In Vitro Effects of the Endocrine Disruptor p,p’-DDT on Human Follitropin Receptor

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Résumé en anglais	BACKGROUND: 1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene (p,p'-DDT) is a persistent environmental endocrine disruptor (ED). Several studies have shown an association between p,p'-DDT exposure and reproductive abnormalities. OBJECTIVES: To investigate the putative effects of p,p'-DDT on the human follitropin receptor (FSHR) function. METHODS AND RESULTS: We used Chinese hamster ovary (CHO) cells stably expressing human FSHR to investigate the impact of p,p'-DDT on FSHR activity and its interaction with the receptor. At a concentration of 5 µM p,p'-DDT increased the maximum response of the FSHR to follitropin by 32 ± 7.45%. However, 5 µM p,p'-DDT decreased the basal activity and did not influence the maximal response of the closely related LH/hCG receptor to human chorionic gonadotropin (hCG). The potentiating effect of p,p'-DDT was specific for the FSHR. Moreover, in cells that did not express FSHR, p,p'-DDT had no effect on cAMP response. Thus, the potentiating effect of p,p'-DDT was dependent on the FSHR. In addition, p,p'-DDT increased the sensitivity of FSHR to hCG and to a low molecular weight agonist of the FSHR, 3-((5methyl)-2-(4-benzyloxy-phenyl)-5-{[2-[3-ethoxy-4-methoxy-phenyl)-ethylcarbamoyl]-methyl}-4-oxo-thiazolidin-3-yl)-benzamide (16a). Basal activity in response to p,p'-DDT and potentiation of the FSHR response to FSH by p,p'-DDT varied among FSHR mutants with altered transmembrane domains (TMDs), consistent with an effect of p,p'-DDT via TMD binding. This finding was corroborated by the results of simultaneously docking p,p'-DDT and 16a into the FSHR transmembrane bundle. CONCLUSION:p,p'-DDT acted as a positive allosteric modulator of the FSHR in our experimental model. These findings suggest that G protein-coupled receptors are additional targets of endocrine disruptors
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