGN cells. Exogenous SF-1 conveyed atrazine-responsiveness to otherwise non-responsive KGN and NIH/3T3 cells. Atrazine induced binding of SF-1 to chromatin and mutation of the SF-1 binding site in ArPII eliminated SF-1 binding and atrazine-responsiveness in H295R cells. Atrazine bound directly to SF-1, showing that atrazine is a ligand for this "orphan" receptor.

Implications: The current findings are consistent with atrazine's induction of developmental malformations of the reproductive tract and organs, the induction of mammary and prostate cancer in laboratory rodents, and correlations between atrazine and similar reproductive cancers in humans. This study highlights the importance of atrazine as a risk factor in endocrine disruption in wildlife and reproductive cancers in laboratory rodents and humans.