The Influence of Diethylstilbestrol on Cervical Cancer in a Rodent Model

Tyra Wu

Carlsbad High

Objective

Diethylstilbestrol was a hormone administered for recurred first trimester miscarriage in the 1970's that was found to cause damaging abnormalities in the female reproductive tract in 1971. Mice were utilized to elucidate the role of DES in cervical abnormalities. In researching diethylstilbestrol, this poster aims to effectively determine what role it has in increased cervical cancer incidents.

Abstract

In the 1970's, diethylstilbestrol (DES), a synthetic form of the hormone estrogen, was prescribed to 2 to 4 million pregnant women for recurred first trimester miscarriage. In 1971, this medication was found to cause several complications in the reproductive tract, including increased risks of cervical cancer[1]. DES is thought to be able to alter the base structure of DNA, as well as cause epigenetic change[5]. If this change occurs in the germ line, it could continue onto the next generation. There is also evidence that maternal ingestion of DES not only has effects on the daughters, but can also have effects of the granddaughters[2]. These effects can be studied on a smaller scale, particularly in mice due to their rapid reproduction rates. In a recent study, pregnant mice were treated with daily doses of DES ranging from 0.01 to 100 µg/kg on days 9 to 16 of gestation. In the DES exposed offspring, the cervix was enlarged, a variety of malignant lesions were found, and malformed cervical canals occurred[4]. These results found in DES-exposed mice mirror those found in DES-exposed women. These results show that the developing fetus is particularly sensitive to exogenous estrogens[3]. This data allows us more insight on the effects DES has on a smaller scale, which can then be compared to a larger scale, allowing for more effective cures and a ceasing of usage of detrimental estrogens. Thus, DES studies in mice can provide useful insight on the long-term effects of estrogens on the cervix.

Materials and Methods

In this experiment, twenty CD-1 mice were treated with daily doses of DES ranging from .01 to 100 µg/kg on days 9 to 16 of gestation. These doses equal those given to pregnant women. Both female and male offspring were born on day 19 of gestation. Female mice were sacrificed at 12 to 18 months of age to assess the long-term effects of prenatal DES exposure and their reproductive tract tissues were examined for histological alterations.

Results

After day 19 of gestation, structural abnormalities were observed in the cervix, which contributed to subfertility. After the sacrifice of female mice at 12 to 18 months of age, the cervix of the DES-exposed offspring was found to be enlarged. A variety of abnormalities such as leiomyoma, papilloma, stromal cell sarcoma, epithelial atypia, and leiomysarcoma were also found. These findings in mice are relevant to similarly exposed humans, as many abnormalities that occurred in mice also occurred in humans. The extreme sensitivity of the developing fetus is demonstrated here. It is suggested that this sensitivity is due to undeveloped DNA repair mechanisms, an immature immune system, lack of detoxifying enzymes, increased metabolic rate, and more. DES is also thought to possess mutagenic potential, allowing harmful effects to be passed down to the granddaughters of DES-exposed individuals.

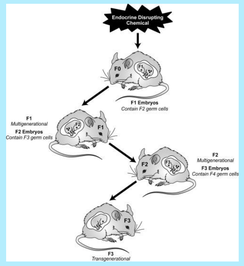

Figure 1. Exposure to a endocrine-disrupting hormone causes epigenetic change, which can alter the germ cell line causing subsequent generations to be afflicted.
Schug, T. (2011) Endocrine disrupting chemicals and disease susceptibility. Retrieved from http://www.sciencedirect.com/science/article/pii/S096007601100166X.

Discussion

Today DES and its detrimental effects are a particular concern as the DES-exposed children are just reaching middle-aged, and many of the long-term effects are starting to appear. It can be concluded that prenatal DES-exposure causes significant changes in the cervix of both mothers and daughters. It increases risks of cervical neoplasia by 2.3 times, which is the growth of abnormal precancerous cells on the surface of the cervix. When untreated, it can lead to cervical cancer. DES-exposed women also reported a incompetent cervix, which could lead to second trimester pregnancy losses. Prenatal DES exposure has been found to cause structural abnormalities of the cervix. DES's mutagenic potential is particularly alarming for the offspring of DES-exposed women, as these abnormalities may appear in their children as well. It accomplishes this feat by altering the genes of the target cells. If the change occurs in germ line cells, the effects may carry onto the next generation. A possible reason for this is DES's ability to cause epigenetic change is its capability for altering genes.

This process involves the addition of methyl groups to specific bases in specific parts of genes. It has been shown to regulate gene expression, meaning it underlies cell differentiation. DES causes persistent epigenetic changes to some genes and not others, thus, altering the fate of certain tissues and organs. Thus, it can be concluded from evidence from the experiment that fetal exposure to DES causes several abnormalities of the cervix, including cervical cancer due to its mutagenic and epigenetic ability.

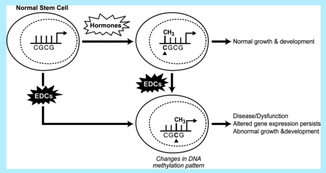

Figure 2. Model depicts epigenetic programming in cells. Alterations in somatic cells leads to disease in developing tissues. Alterations in stem cells cause effects to pass onto offspring. Schug, T. Endocrine disrupting chemicals and disease susceptibility. Retrieved from http://ars.els-cdn.com/content/image/1-s2.0-S096007601100166X-gr4.gif.

Relevant Applications to Biotechnology

DES is not unique. Several other environmental hormones have been tested at equal doses and results have been similar to those caused by DES. Studies on mice are effective due to less ethical issues, and well as cost-convenience as well as rapid reproduction rates. Through tests on mice, insight may be gained to prevent a widespread distribution of harmful estrogens from occurring again. With this knowledge, more effective cures may be developed, therefore increasing the number of cervical cancer survivors.

Acknowledgements

A sincere thanks to Dr. Ericka Senegar-Mitchell, Patricia Winter, Dr. Saunders, Dr. Chang, and all my OSA sisters for all their guidance and support.

References

1 McLachlan, J., Newbold, R., Bullock, B. (1979, November 20) Long-Term Effects on the Female Mouse Genital Tract Associated with Prenatal Exposure to Diethylstilbestrol. In aacrjournals.org. Retrieved July 24, 2012, from http://cancerres.aacrjournals.org/content/40/11/3988.short.

3 McLachlan, J. (2006) *Commentary: Prenatal exposure to diethylstilbestrol (DES): a continuing story.* Advance Access Publication. Retrieved July 23, 2012, from http://ije.oxfordjournals.org/content/35/4/868.full.pdf+html

2 Newbold, R., Padilla-Banks, E., Jefferson, W. (2005, September 12) Adverse Effects of the Model Environmental Estrogen Diethylstilbestrol Are Transmitted to Subsequent Generations. In endojournals.org. Retrieved July 23, 2012, from http://endo.endojournals.org/content/147/6/s11.short.

5 Newbold R. (1995 March 15) Cellular and Molecular Effects of Developmental Exposure to Diethylstilbestrol: Implications for Other Environmental Estrogens. In ncbi.nlm.nih.gov. Retrieved July 27, 2012, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1518878/pdf/envhper00367-0085.pdf.

4 Yoshida, A., Newbold, R., Dixon, D. (1999, May 1) Effects of Neonatal Diethylstilbestrol (DES) Exposure on Morphology and Growth Patterns of Endometrial Epithelial Cells in CD-1 Mice. In sagepub.com. Retrieved July 23, 2012, from http://tpx.sagepub.com/content/27/3/325.full.pdf+html.