Endometriosis is a gynecologic disorder characterized by the growth of endometrial tissue in ectopic sites, causing infertility in reproductive-aged women. Evidence has emerged regarding the relation between organochlorine pollutants and endometriosis. Hexachlorobenzene (HCB) is a widely distributed pesticide that induces toxic reproductive effects by acting as an endocrine disruptor. Cyclooxygenase-2 (COX-2) is involved in pathogenesis of endometriosis regulating the activity of metalloproteases (MMPs), and it has been reported that MMPs play critical roles in endometriosis. In the present study, we evaluated the HCB effects on MMP2 and MMP9 protein expression and activity, and also COX-2 protein levels, in Human Uterine Fibroblast (HUF) cells, in Human Endometrial Stromal Cells (HESCs) cell line, and in human endometrial stromal primary cultures. Cell cultures were exposure to HCB (0.005, 0.05, 0.5 and 5 µM) during 3 and 24 h, afterward protein levels were analyzed by Western Blotting and MMPs activities by gel zymography. In HUF and T-HESCs cells, HCB 0.5 µM increases: (a) MMP9 activity (45.80%, p < 0.01), MMP9 expression (105.53%, p < 0.05) and MMP2 activity (49.53%, p < 0.05) at 24 h; (b) COX-2 levels (78.125%, p < 0.05) at 3 h. In endometrial stromal primary cultures derived from control patients, HCB 0.05 µM enhances: (a) MMP9-MMP2 activities (100.145%, p < 0.05) and expression (690.191%, p < 0.01); (b) COX-2 levels (303%, p < 0.05). However, the pesticide has a moderate effect in eutopic endometrial stromal primary cultures from patients with endometriosis, showing a trend to increase MMP9 and MMP2 protein expression and activity. Our results show that HCB could contribute to endometriosis development, affecting inflammation and invasion parameters of human endometrial cells.

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Action of the dioxin-like compound hexachlorobenzene in an experimental model of endometriosis in rats

Marcela Sánchez 1, Florencia Chiappini 1, Mariela Bilotas 2, Carolina Pontillo 1, Elsa Zotta 3, Claudia Cocca 4, Gabriela Meresman 2, Andrea Randi 1,∗

1 Laboratorio de Efectos Biológicos de Contaminantes Ambientales, Depto de Bioquímica HUMANA, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina. 2 Laboratorio de Genética y Medicina Experimental, IBYME-CONICET, Buenos Aires, Argentina. 3 Laboratorio de Fisiopatogenia, Sección Patología, Depto de Ciencias Fisiológicas, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina. 4 Laboratorio de Radiosíntesis, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina. 5 Laboratorio de Fisiopatología Endometrial, Instituto de Biología y Medicina Experimental, IBYME-CONICET, Buenos Aires, Argentina.

Hexachlorobenzene (HCB) is a dioxin-like environmental pollutant associated with a broad spectrum of toxic effects, including endocrine disruption and immunological disorders. Endometriosis is a gynecologic disease characterized by growth of endometrial tissue in ectopic sites, causing infertility in women of reproductive age. It has been proposed that endocrine-disrupting compounds could play a role in the onset or the growth of endometriosis. The severity of endometrial lesions is associated with expression of metalloproteases (MMPs). Inhibition of Cyclooxygenase-2 (COX-2) decreases invasion of ectopic lesions by suppressing MMP2-MMP9 activities. Besides, the development of the disease depends on the recruitment of new blood vessels. Our aim was to evaluate the effect of HCB on an experimentally induced endometriosis rat model. Fragments of endometrium were autotransplanted to the gut mesothelium of Sprague Dawley rats. Fifteen days post-surgery, rats were exposed to HCB (0, 1 and 100 mg/kg body weight) during 30 days. We analyzed endometriotic lesions (L) and eutopic endometrium (E), by evaluating vascular density by von Willebrand (vW+) immunohistochemistry; and MMPs and COX-2 expression by Western Blotting. We observed that HCB increases: (a) endometriotic lesion volume (HCB100:107%, p < 0.05), (b) vascularized area (VA) (vW+/total area) in L (HCB1:138%, p < 0.05; HCB100:209%, p < 0.01) and E (HCB100:203%, p < 0.05), (c) number of microvessels (vW+/TA) in L (HCB100:85%, p < 0.05) and E (HCB100:112%, p < 0.05), (d) MMP2 expression in L (HCB100:125%, p < 0.05) and E (HCB100:60%, p < 0.05); (e) MMP9 expression in L (HCB100:130%, p < 0.05) and E (HCB100:60%, p < 0.05; HCB100:130%, p < 0.05); and (f) COX-2 protein levels in E (HCB100:120%, p < 0.05). Our results suggest that HCB treatment promotes the development of endometriosis through its angiogenic and inflammatory properties in an experimental endometriosis model in rats.

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New thioxanthones and dihydroxylated xanthones as P-glycoprotein inducers/activators

Renata Silva 1, Marilíne Gameiro 1, Emília Sousa 2,3, Helena Carmo 1, Mafalda Paiva 2, Andreia Palmeira 2, Daniel Barbosa 1, Madalena Pinto 2,3, Maria Lourdes Bastos 1, Fernando Remião 1,∗

1 REQUIMTE, Laboratório de Toxicologia, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal. 2 Centro de Química Medicinal (CEQUIMED-UP), Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal. 3 Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR/CIMAR), Universidade do Porto, Porto, Portugal.

The aim of this study was to investigate the potential of newly synthesized compounds, five thioxanthones (TXs) and five dihydroxylated xanthones (Xs), as inducers of P-gp expression and/or activity, and their capacity to protect Caco-2 cells against the cytotoxicity of the herbicide Paraquat (PQ).

Tested compounds were incubated (0–100 µM) for 24 h in Caco-2 cell culture and their cytotoxicity were evaluated by the MTT reduction and by the neutral red uptake assays. P-gp expression (UIC2 antibody) and activity (Rhodamine 123) were evaluated by flow cytometry after 24 h incubation of the Caco-2 cells to a non-cytotoxic (20.0 µM) concentration of the tested TXs and Xs. P-gp ATPase activity was studied using the MDR1 Predeasy ATPase assay kit. PQ cytotoxicity was evaluated in Caco-2 cells by the Neutral Red uptake assay, with and without simultaneous incubation with the tested TXs and Xs, 24 h after exposure. To confirm the involvement of P-gp in the tested compounds protective effects, similar incubations were repeated in the presence of a P-gp inhibitor (GF120918).

All tested TXs and Xs simultaneously increased P-gp expression and activity. Some results showed direct pump activation without increased P-gp protein expression. These compounds caused a significant increase in P-gp vanadate-sensitive ATPase activity, demonstrating to be P-gp substrates. Moreover, when simultaneously incubated with PQ, used model of a toxic P-gp substrate, all tested compounds significantly reduced the toxicity mediated by PQ, with increases in the EC50 of the PQ+TXs or Xs. These protective effects were completely abolished upon incubation with GF120918.


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