The Effects of Diethylstilbestrol on Embryonic Development [1]

By: Cooper-Roth, Tristan Keywords: Estrogen [2] Human development [3]

Estrogen plays a key role in the regulation [5] of gene transcription. This is accomplished by its ability to act as a ligand and to bind to specific estrogen receptor [6] (ER) molecules, such as ERα and ERβ, which act as nuclear transcription factors. There are three major nuclear estrogen receptor [6] protein domains: the estrogen [7] binding domain, the protein interaction domain, and the DNA binding domain. The domain responsible for the regulation [5] of transcription is the DNA binding domain, which binds to DNA sequences called estrogen [7]-responsive elements (EREs), found in enhancer regions of specific genes [8]. By the binding of estrogen [7] or an estrogen [7] mimic to these enhancers, the target genes [8] become activated and the proteins produced are involved in numerous cellular processes. With an estrogen [7] mimic or xenoestrogen [9], such as diethylstilbestrol (DES), the negative regulation [5] of certain genes [8] during embryonic development can be devastating to the developing anatomy, especially the reproductive system.

DES was first synthesized by Sir Charles Dodds [10] and colleagues in 1938, two years after their creation of a similar chemical named bisphenol A [11] (BPA). DES was also found to be an effective estrogen [7] mimic, and was mainly prescribed to pregnant women to alleviate hormonal imbalances that could potentially lead to miscarriage [12] or premature labor [13]. Advertised as a "miracle drug," this artificially synthesized xenoestrogen [9] in fact produced in serious side effects in developing fetuses, side effects that the US Food and Drug Administration [14] (FDA) failed to identify.

A controlled, double-blind study involving 1,646 women at the University of Chicago [15], conducted by William J. Dieckmann [16] and colleagues in 1953, showed that DES provided no improvement to pregnancy [17] outcome. Even with this evidence, doctors continued to prescribe the drug for use during pregnancy [17] for almost another two decades. Then in 1971 Arthur Herbst [18] and Robert Scully [19] published the results of a study of women who had been exposed to DES during their eighteenth week of development in the womb [20]. Herbst and Scully found clear cell adenocarcinoma (CCA) of the vagina [21] and the cervix [22] of many of these now-adult women. CCA in young women came as a rather odd finding because this type of cancer is rarely seen in younger women. The basis for an apparent association between DES exposure *in utero* and a potential genital abnormality was then established, thus giving ample reason for its banning by the FDA in 1971. An estimated one million fetuses were exposed to DES between the years 1947 to 1971, providing a paradigmatic model of how synthesized chemicals disrupt endocrine functionality and negatively affect sexual organ development *in utero*.

Specific regions, such as the mullerian duct [23] in the female reproductive system, develop by the dictation of *HOXA* gene expression. Hox genes [24], found on human chromosome 7 [25], are a conserved group of genes [8] that specify axis and pattern formation [26] during embryonic development. Specifically, *HOXA-9*, *10*, *11*, and *13* are responsible for pattern formation [26] in the female reproductive system. To understand how xenoestrogens affect sexual development, in respect to these genes [8], Gail V. Benson and colleagues studied the effects of DES on the female mouse [27] reproductive tract in 1996. They found that DES-affected female offspring had an altered *Hoxa-10* expression in the mullerian duct [23]. They then pinpointed where DES affects the female reproductive system by finding *Hoxa-10* repression predominantly in the mesenchyme [28] of the oviduct [29]. By this repression, the proximal quarter of the uterus [30] transforms into oviduct [29] tissue, which results in a deformity between the uterus [30] and the oviduct [29].

The mechanism behind *Hoxa-10* gene repression in these regions can be linked to Wnt protein [31] signaling. The Wnt7a protein, responsible for cell proliferation and the prevention of apoptosis [32], is found in the epithelium [33] and communicates with *Hoxa-10* in the mesenchyme [28] to become transcriptionally active. Wnt7a also induces expression of the *Wnt5a* gene, which encodes for a protein responsible for cell proliferation, as well as the maintenance of *Wnt7a* gene expression. With DES inducing a hyperestrogenic state upon the developing embryo, the Wnt7a pathway becomes repressed leading to the repression of *Hoxa-10* and *Wnt5a*. This then leads to improper cell specification and disorganization of the smooth muscle through uterine cell death.

The *Wnt* pathway may also play a role in regulating embryonic development epigenetically by means of DNA methylation [34]. DNA methylation [34] directly affects the stability of the chromosome and gene expression by the addition of methyl groups to the DNA backbone. The effects of DNA methylation [34] on female mice were tested by Sheng Li [35] and colleagues in 2003. They showed that DES exposure to mice during the critical stages of sexual reproductive organ development *in utero* resulted in

abnormal DNA methylation [34] patterns in the promoters of estrogen [7] responsive genes [8]. This leads to an unusual expression of genes [8] in these organs. Abnormal DNA methylation [34] patterns are also seen in tumors, such as clear cell adenocarcinoma.

Sources

1. Gail V. Benson, Hyunjung Lim, B. C. Paria, Ichiro Satokata, Sudhansu K. Dey, and Richard L. Maas. “Mechanisms of Reduced Fertility in Hoxa-10 Mutant Mice: Uterine Homeosis and Loss of Maternal Hoxa-10 expression.” *Development* 122 (1996): 2687–96.
2. Gilbert, Scott F. *Developmental Biology* [36], 8th ed. Sunderland, MA; Sinauer Associates, 2006, 671–72.
3. Li, Sheng, S. D. Hursting, B. J. Davis, J. A. McLachlan, and J. C. Barrett. “Environmental Exposure, DNA Methylation and Gene Regulation: Lessons from Diethylstilbestrol-Induced Cancers.” *Annals of the New York Academy of Sciences* 983 (2003): 161–69.

Estrogen plays a key role in the regulation of gene transcription. This is accomplished by its ability to act as a ligand and to bind to specific estrogen receptor (ER) molecules, such as ERα and ERβ, which act as nuclear transcription factors. There are three major nuclear estrogen receptor protein domains: the estrogen binding domain, the protein interaction domain, and the DNA binding domain. The domain responsible for the regulation of transcription is the DNA binding domain, which binds to DNA sequences called estrogen-responsive elements (EREs), found in enhancer regions of specific genes. By the binding of estrogen or an estrogen mimic to these enhancers, the target genes become activated and the proteins produced are involved in numerous cellular processes. With an estrogen mimic or xenoestrogen, such as diethylstilbestrol (DES), the negative regulation of certain genes during embryonic development can be devastating to the developing anatomy, especially the reproductive system.

Subject
Diethylstilbestrol [37] Diethylstilbestrol [38]

Topic
Disorders [39]

Publisher
Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

Rights
© Arizona Board of Regents Licensed as Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported (CC BY-NC-SA 3.0) http://creativecommons.org/licenses/by-nc-sa/3.0/

Format
Articles [40]

Last Modified
Wednesday, July 4, 2018 - 04:40

DC Date Accessioned
Thursday, May 10, 2012 - 14:06

DC Date Available
Thursday, May 10, 2012 - 14:06

DC Date Created
2010-09-12

DC Date Created Standard
Sunday, September 12, 2010 - 07:00

- Contact Us

© 2019 Arizona Board of Regents

- The Embryo Project at Arizona State University, 1711 South Rural Road, Tempe Arizona 85287, United States

---

Source URL: https://embryo.asu.edu/pages/effects-diethylstilbestrol-embryonic-development

Links
[1] https://embryo.asu.edu/pages/effects-diethylstilbestrol-embryonic-development
[2] https://embryo.asu.edu/keywords/estrogen
[3] https://embryo.asu.edu/keywords/human-development
[4] https://embryo.asu.edu/search?text=The%20Effects%20of%20Diethylstilbestrol%20on%20Embryonic%20Development
[5] https://embryo.asu.edu/search?text=regulation
[6] https://embryo.asu.edu/search?text=estrogen%20receptor
[7] https://embryo.asu.edu/search?text=estrogen
[8] https://embryo.asu.edu/search?text=genes
[9] https://embryo.asu.edu/search?text=xenoestrogen
[10] https://embryo.asu.edu/search?text=Charles%20Dodds
[11] https://embryo.asu.edu/search?text=bisphenol%20A
[12] https://embryo.asu.edu/search?text=miscarriage
[13] https://embryo.asu.edu/search?text=premature%20labor
[14] https://embryo.asu.edu/search?text=Food%20and%20Drug%20Administration
[15] https://embryo.asu.edu/search?text=University%20of%20Chicago
[16] https://embryo.asu.edu/search?text=William%20J.%20Dieckmann
[17] https://embryo.asu.edu/search?text=pregnancy
[18] https://embryo.asu.edu/search?text=Arthur%20Herbst
[19] https://embryo.asu.edu/search?text=Robert%20Scully
[20] https://embryo.asu.edu/search?text=womb
[21] https://embryo.asu.edu/search?text=vagina
[22] https://embryo.asu.edu/search?text=cervix
[23] https://embryo.asu.edu/search?text=mullerian%20duct
[24] https://embryo.asu.edu/search?text=Hox%20genes
[25] https://embryo.asu.edu/search?text=human%20chromosome%207
[26] https://embryo.asu.edu/search?text=pattern%20formation
[27] https://embryo.asu.edu/search?text=mouse
[28] https://embryo.asu.edu/search?text=mesenchyme
[29] https://embryo.asu.edu/search?text=oviduct
[30] https://embryo.asu.edu/search?text=uterus
[31] https://embryo.asu.edu/search?text=Wnt%20protein
[32] https://embryo.asu.edu/search?text=apoptosis
[33] https://embryo.asu.edu/search?text=epithelium
[34] https://embryo.asu.edu/search?text=DNA%20methylation
[35] https://embryo.asu.edu/search?text=Sheng%20Li
[36] https://embryo.asu.edu/search?text=Developmental%20Biology
[37] https://embryo.asu.edu/library-congress-subject-headings/diethylstilbestrol
[38] https://embryo.asu.edu/medical-subject-headings/diethylstilbestrol
[39] https://embryo.asu.edu/topics/disorders
[40] https://embryo.asu.edu/formats/articles