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Oxidative stress and phthalate-induced down-regulation of steroidogenesis in MA-10 Leydig cells

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Highlights

- MEHP induces two defects in steroidogenic pathway of MA-10 Leydig cells.
- Defect in cAMP production may be due to LH receptor or its coupling to Gs protein.
- Reduction in STAR may be involved in the defect in cholesterol transport.
- MEHP increases oxidative stress in MA-10 Leydig cells.
- Glutathione redox affects the susceptibility of MA-10 cells to MEHP treatment.

Abstract

Previous studies have shown that phthalate exposure can suppress steroidogenesis. However, the affected components of the steroidogenic pathway, and the mechanisms involved, remain uncertain. We show that incubating MA-10 Leydig cells with mono-(2-ethylhexyl) phthalate (MEHP) resulted in reductions in luteinizing hormone (LH)-stimulated cAMP and progesterone productions. cAMP did not decrease in response to MEHP when the cells were incubated with cholera toxin or forskolin. Incubation of MEHP-treated cells with dibutyryl-cAMP, 22-hydroxycholesterol or pregnenolone inhibited the reductions in progesterone. Increased levels of reactive oxygen species (ROS) occurred in response to MEHP. In cells in which intracellular glutathione was depleted by buthionine sulfoximine pretreatment, the increases in ROS and decreases in progesterone in response to MEHP treatment were exacerbated. These results

indicate that MEHP inhibits MA-10 Leydig cell steroidogenesis by targeting LH-stimulated cAMP production and cholesterol transport, and that a likely mechanism by which MEHP acts is through increased oxidative stress.

Abbreviations

DEHP, di-(2-ethylhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; LH, luteinizing hormone; dbcAMP, dibutyryl cAMP; 22HC, 22-hydroxycholesterol; P5, pregnenolone; BSO, L-buthionine-sulfoximine; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; DCF, 2',7'-dichlorodihydrofluorescein diacetate; GSH, glutathione; ROS, reactive oxygen species; Gs α , stimulatory G protein α subunit; IBMX, isobutyl-methylxanthine; STAR, steroidogenic acute regulatory protein

Keywords

Phthalate; MEHP; Leydig cell; Oxidative stress; Steroidogenesis

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