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Review Article

Early-life Exposure to Endocrine Disrupting Chemicals and Later-life Health Outcomes: An Epigenetic Bridge?

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ABSTRACT: A growing body of evidence demonstrates that adverse events early in development, and particularly during intrauterine life, may program risks for diseases in adult life. Increasing evidence has been accumulated indicating the important role of epigenetic regulation including DNA methylation, histone modifications and miRNAs in developmental programming. Among the environmental factors which play an important role in programming of chronic pathologies, the endocrine-disrupting chemicals (EDCs) that have estrogenic, anti-estrogenic, and anti-androgenic activity are of specific concern because the developing organism is extremely sensitive to perturbation by substances with hormone-like activity. Among EDCs, there are many substances that are constantly present in the modern human environment or are in widespread use, including dioxin and dioxin-like compounds, phthalates, agricultural pesticides, polychlorinated biphenyls, industrial solvents, pharmaceuticals, and heavy metals. Apart from their common endocrine active properties, several EDCs have been shown to disrupt developmental epigenomic programming. The purpose of this review is to provide a summary of recent research findings which indicate that exposure to EDCs during in-utero and/or neonatal development can cause long-term health outcomes via mechanisms of epigenetic memory.

Key words: endocrine-disrupting chemicals, developmental programming, epigenetics, adult-life disease

A growing body of evidence demonstrates that events during pre- and post-natal periods of development may have long-term effects on adult health and productivity of organism [1]. The 'developmental origins of adult health and disease' (DOHaD) hypothesis postulates that adverse influences early in development, and particularly during intrauterine life, can program the risks for adverse health outcomes in adult life. The DOHaD concept was initially focused primarily on long-term health outcomes of poor in-utero nutrition. Later, it was extended to other, non-nutritional factors that have been shown to modify the organism's physiology. Early-life exposure to environmental contaminants is among the important risk factors for developmental programming of adult-onset disease in modern humans. A report by the World Health Organization (available at www.who.int/ quantifying_ehimpacts/publications/preventingdisease/en/) estimated that each year there are more than 13 million deaths caused by environmental causes. This report also estimated that almost one third of the burden of mortality and morbidity in less developed regions is due to environmental causes. The list of environmental pollutants hazardous to human health (available at www.cdc.gov/exposurereport/) contains many dozens of environmental chemicals. Most of them are able to cross the placenta and can interact with genetic and epigenetic mechanisms to alter the course of normal development [2]. The endocrine-disrupting chemicals (EDCs) are of specific concern among the detrimental environmental factors because they are widespread in the environment

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and because the developing organism is extremely sensitive to perturbation by substances with hormone-like activity [3, 4]. These substances have been shown to disrupt endocrine function by inhibiting or stimulating the hormone production or changing the way hormones travel through the body, thus affecting the functions that these hormones control. EDCs mainly have estrogenic, anti-estrogenic, and anti-androgenic activity and they act by mimicking or inhibiting the actions of endogenous hormones. Most of EDCs are synthetic chemicals that enter the environment and persist there for long periods of time. Among them, there are many substances that are constantly present in the modern human environment or are in widespread use, including dioxin and dioxin-like compounds, phthalates (plastic-softening chemicals), agricultural pesticides, polychlorinated biphenyls, industrial solvents, pharmaceuticals, and heavy metals [3-7]. EDCs interfere with hormonal biosynthesis, metabolism, or action causing deviations from normal homeostatic control [7]. EDCs have also been shown to influence normal reproductive function, as well as the sex-specific physiology and behavior [5, 6]. Moreover, the effects of EDCs were shown to extend beyond the reproductive and neuroendocrine systems to include multiple adult organs and tissues such as kidney and spleen [8].

Presently, the main focus is on the proximal effects of EDCs on neonatal and childhood outcomes. Some evidence also suggest that prenatal and/or early postnatal environmental exposures can increase the risk of developing chronic diseases later in life, including diabetes, obesity, cardiovascular disease, cancer, infertility, and several psychiatric and behavioral impairments such as schizophrenia and mood disorders [8, 9]. The purpose of this review is to provide a summary of recent research findings which indicate that exposure to EDCs during fetal and/or early postnatal development can cause long-term health outcomes via mechanisms of epigenetic memory.

Epigenetic mechanisms linking adverse early-life exposures to long term health outcomes

In the last two decades, DOHaD hypothesis has been repeatedly confirmed by numerous lines of animal and human evidence [10]. However, despite the long history of research in this field, the mechanisms underlying developmental programming of adult disease remain poorly understood. In the recent years, increasing evidence has been accumulated indicating the important role of epigenetic regulation in developmental programming of late-onset pathologies such as cancer, neurodegenerative diseases, and type 2 diabetes [11-14]. Epigenetics is defined as changes in gene expression that occur without changes in DNA sequence and can be transmitted through mitosis and/or meiosis [15, 16]. While the DNA sequence remains relatively static throughout ontogenesis, the epigenetic code is altered dramatically during embryonic development to initiate differential gene expression patterns among developing tissues. The epigenetic code consists of chemical modifications to DNA and histone proteins that package the DNA in the nucleus. The most intensively investigated mechanism of epigenetic regulation is DNA methylation, consisting of the addition of a methyl group at the 5-carbon of the cytosine pyrimidine ring by DNA methyltransferases, resulting in 5-methylcytosine. In mammals, DNA methylation is encountered at cytosine nucleotides that are followed by a guanidine (CpG-context) in CpG-rich regions (so-called “CpG islands”). The methylation of CpG isl ands is typically associated with transcriptional silencing if these islands are part of a gene’s promoter region with its regulatory entities [17]. The other main epigenetic mechanism contributed to transcriptional regulation is post-translational histone modification, such as methylation, phosphorylation, acetylation, and ubiquitination of histone tails [18]. One more recently discovered component of epigenetic regulation of gene expression is the modulation of gene expression by small (~20–30 nucleotides) non-coding RNAs (ncRNAs) that can target messenger RNA to interfere with transcription or translation [19].

During the early ontogenesis, different sets of genes are activated or deactivated in a sequential manner, providing numerous targets for environmental exposures. Therefore, a critically sensitive window of vulnerability is the developmental period during which the epigenome is more labile than during adulthood [20]. In mammalian development, there are two main periods of enhanced sensitivity of the epigenome to environmental stimuli: gametogenesis and early embryogenesis [21]. In human beings, the window of epigenetic developmental plasticity extends from preconception to early childhood and involves epigenetic responses to environmental changes, which exert their effects during life-history phase transitions [22, 23]. The developmentally established epigenetic marks are stably maintained through somatic cell divisions and create unique, lineage-specific patterns of gene expression. Prenatal and early postnatal exposure to environmental toxicants was repeatedly found to be associated with aberrant DNA methylation of regulatory sequences in susceptible genes, leading to inappropriate gene expression and disease pathogenesis in later life [24, 25].

Persistent epigenetic effects of early-life exposure to EDCs: experimental and epidemiological evidence

Hormone signaling is known to induce dynamic changes in cellular function and is normally reversible. During early development, however, steroid hormones were shown to induce epigenetic effects on gene expression persisting into adulthood and prime genes to respond to secondary hormonal cues later in life [8]. Csaba [26] states that 'in the case of hormonal imprinting, the first encounter between a hormone and its developing target cell receptor - usually at the perinatal period - determines the normal receptor-hormone connection for life. However, in this period, molecules similar to the target hormone (members of the same hormone family, synthetic drugs, environmental pollutants, etc), which are also able to bind to the receptor, provoke faulty imprinting also with lifelong - receptorial, behavioral, etc.,- consequences.'

In both animal and human studies, the early-life exposures to EDCs have been shown to disrupt normal development and lead to adverse lifelong consequences such as tumor development [27]. Apart from their common endocrine active properties, several EDCs have been shown to disrupt epigenomic programming [9]. Recently, some agents such as heavy metals that do not act directly on hormone receptors or DES that are structurally similar to hormones were also found to induce epigenetic changes through interaction with hormone receptors [28]. In the sections below, the evidence supporting the involvement of epigenetic mechanisms in long-term programming effects of EDCs will be reviewed.

Bisphenol A

One of the well-studied EDCs that had been shown to have an impact on epigenetic regulation of gene expression is bisphenol A (BPA), a man-made carbon-based synthetic compound with estrogenic activity which is widely used in the manufacture of polycarbonate plastics and epoxy resins. This xenoestrogen is contained in food cans, bottle tops, food and drink packaging, such as plastic water containers and baby bottles, as well as in dental materials [8, 29]. There is several evidence that BPA may accumulate in early human fetuses. In the Ikezuki et al [30] study, an approximately 5-fold higher concentration of BPA was revealed in amniotic fluid at 15-18 weeks gestation when compared to maternal serum. These data suggest that a fetus is likely unable to metabolize BPA effectively; therefore, it may cross the placenta and accumulate in fetal tissues. Because of the estrogenic properties of this compound, there is increasing concern relative to risks from its exposure during critical periods of development. There is increasing evidence from animal studies that in-utero and/or neonatal exposure to BPA produce a broad range of adverse adult outcomes, including impaired sexual behavior and reproductive function, immune system dysregulation, and cancer [31-34].

In several studies, it has been found that in-utero BPA exposure may affect gene expression in different tissues, including brain and spleen, and these BPA-induced changes in gene expression may persist into adulthood. Data from several recent studies indicate that early-life exposure to BPA can influence epigenetic programming of endocrine signaling and other important physiological pathways. The exposure to BPA from days 30 to 90 of gestation altered the level of expression of fetal ovarian steroidogenic gene and microRNAs related to gonadal differentiation, folliculogenesis, and insulin homeostasis of Suffolk ewes [33]. The developmental exposure of rats to low-dose BPA has been found to increase prostate gland susceptibility to adult-onset precancerous lesions and hormonal carcinogenesis [34]. These adverse adult outcomes were accompanied by permanent alterations in the DNA methylation patterns of multiple cell signaling genes, suggesting that epigenetic processes can play a role in this estrogen imprinting. Specifically, the transient neonatal exposure to BPA resulted in persistent promoter hypomethylation of gene encoding phosphodiesterase type 4 variant 4 (PDE4D4), an enzyme responsible for intracellular cyclic adenosine monophosphate breakdown, and in up-regulation of this gene [35]. In the study by Dolinoy et al. [36], exposure of agouti (*Avy*) mice to BPA two weeks prior to mating with *Avy/a* males and throughout gestation and lactation resulted in shifting the coat color of *Avy/a* offspring toward yellow, as well as in obesity, diabetes, and tumorigenesis. These changes were accompanied by significant epigenetic alterations, namely, by hypomethylation and increased expression of the *Avy* gene. In this study, the BPA-induced hypomethylation of the fetal epigenome was abolished by maternal dietary supplementation with some methyl donors, including folic acid, betaine, vitamin B12, and choline. These findings suggest that the deleterious effects of environmental toxicants such as BPA on the fetal epigenome may be ameliorated by specific nutritional interventions. In the study by Smith and Taylor [37], in-utero BPA exposure resulted in the alterations of uterine homeobox Hoxa10 gene expression that plays an important role in uterine organogenesis in mice, and these changes persisted into adulthood. In the Bromer et al. [38] study, both the level of mRNA and protein expression of Hoxa10 gene were increased by 25% in the reproductive tract of mice exposed to BPA in utero. The low-dose BPA

administration to pregnant mice has also been found to alter the epigenome in the forebrain of the offspring [39]. In particular, such exposure caused hypomethylation at NotI loci that is involved in brain development. Experimental evidence was also found which suggests that the neonatal exposure to BPA led to hypermethylation of estrogen receptor promoter region in adult rat testis [40], indicating that epigenetic changes may be one of the mechanisms contributing to BPA-induced adverse effects on spermatogenesis and fertility.

In the rat model, it has been also demonstrated that postnatal BPA exposure can impair the uterine response to ovarian steroids accompanied by a silencing of Hoxa10 in the uterine subepithelial stroma in adulthood [41]. In several rat studies, it has been reported that in-utero exposure to BPA may have long-term consequences on pancreatic function and metabolic parameters in offspring rats [42, 43]. A recent study by Ma et al. [44] found that modifications in hepatic DNA methylation caused by perinatal exposure to BPA have been implicated in development of insulin resistance in adult animals. Low-dose exposures to BPA were shown to be able to affect the prostate epigenome during development and, as a consequence, promote prostate disease with aging [34]. The alterations in DNA methylation patterns in multiple cell signaling genes in BPA-exposed prostates were obtained suggesting that exposure to the environmentally relevant doses of BPA can be imprinted in the developing prostate through epigenetic alterations [34, 35]. In human studies, it has also been indicated that exposure to BPA during early development may increase breast cancer risk later in life [45].

Diethylstilbestrol

In the 1970s, maternal exposure to diethylstilbestrol (DES), a synthetic non-steroidal estrogen agonist that was used to prevent miscarriage and other pregnancy complications between 1938 and 1971, has been shown to cause vaginal clear-cell adenocarcinoma in adult female offspring exposed in utero [46]. Since then, DES has been repeatedly shown to be associated with developmental programming of adult-onset chronic diseases including several reproductive tract abnormalities and increased vaginal and cervical cancer risk in women [24, 47]. In utero exposure to DES was also found to induce persistent epigenetic changes in the developing uterus. DES was the first estrogenic xenobiotic, which was found to elicit demethylation of an estrogen-responsive gene during rodent development associated with persistent abnormal gene expression and adult tumorigenesis [48]. Importantly, such programming effects of DES have been shown to be able to be epigenetically transmitted to next generations [49]. In the Doherty et al. [31] study, in utero exposure of mice to DES resulted in a >2-fold increase in the expression level of Enhancer of Zeste Homolog 2 (Ezh2), a histone methyltransferase that is linked to breast cancer risk and epigenetic regulation of tumorigenesis, in adult mammary tissue compared with controls. In the study by Bromer et al. [50], the expression of Hoxa10 gene was increased in human endometrial cells after DES exposure, whereas in mice, in-utero DES exposure resulted in hypermethylation and long-term altered expression of the Hoxa10.

Methoxychlor

Early life exposures to environmental toxins such as insecticides have been shown to cause long-term alterations in the structure and function of different organs. One of them, methoxychlor (MXC), is a synthetic organochlorine insecticide that was widely used as an alternative for DDT. MXC is EDC which along with its metabolites possesses estrogenic, antiestrogenic, and antiandrogenic activities. In a number of experimental studies, MXC administration in early pregnancy or during the perinatal and neonatal periods has been shown to cause adult-onset abnormalities, such as reduced pregnancy outcome, ovarian functions and ovulatory rates in female rats, and to a decrease in sexual arousal, an increase in sexual maturation, a decrease in the circulating testosterone level, and decrease in testis weight, Sertoli cell number, and spermatogenesis potential in male rodents [51].

The fetal and neonatal exposure to MXC has been shown to cause adult ovarian dysfunction in rats due to altered expression of key ovarian genes including down-regulation of the estrogen receptor (ER)-beta gene [52]. These data were subsequently confirmed in the study by Zama and Uzumcu [53], where developmental exposure to MXC led to significant hypermethylation in the (ER)-beta promoter regions and to an increased level of expression of DNA methyltransferase 3b (Dnmt3b). Prenatal administration to MXC also resulted in transgenerational imprinting effects on male gametes in mice [51]. Specifically, MXC treatment of female mice during pregnancy altered the methylation pattern of several paternally imprinted genes [H19 and Meg3 (Gtl2)] and maternally imprinted genes [Mest (Peg1), Snrpn, and Peg3] in the sperm of their offspring. These effects persisted through the three generations, but disappeared gradually from F1 to F3 generations.

Permethrin

Another widely used insecticide, permethrin, has also been found to exhibit the characteristics of the EDC, based on their effects found in the female and male reproductive systems. In the Vadhana et al. [54] study, neonatal administration to permethrin led to heart damage in adult rats. Specifically, permethrin treatment resulted in increased DNA damage, decreased heart cell membrane fluidity, increased cholesterol content, and protein and lipid oxidation in heart cells. Carloni et al. [55] evaluated the effect of a low dose of permethrin administered during early life on development of neurodegeneration in adulthood. The results obtained suggest that permethrin intake during the perinatal period can interact with transcription factor Nurr1 by reducing its expression on striatum nucleus. Consequently, the maintenance of dopaminergic neurons as well as Nurr1 inhibitory effect on the production of proinflammatory mediators fails. In the Fedeli et al. [56] study, the effect of permethrin was also evaluated on leukocytes inflammation mediators in 300- and 500-day-old rats. Early-life treatment with a low dose of the permethrin induced a significant increase of Nurr1 and lipid peroxidation in oldest rats. Tumor necrosis factor alpha (TNF-α) and a chemokine Rantes increased, while interleukins (IL-1β, IL-2 and IL-13) decreased in oldest treated rats.

Vinclozolin

Vinclozolin is a well-characterized anti-androgenic pesticide. In rodent models, it has been demonstrated that prenatal exposure to this chemical can decrease the adult sperm concentration and motility, and also can increase the risk of hypercholesterolemia, kidney and prostate disease, abnormalities in immune system function, and cancer in F1 male offspring [28, 57-60]. In the study by Anway et al. [57], these adverse effects were persisted through F1 to F4 generations of male offspring. This research was the first study which indicated the possibility of transgenerational inheritance of adult-onset disease in EDC-exposed rodents. Subsequently, these findings were substantially replicated in several rodent studies [58-63], while in others no evidence for such transgenerational effects was demonstrated [64-66]. If detected, these transgenerational effects of early-life vinclozolin exposure were accompanied by alterations in the sperm methylation profile in the F1–F3 offspring generations [57, 61-63, 67-69]. For example, in the study by Stouder and Paoloni-Giacobino [63], exposure of pregnant mice to vinclozolin at the time of embryo sex determination caused decrease in percentage of methylated CpGs of paternally imprinted genes (H19 and Gtl2) and increase those of maternally imprinted genes (Peg1, Snrpn, and Peg3) in the F1–F3 offspring's sperm. In the research by Chang et al. [67], alterations in the epigenetic pattern (i.e. methylation) of 15 of the 25 candidate genes/DNA sequences studied were detected in the F2 and F3 generation germline.

Dioxin

Dioxin is a general name for a family of chlorinated hydrocarbons, C12H4Cl4O2, typically used to refer to one isomer, TCDD, a toxic by-product of pesticide manufacture. Developmental dioxin exposure has been repeatedly shown to cause developmental, reproductive and immune impairments and also cancer. TCDD has also shown to have anti-estrogenic effects and it was classified as an EDC affecting the human reproductive system. In the Somm et al. [70] study, the effects of TCDD administration to pregnant mice on imprinted genes of male offspring were evaluated. In the sperm, skeletal muscle and liver, prenatal TCDD administration (10 ng/kg/day) did not affect methylation but increased mRNA expression of Snrpn, Peg3, and Igf2r genes. In muscle and liver, TCDD induced increases in methylation and decreases in mRNA expression of Igf2r gene. To determine whether exposure of preimplantation embryos to TCDD affects fetal mice growth, Wu et al. [71] exposed embryos to TCDD from the 1-cell stage to the blastocyst stage and then transferred them to unexposed recipient mice. On the 14th embryonic day, the fetuses exposed to TCDD weighed less than the fetuses in control group. This exposure caused decrease in the expression levels of the imprinted genes, H19 and Igf2. The methyltransferase activity and the methylation level of the 430-base pair H19/Igf2 imprint control region were both higher in TCDD-exposed embryos and fetuses than in the controls. In the Aragon et al. [72] study, in-utero and lactational TCDD exposure caused disruption of the expression of cardiac genes involved in extracellular matrix remodeling (matrix metalloproteinase 9 and 13, and preproendothelin-1), cardiac hypertrophy (atrial natriuretic peptide, beta-myosin heavy chain, and osteopontin), and aryl hydrocarbon receptor (AHR) activation (cytochrome P4501A1 and AHR repressor), that was associated with changes in cardiac and renal morphology in adulthood. In utero exposure to dioxin also was shown to induce changes in the expression of genes encoding the epidermal growth factor receptor and its cognate ligands in the developing mouse ureter [73].

In rats, maternal exposure to a low dose of TCDD resulted in both a dose-dependent increase in 5alpha-reductase type 2 (5alphaR-II) mRNA level and a dose-

dependent decrease in androgen receptor (AR) mRNA level in the ventral prostates of offspring [74]. A decrease in Ccl5/Rantes RNA levels and a transitory decline in sperm reserves in the testes of male offspring of TCDD-exposed Sprague-Dawley dams have been found in the Rebourcet et al. [75] study.

Heavy metals

This is consistent evidence that heavy metals such as cadmium, mercury, arsenic and lead may have endocrine disrupting activity [76, 77]. For example, cadmium has been found to have the ability to produce estrogenic effects in rodents, including proliferation of the uterine and mammary tissues, and these effects might be suppressed by co-treatment with specific estrogen receptor antagonists, suggesting mediation via the estrogen receptor [78].

Recent animal studies have reported that early-life exposure to heavy metals can lead to marked changes in epigenetic regulation of gene expression. In the Castillo et al. [79] study, exposure to cadmium during pregnancy has been found to affect the fetal liver DNA methyltransferase 3a (DNMT3a) resulting in sex-dependent changes in methylation and expression of glucocorticoid receptor promoter (GR) gene exon 1(10). Developmental exposure to lead has been repeatedly shown to cause adverse effects on cognitive functioning and behavior that can persist into adulthood. Both prenatal and early postnatal exposure of Long-Evans dams to low doses of lead resulted in significant changes in DNA methyltransferases (DNMT1 and DNMT3a), and methyl cytosine-binding protein (MeCP2) expression in the hippocampus of offspring at 55 days of age [80]. In recent study by Faulk et al. [81], the viable yellow agouti (Avy) mouse dams were exposed to different doses of lead acetate before conception through weaning. Lead exposure was associated with a trend of increased wean body weight in males and altered coat color in Avy/a offspring. These phenotypic changes were accompanied by altered levels of DNA methylation at Avy and the CDK5 activator-binding protein intracisternal A-particle element, with male-specific effects at the Avy locus. In the chick model, DNMT3A/3B gene expression levels were significantly downregulated in chick embryos at 4 h after treatment with cadmium compared to unexposed controls [82].

In humans, prenatal cadmium exposure was associated with cord blood DNA methylation level [83]. This association was markedly sex-specific. In boys, 96% of the top 500 CpG sites showed positive correlations, while most associations in girls were negative. In girls, overrepresentation of methylation changes in genes associated with organ development, morphology and mineralization of bone was evident, whereas in boys, changes in cell death-related genes have been showed. In the Fry et al. [84] study, the altered gene expression profiles in the cord blood have been found in a population of newborns whose mothers experienced varying levels of arsenic exposure during pregnancy in the Ron Pibul and Bangkok districts of Thailand. The network analysis of the arsenic-modulated transcripts conducted in this study revealed the activation of extensive molecular networks that are indicative of stress, inflammation, metal exposure, and apoptosis.

Conclusion

The plausible link between EDCs exposure during critical periods of early development and risk of chronic diseases later in life has been reported in a number of recent studies. The key role of epigenetic mechanisms in mediating the relationship between endocrine disruption early in life and life-long health outcomes has been highlighted by many authors. Over the last years, a large number of experimental studies aimed at understanding the specific epigenetic mechanisms underlying the developmental programming of later-life pathology by early-life exposure to EDCs have been performed. Until now, DNA methylation is the most studied epigenetic mechanism underlying this association. A summary of main findings in this area is provided in Table 1. The possibility of transgenerational epigenetic effects of EDCs has also been shown. These findings raise concerns regarding the persistent effects of endocrine disruption, not just to individuals who were directly exposed, but also to further generations.

Given the potential reversibility of environmentally-induced epigenetic modifications [85], the deeper understanding of mechanisms underlying the life-long (and sometimes transgenerational) consequences of the perinatal endocrine disruption may in future lead to development of efficient diagnostic tools and therapeutic approaches for the prevention and removal of the adverse effects of EDCs. If one can modify the disrupted epigenetic patterns through specific nutritional or pharmacological interventions, than it would be possible to correct the impaired gene expression patterns to treat EDC-caused disorders and to improve human health and longevity.

Table 1. Summary of studies reporting associations between early-life exposure to EDCs and epigenetic alterations in adult life

Compound	Model	Stage	Epigenetic changes in adulthood	Ref.
Bisphenol A	Mice	In utero	Increased Ezh2 gene expression in the mammary gland	[31]
		Neonatal	Promoter hypomethylation of Pde4d4 gene	[35]
		Preconception to weaning	Hypomethylation and increased expression of the A^{vy} gene in agouti mouse model	[36]
		In utero	Increased Hoxa10 expression in uterine stromal cells	[37]
		In utero	Increased level of mRNA and protein expression of Hoxa10 gene	[38]
		In utero	Hypomethylation at NotI loci	[39]
	Rat	Neonatal	Promoter hypomethylation and up-regulation of Pde4d4 gene	[34]
		Neonatal	Hypermethylation of estrogen receptor promoter region in adult testis	[40]
		Postnatal	Transcriptional silencing of Hoxa10 gene in the uterine subepithelial stroma	[41]
		Perinatal	Modified hepatic DNA methylation	[44]
Diethylstilbestrol	Mice	In utero	Increased Ezh2 gene expression in the mammary gland	[31]
		In utero	Hypermethylation and long-term altered expression of the Hoxa10 gene	[50]
Methoxychlor	Mice	In utero	Altered methylation pattern of paternally imprinted genes, H19 and Meg3/Gtl2, and maternally imprinted genes, Mest/Peg1, Snrpn, and Peg3, in the F1-F3 offspring sperm	[51]
	Rat	Fetal and neonatal	Down-regulation of the (ER)-beta gene	[52]
		Fetal and neonatal	Hypermethylation in the (ER)-beta promoter regions	[53]
Permethrin	Mice	Neonatal	Increase in TNF-α and a chemokine Rantes, and decrease in interleukins (IL-1β, IL-2 and IL-13)	[56]
Vinclozolin	Mice	In utero	Decrease in percentage of methylated CpGs of paternally imprinted genes (H19 and Gtl2) and increase those of maternally imprinted genes (Peg1, Snrpn, and Peg3) in the F1–F3 offspring sperm	[63]
Dioxin	Mice	In utero	Increase in mRNA expression of Snrpn, Peg3, and Igf2r genes, and increase in methylation and decrease in mRNA expression of Igf2r gene in muscle and liver	[70]
		In-utero and lactation	Disruption of the expression of cardiac genes involved in extracellular matrix remodeling, cardiac hypertrophy, and aryl hydrocarbon receptor activation	[72]
	Rat	In utero	Increase in 5alpha-reductase type 2 and decrease in androgen receptor mRNA levels in the offspring ventral prostates	[74]
		In utero	Decrease in Ccl5/Rantes RNA levels	[75]

Ezh2: enhancer of zeste homolog 2, *Pde4d4*: phosphodiesterase type 4 variant 4, A^{vy}: agouti, *Hoxa10*: homeobox A10, *Meg3*/*Gtl2*: maternally expressed gene 3/gene-trap locus 2, *Mest*/*Peg1*: mesoderm-specific transcript/paternally expressed gene 1, *Snrpn*: small nuclear ribonucleoprotein polypeptide N, (*ER)-beta*: estrogen receptor beta, TNF-α: tumor necrosis factor alpha, Rantes: regulated on activation, normal T cell expressed and secreted, IL: interleukin, *Igf2r*: insulin-like growth factor 2 receptor, Ccl5: CC chemokine ligand 5.

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