Current Neuropharmacology, 2022, *20*, 766-776

REVIEW ARTICLE

Effects of Di-2-Ethylhexyl Phthalate on Central Nervous System Functions: A Narrative Review

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ARTICLE HISTORY

Received: May 15, 2021
Revised: June 23, 2021
Accepted: July 03, 2021

DOI:
10.2174/1570159X19666210713122517

Abstract: ***Background*:** Phthalates are widely used in the plastics industry. Di-2-Ethylhexyl Phthalate (DEHP) is one of the most important phthalate metabolites that disrupt the function of endocrine glands. Exposure to DEHP causes numerous effects on animals, humans, and the environment. Low doses of DEHP increase neurotoxicity in the nervous system that has arisen deep concerns due to the widespread nature of DEHP exposure and its high absorption during brain development.

***Objective*:** In this review article, we evaluated the impacts of DEHP exposure from birth to adulthood on neurobehavioral damages. Then, the possible mechanisms of DEHP-induced neurobehavioral impairment were discussed.

***Methodology*:** Peer-reviewed articles were extracted through Embase, PubMed, and Google Scholar till the year 2021.

***Results*:** The results showed that exposure to DEHP during pregnancy and infancy leads to memory loss and irreversible nervous system damage.

***Conclusion*:** Overall, it seems that increased levels of oxidative stress and inflammatory mediators possess a pivotal role in DEHP-induced neurobehavioral impairment.

Keywords: Endocrine disruptors, phthalates, di-2-ethylhexyl phthalate, neurotoxicity, memory deficits, neurobehavioral impairment.

1. INTRODUCTION

Phthalates are one of the most important plasticizers that increase the durability of plastic polymers [1]. Diisononyl phthalates (DINPs), dibutyl phthalates (DBP), diisodecyl phthalates (DIDPs), Di(2-ethylhexyl)phthalate (DEHP) and Benzyl Butyl Phthalates (BBP) are the most commonly used phthalates in the plastics industry [2].

DEHP (also named diethyl phthalate (DOP) or bis (2-Ethylhexyl) phthalate) is the most pivotal member of phthalates. It is a colorless, lipophilic, and viscous liquid that is almost insoluble in water [3]. DEHP is available in various products including plastic containers, toys, cosmetics, and medical equipment [4, 5]. People may be exposed to different concentrations of phthalates *via* inhalation, oral, and dermal exposure [6]. Over 2 million tons of DEHP are produced annually in the world [7]. DEHP can strongly attach to dust particles in the air and soil and is dissolved in the groundwater. Therefore, DEHP is one of the broadest water pollutants [8, 9]. There are increasing worries about the continued exposure of human beings to the increasing environmental DEHP levels. The permissible amount of human contact per day is between 4-30 μg of DEHP. However, some people are at a greater risk of this substance due to high contact with medical equipment containing plastic materials [10].

After entering the body, DEHP is converted to various metabolites. These major metabolites are D-n-butyl phthalate (DnBP), di-n-octylphthalate (DnOP), diethyl phthalate (DEP), and benzylbutylphthalate (BBzP) [11]. Secondary oxidized DEHP metabolites are mono [2- (carboxymethyl) hexyl] phthalate (2cx-MMHP), mono (2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), and mono (2-ethyl-5-carbo) phthalate (5cx-MEPP) [12]. DEHP is converted to monoethylhexyl phthalate (MEHP) by lipase. MEHP is more toxic than DEHP and absorbed by tissues due to its lower viscosity.

DEHP induces toxicity in several targets including the endocrine system [13], renal system [14], liver [15], ovary

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1875-6190/22 $65.00+.00

[16], testis [17], and heart [18]. Brain tissue is one of the most important targets threatened by phthalates [19, 20]. Since DEHP can pass the placenta, Blood-Brain Barrier (BBB), and breast milk, it affects the neural development of the fetal brain, mental ability and social behaviors [21, 22].

Due to daily contact with phthalates and their high absorption, especially in sensitive periods of brain development, this study aimed to investigate the possible impacts of DEHP on the function of the nervous system. Furthermore, the possible mechanisms of DEHP-induced neurobehavioral deficits were discussed. The neurobehavioral impacts of DEHP were also compared in males and females.

2. DEHP-INDUCED NEUROBEHAVIORAL TOXICITY

Phthalates play an important role in the incidence of numerous neuropsychiatric disorders in humans such as Attention Deficit Hyperactivity Disorder (ADHD) [23], autism [24], and learning disabilities. Surprisingly, the prevalence of these impairments is higher in males [25].

In rodents, several studies have shown that DEHP may impair brain growth [3] and cause neurodegeneration [26]. DEHP exposure decreases neuronal growth and increases axonal degeneration, sphingomyelin, and phosphatidylcholine levels in rat hippocampus [27]. It also diminishes cognitive functions and impairs neural function by increasing inflammatory factors and reducing testosterone levels [28]. Additionally, DEHP reduces social interactions and augments anxiety-like behaviors and neurological impairments in first-generation puppies. Many studies have reported that the adverse effects of DEHP on behavioral parameters persist for several generations [29]. In a previous study, mothers were subjected to DEHP for 10 days during pregnancy. The obtained results using the Morris Water Maze test showed that DEHP significantly reduces the spatial learning and memory of male rat pups in adulthood [3]. A recent study also showed that administration of DEHP at doses of 50 and 200 mg/kg during pregnancy and lactation significantly decreases the spatial learning and memory in mice puppies [30]. The effects of prenatal exposure to DEHP on anxiety-like behavior were also investigated using a plus-maze test in male and female mice at different stages of sexual development. The results indicated that exposure to DEHP significantly reduces the percentage of open arm entry and promotes closed-arm entry [31]. Another study examined the effects of DEHP at high (750 mg/kg) and low (200 μg/kg) doses on the behavioral parameters of mice puppies born between the age of 16 and 22 months. The levels of anxiety and behavioral deficits were measured using the Y-Maze Test and Novel Object Recognition Test. The results demonstrated that DEHP causes behavioral impairments and reduces the spatial and short-term memories of male progeny [26]. In addition, exposure to DEHP at doses 10 to 200 mg/kg during pregnancy and lactation increased the anxiety and incidence of severe depressive behavior in male and female progenies [32].

3. EFFECTS OF DEHP EXPOSURE ON NERVOUS SYSTEM FUNCTION OF ANIMALS

Hippocampus is very vulnerable to environmental toxicants including phthalate in the early development of the brain. In rodents, days 16 to 21 of pregnancy are considered critical periods for hippocampus development and hippocampal-based cognitive functions are emerged at this period [30]. Similar to DEHP, the primary metabolite of DEHP, mono-(2-Ethylhexyl) phthalate, can also be transferred through the placenta to the fetus and breast milk to the infants. Neurotoxicity and brain growth abnormalities can be initiated in the pregnancy and lactation periods [19, 33]. Exposure to DEHP (1500 mg/kg) from Gestational Day (GD) 0 to GD 19 disrupts the lipid metabolism of mice brains. Fats, particularly Essential Fatty Acids (EFAs), have an important role in fetal growth and being in contact with plasticizes they may change the lipid transport to the fetus [21]. The alternation in the above-mentioned lipids reduces the cell membrane stability, hippocampal neuronal growth, and the abundance of some lipid species, including sphingomyelin and phosphatidylcholine which can alter neural development [27]. DEHP exposure (200 μg, 500 mg, or 750 mg/kg/day) from GD 11 until birth caused neurodegeneration in the nervous system of mice [26]. It has been indicated that DEHP drastically reduces the brain weight of rodent newborns [33]. A recent study illustrated that DEHP causes irreversible brain damage in the fetus by raising the malondialdehyde (MDA) levels or peroxisomal changes in supplying the essential fatty acids. In the developing fetus, unsaturated fatty acids are primarily produced and transported through carrier proteins all over the placenta [22, 34]. The amount of arachidonic acid and docosahexaenoic acid exerts a significant influence on neurodevelopment, regulation of sex hormones, and the normal growth of the fetal brain. Diethylhexyl phthalate, as an anti-androgenic compound, can affect fetal brain development [35, 36]. Additionally, infant exposure to phthalates causes a severe decline in the number of neurons, movement impairment, and hyperactivity *via* increasing oxidative stress in the brain tissue [33, 37].

DEHP exposure in lactation and pregnancy had influences on the activity of aromatase in the hypothalamus. The action of aromatase in male rats (postnatal days (PND) 1) was hampered in low concentrations of DEHP (less than 0.405 mg/kg/day) and raised in high concentrations (more than 15 mg/kg/day) [38]. In our recent study, DEHP exposure at low doses during pregnancy and lactation (GD 0-PND 21) caused memory impairment in the adult offspring rats [39]. Actually, DEHP changes the hippocampal lipid profile and results in higher levels of sphingomyelin and phosphatidylcholine in the female compared to the male mice. Therefore, since lipids play a vital role in neuroprotection, the resistance of females to destructive impacts of DEHP may be associated with cerebral lipid metabolism [27, 40, 41]. Table **1** [42-50] summarizes some evidence of DEHP-induced neurobehavioral impairment in animals.

4. IMPACTS OF DEHP EXPOSURE DURING CHILDHOOD AND ADULTHOOD PERIODS ON NERVOUS SYSTEM FUNCTION OF HUMAN

Many studies have demonstrated that maternal exposure to DEHP in the gestation time may impair neural development and behavior. In addition, DEHP decreases learning, memory, and intelligence and enhances depression, anxious behaviors, cognitive impairment, and risk of autism in offspring [24, 51-53]. DEHP increases the learning disabilities,

Table 1. DEHP-induced neurobehavioral impairment in animals.

Animal	Time	Exposure of DEHP	Dose or Concentration	Outcome	References
Rat	GD 12 - GD 21	Gavage	10, 750 mg/kg/day	Inhibition of important genes for the proliferation (*Ccnd1* and *Cdc2)*	[3]
Mouse	GD 7 - PND 21	Oral	10, 50, 200 mg/kg/day	Down-regulation of estrogen receptor β in females, androgen receptor in males, and inhibited phosphorylation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2)	[32]
Rat	GD 2 - GD 21	Gavage	1.25 mg/kg/day	Enhancement of Tau phosphorylation	[42]
Rat	PND 16 - PND 22	Intraperitoneal	10 mg/kg/day	Down-regulation of BDNF expression	[43]
Caenorhabditis elegans	24 h	-	2, 20 ppm	Inhibition of important genes for the differentiation of neurons (TTX-1, TAX-2, TAX-4, and CEH-14)	[44]
Mouse	24 h	-	0-20 μM	Increased levels of apoptosis-related proteins such as cleaved Caspase-3 and Bax, as well as decreased Bcl-2 protein level	[45]
Rat	GD 14 - GD 18	Gavage	500 mg/kg/day	Intervention in steroidogenic enzyme expression and reduction of testosterone production	[46]
Mouse	24 h	-	1 nM -100 μM	Dysregulated AhR/Cyp1a and disruption of the defense processes of neocortical cells	[47]
Mouse	2 weeks	Gavage	1-200 mg/kg/day	Decreased activity of ERK1/2 and down-regulation of dopamine receptor 2 and Erβ	[48]
Rat	GD 0 - PND 21	Gavage	30, 300, 750 mg/kg/day	Dysregulation of phosphorylated and total MAP2c and stathmin mediated *via* JNK1	[49]
Quail	45 Days	Gavage	250, 500, 1000 mg/kg/day	Activation of nuclear factor erythroid 2-related factor 2 (Nrf2)	[50]

risks of attention deficit and intellectual development disorders in childhood and adolescence [41, 54]. Children are more vulnerable to the negative effects of DEHP exposure. Critical growth processes including cell proliferation and migration, myelination, neural junction formation, and dendritic and axonal growth are occurring in this period of life. Thus, exposure to DEHP can delay these growth parameters and have severe negative impacts on cognitive function and mental health throughout life [43].

In a previous report, the amount of DEHP metabolites in the urine of children (2 to 6 years old) was twice as much in the urine of their parents. This may indicate an increase in the oxidative metabolism of children [55]. A previous study displayed that higher phthalate intake than other metabolites can be detectable in children due to putting their toys in their mouths [56]. The presence of phthalate metabolites in the urine of children aged 6 to 15 years in the United States was associated with behavioral impairments and learning disabilities [54]. Another study was performed to assess the levels of phthalate metabolites in students ranging from 19 to 29 years in both men and women between 2002 and 2008. This study indicated the epidemic exposure of people living in Germany *via* detecting the presence of urinary phthalate metabolites [57]. In 2014, a study was conducted to estimate dietary intake of phthalates in foods and beverages of adults. This study showed that DEHP is remarkably present in all commonly consumed foods and beverages. Cereals and meat products were the most common causes of exposure to these chemicals in the adult population [58]. Exposure of mothers to DEHP during pregnancy triggers such neurobehavioral impairments as increased hyperactivity in their children [59]. Previous evidence also indicated a direct relationship between the urine phthalates in the 6 to 7 months pregnant mothers and cognitive impairments of children [60]. In addition, a reverse correlation between DEHP and intelligence was also found among school-age children [59]. Table **2** [61-66] summarizes some evidence of DEHP-induced neurotoxicity in humans.

5. MECHANISMS OF DEHP-INDUCED NEUROBEHAVIORAL IMPAIRMENTS

Since phthalates are abundant in the environment and are absorbed during brain development, exposure to these

Table 2. Neurotoxicity of DEHP in humans.

DEHP Performance	References
Down-regulation of *FGD1* and *PAFAH1B* that are essential for fetal brain development	[61]
Correlation between DEHP concentration in maternal urine and increased risk of ADHD in newborns and school-age children	[59] [62]
Over expression of PPARγ and increased levels of apoptosis in undifferentiated neurons	[63]
An important role in the pathogenesis of autism spectrum disorders	[64]
Up-regulation of NF-kB/STAT3 in monocytes of autistic children	[65]
DEHP increases internalizing behaviors and decreases child mental and motor development.	[66]

substances is probably caused by permanent epigenetic changes in the human genome resulting in cognitive impairment. Phthalates reduce the mRNA level of genes engaged in the differentiation and function of neurons [41, 67]. Exposure to phthalates during pregnancy reduces learning and memory by affecting the profiles of two important genes for neuronal proliferation including *Ccnd1* and *Cdc2*. This causes cognitive dysfunction in adulthood. In addition, DEHP inhibits the expression level of crucial genes for the differentiation of sensory neurons including *TTX*-1, *TAX-2*, *TAX-4*, and *CEH-14*(44). DEHP-induced neurotoxicity is also mediated through oxidative stress and its effect on N-acetyl-L-cysteine (NAC) and oxidative stress inhibitors. Reactive oxygen species (ROS) such as superoxide (O2•−), hydroxyl radical (OH•), nitric oxide (NO•) and peroxides are products of mitochondrial respiration under physiological conditions [50, 68]. Antioxidant enzymes like glutathione peroxidase (G*PX*) and superoxide dismutase (SOD) maintain the intracellular ROS content at low levels. DEHP causes oxidative stress by increasing the oxidative products and inhibiting the antioxidant enzymes. Besides this, some doses of DEHP activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway. Oxidative stress maintains the accumulation of Nrf2 and blocks Nrf2-modulated defense responses. Nrf2 is a vital protein to modulate the protein expression that has a protective role against oxidative damage [45, 50]. Furthermore, DEHP affects the balance between oxidants and antioxidants by increasing the content of MDA, excessive ROS generation, and inducing lipid peroxidation in the brain [22]. In addition, DEHP exposure in a species of nematode (*Caenorhabditis elegans*) has been caused by the intracellular accumulation of ROS [44]. Oxidative stress is engaged with DEHP-induced apoptosis [45, 63, 68]. Increased level of oxidative stress in the brain causes DNA damage, which is considered as the main stimulus for brain aging and inducing Alzheimer's disease (AD) [69, 70]. Overall, oxidation of DNA following DEHP exposure may have a role in neurodegeneration and neurobehavioral abnormalities [69]. Imbalance of antioxidant parameters and alterations in the apoptosis-related protein expression (a decrement in B-cell lymphoma 2 (BCL-2) and increment of BCL2 associated X (BAX) protein and caspase-3) are other mechanisms of DEHP-induced neurotoxicity [63, 71]. DEHP may increase the expression of cyclooxygenase-2 (COX-2), a rate-restricting enzyme to produce prostaglandin E2 as a pro-inflammatory factor [72]. The expression of COX-2 in the nerve cells causes neuroinflammation and some neurological disorders such as AD [73]. Inhibitors of COX-2 mostly prevent neural damages and protect neural cells from inflammation caused by nerve injury [74, 75]. Persistent inflammation increases the COX-2 expression and decreases the hippocampal neuronal number [76]. Furthermore, exposure to phthalate before and after childbirth leads to an impairment in brain development and long-lasting neuro-developmental damages [77]. DEHP can also destroy the nerve cells involved in sex differentiation [46].

Endogenous androgens such as testosterone showed a critical role in controlling anxiety and memory function during maturity [32, 78]. DEHP reduces the testosterone levels by interfering with the expression of steroidogenic enzymes [46]. Aromatase enzyme has a neuroprotective role and DEHP exposure reduces its activity in the hypothalamus. Indeed, aromatase activity is essential to convert androstenedione to estrogen and testosterone to estradiol, which accelerates the last, rate-restricting step in the conversion of the androgen to estrogen. Over activity of aromatase causes gynecomastia or precocious puberty in men or gigantomastia in women. Thus, DEHP may alter the brain's sexual distinction and influence behavior and cognitive functions [28, 79]. There is a significant correlation between the age-related decrease of testosterone and dysfunction in some androgen-responsive tissues such as the brain [80]. Experimental studies indicated that reduced testosterone level is associated with decreased levels of neuronal survival and synapse formation, and inducing neurodegenerative diseases such as AD [81, 82].

Hypoandrogenism may be the consequence of a permanent epigenetics modification of the genes that have an impact on the production of testosterone. Testosterone and estradiol derivatives have an important neuroprotective role [83, 84]. There is a significant correlation between decreased levels of testosterone and neuronal loss. Hence, decrement in testosterone levels is a risk factor for nervous system disorders such as AD [85, 86]. According to a study, testosterone promotes the survival of hippocampal neurons and is vital to maintain learning and memory [87]. Therefore, low levels of testosterone in mice subjected to DEHP may trigger anxious behavior, cognitive deficits, and degeneration of the nerve cells [88]. Prenatal DEHP exposure reduced testosterone circulation and decreased the expression of Aryl Hydrocarbon (AR) in the hypothalamus, prefrontal cortex, and cerebellum which results in anxious-like behaviors during puberty. DEHP may have a lifelong effect on neurological behav-

iors [47, 89]. Aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor involved in the regulation of dendritic cell function and maturation. DEHP disrupts the AhR signaling in nerve cells and can increase the mRNA level of cytochrome P450 *(CYP1B1* and *CYP1A1)* and protein level of AhR. In addition, DEHP affects the expression of estrogen receptors (Er) b or AR in adult mice [90-92]. Disruption of gonadal hormones due to decreased ERbor AR in the hippocampus may lead to depression and anxiety-like behaviors [48]. The ERais essential for regulating reproductive functions in the brain, and ERb has non-reproductive functions such as learning, memory, anxiety, and depression. The ERb expression is high in the regions related to anxiety and depression, including the hypothalamus, hippocampus, and amygdala [93, 94]. DEHP can interfere with Brain-Derived Neurotrophic Factor (BDNF) and cAMP-Response Element-Binding Protein (CREB) signaling pathways by affecting ER-β expression and impairing the flexibility of hippocampal function. Another study illustrated that DEHP leads to hippocampal atrophy by reducing BDNF synthesis in male rats. BDNF plays a crucial role in the survival of neurons and dendritic growth and triggers synaptic connections between neurons. The low dosage of DEHP (10 mg/kg) affects the BDNF expression in the hippocampus of male rats [95] and declines the branching and length of dendrites in the cornu ammonis1 (CA1) area of the hippocampus only in the male [10].

Microtubule-Associated Proteins (MAPs) play major roles in tubulin assemble, binding and fixation of microtubules (MTs), shaping cross-connect structures among MTs, and regulating kinesin- and dynein-dependent transports along MTs. MAP2, as an important member of MAPs, is essential for dendritic extension both *in vitro* and *in vivo* [96, 97]. Furthermore, the MAP2 phosphorylation involved in the polymerization of MTs, may control the expansion of dendrites in the growth phase [98]. Hence, MAP2 has a critical role in stabilizing dendritic MTs and modulating the expansion of dendrites through changing the phosphorylation in dendrites [99]. DEHP reduces the phospho-MAP2c and expression of total MAP2c in the male hippocampus. MAP2 and stathmin are phosphorylated *via* c-Jun N-terminal kinase (JNK) [100, 101] and are pivotal for the development of dendrites. A reduced level of total MAP2c helps with the indirect decrease in phosphorylated MAP2c and can result in dendritic impairments. DEHP exposure disturbs the cytoskeleton proteins not only in their normal function, but also in the phosphorylated form. Therefore, maternal exposure to DEHP, the phospho-MAP2c, and down-regulation of total MAP2c may lead to impairments of neuronal dendrites in the CA1 area. DEHP disrupts the dendritic growth of pyramidal nerve cells and reduces the regulation of some basic proteins in the brain such as MAP2c and stathmin [49, 102] .It seems that the lack of these key proteins leads to dendritic degeneration and CNS-related disorders [99]. Another mechanism of DEHP-induced neurotoxicity is impairment in the homeostasis of thyroid hormone. DEHP reduces the activity of Peroxisome Proliferator-Activated Receptors (PPARs), which alters the transcriptional activity of the sodium/iodide symporter and consequently worsens the iodine uptake into the thyroid gland. Maternal hypothyroxinemia is associated with delayed cognitive function and decreased Intelligence Quotient (IQ). DEHP may cause the over expression of PPAR-γ in undifferentiated neurons [63, 103, 104]. DEHP probably causes impairment of spatial memory, mental and motor activity by reducing N-methyl-d-aspartic receptors (NMDA) levels and inhibiting *NR2B* and *NR1* subunits (30). Fig. (**1**) summarizes the possible mechanisms of DEHP-induced neurotoxicity.

DEHP reduces the mRNA level of genes involved in the differentiation and function of neurons. DEHP-induced neurotoxicity is also mediated through oxidative stress and its effect on N-acetyl-L-cysteine (NAC). DEHP causes oxidative stress by increasing the oxidative products and inhibiting the antioxidant enzymes. Alterations in the apoptosis-related protein expression and increased level of COX-2 are also other mechanisms of DEHP-induced neurotoxicity. DEHP reduces the activity of Peroxisome Proliferator-Activated Receptors (PPARs) which alters the transcriptional activity of the sodium/iodide symporter and Intelligence Quotient (IQ). Furthermore, DEHP diminishes testosterone levels and phosphorylated MAP2c. In addition, it can interfere with BDNF and CREB signaling pathways by affecting ER-β expression. DEHP causes memory impairment by declining NMDA levels and inhibiting NR2B and NR1 subunits.

6. COMPARISON OF NEUROTOXIC EFFECTS OF DEHP BETWEEN MALES AND FEMALES

According to studies conducted in recent years, DEHP has more destructive effects on males and less on females. A study demonstrated that exposure to DEHP in male rats causes hippocampal atrophy [43]. Another study also demonstrated that DEHP has anti-androgenic function. Anxiety-like behaviors were observed only in males. However, no change in anxiety-like behavior was found in DEHP-receiving female mice at puberty [31]. A study in 2018 showed that DEHP significantly reduces the number of hippocampal pyramidal neurons in adult male mice born from mothers exposed to DEHP [26]. Acute postpartum DEHP exposure also reduces the number of CA3 neurons in male mice. However, no significant effect was observed in females [40]. DEHP exerts an influence on the expression of steroid enzymes involved in androgen biosynthesis and declines the levels of testosterone [46]. Testosterone plays an crucial role in neural repair and promotes the survival of neural cells [105]. DEHP affects the expression of Estrogen Receptor (ER) β in the female and Androgen Receptor (AR) as well as the phosphorylation of ERK1/2 in the hippocampus of male mice [32]. DEHP interferes with testosterone function in nerve differentiation by reducing testosterone concentration and expression of androgen receptors in the brain [34]. Protective lipids such as hippocampal phosphatidylcholine and sphingomyelin are augmented in female rats following DEHP exposure, which explains the different impacts of DEHP in males and females [27].

7. NON-MONOTONIC DOSE-RESPONSE RELATIONSHIPS OF DEHP

According to previous studies, some high or low doses of DEHP have serious impacts. However, some intermediate doses of DEHP have fewer destructive effects, indicating a non-uniform dose-response curve (NMDR) that resembles a

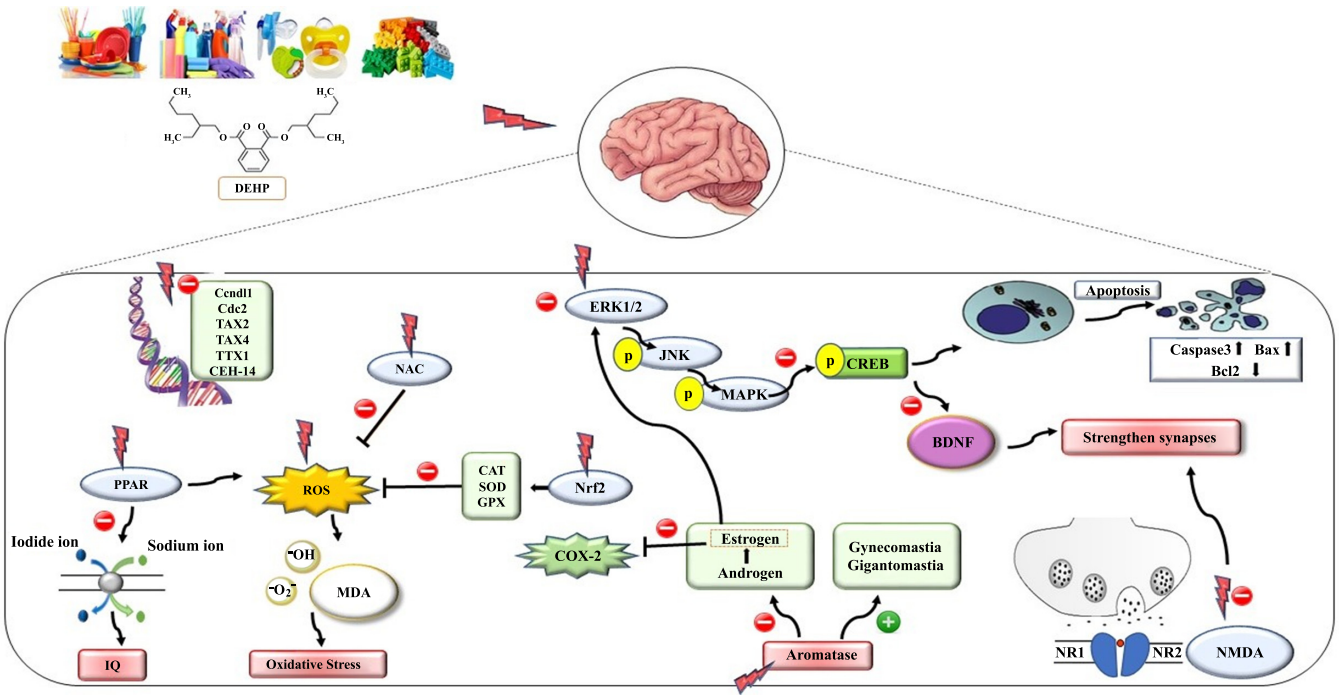

Fig. (1). Schematic representation of the mechanisms of DEHP-induced neurotoxicity. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

J-shaped curve. The effect of DEHP on aromatase activity was varied at different doses of DEHP [38]. The biphasic response can be characterized by values less than control at low doses followed by an increase at high doses (U-shaped or J-shaped curves) or vice versa (inverted U-shaped curve) [106]. Another study in 2012 also illustrated on-uniform dose-response curves of DEHP [17] which are not common in pharmacology and physiology [107]. Thus, various doses of DEHP result in diverse effects, including differences in ligand affinity and signal transduction, saturation of biological transmission pathways or protein binding sites, and compensatory responses in the body [106, 108].

CONCLUSION

Endocrine-disrupting chemicals such as DEHP are widely used in our daily lives. They are very toxic and dangerous for public health. Previous data showed that exposure to DEHP even at low concentrations, especially during pregnancy and infancy, causes memory loss and irreversible nerve damage. High levels of estrogen and protective lipids in females likely have more protective effects than males against the destructive impacts of DEHP. Finally, it is difficult to quantify the effects of DEHP on the nervous system functions because we are constantly exposed to numerous environmental toxicants. Further studies are required in the future to elucidate the exact mechanisms of DEHP-induced neurobehavioral impairment.

LIST OF ABBREVIATIONS

DINPs = Diisononyl phthalates

DBP = Dibutyl phthalates

DIDPs = Diisodecyl phthalates

DEHP = Di-2-ethylhexyl phthalate

BBP = Benzyl butyl phthalates

DOP = Diethyl phthalate

DnBP = D-n-butyl phthalate

DnOP = Di-n-octyl phthalate

DEP = Diethyl phthalate

2cx-MMHP = Mono [2- (carboxymethyl) hexyl] phthalate

5oxo-MEHP = Mono (2-ethyl-5-oxoxyl) phthalate

5OH-MEHP = Mono (2-ethyl-5-hydroxyhexyl) phthalate

5cx-MEPP = Mono (2-ethyl-5-carbo) Phthalate

MEHP = Monoethylhexyl phthalate

BBB = Blood-Brain Barrier

ADHD = Attention Deficit Hyperactivity Disorder

GD = Gestational Day

EFAs = Essential Fatty Acids

MDA = Malondialdehyde

PND = Postnatal Day

U.S = United States

mRNA = Messenger RNA

Ccnd1 = Cyclin D1

Cdc2 = Cell Division Control Protein 2

NAC	=	N-acetyl-L-cysteine
ROS	=	Reactive Oxygen Species
O2•−	=	Superoxide
OH•	=	Hydroxyl Radical
NO•	=	Nitric Oxide
GPX	=	Glutathione Peroxidase
SOD	=	Superoxide Dismutase
Nrf2	=	Nuclear Factor Erythroid 2–related Factor 2
AD	=	Alzheimer's Disease
BCL-2	=	B-cell Lymphoma 2
BAX	=	BCL2 Associated X
COX-2	=	Cyclooxygenase-2
AhR	=	Aryl Hydrocarbon Receptor
CYP	=	Cytochrome P450
ERs	=	Estrogen Receptors
AR	=	Androgen Receptor
BDNF	=	Brain-derived Neurotrophic Factor
CREB	=	cAMP-response Element Binding Protein
CA1	=	Cornu Ammonis1
MAPs	=	Microtubule-associated Proteins
MTs	=	Microtubules
JNKs	=	c-Jun N-terminal Kinases
PPARs	=	Peroxisome Proliferator-activated Receptors
T4	=	Thyroxine
IQ	=	Intelligence Quotient
NMDA	=	N-methyl-d-aspartic Receptor
CA3	=	Cornu Ammonis3
ERKs	=	Extracellular Signal-regulated Kinases
NMDR	=	Non-monotonic Dose-response

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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