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Impact of prenatal environmental stress on cortical development

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Summary

Prenatal exposure of the developing brain to various types of environmental stress increases susceptibility to neuropsychiatric disorders such as autism, attention deficit hyperactivity disorder and schizophrenia. Given that even subtle perturbations by prenatal environmental stress in the cerebral cortex impair the cognitive and memory functions, this review focuses on underlying molecular mechanisms of pathological cortical development. We especially highlight recent works that utilized animal exposure models, human specimens or/and induced Pluripotent Stem (iPS) cells to demonstrate: 1. molecular mechanisms shared by various types of environmental stressors, 2. the mechanisms by which the affected extracortical tissues indirectly impact the cortical development and function, and 3. interaction between prenatal environmental stress and the genetic predisposition of neuropsychiatric disorders. Finally, we discuss current challenges for achieving a comprehensive understanding of the role of environmentally disturbed molecular expressions in cortical maldevelopment, knowledge of which may eventually facilitate discovery of interventions for prenatal environment-linked neuropsychiatric disorders.

Running title

Cortical development and environmental stress

Keywords

Cortical development, prenatal environmental stress, alcohol, autism, schizophrenia, maternal immune activation, gene-environment interaction, iPS cells

Introduction

The development of the cerebral cortex consists of very intricate multifaceted steps including proliferation/differentiation of neural progenitor cells, neuronal migration and maturation [1] [2] [3] [4] [5] [6] [7] [8] [9], and it can be impaired by exposure to environmental stress [10] [11] [12]. Even subtle disturbances in the development of the cerebral cortex impair cognitive and memory functions [13] [14]. Accordingly, ever increasing attention is being paid to understanding the underlying non-genomic alterations thought to govern impairment.

Alcohol is known as one of the most prevalent prenatal environmental stress, and prenatal alcohol exposure-linked impairments are categorized under the term “Fetal Alcohol Spectrum Disorder (FASD)”. FASD patients show higher rates of co-morbidity with various types of neuropsychiatric problems, such as attention deficit hyperactivity disorder (ADHD) and epilepsy [15]. Histological analysis using postmortem tissues from FASD patients documented various anomalies in the brain, including heterotopias, microcephaly, hydrocephaly and agenesis of the corpus callosum [16] [17] [18]. Many of

these morphological phenotypes, as well as behavioral phenotypes of human patients, have been reproduced by non-human primate, rodent and other vertebrate models of fetal alcohol exposure, and therefore, these animal models have been used for understanding etiology of FASD and other health problems linked to prenatal alcohol exposure [19] [20] [21] [22]. Furthermore, these animal studies found that fetal alcohol exposure particularly affects the development of the cerebral cortex, in multiple cellular events including proliferation, differentiation, apoptosis, migration, synaptogenesis and dendritogenesis, depending on the regimens and timing of exposure [11] [23] [24].

Similarly, clinical and epidemiological studies identified a variety of environmental stressors, exposure to which increases the risk of neuropsychiatric diseases [25]. Importantly, rodent and non-human primate models of prenatal exposure to those environmental factors, including hypoxia [26] [27], drugs such as cocaine [11] [28] [29] [30] [31] [32] [33], and heavy metals such as methylmercury [34] [35], have shown that these factors cause similar structural anomalies in the cortex as well as similar abnormal behaviors [11]. These findings imply that different environmental challenges provide

common impacts on cortical development, thereby resulting in similar endophenotypes.

Here, we review recent publications that found molecular mechanisms underlying pathological cortical development elicited by exposure to prenatal environmental stress and discuss how various types of prenatal environmental stress similarly affect cortical development and increase the risk of neuropsychiatric disorders.

Early response genes that protect or disturb cortical development under the conditions of exposure to environmental stress

Based on recent findings using prokaryotes, genes that respond (either by increase or decrease of expression) to environmental stress can be classified mainly into 2 groups [36] [37] [38]. The first group consists of genes that exhibit altered expression immediately upon exposure to multiple types of environmental insult. The second group consists of genes that exhibit altered expression profiles only upon exposure to specific types of environmental stress and are generally altered gradually post exposure. Thus, orchestrated changes in the activities of these two types of genes are likely to occur in developing

cortices. The following section focuses on the first group of genes that immediately respond to environmental stress and may lead to common endophenotypes [39], discussing how these genes change the molecular landscape of cortical development and contribute to the pathogenesis elicited by prenatal environmental stress.

1. Stress responsive signaling

The cellular stress activates multiple signaling pathways that are well positioned to help restore homeostasis upon sudden environmental changes, or, in the long run, enforce a new gene expression program so cells can tolerate the new environment. These signaling pathways and genes include molecular chaperone encoding genes, genes involved in the unfolded protein response, Mitogen-Activated Protein Kinase (MAPK) and Growth Arrest and DNA Damage 45 (GADD45) signaling pathways [40]. The Heat Shock Protein (HSP) pathway is a major molecular chaperone signaling pathway, the activation of which has been identified as one of immediate molecular responses to various types of environmental stress, including alcohol, heat, heavy metals and viral infection [35] [41] [42].

Our recent study using knockout mice of *Heat shock factor 1* (*Hsf1*), a canonical transcription factor that controls transcription of *Hsp* genes revealed that activation of this signaling is required to reduce the risk of cortical malformation, such as heterotopias and small size of the cortex, upon prenatal exposure to various types of environmental stress, thereby reducing susceptibility to epilepsy [35]. Histological analysis immediately after prenatal stress exposure revealed that the increase of these cortical malformations in *Hsf1* knockout mice is due to the increase of cell death and suspension of cell cycling, suggesting *Hsf1*'s roles in cellular protection against environmental stress. Interestingly, the canonical downstream targets of *Hsf1*, *Hsps* mediate proapoptotic effects of *Hsf1* but not the effects on cell cycling (Fig.1). El Fatimy et al., (2014) showed that, many cortical genes that are critically involved in the control of cell cycling/proliferation and the neuronal migration are under the control of *Hsf1* and the family gene *Hsf2* [43]. Thus the activation of HSF1 immediately alters expressions of various types of genes to protect the embryonic cortex from environmental stress.

Another example of a stress responsive transcriptional factor that protects the fetal

brain from prenatal environmental stress is Nuclear Factor Erythroid 2-Related Factor 2 (Nfe2l2/Nrf2). The transcriptional activity is increased in response to such as alcohol [44], kainate induced excitotoxic damage [45] and hydrogen peroxide induced oxidative stress [46]. The target genes include multiple genes that encode antioxidant proteins [47] [48]. Prenatal exposure to methamphetamine (speed) plus *Nrf2* loss of function lead to reduced motor activity, smaller body weight etc. in the offspring [49]. Interestingly, the gender dependent differences were observed in the severity of the phenotypes.

These lines of evidence suggest that multiple cellular mechanisms provoked by the stress response genes act to ensure fetal cortical tolerance to environmental stress, and thus decrease the prevalence and severity of ensuing neuropsychiatric diseases [35].

2. MicroRNAs

Post-transcriptional controls have been demonstrated to be critically involved in the control of normal cortical development [50] [51] [52]. MicroRNAs (miRNAs) are non-coding RNAs that are involved in post-transcriptional regulation of the expression of a wide

variety of genes [53]. Because of their nature as short RNAs for post-transcriptional regulation of genes, they are likely to change the molecular landscape of the cell immediately and temporally in response to environmental challenges [54].

In a comprehensive miRNA profiling study using a neurosphere model of alcohol exposure, Miranda and his colleagues found a reduction in expressions of *miR-21*, *miR-335*, *miR-9*, and *miR-153* 24 hours after exposure [55].

MiR-9 knockout mouse displays smaller brain size [56]. The analysis of those embryonic brains suggested that impaired proliferation and differentiation of neural progenitor cells in stage dependent manner may lead to the smaller brain. Consistent with this *in vivo* observation, *miR-9* knockdown inhibited the proliferation and promoted the migration of the neural progenitor cells *in vitro* [57]. The control of these biological events by *miR-9* may be mediated by controlling expression levels of the downstream targets such as *Forkhead box G1* (*Foxg1*/*Bf1*) [56] [58], *embryonic lethal, abnormal vision, Drosophila like 2* (*Elavl2*/*HuB*) [55], *Fibroblast growth factor receptor 1* (*Fgfr1*) [59], *Forkhead box P2* (*Foxp2*) [59], *Stathmin 1* (*Stmn1*) [57], *Nuclear receptor subfamily 2, group E, member*

1 (*Nr2e1*/*Tlx*) [56] [60], *Inhibitor of DNA binding 4* (*Id4*) [58], *Paired box 6* (*Pax6*) [56], *Meis homeobox 2* (*Meis2*) [56], *GS homeobox 2* (*Gsh2*) [56], *Islet1* (*Isl1*) [56], *RE1-silencing transcription factor* (*Rest*) [61], and *Actin-like 6A* (*Actl6a*/*BAF53a*) [62]. Thus reduced expression of *miR-9* by alcohol exposure is also likely to inhibit those events by the similar mechanism. The miR-153 and miR-21 also similarly control the cellular proliferation [63] [64].

Reduction of *miR-9* expression and the target gene expressions in the zebrafish whole-embryo [65] and the embryonic forebrain [59] exposed to alcohol also supports this hypothesis. However, in the conditions of exposure to different contexts of maternal stress induced by such as restraint of the body and forced swimming, expression of *miR-9* was increased in the brain of offspring [66]. Similarly, the expression of *miR-21* has also been reported to be increased in the different ambience, such as in the mouse brain exposed to ionizing radiation [67], in the endothelial cells under the exposure to shear stress [68], and in the embryonic fibroblasts exposed to arsenite [69]. The expression of *miR-153* is also upregulated by hydrogen peroxidase induced oxidative stress [70] and nicotine exposure

[71]. These lines of evidence indicate that the microRNAs are susceptible to the environmental changes and that the overall changes of various types of microRNAs may determine the phenotypes specific to types/regimens of the environmental stress exposure. The fact that miR-335 knockdown reverses the effects of miR-21 knockdown in the cell proliferation and death also supports this possibility [55].

Maternal, placental and extracortical tissues exhibit indirect effects as a result of environmental stress.

Beside direct molecular changes within embryonic cortical cells, evidences exist that indirect impacts of environmental stress from maternal, placental and other extracortical tissues exert a critical influence on cortical development [72].

Maternal infection is well defined by epidemiological studies as a risk factor for neurodevelopmental disorders such as autism and schizophrenia [73] [74] [75]. Mouse offspring that have been exposed to maternal infection display abnormalities reminiscent of the behavioral, histological and molecular characteristics of autism [76], while fetal brain

infection does not cause these abnormalities [74]. Mouse offspring exposed to maternal immune activation (MIA), which is elicited by poly-riboinosinic-polyribocytidylic acid or lipopolysaccharide, also reproduce the behavioral and histological abnormalities of autism [77] [78] [79] [80], suggesting that activation of maternal immune system triggered by infection is critical for manifestation of deficits. These early findings have proven MIA model useful in the investigation of the molecular mechanisms at play in unraveling maternal effects on the pathophysiology of autism.

Smith and colleagues demonstrated that a proinflammatory cytokine interleukin-6 (IL-6) supplied from the maternal tissues might mediate the MIA effects on the fetal cortex [78]. A single maternal injection of IL-6 in the middle of corticogenesis causes deficits in prepulse inhibition and lateral inhibition in the offspring [78], both of which are linked to autism and schizophrenia [81] [82] [83] [84]. They also demonstrated that inhibition of IL-6 by application of the antibody or using the knockout dam, significantly ameliorated such as cognitive and exploratory deficits in mouse offspring exposed to MIA [78]. The gene expression profiles were also reversed by inhibition of IL-6 in the cortices of the MIA

offspring. These results provided evidence that IL-6 may owe the indirect effects of MIA on fetal cortical development.

Indirect effects of MIA on cortical development may also involve the effects from gastrointestinal tissues of offspring. Autism is often associated with gastrointestinal barrier defects [85] [86], and rodent MIA models reproduce these defects [87]. Hsiao E. and colleagues made an interesting observation that probiotic treatment of gastrointestinal barrier defects improved behavioral abnormalities such as anxiety-like behavior, decreased prepulse inhibition, and deficits in ultrasonic vocal communication in the MIA offspring. Their study also suggested the possibility that gastrointestinal barrier deficit-induced increase of serum metabolites such as 4-ethylphenylsulfate, indolepyruvate, glycolate, imidazole propionate, and N-acetylserine, may contribute to behavior abnormality in the MIA offspring [87]. Of these, the most dramatically affected metabolite, 4-ethylphenylsulfate, has been known as a uremic toxin, and the administration of this metabolite induces anxiety-like behavior in the mouse [87]. As a recent study suggested the link between the uremic toxin and the depression in the chronic kidney disease [88], the 4-

ethylphenylsulfate in serum may be the common factor that affects the brain function in various pathophysiological conditions.

Serotonin derived from placenta may also indirectly affect embryonic brain development. Recent studies demonstrated that the placenta is the major source of serotonin at early embryonic stage, while the dorsal raphe nuclei in the hindbrain take over from late embryonic stage to adulthood [89]. Abnormal serotonin levels in the brain have been linked to autism [90] [91] [92], and the role of serotonin in the normal development of thalamocortical projections also has been reported [93]. In addition, it has been demonstrated that prenatal intake of selective serotonin reuptake inhibitors increases the risk of cognitive impairment in mouse progeny [94] [95]. Importantly, serotonin level is lower in the cortices of the offspring exposed to environmental stress such as maternal infection [96] [97] and cocaine [29]. Therefore environmental stressors may indirectly affect the cortical development as a result of disruption in the synthesis/release of serotonin in/from the placenta [72].

Interaction between a susceptible genotype and environmental risk factors

Genome wide association studies have shown a polygenic component contributes to the risk of schizophrenia and autism [98]. Similarly, many epidemiological studies as well as the aforementioned results from studies of animal exposure models have shown these disorders also include a “polyepigenetic” component that is influenced by various types of environmental stress [10] [99] [100] [101] [102]. However, just how the polyepigenetic component increases the risk of disease manifestation by interacting with polygenic component is largely unknown.

One relatively new approach to help answering this question is the use of induced Pluripotent Stem (iPS) cells taken from subjects diagnosed with polygenic diseases such as schizophrenia or autism. iPS cells are not only becoming useful tools to obtain functional human cortical neurons [103] [104] [105] [106] for understanding the pathogenesis of disease, but are also being utilized for drug screening [107]. To examine potential interactions between genetic predisposition and the environmental risk factors, we recently used iPS cells derived from schizophrenia patients, and exposed the differentiated neural progenitor cells to environmental stress including alcohol, methylmercury and hydrogen

peroxide. Single cell RNA detection revealed augmented cell-to-cell variable activation of HSF1-HSP signaling in the schizophrenia patients' neural progenitor cells, individual cell lines of which carry different genetic risks for schizophrenia (Fig.2). This finding suggests that variable responses of HSF1-HSP signaling among a population of neural progenitor cells exposed to environmental stress is predetermined by genetic predisposition and may increase the risk of the onset of schizophrenia as well as other neuropsychiatric diseases [35] [108].

Using *Disrupted-in-schizophrenia-1* gene (*Disc1*) mutant mice combined with MIA, *in vivo* evidence for the interaction of gene and prenatal environment in the pathogenesis of schizophrenia and depression was also provided. The *Disc1* is one of the risk genes for psychiatric disorders such as schizophrenia and mood disorders [109] [110]. The transgenic mice expressing the dominant negative form of *Disc1* that was found in the patient [110], displayed hyperactivity and impaired social interaction [111]. When this transgenic mouse was subjected to MIA, neurobehavioral phenotypes such as anxiety, depression-like behavior, and a decrease in social interaction and an increase in aggressiveness were

unraveled [112]. Two other *Disc1* mutant mouse lines with point mutations at Q31L and L100P, which show schizophrenia and depression related phenotypes, respectively [113], were also subjected to MIA. MIA exposure augmented the impairment in prepulse inhibition, lateral inhibition, spatial object recognition, and social motivation of those *Disc1* mutant mice [114]. Importantly, the production of IL-6 was concomitantly increased by the combination of *Disc1* mutations and the MIA in the fetal mouse brains [114]. Thus these mouse models that combine *Disc1* mutation and MIA will become powerful models for understanding the molecular mechanisms underlying interactions between the gene and prenatal environmental factors that increase the risk of the psychiatric diseases.

Outlook

As outlined in this review, research on polyepigenetic mechanisms associated with many types of environmental stress that disturb cortical development and on potential prophylactic or preventative interventions of these disturbances are just beginning to emerge. To further facilitate this type of research, patient-derived iPS cells will become one

of several powerful tools. Although there are a number of limitations in their use, easy application of environmental stress and the potential for high throughput analysis substantiate their usefulness. Challenges include: 1. limited availability of iPS cell lines that are fully characterized; 2. lack of validated differentiation protocols for specific types of neurons; and 3. lack of validated *in vivo* approaches (e.g., efficient transplantation methods to animal models, etc.) that allow observation of the iPS cells during cortical development.

A type of the environmental stress can lead to various phenotypes in the cerebral cortex, however this variability cannot be explained exclusively by different regimens of exposure. Recent studies have revealed potential factors that may affect the resultant phenotypes, including gender [49] [115] and probabilistic molecular responses of individual cells to the environmental stress [35] (Fig.2) etc. Thus the next important questions will be: 1. if such molecular differences of individual cells elicited by environmental stress are sustained for long periods of time and ultimately result in altered cortical function, and 2. which molecules mediate the gender specific effects of prenatal environmental stress.

Another recent interesting observation that needs to be addressed at the molecular

level is the transgenerational effects of prenatal exposure to environmental stress, as reported in the cases of alcohol [116]. This observation opens up a whole new field of research that might eventually lead to an understanding of why FASD and other environment-linked disorders show familial and geographical linkages.

Abbreviations

induced Pluripotent Stem cells; iPS cells, fetal alcohol spectrum disorder; FASD, Heat Shock Protein(s); HSP(s), Heat Shock Factor 1; HSF1, maternal immune activation; MIA, interleukin-6; IL-6, disrupted-in-schizophrenia-1; DISC1.

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Legends

Figure 1

HSF1-mediated protection of neural progenitor cells from various types of environmental stress

Upon exposure to environmental stress, HSF1 is activated and HSPs transcribed by HSF1 inhibit cell death. HSF1 also keeps cell cycling/proliferation under stress exposure. The downstream player X is still unknown.

Figure 2

Cell-to-cell variability of HSF1 activation in response to environmental challenges is increased in schizophrenia neural progenitor cells.

The number of cells that are in the levels of excess or very little activation of HSF1 was increased in the schizophrenia cells [35]. These outlier cells may be at the risk of manifesting pathophysiological features (indicated by the cells surrounded by broken lines).

Figure 1.TIF

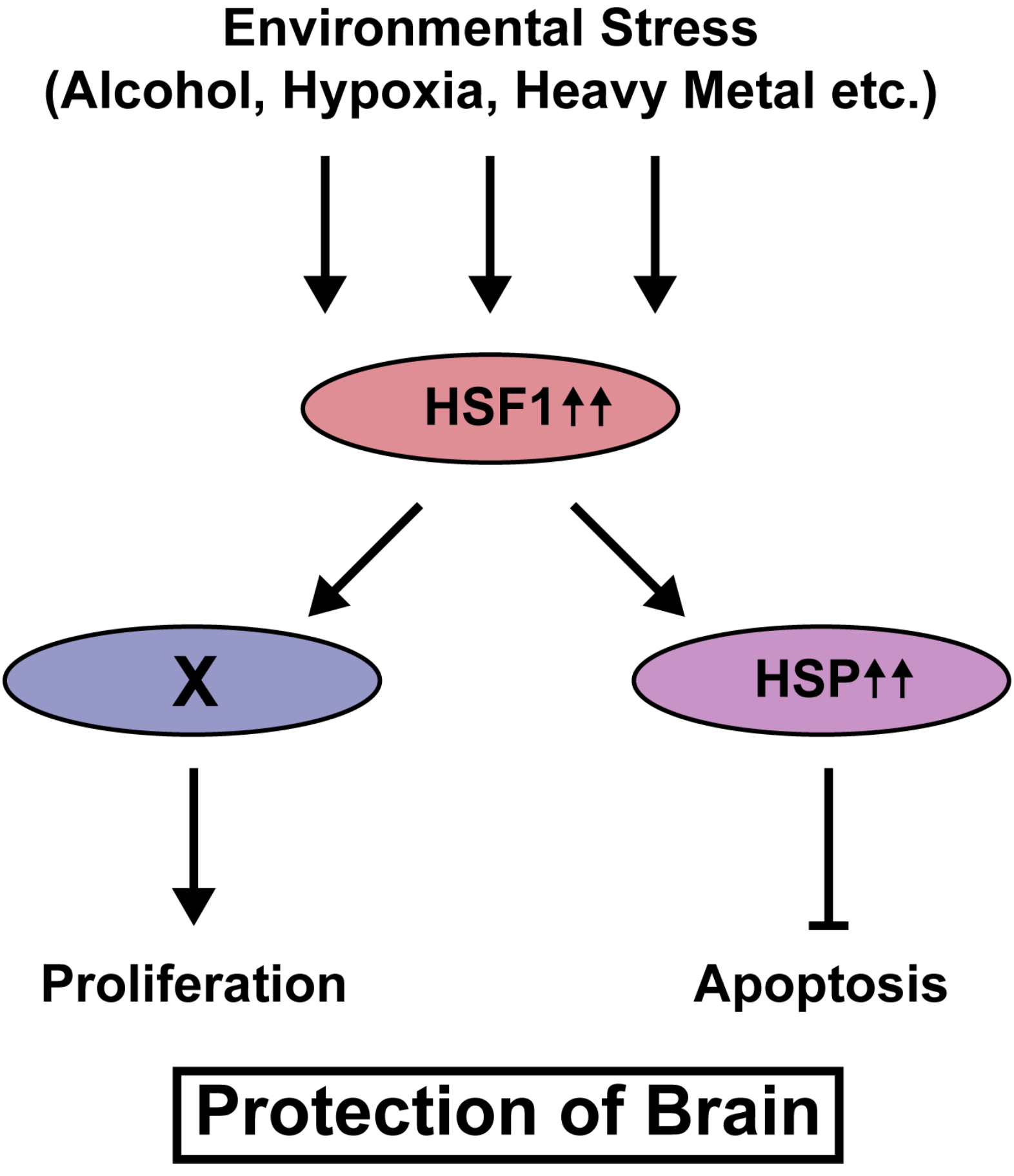
Environmental Stress
(Alcohol, Hypoxia, Heavy Metal etc.)
HSF1↑↑
X
HSP↑↑
Proliferation
Apoptosis
Protection of Brain

Figure 2.TIF