Saudi Journal of Biological Sciences 27 (2020) 3655–3659

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

Developmental exposure to endocrine disrupter dichlorodiphenyltrichloroethane alters transcriptional regulation of postnatal morphogenesis of adrenal zona fasciculata

Nataliya Yaglova *, Sergey Obernikhin, Svetlana Nazimova, Valentin Yaglov

Laboratory of Endocrine System Development, Federal State Budgetary Institution Research Institute of Human Morphology, 117418, Tsurupa st., 3, Moscow, Russia

ARTICLE INFO

Article history:
Received 13 December 2019
Revised 4 August 2020
Accepted 5 August 2020
Available online 13 August 2020

Keywords:
Dichlorodiphenyltrichloroethane
Zona fasciculata
Adrenal gland
Oct4
Sonic hedgehog
Wnt signaling

ABSTRACT

The present study is aimed to validate expression of transcriptional factors mediating postnatal development of adrenal zona fasciculata in rats exposed to low doses of endocrine disrupter dichlorodiphenyltrichloroethane prenatally and postnatally. Histological and immunohistochemical examination of the adrenals was performed. Impaired blood circulation, dystrophy and cell death were found in zona fasciculata of pubertal rats after developmental exposure to low doses of dichlorodiphenyltrichloroethane. Reparation of zona fasciculata was associated with increased number of Sonic hedgehog- and Oct4-expressing adrenal cortical cells but not in areas of regeneration. These data suggest that cell death may promote upregulation of factors inducing and maintaining pluripotent state in fasciculata cells for restoration of tissue homeostasis. Termination of growth of the adrenals after puberty was associated with upregulation of antiproliferative factor Hhex and decrease of cell proliferation. Dichlorodiphenyltrichloroethane exposure disrupted transcriptional control of cell proliferation by downregulation of Hhex expression in fasciculata cells. Decrease of proliferation in the exposed rats was mediated by inhibition of Sonic hedgehog and Oct4 expression and suppression of canonical Wnt signaling. The present study elucidated an alternative mechanism of proliferation control activated by endocrine disrupter dichlorodiphenyltrichloroethane through transition of fasciculata cells from pluripotent state and higher proliferative potential to differentiation. Activation of the alternative mechanism of growth control may probably affect maintenance of tissue homeostasis of zona fasciculata in postnatal development.

1. Introduction

Exposure to endocrine disrupters in humans and wild life is a global problem. World Health organization and International Programme of Chemical Safety defined adverse effects of endocrine disrupters as "a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences" [WHO, 2012]. Some endocrine disrupters have demonstrated the ability to interfere with epigenetic regulation of prenatal developmental processes [Walker and Gore, 2011; Li et al., 2014; Martinez-Arguelles and Papadopoulos, 2015; Cianfarani and Soder, 2016; Alavian-Ghavanini and Ruegg, 2018; Skinner et al., 2018]. Less knowledge on transcriptional regulation of postnatal morphogenetic processes in endocrine glands complicates further elucidation of impact of endocrine disrupter exposure on human health. Dichlorodiphenyltrichloroethane (DDT) is one of the most widespread endocrine disrupting chemical on the planet [WHO, 2017]. It was extensively used in the 20th century as a pesticide and still is used for vector disease control under recommendations of World Health Organization [WHO, 2011]. Detectable levels of DDT metabolites are still found in 90% blood and urine samples of children and their mothers even in countries, which banned use of DDT in 1970th [Haug et al., 2018]. Ubiquitous persistence of DDT and its metabolites provides daily low-dose exposure on

* Corresponding author.
E-mail address: yaglova@mail.ru (N. Yaglova).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2020.08.009
1319-562X/

humans and endocrine disruption of steroid hormone function [Zoeller et al., 2012]. DDT has been found to affect androgen signaling by bounding androgen receptors and induce malformations of reproductive system [Zoeller et al., 2012; De Falco et al., 2015]. Impact of low-dose DDT exposure on development of adrenal glands is less studied. Our previous studies revealed patterns of β-catenin postnatal expression in the rat adrenal cortex and its alterations evoked by developmental exposure to endocrine disrupter (DDT) [Tsomartova et al., 2018; Obernikhin et al., 2019]. These data indicate initiation of another, different from normal developmental program, mechanism of cell proliferation and differentiation control in the adrenal gland. Morphogenesis and self-renewal of tissues is known to be provided by maintenance or migration of pluripotent cells and regulation of cell division and maturation. The present study was focused on expression of transcriptional factors regulating postnatal morphogenesis of adrenal zona fasciculata in rats after developmental exposure to endocrine disrupter DDT.

2. Materials and methods

2.1. Laboratory animals and experimental design

Wistar rats were obtained from Scientific center of biomedical technologies of Federal Medical and Biological Agency of Russia. The rats were housed at +22–23 °C with a 12/12-hr light-dark cycle and given a pelleted standard chow ad libitum.

The female rats received solution of o,p-DDT 20 μg/l ("Sigma-Aldrich", USA) ad libitum instead of tap water since mating during pregnancy and lactation. After weaning the progeny of the rat dams received the same solution of o,p-DDT during postnatal development. The main experimental group included male Wistar rats (n = 20) exposed to low doses of o,p-DDT prenatally and postnatally (group PPE) and sacrificed at 42nd day, which corresponds to pubertal period when adrenals develop intensively, and 70th day of postnatal development when adrenal cortex reaches its maximal size [Pignatelli et al., 2006]. An additional group of male Wistar rats (n = 20) exposed to DDT only during postnatal development (group PE) was included in the experiment to differentiate outcomes of prenatal exposure. The postnatally exposed rats were sacrificed at the same age of 42nd and 70th days. The average daily DDT consumption by the pregnant dams was 2.70 ± 0.19 μg/kg, the lactating dams – 2.47 ± 0.11 μg/kg, by the offspring – 3.30 ± 0.14 μg/kg. The received doses correspond to rates of daily dietary exposure of humans to DDT [WHO, 2017]. The male offspring of intact rat dams (n = 32) was used as a control.

2.2. Histology

The adrenal glands were fixed in Bouen solution. After histological processing the adrenals were embedded in paraffin. Sections of the adrenals were stained with haematoxylin and eosin. Only equatorial sections were used for examination. Morphological parameters of zona fasciculata were assessed using "Image Scope Color" software (Leica Microsystems Gmbh).

2.3. Immunohistochemistry

Expression of transcriptional factors Oct4, Sonic hedgehog (Shh), Hhex, as well as β-catenin and Ki-67 in zona fasciculata were determined by immunohistochemistry with polyclonal rat antibodies (Abcam).

After antigen retrieval with 10 mM sodium citrate (pH 6.0) endogenous peroxidase and endogenous immunoglobulins were blocked with Hydrogen Peroxide Block and Protein Block (Thermo Fisher Scientific). The slides were incubated with primary antibodies Oct4 (1:5000, Abcam, USA), Shh (1:Abcam, USA), Hhex (1:Santa Cruz Biotechnology, USA), β-catenin (1:100, Cell Marque, USA), Ki-67 (1:100, Cell Marque, CA, USA) overnight at 8 °C. The reaction was visualized with UltraVision LP Detection System reagent kit (Thermo Fisher Scientific, USA) according to manufacturer's recommendations. The sections were counterstained with Mayer's haematoxylin.

2.4. Evaluation of the immuohistichemical reactions

Expression oh Hhex was assessed as a percent of immunopositive cells. Because lower rate of Oct4- and Shh-positive cells they were expressed as a number in 1 mm^2 of zona fasciculata. Activation of canonical Wnt signaling was assessed by percent of fasciculata cells with β-catenin positive nuclei revealed by immunohistochemical reaction with monoclonal antibodies (Cell Marque) [Berthon et al., 2012; Kim et al., 2013]. Rate of cell proliferation was determined by calculation of percent of Ki-67-positive cells (Cell Marque). The immunohistochemical reactions were visualized with "UltraVision LP Detection System" (ThermoScientific).

2.5. Statistical analysis

The data were processed using Statistica 7.0 software (StatSoft, Inc.). Quantitative data were expressed as mean and standard error of mean (M ± m). Comparison of the groups was performed using one way ANOVA and Student's *t*-test. The differences were significant at $p < 0.01$.

3. Results

3.1. Age-dependent dynamics of adrenal cortex morphology

The examination of histological sections of the control adrenals revealed significant enlargement of zona fasciculata and reduction of cell proliferation activity with age (Table 1).

The size of zona fasciculata in adrenal cortex of DDT-exposed rats did not differ from the control rats at the age of 42 days (Table 1). Prenatally and postnatally exposed rats exhibited microcirculatory disorders like dilated and obturated by red blood cells capillaries in the outer layer of zona fasciculata. Local dystrophy and death of cortical cells associated with impaired microcirculation were found. Histological examination also revealed areas of tissue reparation with diffusely located cells and cells which began to form typical bundle architectonics. Proliferative activity of the

Table 1
Changes in zona fasciculata morphology of DDT-exposed rats (mean ± SE).

Age	Group	Surface size of zona fasciculata, mm^2	Ki-67(+) cells, %	Diameter of capillaries, μm
42 days	control	2.32 ± 0.15	4.07 ± 0.15	3.16 ± 0.11
	Prenatal and postnatal exposure	2.42 ± 0.08	5.64 ± 0.29*	3.63 ± 0.13*
	Postnatal exposure	2.35 ± 0.16	4.50 ± 0.25+	3.25 ± 0.12
70 days	control	3.68 ± 0.15#	1.26 ± 0.11#	2.39 ± 0.05#
	Prenatal and postnatal exposure	3.68 ± 0.20#	0.99 ± 0.09#	3.33 ± 0.16*
	Postnatal exposure	3.22 ± 0.18*#	1.66 ± 0.12+#	2.80 ± 0.13*+#

Note: statistically significant changes compared: * – to the control group of appropriate age, + – to prenatally and postnatally exposed rats, # – to 42nd day.

fasciculata cells exceeded the control values (Table 1). Ki-67-positive cells were found mainly in unaffected regions of zona fasciculata but in areas of reparation proliferating cells were rarely seen (Fig. 1). Postnatally exposed rats showed similar but less pronounced histological changes and no significant increase in rate of proliferation (Table 1).

On the 70th day of postnatal development the exposed rats also showed increase of zona fasciculata volume with age. Its surface area in the prenatally and postnatally exposed rats did not differ from the control (Table 1). Complete restoration of typical bundle structure of zona fasciculata was observed. Zona fasciculata in the postnatally exposed rats were less developed (Table 1). This

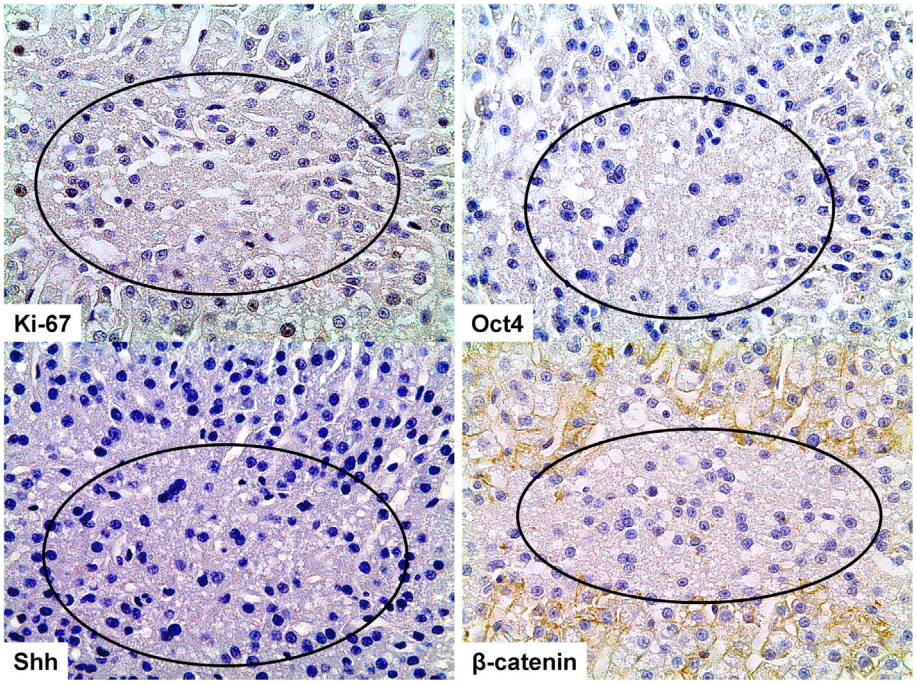

Fig. 1. Absence of proliferating Ki-67-positive cells and downregulated expression of Oct4, Shh, and β-cathenin in areas of reparation in adrenal zona fasciculata of pubertal rats exposed to low doses of DDT during prenatal and postnatal development. Immunohistochemical detection. x400.

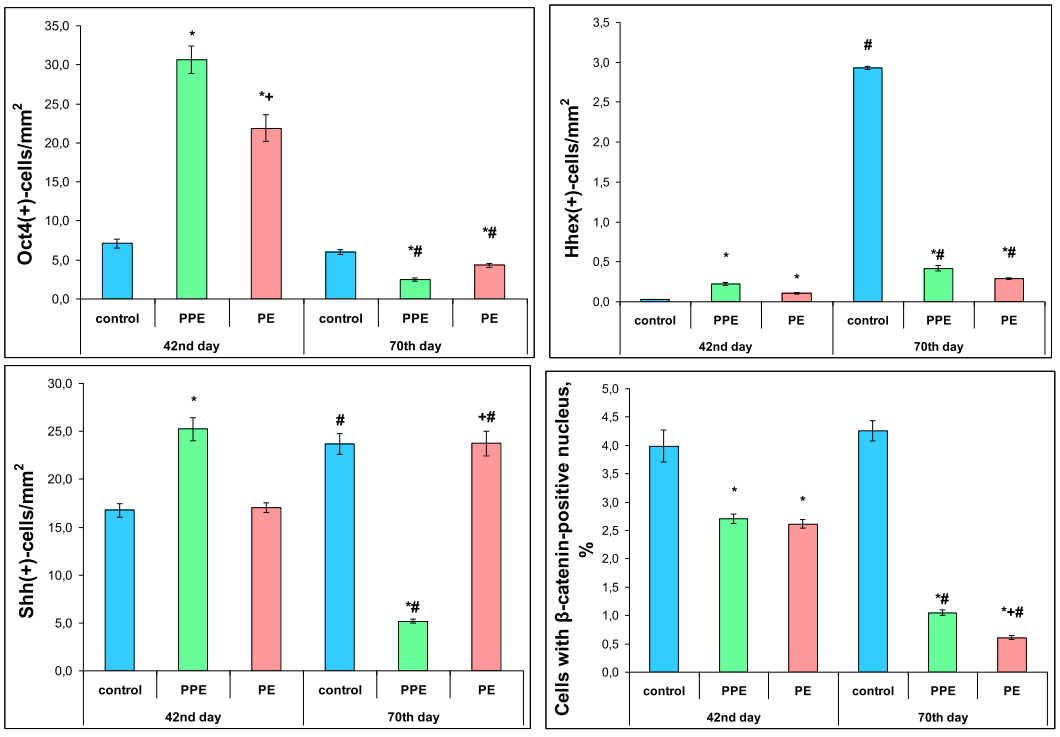

Fig. 2. Age-dependent changes in expression of the transcriptional factors Oct4, Hhex, Shh and translocation of β-catenin to nucleus in adrenal zona fasciculata cells after developmental exposure to low doses of DDT as confirmed by immunohistochemical evaluation (mean ± SE). Statistically significant changes compared: * – to the control group of appropriate age, + – to prenatally and postnatally exposed rats, # – to 42nd day.

group demonstrated local cell death and reparation of zona fasciculata, and, consequently, higher cell proliferation than the previous group. Reduction of proliferation rate was found in both experimental groups and no significant differences in the percent of Ki-67-positive cells between the exposed and the control rats were found (Table 1).

Immunohistochemical detection revealed Oct4-positive cells both in inner and outer layers of zona fasciculata of the control rats. Their number did not change with age (Fig. 2). All DDT-exposed rats demonstrated higher content of Oct4-expressing cells in zona fasciculata except areas of reparation. Unlike the control the both experimental groups showed significant age-dependent down-regulation of Oct4 expression. On the 70th day the exposed rats had less number of Oct4-positive cells in zona fasciculata (Fig. 2).

Evaluation of Shh revealed prevalence of number of Shh-positive cells over Oct4 expressing cells in zona fasciculata of the control animals (Fig. 2). Unlike Oct4 number of Shh-positive cells increased with age. They were diffusely distributed throughout zona fasciculata. Postnatally exposed rats demonstrated the same pattern of Shh expression (Fig. 2). Prenatally and postnatally exposed rats showed elevated expression of Shh on the 42nd day followed by downregulation of expression on the 70th day. Single Shh-positive cells were observed in areas of reparation (Figs. 1 and 2).

Hhex-positive cells in zona fasciculata of the control animals were rarely seen on the 42nd day but on the 70th day their number significantly increased (Fig. 2). Higher number of Hhex-expressing cells was found on the 42nd day in both experimental groups. Age-dependent increase of Hhex expression in the exposed rats was less pronounced. On the 70th day of postnatal development the exposed rats demonstrated lower content of Hhex-positive cells in zona fasciculata. No significant differences in number of Hhex-expressing cells were found between the groups of prenatal and postnatal and only postnatal exposure to DDT (Fig. 2).

Evaluation of fasciculata cells with β-catenin-positive nuclei in the control rats on the 42nd and 70th days of postnatal development revealed absence of age-dependent changes in their percentage (Fig. 2). The exposed rats showed lowered content of cells with β-catenin-positive nuclei both on the 42nd and 70th day. Number of cells with β-catenin-positive nuclei in areas of reparation were extremely low (Fig. 1). Unlike the control transition of β-catenin into the nucleus decreased with age in the DDT-exposed animals (Fig. 2).

4. Discussion

Histological examination of adrenal glands showed that prenatal and postnatal exposure to low doses of DDT did not significantly alter postnatal development of zona fasciculata, but initiated cell death in pubertal period when zona fasciculata actively grows. Our previous investigations found that developmental exposure to DDT reduces production of adrenal epinephrine [Yaglova et al., 2018]. It resulted in compensatory redirection of venous blood from the adrenal medulla to cortical blood vessels and vena porta which produced microcirculatory disorders in zona glomerulosa and outer layer of zona fasciculata, dystrophia and death of fasciculata cells [Yaglova et al., 2019]. Cell death triggered reactive increase of proliferation activity and consequently of proliferation control by upregulation of Hhex expression. Reparation of zona fasciculata requires activation of cell differentiation. Wnt signaling is known as one of the key signaling pathways regulating cell growth and differentiation [El Wakil and Lalli, 2011]. Activation of gene transcription is stimulated by nuclear accumulation of β-catenin [Fuerer et al., 2008]. Canonical Wnt signaling is an essential factor of formation of adrenal zona glomerulosa, but its role in development and function of zona fasciculata is still poorly understood [Drelon et al., 2015]. Recent findings have demonstrated that Wnt signaling may inhibit fasciculata cell differentiation [Walczak et al., 2014]. The results of the present study showed that normal development of the rat adrenal gland was associated with stable level of activation of canonical Wnt signaling pathway, and termination of adrenal cortex growth by the 70th day did not change percentage of cells with β-catenin-positive nuclei. Developmental exposure to DDT downregulated activation of Wnt signaling on the 42nd day, when reparation of fasciculata cells was observed along with cell death, and especially on the 70th day when zona fasciculata had completely restored structure. The postnatally exposed rats demonstrated later development of lesions in zona fasciculata and their reparation accompanied by more pronounced down-regulation of Wnt signaling on the 70th day. These facts indicate that reparation of zona fasciculata requires inhibition of Wnt signaling pathway and provide further support of the hypothesis of attenuation of fasciculata cell differentiation by canonical Wnt signaling.

Expression Oct4, a transcription factor controlling early stages of mammalian embryogenesis, is associated with pluripotent properties of embryonic stem cells [Boiani and Scholer, 2005; Zeineddine et al., 2014]. Involvement of this protein in postnatal morphogenesis and regeneration is still unclear. Shh is a member of hedgehog signaling pathway with well known mitogenic and morphogenic function during embryonic development [Ingham et al., 2011; Laufer et al., 2012]. Recent studies demonstrate implication of Shh signaling in regulation of adult stem cells involved in physiological regeneration of adult tissues [Shin et al., 2011; Peng et al., 2013; Petrova and Joyner, 2014; Penni et al., 2017; Das et al., 2020]. Low proliferation rate in adrenal cortex of Shh mutants supports the idea that Shh is implicated in regulation of adult tissue homeostasis [Ching and Vilain, 2009]. Role of Shh signaling in the three zones of adrenal cortex during normal postnatal development is still to be elucidated. Our findings demonstrate presence of Oct4 and Shh in the nuclei of fasciculata cells indicating their pluripotent potential. Constant number of Oct4- and increasing with age content of Shh-positive cells found in the control rats suggest implication of cells with pluripotent potential in postnatal development and function of zona fasciculata. Activation of Oct4 and Shh expression in zona fasciculata beyond the areas of reparation found in DDT-exposed animals in pubertal period when zona fasciculata intensively grows proves that increased number of cells with pluripotent potential is required both for development and maintenance of tissue homeostasis. Termination of growth and reparation in zona fasciculata by the 70th day in the prenatally and postnatally exposed rats was found to be associated with decrease in number of Oct4- and Shh-expressing cells. It indicates that restoration of cell mass depletes the pool required for fasciculata cell turnover.

Comparative analysis of different regimens of exposure to DDT revealed earlier development of changes in morphology and expression of transcription factors in rats exposed during prenatal and postnatal period, which was probably caused by earlier initiation of microcirculatory disorders and cell death. Similar to control pattern of Shh expression in postnatally exposed rats and age-dependent changes in of Oct4 expression like in prenatally and postnatally exposed rats indicate later implication of Shh signaling in regulation of postnatal morphogenesis. Inhibition of proliferation on the 70th day in the control rats was associated with overexpression of antiproliferative factor Hhex. The DDT-exposed rats demonstrated more profound decrease of cell proliferation rate but significantly smaller increase of Hhex-expressing cells with age. It discloses a putative mechanism of dysregulation of morphogenesis by the endocrine disrupter DDT. Our findings provide support for the idea that termination of zona fasciculata growth

in the DDT-exposed rat is mediated by inhibition of canonical Wnt signaling pathway required for fasciculata cell differentiation and downregulation of Oct4 and Shh, i.e. factors inhibiting differentiation and increasing cell proliferation potential. In the prenatally and postnatally exposed rats depletion of reserve pool of Oct4- and Shh-expressing cells resulted in more pronounced inhibition of cell proliferation in zona fasciculata compared to the postnatally exposed rats. In the latter later onset of circulatory disorders and cell death contributed to a slower rate of postnatal development of zona fasciculata. Higher proliferation rates in postnatally exposed rats on the 70th day might be mediated by overexpression of Shh.

Thus, developmental exposure to endocrine disrupter alters transcriptional regulation of morphogenetic processes in adrenal zona fasciculata. Reparation of DDT-induced lesions requires activation of Oct4 and Shh expression throughout zona fasciculata. Exposure to DDT also impairs expression of antiproliferative factor Hhex and changes pattern of proliferative control after termination of adrenal development for inhibition of proliferation by downregulation of factors responsive for transition and maintenance of low-differentiated state of cells like Oct4, Shh, and canonical Wnt signaling pathway. This pattern suggests reduction of pool of cells in zona fasciculata required for tissue self renewal. Exposure to the endocrine disrupter from prenatal period results in earlier depletion of the pool of cells maintaining tissue homeostasis.

Funding

The research was financially supported by the Ministry of Science and Higher Education of the Russian Federation (No. AAAA-A17-117013050048-6).

Declaration of Competing Interest

None declared conflict.

References

Alavian-Ghavanini, A., Ruegg, J., 2018. Understanding epigenetic effects of endocrine disrupting chemicals: from mechanisms to novel test methods. Basic Clin. Pharmacol. Toxicol. 122, 38–45. https://doi.org/10.1111/bcpt.12878.

Berthon, A., Martinez, A., Bertherat, J., Val, P., 2012. Wnt/b-catenin signalling in adrenal physiology and tumour development. Mol. Cell. Endocrinol. 35, 87–95. https://doi.org/10.1016/j.mce.2011.09.009.

Boiani, M., Scholer, H.R., 2005. Regulatory networks in embryo-derived pluripotent stem cells. Nat. Rev. Mol. Cell Biol. 6, 872–884. https://doi.org/10.1038/nrm1744.

Ching, S., Vilain, E., 2009. Targeted disruption of Sonic hedgehog in the mouse adrenal leads to adrenocortical hypoplasia. Genesis. 47, 628–637. https://doi.org/10.1002/dvg.20532.

Cianfarani, S., Soder, O., 2016. Endocrine disrupters and children health. Horm. Res. Paediatr. 86, 212–220. https://doi.org/10.1159/000449273.

Das, D., Fletcher, R., Ngai, J., 2020. Cellular mechanisms of epithelial stem cell self-renewal and differentiation during homeostasis and repair. Wiley Interdiscip. Rev Dev. Biol. 9,. https://doi.org/10.1002/wdev.361 e361.

De Falco, M., Forte, M., Laforgia, V., 2015. Estrogenic and anti-androgenic disrupting chemicals and their impact on the male reproductive system. Front. Environ. Sci. 3, Art. 3. https://doi.org/10.3389/fenvs.2015.00003.

Drelon, C., Berthon, A., Mathieu, M., Martinez, A., Val, P., 2015. Adrenal cortex tissue homeostasis and zonation: A WNT perspective. Mol. Cell. Endocrinol. 408, 156–164. https://doi.org/10.1016/j.mce.2014.12.014.

El Wakil, A., Lalli, E., 2011. The Wnt/beta-catenin pathway in adrenocortical development and cancer. Mol. Cell. Endocrinol. 332, 32–37. https://doi.org/10.1016/j.mce.2010.11.014.

Fuerer, C., Nusse, R. Ten, Berge, D., 2008. Wnt signalling in development and disease. Max Delbruck Center for Molecular Medicine meeting on Wnt signaling in Development and Disease. EMBO Rep. 9, 134–138. https://doi.org/10.1038/sj.embor.7401159.

Haug, L., Sakhi, A., Cequier, E., Casas, M., Maitre, L., Basagana, X., Andrusaityte, S., Chalkiadaki, G., Chatzi, L., Coen, M., de Bont, J., Dedele, A., Ferrand, J., Grazuleviciene, R., Gonzalez, J., Gutzkow, K., Keun, H., McEachan, R., Meltzer, H., Petraviciene, I., Robinson, O., Saulnier, P., Slama, R., Sunyer, J., Urquiza, J., Vafeiadi, M., Wright, J., Vrijheid, M., Thomsen, C., 2018. In-utero and childhood chemical exposome in six European mother-child cohorts. Environ Int. 121 (Pt 1), 751–763. https://doi.org/10.1016/j.envint.2018.09.056.

Ingham, P.W., Nakano, Y., Seger, C., 2011. Mechanisms and functions of Hedgehog signalling across the metazoa. Nat. Rev. Genet. 12, 393–406. https://doi.org/10.1038/nrg2984.

Kim, W., Kim, M., Jho, E. h. 2013. Wnt/β-catenin signalling: from plasma membrane to nucleus. Biochem. J. 450, 9–21. https://doi.org/10.1042/BJ20121284.

Laufer, E., Kesper, D., Vortkamp, A., King, P., 2012. Sonic hedgehog signaling during adrenal development. Mol. Cell. Endocrinol. 351 (19–27). https://doi.org/10.1016/j.mce.2011.10.002.

Li, Y., Hamilton, K.J., Lay, A.Y., Burns, K.A., Li, L., Wade, P.A., Korach, K.S., 2014. Diethylstilbestrol (DES)-stimulated hormonal toxicity is mediated by ERalpha alteration of target gene methylation patterns and epigenetic modifiers (DNMT3A, MBD2, and HDAC2) in the mouse seminal vesicle. Environ. Health Perspect. 122, 262–268. https://doi.org/10.1289/ehp.1307351.

Martinez-Arguelles, D., Papadopoulos, V., 2015. Mechanisms mediating environmental chemical-induced endocrine disruption in the adrenal gland. Front. Endocrinol. 6, Art. 29. https://doi.org/10.3389/fendo.2015.00029.

Obernikhin S.S., Yaglova N.V., Nazimova S.V., Yaglov V.V., Timokhina E.P. Transcriptional regulation of morphogenesis of rat adrenal zona glomerulosa during postnatal development // Clinical and Experimental Morphology. 2019. Vol. 8 No. 2. P.48-54. https:// doi.org/10.31088/2226-5988-2019-30-2-48-54.

Peng, Y.C., Levine, C.M., Zahid, S., Wilson, E.L., Joyner, A.L., 2013. Sonic hedgehog signals to multiple prostate stromal stem cells that replenish distinct stromal subtypes during regeneration. Proc. Natl. Acad. Sci. USA 110, 20611–20616. https://doi.org/10.1073/pnas.1315729110.

Penni, M., Finco, I., Hammer, G., 2017. Cell signaling pathways in the adrenal cortex: Links to stem/progenitor biology and neoplasia. Mol. Cell. Endocrinol. 445, 42–54. https://doi.org/10.1016/j.mce.2016.12.005.

Petrova, R., Joyner, A., 2014. Roles for Hedgehog signaling in adult organ homeostasis and repair. Development 141, 3445–3457. https://doi.org/10.1242/dev.083691.

Pignatelli, D., Xiao, F., Gouvtia, A., Ferreira, J., Vinson, G., 2006. Adrenarche in the rat. J. Endocrinol. 191, 301–308.

Shin, K., Lee, J., Guo, N., Kim, J., Lim, A., Qu, L., Mysorekar, I.U., Beachy, P.A., 2011. Hedgehog/Wnt feedback supports regenerative proliferation of epithelial stem cells in bladder. Nature 472, 110–114. https://doi.org/10.1038/nature09851.

Skinner, M., Ben Maamar, M., Sadler-Riggleman, I., Beck, D., Nilsson, E., McBirney, M., Klukovich, R., Xie, Y., Tang, C., Yan, W., 2018. Alterations in sperm DNA methylation, non-coding RNA and histone retention associate with DDT-induced epigenetic transgenerational inheritance of disease. Epigenetics and Chromatin. 11, 8. https://doi.org/10.1186/s13072-018-0178-0.

Tsomartova, D.A., Yaglova, N.V., Yaglov, V.V., 2018. Changes in canonical β-catenin/Wnt signaling activation in the adrenal cortex of rats exposed to endocrine disruptor dichlorodiphenyltrichloroethane (DDT) during prenatal and postnatal ontogeny. Bull. Exp. Biol. Med. 164, 4. https://doi.org/10.1007/s10517-018-4019-8. 493–496.

Walczak, E., Kuick, R., Finco, I., Bohin, N., Hrycaj, S., Wellik, D., Hammer, G., 2014. Wnt signaling inhibits adrenal steroidogenesis by cell-autonomous and non-cell-autonomous mechanisms. Mol. Endocrinol. 28, 1471–1486. https://doi.org/10.1210/me.2014-1060.

Walker, D.M., Gore, A.C., 2011. Transgenerational neuroendocrine disruption of reproduction. Nat. Rev. Endocrinol. 7, 197–207. https://doi.org/10.1038/nrendo.2010.215.

World Health Organization. 2012. Endocrine disrupters and child health - Possible developmental early effects of endocrine disrupters on child health. Geneva.

World Health Organization. 2011. The use of DDT in malaria vector control. Geneva.

World Health Organization, 2017. Pesticide residues in food - 2016 evaluations. Part II - Toxicological, Geneva.

Yaglova, N.V., Tsomartova, D.A., Yaglov, V.V., 2018. Effect of prenatal and postnatal exposure to low doses of DDT on catecholamine secretion in rats in different period of ontogeny. Bull. Exp. Biol. Med. 163, 422–424. https://doi.org/10.1007/s10517-017-3819-6.

Yaglova, N.V., Tsomartova, D.A., Obernikhin, S.S., Nazimova, S.V., 2019. The role of the canonical wnt-signaling pathway in morphogenesis and regeneration of the adrenal cortex in rats exposed to the endocrine disruptor dichlorodiphenyltrichloroethane during prenatal and postnatal development. Biology Bulletin. 46, 74–81. https://doi.org/10.1134/S1062359018060122.

Zeineddine, D., Abou Hammoud, A., Mortada, M., Boeuf, H., 2014. The Oct4 protein: more than a magic stemness marker. Am. J. Stem Cells. 3, 74–82.

Zoeller, R.T., Brown, T.R., Doan, L.L., Gore, A.C., Skakkebaek, N.E., Soto, A.M., Woodruff, T.J., Vom Saal, F.S., 2012. Endocrine-disrupting chemicals and public health protection: A statement of principles from The Endocrine Society. Endocrinology 153, 4097–4110. https://doi.org/10.1210/en.2012-1422.