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

Submitted by Daniel Henrion on Mon, 11/14/2016 - 20:52

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

**Type de publication:** Article de revue

**Auteur:** Munier, Mathilde [1], Grouleff, Julie [2], Gourdin, Louis [3], Fauchard, Mathilde [4], Chantreau, Vanessa [5], Henrion, Daniel [6], Coutant, Régis [7], Schiøtt, Birgit [8], Chabbert, Marie [9], Rodien, Patrice [10]

**Pays:** Etats-Unis

**Editeur:** National Institute of Environmental Health Sciences

**Type:** Article scientifique dans une revue à comité de lecture

**Année:** 2016

**Langue:** Anglais

**Date:** 19 Fév. 2016

**Numéro:** 7

**Pagination:** 991-999

**Volume:** 124

**Titre de la revue:** Environmental Health Perspectives

**ISSN:** 1552-9924

**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.

**URL de la notice:** http://okina.univ-angers.fr/publications/ua15167 [11]

**DOI:** 10.1289/ehp.1510006 [12]

**Lien vers le document:** http://ehp.niehs.nih.gov/15-10006/#tab2 [13]

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