Approaches to Understanding Mechanisms between Environmental Chemical Exposure and Brain Development


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Abstract- Environmental chemicals are not without effects on the developmental processes taking place in the brain, considering their involvement in its pathogenesis. Of importance is the finding in a 2006 survey which showed several environmental chemicals to be implicated in neurobehavioral deficits in children following prenatal exposures. Worrisome on the other hand, quantifying chemical exposure effects on neurodevelopment and brain disorders usually prove difficult being that the brain; the target organ of neurotoxicants, requires highly invasive or extremely costly (e.g. neuroimaging) methods to access. To date paucity of central nervous system (CNS) or peripheral biomarkers are available as validated indicators for the mechanisms responsible for brain disorders. Available biomarkers so far for many environmental chemicals are indeed poor predictors. Combining insights from epidemiological studies and anecdotal clinical evidences in the field of neuroscience, this review discusses existing literatures/experimental researches that have attempted to explain links between environmental chemicals and brain disorders. This paper aims at contributing to the field of neuroscience by clarifying key processes, noting unresolved issues in previous experimental works and illuminating on mechanistic approaches to be tested with proper and robust research design of the 21st century.

Keywords: Environmental chemicals, Brain disorders, Mechanisms, Brain, Neuro-development, biomarkers, developmental neurotoxicity.

1. Introduction

The brain requires several and interacting steps in its developmental processes, which are controlled by intrinsic factors modulated by external influences. At third gestational week, the human brain development begins with the differentiation of the neural progenitor cells and extends at least through late adolescence, and throughout life span. The processes involved in brain development range from the molecular events of gene expression to environmental inputs. Neuron production in humans begins on embryonic day of 42 [1,2] and almost complete by mid gestation. During this developmental period, the shape of m primitive nervous system change. Before neural tube closure, the anterior end of the tube begins to expand forming the three primary brain vesicles – prosencephalon, mesencephalon and rhombencephalon. Upon production, the neurons begin to make connections with other neurons establishing rudimentary neural works in different brain areas. By the end of gestation, most of the pathways, including the thalamocortical pathway have been completed and the five secondary brain vesicles are present. In human fetus, cell migration is nearly complete in most of the brain by the sixth month of gestation [3].

Furthermore, the production and migration of neurons are largely prenatal events, migration and proliferation of progenitor glial cells continues for and extended period postnatally with maturation and differentiation of these cells continuing throughout childhood.

For the proper functioning and responsiveness of the human, brain receives information from the environment and this is redefined to re-shape the brain circuitry system. This can be attributed to various researches showing the important role of sensory input during developmental stages for appropriate build up of connections in the visual cortex [4], culminating into intention-action (behavior) of the human.

In its immature stage, formation of brain basic circuits is susceptible to adverse impacts. Adverse environmental condition/factors have been implicated in the etiology of brain disorders, characterized by abnormal brain morphology and functional activity. Environmental stress, drugs, infection, chemical pollutants etc are among the several environmental factors that play a role in the modulation of brain development, thus increasing the risk of brain disorders. When these factors (e.g. chemicals) reach certain dangerous levels particularly at sensitive points, they can disrupt developmental processes; weaken foundational structures leading to long life impact on the brain. A report from Grandjean and Landrigan et al [5] showed about 201 chemicals (metals, organic and inorganic compounds, pesticides and other organic substances) were identified as neurotoxic. The appropriate mechanism of action of these chemicals remains or partially unresolved.

Neuro-disorders comprises of a series of clinical heterogeneous conditions. These disorders can manifest early or later in life’s development, thus, leading to impairments of total well-being. Also, a number of variations (i.e. mutations, deletion and replication of number variants, polymorphisms) in different genes predisposes to adverse environmental factors such as exposure to drugs [6].
The present review focuses on understanding the possible mechanisms underlying the effect of exposure to environmental chemicals. We give an in depth analysis of epidemiological studies showing the association between environmental chemical exposure and altered brain disorders. Fundamental issues unresolved in environmental chemical exposure and brain disorders, noting the pitfalls of research design (in most cases the presence of adverse conditions). We mention studies on the mechanism of action which explains the possible link to brain disorders. We describe the possible mechanistic approaches that could provide a better framework to unraveling the environmental chemical and brain disorder interaction.

2. Epidemiological Studies Showing the Association between Environmental Chemical Exposure and Brain Disorders

A number of researchers have implicated chemicals to be neurotoxic. According to literature, the relationship between chemical exposures and neurotoxicity was first recorded on the toxicity of lead exposure to brain development [7-10]. Several other environmental chemicals have also been implicated in the different stages of neurodevelopment. Such described include heavy metals [11,12], different classes of pesticides [13-16], polychlorobiphenyls (PCB) [17], polybrominated diphenyl ethers (PBDE) [18] and phthalates [19].

A significant proportion of autism spectrum disorder (ASD) children prenatally exposed to either thalidomide or valproic acid in pregnancy [20,21] have been closely associated with the etiology of ASD. This is further corroborated by the reports of [22,23], maternal exposure to air pollution [24] and environmental toxicants. The association between attention deficit/hyperactivity disorder (ADHD) and environmental chemical is substantial based on the evidences such as polychlorobiphenyls (PCB) [25,26], heavy metals such as lead (Pb) [27-29] and mercury (Hg) [30,31], organophosphate (OP) pesticide [13,32,33] being linked to ADHD symptoms (attention problems, impulsivity and hyperactivity). Though the results of these researchers are still largely inconsistent, the etiologies of ADHD by phthalates, polyfluoroalkyl chemicals, bisphenol-A (BPA) and polycyclic aromatic hydrocarbons have been stated [34]. In a similar vain, studies conducted in Faroe Islands, showed that children between the ages of 7-14 years had a significant deficit in motor, attention and language function with elevated cord blood Hg levels [35,36]. In contrast, no association was found between elevated Hg levels and neurodevelopment functions in Seychelles Islands, regarded as the world’s highest level of Hg exposure [37-39]. Similarly, perspective birth cohort study in Northern Italy did not show any significant effect between prenatal Hg exposure and child neurodevelopment [40], while there was an inverse relationship between Hg levels in hairs and children’s motor and cognitive abilities [41].

Both humans and animals have been shown to be toxic to organophosphate (OP) pesticides despite low doses [42,43]. Specifically in humans prenatal exposure to Ops was inversely associated with abnormal reflexes [44], smaller head circumference [45], lower intelligence quotient (IQ) and increased risk of neurodevelopmental delay in childhood [13,46,47,48].

3. Fundamental Issues Unresolved In Environmental Chemical Exposure and Brain Disorders

Despite the vast amount of articles published in specialized journals on chemical exposure and brain disorders over the last decade, no consensus has been reached upon certain key concepts and/or fundamental research questions.

We argue that studying effect of environmental chemicals on brain disorders in its various forms is indispensable to the essential aspects of the phenomenon that make it unique and that will help scholars reach consensus on the fundamental research question and develop a unifying paradigm.

A review of literature reveals several pitfalls and loop holes which contributes to a more complicated understanding of the specific effects of these chemicals in neurotoxicity.

We start by stating the differences in the design of the experimental work which included other adverse conditions in their attempt to find the relationship between environmental chemicals and brain disorders. A comparison of various existing studies has combined factors such as stressful life events (mediated by mother or occurring during prenatal period) with chemical exposure.

Hougaard and Hansen [49] showed an association between chemical exposure to various chemicals (metals inclusive), taking neuro-developmental toxicity variables (such as reflex development, apoptosis in brain tissue), and implicated gestational stress on its findings. This means that neuro-developmental toxicity of most of the chemicals analyzed could be exacerbated by association with maternal stress, culminating to the inability to define a definite path of mechanism of action. This is further suggestive of the fact that developmental toxicity studies with bisphenol-A have recently suggested that oral gavage per se include a maternal stress-component able to modulate the effects of this chemical, representing a co-founder of which not all researchers are aware [50]. In sum, most of the studies carried out based their results on neuro-behavioral changes observed leaving out identifiable and validating biomarkers, hence unable to predict and trace the underlying mechanisms of action of these chemicals.

Also, exposure to the environmental toxicants are mainly through the mother either prenatally (in utero) or postnatal (via lactation). This shows that the offspring is not only directly affected by reaching the target systems (nervous or neuroendocrine), but also interfering with
dams’s maternal care in both qualitative and quantitative terms indirectly [51]. However, the morphological and physiological changes defining this transitional process is rarely and/or of at all available is poorly looked into by researchers. Therefore, taking appropriate account to better understand causes and pathways these chemicals exert its effects from mother to child i.e. paying particular interest to series of bio chemical occurring in the mother fetus (neonatal and juvenile period) before/after transmission, will pave way for potential mechanistic approaches predictive of later brain disorders. 

Apart from the aforementioned limitations, most research designs fail to consider variations in interactions of these chemicals with the population under study based on their genetic dispositions. This is more so with the difference in results observed from the findings in Seychelles Islands [37-39] and Spain [41] as reported earlier in this review.

In particular, it is suggested that variations in a group of so called “environmental responsive genes” may confer higher vulnerability to the adverse effects of environmental toxicants [52]. Several studies have identified Single Nucleotide Polymorphisms (SNPs) in genes involved in the detoxification of environmental pollutants in some individuals with ASD. It is estimated that more than 100 such genes may contribute to ASD risk [53].

4. Mechanistic Framework to Unraveling Environmental Chemical and Brain Disorder Interaction

A meta-analysis on the available mechanistic experiments carried out in vivo and in vitro presents multiple targets and pathways of toxicity for these chemicals. Chemicals may directly interfere with formation and closure of the neural tube, cell proliferation, migration, death or synapse formation [54] inducing changes ranging from overt morphological alterations [55] to subtle dysfunction in synaptic connectivity [56]. A particular chemical can affect different developmental processes or different cell types, depending on the time window of exposure [57]. Also of particular concern is that chemicals of same classes and having similar properties may have dissimilar mechanisms of action.

Another dimension of this multifaceted concept is that the same chemical may have multiple mechanisms of actions. An agent/chemical may mimic endocrine activity, thus affecting neurobehavioral development by directly binding with receptors in brain cells or periphery and simultaneously adversely affect the density of synaptic connections in specific brain areas with mechanisms possibly independent from their hormone-like action [58].

While we acknowledge the various hindrances to understanding the mechanistic approaches underlying the toxic effects of these chemicals on the brain, in this section, we focus on key based experimental articles published till date to unravel the feasibility and suggestive studies on the critical gap relating to mechanisms by which different classes of chemicals act on brain disorders.

On the other hand, bridging the links between environmental chemicals exposure and brain disorders at different levels of biological organization will be discussed in the succeeding paragraphs of this review. This will provide a platform and support further mechanistic approaches yet attempted in multi cellular and human subjects.

5. Gene Studies

It is imperative to note that specific research in neuroscience indicate that dilation, mutation of gene is an etiology/cofounder to multiple brain disorders. A body of evidence exist linking dopamine receptors DRD4 and DRD1 variants, a dopamine transporter gene DAT1 (SLC6A3) regulating the reuptake of dopamine in pre synaptic cleft to be associated with ADHD [59]. This is same for synaptosomal protein SNAP-25 [60]. The association between ADHD and prenatal chemical exposure showed several polymorphisms in the candidate gene in ADHD. For example, the valine/methionine of the gene encoding catalhoo-o-methyltransferase (COMT), which affects the catalytic activity of the enzyme for the degradation of dopamine and the C102T polymorphism of the serotonin receptor gene 5-HT2A [61]. Although previous researches by Echevarria et al [62] confer coproporphyrinase oxidase (CPOX) – gene encoding the heme biosynthetic pathway enzyme to be responsible for the susceptibility to neurobehavioral effects upon elemental Hg exposure in humans. Woods et al [63] found a strong association between Hg exposure and males carrying the CPOX4 allele resulting in reduction in cognitive performance. However, the mechanisms by which COPX4 allele lead to degenerative disorders to Hg exposure are not clear. It is suggestive to say that since the heme biosynthetic pathway plays an important regulatory role in neural pathway and synaptic development, there is the possibility that Hg and COPX4 allele acts synergistically on same pathway to effect neurodevelopment [64].

Another possible pathway in this direction could be high mean urinary porphyrin concentrations detected in children with ASD. This means that environmental chemicals acts through the mechanisms that change porphyrin excretion hence related with processes involved in ASD pathogenesis [24].

Another diverse opinion involve metallothionein (MTs) proteins. MT1M and MT2A are two different isoforms in humans identified to disperse and store metals such as Hg in the body [65] and modify its toxicokinetics in adults [66]. Deletion of MT1/2 genes (i.e. both isoforms) worsens learning and memory impairments and exacerbated adverse neurological functions in children (verbal learning, memory and executive function) [67,68].

Apolipoprotein E (gene product) is a protein transfer expressed in the brain. It has several alleles including Epsilon 4. Epsilon 4 alleles have been found to be associated with poor neural repair function and modulate neurobehavioral toxicity of lead in adults [69][142]. Measurement of apolipoprotein E in cord blood,
indicating individuals carrying Epsilon 4 allele is a target for Hg on adverse effects on neurodevelopment [70].

More intriguing is the fact that Methylmercury (MeHg) is able to cross the placenta through ATP binding (ABC) transporters (specific transporter proteins) widely responsible for active transport of various xenobiotics across the cell membranes. An alternative way to test Hg intoxication was implicated in placental transfer of xenobiotics.

An interesting issue was addressed by Llop et al [71]. To study this relationship, they compared the relationship between prenatal exposure to MeHg and ABC genes (ABCB1, ABCC1 and ABCC2) in two Mediterranean birth cohorts and found an association between mercury in cord blood and maternal fish intake. From this perspective one may argue that the genotype for ABC transporters of a child determines the accumulation of MeHg during early development to have its effect on the brain disorders.

A link between environmental chemicals and neurotrophic enzyme inhibition has been stressed by available literature. Certain chemicals such as organophosphate pesticides (OPs) exert their neurotoxic actions primarily by inhibiting the enzyme acetylcholinesterase (AchE), thus preventing the degradation of the neurotransmitter acetylcholine and consequently increasing both its concentration and presence in the synapse [72].

Prenatal MeHg exposure and IQ scores have been found to be associated according to a finding by the Avon Longitudinal Study of Parents and Children (Bristol, UK). Wood et al., [73] identified 13 candidate genes to be associated with various neuropsychiatric disorders and also with alterations in Hg toxicity and tissue distribution. Taken together, these data clearly show that MeHg interactions with IQ cores were detected for Paraoxonase 1 (PON1), progesterone receptor, brain-derived neurotrophic factors and transferring. They also indicate that, these genes modify the effects of Hg exposure.

In another perspective supporting the implication of Paraoxonase (PON 1) in neurodevelopmental disorders (NDD) findings by OP exposure as first evidenced by Berkowitz et al [45], the delivery of functional polymorphisms of PON such as PON1_162, PON1_108, PON1_155, PON1_192 [74] prompted a series of experiments aimed at finding the key role played by PON1 enzyme at different stages in life upon OP exposure.

Prompted by these considerations, Costa et al [75] and Eskenazi et al [76] reported PON1 enzyme metabolizes activated OP and detoxification pathways, conferring a degree of protection from OP exposure [74]. It is important to note that PON1 expression in humans is race and age-dependent as adults have higher PON1 levels than children [77,78]. Not all alloforms of PON acts through same mechanism. In any case the studies by Humbert et al [79] associated PON1_192 alloform to determine the glutamate (Q)/arginine (R) substitution thus hydrolyzes OP oxon and Paraoxon more efficiently than does PON1_1892 – which determines the leucine (L)/Methionine (M). Also several other studies measuring dialkylphosphates (DAPs) representative of total OP exposure have been negatively associated to neurodevelopment in humans having deficit in PON1 (PON1_192) and PON1_1892 alleles [44,49,76,80].

It is more likely, therefore to speculate that based on the prominent role played by PON1 enzymes and its allel in mitigating damages caused by reactive oxygen species in the brain (in its absence vulnerable) an important mechanism approach can be deduced.

6. Suggested Mechanistic Approaches

Several epidemiological and clinical studies enumerated above establish a link between environmental chemical exposures to brain disorders. However, there is still a gap in establishing causal links between each of these chemicals and brain disorders.

More specifically, this scenario assumes that in the case discussed above, simultaneous exposure to multiple risk factors together with these chemicals tend to interact in an additive, synergistic or antagonistic way, not giving a definite mechanistic perspective.

If the homology just described is correct, useful predictors (methods) in terms of neuroimaging and biomarker indicating the effect of these environmental chemicals on the CNS is of critical essence. Considering the complexity, estimating the concentration of a toxic compound or metabolite in the brain on the basis of concentrations found in other matrices may lead to exposure misclassification [81].

Reelin is a protein of the extracellular matrix with a role in neuronal migration. It has been observed that reeler mice bear a spontaneous mutation for the reelin gene and display neuroanatomical and behavioral alterations partly resembling those found in ASD and schizophrenic patients [82,83]. Although reports by Laviola et al [84] and Mullen et al [85] in their works showed decreased level of reelin, the neurodevelopmental disorders have not been established. This could proffer more understanding to mechanisms of environmental chemicals in brain disorders.

Deoxyribonucleic acid (DNA) methylation is an important debilitating factor in brain disorders. Measurement of this marker have been reported in prenatal polybrominated diphenyl ethers (PBDE) exposure, but barely studied among other conventional and prevalent environmental chemicals.

Another rarely measured biomarker is the DISCI level in rodents. Findings by [86] stated in their work that DISCI pathway provided a mechanistic approach through which lead may contribute to the pathogenesis of brain disorders in susceptible individuals.

Oxidative stress can be in no way excluded from developmental neurotoxicity. Measurement of intracellular Glutathione (GSH) level and its gene modifiers (e.g. Glutathione-S-transferase μ1 - GSTM1) in vitro and especially in vivo experiments will provide more information on several environmental chemicals. Important studies in this regard has however been looked into by [87,88] for susceptibility to PBDE effects and GSH levels and [89] for deletions in (GSTM1) gene.

The proper functioning of the brain is dependent on the active and regulated secretion of neurotransmitters (monoamine neurotransmitters and corticosteroids).
Serotonin and nor epinephrine levels as well as dopamine and their turnover are important determinants of brain functions. Chemicals such as Pb though in combination with other stressors have been found to change serotonin and nor epinephrine levels as well as dopamine and serotonin turnover, with no combined effect on corticosterone [90].

Furthermore, anti-inflammatory cytokines in the brain such as interleukins and kinins are potential targets to etiology of neurodevelopment disorders. Caspases present in the neuronal development also have the potential of being disturbed by environmental chemicals. This template has been partially set by Bolton and coworkers [91] where they studied diesel exposure combined with maternal stress.

As discussed above about the PON family and its implication in NDDs. Two other members of PON family: PON2 and PON3 have been identified located in the long arm of the human chromosome 7. Experimental signs portraying its knockout stages and presence will share more light on its mechanistic roles.

Epigenetic mechanisms are a recent frontier in research within the last decade. Till date, very little is known and applied to brain disorders in unraveling the mechanism. Epigenetic mechanisms involve modifications in gene expression with nucleotide sequence intact. They are important tools by which neurons modify their transcriptional response to development and environmental factors [92] and studying alterations these environmental chemicals on how they alter DNA methylation, histone modification, chromatin organization and micro ribonucleic acids (RNAs) at different stages of pre and post natal development, provided a useful background to typical brain development disorders. A light in this direction is the epigenetic regulation of Valproic acid (VPA) a non-selective inhibitor of histone deacyetylase of class I and II (HDAC1 and HDAC2) expressed in the brain [93].

Several enzymes play important manufacturing as well as transmitting roles in the brain. Of most recently researched enzymes is the O-GlcNAc enzyme. Studies suggest that O-GlcNAc represents a key regulatory modification in the brain, contributing to transcriptional regulation, neuronal communication and neurodegenerative disease [94]. So therefore, enzyme quantification in the brain is a mechanism target. In addition, protein glycation can occur in the brain upon exposure to these heavy metals and chemicals. These chemicals can form complexes with proteins in the brain, in which carboxylic acid (-COOH), amine (-NH2) and thiol (-SH) groups are involved. These modified biological molecules have the tendency to lose their ability to function properly and result in the malfunction/death of the brain cells. Furthermore, metals bind to these groups, leading to inactivation of important enzyme systems or affect protein structures which is linked to the catalytic properties of enzymes. Hence, the biomarkers indicative of brain protein denature is important tool for mechanism approaches.

Again, the ionic components of the brain can also be a tool to envisage mechanism approaches. According to Garza et al [95], the toxic mechanism of lead is caused by its ability to substitute for other polyvalent cations (particularly divalent cations, such as calcium [Ca^{2+}], zinc [Zn^{2+}]), and these molecules in the molecular machinery of living organisms. These interactions allow lead to affect different biologically significant processes, including metal transport, energy metabolism, apoptosis, ionic conduction, cell adhesion, inter- and intracellular signaling, diverse enzymatic processes, protein maturation, and genetic regulation. Membrane ionic channels and signaling molecules seem to be one of the most relevant molecular targets contributing to lead's neurotoxicity; the developing central nervous system is particularly susceptible [95].

One dominant approach yet overlooked are the receptors of the brain. It has been demonstrated that environmental chemicals alter thyroid hormone receptor and its analog in the brain [96]. So therefore, it is possible to address specifically the environmental chemical-brain interaction from the effect of these chemicals on receptor morphology changes and destruction.

7. Conclusion

The human population is exposed to a large number of environmental chemicals. Increasing evidences are revealing that these chemicals can disrupt normal neurodevelopment, predictable of causing numerous brain disorders. Mechanisms of environmental chemical action in the developing brain are less well understood due limited information on adequate CNS biomarkers. Thus, it will be important to define the role and identify mechanisms by which these chemicals exert these actions, if we are to understand the potential health implications of persistent exposure and proper/adequate interventions were necessary. Given the complexity of the topic, this review aimed at providing a parsimonious rather than a comprehensive definite model to explain the link between environmental chemical exposure and brain disorder. This paper notes the fact that the mechanistic approaches chosen are not free of modifications. The recommendation on additional conceptual and empirical works to enhance our understanding of the whole process cannot be overemphasized.

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Abbreviations

autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), lead (Pb), mercury (Hg), organophosphate (OP), intelligence quotient (IQ), bisphenol-A (BPA), Single Nucleotide Polymorphisms (SNPs), catechol-o-methyltransferase (COMT), metallothionein (MTs), Methylmercury (MeHg), acetylcholinesterase (AchE), Paraoxonase 1 (PON1), neurodevelopmental disorders (NDD), diallylphosphates (DAPs), central nervous system (CNS),
Deoxyribonucleic acid (DNA), ribonucleic acids (RNAs), polychlorobiphenyls (PCB), polynbrominated diphenyl ethers (PBDE), coproporphyrinase oxidase (CPOX), ATP binding cassette (ABC), Glutathione-S-transferase µ1 (GSTM1), Valproic acid (VPA), histone deacetylase of class I (HDAC1) and histone deacetylase of class II (HDAC2).

**Author contribution**

The author worked on all aspects of the manuscript

**Competing interests**

The author declare no competing interest.

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