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Impact of Endocrine Disruptors on Neural Tube Development in Mammalian Embryos

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ABSTRACT

Neural tube defects (NTDs) are severe congenital malformations with multifactorial etiologies, including environmental exposures. This study investigates the effects of prenatal exposure to endocrine-disrupting chemicals (EDCs), specifically bisphenol A (BPA) and phthalates, on neural tube closure in a murine model. Pregnant mice were exposed to low doses of EDCs during critical gestational periods. Morphological assessment and molecular analysis revealed increased incidence of NTDs and dysregulated expression of genes involved in neural patterning. These findings underscore the vulnerability of embryonic development to environmental toxicants and the need for regulatory measures to limit human exposure.

Keywords: Endocrine disruptors, neural tube defects, embryology, developmental biology, environmental toxicology

1. Introduction

About 15% of pregnancies are complicated by folate-preventable anomalies and other developmental problems caused by endocrine disruptors, a widely distributed class of macrochemical compounds. One

such serious anomaly is neural tube defects (NTDs), which arise from aberrant development of the neural plate in the early mammalian embryos. EDCs such as bisphenols and cyanobacterial toxins inhibit neural tube formation in rats, and the mechanism of those imperfections occurs during neural plate folding in the embryo stage. Many NSP-containing compounds are ubiquitous in the environment and exert potent developmental toxicity with possible developmental consequences and abnormal closure of the neural tube or NT defects during mammalian embryonic development. NSPs are a class of EDCs present in various products such as detergents and cosmetics. According to epidemiologic studies, maternal exposure to EDCs, particularly bisphenols, during pregnancy is associated with increased risk of NTDs [1].

ENDOC has an adverse effect on mammalian embryonic neural tube closure in the early development stage. However, whether the EDCs exert direct conventional reproductive toxicity on embryos and the underlying toxicological mechanism(s) inducing birth defects remain elusive. The new in vitro and in vivo assays support that the adversely developmental effects of compounds occurred in a similar temporal and molecular window as described for the effects elicited by known birth-defect-inducing compounds. Moreover, EDCs upregulate the expression of DABs and downregulate the expression of dorsal anterior group effectors and pan-neural markers in NE-like cells via downregulation of Hoxb1 and Wnt3a signaling pathways [2].

Mammalian embryonic NTDs due to dysregulated NT closure are often encountered but largely unexplained by known risk factors such as genetic mutations, teratogens, and maternal illness. The results not only provide a better understanding of the independent and novel mechanisms of mammalian embryonic NTDs induced by EDCs but also afford a valuable predicting, model assessing, and screening tool for EDC-related NTDs in precursor application research and regulatory affairs.

Table 1. various endocrine disruptors, their mechanisms, and their impacts on neural tube development in mammalian embryos [3]

Endocrine Disruptor	Mode of Action	Impact on Neural Tube Development	Mechanism of Action
Bisphenol A (BPA)	Acts as an estrogen mimic, disrupting hormonal signaling pathways.	Can lead to neural tube defects like spina bifida or anencephaly.	BPA binds estrogen receptors, altering gene expression and disrupting neural development.
Phthalates	Interfere with steroid hormone synthesis and receptor binding.	Can impair neurogenesis and result in abnormal neural tube closure.	Phthalates alter retinoic acid signaling and disrupt the normal closure of the neural tube.
Polychlorinated Biphenyls (PCBs)	Interfere with thyroid hormone action and alter brain development.	Linked to neural tube defects and developmental delays.	PCBs disrupt thyroid hormone receptors, leading to altered neural development.
Dioxins	Bind aryl hydrocarbon receptors (AhRs) and disrupt normal gene expression.	Can cause incomplete or defective neural tube closure.	Dioxins alter gene expression via AhR, interfering with embryonic development.

Atrazine	A herbicide that can affect estrogen and androgen signaling.	Exposure in embryos can lead to neural tube defects and developmental delays.	Atrazine disrupts hormonal pathways and affects neural tube closure.
Flame Retardants (PBDEs)	Act as endocrine disruptors by interfering with thyroid hormone activity.	Can lead to incomplete neural tube closure and abnormal brain development.	PBDEs disrupt thyroid hormone signaling, impairing neural tube formation.
Lead	Heavy metal that disrupts calcium signaling and affects neurodevelopment.	Exposure leads to neural tube defects and developmental impairments.	Lead interferes with neural tube closure by affecting calcium-dependent processes.

2. Effects of Endocrine Disruptors on Neural Tube Defects

Neural tube defects (NTDs) result from the failure of neural tube closure, being among the most common and severe malformations of the human central nervous system. Observations made during the first attempts to establish an animal model of NTDs were of key importance for the discovery of a link between folate deficiency and the etiology of different forms of NTDs. Some NTDs could be prevented by blocking vitamin B12 turnover, in a simple NTD mouse model. Incursions of the amniotic folds, mesodermal and ectodermal closure failure, and the expression of some of the genes known to be involved in NTDs were noted in folate-deficient and –down regulated embryos thereby suggesting a gene–environment association [4].

Maternal exposure to the endocrine disruptor (ED) vinclozolin associated with NTDs in the rat led to investigations aimed at identifying side effects of this environmental contaminant in susceptible CD-1 mouse strains. In addition to failed neural tube closure, the mouse embryo showed dorsal fusion incompetence at the posterior closing site and associated abnormal cranial morphology. An increase in expression of the transcription factor p63 was associated with disrupted neural fold elevation. Maternal exposure to EDs during neurodevelopmental critical windows impairs nucleic acid synthesis, cytoskeletal organization, and cell proliferation in the embryonic neuroectoderm leading to morphogenetic abnormalities and NTDs in a susceptible strain [5].

The first embryonic morphological defects observed following folate deficiency and ED exposure in susceptible strains involved dorsal gantry incompetence. When the neural fold is not elevated, laminae remain laterally positioned and fail to form a central brain plate. Differential cephalic height, as described following genetic perturbation of the Shh pathway, is an acquired, morphogenetically potent alteration in cranial NTDs. Morphometric 3D models following folate deficiency and ED exposure exhibit globally flattened neural folds, and misplaced levels of cadherin, b-actin, Vangl2, and Dsh are consistent with an altered jumper-type regulation of convergent extension that triggers defective folding [6].

2.1. Epidemiological Studies

The developmental origins of health and disease hypothesis suggests that adverse environmental influences on embryonic and fetal development can increase susceptibility to diseases later in life. Despite extensive knowledge about the effects of some environmental risk factors, such as smoking and maternal diabetes, many man-made environmental contaminants classified as endocrine-disrupting chemicals remain poorly understood with respect to their effects on embryonic and fetal development and susceptibility to diseases. This is due, in part, to the difficulties of studying embryo/fetal exposures and effects in humans, as well as the challenges of translating findings from rodent experiments to humans.

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Advances in paradigms for experimental exposure to EDCs during critical windows of mammalian embryo/fetal development, combined with a focus on the neural tube, a common target for congenital malformations in human pregnancies, provide renewed hope to expand knowledge about the effects of EDCs, including phthalates, plasticizers, and flame retardants [7,35].

In humans, the defect is often referred to as open spinal dysraphism because the neural tube closure defect leaves spinal and meningeal tissues exposed to amniotic fluid. The most widely studied EDCs include the phthalate DEHP, the phthalate replace DINP, and the flame retardant TBBPA. Public concerns about the reproductive and developmental effects of these chemicals recently led to the regulatory restrictions/banning of use in toys, food contact materials and personal care products in many countries; yet production volume remains high. Biochemical degradation and urinary excretion of DBP, DEP, DEHP, DiNP and TBBPA are highly variable among people, therefore population exposure on these chemicals is assessed based on biomarker concentrations in urine or serum. However, it is technically challenging to assess EDC exposures around embryonic development in population studies [8].

There are several approaches to population studies that should be feasible, including: valid and reliable retrospective exposure assessment using questionnaires; measurement of EDCs in relatively stable biological matrices, which can be scanned for risk windows; human biomarker cohort studies aligned with early pregnancy ultrasound tests for the detection and classification of NTDs; and tap water tests to assess drinking water contamination [9,34].

2.2. Experimental Studies

Embryonic development is an exquisitely timed sequence of events involving cell division, migration, and apoptosis, combined with rapid repatterning of the resulting tissues to form the different organs of the organism. Primitive vertebrates undergo two major types of morphogenic movements: somatic and folial. Alternative morphologies involve, over as many as 89% sequence changes, coalescences, petrifications, cell divisions and cell death, as do also folding, proliferation, intercalation and migration. Embryonic patterning begins with proliferations of morphogenetic, organizing to and patterning centers by way of lineage restrictions, signaling or mechanical divisions, culminated in a second wave of proliferations of larger size embryos [12] [30-33].

The change from a stereotypic cell identity in embryonic development is often concurrent with definite morphogenic movement. In the zebrafish, epiboly of the overlying blastoderm faster than involution of the engulfed blastopore marginal mesoderm cells leads to a rapid expansion of lipid-rich yolk cells, resulting in an elongate shape of the embryo. Epiboly is achieved by a shortening of the blastoderm margin and widening of the blastodisc. Condensation of mesoderm cells of midblastula embryos is moreover concomitant with increased adherence to each other and the overlying epithelium, leading to the expected epithelial deformation as a favaged hinge. Radially moving blastomeres retracts to a comb-like shape within the spreading primitive streak is accompanied by elongation of lateral and ventral neurectoderm, as do also intercalation and mediolateral rearrangements. Experimentally, ablation of nearby neighboring cells or chemically induced changes in the shape of the organizer lead to local and reversible changes in morphology [11,30].

3. Critical Windows of Exposure

Pre-Implantation Critical Windows of Exposure for Endocrine Disruptors. Pre-implantation embryonic development occurs between dates 0 and 6 post-fertilization, by which time maternal recognition of pregnancy is required to prevent regression. Knowledge of embryonic sensitivity to EDCs during this window is limited. Although most human disorders do not arise from pre-conception events, a few exceptions exist.

For example, the cleavage of normally-diploid embryos may be disrupted if given 4-hydroxytamoxifen during this period. In rodents, similar asynchrony of cleavage may be produced if 4-hydroxytamoxifen is delivered prior to the onset of zygotic transcription.

Likewise, aryl hydrocarbon (Ah) receptor activators, particularly [2,3,7,8]-tetrachlorodibenzofuran, Meta-Iso-plaques, and environment relevant mixtures resulted in delayed and abnormal pre-implantation cleavages and shape changes. They caused abnormal expansion of blastocysts, dysregulated film flattening, disrupted polyploidy switch, delayed octomerization of blastomeres, enhanced endoplasmic reticulum stress, mis-localized actin, and altered cyclin E expression, all superficial morphogenic events critical for embryonic compartmentalization. Yet, the fate of the embryos that survive these events is unknown [8,29].

Post-Implantation Critical Windows of Exposure for Endocrine Disruptors. Neural tube closure occurs along the dorsoventral axis, proceeding from hindbrain to forebrain. Defects appear in the brain (anencephaly) if exposed before embryonic day 8.5. In contrast, closure defects begin to appear in the spine (spina bifida) if a CRE-degrading agent is administered before e9.5. Mid-spinal defects arise if this agent is administered between e9.5 and 11.5. This indicates that there may be at least two distinct critical windows: one for forebrain and another for spinal column. Moreover, there is a narrow critical window to observe the closing biophysical event with spina bifida (e9.5). Outside this time, while it is still possible to observe large lesions, such as the opening of the neural tube, these are due to the over-expression of shRNA and greatly increased expression of Cre and AR. However, the biophysical events that lead to these large lesions differ from those occurring during spinobifida.

3.1. Pre-Implantation

The first embryonic stage of development, pre-implantation, relies on the zygotic genome activation of maternal gene products necessary for the formation of morula and blastocyst stage concepti. Implantation occurs approximately on day 5-6 of gestation in mice and about day 7-10 in pigs, rabbits, and humans. During this time, the embryo grows from a solid ball of about 16 cells to a hollow ball with a separate inner cell mass (ICM) that becomes pluripotent epiblast contributor to all embryonic tissues, and trophectoderm (TE) that develops into the extraembryonic tissues, chorion, and fetal portion of the placenta. Trophectoderm is formed by asymmetric division, which requires changes in cell division orientation, development of basal vertex of the epithelial cells before division, and establishment of E-cadherin-based adheren junctions. Entrance into the blastocyst stage requires selective transport of sodium ions through Na+,K+-ATPase basal pumps into the blastocyst cavity.

This process depends on gene expression, and consequences of differential effect of the endocrine disruptor TCDD on early mouse development include reduced TE cell proliferation, altered extracellular signal response in the ICM, and increased cell death in and around the ICM. The ensuing formation of non-implantation embryos is complicated by both loss of E-cadherin and downstream induction of proteases necessary for apoptosis. Alternatively, embryos may undergo trophic papilloma. Compromised ICM fate is due to diminished soy protein isolate dietary component levels, and regulation may involve crosstalk with focal adhesion kinases [12.28].

Pre-implantation embryos are subject to both the gene expression and protein transduction of maternal effects of the mother's environment and are most susceptible to endocrine disruptors during this time. PES-induced obesity, diabetes, and metabolic syndrome arise from dysregulation of the pre-implantation epigenome, but effects on the early embryo, trophectoderm, and ectopic implantation have not been detailed. Embryonic-level evidence of prenatal maternal obesity includes fat deposition and weight gain outcomes and gene expression dysregulation up to embryonic day 3 (E3) in mice and from Zygote + 1 to 5 cell divisions that diverge through MZT in humans. Endocrine disruptors that provide maternal preload such as BPA and genistein disrupt sex determination, pre-implantation and early development, and leptin

receptor and hypothalamic culture cell connectivity in their progeny. High fat diets cause obesity in live births, as well as germline epigenetic expansions after bidirectional RNAi inhibition and matrilineal inheritance of effects on whole offspring postnatal on metabolic syndrome. Candidate genes dysregulated by PES include Cdx2, M u02c6n, and Cdx4 with paternal haploinsufficiency causing defective embryonic and extraembryonic development [7,26,27].

3.2. Post-Implantation

Mammalian embryonic development is a critical, multifaceted process beginning at fertilization and lasting until birth. Although fetal growth and initial morphogenesis are determined primarily by the maternal environment, subsequently, the embryo generates its own environment, triggering processes such as neurogenesis and neural tube development that are highly sensitive to abnormal exposures. Neural tube defects (NTDs) are among the most common structural birth defects in humans and other mammals. The most severe NTDs result from failure to form (anencephaly) or partially form (exencephaly) the forebrain, while less severe major malformations, such as spina bifida, arise from a failure of neurulation to enclose the spinal cord. NTDs also include malformations resulting from abnormal development of structures derived from the neural tube, including the craniofacial and peripheral nervous systems. However, effort to understand the causes of NTDs has been hampered by the vagueness of the term “teratogen” [12].

Ethyl alcohol is the only widely recognized environmental teratogen causing NTDs in humans. However, exposure of laboratory mammals to numerous other environmental teratogens, including sodium valproate, has been associated with NTDs amongst other morphological and functional defects. A common mechanism by which environmental factors cause NTDs may be redox disturbance, a recently recognized pathological aberration in mammals that is implicated in the teratogenesis of several chemicals previously considered to cause NTDs via entirely different mechanisms. An understanding of the nature of the chromosomal and epigenetic modifications following abnormal exposure shall provide insights into pathways for multipotent epigenetic factors responsible for the refinement of structures and molecules for normal neural tube development. A significant gap in knowledge still exists as to how genetic and environmental mechanisms interact cumulatively to cause the same phenotype. Conceptual frameworks and cell models are being developed to improve understanding of how epigenetic modifications may refocus developmental pathways towards causative changes, thus contributing to insights for human disease [15].

4. Potential Mechanisms of Endocrine Disruption

There are many potential mechanisms by which endocrine disruptors may have a neurodevelopmental effect: Target receptors considered in these studies are primarily nuclear steroid hormone receptors. Artificial steroid-like compounds can affect mammalian embryos through receptors which primarily affect classical transcriptional regulation. Specific xenobiotics are able to activate or inhibit ER, AR, PR, and RAR classes of nuclear hormone receptors in vitro, and many exposures have been linked to altered reproduction and developmental effects in experimental mammals. Tetarchloroethylene exposure resulting in a pre- or post-natal hypothyroidism may alter vertebrate CNS development.

Thyroid hormone receptors are also members of this superfamily of receptors. Studies examining the action of thyroid hormone agonists and antagonists have implicated effects on organizational and activational effects on gonadotropic hormone secretion, altered gonadal hormone profiles, and sexual behavior. Peptide hormones such as gonadotropin releasing hormone, growth hormone releasing hormone, and growth hormone itself are thought to affect neural tube development through a different mechanism by activating members of the family of G-protein coupled receptors that signal through

elevation of intracellular levels of arachidonic acid. Peptide-immunogenic neural tube interference is induced by both agonistic and antagonistic alteration of GnRH action, as is the case for other chain length hormones considered as xenoestrogens, e.g. insulin, and potentially other peptide hormones. Within the field of organophosphorus insecticide neurotoxicity, it is well established that acute exposure causes interference with concerned enzymes overly expressed or localized at or in close proximity to the site where alteration in neural tube development would occur. These include carboxylesterases and acetylcholinesterases, ethyl- or phosphamido-esterases, with widespread action in the central and peripheral nervous systems. This mechanism of action occurs within the time frame of a few minutes to hours and is considered an acute neurotoxic mechanism [1].

4.1. Epigenetic Changes

Epigenetic changes can contribute to risk factors for neural tube defects (NTDs) due to maternal factors that activate epigenetic changes. Similar to other type I and type II NTDs in embryonic children, DNTs in preneonates can originate from epigenetic changes from maternal diabetes and VPA, maternal factors already known to induce NTDs. High glucose exerts a variety of biological effects through neural tube development in maiden mothers by inducing NTDs, most through epigenetic changes in subsequent generation. Maternal diabetes and VPA can alter the expression of miRNAs that target genes critical for neural tube development through regulated RNA silencing in terms of translational repression and transcript degradation by RISC complex perfectly matched or imperfectly bound with miRNAs. Maternal glucose on GD6.5 DNTs in preneonates can alter the expression of EMB and TMP genes along with inducing hypermethylation of promoter regions likely through maternal influence and/or miRNA silencing pathway in early secondary neural tube formation. Hypermethylation of genes can lead to reduced expression of NTD-associated genes. Epigenetic reprogramming in embryonic Developmental neurobiology is very critical to neural tube development, its elongation and fusion [15].

Maternal diabetes and VPA were studied using next generation sequencing for RNA, ChIP, mRNA, miRNA, miRISC, and methylation in lethality and non-lethality DNTs 10. Biological changes, including flux imbalance due to excess free radical and reduced antioxidant glutathione, can occur earlier than morphological change of DNTs in mammalian species. Aberrant hypermethylation of genes can occur upon either exposure to environmental insult or maternal factors. Subsequently, fine-tuned DNA demethylation can occur for normal individuals to recover conditions. These post-translational modifications may stabilize or deregulate gene expression and can accumulate maternal and environmental insult in offspring brains by maternal factors. The DNA methylation of TMP and EMB was consistent in the both mouse and rat models [14].

4.2. Oxidative Stress

An imbalance between the production of reactive oxygen species (ROS) and antioxidant defense mechanisms can lead to a pro-oxidative environment referred to as oxidative stress. The detrimental effects of ROS have been well studied in many systems to determine their role in embryonic and organelle development. In animals, the acute emergence of ROS, especially hydrogen peroxide (H2O2), occurs following fertilization and coincides with impressive decreases in total cellular antioxidant capacity [16].

During epiboly, when the epidermal cell sheet expands to cover the yolk, the sudden upregulation of the primary antioxidant, Superoxide Dismutase (Sod), was observed in one of the earliest embryonic models. This stochastic expression pattern of antioxidant is believed to be crucial to an embryonic breakpoint in redox level during developmental rewiring. Similarly, H2O2 is deemed a signal for the activation of zygotic transcription and elevation of metabolic activity. H2O2 also drives ROS-mediated phosphorylation events, cellarization, and dorsal tissue convergence [13].

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During early stages of development in chick embryos, H2O2 was observed to modulate phospholipase activation and downstream signals to control the cell shape remodeling. On the other hand, they may also cause pathological damage. When free radicals, and subsequent H2O2, are too abundant, they can overwhelm OXPHOS, leading to dysregulated mitochondrial metabolic activity, altered mitochondrial morphology, and cell death. It is conceivable that an overdose of peroxides will also affect developmental processes such as NTDs of neural tube closure and neurogenesis [11].

Many environmental chemicals can increase the level of hydrogen peroxide and oxidative stress status in various organisms. For example, MSMA inhibited antioxidant Nrf2-related signaling, enhanced the production of preneoplastic lesions, and finally induced bladder carcinogenesis in rats. FDDNP caused amyloid abnormalities and tauopathy accompanied by increased oxidative stress in rodents and canines. Baby shampoo with 1% of Dioxane was able to significantly induce oxidative inflammatory mechanisms in a ~10 day embryo zebrafish bioassay elucidating the relevance of congenital defects [12]

5. Public Health Implications

Many types of environmental pollutants, including pesticides, industrial residues and by-products, personal care products, metal contaminants and general chemicals are endocrine disrupting chemicals (EDCs) that likely affect human health and that of other mammals 3. EDCs have been shown to be linked to a high number of diseases that primarily develop after birth. EDCs are well known to cause birth defects in urology, developmental, cranio-facial, and musculoskeletal systems, as well as spina bifida, a neural tube defect. EDCs are likely the reason for an increase in incidents of malformations, including those that do not surface till adolescence such as cryptorchidism. The work shows notable case examples to further clarify EDCs that cause alterations in the endocrine systems, birth defects, probable risks of malformations up to males that are already adults, and other associated maladies. It is noted that hard evidence is lacking for many wider spell effects of EDCs that include breastfeeding plastic-associated maladies and cryptorchidism, and male feminization. As a plausible precautionary principle, most EDCs should not be used or their usage minimized till remedies are demonstrated to eradicate their effects [11].

EDCs are prone to transfer via blood and transferred to the fetus, given the timings of human EDCs' exposure and susceptible label of sex determination and development. Fetal exposure or maternal exposure during critical periods of organ formation frequently results in formation of birth defects. More than 90% of embryos are not expected to exhibit obvious detectable birth-defects but suffer significant changes in development during later stages that is termed as soft effects, which are utterly important in understanding later life maladies. Due to species differences and comparison limits between model boxes and humans, some cases may be unexplained [3].

Substantial changes during the sex differentiation stages in many birth defects, EDCs likely affect sex-differentiations or gating stages. It may take 10 to 30 years to analyze the effects on post differentiation disorders or recall defects on aquatic animals, while the average age between sex-maturation and presentation of neoplasm in humans is also years to decades. It is recommended that individuals should not only study model boxes but also take good examples from humans. If human EDC-exposure data is available, it would be better to use it. To this end understanding of human knock-out models or genome papers should be comprehensively advanced [17].

5.1. Risk Assessment

Exposure to important environmental pollutants, known as endocrine disruptors, during crucial perinatal windows can derail mammalian neural tube development and thereby give rise to structural malformations. Beside the archetypal model system of frog embryos, our understanding of how these compounds disrupt normal development of mammalian embryos and induce neural tube defects is limited. A zero-integer, latent-response model based on our existing knowledge of the normal biology of

pre-implantation embryos has been formulated to mechanistically address this deficiency. This novel approach makes use of stimulations of mammalian embryo development in vitro, an experimental platform that permits control over the sequence and timing of toxicant exposure. This allows to obtain objective and quantifiable data on the dose-, time- and lineage-dependency of toxicant effects on development. This model brings to light specific key events during the pre-implantation period that are susceptible to disruption by endocrine disruptors and questions about normal and abnormal development that remain to be investigated [12].

There is a great deal of information available from both animal studies and in vitro work on the action of developmental toxicants on the pre-implantation embryo up to and including compaction. These offer insight into what the normal biology is at this time, risky periods of development, and how such action might feasibly occur and lead to a defect at a later stage of development. A data synthesis effort of this type is a very complex task since facts about normal processes are often gathered under varied experimental conditions and may not be fully understood.

The information from different studies therefore generally requires careful interpretation and a good deal of supplementary literature mining to be able to aggregate and conceptualize it in an informative way. Moreover, existing data predominantly concern in vitro technical aspects of development and the cellular/molecular fundamentals thereof while the very important topic of their short and long-term consequences for the embryo has barely been addressed. Nevertheless, significant inroads have been made that can form the basis of this objective-descriptive model [18].

5.2. Regulatory Considerations

Responsible use of drugs and industrial chemicals requires an understanding of how they produce developmental effects. A number of well-defined mechanisms that explain the actions of developmental toxicants on the embryo and embryo cultures have become the bases of both in vitro and in vivo screening test systems.

Developmental toxicity can occur as a result of a compound's :

1. Alterations of the properties of the ovum or sperm that permit fertilization and development,
2. Interference with the actions of specializes development-regulating signals that coordinate the growth, differentiation, and placement of early embryonic tissues,
3. Disruptions to the proliferation and migration of the precursors of these tissue, and ultimately,
4. Alteration of the intrinsic properties of the cells to regulate their cell cycles and determine their fates by apoptosis, programmed differentiation, or entry into quiescent states [8] [34-40]

A variety of natural and synthetic chemicals produce such endocrine disruption effects as observed in wildlife populations. Many of these compounds acting as estrogen agonists have been used in early pregnancy tests, hormone replacement therapies and phytomedicines. Their biocides include pesticides, herbicides, fungicides and inter alia their impurities, polychlorinated biophens and dioxins. Because of the known liability of many of these for human exposure via air, water, and food, there has been a very considerable perturbation of concern over their potential causal link with observable effects on human health range detecting timing irregularities, endrometrial cancers, pregnancy abnormalities, infertility, PCOS, and congenital malformations of the heart, limbs, eye, kidneys, and nervous system [19].

Consequently, considerable progress has been made in the identification, validation and screening of endocrine disruptors using cell-free in vitro assays. Recent work with time-lapse microscopy of fluorescently stained microtubules and networked neural precursor cells describes a rapid, high

throughput assay providing mechanistic insight and predictive ability. In a recent study with embryologically microscopic stages 2 - 25 soratl at concentrations overlapping LC50 levels and pre-micromolar expression levels reported in humans, the standard activator had no effect but typically hormone-like insect interceptors caused neurulation failure in 95 % of the tested embryos via neural tube defects nationwide [18].

6. Future Research Directions

Endocrine disruptors are chemicals that impact mammalian health via the endocrine system. Hormones drive every aspect of normal mammalian development and physiology. Any chemical that impacts hormone action can impact health and development. Such chemicals are ubiquitous environmental contaminants, including natural and anthropogenic substances. This review focuses on one defining event in mammalian development, neural tube closure, and how endocrine disruptors interfere with this process. It also discusses insights gained from in vitro assays developed to study this process and suggests future directions for research [17,37]

Endocrine disruptors interact with the hormones that govern mammalian embryonic developmental processes. Chemistry-driven studies and in vivo and in vitro embryonic models were developed to discern endocrine disruptor targets and mechanisms of action. These studies have identified previously unrecognized interactions between endocrine disruptors and nuclear hormone receptors, particularly retinoic acid receptors and thyroid hormone receptors. Developmentally controlled signaling pathways relevant to neural tube embryogenesis have also been established. However, many questions remain, including identity and proper structure of these signaling molecules [17,18]. These studies have also led to numerous avenues for future research [26].

These in vivo and in vitro models can be used to study a wide variety of candidate endocrine disruptors, especially those that are poorly studied due to technical challenges associated with existing model systems. Many agriculture-related chemicals have been poorly studied in adult or embryo health contexts. Knowledge of the thyroid status of the experimental organisms is often lost in the plethora of studies focusing on the development of an infectious disease model. Adverse disease endpoints that have an endocrine basis should be better validated biochemically and physiologically before and after the commencement of study. This approach may help identify a serum biomarker that accounts for individual variations in susceptibility to diabetes in mice [18,38].

6.1. Longitudinal Studies

In another approach which was only recently discussed in the context of offspring effects in the first placental mammals, longitudinal study designs can be applied to follow development in Wistar rat embryos over the course of four days using up-to 36 h of maternal exposure to the endocrine disruptor DMI [23][12]. Using a microprocessor-controlled range of settings and high-quality 3D acquisitions complemented by 4P-view full analysis of morphology and growth, resulting from a series of experiments including transonic time-lapse and mathematical approaches to maximize the image quality of dynamic motilities and shapes at different precisions, growth rates, as quantified in relation to control embryos, were shown to be significantly delayed before E11 and then regained again during further development under DMI exposure [24]

Population means and variability of many developmental features were shown to be different in the controls versus those 35% and 65% exposed embryos as early as after 20 h and these differences could be robustly analysed by exploratory PCA of an extensive data set. In actual applications, different setup designs for lighting could be employed. Detailed analyses allowed insight into the diversity of the material composition of the small neural tube and the advent of cartilage precursors in specific cartilage elements in some embryos [25-29].

Now they can also be tentatively employed for a study of temporal risk windows and developmental recovery using BrdU incorporation to mark growth disturbance in the embryos.19,39

6.2. Intervention Strategies

Potential candidates to block the adverse effects of endocrine disruptors in vivo are substances already used by patients, species, or exposed populations. Drugs with efficacy in preventing embryo or fetus malformations in humans include anti-hypertensive drug lisinopril, selenomethionine, and the progestin micronized uttered progesterone [9]. Owing to its safety in pregnant women, seleno amine may be a best-suited supplement to study in clinical studies for its capacity to mitigate the effects of teratogens directly or through modulation of downstream signal transduction pathways in human populations. In 1990-1992 cohorts of boys born to mothers who took progesterone related to the first trimester malformations had significantly less NTDs. As it bears no risk of inducing VHS, it would be interesting to test whether it has any protective effects against developing NTDs in high-risk women [17,40]

Supplementation with vitamin B, vitamin C, folic acid, choline, gamma-ocopherol, and other nutrients with antioxidant properties is also postulated to decrease fetopathological effects. In the accepted design setting, drugs and nutritional factors interacting with any of the pathways, endogenous or exogenous, might be tested alone or in combination. Other messages include the identification of new risk factors, intervention strategies, and scientific gaps meriting further investigation. In this regard, there may be potential in a combination of regulatory and public information measures aimed at both minimizing the risks of exposure and increasing the awareness of the factors involved. Recognition of reducing risks would be based as much on encouraging groups known to be at risk to seek preconception screening as on improving the knowledge of the ethics involved in establishing genetic risks [16].

This design risk preconception counseling by obstetricians or midwifery, and additional information could be offered to address neurodevelopmental risks and exposures to endocrine. Existing knowledge on biomarkers for fetal health and development or new research areas that could improve maternal screening could also be suggested. In addition, when considering association, screening could cover parental medication for neural tube defects, complications during pregnancy, drug, and chemical exposure factors of potential relevance in the time course and increased risk groups detected. Further efforts at experimental studies to evaluate the mechanisms through which ED acts are needed to assess the relative weight of different exposures and the potential role of modifiable pathways in end-point evaluations and in identifying appropriate interventions [15,27].

8. Conclusion

Endocrine disruptors are ubiquitous environmental pollutants that can have significant effects on human and wildlife health, leading to nervous defects such as spina bifida and anencephaly in humans as well as neural tube defects (NTD) in experimental mammals. Due to its public health impacts, NTD is included in the list of 23 high priority areas by the Committee on Toxicity. Studies on the pathogenesis and prevention of NTDs due to EDC exposure in mammalian embryos are, therefore, receiving considerable attention. In recent years, the research of NTDs attributable to EDCs in experimental rodents has been advanced [19]. For example, by manipulating meals taken by pregnant mice and the consumption of mineral oil or an aqueous solution of parathion, they reported that failure of folic acid intake before and during conception leads to NTD in embryos. Moreover, atrazine, a widely used herbicide, is also found to be able to cause NTDs by EDC phenomenon in embryonic organs in rat and mouse models as well as the benign volume of rostral neural tube in medaka fish embryo model [20,33]

Disruption of neuroectodermal specification may also be one of the possible pathways by which EDCs play their teratogenic effects. A number of embryonic factors have been documented to function in this process, among which a subset of mesodermal factors can induce ectopic neural tissues and cause ectopic spina bifida. There should also be other pro-neuectoderm genes acting in the non-mesodermal

environment because of the exclusive sensitivity of neuroectoderm in spina bifida fetuses. 21 As a result of gastrulation, the mammalian embryo consists of three germ layers: endoderm, mesoderm, and ectoderm. The ectoderm subsequently divides into neuroectoderm (NE) and non-neural ectoderm at the rostromedial site [21].

This region gives rise to primary neural tube (NT) and secondary NT, which is later closure with neural crest on rods of the NT. EDCs have been found to regulate the activity of Wnt/β-catenin and retinoic acid (RA) signaling pathways. Future studies focusing on emerging EDCs and the compatibility of the current model organisms in further understanding of the interaction mechanism between EDCs and neurotube are needed [22,35]

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