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Review

Adverse effects of early-life stress: focus on the rodent neuroendocrine system

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Abstract

Early-life stress is associated with a high prevalence of mental illnesses such as post-traumatic stress disorders, attention-deficit/hyperactivity disorder, schizophrenia, and anxiety or depressive behavior, which constitute major public health problems. In the early stages of brain development after birth, events such as synaptogenesis, neuron maturation, and glial differentiation occur in a highly orchestrated manner, and external stress can cause adverse long-term effects throughout life. Our body utilizes multifaceted mechanisms, including neuroendocrine and neurotransmitter signaling pathways, to appropriately process external stress. Newborn individuals first exposed to early-life stress deploy neurogenesis as a stress-defense mechanism; however, in adulthood, early-life stress induces apoptosis of mature neurons, activation of immune responses, and reduction of neurotrophic factors, leading to anxiety, depression, and cognitive and memory dysfunction. This process involves the hypothalamus-pituitary-adrenal axis and neurotransmitters secreted by the central nervous system, including norepinephrine, dopamine, and serotonin. The rodent early-life stress model is generally used to experimentally assess the effects of stress during neurodevelopment. This paper reviews the use of the early-life stress model and stress response mechanisms of the body and discusses the experimental results regarding how early-life stress mediates stress-related pathways at a high vulnerability of psychiatric disorder in adulthood.

Key Words: early-life stress; hypothalamic-pituitary-adrenergic axis; maternal separation; mental illness; neurodevelopmental disorder; neuroendocrine system; neurotransmitter

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Introduction

Early life is a stage in which an individual's physical, emotional, and cognitive functions can undergo extensive development, and experiences during the postnatal developmental period can have long-term effects throughout their lifetime (Duffy et al., 2018). In terms of brain development, postnatal brain growth includes synaptogenesis, synapse pruning, neuronal arborization, gliogenesis, and myelination, which are processes that help an individual perform, recognize, and think normally (van Dyck and Morrow, 2017). Early-life stress (ELS) or early-life adversity includes exposure to stressful environmental circumstances such as separation from parents, substance abuse, violence, starvation, and neglect during the developmental period (Kessler et al., 2010). Over the past several decades, many studies have reported that stress experiences in infancy and childhood are related to the probability of adverse outcomes of neuropsychiatric symptoms such as mood disorders (anxiety, depression, bipolar disorder), post-traumatic stress disorder (PTSD), and attention-deficit/hyperactivity disorder (Carr et al., 2013). Indeed, these stress-induced mental illnesses are thought to be associated with dysregulation in neurophysiology, such as the hypothalamic-pituitary-adrenergic (HPA) axis, noradrenergic system, serotonergic system, and dopaminergic pathway in the brain (Koob, 1999; Ventriglio et al., 2015; van Bodegom et al., 2017). When a neonate is exposed to stress, biological activities are elevated to respond appropriately to the stress and participate in neurotransmitter delivery and shaping of neuronal circuits, ultimately resulting in persistent and pervasive alterations that manifest as detrimental psychological and behavioral outcomes (Agorastos et al., 2018). It is important to understand the neurobiological processes affected by ELS and cues mediating the prevalence of neuropsychiatric disorders in adulthood in order to identify possibilities for new therapeutic approaches to mental illness (Fogelman and Canli, 2019).

Although numerous studies have reported that ELS affects mental health by contributing to the onset of psychopathology, the biological mechanisms underlying this association have not yet been clearly defined. Due to the temporal and ethical constraints of human studies, researchers have devised methods for reliable and useful animal models subjected to ELS (Murthy and Gould, 2018). For the past several decades, rodent models have been commonly used to identify neurobiological processes and behavioral abnormalities under ELS conditions (Levine, 1957). ELS models using rodents are thought to reflect human stress responses and phenotypes, such as representing anxiety and depressive behaviors, and increases in stress hormone levels in the blood (Orso et al., 2019). Here, we review the methods of the ELS model using rodents and recent studies on the effects of ELS, focusing in particular on the neuroendocrine system of the HPA axis and neurotransmitter systems, such as the norepinephrine system, dopaminergic pathways, and serotonergic system in adult rodents.

Literature Search Strategy

Publications included in this narrative review were retrieved by a computer-based online search of the PubMed database updated until March 2023. Search specificity and sensitivity were maximized using a combination of the following terms: "early-life stress", "early-life adversity", "model", "mouse", "maternal separation", "response", "system", "neurodevelopment", "neuroendocrine", "behavior", "neurotransmitter", "HPA axis", "norepinephrine", "dopamine", and "serotonin". Search results were further screened by title and abstract and retrieved further articles using the PubMed function of relevant article tracking.

Models of Early-Life Stress

ELS models using rodents have been established and applied to study the

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etiology of psychiatric disorders involving adverse experiences in early life (Murthy and Gould, 2018). For each model, dams or offspring mice are subjected to a range of stimuli during different neurodevelopmental stages: gestational stress and postnatal stress (Fareri and Tottenham, 2016; Orso et al., 2019; Adjimann et al., 2021). The first involves daily physical body restraint and exposure to variable stress for the gestational period of dams. Following the daily application of gestational stress, offspring mice display abnormal behavioral patterns, including increases in anxiety behaviors or stress-related responses such as compulsive addictive behaviors later in life (Estanislau and Morato, 2006; Dong et al., 2018).

Postnatal stress of ELS involves maternal separation (MS) or limitation of bedding or nesting (LBD) (Adjimann et al., 2021; **Figure 1**). MS is one of the most commonly applied ELS manipulations. In this model, pups are repeatedly separated from the dams, typically for 3–4 hours a day during the first 2–3 postnatal weeks, resulting in the loss of maternal care and lactation. It is considered valid in translation because it mimics separation from the mother well, induces depressive behavior, and reduces exploratory activity in adult mice (Andersen, 2015). Another manipulation of the postnatal ELS model is LBD, which creates a stressful environment, and dams experience difficulty with maternal care. The most severe version of this model involves housing dams and pups on wire mesh platforms without bedding or nesting (Cui et al., 2006; Molet et al., 2014). In this version, dams are disturbed from postnatal day 2 (PND2) to PND10 in empty regular cages with a floating mesh platform approximately 2.5 cm above the cage floor (Al-Chami et al., 2020).

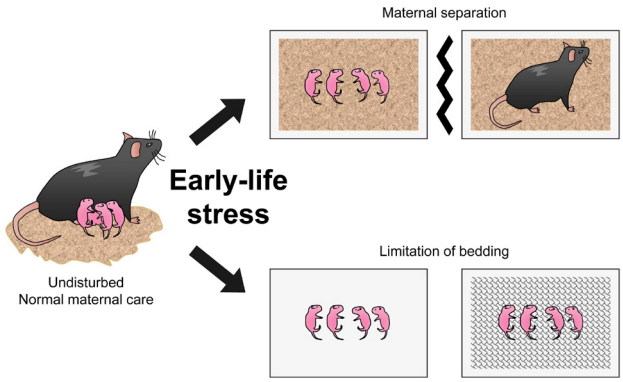

Figure 1 | **Manipulations of early-life stress model using rodents.**
separation model, pups are separated from the dams during the early-postnatal period. In the limitation of the bedding model, pups are raised on minimal bedding or wire mesh platform. These models induce deprivation of maternal care, resulting in depressive behavior or cognitive deficit in adult offspring. Created using Microsoft PowerPoint 2021.

Individuals subjected to ELS tend to respond to stress by comprehensively modulating the neuroendocrine system, the sympathetic nervous system, and inflammatory cytokines, and these dramatic alterations of neurobiological factors during the developmental period may result in long-lasting damage to the brain by induction of epigenetic changes in gene expression (Fogelman and Canli, 2019; Cheng et al., 2022). Several studies using these ELS paradigms have demonstrated that exposure to ELS negatively affects the developing nervous system (Walker et al., 2017; Shin et al., 2023; **Table 1**). Rodents exposed to ELS exhibit depressive-like behaviors, such as anhedonia under reduced sucrose preference (Molet et al., 2016) and anxiety-like behaviors in the elevated plus-maze test (Dalle Molle et al., 2012). The LBD paradigm increased plasma corticosterone levels and induced activation of the HPA axis in PND9 rats (Brunson et al., 2005). In the LBD model, developmental neurogenesis increased in the hippocampus of PND9 male mice but reduced the survival of neurons and impaired cognition function in adult male offspring (Naninck et al., 2015). In addition, it has been suggested that recognition dysfunction provoked by ELS is related to the development and pathology of neurodegenerative disorders, such as Alzheimer's disease. Increased microglial activity and pro-inflammatory cytokine expression in the hippocampus have been observed in adult mice exposed to ELS, but these effects appear to decline in older rodents (Lumertz et al., 2022). Early maternal deprivation decreases the expression of brain-derived neurotrophic factor (BDNF) in the rat brain, neurotrophins that modulate biological processes in the brain (Roceri et al., 2002), and enhances c-fos levels in the hypothalamus of the mouse brain (Benner et al., 2014). These results may be influenced by epigenetic factors because an increasing number of studies have reported that ELS induces the expression of epigenetic-related genes, such as histone deacetylase and histone acetylase (Alameda et al., 2022).

However, several studies using the maternal separation paradigm have reported that dams exhibit inconsistent behavioral patterns and even increased maternal care after ELS, raising concerns that stress-induced behavioral outcomes in offspring are not consistent (Millstein and Holmes, 2007; George et al., 2010). Therefore, researchers have developed a novel ELS model that minimizes the lethal impact on developing offspring, while manifesting the physiological or behavioral effects of early-life challenges. For example, maternal separation combined with an early weaning model causes anxiety and depressive behavior in the elevated plus-maze and forced swim test in mice (George et al., 2010). A recent study using maternal deprivation demonstrated that when the developmental period involves exposure to ELS, neurogenesis activities are affected in the adult mouse brain (Daun et al., 2020). As such, the ELS paradigm contains several modifications, including a combination of other stresses, separation methods, and periods, and it is difficult to compare the results obtained by different research groups. Therefore, the application of stress should be strictly regulated, and variables should be minimized to increase reproductivity (Azevedo et al., 2010). Although there are some differences or discrepancies in experimental results depending on the strain, sex, and modifications of the experimental methods, the rodent ELS model is widely used to understand childhood maltreatment (Murthy and Gould, 2018; Goodwill et al., 2019; Zeng et al., 2021).

Table 1 | **Rodent studies on adverse effects of different early-life stress models**

Type of ELS model	Possible effect in rodent model	Reference
MS	Increased anxiety-, depressive-, and aversion behavior	Gracia-Rubio et al., 2016; Frau et al., 2019
	Impaired cognitive function	Yang et al., 2017; Sinani et al., 2022
	Enhanced neuroinflammation in the prefrontal cortex and hippocampus	Gracia-Rubio et al., 2016
	Persistent activation of the HPA axis and CRH signaling in BNST	Hu et al., 2020
	Increased NE release in the hippocampus	Sterley et al., 2013
	Reduced mRNA level of SERT and BDNF in DRN	Bravo et al., 2014
LBD	Increased anxiety, depressive-like behaviors, and anhedonia in adolescent	Dalle Molle et al., 2012; Molet et al., 2016; Goodwill et al., 2019
	Impaired cognitive function	Naninck et al., 2015
	Activation of the neuroinflammatory response in the hippocampus	Hoeijmakers et al., 2017; Lumertz et al., 2022
	Activation of HPA axis; increased ACTH and GCs levels in plasma	Brunson et al., 2005
MS + LBD	Abnormal behavior with increased anxiety and depressive behavior, sociability deficits, cognition impairment	Shin et al., 2023
	Disruption of reward circuitry and increased stress susceptibility	Peña et al., 2019
	Increased CRH level in the hypothalamus	Orso et al., 2020
MS + early weaning	Increased anxiety and depressive behavior	George et al., 2010
MS + social isolation	Reduced reward-seeking behavior; decreased expression level of DRD1	Sasagawa et al., 2017

ACTH: Adrenocorticotropic hormone; BDNF: brain-derived neurotrophic factor; BNST: bed nucleus of stria terminalis; CRH: corticotropin-releasing hormone; DRD1: dopamine receptor D1; DRN: dorsal raphe nucleus; GC: glucocorticoid; HPA: hypothalamus-pituitary-adrenal axis; LBD: limitation of bedding or nesting; MS: maternal separation; NE: norepinephrine; SERT: serotonin transporter.

The Effects of Early-Life Stress on the Hypothalamic-Pituitary-Adrenergic Axis

The stress response comprises a wide range of processes in which peripheral tissues receive and convey environmental stimuli to the central nervous system, resulting in the regulation of a chain of biological factors (Charmandari et al., 2005). The HPA axis is one of the key stress response systems involving three organs, namely the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary gland, and the adrenal gland, that interact with neuroendocrine factors and coordinate physiological responses. When stressors are encountered, the HPA axis triggers the 'fight-or-flight' response. The hypothalamus is modulated by various neurotransmitters, either excitatory (norepinephrine and serotonin) or inhibitory (γ-aminobutyric acid and opioids) (Stephens and Wand, 2012). Corticotropin-releasing factor (CRF), which is a key regulator of the HPA axis, is synthesized in parvocellular neurons in the PVN and released into the hypophyseal portal vessels (Herman and Tasker, 2016). CRF reaches the pituitary gland and binds to CRF R1 receptors in the anterior pituitary corticotropes, leading to the synthesis and release of adrenocorticotropic hormone (ACTH), which then travels via the blood vessels to the adrenal cortex, where it synthesizes and releases glucocorticoids (GCs) (Smith and Vale, 2006). GCs act in various parts of the body to provide an energy source for stress responses, suppress immune responses, and modulate sympathetic nervous systems, including adrenergic and norepinephrine systems, by binding mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (Sapolsky et al., 2000). Because GCs have a higher affinity for MRs than for GRs, they usually bind more to MRs at low GC levels. However, with high levels of GCs, such as under stress conditions, GCs bind GRs and can pass freely through the blood-brain barrier and affect brain function. When GC levels reach a specific threshold, they suppress their own

release and exert tight control of the two upstream targets of the HPA axis by negative feedback loops (Koning et al., 2019).

The HPA axis is essential for coping with and normalizing the body system against external stress disrupting homeostasis. However, upon exposure to severe or chronic stress, GCs may be aberrantly released and cause disturbances in normal stress responses to the detriment of mental health (Varghese and Brown, 2001). Dysfunction of the HPA axis is associated with blunting of ACTH responses and alterations in GR sensitivity and expression levels, which are direct upstream signals (Karin et al., 2020). There is considerable evidence of dysregulation of the HPA axis in stress-related mental illnesses. For example, a large proportion of patients with PTSD exhibit excessive GCs levels in the blood, and pharmacological treatment that inhibits GC secretion or blocks GRs has a therapeutic effect on depressive symptoms (Gerritsen et al., 2017). In a rodent model, exposure to unpredictable chronic mild stress for eight weeks increased GC secretion but reduced the expression level and ligand-binding affinity of GRs in the hippocampus (Hill et al., 2012). In addition, exposure to social defeat stress induces anxiety- and despair-related behavior in mouse models, and susceptible mice exhibit hypercortisolemia with significantly less GR nuclear translocation in the hippocampus (Han et al., 2017). These results demonstrate that a variety of stresses induce HPA axis collapse and contribute to the onset of neuropsychiatric symptoms.

There are many studies on changes in the HPA axis in the ELS paradigm. PND1–12 mice and PND3–14 rats have low stress-responsiveness periods with low corticosteroid exposure in the brain, and pups exhibited low levels of basal ACTH and corticosteroid concentrations. During this period, the alteration of ACTH/GC levels has multiple effects on nervous development (Schmidt et al., 2003). Pups and adult mice subjected to the LBD model exhibited increases in ACTH and GC levels in plasma (Moussaoui et al., 2017) and elevated relative adrenal weight, which represents the effects of chronic stress. In addition, a decline in the negative feedback of the HPA axis was observed as a result of decreased CRF levels in the PVN compared with the increase in the level of GCs in the mouse brain (Avishai-Eliner et al., 2001). Long-term overproduction of GCs may induce atrophy of hippocampal dendrites and perpetual loss of memory and recognition function, which is the usual phenotype of PTSD and depression (Sapolsky, 1996). GCs are also involved in epigenetic processes, such as methylation, because GRs are nuclear receptors that can act as transcriptional factors. For example, GCs alter the methylation pattern of the Fkbp5 gene in adolescent mice, which is associated with increased anxiety (Lee et al., 2010). Thus, elevated GC levels may play a role in representing phenotypes caused by ELS. Maternal care, including licking and grooming of dams, induces GR expression, accompanied by increased histone acetyltransferase activity in mice. These results suggest that the absence of maternal care may contribute to the dysfunction of the HPA axis by altering the level of GR expression (Weaver, 2009).

The Effects of Early-Life Stress on the Norepinephrine System

The sympathetic-adrenal-medullary system, which is controlled by the central autonomic nervous system, is another essential neuroendocrine response mechanism to stress. Norepinephrine (NE) is a catecholamine neurotransmitter synthesized in the locus coeruleus (Bourdy et al., 2014) and is an important factor in the rapid response to external or internal stress stimuli by activation of the autonomic nervous system (Habib et al., 2001; Chrousos, 2009; Agorastos et al., 2018). NE controls and increases arousal and physiological responses to stress. Moreover, it involves recognition and memory function through LC neurons projected into the prefrontal cortex, hippocampus, and amygdala (Schwarz and Luo, 2015; Wood and Valentino, 2017). Diverse stressors, such as electric shock, auditory stress, and bladder pressure, are recognized as stimuli that activate the LC-NE system in conjunction with the activation of the HPA axis. Activation of the LC-NE system includes the firing of neuronal activity, increases in NE turnover, and NE secretion. The released NE transmits signals globally to target organs governed by the central nervous system, including the adrenal medulla, cardiovascular system, respiratory system, and renal system, which results in behavioral changes. In the adrenal medulla, both NE and epinephrine, an analog of NE, are secreted and result in physiological responses (Koob, 1999; Herrmann et al., 2004; Morilak et al., 2005). These processes are controlled by negative feedback via the α2 adrenoreceptor, which inhibits NE release. In addition, HPA axis-related factors are involved in the activation of the autonomous nervous system (Koob, 1999). Pre-opiomelanocortin, a precursor polypeptide synthesized in corticotrophs of the anterior pituitary, produces ACTH, β-endorphin, and melatonin. ACTH stimulates epinephrine secretion in the adrenal medulla and GC secretion in the adrenal cortex. β-endorphin is related to the release of epinephrine in the adrenal medulla (Wurtman and Axelrod, 1966; Amir et al., 1980).

Dysfunction of the LC/NE system has been implicated in the etiology of neuropsychiatric and stress-related disorders. Acute stress activates LC neurons autonomously, whereas chronic stress may induce over-responsiveness, enhancing the activity of LC neurons on excitability and NE synthesis (Southwick et al., 1999; Hillhouse and Grammatopoulos, 2006). Concerning the ELS paradigm, there are a limited number of studies on alterations in autonomic activity and NE responses following ELS exposure. A study using an MS model combined with odorless clean bedding observed that repeated exposure to olfactory experiences induced downregulation of α1 adrenoreceptors in somatosensory cortices and anhedonic-like behavior in adult mice (Coccurello et al., 2014). In addition, expression of the anti-apoptotic factor Bcl-2 in the hippocampus was enhanced, which indicates that neuroprotection to subsequent adversity is activated in terms of information processing (Coccurello et al., 2014).

Many clinical studies on depression have highlighted mediators contributing to psychiatric pathology due to the monoamine depletion hypothesis and alteration in neurotransmitter receptor density (Hillhouse and Grammatopoulos, 2006). However, chronic stress-induced cognitive deterioration is reversed by chronically blocking the norepinephrine system (Jett and Morilak, 2013). Because NE functions in various ways, further research and analysis of changes in the NE system using the ELS model are needed, and this will help with a systematical understanding of the overall responses induced by stress on norepinephrine activity.

The Effects of Early-Life Stress on the Dopaminergic Pathways

Dopamine (DA) is a catecholamine neurotransmitter synthesized in the substantia nigra and ventral tegmental area (VTA) of the midbrain. Although dopaminergic neurons account for less than 1% of the total number of neurons in the brain, they control important functions of the brain, including motor behavior, reinforcement, motivation, and working memory, by projecting to various areas of the brain (Schultz, 1997; Iversen and Iversen, 2007; Luo and Huang, 2016). When tyrosine is converted into DA by tyrosine hydroxylase (TH) at axon terminals, it can bind to DA receptors of downstream neural circuits or lead to various biological functions by uptake of the DA transporter (DAT) in postsynaptic neurons (Faber and Haring, 1999; Daubner et al., 2011). There are four dopamine pathways, each with a different function. The nigrostriatal pathway arises from the substantia nigra pars compacta and projects to the dorsal striatum, which plays a key role in motor function or cognition (Bourdy et al., 2014). The mesocortical pathway projects from the VTA to the frontal and temporal cortices, which are thought to be relevant to learning, working memory, and concentration (Hauser et al., 2017). The mesolimbic pathway controls motivation, experiences of reward, and pleasures that project from the VTA to the ventral striatum, hippocampus, amygdala, and bed nucleus of the stria terminalis (Tritsch and Sabatini, 2012). The tuberoinfundibular dopaminergic pathway arises from periventricular nuclei and sends projections to the hypothalamus, which inhibits prolactin releases (Stagkourakis et al., 2019).

The pathological hallmarks of malfunction of the dopaminergic system include many neuropsychiatric disorders, such as anxiety, depression, and drug addiction. A representative example is the collapse of the reward function due to DA receptor D2 (DRD2) defects, which keep dopamine at a low level in the brain, endangering an individual at risk of substance addiction (Brown and Gershon, 1993; Dailly et al., 2004). Several studies have reported that patients with psychiatric disorders have lower levels of BDNF, which controls the expression of DRD3 and upregulation of DAT in a compensatory manner (Huang et al., 2011; Kordi-Tamandani et al., 2012; Han and Deng, 2020). DAT1 and DRD4 have been considered candidate dopamine genes that contribute to the onset of attention-deficit/hyperactivity disorder in twin and family studies (Swanson et al., 2000). In addition, the dopaminergic pathway can communicate with the HPA axis and serotonergic system under chronic stress conditions in rats (Mizoguchi et al., 2008). These results indicate a relationship between depression and dopamine transmission.

ELS can induce epigenetic alterations in neurotransmitter-related genes in animal models. Mice exposed to the MS paradigm with social isolation stress had higher methylation of the promoter of the Drd1a gene, and its mRNA expression level was reduced in the nucleus accumbens (Sasagawa et al., 2017). A study using a mouse model reported that acute ELS enhanced DRD1 expression and dopamine- and cAMP-regulated neuronal phosphoprotein in the hippocampus; however, upregulation of its expression and no alteration of DRD1 expression were observed in the chronic ELS model. These experimental results suggest that ELS may induce the reconstruction of the dopaminergic system (Köhler et al., 2019). In addition, a recent study has demonstrated that the MS model affects the binding levels of striatal DRD1, which is strongly associated with the discrimination index of the novel object recognition test in adolescent and adult rats (Sinani et al., 2022). Monoamine-oxidase A (MAO-A), a key enzyme that oxidizes neurotransmitters such as catecholamine, may be relevant to the vulnerability of ELS (Xu et al., 2020). Mice having hypomorphic mutation of MAO-A, which exposed to ELS, exhibited reduction of MAO-A level, aberrant neuronal plasticity in the prefrontal cortex, and increased aversion behavior as a result of dysfunction of the mesocortical dopamine circuit (Frau et al., 2019). Consequently, ELS may induce disruption of the dopaminergic circuit during the developmental programming period, resulting in vulnerability to psychosis.

The Effect of Early-Life Stress on the Serotonergic System

5-Hydroxytryptamine (5-HT), also known as serotonin, is a major neurotransmitter that plays an important role in diverse biological processes. In the brain, 5-HT is expressed in various areas, such as the striatum, amygdala, and prefrontal cortex, and is especially abundant in the dorsal raphe nucleus, which is a brain stem nuclei region located in the midbrain

and pons (Paquelet et al., 2022). Serotonergic neurons in the DRN send projections into large areas of the brain and are involved in social interaction, reward processing, aggressive behaviors, and anxiety or depressive behavior by influencing not only the brain but also the peripheral nervous system, such as thermoregulation and cardiovascular regulation (Li et al., 2016). In recent decades, several studies have suggested that defects in the serotonin system are associated with depressive symptoms (Haleem, 2019; Pourhamzeh et al., 2022). The proposed possibilities of the serotonin hypothesis include decreases in 5-HT levels, higher levels of serotonin transporter (SERT), and alterations in serotonin receptor activities in the brain (Roth, 2008). Clinical attempts have been made to use serotonin receptor inhibitors in pharmacological interventions for patients with depression (Cowen and Browning, 2015). However, a recent systematic review using large data meta-analyses reported no consistent link between serotonin and depression (Moncrieff et al., 2022). This makes it clear that 5-HT is not a key contributor to depression; nevertheless, it is still evident that 5-HT is involved in various functions, including mood, sleep, appetite, and defensive mechanism activities, and most mental disorders are associated with abnormalities in the serotonergic system (Pourhamzeh et al., 2022).

An increasing number of studies have suggested that serotonin plays a significant role in brain development and synaptic plasticity (Daubert and Condron, 2010; Booij et al., 2015). In both rodents and humans, serotonin levels increase during the immature period, and the turnover speed of serotonin is higher in developing brains because serotonin is produced earlier than other monoamine neurotransmitters (Azmitia, 2007). Serotonin release may alter the dendritic length, synaptic plasticity, and neuronal cell growth in a highly orchestrated manner (Faber and Haring, 1999). External stress stimuli during the developmental period can disturb the growth of serotonergic neurons by affecting serotonergic neurons afferented to the downstream region of the DRN, such as the central amygdala. The effect of ELS on the serotonin system is mainly been investigated in terms of association with the dysregulation of serotonin receptors (Chaouloff et al., 1999). For example, male rats exposed to early deprivation exhibited a decline in reward motivation in compliance with a reduction in the binding affinity of the serotonin type 1A receptor in the anterior cingulate region, hippocampus, and DRN (Leventopoulos et al., 2009). Maternal separation entails increased pre-mRNA levels of Htr2c and Gαq subunits, which participate in binding to the 5-HT receptor in adult mice (Bhansali et al., 2007). These experimental results are consistent with the clinical results of increased serotonin turnover and binding affinity of the 5-HT receptor observed in patients with anxiety and mood disorders (Bach-Mizrachi et al., 2006). Moreover, the MS model reduced SERT and BDNF mRNA expression levels in the DRN of adult rats (Bravo et al., 2014), and the transcription level and uptake functionality of SERT were determined depending on the SERT genotype. These results suggest that SERT may be associated with ELS susceptibility (Houwing et al., 2017). Furthermore, one of the functions of 5-HT is likely to indirectly participate in neuroendocrine regulation by modulating mRNA levels of CRF in the PVN (Jørgensen et al., 2002), which indicates that serotonin responds to stress not only by direct regulation but also via indirect circuits involving other stress-related factors.

Limitations

This paper has some limitations at the review level. It discussed the adverse effects of ELS in rodent experimental models in terms of neuroendocrinology but does not provide an in-depth explanation of the interactions of each system. It does not include profound descriptions of the alteration of neuronal dynamics at synapse and network levels. It does not address a systematic review and meta-analysis of experimental studies investigating the effects of ELS.

Conclusion

Our stress system includes the HPA axis and catecholamine neurotransmitter pathways, which respond to environmental and physiological stresses (**Figure 2**). Activation of the stress system during the neurodevelopmental period is associated with the development of mental diseases such as depression, and there is a limitation in considering changes in single factors as the etiology of psychiatric disorders. Several studies on stress-related neurotransmitters have revealed how stress systems interact with each other and cooperate in a complex manner for development or survival. Their activities affect all processes, including physiological responses such as breathing, control of body temperature, and arousal, as well as functions such as cognition, memory, learning, and mood control.

ELS model using rodents is an experimental system for the manipulation of the effects of environmental factors, such as maternal separation and severe housing conditions, on neurodevelopmental processes. ELS causes neuropsychiatric disorders in adults and induces stress response dysfunctions. There are an increasing number of reports that epigenetic factors are involved in neurodevelopmental processes. An epigenetic approach needs to be investigated given that the effects of ELS are not limited to the early stages of life by influencing histone modifications but persist into adulthood as well. Despite variable and inconsistent experimental results due to sex, time, and stress methods, it is helpful to understand the pathological aspects of mental illness caused by environmental factors, considering that ELS can explain universal childhood maltreatment.

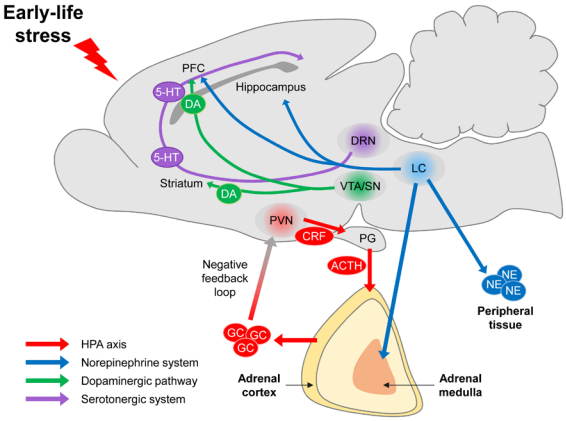

Figure 2 | **Stress response-related system in mouse brain.**
Stress response-related system includes the hypothalamic-pituitary-adrenergic axis (HPA axis), norepinephrine system, dopaminergic pathway, and serotonergic system. Stress-related neurotransmitters and hormone modulate physiological responses, mood, cognition behavior to stress by interaction with each other. Created using Microsoft PowerPoint 2021. ACTH: Adrenocorticotropic hormone; CRF: corticotropin-releasing factor; DA: dopamine; DRN: dorsal raphe nucleus; GC: glucocorticoid; LC: locus coeruleus; NE: norepinephrine; PFC: prefrontal cortex; PG: pituitary gland; PVN: paraventricular nucleus; SN: substantia nigra; VTA: ventral tegmental area; 5-HT: 5-hydroxytryptamine.

In human research, a longitudinal study has suggested that MS before age 5 years may be a risk factor for long-term borderline personality disorder symptoms (Crawford et al., 2009). Several studies have reported that individuals who experienced childhood neglect or PTSD show abnormalities in brain development (Teicher et al., 2004; Woon and Hedges, 2008; VanTieghem and Tottenham, 2018). The other human study using functional magnetic resonance imaging has reported that adolescents who experienced early caregiver deprivation represent impaired cognitive control than control adolescents (Mueller et al., 2010). There are some studies on how ELS affects the human brain using longitudinal studies, imaging techniques, and meta-analysis, but it is difficult to identify the molecular mechanism because of the small sample or absence of a well-organized longitudinal cohort (Dillon et al., 2009). Therefore, researchers use the rodent model for clarifying details about how ELS impacts neurodevelopment and behavior. Although there are obvious limitations or contradictory results for rodent model studies in terms of understanding the function of the human brain, the rodent models will be effective tools for exploring links between ELS and long-lasting outcomes because of their genetic and behavioral similarity with humans.

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Conflicts of interest: *The author declares no conflicts of interest.*
Data availability statement: *Not applicable.*

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