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MECHANISM OF PHENOXY COMPOUNDS AS ANDROGENIC ENDOCRINE DISRUPTORS

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Phenxoy compounds, 2,4-Dichlorophenol acetoxyacid (2,4-D) and 2,4-dichlorophenol (DCP), are widely used as a herbicide and intermediate for pesticide manufacturing, respectively. In order to assess the potential of these compounds as endocrine disruptors, we studied the androgenicity of them using in vivo and in vitro assay system. In Hershberger assay, administration of 2,4-D (50 mg/kg/day, p.o.) or DCP (100 mg/kg/day, p.o.) to rats caused an increase in the tissue weight of ventral prostate, Cowpers gland and glands penis. These increases of androgen-dependent tissues were additively potentiated when rats were simultaneously treated with low dose of testosterone (1g/kg, s.c.). 2,4-D increased about 350% of the luciferase activity in the PC cells transiently cotransfected phAR and pMMTV-Luc at concentration of 10-9M. In 2,4-D or DCP-treated castrated rats co-treated with or without testosterone did not testosterone 6β-hydroxylase activity was not significantly modulated. In vitro incubation of 2,4-D and DCP with microsomes at 50uM inhibited testosterone 6β-hydroxylase activity about 27-66% in rat liver microsomes, human liver microsomes and recombinant CYP3A4 system. And the amounts of total testosterone metabolites were inhibited about 33-75% by 2,4-D or DCP, respectively. These results collectively suggested that 2,4-D and DCP may act as androgenic endocrine disruptor by binding to the androgen receptor as well as by inhibiting the metabolism of testosterone.

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