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Effects of Atypical Neurotoxins on the Developing Fetal Brain

Chia-Yi Tseng

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. Macro-manifestations 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 tropomyosin-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 -Ca²⁺, NF- κ B, 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], astrogliosis, ventriculomegaly, changes in oligodendrocyte precursors [98], reduction of oligodendrocyte number, hypomyelination of brain [99] and a decrease of dopaminergic and serotonergic 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]. MAAs 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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References

- [1] Abdel-Aal RA, Assi AA, Kostandy BB. Memantine prevents aluminum-induced cognitive deficit in rats. *Behavioural Brain Research*. 2011;**225**(1):31-38
- [2] Volpe BT et al. Loss of hippocampal CA1 pyramidal neurons correlates with memory impairment in rats with ischemic or neurotoxin lesions. *Behavioral Neuroscience*. 1992;**106**(3):457-464
- [3] Mainardi M et al. Tetanus neurotoxin-induced epilepsy in mouse visual cortex. *Epilepsia*. 2012;**53**(7):e132-e136
- [4] Eiser AR. Why does Finland have the highest dementia mortality rate? Environmental factors may be generalizable. *Brain Research*. 2017;**1671**:14-17
- [5] Ronnback C, Hansson E. The importance and control of low-grade inflammation due to damage of cellular barrier systems that may lead to systemic inflammation. *Frontiers in Neurology*. 2019;**10**:533
- [6] Zhu X et al. Perceptual training restores impaired cortical temporal processing due to lead exposure. *Cerebral Cortex*. 2016;**26**(1):334-345
- [7] Wang M et al. Effects of carbachol on lead-induced impairment of the long-term potentiation/depotential in rat dentate gyrus in vivo. *Food and Chemical Toxicology*. 2007;**45**(3):412-418
- [8] Dolinsky ZS et al. Behavioral effects of lead and *Toxocara canis* in mice. *Science*. 1981;**213**(4512):1142-1144
- [9] Hietanen E et al. Biotransformational and neurophysiological changes in rabbits exposed to lead. *Archives of Environmental Contamination and Toxicology*. 1980;**9**(3):337-347
- [10] Ghose AK et al. Knowledge-based, central nervous system (CNS) lead selection and lead optimization for CNS drug discovery. *ACS Chemical Neuroscience*. 2012;**3**(1):50-68
- [11] Lee JW et al. Toxic effects of lead exposure on bioaccumulation, oxidative stress, neurotoxicity, and immune responses in fish: A review. *Environmental Toxicology and Pharmacology*. 2019;**68**:101-108
- [12] Hassel B. Tetanus: Pathophysiology, treatment, and the possibility of using botulinum toxin against tetanus-induced rigidity and spasms. *Toxins (Basel)*. 2013;**5**(1):73-83
- [13] Poulain B. Molecular mechanism of action of tetanus toxin and botulinum neurotoxins. *Pathologie Biologie*. 1994;**42**(2):173-182
- [14] Malgorzata P, Piotr C, Edward K. The mechanism of the beneficial effect of botulinum toxin type a used in the treatment of temporomandibular joints dysfunction. *Mini Reviews in Medicinal Chemistry*. 2017;**17**(5):445-450
- [15] Toczyska I, Plusa T. Shiga toxin and tetanus toxin as a potential biologic weapon. *Polski Merkuriusz Lekarski*. 2015;**39**(231):157-161
- [16] Sellin LC. The action of batulinum toxin at the neuromuscular junction. *Medical Biology*. 1981;**59**(1):11-20
- [17] Surana S et al. The travel diaries of tetanus and botulinum neurotoxins. *Toxicon*. 2018;**147**:58-67
- [18] Rossetto O, Pirazzini M, Montecucco C. Botulinum neurotoxins: Genetic, structural and mechanistic insights. *Nature Reviews. Microbiology*. 2014;**12**(8):535-549
- [19] Bradford AB et al. 3,4-Diaminopyridine reverses paralysis

- in botulinum neurotoxin-intoxicated diaphragms through two functionally distinct mechanisms. *Toxicology and Applied Pharmacology*. 2018;**341**:77-86
- [20] Morton DB et al. Synaptic transmission in neurons that express the *Drosophila* atypical soluble guanylyl cyclases, Gyc-89Da and Gyc-89Db, is necessary for the successful completion of larval and adult ecdysis. *The Journal of Experimental Biology*. 2008. **211** (Pt 10):1645-1656
- [21] Chulanetra M et al. Human ScFv that block sodium ion channel activity of tetrodotoxin. *Toxicon*. 2012;**59**(2):272-282
- [22] Tisa LS, Olivera BM, Adler J. Inhibition of *Escherichia coli* chemotaxis by omega-conotoxin, a calcium ion channel blocker. *Journal of Bacteriology*. 1993;**175**(5):1235-1238
- [23] Clarke PB. The fall and rise of neuronal alpha-bungarotoxin binding proteins. *Trends in Pharmacological Sciences*. 1992;**13**(11):407-413
- [24] Roux A et al. Ethanol induced brain lipid changes in mice assessed by mass spectrometry. *ACS Chemical Neuroscience*. 2016;**7**(8):1148-1156
- [25] Hermenegildo C et al. NMDA receptor antagonists prevent acute ammonia toxicity in mice. *Neurochemical Research*. 1996;**21**(10):1237-1244
- [26] Woodward JJ. Ethanol and NMDA receptor signaling. *Critical Reviews in Neurobiology*. 2000;**14**(1):69-89
- [27] Huang W et al. Fatty acid ethyl ester synthase inhibition ameliorates ethanol-induced Ca^{2+} -dependent mitochondrial dysfunction and acute pancreatitis. *Gut*. 2014;**63**(8):1313-1324
- [28] Luo J. Autophagy and ethanol neurotoxicity. *Autophagy*. 2014;**10**(12):2099-2108
- [29] Davis KM, Wu JY. Role of glutamatergic and GABAergic systems in alcoholism. *Journal of Biomedical Science*. 2001;**8**(1):7-19
- [30] Kiecker C. The chick embryo as a model for the effects of prenatal exposure to alcohol on craniofacial development. *Developmental Biology*. 2016;**415**(2):314-325
- [31] Savolainen KM, Loikkanen J, Naarala J. Amplification of glutamate-induced oxidative stress. *Toxicology Letters*. 1995;**82-83**:399-405
- [32] Zadori D et al. Mitochondrial disturbances, excitotoxicity, neuroinflammation and kynurenes: Novel therapeutic strategies for neurodegenerative disorders. *Journal of the Neurological Sciences*. 2012;**322**(1-2):187-191
- [33] Hardingham N, Dachtler J, Fox K. The role of nitric oxide in pre-synaptic plasticity and homeostasis. *Frontiers in Cellular Neuroscience*. 2013;**7**:190
- [34] Cui X et al. Role of endothelial nitric oxide synthetase in arteriogenesis after stroke in mice. *Neuroscience*. 2009;**159**(2):744-750
- [35] Nasyrova RF et al. Role of nitric oxide and related molecules in schizophrenia pathogenesis: Biochemical, genetic and clinical aspects. *Frontiers in Physiology*. 2015;**6**:139
- [36] Kumar P, Kalonia H, Kumar A. Cyclosporine A attenuates 3-nitropropionic acid-induced Huntington-like symptoms in rats: Possible nitric oxide mechanism. *International Journal of Toxicology*. 2010;**29**(3):318-325
- [37] Kim YH et al. Association of extended nitric oxide parameters with bronchial hyperresponsiveness and

bronchodilator response in children with asthma. *Journal of Breath Research*. 2017;**11**(4):046003

[38] Chabrier PE, Demerle-Pallardy C, Auguet M. Nitric oxide synthases: Targets for therapeutic strategies in neurological diseases. *Cellular and Molecular Life Sciences*. 1999;**55**(8-9):1029-1035

[39] Pucca MB et al. History of envenoming therapy and current perspectives. *Frontiers in Immunology*. 2019;**10**:1598

[40] Kita T et al. Protective effects of phytochemical antioxidants against neurotoxin-induced degeneration of dopaminergic neurons. *Journal of Pharmacological Sciences*. 2014;**124**(3):313-319

[41] Wasik A, Antkiewicz-Michaluk L. The mechanism of neuroprotective action of natural compounds. *Pharmacological Reports*. 2017;**69**(5):851-860

[42] Koibuchi N, Iwasaki T. Regulation of brain development by thyroid hormone and its modulation by environmental chemicals. *Endocrine Journal*. 2006;**53**(3):295-303

[43] Beard J. Iron deficiency alters brain development and functioning. *The Journal of Nutrition*. 2003;**133**(5 Suppl. 1):1468S-1472S

[44] Netchine I et al. IGF1 molecular anomalies demonstrate its critical role in fetal, postnatal growth and brain development. *Best Practice & Research. Clinical Endocrinology & Metabolism*. 2011;**25**(1):181-190

[45] Su SC, Tsai LH. Cyclin-dependent kinases in brain development and disease. *Annual Review of Cell and Developmental Biology*. 2011;**27**:465-491

[46] de Escobar GM, Obregon MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. *Public Health Nutrition*. 2007;**10**(12A):1554-1570

[47] Innis SM. Dietary (n-3) fatty acids and brain development. *The Journal of Nutrition*. 2007;**137**(4):855-859

[48] Stagni F et al. Timing of therapies for down syndrome: The sooner, the better. *Frontiers in Behavioral Neuroscience*. 2015;**9**:265

[49] Dehay C, Kennedy H. Cell-cycle control and cortical development. *Nature Reviews. Neuroscience*. 2007;**8**(6):438-450

[50] Kwan KY, Sestan N, Anton ES. Transcriptional co-regulation of neuronal migration and laminar identity in the neocortex. *Development*. 2012;**139**(9):1535-1546

[51] Stiles J, Jernigan TL. The basics of brain development. *Neuropsychology Review*. 2010;**20**(4):327-348

[52] De Carlos JA, O'Leary DD. Growth and targeting of subplate axons and establishment of major cortical pathways. *The Journal of Neuroscience*. 1992;**12**(4):1194-1211

[53] Han W et al. TBR1 directly represses Fezf2 to control the laminar origin and development of the corticospinal tract. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;**108**(7):3041-3046

[54] Hevner RF et al. Tbr1 regulates differentiation of the preplate and layer 6. *Neuron*. 2001;**29**(2):353-366

[55] McKenna WL et al. Tbr1 and Fezf2 regulate alternate corticofugal neuronal identities during neocortical development. *The Journal of Neuroscience*. 2011;**31**(2):549-564

- [56] Lam YW, Sherman SM. Functional organization of the somatosensory cortical layer 6 feedback to the thalamus. *Cerebral Cortex*. 2010;**20**(1):13-24
- [57] Hall JE. *Guyton and Hall Textbook of Medical Physiology*. Elsevier Health Sciences; 2010
- [58] Zhang L et al. Satb2 is required for dendritic arborization and soma spacing in mouse cerebral cortex. *Cerebral Cortex*. 2012;**22**(7):1510-1519
- [59] Clancy B, Darlington RB, Finlay BL. Translating developmental time across mammalian species. *Neuroscience*. 2001;**105**(1):7-17
- [60] Bouwmeester H, Smits K, Van Ree JM. Neonatal development of projections to the basolateral amygdala from prefrontal and thalamic structures in rat. *The Journal of Comparative Neurology*. 2002;**450**(3):241-255
- [61] MacNeil MA, Masland RH. Extreme diversity among amacrine cells: Implications for function. *Neuron*. 1998;**20**(5):971-982
- [62] McAllister AK. Cellular and molecular mechanisms of dendrite growth. *Cerebral Cortex*. 2000;**10**(10):963-973
- [63] Mandell JW, Banker GA. The microtubule cytoskeleton and the development of neuronal polarity. *Neurobiology of Aging*. 1995;**16**(3):229-237 discussion 238
- [64] Urbanska M, Blazejczyk M, Jaworski J. Molecular basis of dendritic arborization. *Acta Neurobiologiae Experimentalis (Wars)*. 2008;**68**(2):264-288
- [65] Araki M et al. Developmentally regulated expression of neuro-p24 and its possible function in neurite extension. *Neuroscience Research*. 2002;**44**(4):379-389
- [66] Michelson P et al. Missense mutations in the extracellular domain of the human neural cell adhesion molecule L1 reduce neurite outgrowth of murine cerebellar neurons. *Human Mutation*. 2002;**20**(6):481-482
- [67] Zoghbi HY. Postnatal neurodevelopmental disorders: Meeting at the synapse? *Science*. 2003;**302**(5646):826-830
- [68] Kaufmann WE, Moser HW. Dendritic anomalies in disorders associated with mental retardation. *Cerebral Cortex*. 2000;**10**(10):981-991
- [69] Liu JS. Molecular genetics of neuronal migration disorders. *Current Neurology and Neuroscience Reports*. 2011;**11**(2):171-178
- [70] Molyneaux BJ et al. Neuronal subtype specification in the cerebral cortex. *Nature Reviews. Neuroscience*. 2007;**8**(6):427-437
- [71] MacKenzie AR et al. The atmospheric chemistry of trace gases and particulate matter emitted by different land uses in Borneo. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. 2011;**366**(1582):3177-3195
- [72] Chao MV. Neurotrophins and their receptors: A convergence point for many signalling pathways. *Nature Reviews. Neuroscience*. 2003;**4**(4):299-309
- [73] Huang EJ, Reichardt LF. Trk receptors: Roles in neuronal signal transduction. *Annual Review of Biochemistry*. 2003;**72**:609-642
- [74] Segal RA. Selectivity in neurotrophin signaling: Theme and variations. *Annual Review of Neuroscience*. 2003;**26**:299-330

- [75] Yoshizawa M et al. Involvement of a Rac activator, P-Rex1, in neurotrophin-derived signaling and neuronal migration. *The Journal of Neuroscience*. 2005;**25**(17):4406-4419
- [76] Tan X, Shi SH. Neocortical neurogenesis and neuronal migration. *Wiley Interdisciplinary Reviews: Developmental Biology*. 2013;**2**(4):443-459
- [77] Douet V et al. Genetic influences on brain developmental trajectories on neuroimaging studies: From infancy to young adulthood. *Brain Imaging and Behavior*. 2014;**8**(2):234-250
- [78] Barth PG. Disorders of neuronal migration. *The Canadian Journal of Neurological Sciences*. 1987;**14**(1):1-16
- [79] Folsom TD, Fatemi SH. The involvement of Reelin in neurodevelopmental disorders. *Neuropharmacology*. 2013;**68**:122-135
- [80] Gressens P. Pathogenesis of migration disorders. *Current Opinion in Neurology*. 2006;**19**(2):135-140
- [81] Goasdoue K et al. Review: The blood-brain barrier; protecting the developing fetal brain. *Placenta*. 2017;**54**:111-116
- [82] Sanders T et al. Neurotoxic effects and biomarkers of lead exposure: A review. *Reviews on Environmental Health*. 2009;**24**(1):15-45
- [83] Abdel-Rahman A et al. Maternal exposure of rats to nicotine via infusion during gestation produces neurobehavioral deficits and elevated expression of glial fibrillary acidic protein in the cerebellum and CA1 subfield in the offspring at puberty. *Toxicology*. 2005;**209**(3):245-261
- [84] Slotkin TA. Cholinergic systems in brain development and disruption by neurotoxicants: Nicotine, environmental tobacco smoke, organophosphates. *Toxicology and Applied Pharmacology*. 2004;**198**(2):132-151
- [85] Archer T. Effects of exogenous agents on brain development: Stress, abuse and therapeutic compounds. *CNS Neuroscience & Therapeutics*. 2011;**17**(5):470-489
- [86] Jang MH et al. Influence of maternal alcohol administration on c-Fos expression in the hippocampus of infant rats. *Neuroscience Letters*. 2005;**378**(1):44-48
- [87] Mishra D et al. Prenatal carbofuran exposure inhibits hippocampal neurogenesis and causes learning and memory deficits in offspring. *Toxicological Sciences*. 2012;**127**(1):84-100
- [88] Esmat A et al. Dichloroacetonitrile induces oxidative stress and developmental apoptotic imbalance in mouse fetal brain. *Environmental Toxicology and Pharmacology*. 2012;**33**(1):78-84
- [89] Kockaya EA, Kilic A. Developmental toxicity of benzyl benzoate in rats after maternal exposure throughout pregnancy. *Environmental Toxicology*. 2014;**29**(1):40-53
- [90] Paule MG et al. Developmental toxicology of trimethyltin in the rat. *Toxicology and Applied Pharmacology*. 1986;**84**(2):412-417
- [91] Yoon BH et al. Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. *American Journal of Obstetrics and Gynecology*. 2000;**182**(3):675-681
- [92] Yoon BH et al. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with

white matter lesions associated with periventricular leukomalacia. *American Journal of Obstetrics and Gynecology*. 1996;**174**(5):1433-1440

[93] Shatrov JG et al. Chorioamnionitis and cerebral palsy: A meta-analysis. *Obstetrics & Gynecology*. 2010;**116**(2 Pt 1):387-392

[94] Wu YW et al. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA*. 2003;**290**(20):2677-2684

[95] Brown AS et al. Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: A prospective birth cohort study. *Schizophrenia Bulletin*. 2000;**26**(2):287-295

[96] Beversdorf DQ et al. Timing of prenatal stressors and autism. *Journal of Autism and Developmental Disorders*. 2005;**35**(4):471-478

[97] Burd I, Balakrishnan B, Kannan S. Models of fetal brain injury, intrauterine inflammation, and preterm birth. *American Journal of Reproductive Immunology*. 2012;**67**(4):287-294

[98] Rodts-Palenik S et al. Maternal infection-induced white matter injury is reduced by treatment with interleukin-10. *American Journal of Obstetrics and Gynecology*. 2004;**191**(4):1387-1392

[99] Pang Y et al. Suppression of glial activation is involved in the protection of IL-10 on maternal *E. coli* induced neonatal white matter injury. *Brain Research. Developmental Brain Research*. 2005;**157**(2):141-149

[100] Lin YL, Lin SY, Wang S. Prenatal lipopolysaccharide exposure increases anxiety-like behaviors and enhances stress-induced corticosterone responses in adult rats. *Brain, Behavior, and Immunity*. 2012;**26**(3):459-468

[101] Chao MW et al. N-acetylcysteine attenuates lipopolysaccharide-induced impairment in lamination of Ctip2- and Tbr1-expressing cortical neurons in the developing rat fetal brain. *Scientific Reports*. 2016;**6**:32373

[102] Boksa P. Effects of prenatal infection on brain development and behavior: A review of findings from animal models. *Brain, Behavior, and Immunity*. 2010;**24**(6):881-897

[103] Skipper PL et al. Monocyclic aromatic amines as potential human carcinogens: Old is new again. *Carcinogenesis*. 2010;**31**(1):50-58

[104] Koujitani T et al. Tumor-promoting activity of 2,6-dimethylaniline in a two-stage nasal carcinogenesis model in N-bis(2-hydroxypropyl)nitrosamine-treated rats. *Cancer Letters*. 1999;**142**(2):161-171

[105] Gan J et al. Alkylaniline-hemoglobin adducts and risk of non-smoking-related bladder cancer. *Journal of the National Cancer Institute*. 2004;**96**(19):1425-1431

[106] USNT Program. Toxicology and carcinogenesis studies of 2,6-xylidine (2,6-dimethylaniline) (CAS No. 87-62-7). Charles River CD Rats. Research Triangle Park, NC; 1990

[107] Skipper PL et al. DNA adduct formation by 2,6-dimethyl-, 3,5-dimethyl-, and 3-ethylaniline in vivo in mice. *Chemical Research in Toxicology*. 2006;**19**(8):1086-1090

[108] Chao MW et al. Genotoxicity of 2,6- and 3,5-dimethylaniline in cultured mammalian cells: The role of reactive oxygen species. *Toxicological Sciences*. 2012;**130**(1):48-59

[109] Cui L et al. Identification of adducts formed by reaction of N-acetoxy-3,5-dimethylaniline with DNA. *Chemical Research in Toxicology*. 2007;**20**(11):1730-1736

- [110] Eyer P. Reactions of oxidatively activated arylamines with thiols: Reaction mechanisms and biologic implications. An overview. *Environmental Health Perspectives*. 1994;**102**(Suppl 6):123-132
- [111] Slaughter DE, Hanzlik RP. Identification of epoxide- and quinone-derived bromobenzene adducts to protein sulfur nucleophiles. *Chemical Research in Toxicology*. 1991;**4**(3):349-359
- [112] Towndrow KM et al. Stress- and growth-related gene expression are independent of chemical-induced prostaglandin E(2) synthesis in renal epithelial cells. *Chemical Research in Toxicology*. 2000;**13**(2):111-117
- [113] Chao MW et al. Intracellular generation of ROS by 3,5-dimethylaminophenol: Persistence, cellular response, and impact of molecular toxicity. *Toxicological Sciences*. 2014;**141**(1):300-313
- [114] Erkekoglu P et al. Antioxidants and selenocompounds inhibit 3,5-dimethylaminophenol toxicity to human urothelial cells. *Arhiv za Higijenu Rada i Toksikologiju*. 2019;**70**(1):18-29
- [115] Chao MW et al. In vitro and In vivo analysis of the effects of 3,5-DMA and its metabolites in neural oxidative stress and neurodevelopmental toxicity. *Toxicological Sciences*. 2019;**168**(2):405-419
- [116] Chao MW et al. Exposure to PM2.5 causes genetic changes in fetal rat cerebral cortex and hippocampus. *Environmental Toxicology*. 2017;**32**(4):1412-1425
- [117] Tseng CY et al. The effect of *Ganoderma microsporum* immunomodulatory proteins on alleviating PM2.5-induced inflammatory responses in pregnant rats and fine particulate matter-induced neurological damage in the offsprings. *Scientific Reports*. 2019;**9**(1):6854
- [118] Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. *Lancet Neurology*. 2014;**13**(3):330-338
- [119] Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet*. 2006;**368**(9553):2167-2178
- [120] Chinta SJ et al. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. *Cell Reports*. 2018;**22**(4):930-940
- [121] Spencer PS, Palmer VS, Kisby GE. Seeking environmental causes of neurodegenerative disease and envisioning primary prevention. *Neurotoxicology*. 2016;**56**:269-283