Chapter 1
Maternal Exposure to Environmental Chemicals and Health Outcomes Later in Life

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Abstract The developmental origins of health and disease (DOHaD) paradigm, which was first presented as the Barker hypothesis, has been widely accepted in a variety of medical disciplines, ranging from public health to internal medicine, nutritional sciences, gynecology, pediatrics, and environmental health. Prenatal exposure to industrial chemicals at low doses has been shown to have a critical window during gestation and induce abnormalities later in life following a definite latent period. Such exposure scenarios can now be considered as a critical component that may act as initiating or modifying factors for health and disease status later in life and support the DOHaD paradigm. Exogenous chemicals include methylmercury, pesticides (organophosphates and neonicotinoids), tobacco, polychlorinated biphenyls and dioxins, and diethylstilbestrol, and their late-onset health outcomes include cancers and neurocognitive behavioral abnormalities. In order to understand the DOHaD paradigm, attention needs to be drawn to chemical exposure during the early life stages. Subtle alterations in developmental neurotoxicity that can only be detected by cutting-edge technology using a hypothesis-driven approach are discussed in the present study.

Keywords Chemical exposure · Dioxins · Environmental endocrine disruptors · Industrial chemicals · Methylmercury · Pesticides

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Abbreviations

ADI	Allowable daily intake
AhR	Aryl hydrocarbon receptor
AVPV	Anteroventral periventricular nucleus
BPA	Bisphenol A
CPF	Chlorpyrifos
DES	Diethylstilbestrol
DL	Dioxin-like
DOHaD	Developmental origins of health and disease
EDCs	Endocrine-disrupting chemicals
FOAD	Fetal origins of adult disease
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MPOA	Medial preoptic area
nAChR	Nicotinic acetylcholine receptor
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-*p*-dioxin
PCDF	Polychlorinated dibenzofuran
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin

1.1 Introduction

Human health status is governed by predisposing factors determined by the genome of each individual, as well as by homeostatic regulation of the human body. Predisposition can develop during the evolution processes over a very long period of time, but it can be modulated in response to environmental stimuli, possibly by epigenetic mechanisms, and may be inherited by subsequent generations. Genetic factors were historically believed to play predominant roles in the etiology of chronic diseases, including cancers, cardiovascular disease, and type 2 diabetes mellitus, whereas lifestyle, including high-calorie diet, low level of physical activity, high-salt intake, tobacco, and alcohol, is now considered to significantly contribute to the incidence of these diseases [1]. The etiology of these diseases was challenged by the late Sir David Barker and his associates, who reported a number of epidemiologic studies describing that poor nutritional status during pregnancy is associated with increased rates of coronary heart disease, stroke, type 2 diabetes mellitus, adiposity, the metabolic syndrome, and osteoporosis in adult life [2, 3]. They proposed the "thrifty phenotype" hypothesis, stating that poor nutritional status in fetal and early infant life is detrimental to the development and function of the individuals' organism, predisposing them to the development of adult chronic diseases. This theory indicates that causal factors of adult-onset diseases may exist during early life, which lead to alteration of health status and disease phenotypes. With a greater number of observations that support the Barker theory by epidemiologic and clinical studies as well

as laboratory animal studies, the term "Barker theory" was renamed FOAD (fetal origins of adult disease) and subsequently to DOHaD to recognize and broaden the concept that perinatal environment can shape both health and disease in resulting offspring [4]. Readers are suggested to refer to other articles in this book.

Because major health outcomes on which the DOHaD paradigm relies were lifestyle-related diseases, it was natural that the majority of researchers who led the study of the DOHaD paradigm at the initial stage were clinical or public health oriented and nutritional status was intensively investigated as a main environmental factor. However, researchers in the field of environmental health and toxicology who have been studying environmental pollutants as well as endocrine-disrupting chemicals (EDCs) realized that some of the important properties of these chemicals, such as late-onset toxicity, critical window, and latency, could have commonalities, although not entirely, with the DOHaD paradigm.

Until the late 1990s, the majority of scientific concerns on the possible impacts of environmental pollutants on public health have been directed to the occurrence of catastrophic diseases which occurred in various parts of the world. These include *Minamata* disease, *itai-itai* disease, chronic obstructive pulmonary diseases from air pollution, dioxin, and PCB-induced poisoning, chronic arsenic poisoning, and various types of cancers caused by exposure to asbestos, chromium, and other chemicals. In addition, toxicological research became institutionalized in the USA in response to public concern about cancer and acute mortality [5]. Little attention was paid to pesticides and industrial synthetic chemicals that have adverse effects on endocrine function. Incidentally, since the late 1990s, environmental chemicals that may act as "environmental estrogens" have gained increasing attention of researchers in toxicology, endocrinology and developmental biology, and epidemiology. In the late 1990s, the term "environmental hormones" was coined and used in official governmental documents and also used by Japanese media for some time. However, the use of this term has now been discontinued in official documents due to possible imprecise interpretations.

Scientists as well as stakeholders were challenged to hypothesize that humans and wildlife species have suffered adverse health effects after exposure to endocrine-disrupting chemicals (EDCs). The book, entitled *Our Stolen Future* by Colborn and associates [6], has become a milestone in research on the health of humans and wildlife. EDCs is defined as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations" [7]. In particular, the mode of action of EDCs is unique. Low-dose exposure to EDCs during early life (gestation and lactation periods) does not exert overt toxicity in mothers or offspring; there is often a critical window in gestational or neonatal periods. However, the latency period, between chemical exposure and the onset of symptoms later in life, is a premise of the DOHaD paradigm, but not necessarily for the mode of action of the EDCs.

1.2 Chemical Exposure and the DOHaD Paradigm

To examine when the "DOHaD" paradigm was intentionally internalized in the research on chemical exposure, in this review, I surveyed literature on Medline. A PubMed search using the term "DOHaD" in "all fields" yielded 269 papers as of April 21, 2017. The first paper that had the term "DOHaD" was published in 2005 [8]. When the terms "DOHaD" and "chemical" were searched together in "all fields," only 16 papers were found. A paper by Grun and Blumberg [9] specifically described an obesogen concept of chemicals, such as tributyltin, in the context of DOHaD. Bezek's short review [10] mentions chemical exposure in the context in DOHaD, but there is no detailed discussion. In a conference statement [11], the importance of research on the effects of prenatal and early postnatal exposure to chemical agents and their sustained effects on the individual throughout the lifespan was emphasized, and this concept was developed as the DOHaD paradigm. A review article by Rosenfeld [12] may be the first to comprehensively place chemical exposures in the DOHaD paradigm. In this review article, however, the endpoint of environmental chemical exposure was focused on an association of sex dimorphic responses of zygotes and conceptuses in response to exposure to EDCs, with neurobehavioral changes later in life as a DOHaD outcome.

Recently, Heindel and associates [13] reported a review article, based on their extensive survey of original papers in environmental epidemiology with regard to the DOHaD paradigm. The authors reviewed 2675 publications in environmental epidemiology and 425 publications published by the end of year 2014. They selected papers with contents essentially related to the DOHaD paradigm, or proof of concept approach, even if there was no mention on DOHaD in a given paper. The papers examined were original research in humans that examined the association between prenatal and/or early childhood exposures (up to 8 years old) to environmental chemicals and adverse health outcomes later in life. Based on their analysis, these papers dealt with perinatal exposure to 60 different chemicals (excluding tobacco, alcohol, and pharmaceuticals but including diethylstilbestrol as a prototypical chemical for the proof of concept) to the health effects later in life [13]. By a trend analysis of health outcomes, DOHaD epidemiology publications on adverse health outcomes are related to neurological/cognitive outcomes (n = 211 publications), followed by cancer (n = 59), respiratory (n = 50), metabolic outcomes including obesity (n = 35), reproductive health (n = 31), immune disorders (n = 29), endocrine (n = 22), and cardiovascular dysfunctions (n = 12) with less than 10 publications each focusing on the skin, musculoskeletal, visual problems, gastrointestinal, and liver. This review article claims that many papers on environmental chemical exposure that were published before the emergence of the Barker theory or DOHaD paradigm described phenomena that could still be explained by the DOHaD paradigm. Whether each paper cited in this review appropriately represents a DOHaD paradigm from the chemical exposure point of view should be evaluated by readers. It should be pointed out that the dataset of all the selected literature which is available to readers might be useful as a common platform for the literature survey on the DOHaD and chemical exposure research.

To sum up the two independent results on the literature surveys as described above, the DOHaD paradigm conceived by unique observations on poor nutritional status during early life was also influenced by environmental chemical exposure during this period. The influence of chemical exposure opened up a new avenue of research field in the context of the DOHaD paradigm. Since the majority of papers on chemical exposure-related DOHaD tend to deal with neurological/cognitive outcomes and cancer [13], this review mainly describes these types of disorders.

1.3 A Wide Spectrum of Health Outcomes by Chemical Exposure

The life of mammals, including humans, is regulated to maintain homeostasis in response to environmental stress. However, when the degree of stress, such as dose of a chemical, overwhelms the physiological capacity, homeostasis is disrupted, and abnormal signs and symptoms manifest. In case of chemical exposure, there are many examples in which the exposure level and timing of a chemical can induce severe systemic abnormalities. In the context of the DOHaD paradigm, such cases may represent an extreme end of the spectrum of abnormalities.

A prototypical example is *Minamata* disease, caused by methylmercury poisoning in Japan. The officially certified year of outbreak of this human tragedy was 1956. Many people living around *Minamata* Bay have been suffering from the effects of this chemical for several decades after exposure. Humans are protected from xenobiotic chemicals by barrier systems in the body. The most well-known barrier system is the blood-brain barrier, which is composed of a complex structure of astrocytes and unfenestrated endothelial cells in the capillaries. Another barrier system is the fetoplacental barrier, in which maternal and fetal circulation are separate and do not mix. However, these barrier systems are overwhelmed by excessive exposure to methylmercury. The inability of these barrier systems and the presence of a critical window of vulnerability were shown in *Minamata* disease. Methylmercury, a lipophilic low molecular weight chemical, can be easily transferred through the fetoplacental barrier and also through the blood-brain barrier even in adults. When pregnant women regularly ate heavily contaminated fish, methylmercury was transferred from mother to fetus via the placenta. The developing brain of the fetus was thus heavily exposed to methylmercury. Consequently, fetuses were more severely afflicted with central nervous system disorders, named "congenital *Minamata* disease." The affected fetuses are considered to act as a sink for methylmercury, thus mitigating the severity of toxicity in the mother [14]. However, it should be pointed out that congenital *Minamata* disease does not directly go with the DOHaD theory because newborn babies have manifested devastatingly abnormal signs and symptoms soon after birth without a latency period. In addition, histopathologic examination of brain tissue obtained from patients at necropsy revealed conspicuous degeneration of neuronal tissue. It should be noted that the congenital *Minamata* disease is regarded as the most extreme end of the

spectrum of methylmercury poisoning. However, it is conceivable that pregnant women who are exposed to methylmercury at low doses that do not induce conspicuous abnormalities may deliver newborn babies who might develop behavioral or cognitive abnormalities later in life, which may fit into the DOHaD paradigm, as described below. Besides methylmercury poisoning, other chemical poisoning cases, including DES, dioxin/PCBs, and arsenic, may also reflect the extreme end of the spectrum of abnormal phenotypes.

1.4 Prenatal Chemical Exposure and Late-Onset Cancers in Offspring

Prenatal exposure to the pharmaceutical diethylstilbestrol (DES) is considered to be adopted as a proof of principle to study the DOHaD paradigm [15]. DES is a potent synthetic estrogen and was extensively prescribed in the USA, Canada, and some European countries to pregnant women from the 1940s to the 1970s. In these countries, this drug was mistakenly believed to prevent miscarriage, premature labor, and related complications of pregnancy [16]. It is estimated that over ten million people were exposed only in the USA and that 1/1000 developed cancer of the cervix and vagina in offspring who were born to DES-prescribed mothers during pregnancy. Furthermore, other health problems including a higher incidence of breast cancer in women and testicular abnormalities (undescended testicles and epididymal cysts) in men born to mothers who were treated with DES have been noted. However, the association is not clear-cut, and definitive conclusions cannot be drawn [16, 17].

As to the possible occurrence of DES-related health problems in Japan, no English language papers that report the prescription of DES to pregnant women in Japan are available. Mizutani intensively examined Japanese literature that reported the DES situation in Japan and published a book on DES poisoning [18]. Since this is the only book so far published on the DES situation in Japan, I briefly present his findings, although this topic may not be in the mainstream of this review. First, in Japan, DES and its derivatives were introduced to the market between 1940 and 1960 but banned for use in pregnant women by the Ministry of Health in December, 1971. Second, the dose of DES contained in a pellet sold in Japan was approximately 1 mg/day, which was much lower than the dose recommended for use in the USA (5–125 mg/day). Third, literature analysis indicated that hormone treatment for premature delivery or miscarriage using DES and its derivatives adopted in the USA and other countries did not receive strong support from Japanese obstetricians/gynecologists after its introduction in Japan but instead received criticism. Overall, Mizutani [18] concluded that DES treatment was introduced to obstetrics and gynecology practice in Japan on a very limited scale and did not become common practice.

The late-onset abnormalities observed in the offspring born to mothers administered DES during gestation have been supported by many experimental studies. McLachlan and colleagues [19] showed that male mice offspring (60%) born to dams exposed to DES were sterile with intra-abdominal or fibrotic testes or both

and that nodular masses were observed in the ampullary region of the reproductive tract in 6 of 24 animals, with 1 undergoing a seemingly preneoplastic change. Nomura and associates [20] reported that DES was transferred to the fetus via placenta and that a critical window exists during gestation (days 15–19). They found that female offspring was sensitive to abnormalities in the uterus and vagina and that male offspring was susceptible to have undescended testes and hypogenesis. They also found that the incidence of various tumors (lung adenoma, granulosa cell tumor, etc.) increased significantly when DES was given in the critical window (days 15 and 17), which correspond to the stage that is sensitive to other carcinogens. However, adenosis and adenocarcinoma of the vagina were not observed in the offspring. These animal models as well as other later studies strongly support the mechanism of DES toxicity in human cases.

It is well-known that a prolonged latency period, often up to several years, is required for the pathogenesis of cancers, regardless of the cause. Yamagiwa and Ichikawa first established a chemical carcinogenesis animal model in 1915, by topically applying coal tar for hundreds of days to produce carcinoma in the rabbit ear [21]. A representative chemical carcinogenesis model has been established as two-stage or multistage model. The stages comprise of initiation, promotion, and progression [22]. The DES-induced cancers may fit into a model of a chemical carcinogenesis. However, DES-induced cancers have features distinct from the chemically induced skin or colon cancers; the former has a very narrow critical window in the neonatal period [23], whereas the latter does not and occurs during adulthood.

1.5 Prenatal Chemical Exposure and Neurobehavioral and Cognitive Abnormalities

Epidemiologic and animal studies have shown that the developing brain is extremely vulnerable to exogenous chemicals (Fig. 1.1). Although at least 80,000 synthetic chemicals have been on the market, many potential neurotoxicants have not been identified or examined for developmental neurotoxicity because of the costs involved or absence of a legal requirement [24]. It should be pointed out that in the Heindel review [13], tobacco- and alcohol-related papers were not included; had they been included as keywords, the number of papers may have increased. Grandjean and Landrigan [25] reported that at least a dozen exogenous chemicals act as neurotoxicants, which include lead, methylmercury, polychlorinated biphenyls, arsenic, toluene, manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and polybrominated diphenyl ethers. From risk assessment based on environmental health point of view, we need to consider that late-onset abnormalities may be caused by prenatal exposure to low-dose chemicals that do not overly harm pregnant women as well as their fetuses. Moreover, subtle alterations not detected by routine diagnostic procedures, presumably induced by epigenetic mechanisms, may also cause such abnormalities. Such exposure scenarios may fall into the DOHaD paradigm.

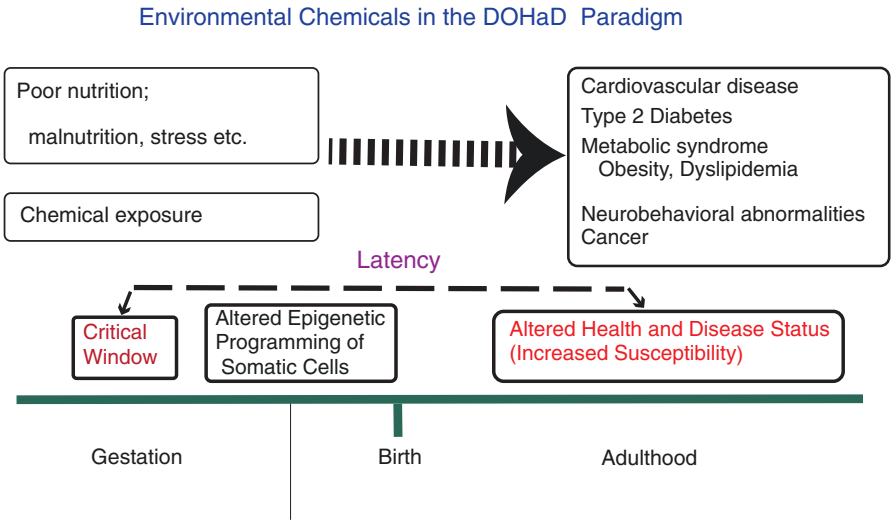

Fig. 1.1 A scheme of the DOHaD paradigm with regard to chemical exposure

Majority of the neurotoxicants have physicochemical properties like low molecular weight and high lipophilicity that help them penetrate the fetoplacental and blood-brain barriers and may elicit toxicity because these barriers normally block the entry of chemicals into the brain parenchyma. Exposure assessment data show that environmental levels of these chemicals are frequently detected in food material. Thus, it is conceivable that they are ingested by pregnant women through food and transferred to the fetus, leading to adverse effects on growth and development of fetal tissue and eventually inducing late-onset abnormalities in their developing brain. If prenatal rather than postnatal exposure is more likely to lead to adverse health outcomes, the etiology can be considered to fall in into the spectrum of DOHaD.

The following are some examples of the chemicals that induce developmental neurotoxicity that fits into the DOHaD concept.

Methylmercury. The primary source of methylmercury exposure in daily life is consumption of higher trophic level fish, like bluefin tuna and swordfish, and marine mammals, like whales and dolphins. No conspicuous abnormalities are diagnosed by physicians with daily exposure to environmental levels of methylmercury, which is in contrast to the severe symptoms of *Minamata* disease or Iraqi poisoning victims. However, subtle neurodevelopmental effects have been observed in populations with moderate methylmercury exposures in a cohort study in the Faeroe Islands where whales have been traditionally caught and consumed for a living. For example, in a study on 878 offspring, who were 14 years old, indicators of prenatal methylmercury exposure were significantly associated with deficits in finger tapping speed, reaction time on a continued performance task, and cued naming. In the islands belonging to the Republic of Seychelles, a target population of pairs of

mothers and infants who were exposed to methylmercury mainly via various kinds of fish were subjected to a cohort study. Results from the Seychelles cohort studies were used to derive NOAEL of methylmercury in infants. These epidemiological study results were used to derive provisional tolerable intake level by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) [26].

Arsenic. Over 20 million people are exposed to arsenic-contaminated water worldwide, such as Bangladesh, China, India, Chile, and many other countries. The WHO's current recommended limit of arsenic in drinking water is 10 μg/L, although this level is designated as provisional because of measurement difficulties and the practical difficulties in removing arsenic from drinking water [27]. In the city of Antofagasta in northern Chile, more than 250,000 people were exposed to a high arsenic content in drinking water (870 μg/L) from 1958 until 1970 when exposure was terminated by installation and operation of an arsenic removal plant. The epidemiologic studies carried out in this area have some advantages over similar studies in other parts of the world for clarifying dose-response relationship. The lifetime exposure and long-term latency patterns can be assessed with better accuracy from the Antofagasta studies because of its unique geology, limited water sources, and good historical records [28]. Evidence of increased mortality from lung cancer, bronchiectasis, myocardial infarction, and kidney cancer has been reported among young adults who were born when tap water was highly contaminated with arsenic between 1958 and 1970 or were less than 18 years old. In addition, epidemiologic studies carried out between 2007 and 2010, approximately 40 years after the cessation of high-level arsenic exposure, indicate a high prevalence of lung and bladder cancer. It is concluded that exposure to arsenic in utero or during infancy may enhance the tendency to getting afflicted with the abovementioned diseases [29]. These observations are important in terms of risk assessment of arsenic because some food commodities contained non-negligible concentrations of inorganic arsenic, including *hijiki*, a kind of seaweed. An alert not to eat this seaweed has been issued in the UK, whereas *hijiki* is commonly consumed by the Japanese population.

Tobacco. Smoking during pregnancy predisposes the fetus to many kinds of potentially hazardous chemicals. Nicotine and carbon monoxide are typical chemicals, both of which penetrate the fetoplacental barrier. Adverse effects of prenatal smoking exposure have been well-documented. Growth of the body and the head of the fetus can be hampered, and alterations in brain structure and function can be seen in children who are exposed to prenatal smoking. In addition to these short-term effects, prenatal smoking was found to alter cardiovascular function (blood pressure control and heart rate response) 1 year after birth [30]. Altered function of the nicotinic acetylcholine receptor (nAChR) by prenatal nicotine exposure is closely involved in the abnormal development of the brain. Nicotine exposure during pregnancy has been shown to affect brain cell replication and differentiation, leading to changes in brain structure, such as impaired growth of the rat forebrain [31]. Tobacco smoking during pregnancy also elevates carbon monoxide concentration not only in maternal blood but also in fetal blood because it can pass through the placenta. Carbon monoxide binds to hemoglobin and produces carboxyhemoglobin, which

impairs oxygen delivery to the fetus. Furthermore, prenatal nicotine exposure was found to affect the contractility of the uterine arteries and to decrease uterine blood flow in pregnant animals [32]. Therefore, maternal smoking during pregnancy can lead to fetal hypoxia and ischemia, which may disrupt normal growth and development of the fetal brain.

Prenatal passive smoking was inversely associated with neurodevelopmental outcomes in young children, whereas postnatal passive smoking was associated with poor academic achievement and neurocognitive performance in older children and adolescents. Furthermore, Chen and associates [33] systematically reviewed articles (dated 1989–2012) that investigated the association between passive smoking, focusing on prenatal exposure by pregnant women, and performance on neurocognitive and academic tests. It was confirmed that passive smoking by pregnant women showed a strong association with reduced neurodevelopment especially in children aged younger than 5 years, even after controlling for postnatal passive smoking. Children, on an individual basis, who were prenatally exposed to passive smoking were in a normal range in cognitive performance, but on a group basis, their cognitive performance was lower than those who were not exposed. The literature on passive smoking during prenatal and postnatal periods consistently indicates associations with increased rates of behavior problems, including irritability, oppositional defiant behavior, conduct disorders, and attention deficit hyperactivity disorder, although the relative roles of prenatal vs. postnatal exposure have not been studied [34].

Humans are exposed to pesticides through food and environment. Because of the accumulated knowledge on health problems in children from daily exposure to pesticides, the American Academy of Pediatrics [35] published a position paper, stating that epidemiologic evidence demonstrates associations between early life exposure to pesticides and pediatric cancers, decreased cognitive function, and behavioral problems. Biomonitoring of urinary organophosphate metabolites indicated associations of exposure to organophosphates with neurotoxicity outcomes, including poor mental development, attention-deficit/hyperactivity disorder, low IQ scores, and parent-reported behavioral problems [36–41].

Among OP pesticides, chlorpyrifos (CPF) has been widely used as a broad-spectrum organophosphate insecticide for pest control. Prenatal exposure to CPF is associated with neurobehavioral deficits in humans and animal models. Rauh and associates [39] investigated the association between CPF exposure and brain morphology using magnetic resonance imaging in 40 children (5.9–11.2 years old), selected from a nonclinical, representative community-based cohort. When the subjects were categorized by CPF concentrations in umbilical cord blood, a significant association was observed between prenatal exposure to CPF and structural changes in the developing human brain. Although the route of exposure to pesticides can be multiple, an intervention study clearly demonstrated that the most influential route of exposure is through the diet. In that study, diet was replaced with organic food items for 5 consecutive days, and urine specimens were collected from 23 children for 2 weeks including the intervention period. Urinary levels of organophosphates pesticides showed that metabolites for malathion and chlorpyrifos decreased to the

undetectable levels immediately after the introduction of organic diet and remained so until conventional diet was reintroduced [42].

Recently, organophosphorus pesticides have been gradually replaced with neonicotinoid pesticides, and the total amounts of production of OPs decreased from approximately 6000 tons in 2000 to approximately 2000 tons in 2011. The use of neonicotinoid pesticides for pest control has been registered in more than 120 countries in the world, with global production being valued at US$2.5 billion [43]. According to a recent study on exposure assessment of OPs and neonicotinoids [44], urine specimens obtained from Japanese women during the period 1994–2011 indicate a decreasing trend of the excreted amounts of OPs and an increasing trend of neonicotinoids (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam). More importantly, it should be borne in mind that neonicotinoids, as well as organophosphates and pyrethroids, that were not naturally present in humans were detected in urine specimens from infants ([45]; Ikenaka et al., personal communication). Sano et al. [46] reported that only male mice born to dams administered with acetamiprid from gestational day 6 to lactation day 21 showed abnormalities in sociosexual and anxiety-related behaviors, without a change in the testosterone level. An excitatory action of acetamiprid or imidacloprid on neurons via nicotinic acetylcholine receptor subtypes was shown by an in vitro study using primary cultures of cerebellar neurons from neonatal rats [47]. Thus, it is reasonable to consider that OPs, neonicotinoids, and possibly PYRs in food commodities are absorbed by pregnant women and infants and retained for a prolonged time to induce abnormalities in the developing brain and lead to other disease states.

Dioxins. Polychlorinated dibenzo-*p*-dioxin (PCDD), dibenzofuran (PCDF), and biphenyl (PCB) congeners are persistent, and ubiquitous environmental contaminants that are found in air, water, soil, and sediment bioaccumulate in various animal species including humans worldwide. PCDDs and PCDFs are unintentional byproducts of combustion and various industrial activities. PCB mixtures were commercial products widely used as heat-resistant solvents and lubricants and in fluorescent light ballasts before they were banned. A subset of PCDD, PCDF, and PCB congeners can bind and activate aryl hydrocarbon receptor (AhR) to exert various kinds of toxicities, such as metabolic disorders, reproductive toxicity and neurodevelopmental toxicity, immunosuppression, and carcinogenicity, and referred as dioxin-like (DL) congeners or simply as dioxins [48]. Among them, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the most potent in causing toxicity and is the prototype to which biological and toxicological actions of all other DL-congeners are compared. With regard to the DOHaD paradigm, it is important to point out that in utero and lactational exposure to low dose of TCDD was shown to induce toxicity phenotypes in rodents and nonhuman primates, such as abnormalities in higher brain function, sexual differentiation (demasculinization), and immune dysfunction, in offspring during adulthood. It has been established that AhR is essential for the manifestation of the majority of toxicity phenotypes, but the morphological and functional cause that determines toxicity phenotypes beyond AhR signaling remains largely unstudied [49].

1.6 Alterations During Gestation That May Link Chemical Exposure and the DOHaD Phenotypes

Pathogenesis of lifestyle-related diseases that the DOHaD paradigm relies on differs by disease phenotypes, although the commonality of the pathogenesis is that a factor(s) during the gestational and neonatal periods could affect the health status of the offspring. In the case of chemical exposure, perinatal exposure to low-dose chemical exposure has been known to affect function of the developing brain, which results in abnormalities in cognitive and behavioral functions later in adulthood. However, the underlying mechanisms that link chemical exposure and the health outcomes are largely unknown.

A battery of behavioral tests as well as histopathologic techniques recommended for use in developmental toxicity testing by OECD test guideline 426 may lack reliability and detection sensitivity [24]. For example, the number of pesticides that were said to be subjected to these DNT test guidelines is extremely limited, and almost no endpoints have been used to derive allowable daily intake (ADI) [24]. In other words, in order to minimize the potential for developmental neurotoxicity, the application of cutting-edge techniques to the hypothesis-driven DNT testing is likely to be able to detect subtle or early-phase alteratons in the offspring [50].

A given chemical, which belongs to a group of EDCs and has an estrogenic or androgenic activity, may induce neurobehavioral disturbances by disrupting sex hormone receptor-mediated mechanisms. Mammalian brain is sexually differentiated during perinatal period by estradiol, which is aromatized in the brain from androgen synthesized in the fetal and neonatal testis. Female brains were protected by plasma glycoproteins that bind circulating estrogens. The amount of steroid in well-established sexually dimorphic regions is typically higher than that in the hippocampus and cortex and may be due to a combination of regionally specific uptake, synthesis, and metabolism [51]. Thus, it is reasonable to suspect that bisphenol A (BPA) may have such an effect.

Bisphenol A has been widely used in the production of polycarbonate plastics, epoxy resins used to line metal cans, and numerous plastic consumer products and has been most extensively studied and evaluated for endocrine-disrupting activities with regard to risk assessment purposes [52]. Perinatal exposure to low doses of BPA downregulated the expression levels of estrogen receptor α and β in sexual dimorphic regions, anteroventral periventricular nucleus (AVPV), and medial preoptic area (MPOA) in the hypothalamus of rats. BPA has been known to interact with ERα and ERβ and has been shown to interfere with hippocampal synaptogenesis [53, 54].

An application of cutting-edge techniques, which are not meant to be used in the toxicology test guidelines, revealed that perinatal exposure of BPA, TCDD, or other chemicals may induce abnormalities at the neuronal micromorphology level in brain regions, such as hippocampus and amygdala that govern learning/memory and memory, respectively. Perinatal BPA exposure to rodents was found to induce morphological abnormalities in neuronal development [55]. Prenatal exposure to a low-dose BPA

(40 or 400 μg/kg body weight per day) impaired not only the branching of dendrites of hippocampal neurons at an earlier developmental stage but also dendritic spine density in a hippocampal subregion during adulthood. It is shown that such alterations that occurred during brain development persist to adulthood and lead to behavioral and cognitive abnormalities, such as anxiety-like behavior, loss of exploration, learning/and memory, socio-sexual behaviors across mammalian species [56–59], and social recognition difficulties [60]. However, the molecular basis of such behavioral and cognitive disorders is not fully understood. No study has conclusively shown that BPA altered Dnmt expression or chromatin modification after BPA exposure influences sexual differentiation of the brain in adulthood [61].

Rodent offspring born to dams administered with a low-dose TCDD has been shown to manifest cognitive and behavioral abnormalities, such as spatial, reversal, and alternate and paired associate learning and memory, as well as anxiety and sociality in adulthood [62–69]. In mice offspring under the identical TCDD exposure conditions as in our laboratory, 14-day-old mice exhibited disrupted dendritic branch growth in both the hippocampus and amygdala, and 16-month-old mice had significantly reduced spine densities in the hippocampus [70]. Prenatal exposure to TCDD was found to disrupt the gene expression of glutamate receptor subunits and BDNF, the molecules that control spatial learning and epigenetic-mediated learning, respectively, in the hippocampus and cerebral cortex [71, 72] and induced imbalance of neural activity between the prefrontal cortex and amygdala [62].

Taken together, it is concluded that the micromorphological evidence on BPA- or TCDD-exposed developing brain links chemical exposure with cognitive and behavioral abnormalities. It is implicated that scrutiny using the most appropriate and sensitive state-of-the-art assays [50] that can determine minute alterations, such as neuronal morphology, is needed in developmental neurotoxicity testing in order to clarify the underlying mechanisms of the DOHaD paradigm.

1.7 Conclusion

The DOHaD paradigm has been gaining increasing interest from various disciplines of medical science. Researches on the prenatal low-dose exposure to environmental and industrial chemicals, such as heavy metals, pesticides, tobacco, alcohol, dioxins, and diethylstilbestrol, have revealed that not only the poor nutritional status during gestation but also prenatal chemical exposure may have some characteristics, such as critical window and latency between the time of exposure and health outcomes, in common with the DOHaD paradigm. The nature of the mechanisms underlying the abnormal health outcomes induced by chemical exposure with regard to the DOHaD paradigm is largely unknown. In particular, to clarify the underlying mechanisms of developmental neurotoxicity in the context of the DOHaD paradigm, the most appropriate and sensitive state-of-the-art assays that can detect subtle changes at the micromorphological or molecular levels based on a hypothesis-driven approach are needed.

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