Uterine response to estradiol: low-dose facilitation and high-dose inhibition due to fetal exposure to diethylstilbestrol and methoxychlor in CD-1 mice

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We have previously reported that prenatal exposure to low doses of diethylstilbestrol (DES) and other manmade estrogenic chemicals, such as methoxychlor (MXC), permanently increased prostate size in male mice. In contrast, a high dose of DES had the opposite effect and significantly decreased prostate size. We thus examined whether fetal exposure to a low dose of DES (0.1 µg/kg/day) or MXC (10 µg/kg/day)) would produce an opposite effect on the uterus in adult female CD-1 mice relative to a high dose of DES (100 µg/kg/day) or MXC (10,000 µg/kg/day). Pregnant females were injected s.c. with DES or fed methoxychlor in tocpherol-stripped corn oil once per day on gestation days 12-18, while appropriate controls received only vehicle. At 7 months of age, randomly selected females were ovariectomized and implanted for 7 days with a Silastic capsule containing 0.5 µg estradiol, which results in about 50% of maximum uterine size relative to ovariectomized females receiving a blank implant. The 100 µg/kg prenatal dose of DES significantly increased body weight by 19% relative to control females, while body weight was unaffected by other treatments. Relative to controls, females exposed to the 0.1 µg DES dose showed significantly heavier uteri (by 27%), while females exposed to the 100 µg DES dose showed significantly lighter uteri (by 49%). Females exposed prenatally to the 10 µg/kg dose of MXC had significantly heavier uteri relative to females exposed to the 10,000 µg/kg dose of MXC, but neither group differed significantly from controls. For DES there was a dose-related increase in liver weight, with females exposed to both doses of DES showing significant enlargement of the liver relative to controls.

At 8 months of age, the remaining females were ovariectomized and implanted for 7 days with Silastic capsules containing one of 4 doses of estradiol: 0 (vehicle only), 2.5, 5 and 1 µg per Silastic capsule. The lowest estradiol dose (0.25 µg) had previously been shown to result in a slight, but significant, increase in uterine weight, while the highest estradiol dose (1.0 µg) maximally stimulated uterine growth. For prenatal control females, uterine weight increased by 458%, from 57 to 261 mg between the 0 and 1.0 µg doses of estradiol per Silastic capsule. In sharp contrast, the 100 µg dose of DES resulted in a markedly attenuated uterine weight response to increasing doses of estradiol of less than 2-fold from 52 to 94 mg. The prenatal 0.1 µg dose of DES resulted in a 496% increase in uterine weight from 72 to 357 mg between the 0 and 1.0 µg doses of estradiol, which differed significantly from increase seen in control females. Females exposed to the low and high doses of methoxychlor also showed enhanced and attenuated responses to increasing doses of estradiol. The prenatal 10 µg dose of MXC resulted in a 527% increase in uterine weight from 63 to 332 mg, while the 10,000 µg/kg dose of MXC resulted in a 418% increase in uterine weight from 49 to 205 mg between the 0 and 1.0 µg doses of estradiol. Both the low and high doses of DES resulted in a significantly enlarged liver, and the 100 µg/kg/day dose of DES also significantly increased kidney and spleen weight. We thus found opposite effects of fetal exposure to low and high doses of DES and MXC on the uterine response to estradiol in adult female mice. These findings are important for risk assessment, which assumes that effects caused by high doses of a chemical will always be greater than effects at much lower doses. For endocrine disrupting chemicals, this is an invalid assumption. Supported by NIH grant ES08293.