Chapter 8
Advance in Stress for Depressive Disorder

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Abstract Stress is an adaptive response to environment aversive stimuli and a common life experience of one's daily life. Chronic or excessive stress especially that happened in early life is found to be deleterious to individual's physical and mental health, which is highly related to depressive disorders onset. Stressful life events are consistently considered to be the high-risk factors of environment for predisposing depressive disorders. In linking stressful life events with depressive disorder onset, dysregulated HPA axis activity is supposed to play an important role in mediating aversive impacts of life stress on brain structure and function. Increasing evidence have indicated the strong association of stress, especially the chronic stress and early life stress, with depressive disorders development, while the association of stress with depression is moderated by genetic risk factors, including polymorphism of *SERT*, *BDNF*, *GR*, *FKBP5*, *MR*, and *CRHR1*. Meanwhile, stressful life experience particularly early life stress will exert epigenetic modification in these risk genes via DNA methylation and miRNA regulation to generate long-lasting effects on these genes expression, which in turn cause brain structural and functional alteration, and finally increase the vulnerability to depressive disorders. Therefore, the interaction of environment with gene, in which stressful life exposure interplay with genetic risk factors and epigenetic modification, is essential in predicting depressive disorders development. As the mediator of environmental risk factors, stress will function together with genetic and epigenetic mechanism to influence brain structure and function, physiology and psychology, and finally the vulnerability to depressive disorders.

Keywords Stress · Depressive disorder · Stressful life events · HPA axis · Epigenetic modification

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8.1 Introduction

Stress, including physiological and psychological stress, is a common experience of individual life. In general, the stress refers to the response to the stressful life events which are challenging, taxing, harmful, and even threating to individual. Disagreeable emotions like anxiety, anger, and bitterness could be evoked, leading to psychological tension. Stressed individuals may become tense, irritable, aggressive, disinterested, anxious, or agitated, being accompanied by disturbed sleep, decreased or increased appetite, and declined sexual desire. In addition, physiological alterations containing activation of hypothalamic–pituitary–adrenal (HPA) axis (Belda et al. 2015; Bonfiglio et al. 2011), and changes in catecholaminergic systems and immune system, will be induced. Does stress cause depression? This essential issue has drawn a great deal of attention but still remained to be fully addressed. A large body of studies from human and animal models focusing on the association between stress and depressive disorders defined the strong impact of stress on risk of developing depressive disorders, supporting the causal association of stress with depressive disorders onset (Hammen 2005; Kendler et al. 1999).

Depressive disorder, also simply known as depression, is a common but serious mood disorder characterized by persistent feelings (at least 2 weeks) of sadness, hopelessness, and worthlessness, which is usually accompanied by loss of interest in normally pleasurable activities, irritability, impaired cognition, low energy, sleeping or eating problem, pain without a clear cause, and even tendency to suicide (Otte et al. 2016; Schulz and Arora 2015). Depression is a highly prevalent psychiatric disorder in current society, and is associated with high levels of morbidity and mortality (Chirita et al. 2015; Kessler and Bromet 2013; Laursen et al. 2016; Otte et al. 2016). Although large attentions and research have been attracted to the exact cause of depressive disorder, the etiology of depression is still not fully understood.

Unlike other diseases determined by specific gene malfunction, no true depression genes are identified to be directly responsible for the onset and cure of the depression due to the heterogeneity and complexity of depressive disorders. Several genetic factors have been recognized to be associated with increased risk for depressive disorders like major depressive disorder based on family, twin, and epidemiologic studies (Clarke et al. 2010; Dunn et al. 2015; Flint and Kendler 2014; Gao et al. 2012; Gatt et al. 2015; Kishi et al.2013; Lee et al. 2012; Lopez-Leon et al. 2008; Shadrina et al. 2018; Smoller 2016; Wray et al. 2012; Zhao et al. 2014). Each susceptibility gene contributes to a small fraction of the total genetic risk. It was estimated that genetic contribution to the risk of depression is probably ~40% and can be increased to 75% in recurrent depression (McGuffin et al. 1996; Sullivan et al. 2000), the remaining main risk for depression development was attributed to environmental factors (Klengel and Binder 2013; Lopizzo et al. 2015; Richter-Levin and Xu 2018). The role of environmental factors in predisposing depressive disorders essentially reflects the crucial effects of stress on etiology of depressive disorders, since environmental risking factors actually trigger stress and dysregulated stress response are supposed to mediate environmental impact on depression

onset. These environmental risk factors, which have been found to be correlated with depressive disorders vulnerability, include prenatal infection, maternal stress, child abuse and neglect, social stress, traumatic events, cancers, endocrine abnormalities, and so on (Glover 2014; Heim et al. 2010; Hollis and Kabbaj 2014; Horowitz and Zunszain 2015; Larrieu and Sandi 2018; Laugharne et al. 2010; Lin and Wang 2014; Lindert et al. 2014; Nemeroff 2016; Sotelo et al. 2014; Sperner-Unterweger 2015; Takahashi et al. 2018; Verdolini et al. 2015; Weinstock 2017). It is noticeable that the effect of environmental risk factors in pathology of depressive disorder can happen as early as in embryonic stage, since prenatal maternal stress (e.g., mother's anxiety or depression) has been shown to be correlated with increased risk of psychological disorders including depression in offspring (Babenko et al. 2015; Barker et al. 2011; Braithwaite et al. 2014; Fatima et al. 2017; Weinstock 2017).

Among these environmental risk factors, stressful life events (SLEs) like cancers, losing job or beloved one, which can evoke psychic tension to trigger a series of stress response including physiological, psychological, and behavioral changes, have attracted much attention and been demonstrated to exert important effect on etiology of depression (Chirita et al. 2015; Hammen 2005; Kendler et al. 1999; Kessing and Bukh 2013; Palazidou 2012; Park et al. 2015; Richter-Levin and Xu 2018; Yang et al. 2015). Stress induced by stressful life events, especially traumatic and chronic life stress, is considered to be a crucial linker of stressful life events with etiology of depressive disorder, and the increasing attention has been focused on the possible mechanisms of life stress in depression development. Stress exposure across the life span can cumulatively increase the risk for the development of depressive disorder (Abravanel and Sinha 2015; Agorastos et al. 2014; Steine et al. 2017; Vinkers et al. 2014). The severity and number of stressful life events are shown to be positively correlated with depressive disorders (Chapman et al. 2004; Kendler et al. 1998; Lueboonthavatchai 2009; Roca et al. 2013; You and Conner 2009). Many changes in the brain happened during depression are found to resemble the effects of severe and prolonged stress, suggesting a strong association of stress with depression. More appropriate animal models, which are easy and faithful methods to induce physical and psychological stress, are developed for addressing pathological mechanism of stress in depressive disorders.

Although stress is a major risk factor for depression, most people do not develop a depression with stress exposure. This is supposed to be due to the moderating effect of genetic factors on the role of stress in depression development (Kessing and Bukh 2013; Klengel and Binder 2013; Lopizzo et al. 2015). Although no true depression genes are identified to be responsible for the onset and cure of depression, genetic background is considered to be an important risk factor in predisposing depressive disorder by interacting with environment factors (Kessing and Bukh 2013; Klengel and Binder 2013; Lopizzo et al. 2015). Many studies have focused on identifying genetic factors that are interacted with stressful life exposure in modulating vulnerability and severity of depressive disorders. Several genes' polymorphisms including serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR), brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, and SNP

polymorphism of key factors involved in stress response [glucocorticoid receptor (GR) gene, mineralocorticoid receptor (MR) gene, FK506 binding protein 51 gene (*FKBP5*), and corticotropin-releasing hormone receptor 1 gene (*CRHR1*)] are shown to contribute to the predictive role of stressful life events in depressive disorders (Kessing and Bukh 2013; Klengel and Binder 2013; Lopizzo et al. 2015).

Now, it is believed that genetic vulnerable genes and environmental factors (mainly stressful life events such as early life stress, traumatic events) are combinatorially and cumulatively involved in the onset of depressive disorder (Chirita et al. 2015; Januar et al. 2015; Klengel and Binder 2013; Lopizzo et al. 2015; Mullins et al. 2016; Northoff 2013; Uher 2014), in which multiple and partial overlapping susceptible genes interact with each other and with environment to predispose individuals to depressive disorders. The gene–environment interaction is considered to be accountable for the etiopathogenesis of depression, implying that stress and gene function together in predicting depression development. Meanwhile, environment-risk factor can induce epigenetic modification to cause brain structural and functional alterations, finally increasing the vulnerability to mental disorders including depressive disorders.

In this chapter, based on human and animal model studies, we will summarize and discuss the effects of stress caused by stressful life events in the onset of depressive disorders, the genetic contributions to the vulnerability of depression by stressful life events, and epigenetic modification in linking stress with depression, to elucidate the correlation of stress with depressive disorders. More recent findings and proposals dedicated to uncovering the interconnections between life stress and depression will be included.

8.2 Biology of Stress

Human being and other living organisms need to keep homeostasis, which can be threatened by external and internal, or physiological (e.g., injury, pain, infection) and psychological (can be real or perceived) stimuli, namely, stressors. In response to stressors, the organism will generate a series of physiological, psychological, and behavioral changes to maintain or re-establish its homeostasis. All of these adaptive responses are collectively called stress response, in short, namely, stress. Thus, stress is the physical, psychological, and behavioral responses evoked by the stressor to cope with it, which is a fundamental requirement for survival and well-being. Stress is an adaptive process in coping with stressors during evolution and a common experience of daily life.

During the process of stress response, autonomic nervous system and HPA axis are two primary systems being activated and functioning (Belda et al. 2015; Ulrich-Lai and Herman 2009). The activation of autonomic nervous system evokes the most immediate physiological response to stressor via its sympathetic (sympathoadrenal medullary axis) and parasympathetic branches with opposing activity, which play an important role in translating stress into a response. Excitation of

sympathoadrenal medullary axis increases adrenaline and noradrenaline level in blood, heart rate, vasoconstriction, and energy dedication, representing classical fight-or-flight response, while the parasympathetic arm activation attenuates sympathetic excitation and returns the body to homeostasis. The second major physiological response under stress, HPA axis activation, causes the release of corticotropin-releasing factor (CRF) from the parvocellular part of paraventricular neurons (PVN) of hypothalamus to trigger the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary, and finally lead to the liberation of glucocorticoids (GCs; named cortisol in human and corticosterone in rodent, respectively) into blood, which influence many bodily functions such as metabolic, psychological, and immunological functions. The GCs can also exert self-limiting effect through negative feedback on HPA axis to prevent the rise of GCs level, which otherwise fail in some cases like chronic stress. Normally, the activation of HPA axis and autonomic nervous system is tightly regulated, ensuring the body quickly respond to stressful events and return to homeostasis rapidly. There are much complementary actions between HPA axis and sympathetic system in bodily responses such as energy mobilization and blood pressure maintenance, as circulating GCs can potentiate sympathetically mediated effects; conversely, sympathetic nervous system can facilitate GCs release via its innervation of adrenal cortex.

Besides the activation of physiological function for survival under stress (e.g., increasing energy availability and accelerating oxygen supply), other physical functions which are not for immediate survival, including appetite, digestion, and immune, will be downregulated. Meanwhile, stressed subjects will also exhibit increased alertness, vigilance, and attention, which are thought to be good for responding to threatening situation. Moreover, stress may also affect memory, reward, and susceptibility to diseases (Aich et al. 2009; Ragen et al. 2016; Gilpin 2014; Becker 2010; Laudenslager 1987; Musić and Rossell 2016; Myruski et al. 2018; Wolf 2017). In emotion, based on the appraisal of stressor by exposed individuals as routine or challenging, gratifying or taxing, benign or harmful if taxing, manageable or overpowering in the case of negative appraisal, a diversity of emotions will be generated, ranging from joy to despondency, from tranquility to anxiety, and from self-confidence to sham. Under psychic tension evoked by aggravating and disagreeable emotions, stressed subjects may become irritable, aggressive, anxious, agitated, and distracted. Meanwhile, behavior changes including disturbed sleep, decreased sex, declined, or ravenous appetite will be caused.

These physiological, psychological, and behavioral responses under stress are mediated and regulated by multiple brain regions including brain stem, hypothalamus, amygdala, prefrontal cortex, as well as hippocampus (Ulrich-Lai and Herman 2009). It is noteworthy that the effect of stress on an individual is not a uniform syndrome, but is strongly dependent on not only the stressor characteristics including nature, number, or persistence (acute or chronic) but also individual factors such as age, physical and psychological well-being, genetic vulnerability, past stressful experiences, especially coping ability and personality characteristics (Schneiderman et al. 2005).

As mentioned that these stress responses are indispensable for individual homeostasis, the stress should be properly initiated when needed and terminated when homeostasis is re-established. In general, short-term, slight, and mild stress can be beneficial and healthy, which can improve individual motivation, adaptation, and reaction to the environment. However, in some circumstances like intense stressor, chronic stressor, or acute stressor with long-lasting effect, stress response may be improper, excessive, even prolonged, which is thought to be harmful, and also increase the risk of illness including psychological disease such as anxiety and depression (Jeon and Kim 2018; Lucassen et al. 2014). Chronic stressors (e.g., divorce, unemployment, living in a dangerous neighborhood) may be not intense like a natural disaster or a severe accident, but they last for longer periods of time and may be hard to be avoided or coped with, which tend to have more negative effects on individual health and provoke more frequent and excessive stress response (Jeon and Kim 2018). Too much or chronic stress will over-activate HPA axis to cause prolonged increase of stress hormone glucocorticoid levels, which may induce inertia, fatigue, amotivational syndrome, loss of bone mass, hippocampal atrophy, and acceleration of aging (Myers et al. 2014; van Praag et al. 2004). Many studies showed that human exposed to chronic stressor (e.g., caregivers of patients, job stress, chronic illness) and animal model with persistent stress (e.g., unpredictable chronic mild stress, long-term corticosterone exposure) represent slightly worse physical health, higher levels of depression, and defective cognition (Benson 2018; Jeon and Kim 2018; Ngoupaye et al. 2018; Pinquart and Sorensen 2003; van Donkelaar et al. 2014; Yin et al. 2018; Zhu et al. 2014). In addition, chronic stresses are found to be correlated with high rates of several diseases (e.g., cardiovascular disease, diabetes) and mortality, precipitate a serious or relapse into alcohol abuse (Eisenmann et al. 2016; Golbidi et al. 2015; Kivimaki and Steptoe 2018; Ohlin et al. 2004; Pashkow 1999; Rutters et al. 2014; Schneiderman et al. 2005; Sinha 2012; Spanagel et al. 2014; Steptoe and Kivimaki 2012). Thus, excessive or chronic stresses are harmful to not only physical health but also psychological health.

8.3 Association of Stress with Depressive Disorders

The etiology of depressive disorders is heterogeneous and multifactorial, which is considered to depend on the interaction of environmental and multi-genetic risking factors. Environment-risk factors have been shown to exert strong impact on the vulnerability to depressive disorders, of which stressful life events (maternal stress, social defeat and maltreatment, traumatic events, childhood abuse and neglect, cancers, and so on) are widely studied in predisposing depression (Braithwaite et al. 2014; Hollis and Kabbaj 2014; Lindert et al. 2014; Nemeroff 2016; Park et al. 2015; Sperner-Unterweger 2015; Takahashi et al. 2018; Verdolini et al. 2015). Exposure to stressful live events (SLEs) has been consistently implicated in the pathophysiology of depression disorders like major depressive disorder, especially those life stress exposure in early life (childhood and adolescence). Although depressive disorders can arise without any stressful life events exposure and most people do not develop

depression even if they experience life stress, most depressive episodes often develop after stressful life events. So SLEs are considered to be high-risk factors for predicting depressive disorder. Stressful life events such as divorce, losing job, or beloved one, which exceed one's ability to effectively cope with, could evoke a series of psychological and physiological changes including activation of HPA axis and autonomous system, which can be referred to as psychological stress. The psychological stress is a perspective of stress from psychology, which is a feeling of strain and pressure, and a kind of psychological pain. The effects of SLEs in depression development actually reflect a crucial role of stress in etiology of depression. A vast majority of research supports the causal association of stressful life events, essentially stress, with depressive disorder onset (Cohen et al. 2007; Colman and Ataullahjan 2010; Hammen 2005; Kendler et al. 1999; Mothersill and Donohoe 2016; Paykel 2003; Richter-Levin and Xu 2018; Tafet and Nemeroff 2016; Tennant 2002). Besides, most animal models of depressive behaviors are established on chronic and inescapable stress paradigms such as social defeat stress and early life stress, further supporting the causal association of stress with depressive disorder development.

Stress could be evoked when an individual perceives that a situation (e.g., stressful life event) exceed his or her adaptive capacity to handle, including a feature of uncontrollability and (or) inescapability (Richter-Levin and Xu 2018). According to the duration, stress can be acute (e.g., under traumatic events, surgical operation) or chronic (e.g., under chronic illness, marital conflicts), of which chronic stress could be disconnected or persistent. The level of stress is not only affected by the intensity, duration, and frequency of triggering events but also by individual genetic predisposition, personality characteristics, coping abilities, as well as subjective perception on how a traumatic event is. Chronic stresses are more strongly related to depressive symptom than acute stresses (Avison and Turner 1988; Eckenrode 1984). Under chronic or traumatic stress, more or sustained glucocorticoids (GCs) will be released due to dysregulation of HPA axis activation, exerting deleterious impacts on multiple brain functions including neurogenesis, synaptic plasticity, learning and memory, hippocampal size, emotional appraisal of events, as well as periphery functions such as metabolism and immunity (Murray et al. 2008; Palazidou 2012; Pariante and Lightman 2008; Teicher et al. 2012). Hyperactivity of HPA axis is one of the commonest neurobiological changes in depressive patients (Pariante and Lightman 2008). And reduced hippocampal size, decreased neurotrophic factors, and neurogenesis is also characteristic feature of depressed patients and depressive-like animal models (Luo et al. 2014; Sheline et al. 1996; Treadway et al. 2015). Meanwhile, sustained overproduction of cortisol induced by chronic stress leads to reduced activity of dopaminergic (DAergic) system, noradrenergic (NAergic) system, and serotonergic (5-HTergic) system, of which changes are shared by some depressed patients presenting indiscriminate NAergic activity, and diminished DAergic and 5-HTergic activity (van Praag et al. 2004; Yang et al. 2015). Thus, stress response and depressive disorder shared many mediators, circuitries, and phenomenology, in which depression represents a dysregulation of stress response, indicating a strong association between stress and depressive disorder onset. Besides, the severity and number of SLEs are positively correlated with probability of depression onset

(Chapman et al. 2004; Kendler et al. 1998; Lueboonthavatchai 2009; Roca et al. 2013; You and Conner 2009), in which moderate to severe stress predisposes higher risk of depressive disorder than mild stress in subjected people, meanwhile the depressed subjects also experienced more stressful life events than the nondepressed subjects. More importantly, cumulative stress exposures across the life span are related with increased risk for the development of depressive disorder (Abravanel and Sinha 2015; Agorastos et al. 2014; Steine et al. 2017; Vinkers et al. 2014).

The effect of stress on the vulnerability of depressive disorder can happen as early as in utero. Epidemiological studies of human populations and studies on animal models indicate that prenatal maternal stress is linked with adverse health outcomes in the offspring (Beydoun and Saftlas 2008). More and more studies show that prenatal maternal psychological stress (e.g., mother's anxiety and depression) is correlated with increased risk of psychological disorders including depression onset in offspring (Babenko et al. 2015; Barker et al. 2011; Braithwaite et al. 2014; Fatima et al. 2017; Monti and Rudolph 2017; Slykerman et al. 2015; Weinstock 2017), reflecting an intergenerational effect of stress. During pregnancy, maternal stress can exert a major impact on brain development and thereby contribute to the pathogenesis of neuropsychiatric illnesses including depression in offspring. In this process, cortisol which is highly lipophilic to pass placenta has generally been identified as the major mediator in transferring maternal stress to the fetus (Osborne et al. 2018; Rakers et al. 2017; Van den Bergh et al. 2005). Excessive maternal cortisol could persistently impair the development of the fetal HPA axis and crucial brain areas including amygdala, hippocampus, and frontal cortex (Nemoda and Szyf 2017; Van den Bergh 2011; Van den Bergh et al. 2005). Importantly, exogenous glucocorticoids treatment of pregnant women can result in similar deficits in offspring development to those related to postpartum depression, supporting the view that the stress response may mediate the adverse effects of maternal depression on offspring (Conti et al. 2017; Owen et al. 2005). Depressive symptoms during pregnancy are very common, and about 10% of pregnant women have major depressive disorder, which can be increased to higher frequency (about 17%) in low- and middle-income countries (Bennett et al. 2004; Fellmeth et al. 2017; Gelaye et al. 2016). So the impact of maternal depression on vulnerability of depressive disorders in offspring has drawn a lot of attention. It is considered that the prenatal maternal depression could also have a long-term indirect effect on offspring depression via poor physical health in early childhood and its psychosocial consequences, in which the prenatal maternal depressive symptoms predict worse physical health of offspring during early childhood to further predict increased health-related stress and poor social functioning, finally predicting increased risk of depressive symptoms later in young adulthood (Raposa et al. 2014).

Childhood and adolescence period are particularly sensitive to stressful life events, which increase the vulnerability to depressive disorder (Andersen and Teicher 2008; Fuhrmann et al. 2015; Laceulle et al. 2014). During these periods, neural plasticity, brain regions involved in regulating emotion and mediating the stress response appear to be particularly sensitive to the effects of stressful events. Excessive or chronic stress evoked by intense or chronic stressful life events (such as child abuse and

neglect, parental loss, marital conflict of parents) during childhood and adolescence can have long-lasting neurobiological effects and increase the risk for psychological disorders including depression (Heim and Binder 2012; Infurna et al. 2016; Lopizzo et al. 2015; Mandelli et al. 2015; Oldehinkel et al. 2014). It is suggested that early programming of neurobiological systems in regulating emotion and stress responses can mediate the increased stress vulnerability and depression risk in later life (Chen and Baram 2016; Heim and Binder 2012; Lopizzo et al. 2015; van Bodegom et al. 2017).

During early childhood, postpartum maternal depression, which is more common than prenatal depression, can also negatively impact offspring mental health. So the intergenerational effects of maternal stress also happen at early childhood. Research focused on the impact of maternal postnatal depression on offspring depressive psychopathology has documented a link between them, in which offspring of postnatally depressed mothers are at increased vulnerability for depression (Halligan et al. 2007b; Hammen and Brennan 2003; Murray et al. 2011; Pearson et al. 2013; Sanger et al. 2015). Elevated basal levels of the cortisol have been found in offspring of mothers with postnatal depression and been associated with the presence of maternal postnatal depression (Brennan et al. 2008; Essex et al. 2002; Halligan et al. 2004; Murray et al. 2010). And biological sensitivity to social stress in adulthood is also increased in the offspring of mothers with postnatal depression, as indicated by greater cortisol reactivity to the stress test (Barry et al. 2015). The over-activated HPA axis is supposed to mediate the deleterious impact of maternal depression on offspring in early childhood (Halligan et al. 2007a; Murray et al. 2010). Studies in animal models also suggest that hyperactivity of the HPA axis may mediate the adverse effects of maternal depression on offspring behavior (Maguire and Mody 2016).

As humans are social beings, keeping good social relationship is fundamentally important and beneficial for one's life. Thus, any stimulant disrupting or threatening one's social relationship, esteem, or sense of belonging in a social group can lead to stress. Social stress is the most frequent and intense stress experienced by us in daily lives, including life events characterized by abrupt and severe incidents (e.g., death of loved one, sexual assault), chronic strains (e.g., marital conflict, unemployment, bullying), and daily hassles (e.g., traffic jams, argument). Persistent social stress such as workplace bullying and adolescent bullying has been shown to increase the risk of developing mental disorders such as anxiety and depression in stressed subjects (Pitney et al. 2016; Ttofi 2015; Williams et al. 2017). A lot of supportive views on the association of social stress with depressive disorders are from animal model studies. Two common social stress paradigms, social defeat, and social isolation are introduced in rodent models to explore the neurological mechanism of social stress and the correlation with mental disorders (Chaouloff 2013; Hollis and Kabbaj 2014; Zanier-Gomes et al. 2015). In social defeat paradigm, social stress can be induced in the nonaggressive male rodent when being attacked by the aggressive intruder. Singly housed animals for 21 days are usually introduced to establish social isolation paradigm. All these social-stressed models can induce an array of behavioral and physiological changes in susceptible rodents, which are reminiscent of depression- and anxiety-related symptoms in human (Chaouloff 2013; Liu et al.

2017b; Zanier-Gomes et al. 2015), suggesting social stress is an important risk factor in pathogenesis of psychiatric disorders including depressive disorders.

As mentioned above, more vulnerability of depressive disorders is observed during childhood and adolescent stages under stressful life events, implicating the age of subjected individual will influence the final aversive outcome of life stress. Besides age sensitivity, as well as event severity and number, the impact of stress on the onset of depressive disorders is also influenced by gender, history of depression (family and individual), and personality characteristics of subjected individuals (Assari and Lankarani 2016; Mazure et al. 2000; Monroe et al. 2014; Morse and Robins 2005; You and Conner 2009). Overall, in response to stressful life events with some exceptions of specific event types, women were found to be more likely than men to develop major depression (Maciejewski et al. 2001). No gender difference was detected in risk for depression associated with loss of beloved ones, marital conflicts, or events corresponding to acute financial or legal difficulties, while increased risk for depression associated with more distant interpersonal losses (death of a close friend or relative) and other types of events (change of residence, physical attack, or life-threatening illness/injury) were found in woman as compared with man (Maciejewski et al. 2001). Elevated risk in women for major depression was found to be related with low but not high level of stress exposure (Kendler et al. 2004). A longitudinal study on the long-term predictive role of stressful life events (SLEs) on the subsequent risk of major depressive disorder found a stronger predictive role of SLEs for subsequent clinical depression for men as compared with women (Assari and Lankarani 2016). In rat model of prenatal stress exposure, increased vulnerability for depression-like behaviors was observed in females (Sickmann et al. 2015). So, gender is an important element to consider when analyzing predictive role of SLE on the risk of depressive disorders. The congruence of cognitive-personality characteristics (sociotropy and autonomy) and life stress can confer susceptibility to depressive disorders, in which congruent interaction of sociotropy with negative interpersonal events and autonomy with negative autonomy events significantly predicted depression (Mazure et al. 2000; Morse and Robins 2005). Moreover, individuals with high neuroticism were at increased risk for major depression and more sensitive to the depressogenic effects of stressful life events (Kendler et al. 2004). Severe life events were significantly associated with current depressive symptoms among women without depression history as compared with women depressed before (You and Conner 2009). Individuals with family history of depression would have more lifetime episodes of depression under a major life event than those without family history of depression (Monroe et al. 2014). And the risk of depression relapse in one's life is higher when the first episode occurs at earlier age or when there is family history of depression (Palazidou 2012). Thus, personality characteristics and depression history are also potential elements to impacting depression onset under stressful life events.

8.4 Genetic Contributions in the Association of Stress with Depressive Disorders

On the etiology of depressive disorders, the interaction of gene–environment is considered to be essential in the development of depressive disorders although environment may have more intense impact (~60%) than genetic factors (~40%). Besides the important role of stressful life experience in predisposing depressive disorders, individual genetic background which can in turn regulate and affect coping mechanism in response to stressful life stimuli is another important effector involved in the final depressive outcome of stressed subjects. So not all people with adverse life exposure develop depression despite the intensity of stressful life events, which is supposed to be due to the moderating effects of genetic factors on individual sensitivity to life stress (Klengel and Binder 2013; Lopizzo et al. 2015; Uher 2014). A large body of research has focused on identifying genetic factors that are interacted with stressful life exposure in modulating vulnerability and severity of depressive disorders (Bleys et al. 2018; Caspi et al. 2003; Dalton et al. 2014; Kessing and Bukh 2013; Klengel and Binder 2013; Lopizzo et al. 2015; Risch et al. 2009; Tafet and Nemeroff 2016).

The first supportive evidence of gene–stressful life experience interaction, or gene–stress interaction, in modulating the risk for depressive disorder development is from the study of Caspi et al. (2003). They found 5-HTTLPR polymorphism involving short or long alleles in the promoter region of serotonin transporter gene (*SERT* or *SLC6A4*) can modulate the influence of stressful life experience on depression, in which subjects with short allele of 5-HTTLPR (homozygotes or heterozygotes) exhibited more depressive symptoms, diagnosable depression, and suicidality than individuals with long allele homozygotes of 5-HTTLPR when exposed to life stress (Caspi et al. 2003). Short allele variant of 5-HTTLPR is associated with lower promoter transcriptional efficiency of *5-HTT* gene as compared with long allele (Heils et al. 1996; Hranilovic et al. 2004). The association of 5-HTTLPR short variant with increased vulnerability to depressive disorders under stressful life exposure is supported by a lot of studies replicating the results of Caspi et al., but still controversial as some others failed to repeat it (Bleys et al. 2018; Caspi et al. 2010; Chipman et al. 2007; Dalton et al. 2014; Karg et al. 2011; Risch et al. 2009; Saul et al. 2018; Sharpley et al. 2014). This disagreement could be mainly due to the methodological differences in the assessment of stress and depression between studies (Wankerl et al. 2010).

Another gene modulating stress impact on the vulnerability of depressive disorders is brain-derived neurotrophic factor (BDNF), an important factor involved in normal brain development and function, as well as pathological changes of brain structure and function in brain disorders including depression (Begni et al. 2017; Brunoni et al. 2008; Bus and Molendijk 2016; Lu et al. 2014). Stress is hypothesized to decrease BDNF activity to result in reduced function of brain regions particularly linked to emotion processing and cognition (e.g., hippocampus, amygdala, neocortex), which finally alters mood and may cause depression (Martinowich et al. 2007; Molendijk et al. 2014; Stein et al. 2008). The *BDNF* gene has been implicated in stress and

depression vulnerability in human, even animal model (Blugeot et al. 2011; Groves 2007; Homberg et al. 2014; La Greca et al. 2013; Seo et al. 2016). Many studies on the effect of *BDNF* gene in predictive role of life stress to depression are focusing on BDNF Val66Met polymorphism, which is valine to methionine substitution at codon 66 (Val66Met) of *BDNF* gene due to a functional SNP (rs6265) in the promoter region, and found a significant interaction between BDNF Val66Met polymorphism and stressful life experience in depression(Gatt et al. 2009; He et al. 2018; Hosang et al. 2014; Jiang et al. 2013; Lopizzo et al. 2015; Zhao et al. 2018). Such Val66Met polymorphism affects BDNF activity including intracellular distribution, packaging, and release of BDNF protein, in which Met allele leads to adverse effect of BDNF activity (Egan et al. 2003). The Met allele of BDNF Val66Met polymorphism is also linked with impaired memory, reduced brain volume, and harm avoidance (Jiang et al. 2005; Lamb et al. 2015; Toh et al. 2018). Interestingly, individuals with Met allele (heterozygotes or homozygotes) show elevated evening cortisol levels and a significantly attenuated HPA axis response to acute psychosocial stressor as compared with Val/Val genotype (Alexander et al. 2010; Shalev et al. 2009; Vinberg et al. 2009). Transgenic mice with Met allele of BDNF Val66Met polymorphism exhibited increased anxiety under stress conditions (Chen et al. 2006). More prominent effects of Met allele are indicated in the impact of early life stress on depression, while the impact of stress in adulthood on depressive symptoms seems more significant in Val/Val genotype individuals, which might due to the different functions of BDNF at different life stages (Aguilera et al. 2009; Gatt et al. 2009; He et al. 2018; Jiang et al. 2013). Meta-analyses consistently indicated that the Met allele of BDNF Val66Met polymorphism significantly moderates the relationship between life stress and depression (Hosang et al. 2014; Zhao et al. 2018). Furthermore, a combinatory effect of 5-HTTLPR and BDNF Val66Met is implicated to interact with early life stress (childhood adversity) in relation to depression, as indicated by more common depressive symptoms among carriers of either the ss/sl +Val/Val or the ll+Met genotypes in the presence of early life adversities (Comasco et al. 2013).

Key factors involved in stress response have also been studied as possible genetic risking factors for depression vulnerability under life stress exposure. Polymorphisms within four critical factors involved in stress including glucocorticoid receptor (GR) gene, mineralocorticoid receptor (MR) gene, FK506 binding protein 51 gene (*FKBP5*), and corticotropin-releasing hormone receptor 1 gene (*CRHR1*) are suggested to be risk factors in predicting depression (Claes 2009; de Kloet et al. 2016; Grabe et al. 2010; Grimm et al. 2017; Szczepankiewicz et al. 2014). During stress response, stress hormone cortisol will be released to bind with GR, while more and more binding of cortisol with GR provides signal for reduction of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone release. GR is kept in an inactive state by binding with FKBP5 without cortisol, which will be activated by binding with cortisol to trigger GR-dependent gene expression. FKBP5 is a significant player in stress response through regulating the GR receptor sensitivity to cortisol, and chronic stress was found to increase FKBP5 expression to generate greater inhibition of GR sensitivity (Guidotti et al. 2013; O'Leary et al. 2013). A dysregulation of GR function, called GR resistance, is a

common feature of depressed subjects and is related with HPA axis hyperactivity (Juruena et al. 2004; Rodriguez et al. 2016). Binding of cortisol with MR receptor will exert tonic inhibitory effects on basal HPA axis activity, and MR is found to be an important stress modulator and influences basal as well as stress-induced HPA axis activity.

Several GR gene polymorphisms (BclI RFLP, N363S, ER22/23EK, 9β, TthI-III, NR3C1-1) and MR gene polymorphisms (-2C/G and I180V) are implicated to affect HPA axis activity to psychosocial stress, and interact with stressful life experience in predicting the development of stress-related disorders like depression (Bet et al. 2009; de Kloet et al. 2016; Derijk and de Kloet 2008; Hardeveld et al. 2015; Juruena et al. 2015; Kumsta et al. 2007; ter Heegde et al. 2015; Vinkers et al. 2015; Wust et al. 2004). Similarly, single nucleotide polymorphisms in *FKBP5* gene (rs1360780, rs3800373, rs9296158, rs4713916, rs9470080), which will affect FKBP5 basal level, are also shown to modulate the risk of depression to stressful life experience (Appel et al. 2011; Binder 2009; Kohrt et al. 2015; Lavebratt et al. 2010; Menke et al. 2013; Szczepankiewicz et al. 2014; Zimmermann et al. 2011). Besides, single nucleotide polymorphisms within *CRHR1* gene (rs4792887, rs12936511, rs4792887, rs17689882, rs7209436, rs110402, and rs242924) can modulate predictive role of early life stress in depression (Grabe et al. 2010; Kranzler et al. 2011; Polanczyk et al. 2009; Rogers et al. 2013; Wasserman et al. 2009). Interaction of 5-HTTLPR S allele with CRHR1 haplotypes moderates effect of child abuse on predicting depressive symptoms (Ressler et al. 2010).

Taken together, in the association of stress with depressive disorders development, genetic element is an important risking factor in increasing vulnerability of depression under environmental life stress. It should be kept in mind that different risking genes will interact with each other and with stressful life events to exert cumulative role in predisposing depressive disorders.

8.5 Epigenetic Modification in Linking Stress with Depression

Epigenetic regulation means stable change of gene expression and function via chromatin structure alteration or noncoding RNA regulation without change of DNA sequence, which is heritable and can be modified by environmental stimuli. Epigenetic modification caused by environment factors, such as stress especially early life stress, is considered as a key mechanism through which environmental risk factors can modify gene function without affecting DNA sequence to cause brain structural and functional alteration, finally increasing the vulnerability to mental disorders including depressive disorders (Bagot et al. 2014; Bakusic et al. 2017; Roy et al. 2017b; Sun et al. 2013; Vialou et al. 2013). And epigenetic mechanism also underlies extraordinary interindividual variability in sensitivity to stressful life exposure and variability in depressive symptoms (Bagot et al. 2014; Sun et al. 2013).

Among epigenetic modification, DNA methylation and histone acetylation are extensively studied in the context of long-term effects of stressful life events on gene transcription and on mental disorders etiology especially depression (Bagot et al. 2014; Bakusic et al. 2017; Deussing and Jakovcevski 2017; Fatima et al. 2017; Klengel et al. 2014; Li et al. 2017; Liu et al. 2014; Nemoda and Szyf 2017; Weder et al. 2014; Zheng et al. 2016). DNA methylation changes within promoter and enhancer regions of genes are closely related to the alteration of gene expression, as they reduce the entry of transcription factors into regulatory elements to promote silencing or downregulation of gene expression. The role of DNA methylation in several genetic risk genes, such as *BDNF*, *5-HTT*, *GR*, and *FKBP5*, has been extensively investigated in the pathology of stress-related depressive disorders. Acetylation of histone is associated with greater level of gene expression, and its alteration in mental disorders and the role in vulnerability to depressive disorder under stressful life exposure are also widely studied. For example, in depressed rat model with chronically unpredicted stress treatment, increased depression-like behaviors were associated with decreased acetylated histone (H3K14, H3K23, H4K16), suggesting the decrease of histone acetylation modification level may contribute to the mechanism of depression-like behaviors (Li et al. 2017).

Environmental factors may also modify gene expression via changing microRNAs (miRNAs) synthesis (Carthew and Sontheimer 2009), a type of small noncoding RNAs (20–22 nt), which play a major role in posttranscriptional regulation of gene expression. Individual miRNAs are able to target hundreds of different mRNAs, and a single gene can be modulated by several different miRNAs. Many studies have observed expression change of miRNAs targeting to important genes for brain development and function in rodent brain with life stress exposure, indicating the contribution of miRNAs in epigenetic modulation by stress to affect the vulnerability of depressive disorders (Babenko et al. 2015; Dirven et al. 2017; Higuchi et al. 2016; Liu et al. 2017a; Lopizzo et al. 2015; Ma et al. 2016). With early life stress exposure, the expression level of two miRNAs which are closely related to 5-HT neurotransmitter system was found to be altered in rat brain, with a reduction of miRNA-135a in the prefrontal cortex and increase of miRNA-16 in the hippocampus (Liu et al. 2017a). In depression-like mice induced by chronic unpredictable mild stress, upregulation of miRNAs responsible for downregulating genes functioning in GABAergic synapses, dopaminergic synapses, myelination, synaptic vesicle cycle, and neuronal growth were detected in the medial prefrontal cortex (Ma et al. 2016). Interestingly, expression change of several miRNAs (such as miR-709, miR-132, miR-124) under life stress can persist for a long time (Babenko et al. 2012; Liu et al. 2017a; Uchida et al. 2010), which might be due to the epigenetic changes of miRNAs, as hypermethylation in 31 miRNAs from adult males exposed to childhood abuse were detected (Suderman et al. 2014).

Due to the high sensitivity of depression risk gene *BDNF* to stress and its decreased level in depressed patients and animal models, epigenetic modification of *BDNF* gene attracted much attention. In rodents studies, stress exposure at gestation, early life and adult stages can induce epigenetic change of *BDNF* gene to decrease its expression level in several brain regions including hippocampus and prefrontal cortex, which

could increase the vulnerability to stress or mental disorder including depression (Roth et al. 2009; Seo et al. 2016; Weinstock 2017; Xu et al. 2018; Zheng et al. 2016). In the hippocampus of rodents with stress exposure, increased methylation within *BDNF* promoter, elevated level of DNA (cytosine-5)-methyltransferase and histone deacetylase (such as HDAC1, HDAC2), as well as decreased expression of acetylated histone and its binding on specific *BDNF* promoters were observed (Seo et al. 2016; Zheng et al. 2016). Similarly, an increase of methylation at CpG sites within the promoter region of the *BDNF* exon IV was detected in the prefrontal cortex of mice with early maltreatment from adolescence till adult stages, which account for the reduced *BDNF* mRNA level in this brain region (Roth et al. 2009). And such increased methylation of *BDNF* gene promoter in the frontal cortex can even be transmitted from one generation to the next generation, as this epigenetic modification was also observed in the offspring of females with early maltreatment (Roth et al. 2009). Changed epigenetic modification of *BDNF* has also been detected in human brain or peripheral blood or saliva from depressive subjects. Fuchikami et al. reported a significant difference of CpG methylation within *BDNF* gene-specific promoter of exon I but not IV, in peripheral blood between depressed patients and controls (Fuchikami et al. 2011). Roy et al. also observed that *BDNF* gene CpG methylation was significantly increased in peripheral blood of depressed patients (Roy et al. 2017b). An increased methylation in *BDNF* gene promoter of exon IV was found to be associated with reduced *BDNF* expression in Wernicke's area of postmortem brain from suicide victims with major depression (Keller et al. 2010). Significant difference of *BDNF* gene methylation from saliva sample between maltreatment children and control was observed, which may confer risk for depression in children (Weder et al. 2014). In contrast, prenatal maternal stress (maternal depression) significantly predicted decreased DNA methylation in *BDNF* IV in both male and female infants, which was proposed to reflect a molecular basis for the rapid maturation induced by adverse prenatal events (Braithwaite et al. 2015). It is noteworthy that BDNF dysregulation may also be contributed by alterations of miRNAs level. In depressed patients and depression-like animal models with early life stress exposure, upregulation of several miRNAs (miR-132, miR-182, miR-16) which can regulate *BDNF* translation are correlated with decreased *BDNF* expression in brain or serum (Bai et al. 2012; Li et al. 2013, 2016; Su et al. 2015).

Another genetic risk gene for depressive disorders, 5-HTT (*SLC6A4* or *SERT*), has also been investigated on its epigenetic modification correlated with life stress exposure and depression pathology. Since *SLC6A4* gene plays an important role in the normal development and function of brain regions, and its malfunctioning is supposed to be involved in the pathology of mental disorders including depressive disorders, the alteration of 5-HTT expression will be closely related to brain structure and function, behavior change, as well as vulnerability of mental disorders. The expression of 5-HTT is dependent not only on genetic variation (5-HTTLPR polymorphism) but also epigenetic modification in response to environmental stress exposure (such as hypermethylation with early life exposure or chronic stress) (Palma-Gudiel and Fananas 2017; Vijayendran et al. 2012). Besides that short(s) 5HTTLPR allele is associated with lower amounts of *5-HTT* mRNA transcription, several in vitro and in vivo studies

consistently observed higher level of specific-site methylation in *SLC6A4* promoter which is associated with its lower mRNA expression (Abdolmaleky et al. 2014; Palma-Gudiel and Fananas 2017; Philibert et al. 2008; Wang et al. 2012). Methylation level of *SLC6A4* has been associated with a number of environmental stresses originated from maternal stress, childhood trauma and abuse, and other early life stress, which is confirmed as an epigenetic biomarker of early adversity exposures in human (Palma-Gudiel and Fananas 2017; Provenzi et al. 2016). In patients with major depression, higher *5-HTT* promoter methylation status was found to be significantly associated with childhood adversities and worse clinical presentation (family history of depression, higher perceived stress, and more severe psychopathology) (Kang et al. 2013). And the increased methylation within *SLC6A4* promoter can affect brain responses to negative stimuli, as indicated by the results that twins with higher peripheral SLC6A4 methylation levels showed greater orbitofrontal cortical (OFC) activity, greater connectivity of left amygdala–anterior cingulate cortex (ACC) and left amygdala–right OFC in response to sadness, as well as greater ACC–left amygdala and ACC–left insula connectivity in response to fearful stimuli (Ismaylova et al. 2018).

Further, miRNAs also contribute to the epigenetic regulation of 5-HTT expression in response to life stress exposure. In depression-like rat model induced by chronic mild stress, the expression of seven miRNAs targeting 5-HTT (miR-18a-5p, miR-34a-5p, miR-135a-5p, miR-195-5p, miR-320-3p, miR-674-3p, miR-872-5p) was increased in ventral tegmental area (VTA) but decreased in prefrontal cortex, and more profound increase of these miRNA in VTA was detected in resilient rat accompanied by lower 5-HTT level (Zurawek et al. 2017). Cell line and animal studies demonstrated that miR-16 (also targeting on BDNF) and miR-15a can also negatively regulate 5-HTT expression, which might be associated with major depressive disorder, as alteration of these two miRNAs level can be detected under life stress and in depression patients and animal models (Baudry et al. 2010; Launay et al. 2011; Moya et al. 2013; Shao et al. 2018; Song et al. 2015). In the same paradigm of chronic mild stress-induced depression, miR-16 level in cerebrospinal fluid (CSF) and raphe nuclei was significantly decreased with obviously increase of 5-HTT protein in raphe (Shao et al. 2018). And with anti-miR-16 treatment, rats exhibited depression-like behaviors, extremely lower CSF miR-16, and obviously higher raphe 5-HTT protein than control (Song et al. 2015). Similarly, CSF miR-16 is also decreased in major depression patients (Song et al. 2015). Interestingly, antidepressants drugs like selective serotonin reuptake inhibitors (SSRI) can increase miR-16 levels in serotonergic raphe nuclei, which was accompanied by reduction of 5-HTT expression in raphe (Baudry et al. 2010; Yang et al. 2017), supporting the role of miR-16 in depressive disorders pathology.

Due to the essential role of HPA axis in stress response under aversive environment stimuli, the involved genes are also investigated on their epigenetic modulation in stress exposure and depressive disorders onset. Numerous studies have focused on the relationship of methylation in glucocorticoid receptor (GR) gene, also known as NR3C1 (nuclear receptor subfamily 3, group C, member 1), with early life stress. And increased methylation of GR promoter in brain or periphery samples from rodent

or human subjected with early life stress (e.g., prenatal or postnatal maternal stress, paternal stress, child abuse, low maternal care) are consistently reported among these studies (Bockmuhl et al. 2015; Braithwaite et al. 2015; Efstathopoulos et al. 2018; Farrell et al. 2018; Smart et al. 2015; Turecki and Meaney 2016). Mainly increased methylation of rat NR3C1 exon 17 and human homolog NR3C1 exon 1F are found to be related with early life stress. Prenatal depressive symptoms were shown to significantly predict increased NR3C1 exon 1F DNA methylation in male infants (Braithwaite et al. 2015). Mean NR3C1 exon 1F DNA methylation levels were significantly increased in depressed patients, and the degree of methylation was positively associated with morning cortisol concentrations (Farrell et al. 2018). Meanwhile, DNA methylation level at specific CG sites in the NR3C1 exon 1F was related to childhood emotional abuse severity (Farrell et al. 2018). The methylation level of NR3C1 exon 1F was also significantly increased in the hippocampus from suicide victims with a history of childhood abuse, as compared with those from suicide victims without childhood abuse or with control samples (McGowan et al. 2009). Furthermore, the severity, number, and types of childhood maltreatments positively correlated with NR3C1 exon 1F methylation (Perroud et al. 2011).

The GR co-chaperone, *FKBP5*, which is also one of the genetic risk factors in depressive disorders, has likewise been widely investigated on its epigenetic changes induced by life stress especially early life stress. The methylation of the *FKBP5* gene is associated with reductions in transcription; conversely, *FKBP5* demethylation will increase FKBP5 level to interfere GR sensitivity to cortisol. In human, childhood maltreatment has been associated with demethylation in *FKBP5* gene, as indicated by lower DNA methylation at *FKBP5* intron 7 in the blood or saliva of maltreated subjects as compared with those unexposed (Klengel et al. 2013; Non et al. 2016; Tyrka et al. 2015). Since polymorphisms of *FKBP5* gene have been shown to influence glucocorticoid receptor sensitivity, stress response regulation, and depression risk in traumatized subjects, the epigenetic modification in these functional variants especially rs1360780 also attracts much attentions (Han et al. 2017; Mulder et al. 2017; Tyrka et al. 2015). For example, *FKBP5* methylation was positively correlated with the thickness of the right transverse frontopolar gyrus in the C allele (FKBP5 rs1360780 polymorphism) homozygote group, suggesting that the FKBP5 genetic and epigenetic changes may affect morphology of emotion-related brain regions, which may be involved in depression development (Han et al. 2017).

Besides DNA methylation affecting HPA axis responsiveness, miRNAs which target key factors in HPA axis have also been shown to be changed under life stress. The miR-124, an important effector in brain development, can also target GR. Chronic stress led to the upregulation of miR-124 in the hippocampus and basolateral amygdala of rats (Bahi et al. 2014; Xu et al. 2017), and a higher level of miR-124 was detected in prefrontal cortex of depressive-like rats and in serum of major depressive patients (Roy et al. 2017a). In rat model, depressive-like behaviors induced by chronic unpredictable mild stress were positively correlated with the level of miR-124a, whereas GR levels were negatively correlated with miR-124a level in both adolescent and adult brain (Xu et al. 2017). Inhibition of miR-124 by its antagomir was shown to reverse the depressive-like behaviors in mice exposed to chronic

corticosterone (Wang et al. 2017). The exact role of increased mir-124 in regulating GR expression and HPA axis response activity under life stress, and in linking stress with depressive disorder need to be investigated. Upregulation of miR-34c in mice exposed to acute and chronic stress was also observed (Haramati et al. 2011), which may regulate stress response by targeting stress-related corticotropin-releasing factor receptor type 1 (CRFR1) mRNA. Under chronic unpredictable mild stress, the expression of another miRNA targeting GR, miR-18a, was found increased in the basolateral amygdala only in adolescent rats but not adult rat (Xu et al. 2017).

Overall, in this part, epigenetic modification including DNA methylation and miRNA on key depression risk genes (*BDNF*, *SERT*, *GR*, and *FKBP5*) are demonstrated. The changes in DNA methylation of these genes or expression of miRNAs targeting on these genes are sensitive to life stress and can generate long-lasting effects on brain structure and function, behavior, and most important the vulnerability to mental disorders including depressive disorders. These epigenetic modifications provide a potential mechanism in linking environmental risk factors such as early life stress with depression disorders onset. It is of noteworthy that these epigenetic regulations will function together with genetic background to affect individual vulnerability to depressive disorders under stressful life events.

8.6 Conclusion

Stress is an adaptive mechanism of individuals to cope with environment aversive stimuli during evolution. However, excessive or prolonged stress triggered by stressful life events will cause deleterious impacts on individuals' both physiological and psychological health. Dysregulated HPA axis activity under overloaded stress is considered to play important role in depression development. More and more evidence have been supporting the causal association of stress, especially the chronic stress and early life stress, with depressive disorders development. Thus, stressful life events are high-risk factors of environment in predisposing depressive disorders.

While the effects of stressful life exposure on the vulnerability to depressive disorders are moderated by individual's genetic background, polymorphism of several high-risk genes including *SERT*, *BDNF*, as well as key genes involved in stress response (*GR*, *FKBP5*, *MR*, and *CRHR1*) have been found to affect aversive outcome of life stress in depression onset. The interaction of environment–gene, meaning the combinatorial function of stressful life exposure with genetic background, actually plays the essential roles in pathology of depressive disorders. Now it is widely accepted that depressive disorders are multifactorial and polygenic mental disorders.

The close association of stressful life exposure to depressive disorders development is also dependent on the epigenetic mechanism. Environmental risk factors will lead to epigenetic modification in depression risk genes (*BDNF*, *SERT*, *GR*, and *FKBP5*) through DNA methylation and miRNA regulation, to generate long-lasting even heritable effects on risk genes expression. Such epigenetic mechanism can cause brain structural and functional alteration, and finally increasing the vulnerability to

depressive disorders. Meanwhile, epigenetic regulation will interact with genetic background to affect the predicting role of stressful life events in vulnerability to depressive disorders.

Therefore, as the mediator of environmental risk factors, stress will function together with genetic risk factors and epigenetic modification to generate impacts on brain structure and function, as well as physiology and psychology, to predispose depressive disorders.

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