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Review

Prenatal stress and elevated seizure susceptibility: Molecular inheritable changes

Ehsan Saboory [a,*], Sedra Mohammadi [b,**], Sina Dindarian [b], Hozan Mohammadi [c]

[a] Neurophysiology Research Center, Urmia University of Medical Sciences, Urmia, Iran
[b] Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran
[c] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Stressful episodes are common during early-life and may have a wide range of negative effects on both physical and mental status of the offspring. In addition to various neurobehavioral complications induced by prenatal stress (PS), seizure is a common complication with no fully explained cause. In this study, the association between PS and seizure susceptibility was reviewed focusing on sex differences and various underlying mechanisms. The role of drugs in the initiation of seizure and the effects of PS on the nervous system that prone the brain for seizure, especially the hypothalamic–pituitary–adrenal (HPA) axis, are also discussed in detail by reviewing the papers studying the effect of PS on glutamatergic, gamma-aminobutyric acid (GABA)ergic, and adrenergic systems in the context of seizure and epilepsy. Finally, epigenetic changes in epilepsy are described, and the underlying mechanisms of this change are expanded. As the effects of PS may be life-lasting, it is possible to prevent future psychiatric and behavioral disorders including epilepsy by preventing avoidable PS risk factors.

1. Prenatal stress (PS) and offspring neurodevelopment

Prenatal stress is defined as the exposure of a mother to distress before giving birth [1]. Prenatal stress can affect the offspring in various ways in the long term [2–5]. Studies on animals demonstrated that fetuses exposed to PS may face preterm birth and low birth weight [6–8]. During pregnancy, environmental elements and genetic changes may affect fetus development, showing the importance of maternal stress in the development of fetus [9]. Several studies have stated that PS can also change the offspring's brain, both morphologically and functionally. These alterations include a wide spectrum of disorders such as schizophrenia, attention-deficit/hyperactivity disorder, autism, learning disorders, anxiety, and behavioral disorders [10–15]. As mentioned above, animal studies suggest a relatively strong association between PS and child outcome. In other words, stressed animals are likely to have stressed offspring.

Studies show that PS affects child outcome also in humans. In a study conducted by Rice et al. [16], they evaluated the effects of PS on in-vitro fertilization-born children related and unrelated to their mothers. They noticed that the association between PS and antisocial behavior is seen in both related and unrelated children mother–offspring pairs. However, in human studies, the association seems to be complicated and multifactorial. That means that prenatal and postnatal stressors accompanying genetic characteristics affect the child outcome. A stressed mother is more likely to be stressed also in her postnatal period which makes her to be a stressed parent. Other covarying factors such as smoking, alcohol consumption, and socioeconomic status may also add to this stressed status. Also, due to common genetic susceptibility, a depressed, anxious, or stressed mother is more probable to have a child with same characteristics [17–19]. Conclusively, it is recommended to evaluate the effect of parent stress on child outcome considering prenatal, postnatal, and genetic status altogether.

On the other hand, neurodevelopmental effects of stress considering its level have also been discussed in number of studies with opposite results. Some studies suggested that low level of PS can help development of neuronal structure. As an example, DiPietro et al. [20] investigated that mild stress was correlated with better motor and cognitive development. However, O'Connor et al. [17] discovered that linear dose response effect might be related to behavioral outcomes; that means different dose response effect of PS can cause different results. For instance, mild dose of stress increases both physical maturation and anxiety. These changes are better to be called evolutionary adaptation, rather than "good" or "bad" [21]. Other studies have demonstrated different results evaluating the effects of maternal stress on the offspring brain and motor development. Polanska et al. [22] have shown that PS only affects the cognitive development, mental operations, and insight of the offspring while it does not have any significant impacts on visual-motor coordination, reflexive behaviors, and primary circular

* Corresponding author at: Department of Physiology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia 5756115111, Iran.
** Corresponding author.
E-mail addresses: saboory@umsu.ac.ir (E. Saboory), d.3dra.sm@gmail.com (S. Mohammadi).

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reactions. Other studies have also confirmed these findings [23–25]. It is also important to consider postnatal environmental effects, since sensitive mothering may protect the child from some of the prenatal environment effects [26] but some forms of insecure attachment can make them worse [27].

2. Stress during prenatal stage and seizure in offspring

According to the studies, seizure induction can be potentiated by PS in the offspring. Seizure is an abnormally high discharge of brain neurons whose cause is not clearly explained yet [28]. A study reported that exposure to PS increases the probability of seizure, especially early in life [29]. As showed in Fig. 1, together with genetic and epigenetic factors, early life stress increases the risk of the development of epilepsy [30]. Generally, prenatal factors may affect the probability of seizure occurrence which encompasses every kind of seizure [31–37].

In case of exposure to stress, the central nervous system (CNS) of the fetus can be influenced by stress hormones released by the pregnant mother's endocrine system. These hormones mostly include glucocorticoids (GCs) and corticotrophin-releasing hormone (CRH) [38]. The neurotransmitter systems of the body may be disturbed by exposure to both endogenous and exogenous GCs [39,40]. It has been demonstrated that excitable parts of the hippocampus are affected by the abnormally high levels of GCs resulting from the activation of the hypothalamic–pituitary–adrenal (HPA) axis in a recurrent manner [41,42]. With regard to the involvement of these regions of the hippocampus in developing seizure, the mechanism of epilepsy due to PS can be explained [43]. Studies have also reported the effect of early-life stresses on seizure susceptibility. In a study, the effects of early-life inflammation on hyperthermia-induced seizures were investigated in infant rats. The findings suggested that, as an early-life stress, neonatal inflammation potentiates hyperthermia-induced seizures and also increases seizure susceptibility at older ages. Decreased blood levels of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) may be the cause of inflammation-induced increased seizure intensity in infants [44]. Thus, the literature generally supports the considerable association between stress in early-life stages and seizure susceptibility later in life.

3. Sex-specific stress effects on seizure

Stressors may affect men and women in completely different ways. Stressful situations may cause men to show a “fight-or-flight” reaction, while women are likely to demonstrate “tend-and-befriend” reactions [45,46]. Some studies have shown that responses to stress are endocrinologically different between males and females [47,48]. The results of a study conducted by Sadaghiani et al. [36] stated a significant difference between corticosterone levels of male and female rats after gestational restraint stress. In the mentioned study, male offspring had higher levels of corticosterone, greater intensity of seizure, and higher mortality rate compared with female offspring. In addition, the study of Finn et al. [49] suggested that the basal seizure risk differs in males and females, as also revealed by other studies on the measurement of seizure susceptibility [50,51]. Thus, prenatal stressors may affect males and females in different ways. Further studies are required in this field in order to discover the difference between males and females in terms of the risk of seizure induced by PS.

4. Effects of corticosteroids in the central stress response and seizure susceptibility

Stressful events and/or exposure to GCs, along with neurotransmitters' alteration during early-life periods, cause changes in the neuronal structure depending on the brain region [52,53]. During the perinatal period, elevation of synaptic plasticity has a critical role in brain development, thus explaining the sensitivity of the brain to external factors, including stress [54,55]. Stressful experiences and GCs affect the structure and function of the brain through various mechanisms such as dendritic retraction or expansion and increased or decreased synapse density on different parts of the brain [56–58]. Glucocorticoids are secreted from the adrenal cortex in response to stress and easily cross the blood–brain barrier to activate two intracellular receptors, glucocorticoid receptors (GRs), and mineralocorticoid receptors (MRs), to regulate gene expression and influence brain function [56,59]. The ligand affinity and distribution of these receptors differ [59]; MR has a tenfold higher affinity than GR. Thus, they are mostly occupied when corticosterone levels are low [60]. This feature is involved in the transfer of information and stability, self-regulatory abilities, and control of the system's response to stress [52,61]. Consequently, the proper balance of MR and GR activation is vital for homeostasis. The binding affinity of MR for aldosterone, cortisol, and corticosterone is almost the same. Glucocorticoids stimulate MR in most tissues at normal levels and GR at stress levels [62].

For long, it was believed that the intracellular GR plays the key role in the stress response by controlling negative feedback on the HPA axis, recovering the brain from stress, and normalizing neuronal activity [52,63]. However, recent studies indicated that, after stress, GRs also become considerably activated in spite of their lower affinity. Thus, after experiencing stress, both groups of GRs and MRs become occupied [64]. Glucocorticoids attach to these membrane receptors and change the excitability and activity of neurons through a nongenomic mechanism [65], and that is why they seem to participate in an acute state of

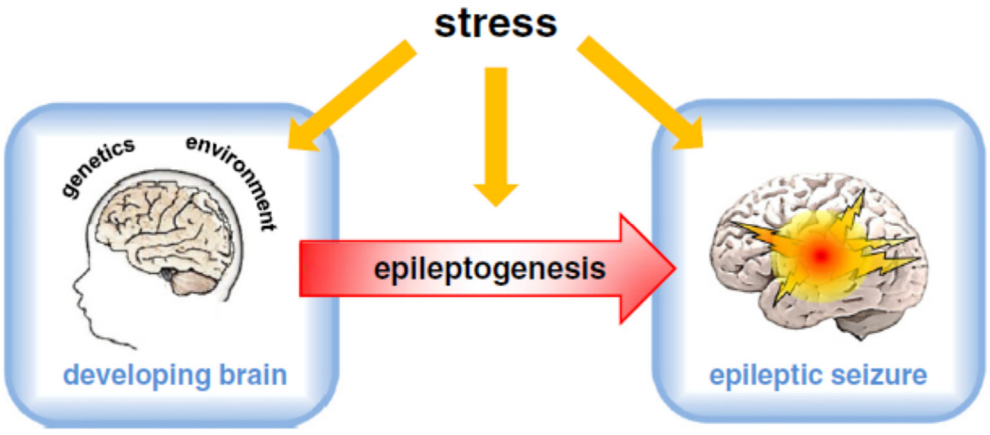

Fig. 1. Effects of stress on epileptogenesis. Exposure to stress affects neuronal structure and function, thus, influences epilepsy at several stages of life. Especially in early life, the developing brain is vulnerable to stress. Together with genetic background and other environmental factors, early-life stress increases the risk of the development of epilepsy.
(Adopted from van Campen et al. [30])

arousal and hypervigilance [59]. Both GR and MR are widely expressed in the developing brain, mostly in hypothalamic CRH neurons and pituitary gland. Expression of MR is predominantly limited to the limbic area, with the highest expression levels found in the hippocampus [52,60]. Corticosteroid receptors binding in the rat brain are shown to be low during gestation but, after birth, a mechanism of induction or repression of the transcription of more than 200 genes [66] provides neuron remodeling and brain maturation [67]. GRs and MRs were firstly detected in hippocampal formation, indicating that steroids influence the brain in more ways than through the hypothalamus. These receptors are known to affect episodic memory and spatial and mood equilibration [58,68]. In addition, studies indicate that MR mediates excitatory effects of corticosteroids on seizure vulnerability. The circadian rhythm in seizure vulnerability varies with the circadian rhythm of blood corticosteroids levels and MR binding. The types of seizures affected by manipulations of MR activity are thought to be of limbic origin, signifying that limbic seizures may be attenuated by the use of specific MR blockers [69].

Upon exposure to stress, GCs seem to cause dendritic retraction and loss of communication branches [58,70]. Studies on rats confirm that the expression of genes can cause variations after the end of stress until 24 h later [71]. At the time of stress effects, stimulatory amino acids can influence neuronal replacement in the adult brain which was first recognized in the hippocampus [72]. Acute and chronic stresses play a different role in different parts of the brain. For instance, acute stress causes an increased spine density on basolateral neurons, and chronic stress develops new branches of dendrites in the amygdala [73], while chronic stress on the medial amygdala induces loss of spines [74]. In the dentate gyrus, chronic stress can alter gene transcription in response to an acute infusion of corticosteroids. Moreover, in the prefrontal cortex, debranching and shrinkage of dendrites can occur in the medial prefrontal cortex which is attributed to cognitive rigidity, whereas neurons in the orbitofrontal area cause dendritic expansion which may be associated with increased vigilance [58,75]. Based on these studies, a history of stress exposure may have a continuous effect on future stress reactivity, seizure susceptibility, and brain function, particularly in the hippocampus.

5. PS may affect seizure via HPA axis programming

Several mechanisms affect the developing brain due to excessive corticosteroid exposure. During the prenatal period, 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) inactivates corticosteroids right after stress exposure [76,77]. In late pregnancy, the mother's HPA axis does not respond to stress as before, and postnatally, the stress hyporesponsive period reduces the developing brain's exposure to corticosteroid [76,78]. The duration of stress hyporesponsive period in humans is not completely clear, but it is believed to happen between 6 and 12 months of age, while the human HPA axis responds to stressful situations up to three months after birth [76]. Findings from animal and human studies demonstrated physiological adaptations, including brain oxytocin and prolactin system (one of the mechanisms in stress hyporesponsive period, which develop to decrease the activity and emotional response of the HPA axis in the peripartum period), associated with the prevention of the opioid and noradrenergic excitatory system of the HPA axis [79]. These adaptations ensure a healthy development by protecting the offspring from prolonged exposure to additional corticosteroids. Repeated exposure to stress during pregnancy can significantly reduce the expression and protective activity of 11β-HSD2 [80]. See Fig. 2 for details of mother-placenta-fetus unit; as illustrated in Fig. 2, placental CRH and 11β-HSD2 play important roles in modulating the programming effects of PS [81].

On the other hand, GCs, particularly synthetic GCs such as dexamethasone, are not appropriate substrates for 11β-HSD2. Therefore, a considerable part of them crosses the placenta, and only 17% of the synthetic GC is metabolized by 11β-HSD2 [82]. Consequently, it not only causes the indirect activation of the HPA axis, but also exposes the fetus to direct circulation of maternal cortisol, thereby altering fetal programming [82,83]. As 11β-HSD2 is the main preventer of prolonged offspring exposure to additional corticosteroids, there may be a difference in 11β-HSD2 activity in male and female pregnancy. Sex differences must be investigated by including both sexes in neurobehavioral studies. Still, further studies are needed to examine the long-life effects of PS in the process of brain maturation. Studies have so far focused on two topics. First, PS can disrupt brain development by affecting neuronal differentiation, gene transcription, and other processes that can lead to defects in neuronal connections and network [76,84]. Between 24 and 32 weeks of gestation, the human brain is at its highest level of sensitivity, when immature and primitive oligodendrocytes have predominantly gathered in the cerebral white matter [85,86]. Furthermore, other neuronal structures which are involved in the process of proliferation, migration, and differentiation, are exclusively vulnerable to injury [86]. Observations demonstrated that in vitro exposure to corticosteroids decreases the rate of cell division, thus leading to the differentiation of cells rather than their proliferation [87,88]. Subsequently, it is assumed that endogenous corticosteroids may play a role in the maturation and development of brain in the late fetal period by inhibiting cell division as well as expressing the genes responsible for the differentiation of mature phenotype [76]. Second, a study suggests that external environmental exposures revealed on the genome as epigenetic mechanisms can have life-long effects on the brain [89].

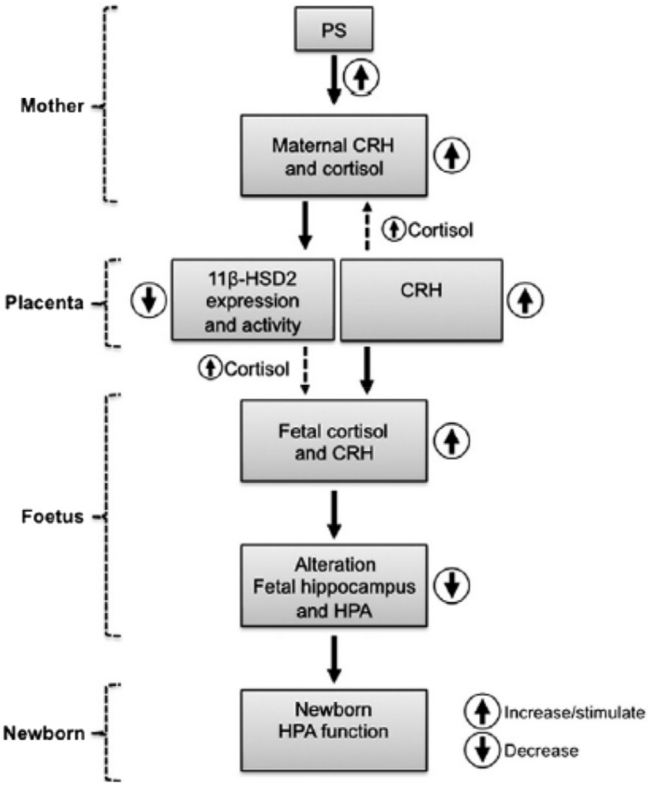

Fig. 2. Role of PS on the mother-placenta-fetus unit. Prenatal stress activates the maternal HPA axis, which increases levels of circulating maternal CRH and cortisol. This, in turn, increases the production and release of placental CRH into the bloodstream. In contrast to hypothalamic CRH production, which is suppressed by stress-induced cortisol, placental CRH is increased by GCs, so that PS leads to progressively higher fetal plasma cortisol and CRH levels. This placental CRH reaches the fetal brain and could influence the fetal hippocampus, presumably by activating CRH receptors. Prenatal stress also reduces the expression and activity of 11β-HSD2, in the placenta, leaving the fetus less well-protected. Downregulation of placental 11β-HSD2 activity increases glucocorticoid exposure of the placenta and the fetus. Alterations of fetal HPA axis remain present in the newborn. PS = prenatal stress; HPA = hypothalamic–pituitary–adrenal; CRH = corticotropin-releasing hormone; 11β-HSD2 = 11β-hydroxysteroid dehydrogenase type 2. (Adopted from Charil et al. [81])

Epigenetics mostly refers to alterations in a chromosome that modulates gene expression and results in phenotype changes [90,91]. Briefly, epigenetics is described as any heritable phenotypic traits that do not involve a change in the Deoxyribonucleic acid (DNA) sequence; such changes can be embedded with mechanisms such as histone modifications and DNA methylation [89]. Prenatal stress affects brain microRNA (miRNA) sections and further leads to disruptions in the adaptation and development of the offspring [92]. In addition, DNA methylation in the 11β-HSD2 gene promoter is considered as a consequence of repeated stress exposure of the mother, which is responsible for reducing the expression of 11β-HSD2 mRNA [93].

Additionally, high levels of GC in the fetus lead to the downregulation of MR and GR in the hypothalamus and HPA axis, particularly inside the paraventricular nucleus, which reduces the feedback mechanism of GC secretion. Under such circumstances, the hypothalamus secretes much more CRH, thus leading to higher levels of Adrenocorticotropic hormone (ACTH) and consequently maintaining higher levels of GC; higher levels of GC increase seizure susceptibility and potentiate seizure intensity. Several studies confirmed this finding, showing that prenatally stressed offspring has a higher concentration of GC and an elevated seizure intensity later in life [31,32,94]. Prenatal stress also increases the GR:MR ratio in the hippocampus, GR and MR expression in the hypothalamus, and GR expression in the pituitary gland. It permanently affects the expression of both receptor types in HPA axis regions. The effects of PS are in accordance with a more efficient negative-feedback within the HPA axis and can thus explain the attenuated stress response observed in many subjects, including humans and rats [94]. Thus, the alterations in receptor density as a consequence of PS exposure may be the mechanism permitting an adaptive response to later-life stressful conditions such as epilepsy [37,94].

6. Epigenetic changes in stress and epilepsy

Evidence suggests that major stress during pregnancy potentiates febrile seizure and causes higher cortisol blood levels [31]. Eventually, chronic epilepsy appears to be associated with the modulation of gene transcription and chromatin structure [95]. An overview of epigenetic mechanisms is shown in Fig. 3 [96].

There are three well-studied epigenetic mechanisms by which stressors may biologically implant themselves and therefore contribute to multiple consequences, including epilepsy, later in life. Studies indicate that stress can induce alterations through each of these mechanisms [97]. Thus, early-life stress may be involved in epigenetics which, in turn, may affect epilepsy through the mechanisms discussed below.

6.1. DNA methylation

The mechanism of methylation suggests that epigenetic changes can be induced by seizure itself and thus aggravate the epileptogenic condition [91,92]. Particularly, the enhancement of DNA methylation enzyme activity as well as the hypermethylation of DNA has been correlated

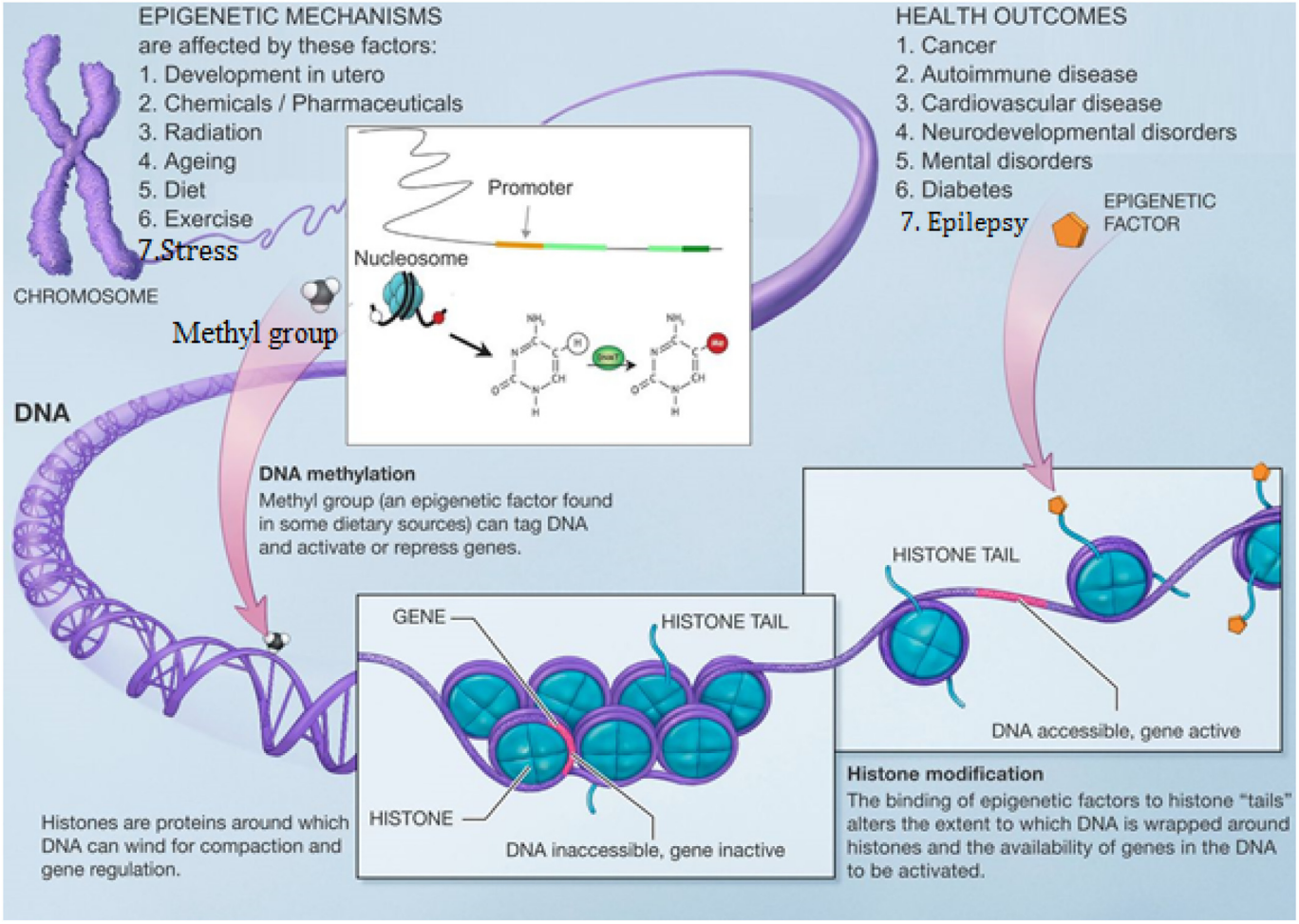

Fig. 3. Epigenetic mechanisms and health outcomes. Environmental factors, including stressors, can affect chromatin by DNA methylation and/or histone modification, thereby, lead to long-lasting outcomes such as mental disease, neurodevelopmental disorders, cancer, and epilepsy.
(Adopted from the National Institutes of Health with modifications.)

with a higher seizure susceptibility [91,98,99]. Adenosine and glycine, regulated by adenosine kinase (ADK) and glycine transporter 1 ($GlyT_1$), respectively, control the transmethylation pathway which is dependent on S-adenosylmethionine [91,100]. For DNA methylation, a methyl group should be separated from S-adenosylmethionine. This is facilitated by DNA methyltransferases (DNMTs). The product, S-adenosylhomocysteine, is then converted to adenosine and homocysteine by S-adenosylhomocysteine hydrolase [99,101]. An increase in S-adenosylhomocysteine levels due to impairments in the metabolic clearance of adenosine through ADK causes DNMT inhibition [91,102]. Considering adenosine's role as an essentially final product of DNA methylation, it is concluded that ADK elevation and subsequent reduction of adenosine can increase the total DNA methylation in the brain which is observed in chronic epilepsy [103,104]. Thus, overexpressed ADK and $GlyT_1$ resulting in pathologic DNA hypermethylation lead to the epilepsy progression [105].

6.2. Histones

Histone methylation is described as the transfer of a methyl group to the amino acids of histone proteins synthesizing nucleosomes which are the basic structural units of chromatin [106,107]. Histones not only provide support for chromatin structure, but also facilitate access to transcription factors and, therefore, determine gene expression [107,108]. Epigenetic alterations occur in N-terminal domains (especially the N-terminals of H_3 and H_4), including acetylation, methylation, phosphorylation, biotinylation, ubiquitination, and adenosine diphosphate (ADP)-ribosylation [107,108]. For instance, 3 h after the induction of status epilepticus with pilocarpine in rats, the hypoacetylation of histone H_4 was found in the promoter of the glutamate 2 receptor ($GluR_2$), in addition to hyperacetylation in the promoter of the brain-derived neurotrophic factor [107,109]. Changes in the acetylation of histone H_3 and H_4 at the Cyclic adenosine monophosphate response element binding protein (CREB) promoter in the rat hippocampus were the results of another animal study, demonstrating the important roles of histone modifications in the control of epileptic activity [107,110].

6.3. microRNA and epilepsy

miRNA plays a potential role in the development of epilepsy. They are expressed in a wide variety of organs and cells, and regulate both pro- and antiinflammatory actions [111]. The biogenesis of miRNAs is regulated as part of the inflammatory response by altering the transcription, processing, or stabilization of mature or precursor miRNA transcripts [111]. Accumulating evidence in animal models has shown the higher expression of miRNA-132 as one of the mechanisms responsible for epileptiform activity in the hippocampal tissue from rats with induced status epilepticus. Initiation of inflammation in the brain may contribute to epileptogenesis [107,112]. There is evidence that inflammation potentiates seizure intensity in rats and humans [113,114]. Also, early-life inflammation leads to higher seizure susceptibility later in life [44,115,116].

7. Seizure-related structural remodeling in the hippocampus

As previously discussed, the oversecretion of stress hormones can cause acute and chronic alterations in specific parts of the brain, particularly in the hippocampus, prefrontal cortex, and amygdala. Although studies have reported that the entire hippocampus shares the same basic structure, the dorsal (DH) and ventral hippocampus (VH) seem to have different functions, particularly in the connectivity and distribution of receptors [117]. It has been revealed that, in spatial learning and memory, DH plays a vital role while, instead, anxiety, defensive behavior, fear, and stressful situation responses are controlled by VH [117–120]. Studies conducted so far have concluded that morphological alterations due to PS mostly influence DH [117]. The hippocampus is formed late in the embryonic life and continues to develop early in postnatal days [117,121,122].

The hippocampus consists of three main sections: the cornu ammonis, dentate gyrus, and subiculum [123,124]. Connections between these intrahippocampal regions comprise excitatory feedback circuits which can generate an epileptic state [123]. Widespread cortical regions' input into hippocampal formation synapses on the entorhinal cortex. The efferent connections of entorhinal cortex project mostly to dentate granule cells but also to CA3 pyramidal ones [125,126]. CA3 pyramidal cells and hilar cells receive excitatory glutamatergic input from projections known as mossy fibers [123]. Through Schaffer collaterals, pyramidal cells in CA3 develop an axonal connection to mossy fibers (Hilar neurons) in order to create recurrent synapses on the granule cell dendrites of the dentate gyrus [123]. Interconnections from granule and hilar cells through recurrent impulses in the hippocampal loop may cause an epileptic state [123,127]. The hilus can return the neuronal activity arising from the dentate granule cell layer through polysynaptic pathways [123,128]. Chronic stress can reduce the dendritic spine density of hippocampal CA3 and granule cells of the dentate gyrus while also leading to dendritic shrinkage in the CA1 area [129]. Feedback connections between CA3 and the dentate gyrus promote memory formation but simultaneously make CA3 vulnerable to seizure-induced excitation [56,129]. Excitatory amino acids (EAAs) and their receptors are also involved. For instance, the debranching of pyramidal cells in the CA3 area due to chronic stress affected by mossy fiber terminals is fully packed with glutamate vesicles [129]. It has been reported that exposure to predatory and restraint stress on gestation days 15, 16, and 17 in rats resulted in higher GC blood levels in pups and dams. Also, in the CA1 area, the amplitude and slope of field excitatory postsynaptic potentials were significantly decreased, ultimately causing a reduction in hippocampal synaptic potentiation and increased mortality rate due to seizure [130]. Prolonged seizure activity causes the progressive loss of GABA in target neurons and leads to epileptogenesis condition [123,131]. In addition, rats exposed to single-prolonged stress demonstrated the downregulation of MR and GR expression [132]. The study by Hwang et al. revealed that, in the hippocampus of seizure-sensitive gerbils, MR and GR levels were higher than those of seizure-resistance gerbils. Thus, changes of MR and GR in the CA1 region and the dentate gyrus may be associated with seizure generation in these animals [126]. In another study, pregnant mice were exposed to restraint stress twice a day for three days. Ten days after birth, hippocampal slices were obtained from the offspring, and spontaneous seizure-like events from the CA1 pyramidal layer were recorded. Both the number and the duration of seizure activity were decreased in stressed pups compared to controls. The results suggested that temporal lobe epilepsy in children who have experienced PS may be decreased [133].

In the following sections, the effects of PS are briefly discussed on the expression of the N-methyl-D-aspartate (NMDA) receptor, and then possible mechanisms involved in premature hippocampal injury are explained.

8. Effect of PS on seizure via the density of NMDA receptors

The consequences of PS can be exerted by changing the expression of the glutamate N-methyl-D aspartate (NMDA) receptor mainly involved in the establishment of long-term potentiation (LTP) in the CA1 area [134]. The GluN2B subunit of the receptor appears to play a role in receptor-dependent synaptic plasticity as well as seizure and memory [37]. Prenatal stress has been shown to alter synaptic plasticity in the hippocampus and impair spatial learning and memory [134]. Glucocorticoid released in response to stress alters mRNA expression for some NMDA receptor subunits in the brain after birth [135]. The impaired development of the corticostriatal and corticolimbic pathway due to NMDA receptor level alteration may provide a suitable condition for the development of epilepsy [136]. In a study, 68 pregnant rats on

the 15th, 16th, and 17th days of gestation were exposed to restraint or predatory stresses. After labor, these pups were compared with those born in unstressed conditions. The results revealed that stress increases GC blood levels and causes a significant elevation in the density of NMDA receptor in different brain regions, including the hippocampus, making the brain vulnerable to seizure [37]. Another study suggests that the reduction in NR1 and NR2B subunits of the NMDA receptor in hippocampal synapses results in a lower interaction between them. Then, it was concluded that exposure to maternal stress for a long time leads to the long-lasting dysfunction of the hippocampus which may continue and be manifested in adulthood [137].

9. Effect of PS on the GABAergic system

The GABA receptors encompass three groups of receptors (A, B, and C), namely GABAA, GABAB, and GABAC. GABAA and GABAC receptors are ionotropic, whereas GABAB receptors are metabotropic. GABAA receptors are GABA-gated chloride channels consisting of 19 known subunits divided into eight classes of α, β, γ, δ, ε, π, θ, and ρ according to sequence identity [138,139]. From among these receptors, the GABAA receptor is mainly involved in the control of neural excitability, anxiety, feeding and drinking behavior, circadian rhythms, cognition, learning, and memory [140]. In addition, genetic mutations in this receptor have a role in some neurological and/or psychiatric disorders such as epilepsy, depression, and disorders related to growth such as autism and schizophrenia [141].

Numerous studies have been conducted in order to assess the effect of PS on the GABAergic system. In a study by Nejatbakhsh et al. [142], the researchers observed that PS increased the α5 subunit of the GABAA receptor in infant rats' hippocampus. They also noticed the significant reduction of first tonic–clonic seizure latency in pups exposed to stress. Furthermore, these pups experienced a longer duration of tonic–clonic seizures. Finally, at P14 and P21, PS increased the total score of seizure in rats. Caraiscos et al. [143] also reported the same finding by observing an increase in the expression of GABAA receptor α5 subunit in patients with epilepsy. In CA1 pyramidal neurons, this subunit mediates tonic GABAergic inhibition. Also, the expression of the GABAA receptor δ subunit increases in patients with epilepsy. This subunit has the same function of the α5 subunit but in dentate gyrus granule cells [144]. Thus, some aspects of PS-induced potentiation in seizure might be mediated via alterations in GABAergic system in certain brain structures such as the hippocampus.

10. Effect of PS on adrenergic systems

The autonomic nervous system has two components: sympathetic and parasympathetic systems. Numerous systems of the body such as cardiovascular, renal, and respiratory ones are affected by these two systems. Adrenal medulla and systemic sympathetic system secrete catecholamines which participate in the response to stress. Corticoids derived from the adrenal cortex have the same effect [145]. All circulating epinephrine and some of the norepinephrine (NE) are secreted by the adrenal medulla to facilitate fight or flight reaction in the stress response [146]. Norepinephrine is released from noradrenergic terminals primarily located in locus coeruleus which sends projections containing NE to different parts of the brain. Brain regions involved in epilepsy also receive these projections [147,148]. Studies demonstrate that NE acts like an anticonvulsant, and agents increasing extracellular NE levels have anticonvulsant effects [149–154]. On the other hand, the decrease in extracellular NE levels or adrenergic receptor antagonists elevates seizure susceptibility [155,156]. Nevertheless, according to the findings of some human and animal studies, under specific circumstances, elevated NE levels may have proconvulsant effects. Therefore, the level of NE determines its role as an anticonvulsant or proconvulsant [157–159]. The mechanisms of drugs used to control seizure are based on these two contradictory findings; carbamazepine decreases the NE level in cerebrospinal fluid in patients with mania [160], while phenytoin and valproic acid elevate NE levels to control epilepsy [161,162]. In a study by Moyer et al. [163], the researchers observed that PS alters NE levels in brain regions. Moreover, results of the study by Peters [164] demonstrated that PS changes NE levels, but the increase or decrease in NE level and the significance of level modification depend on the age of offspring and the brain region. Furthermore, some studies have investigated the effects of PS on the sympathetic nervous system by assessing the heart rate, heart rate variability, and respiratory sinus arrhythmia of fetuses. DiPietro et al. [165], for instance, suggested that PS has a correlation with heart rate and heart rate variability later in infancy. Furthermore, in a study by Alkon et al. [166], the researchers explained that psychosocial risk factors such as poverty decrease the intensity of sympathetic nervous system reactivity from 6 months to 5 years of age. Another study also demonstrated an association between infant respiratory sinus arrhythmia reactivity to a series of frustration tasks and high levels of maternal stress biomarkers at weeks of pregnancy [167]. Prenatal stress was associated with a reduction in α2 adrenergic receptor binding in several brain regions in 60-day-old offspring rats [168], suggesting a mechanism by which stress may increase seizure susceptibility in offspring rats [169]. Maternal stress exposure has also been suggested to influence fetal development via altering brain adrenergic receptors' binding as well as decreasing placental NE transporter protein levels [168,170] and uterine blood flow mediated by α1-adrenergic receptors [171]. Thus, it can be concluded that the effects of PS on adrenergic system and sympathetic nervous system are mainly due to effects on the neurotransmitter system and functioning of autonomic nervous system.

11. Long-lasting and inheritable properties of PS-induced changes

Stressful incidents during early life may have a wide range of negative effects on the brain and behavior of offspring, and numerous psychiatric and behavioral disorders in adulthood may originate from these incidents [172,173]. Several studies have demonstrated that PS is correlated with stress responses and depressive-like behaviors. This phenomenon has been referred to as “fetal programming” in numerous studies [174–176]. Psychiatric disorders result from HPA axis dysfunction caused by the effects of PS on fetal programming [77,177]. In a study conducted by Brunton et al. [176] on rodent offspring, the researchers observed that social stress during pregnancy significantly increased the responses of HPA axis to later physical and psychological stresses. These responses encompass the higher secretion of ACTH and GC in response to stress and higher expression of CRH mRNA in the medial parvocellular division of the paraventricular nucleus. The increased HPA axis in response to PS may be explained by central GC negative feedback regulation impairment. This idea has been supported by Brunton et al. [176] as the decreased mRNA expression in the hippocampus for the MR. On the other hand, Maccari et al. [77] stated that the reduced mRNA expression for the GR plays an important role in addition to the MR. Furthermore, in the study by Grundwald et al. [178], it was found that the effects of PS on HPA axis regulation can be passed to coming generations in a sex-dependent manner, implicating neuropsychiatric disorders with developmental origins. Studies also report that PS may be correlated with the development of schizophrenia in adulthood. In a study conducted by Khashan et al. [179], it was suggested that experiencing maternal stress during the first trimester of pregnancy increases the risk of schizophrenia. Also, some other studies indicated that exposure to stressful events, including hypoxia, starvation, and infections, can be associated with an increased risk of schizophrenia [180–182]. Other psychiatric disorders such as affective disorders can also be correlated with PS. Based on studies, maternal immune and stress responses have a significant relationship with the major depressive disorder [183,184]. Another risk factor for major depressive disorder is maternal exposure to famine in the second and third trimesters, revealing the importance of maternal nutrition in the

neurodevelopment of offspring [185]. In addition to exposure to maternal risk factors, some studies have shown that traumas in early life may also cause long-term complications in the offspring. Maternal separation (MS) in early life has been chosen as a type of trauma to examine these complications [186]. Animal studies examining the effect of MS on the behavioral development of offspring have yielded different outcomes. Some have suggested that the number of MS paradigms causes changes in HPA axis response to stressful events, leading to the induction of anxiety and depressive-like behaviors [187–189]. On the other hand, some studies have revealed that MS may cause animals to take risks and seek novel ways to cope with the new situation [190–192]. In a study by Weiss et al. [193], the effects of unpredictable MS were compared to the effects of a combination of unpredictable MS with maternal stress on behavioral development. They concluded that the combination of unpredicted MS with maternal stress affects behavior more severely. In addition, parental stress before gestation can affect reproduction system both in dams and pups. It has been reported that parental stress before gestation decreases fertility rate in dams and changes sex ratio in favor of females in the pups. Meanwhile, it not only decreases sex hormones in parents (both mother and father), but also diminishes sex steroids in immature pups [194,195]. These are some examples of inheritable properties of early life stress including PS mostly by epigenetics mechanisms.

In conclusion, variations induced by prenatal and early-life stress may have long-lasting and even inheritable molecular and cellular alterations in the offspring. These changes may, in turn, justify many psychiatric and behavioral disorders, including seizure, in adulthood. Thus, appropriate management of pregnant women and their offspring and preventing their exposure to the mentioned risk factors seem to be vital in promoting the health of future generations.

Conflict of interest

There is no conflict of interest between the authors.

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