Chapter

Effects of Atypical Neurotoxins on the Developing Fetal Brain

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Abstract

The brain is not only a control center of the body but also a part of the way that the body can communicate with external environments. The spatial and temporal events of brain development are well-defined. These processes are sequentially regulated by intrinsic and external factors, such as gene. Disruption of these steps results in malformation and malfunction of the brain. Neurotoxin may affect our developing nervous system as a kind of endogenous and exogenous factor. For classical neurotoxins, such as heavy metals, snake venom, and bacterial toxins, the underlying toxin-mediated physiological pathways are relatively clear, and their antidotes are usually available. However, for atypical neurotoxins, such as air pollutants, food additives, and manufactural compounds, their effects on the nervous system are ordinarily extended and not easy to detect. In addition, the corresponding mechanism is too complex to define. A single and effective antidote against these atypical neurotoxins is uncommon, so prevention is better than cure with this kind of toxin. This chapter starts with the introduction of endogenous and exogenous neurotoxins, how they affect nervous system and their potential antidotes, followed by the impact of atypical neurotoxins in fetal brain development and their possible preventative or therapeutic methods.

Keywords: environmental or atypical neurotoxins, neurodevelopmental defects, neurodegenerative disorders

1. Introduction

Neurotoxins are toxic substances that destroy the nervous system. Depending on their origin, it could be divided into endogenous or exogenous neurotoxins. Endogenous is the neurotoxin produced by the human body itself, while exogenous one comes from the surrounding environment. Neurotoxins can damage neurons, nerve fibers, glias, and myelin, causing the atrophy of nerve fibers and neurons, or demyelination, which in turn affects neural circuits and functions. Ultimately, defect in nerve system affects the physiological homeostasis of human body, which results in corresponding signs and symptoms of poisoning. Macromanifestations of neurotoxin exposure may associate a wide range of central nervous system impairments such as cognitive deficit [1], memory impairment [2], epilepsy, and dementia [3, 4].

2. Classic neurotoxins and their possible mechanisms of action that damage the nervous system

2.1 Exogenous neurotoxin

Exogenous toxins are foreign synthetic by name, and common exogenous neurotoxins include metal neurotoxins (e.g., lead), microbial neurotoxins (e.g., botulinum), biotoxins (e.g., tetrodotoxin), and chemical toxoids (e.g., ethanol). Different types of toxins have their different mechanisms of action in nervous system: (1) metal neurotoxins, such as lead and aluminum, usually migrate to the brain through the blood circulation by destroying the structure of or inhibition of the blood-brain barrier (BBB) [5]. Once it penetrates the BBB and reaches the brain, it can cause damage to brain and thus the emergence of diseases such as learning disabilities [6, 7], disorders in motor coordination [8, 9], and Alzheimer's disease [10]. At present, these metal neurotoxins are still widely used in food preparation, like in the packaging factory. Furthermore, due to the environmental pollution, these substances are also widely existing in the food chain [11]. (2) Microbial neurotoxins are produced by microorganisms, mostly from bacteria, such as botulinum, tetanus toxin, and lipopolysaccharide (LPS). The main mechanism of microbial neurotoxins that disturb the nervous system is inhibiting the communication of neurons. Microbial neurotoxins prohibit the release of neurotransmitters from synaptic vesicle [12, 13], thereby terminating nerve messages, which may lead to a decrease in muscle tension [14, 15], muscle atrophy [16], and paralysis [17, 18]. If it affected the respiratory muscles, it could cause asphyxiation and death [19, 20]. (3) Bio-neurotoxins come from organisms that produce these toxins as tetrodotoxin existed inside pufferfish's skin and gastrointestinal tract, snake venom produced by snakes, and chlorotoxin produced by scorpion. Some of which reduce the permeability of the ion channels in neurons and thus decrease neuronal communication. Different bio-neurotoxins can target different ion channels. For example, the tetrodotoxin is specific to the sodium ion channel [21], while the conotoxin produced by the conch is specific to the calcium ion channel [22]. The other bio-neurotoxins may not affect ion channel but have impact on neurotransmitter gated channel, like bungarotoxin, a type of snake venom [23]. (4) Chemical neurotoxins are a class of toxins with a broader mechanism of action. For example, ethanol has been shown to induce nervous system damage and affect the body in various ways: studies show that ethanol can alter the composition of nerve cell membranes [24], inhibiting the activation of NMDA receptors [25], causing the imbalance of cellular calcium ion concentration [26], facilitating the mitochondrial dysfunction [27], and increasing the oxidative stress inside the neurons [28], and that destroy the nervous system, leading to brain atrophy, encephalitis, neurodegeneration, cognitive decline, developmental disorders, and other neurological diseases [29, 30].

2.2 Endogenous neurotoxins

Endogenous neurotoxins, such as nitric oxide and glutamate, originate in the body and usually have their typical physiological role and function in the body. When the concentration of these endogenous compounds becomes higher, it can lead to dangerous effects: (1) glutamate is the primary neurotransmitter of the nervous system, accomplishing the chemical transmission in synapses. The normal concentration of glutamate is responsible for the regular performance of neurons. One of the most critical uses in nervous system is an excitatory neurotransmitter, which is related to the long-term potentiation in memory and learning.

High concentrations of glutamate become toxic to the neurons by increasing the permeability of calcium ions. It leads to an increase in cellular calcium concentration, then over-activates the calcium-associated enzymes, and eventually results in neuronal swelling and cellular death. This phenomenon is known as excitotoxicity. Studies have linked this mechanism to many neurological disorders, such as Huntington's disease, epilepsy, and stroke [31, 32]. (2) Nitric oxide (NO) is a secondary messenger synthesized by neural nitric oxide and commonly used in neurons. It regulates synaptic plasticity of the nervous system, smooth muscle relaxation in nerve and vascular system, and neurovascular dilation [33, 34]. Abnormal concentration of NO is associated with asthma, schizophrenia, and Huntington's disease [35–37]. The neurotoxicity of NO is based on glutamate-induced excitotoxicity. NO is response to glutamate-mediated NMDA activation, which is produced by calcium-dependent signaling. An elevated rate of glutamate excitotoxicity could lead to an increase in neuronal NO level. Over-dose of NO can also increase oxidative stress, which further induces DNA damage and apoptosis [38]. Therefore, an abnormal level of NO inside the nervous system can produce significant neuronal toxic effects.

3. Common antidotes

Common antidotes, such as antioxidants and antitoxins, can effectively reduce nerve damage induced by neurotoxins: (1) Antitoxin or antiserum is an antidote that uses antibodies to neutralize specific action of the toxins. Antitoxin is produced by individual animals, plants, or bacteria that are responded to toxin exposure. Antitoxins are made in organisms and can be injected into other organisms, including humans. Its most common use in the human body is antivenom [39]. (2) Antioxidants are compounds that inhibit oxidative stress, such as glutathione or ascorbic acid (vitamin C). If neurotoxins cause oxidative stress, antioxidants can be used to reduce the toxic reactions and side effects [40, 41].

4. Neurotoxins and the developing nervous system

4.1 Brain development

Brain is the computational core of our nervous system and is a place where animals can process and coherent the stimulus gathering from outside or internal surroundings and then sending out the response. It is responsible for many higher-order functions such as coordination of movement, learning and memory, and language and speech. Therefore, a well and the fully developed brain is essential to regulate these functions. Many intrinsic and external factors are required for brain development. Intrinsic factors are like hormones or regular development-associated gene expression, and external factors are like essential nutrients. Abnormal impact on these factors results in brain malformation and malfunction. For example, abnormal expression of thyroid hormone affects cerebellar development, motor performance, and severe anxiety [42, 43]; dysfunction of cyclin-dependent kinase 5 and insulin-like growth factor-I results in neurological disorders and neurodegenerative diseases [44, 45]; iron deficiency in early life causes irreversible effect on behavioral and neural development [43, 46]; and (n-3) fatty acid plays a role in neurogenesis, neurotransmission, and protection against oxidative stress in whole life span [47].

4.2 General events during the timeline of fetal brain development

During cerebral development, brain cells go through the process that includes replication and migration. The replication of the brain cells is also called neurogenesis, which starts from the 8th week of gestation in humans and the 10th day in rodents [48]. Neurogenesis is the formation of neurons from neural stem cells near the area of lateral ventricles occurring during embryonic development and is responsible for producing all the various types of neurons of the brain. Neuronal migration mainly happens between the 12th and 24th week of gestation in humans and the 11th and 16th day in rodents [49, 50]. Neurons pass the subplate and migrate into the cortical plate along the radial glial process starting from the subventricular zone with an inside out pattern that forms six-layered neocortical laminae [51], also known as cortex. We may look at these processes in detail through rodent studies: neuronal progenitor cells (NPCs) form the earliest cortical neurons and lie inside the preplate on the 10.5th day of pregnancy, which is divided into the superficial marginal zone, the cortical plate, and the subplate. The radial glial cells (RGCs) are also generated from NPCs at around 11th to 12th day of gestation, which owns the unique morphology with their soma inside the ventricular zone, their short processes extending the apical side of ventricle, and their long processes elongating to basal lamina. Newly formed neurons use the processes of RGCs as guiding railroad to migrate from the ventricular zone toward their final destination inside the cortical plate. Early-born neurons give rise to layers I, V, and VI, and later-born neurons migrate from past layers V and VI to the other layers (layers II to IV) of the cortical plate [52]. This is also known as in-side-out migration.

Different cortical layers have different functions; for example, the neurons of the 6th layer remarkably express the T-box brain 1 (Tbr1) protein, which regulates cell migration and differentiation during embryonic development [53–55], and also is responsible for the connection between cortex and thalamus in the developed brain [56]. The cortical neurons of the 5th layer mainly express COUP-TF-interacting protein 2 (Ctip2; also known as Bcl11b), a C2H2 zinc finger transcription factor, and link the cortex with brain stem and spinal cord [57]. Special AT-rich sequence-binding protein 2 (SATB2) also known as DNA-binding protein SATB2 is highly expressed in the neurons with layers II and III, which is associated with neuronal morphogenesis [58]. In adult brain, the neurons in layers II and III mediate communication across cortical regions and with the amygdala [59, 60].

After the nerve cells migrate to the destination, they begin to develop neurites in order to form synapses, which communicate with other brain cells. Neurites are composed of axons and dendrites. Axons transmit messages, and dendrites receive them. Both of which shape neural circuits. Most of the topics discussed are dendritic patterns. Dendrites are highly branched bush-like cellular extensions that mediate the enormous majority of presynaptic and environmental inputs, which regulate neuronal communication. Dendritic patterning is critical for proper neuronal function and has served as the basis for the classification of neuronal subtypes [61, 62]. The development of dendrite is a complicated multistep process. First, neurites initiate and form a structure called lamellipodia. Axons outgrow from minor processes followed by the outgrowth of dendrites. Dendrites then start to branch and form dendritic spines. After the process of pruning, dendritic branches are fully matured, and synapses are formed [62–64]. These steps are regulated by intrinsic genetic signals and extracellular cues [64]. Disruption of these pathways results in abnormal development in dendrite patterning that sequentially affects communication between neurons, which further leads to disruption of neuronal circuitry, and finally, whole nervous system breaks down. For example, mutation in

the human neural cell adhesion molecule L1 and Neuro-p24, a membranous protein, affects neurites' outgrowth and extension [65, 66]. Many well-known neurodegenerative diseases, such as Rett syndrome (RS) and autism, are genetic defects with well-defined anomalies in dendritic patterning [67, 68]. Hence, the integrity of dendrite morphology is crucial for maintaining normal function of brain circuitry and neuronal networks.

4.3 Genetic factors affect brain development

Gene is the main intrinsic factor that affects brain development, which contained highly programmed information related to neurogenesis and migration. These genetic factors include integration of reelin, Lis-1, and doublecortin [50, 69, 70]. The most studied genes are those encoding the dopamine inactivator catechol-O-methyl transferase (COMT), neurotrophin, brain-derived neurotrophic factor (BDNF), the schizophrenia candidate gene neuregulin (NRG1), and the serotonin transporter (5-HTT), for example, take neurotrophins. Neurotrophins play an essential role in mediating neuronal survival and brain development. There are four types of neurotrophins: neuronal growth factor [71], brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5). In their mature forms, these neurotrophins can bind as homodimers to specific tropomycin-related kinase (Trk) receptors. TrkA binds to NGF, TrkB binds to BDNF and NT-4/5, and TrkC binds to NT-3. Trk receptors are part of a group of receptor tyrosine kinases. Ligand binding results in dimerization of the receptor. The dimerized receptors phosphorylate several conserved tyrosine residues on one another [72–74]. This allows for proteins containing phosphotyrosine binding (PTB) or Src homology (SH2) domains to dock, and this docking activates intracellular signaling cascades that include Ras-Raf-Erk, PI3 kinase-Akt, PLC-γ-Ca^{2+}, NF-κB, and some protein kinase C pathways [73]. Neurotrophins exist in two states: proteolytically processed, which is the mature form and can bind the various Trk receptors, or unprocessed, which allows them to bind with high affinity to p75 neurotrophin receptor (NTR). Processed neurotrophins can still bind to p75NTR but with much lower affinity than to the Trk receptors. Binding of processed or unprocessed neurotrophins to p75 may elicit several responses including cell death [72, 73]. Recent studies also show that extracellular stimuli (NGF, BDNF, and epidermal growth factor) induced Rac activity, which is involved in neurotrophin-derived signaling and neuronal migration [75]. Deficiency in these intrinsic regulators disrupts neuronal migration and cortical laminar organization [76, 77], causing morphological abnormalities, such as schizencephaly, porencephaly, lissencephaly, macrogyria, and microgyria [78]. These lead to psychiatric and neurological disorders [69, 79, 80].

4.4 Examples of common neurotoxins on fetal brain development

The blood-brain barrier (BBB) is a crucial example of protection against toxins and other adverse compounds reaching the brain. BBB of the developing brain is not fully formed at the beginning of gestation, and therefore, fetal will be more vulnerable to the neurotoxins [81, 82]. For example, long-term exposure to nicotine during pregnancy directly affects acetylcholine systems and brain cell replication and differentiation, which consequently results in behavioral deficits of the offspring [83, 84]; prenatal, postnatal, and adolescent administration of alcohol affects gene expression (e.g. c-fos), causes abnormalities of brain structure and function, and finally disrupts brain development permanently and irreversibly [85, 86].

4.5 The impact of atypical neurotoxins on the developing brain

In the current industrialized society, atypical neurotoxins may also have hidden influence on normal brain development. The impacts of these agents on the processes of brain development are diverse and the productive time extends from prenatal to adolescent period [85]. Prenatal exposure to carbofuran, a carbamate pesticide, decreases nestin expression, histone-H3 phosphorylation, and the number of glial fibrillary acidic protein and SOX-2 co-labeled cells, which further leads to neurodegeneration and cognitive deficits in offspring [87]; Maternal application of dicholoacetonitrile (a disinfectant in our drinking water), benzyl benzoate (a antiparasitic insecticide), and trimethyltin (a stabilizer for plastics in paints) may induce oxidative stress and then result in neurodegeneration in fetal brain [88–90]; maternal infection is associated with the increased levels of proinflammatory cytokines in the amniotic fluid [91], umbilical cord plasma [92], and cerebral palsy [93, 94] as well as neurodevelopmental disorders such as schizophrenia [95] and autism spectrum disorders [96]. The findings in experimental models of maternal infection manifest the role of inflammatory response in the alteration of fetal neuronal morphology [97], astrocytosis, ventriculomegaly, changes in oligodendrocyte precursors [98], reduction of oligodendrocyte number, hypomyelination of brain [99] and a decrease of dopaminergic and serotoninergic neurons in the offspring [100], all of which are capable of leading to brain formative deficits. Indeed, maternal infection induces changes in brain developmental events, including neurogenesis, myelination, synaptogenesis as well as cell migration [101, 102]. Neuroinflammation has been reported to be highly associated with numbers of neurological and pathological diseases, such as cerebral palsy [94], schizophrenia [95], and autism spectrum disorders [96].

However, the precise molecular mechanisms of these exogenous agents that cause abnormal brain development largely remain unknown. Moreover, there are other possible harmful candidates needed to reveal. For example, monocyclic aromatic amines (MAAs) are a group of chemicals ubiquitously present in the environment. Exposure assessments indicate that most individuals experience lifelong exposure to these compounds from several sources, such as occupational exposure *via* tobacco smoke, herbicides, or hair dye, which are considerable in causing bladder cancer [103]. *In vivo* evidence has demonstrated the carcinogenic potential of most alkyl aniline compounds. For examples, 2,6-dimethylaniline (DMA) is responsible for nasal carcinogenesis [104]; Gan and colleagues indicated that 2,6-DMA, 3,5-dimethylaniline (3,5-DMA), and 3-ethylaniline (3-EA) are strongly associated with bladder cancers [105]. Currently, only 2,6-DMA is categorized as a possible human carcinogen by IARC [106]. However, the threats of other alkyl anilines cannot be neglected that 2,6-DMA, 3,5-DMA, and 3-EA can be metabolized as electrophilic intermediates, which further bind to DNA and form adducts. Skipper and colleagues report that three alkyl anilines can be metabolized as electrophilic intermediates and induce the production of DNA adducts, followed by attacking their putative targets, like bladder. Moreover, their results indicated that the adduct levels were the highest in animals given 3,5-DMA and the lowest in that given 3-EA. Furthermore, 3,5-DMA has been indicated not only to play a significant role in the etiology of bladder cancer in humans but study using *in vivo* experiments also strongly suggested that DNA adducts formed by 3,5-DMA might account for its presumptive activity [107]. A recent study additionally proves that 2,6-DMA and 3,5-DMA cause a single base-pair transition in the guanine-hypoxanthine phosphoribosyltransferase (*gpt*) gene in an *in vitro* model [108]. MMAs are activated through cytochrome P450-catalyzed oxidation of the amino group, followed by extensive esterification of *N*-hydroxylamine and heterolysis of the N—O

bond to produce a reactive nitrenium ion. The ion then interacts with DNA base and forms covalent adducts [108, 109]. Furthermore, the other major product of hydroxylation, aminophenol, also has the ability to damage DNA by electrophilic attack at nucleophilic DNA bases that lead to mutagenesis and carcinogenesis. Aminophenol becomes electrophilic upon 2-electron oxidation to quinine imines, followed by Michael addition reactions as well as nucleophilic addition at the keto and imino carbon centers. Finally, DNA adducts are formed [103, 110]. Moreover, quinines react directly with proteins through thiol addition. Thioether addition products are responsible for the production of reactive oxygen species (ROS) [111, 112]. Accordingly, oxidation of alkyl anilines is generally regarded as a critical bioactivation. Indeed, studies have shown that the major metabolite of 3,5-DMA and 3,5-dimethylaminophenol (3,5-DMAP) is responsible for the ROS production, which contributes to the apoptotic cytotoxicity in mammalian cell lines [113, 114]. Furthermore, a recent *in vivo* study has shown that 3,5-DMA-induced ROS production disrupts the dendrites patterning of the cortical cells and causes the abnormal cortical layer distribution in developing fetal brain [115].

The most popular topic of air pollution, fine particular matter such as $PM_{2.5}$, has been reported to have massive impact on neurodevelopment. A study displays that $PM_{2.5}$ can enter the maternal amniotic fluid system by inhalation and directly causes the delay in brain development of the fetal rat. Besides, microarray data demonstrated that $PM_{2.5}$ mainly increases the risk of neurological diseases in the offspring, such as Alzheimer's disease, epilepsy, autism, learning and memory disorders, and emotional control disorders [116]. Up-to-date study shows that $PM_{2.5}$ increases the number of white blood cell, upregulates the inflammatory response, induces the memory impairment, and declines in dendritic branches of the hippocampi of the offspring [117].

5. Discussion and conclusion

The human brain is the most complex system in biology, and its function depends on the various connections of nerve cells or the interaction between brain regions. Besides, there is growing evidence that many mental and neurological disorders are associated with neurodevelopmental abnormalities, which, according to epidemiological statistics, include autism, attention deficit hyperactivity disorder, dyslexia, and other cognitive impairments affecting millions of children worldwide [118, 119]. During the fetal and infant periods, they are most susceptible to environmental neurotoxin, which can cause permanent brain damage during these sensitive developmental stages [82]. Classical neurotoxins, such as heavy metal neurotoxins, microbial neurotoxins, bio-neurotoxins, and chemical neurotoxins, are mentioned earlier in this chapter. As for atypical neurotoxins, such as 3,5-DMA mentioned in the previous section, their effects are not immediate and not apparent, so their damage to the nervous system is not easy to detect. Instead, once it is detected, the damage is already severe and irreversible, such as neurodegeneration or developmental disorders [120, 121]. Some of these atypical neurotoxins are hidden in the surrounding environment, and some are obvious but neglected because of slow action, such as air pollution. Because there is no immediate risk, it is often ignored in clinical or in research. Therefore, how to find an efficient antidote or effective daily health care methods against this neurotoxin, especially in current aging society, become much more critical.

Conflict of interest

The authors have declared that no competing interests exist.

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