The aryl hydrocarbon receptor and retinoid receptors cross-talk at the CYP1A1 promoter in vitro

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Abstract

The epithelium of the small intestine plays an important role in detoxification processes due to the presence of various xenobiotic-metabolizing enzymes from phase I and II, as well as transport proteins of the ATP-binding cassette superfamily. Exposure to xenobiotics induces the expression of these proteins in the small intestine, with multiple signaling pathways stimulated by exogenous compounds converging at individual gene promoters by mechanisms which have not been fully understood yet. In this context the promoter region of the *CYP1A1* gene, encoding the phase I monooxygenase cytochrome P450 1A1, was analyzed by chromatin immunoprecipitation with regard to binding of xeno-sensing receptors following stimulation of Caco-2 cells with agonists of the aryl hydrocarbon receptor (AHR) and retinoid receptors. Histone acetylation in the regulatory region of *CYP1A1* was enhanced by treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) or all-*trans* retinoic acid (at-RA). Binding of retinoid-X-receptor (RXR) α to the promoter region was detected in response to at-RA, while AHR bound to the gene promoter following its activation by TCDD. Of note, enhanced RXR α binding was also detected after AHR stimulation, and increased AHR binding was observed after retinoid receptor activation by at-RA. Exposure of Caco-2 cells to mixtures of AHR and retinoid receptor agonists yielded synergistic induction of *CYP1A1* mRNA. In conclusion, the present data improve our knowledge on retinoic acid-dependent effects on *CYP1A1* expression and demonstrate unexpected mixture effects by cross-talk of the different receptors.

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