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REVIEW ARTICLE

Stress Can Changes Reward System Function in Second-Generation (F2): A Review

Maryam Salehi[1], Hussein Eimani[1], Hedayat Sahraei[1], Gholam Hossein Meftahi [*1]
[1]-Neuroscience Research Center, Baqiyatallah University of Medical Sciences,Tehran, Iran.
Email: meftahi208@yahoo.com or hossein.meftahi@bmsu.ac.ir

ABSTRACT
Stress is a natural part of life, and has positive or negative effects in human life. One of the important systems that involved in the mammalian stress response is hypothalamic-pituitary-adrenal (HPA) system. Stress increased the release of corticotropin releasing hormone (CRH) into the anterior pituitary gland, which releasing adrenocorticotropic hormone (ACTH). ACTH stimulated the adrenal gland to produce cortisol. Cortisol in physiologic concentration is essential for survival. Additionally, maternal stress can influence brain development in the embryos. High cortisol concentration which occurred after stress can easily crosses from the blood-placenta barrier and reaching the embryonic neurons. PubMed and MEDLINE data bases were searched for English-language articles by using " Maternal Stress ", "ventral tegmental area ", Reward System and "Cortisol" as primary terms. No time or article type constraints were applied. Dopaminergic neurons of ventral tegmental area (VTA), respond strongly to stressful situations. Early life stress can change dopaminergic system in VTA, and can affect brain morphology and also some behaviors of the offspring's. Recent finding showed that probably there are different populations of VTA neurons that are preferentially activated by rewards or stressful situations. Moreover, exposure to acute stress changed reward-related processing in the dorsal striatum and also reduced reward-related responses in the dorsal striatum. Additionally, delightful behaviors can reduce stress by brain reward pathways. Therefore, environmental stress also can change gene expression and induced epigenetic variations in individuals. These variations can transmit to subsequent generations. Taken together, exposure to the stressors in the human initiated organized responses. These coordinated responses are composed of changes in the behavior, autonomic function and endocrine systems.
Key words: *Maternal Stress, Ventral Tegmental Area (VTA), Reward System, Cortisol, Epigenetic*

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INTRODUCTION

Stressful experiences excite a strong set of hormonal, behavioral, cellular and molecular responses that cooperates organisms in adapting to the physical and social environment. The responses of stress have historically concentrated on the hypothalamic-pituitary adrenal (HPA) axis and catecholamine responses [1]. Eventually, a cascade of events leads to high level of cortisol hormone. This hormone is necessary for the survival, but when cortisol is chronically increased or poorly regulated, it can have detrimental impacts on health [2, 3]. However, increasing or decreasing cortisol concentration can change different parts of brain such as prefrontal cortex, hippocampus, amygdala and reward system. The past 30 years evidence showed that dopaminergic neurons in the VTA projected to the limbic regions including the amygdala, nucleus accumbens, hippocampus, and frontal cortex and also responded strongly to the stressful situations [4]. Recent discoveries suggest that there are distinct populations of VTA neurons that are activated by rewards or stress conditions [5]. Moreover, individual variation in VTA responses to stressors has been linked to individual differences in coping responses to stress [6]. These discoveries are contributing to our still concluding understanding of the functions of mesolimbic dopamine neurons in behaviors [7]. Some studies confirmed that exposure to acute stress affects reward-related processing in the dorsal striatum and orbital frontal cortex (OFC) [8]. Additionally, pleasurable behaviors (palatable food intake, sexual activity) can reduce stress via brain reward pathways [9]. As well as foot shock stress

of mice increased mesolimbic dopamine release in the nucleus accumbens septi (NAS) [10]. Therefore, these results suggest that different stressful environments can change reward system and related behaviors. On the other hand, stress during pregnancy can increase the plasma concentration of corticosterone and finally this hormone can cross from placenta barrier and affect growth and development of embryos [11]. As well as the studies also have shown that early life stress can alter dopaminergic system, therefore these changes can affect brain morphology and behavior of the offspring's. Eventually, these changes can transfer to later generations. Studies have shown that a milled constraint stress that can increase plasma corticosterone level in the pregnant mice, can influence the brain laterality in the embryos in F2 generation [11]. In this review, we focus on the studies to deal stress and stress system and this correlation with reward system in prenatal, postnatal and adult periods as well as transmission of stress effects on reward system in second generation.

DIFFERENT TYPES OF STRESS

Stress is a word that used in daily life and biological sciences. Stress is used to explain experiences that are challenging emotionally and physiologically. Selye described, in his first publication in Nature in 1936, stress is as "the nonspecific response of the body to any demand made on it" [12].We can experience stress from four basic sources: The Environment (traffic, weather), Social (deadlines, job interviews), Physiological (menopause, illness, aging), Thoughts (difficult, painful)
[13]. Stress from biological point of view includes good stress or positive stress (Feels exciting, Motivates), bad stress or negative stress (Feels unpleasant, mental and physical problems, anxiety or concern) and non-effect stress [14]. As well as, some studies suggested that stress point of view biological can be divided to acute stress (such as car accident, fire in work place), chronic stress (such as divorce, failing work, addiction) and episodic Stress [15]. Acute stress is created unexpectedly (suddenly) and pressures on individual in spatial time confines. This stress is short term and its symptoms include anxiety, depression, muscular and stomach problems and etc. Chronic stress is long term and produces on individual continuously and longley. Chronic stress symptoms include metabolic disorders (type 2 diabetes mellitus, obesity), atherosclerotic cardiovascular disease, sleep disorders, and etc. Episodic Stress is created by expanding disorder and crisis in individual life. Episodic Stress symptoms include migraines, chest pain [15]. Reach results of chronic stress in animal and human have shown that chronic stress may be expressed by suppressed reproductive cycling, and immune responses or that can reduce growth hormone levels and subsequently inhibited growth rate [16]. This same stress can effect on reducing body weight and behavioral and physiological characterizations in male mice [16]. Animal studies have shown that the stress can lead to increase of food intake in some instance but basically stress decreased food intake and also weight in rat [17]. As well as fear such as chronic psychological stress can cause hyperglycemia and prediabetic situation in male rat [18]. However, acute physical and psychological stresses can effect on behavioral and metabolic signs in animal models [19]. Therefore, different types of stress can be having different effects in body.

STRESS AND HPA AXIS

Some studies reported that stress can change body homeostasis, generating stress-related responses [20-22]. Central effectors (including hypothalamic hormones, such as AVP, CRH, *pro-opiomelanocortin* derived peptides and brainstem derived norepinephrine) and peripheral effectors (including glucocorticoids, norepinephrine and epinephrine) of stress system effect on the different parts of body such as immune systems, wake-sleep centers, reproductive and thyroid hormone axes [23].
The first and important physiological axis that involved in the stress-induced responses is the autonomic nervous system (ANS). Primary ANS monitored general stress-induced responses including control of heart rate, respiratory rate, blood pressure, heart rate variability, cardiac output, and electro-dermal activity [24]. The second major neuroendocrine response to stress is activation of HPA axis. Under stress conditions, the hypothalamus secretes corticotropin-releasing hormone (CRH), and this provokes the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH triggers the secretion of glucocorticoids from the adrenal cortex. In humans, the main glucocorticoid is cortisol. Cortisol is predominantly (90–95%) bound to binding proteins in blood, only 5-10% of the total plasma cortisol circulates as biologically active, unbound, ''free'' cortisol. All of these stress mediators can induce many changes in the several systems such as the fear/anger behaviors, the executive and cognitive responses, the reward systems, the wake-sleep centers of the brain, the gastrointestinal, cardiorespiratory, metabolic, immune systems and the growth, reproductive and thyroid hormone axis. Numerous studies have demonstrated that stress changed the concentration of mediator's in the different axis. For example, the inhibitory effect of immobilization stress on the HPG (Hypothalamic-Pituitary-Gonad) axis may also

cause negative effects on the spermatogenesis process [25, 26] as well as sound and light stress in the pregnancy but only increases HPA axis activity, adrenocorticotropic hormone and adrenal gland weight but also decrease new-born weight [27]. Other studies have shown that vibration stress because of disturbing in HPA axis could decrease hypothalamus neuron formation that this decrement can cause tendency behaviors to homogeneous [28]. Therefore, increasing or decreasing HPA axis activity in effect of stress can cause different disorders in body [29].

STRESS AND REWARD SYSTEM

Reward and punishment or satisfaction and dislike have important role in the individual behaviors. Human learns an experiment and habit it that would have both reward and satisfaction. Therefore, reward stimulation can create strong remembrance in individual memory and create behaviors for seeking again it. Milner and Olds reported that several brain areas have important role in the reward system such as VTA, NAc, venteral singular cortical, amygdale, hippocampus, prefrontal, locus ceruleus, pre-midline brain [30, 31]. Some studies also have shown that several neurotransmitters involved in reward behaviors such as dopamine, GABA, glutamate, serotonin and opioid androgen [32, 33]. However, dopamine mesolimbic pathways are more important in the reward and reinforcement system [34, 35] . The mesolimbic dopamine pathway, consisted of dopaminergic neurons in VTA and their projections to the NAc, allows an organism to identify emotionally salient stimuli in the environment, to learn about outcomes associated with those stimuli, and to express appropriate approach or avoidance responses [36]. Therefore, many stimuli can activate brain reward system, and one important kind of them is stress. Moreover, Stress activates the limbic system, in particular the amygdala and then corticotropin releasing factor (CRF) from the hypothalamus, consequently the HPA axis. Activation of the HPA axis is linked to activation of the mesolimbic reward area activity. There are several examples of the tight interconnection between stress and reward areas. Anatomically, increased CRF secretion impinges on dopamine neurons in the VTA, and increases dopamine secretion over the NAc. As well as stress accompany with released cortisol both enhanced dopamine release from the NAc. Several studies showed that acute stress increased cortisol level which released dopamine in ventral striatum [37-39]. Also, it has been shown that acute stress-induced cortisol elevations mediate reward system activity during subconscious processing of sexual stimuli in young males [40]. These findings indicated that cortisol is crucially involved in the relation between stress and the responsiveness of the reward system. Although, commonly stress decreases activation of the NAc in response to the rewarding stimuli however high stress-induced cortisol levels suppress increases the firing of NAc neurons [40]. Additionally, Animal studies have shown that stressors such as electric shocks and tail pinch induced dopamine secretion in the striatum [41].

PRENATAL STRESS AND REWARD SYSTEM

Stress may be experienced during several phases of the life period; prior to mating (premating stress) during early, mid or late gestation (prenatal stress) or during the early period after birth (postnatal stress). One of the most critical periods is prenatal period. This period is a time of particular vulnerability to stress which has serious consequences on the developing fetus through both maternal behaviors and physiological changes. In human, prenatal stress is linked to an increased vulnerability for developing various psychosocial problems that are perceived both in childhood and adulthood. In children, prenatal stress is associated with cognitive, behavioral, physical and emotional problems [42]. All of these problems are most likely mediated by the effects of maternal stress on the structure and function of the fetal brain, which is the control center for a multitude of systems. During pregnancy, levels of maternal cortisol elevates naturally. This glucocorticoid is essential for fetal growth and the induction of certain enzymes, such as pulmonary surfactant. However, under particular stressful conditions, maternal cortisol concentrations can reach abnormally high levels. Then, increase of maternal cortisol, which is mostly transformed by the fetoplacental into its inactive form (i.e., cortisone), reaches to the fetus in high concentrations, which may potentially alter fetal development and growth [43]. However, stress activates the maternal HPA axis, resulting in increased production and release of placental CRH into the bloodstream. In contrast to hypothalamic CRH production, which is suppressed by stress-induced cortisol, placental CRH is increased by glucocorticoids, so that stress leads to progressively higher fetal plasma CRH levels. This placental CRH reaches the fetal brain [44]. Areas of the brain such as limbic areas are rich in CRH receptors during mid- to late gestation, therefore, could also be influenced by placental CRH [45] [45, 46]. Some studies have shown that hyper-production of glucocorticoids in stressed females may affect the development of embryonic adrenal function and also change neuroendocrine pathways in their offspring and reduced adrenal weight in offspring males [47, 48]. Prenatal stress traces on reward system and neurotransmitter level in embryo and offspring and adult brain. Prenatal stress reduces

neurotransmitter levels such as serotonin (5-HT), noradrenaline and dopamine in the different regions of brain and turn-over in the adult brain [49, 50]. Prenatal stressors with altering opioids, noradrenaline and serotonin levels may effect on male sexual behavior [51]. Prenatally stress with foot shocks of rats induced a higher noradrenaline turnover in the locus coeruleus, which might mediate alterations of attention, affective behavior and anxiety in response to stress [52, 53]. However, dopamine turn-over in the brain of prenatally stressed rats is generally increased; there is a reduced turn-over in NAc, which could explain the reduction of exploratory behaviors in response to novelty [54]. Other studies shown that daily administration of ACTH in the last week of pregnancy alters adult brain monoaminergic activity, blocking of opioid receptors at the time of the prenatal stress decreased the anxiety of prenatally stressed rats in the elevated plus maze later in life [47, 55]. Thus, prenatal glucocorticoid exposure affects the developing dopaminergic system, which is involved in reward- or drug-seeking behaviors, and it has been suggested that the increased sensitivity reward behavior is related to the interaction between prenatal stress, glucocorticoids and dopaminergic neurons as well as an interaction between and corticosterone (CORT), and other stress-induced factors (e.g. neurotransmitters, opioids, neurosteroids, circulating hormones) may be required to induce long-term changes in the HPA axis of prenatally stressed animals [56].

POSTNATAL STRESS AND REWARD SYSTEM

Postnatal and later environmental events might modulate the effects of prenatal programming and also effects of prenatal stress or fetal glucocorticoid exposure extends into the postnatal period. Stress in postnatal period seems to effect on HPA axis and different parts of central nervous system such as the DA and endogenous opioid systems in the offspring. Some Studies shown that separation stress of the pups from the dam (the most important stress in the postnatal) for long separation periods (3 h or more each day) activate the pups' HPA axis ,as evidenced by increased plasma levels of adrenocorticotropic hormone and glucocorticoids with reducing pituitary CRH binding sites [57]. Moreover, this stress reduces exploratory behaviors in adulthood and is associated with locomotor hyperactivity, cognitive impairments and reductions in maternal care [58]. Other studies confirmed that stress in this period produces specific and permanent changes of offspring plasma ACTH and corticosterone (CORT) concentrations and corticosteroid receptor levels in hippocampus [59, 60] PVN and pituitary [61]. Humane studies have reported that glucocorticoid levels increase in these children (children with separation stress of the offspring from the mother) over the day, more so in toddlers than in older preschool-aged children [62, 63] as well as other studies shown that postnatal stress in humans predisposes to developmental delays and behavioral disturbances [64], and possibly also personality disorders [65]. One of postnatal stress consequences is the effect on the dopamine and endogenous opioid systems (as reward system). Some of reports confirmed that postnatal stress (such as maternal separation stress) results in increased dopamine release as well as decreased the number of D_2-dopamine receptors in the VTA and so lowered dopamine transporter levels in the NAc [66]. Also, early postnatal stress (maternal separation) can significantly alter the rewarding or aversive value of μ- and k-opioid agonists when measured using place conditioning (1me) and exposure to repeated stress during postnatal development eliminated the increase of dopamine release that elicited by short stressful experiences in the adult life without affecting the inhibition of dopamine release induced by prolonged stress [67]. Thus, stress in this period seems to effect on different systems of brain such as reward system that can display its destroyer effects in adult.

STRESS IN AN ADULTHOOD AND REWARD SYSTEM

The same as was stated, the one can exposed with stress in different periods of life that one of them is an adulthood time as well as stress seems to effect different parts of brain such as mesolimbic dopamine system (or reward system) [68]. Recent discoveries suggest that there may be distinct populations of VTA neurons that are preferentially activated by stress. However, less is known about how these factors mediate mesolimbic dopamine responses to stress. Moreover, the majority of studies investigating dopaminergic responses to stress have focused on a few species of male rodents under relatively controlled laboratory conditions. Experimental Stressful stimuli such as restraint [69, 70] and foot shock [71, 72] , induced dopamine release or turnover in the NAc shell, but a few studies have examined dopaminergic responses to more natural stressors such as predator odor in male rats. For example, rats exposed to fox odor for 20 min increased dopamine turn-over in the amygdala and frontal cortex but not in the NAc [73]. Several in vivo and ex vivo studies have reported that enhanced dopamine release in the NAS (nucleus accumbens septi) in response to stressful experiences [70, 74] .Other Stress stimuli such as stressful experience of animal attack to conspecifics seems to enhance dopamine release in

mesoaccumbens [75, 76] as well as, other studies shown that tail-pinch stress increases extracellular dopamine levels (as measured by in vivo voltammetry) in the rat NAc and restraint stress enhances dopamine outflow in the Frontal cortex (FC) and in the NAS [77]. Human studies have shown that exposure of stress during adolescence increases risk of drug abuse, a process that is linked to changes in mesolimbic dopamine function [78, 79]. Social stress during adolescence alters the "programming" of the mesolimibic dopamine system, potentially making it more sensitive to drugs of abuse [80]. However, there is also evidence that stress during adolescence can lead to desensitization of the mesolimbic system [81]. For instance, Patients with social anxiety disorder (such as stressful activity) had higher levels of activity in ventral striatum (which includes the NAc and caudate putamen) compared to matched controls [82]. Similarly inconsistent results were found in studies examining D_2 receptor binding in adult populations with social anxiety phenotypes [83]. Thus Stimuli that increase the release of dopamine in the mesoprefrontal cortex (MFC) or NAc, whether natural (water, food, and sex) or artificial (produced by means of drugs or electricity), can be heavily affected by stress [84]. These results indicated that a short exposure to stressors enhances mesolimbic dopamine release, promotes behavioral activation and facilitates reinforced responding, while prolonged exposure leads to inhibition of either the behavioral or the neurochemical responses [74].

STRESS IN F2 GENERATION

Maternal stress can influence offspring development and stress responses with serious consequences that lasting to adulthood [85, 86]. Maternal stress has been reported to programing physiology and behaviour across generations [87]. Trans generational programming of stress responses were suggested to transmit to subsequent generations in the absence of stress by germ line-dependent mechanisms [88]. Some Studies have reported that environmentally stress induced epigenetic variation in the male germ cells with similar modifications of the brain structures and also sperm of F1 offspring, and also in some cases are observed in the F2 and F3 generations [89, 90]. For example, these heritable epigenetic changes may induce the increased levels of Rcan1 and Rcan2 expression in stress-exposed mice and theirF1, F2, and F3 daughters [91]. It was suggested that maternal stress contributes offspring behavioural traits and their stress responses by epigenetic mechanisms [88, 92]. Therefore, the epigenetic imprinting of adult physiology and behaviour by stress suggests that this reciprocal relationship represents a potential target for the prevention and intervention to improve offspring health outcomes. Moreover, fetal antecedents likely lead to adult disease by programming changes in the epigenome. For example, human infants with prenatal exposure to maternal stress showed increased glucocorticoid methylation, which associated with a heightened cortisol response to a mild stressor. These programming effects may transmit to subsequent generations, and also predisposing offspring to disease [93]. Prenatal stress may permanently alter brain development, which may manifest in behaviors (such as nest building and behavioral simplification) when a prenatally stressed rat matures and becomes pregnant [94]. Moreover, corticosterone levels in pregnant rats peak on gestational day 18 and remain high until parturition [95]. The intricate endocrine changes of gestation and the rise in antepartum corticosterone levels in particular may stimulate central dopaminergic systems and lead to greater locomotor activity [96]. All of the issues related to HPA axis activity. Moreover, prenatal stress may alter basal activity of the HPA axis and the response to stress in adulthood [97]. The studies shown that gestational stress can deregulate progesterone formation in juvenile offspring [98] , a change that may persist into adulthood in female F1 and F2 animals to perturb physiological and behavioral adjustments to pregnancy. Then, the result shown that F0 generation exposure to a given environmental factor (such as stress) during pregnancy that directly also affects the phenotype of the F1embryo and F2 primordial germ cells.

EPIGENETIC

Scientists defined that epigenetics more than half a decade ago as being "the interaction of genes with their environment, which bring the phenotype into being". Later, other scientists found that DNA-methylation and other covalent modifications of DNA, to be one of the mechanisms behind Waddingtonian epigenetic regulation, however, today there is a debate concerning the correct definition of epigenetics [99-101]. Epigenetics is the ensemble of processes that induce mitotically or meiotically heritable changes in gene expression without altering the DNA sequence itself. Epigenetic mechanisms occur primarily at the chromatin, and involve multiple mechanisms including DNA methylation, covalent posttranslational modifications of histones (HPTMs), chromatin folding and attachment to the nuclear matrix, and/or nucleosomes repositioning (likely also noncoding RNAs). These mechanisms can act separately or in synergy to modulate chromatin structure and its accessibility to the transcriptional machinery. Epigenetic mechanisms are highly dynamic and can be influenced by environmental factors

such as diet, social/familial settings, and stress. As previously illustrated the prenatal and postnatal periods characterized by rapid changes in the neuronal organization, thus providing a critical window of opportunity during, which environmental experiences can lead to long-term influences on brain and behavior. There are several evidences for the role of epigenetic factors in mediating the relationship between these experiences and long-term outcomes. Primate and rodent studies have shown that maternal environment (in the prenatal and postnatal periods) has a profound influence on offspring phenotype and this influence is mediated by changes of gene expression. As a result, understanding the mechanisms governing these effects requires an investigation of the molecular mechanisms which regulate gene transcription and thus exploration of the epigenetics of gene expression. The molecular mechanisms involved in the epigenetics of the genome are numerous and complex including RNA interference, chromatin remodeling, histone modification and DNA methylation [102]. For example, chronic and unpredictable maternal separation stress also alters the profile of DNA methylation in the promoter of several candidate genes in the germ line of the separated males (mice). Comparable changes of DNA methylation are also present in the brain of the offspring and are associated with altered gene expression [103]. Other studies shown that postnatal maternal separation induces increased stress reactivity associated with reduced glucocorticoid receptors (GRs) expression in the hypothalamus and hippocampus, and regional changes in CRH receptor expression [104, 105]. As well as, pups that received little nurturing stress have shown increased methylation of the GR gene promoter at the NGFI-A binding site in the hippocampus, an epigenetic change that associated with reduced GR expression [92]. Another study showed that prenatal stress in pregnancy was associated with the GR gene methylation in children in their early teens. Increased GR methylation is associated with stronger cortisol responses to stress [106]. As well as, juvenile and adult rats exposed to prenatal stress have decreased numbers of mineralocorticoid receptors (MRs) and GRs in the hippocampus, possibly because of epigenetic effects on gene transcription [107]. Then prenatal stress can adversely influence gene expression in the HPA-axis [108]. These results suggest that the GRs themselves are known to be involved in mediating of epigenetic information by histone remodeling [109]. That is the influence by maternal hormones on the developing embryo and the exposure of postnatal offspring to parental behavior could also be seen as carriers of epigenetic information that ultimately might affect DNA-methylation and the chromatin configuration. Now this question is propounded how early environmental stress effects are sustained into adulthood? The answer to this question involves understanding of epigenetic modifications of gene expression in response to environmental stress. DNA methylation patterns are maintained after cell division and thus passed from parent to daughter cells and it is through this form of epigenetic modification that cellular differentiation occurs [110]. This methylation is perpetuated across successive generations and is present in the germ-line of first-generation males and the brain and germ-line of second-generation progeny [31, 111]. Then stress in the adulthood differentially modulates DNA methylation at specific genes [112]. Also, adult stress can leads to trans generational transmission of some behavioral symptoms [113], these can be transmitted from mother to offspring (F1 generation) and to grand-offspring (F2 generation). For example, it has been shown that DNA methylation of the CRF gene promotor decreased however the methylation of the GR exon 17 promotor regions increased in hypothalamic tissue of adult male mice born to gestationally stressed females [114]. It seems that maternal depression is to be associated with the increased GR 1F promotor methylation in the fetal blood samples and these methylation patterns predicted HPA reactivity in the infants at 3 months of age [115]. Animal studies have shown that the effects of maternal stress emerged in infancy and were maintained into adulthood. Moreover, these effects of stress on BDNF exon IV methylation are perpetuated to the F1 generation, suggesting a role of epigenetic mechanisms in the transgenerational effects [116]. Different epigenetic alterations likely involved in different types of gene and brain areas after stress [110]. For example, epigenetic alterations may involve DNA methyltransferases (DNMTs) like DNMT3a, whose mRNA is persistently increased in NAc after chronic social stress or other DNMTs or DNA methylation regulators [110].

CONCLUSION

Stress is considered as an important factor which can influence embryos growth during the gestation period and other stages of life. Stress has been defined as any condition that changes internal or external melio. Stress reaction differs according to its severity to threats in life. In general, it is highly likely that stress can induce a neuroendocrine response originated from hypothalamus and ends in adrenal gland. Corticosterone and norepinephrine released from adrenal cortex and medulla respectively, and prepared the animals for ameliorate the menace and/or overcome it, when a pregnant animal is exposed to a stressful event, with a possible increase in the plasma concentration of its corticosterone, the overloaded

hormone may readily cross the placenta barrier and affect its embryos growth and development. Moreover, prenatal stress may be linked to a typical laterality in rats. The studies also revealed that the early life stress can alter dopaminergic system activity in rat, which may influence their response to the psycho stimulants, indicating the importance of early life events on later brain activities. All of findings indicated that implication of stress to a pregnant animal could lead to a serious abnormal brain function of its off-springs.

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REFERENCES

1. Herman, J.P., Figueiredo, H., Mueller, N.K., Ulrich-Lai, Y., Ostrander, M.M., Choi, D.C., et al. (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol. 24(3):151-80.
2. Sapolsky, R.M., Romero, L.M., Munck, A.U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 21(1):55-89.
3. Yaghmaee, P., Parivar, K., Kouchesfahan, H., Pirnia, A. (2011). Effect of vibration stress the sexually dimorphic nucleus of hypothalamus of immature male Wistar rats. Medical Science Journal of Islamic Azad University. 20(2):83-9.
4. Herman, J.P., Guillonneau, D., Dantzer, R., Scatton, B., Semerdjian-Rouquier, L., Le Moal,, M. (1984). Differential effects of inescapable footshocks and of stimuli previously paired with inescapable footshocks on dopamine turnover in cortical and limbic areas of the rat. Life Sci. 30:2207–14.
5. Schwabe, L., Wolf, O.T. (2011). Stress-induced modulation of instrumental behavior: from goal-directed to habitual control of action. Behav Brain Res. 219(2):321-8.
6. Krishnan, V, Nestler, E.J. (2010). Linking molecules to mood: new insight into the biology of depression. Am J Psychiatry. 167:1305–20.
7. Berridge, K.C. (2007). The debate over dopamine's role in reward: the case for incentive salience. . Psychopharmacology. 191:391–431.
8. Born, J.M., Lemmens,S.G., Rutters, F., Nieuwenhuizen AG, Formisano, E., et al. (2009). Acute stress and food-related reward activation in the brain during food choice during eating in the absence of hunger. Int J Obes. 34:172–81.
9. Ulrich-Lai, Y.M., Christiansen, A.M., Ostrander, M.M., Jones, A.A., Jones, K.R., Choi, D.C., et al. (2010). Pleasurable behaviors reduce stress via brain reward pathways. Proc Natl Acad Sci U S A. 107(47):20529-34.
10. Puglisi-Allegra, S., Imperato, A., Angelucci, L., Cabib, S. (1991). Acute stress induces time-dependent responses in dopamine mesolimbic system. Brain Res. 19;554(1-2):217-22.
11. Brake, W.G., Zhang, T.Y., Diorio, J., Meaney, M.J., Gratton, A. (2004). Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. Eur J Neurosci. 1863-74.
12. Selye, H. (1974). Stress without distress. Philadelphia, PA: J B Lippincott.
13. Dantzer, R. (1991). Stress, stereotypies and welfare. Behav Processes. 25(2-3):95-102.
14. Nadeem, A., Masood, A., Masood, N., Gilani, R.A., Shah, Z.A. (2006). Immobilization stress causes extra-cellular oxidant-antioxidant imbalance in rats: restoration by L-NAME and vitamin E. Eur Neuropsychopharmacol. 16(4):260-7.
15. Chakraborti, A., Gulati, K., Ray, A. (2008). Age related differences in stress-induced neurobehavioral responses in rats: modulation by antioxidants and nitrergic agents. Behav Brain Res. 194(1):86-91.
16. Chrousos, G.P., Gold, P.W. (1992). The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. Jama. 4;267(9):1244-52.
17. Levine, A.S. (1981). Stress-induced eating in rats. Am J Physiol. 241:72-6.
18. Nirupama, R.D., Yajurvedi, H.N. (2010). Repeated Acute Stress Induced Alterations in Carbohydrate Metabolism in Rat. Journal of stress physiology and biochemistry. 6(3):44-55.
19. Hooshmandi, Z. Eidi, A., Fatahi, Z., Golmanesh, L., Sahraei, H. (2011). Reduction of metabolic and behavioral signs of acute stress in male Wistar rats by saffron water extract and its constituent safranal. Pharm Biol. 49(9):947-54.
20. McEwen, B.S. (1983). Effects of stress on the neurochemistry and morphology of the brain: Counterregulation versus damage. In L. Goldberger & S. Breznitz (Eds.), Handbook of stress: Theoretical and clinical aspects.
21. McEwen, B.S. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. Neuropsychopharmacology. 22(2):108-24.
22. Selye, H. (1976). Stress in health and disease. Reading, MA: Butterworth's.
23. Cannon, W.B. (1963). The Wisdom Of The Body. Rev. and Enl. Ed Edition
24. Sherwood, L. (2010). Human physiology: From cell to system. London, England: Cengage Learning.
25. Dallman, M.F., Cascio, C.S., Darlington, D.N., Jacobson, L., Levin, N. (1987). Regulation of ACTH secretion: variations on a theme of B. Recent Prog Horm Res. 43:113-73.

26. Mozafar, A., Keshavarz, M., Zareian, P., Johary, H., Jahromy, H.K., Hoseini, S. (2013). The Effect of Immobilization Stress on the HPG Axis (Hypothalamic – Pituitary - Gonad) Hormones and the Number of Spermatogonia. Journal of Fasa University of Medical Sciences. 3(3):280-4.
27. Mulatta, S.M. (1990). The effect of mild stress during pregnancy on birthweight and neurmotor maturation in rhesus monkey infants. Winsconsin Madison 28(3):1022-5.
28. Kartapol'tseva, N.V., Katamanova, E.V., Rusanova, D.V. (2007). Features of nervous system involvement under stress influence by occupational physical factors. Med Tr Prom Ekol. (6):43-7.
29. Yoshimura, S.S., Kudo, H., Sassa, S., Kumai, A., Okamoto, R. (2003). Sex-differences in adrenocortical responsiveness during development in rats. Steroids. 68:439–45.
30. Olds, J., Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol. 47(6):419-27.
31. Wise, R.A. (1996). Addictive drugs and brain stimulation reward. Annu Rev Neurosci. 19:319-40.
32. Bahari, Z., Manaheji, H., Hosseinmardi, N., Meftahi, G.H., Sadeghi, M., Danialy, S. (2014). Induction of spinal long-term synaptic potentiation is sensitive to inhibition of neuronal NOS in L5 spinal nerve-transected rats. EXCLI Journal.13:751-60.
33. Nestler, E.J. (2004). Molecular mechanisms of drug addiction. Neuropharmacology. 47-1:24-32.
34. Zarrindast, M.R., Faraji, N., Rostami, P., Sahraei, H., Ghoshouni, H. (2003). Cross-tolerance between morphine- and nicotine-induced conditioned place preference in mice. Pharmacol Biochem Behav. 74(2):363-9.
35. Chalabi-Yani, D., Sahraei, H., Meftahi, G.H., Hosseini, S.B., Ali Beig, H., Bourbour, Z. (2015). Effect of Transient Inactivation of Ventral Tegmental Area on the Expression and Acquisition of Nicotine-Induced Conditioned Place Preference in Rats. Iranian Biomedical Journal 2015;19(4): x-x (October 2015).
36. Cabib, S., Puglisi-Allegra, S. (1994). Opposite responses of mesolimbic dopamine system to controllable and uncontrollable aversive experiences. J Neurosci.14(5 Pt 2):3333-40.
37. Pruessner, J.C., Champagne, F., Meaney, M.J., Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J Neurosci. 17;24(11):2825-31.
38. Wanat, M.J., Hopf, W., Stuber, G.D., Phillips, P.E., Bonci, A. (2008). Corticotropin-releasing factor increases mouse ventral tegmental area dopamine neuron firing through a protein kinase C-dependent enhancement of Ih. J Physiol. 15;586(8):2157-70.
39. Wand, G.S., Oswald, L.M., McCaul, M.E., Wong, D.F., Johnson, E., Zhou, Y. (2007). Association of amphetamine-induced striatal dopamine release and cortisol responses to psychological stress. Neuropsychopharmacology. 32(11):2310-20.
40. Oei, N.Y., Both, S., Van Heemst, D., Van der Grond, J. (2014). Acute stress-induced cortisol elevations mediate reward system activity during subconscious processing of sexual stimuli. Psychoneuroendocrinology. 39:111-20.
41. Abercrombie, E.D., Keefe, K. A., DiFrischia, D.S., Zigmond, M.J. (1989). Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J Neurochem. 52(5):1655-8.
42. King, S., Mancini-Marie, A., Brunet, A., Walker, E., Meaney, M.J., Laplante, D.P. (2009). Prenatal maternal stress from a natural disaster predicts dermatoglyphic asymmetry in humans. Dev Psychopathol. 21(2):343-53.
43. Seckl, J.R., Holmes, M.C. (2007). Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. Nat Clin Pract Endocrinol Metab. 3(6):479-88.
44. Kastin, A.J., Akerstrom, V. (2002). Differential interactions of urocortin/corticotropin-releasing hormone peptides with the blood-brain barrier. Neuroendocrinology. 75(6):367-74.
45. Sandman, C.A., Wadhwa, P., Glynn, L., Chicz-Demet, A., Porto, M., Garite, T.J. (1999). Corticotrophin-releasing hormone and fetal responses in human pregnancy. Ann N Y Acad Sci. 897:66-75.
46. Meftahi, G.H., Ghotbedin, Z., Eslamizade, M.J., Hosseinmardi, N., Janahamadi, M. (2015) Suppressive Effects of Resveratrol Treatment on The Intrinsic Evoked Excitability of CA1 Pyramidal Neurons. Cell Journal(Yakhteh). 17(3):532-9.
47. Fameli, M., Kitraki, E., Stylianopoulou, F. (1994). Effects of hyperactivity of the maternal hypothalamic-pituitary-adrenal (HPA) axis during pregnancy on the development of the HPA axis and brain monoamines of the offspring. Int J Dev Neurosci. 12(7):651-9.
48. Osadchuk, L.V. (1997). Cortisol production in fetal adrenals of the silver fox. Theriogenology. 47(4):903-12.
49. Peters, D.A. (1982). Prenatal stress: effects on brain biogenic amine and plasma corticosterone levels. Pharmacol Biochem Behav. 17(4):721-5.
50. Takahashi, L.K., Turner, J.G., Kalin, N.H. (1992). Prenatal stress alters brain catecholaminergic activity and potentiates stress-induced behavior in adult rats. Brain Res. 6;574(1-2):131-7.
51. Velazquez-Moctezuma, J., Dominguez, S.E., Cruz Rueda, M.L. (1993). The effect of prenatal stress on adult sexual behavior in rats depends on the nature of the stressor. Physiol Behav. 53(3):443-8.
52. Takahashi, L.K., Kalin, N.H. (1991). Early developmental and temporal characteristics of stress-induced secretion of pituitary-adrenal hormones in prenatally stressed rat pups. Brain Res. 30;558(1):75-8.
53. Weinstock, M. (1997). Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? Neurosci Biobehav Rev. 21(1):1-10.
54. Alonso, S.J., Navarro, E., Rodriguez, M. (1994). Permanent dopaminergic alterations in the n. accumbens after prenatal stress. Pharmacol Biochem Behav. 49(2):353-8.

55. Keshet, G.I., Weinstock, M. (1995). Maternal naltrexone prevents morphological and behavioral alterations induced in rats by prenatal stress. Pharmacol Biochem Behav. 150(3):413-9.
56. Piazza, P.V., Le Moal, M.L. (1996). Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. Annu Rev Pharmacol Toxicol. 36:359-78.
57. Levine, S., Wiener, S.G. (1998). Psychoendocrine aspects of mother-infant relationships in nonhuman primates. Psychoneuroendocrinology. 13(1-2):143-54.
58. Gonzalez, A., Fleming, A.S. (2002). Artificial rearing causes changes in maternal behavior and c-fos expression in juvenile female rats. Behav Neurosci. 116(6):999-1013.
59. Meaney, M.J., Aitken, D.H., Viau, V., Sharma, S., Sarrieau, A. (1989). Neonatal handling alters adrenocortical negative feedback sensitivity and hippocampal type II glucocorticoid receptor binding in the rat. Neuroendocrinology. 50(5):597-604.
60. Sutanto, W., Rosenfeld, P., De Kloet, E.R., Levine, S. (1996). Long-term effects of neonatal maternal deprivation and ACTH on hippocampal mineralocorticoid and glucocorticoid receptors. Brain Res Dev Brain Res. 30;92(2):156-63.
61. Rots, N.Y., De Jong, J., Workel, J.O., Levine, S., Cools, A.R., De Kloet, E.R. (1996). Neonatal maternally deprived rats have as adults elevated basal pituitary-adrenal activity and enhanced susceptibility to apomorphine. J Neuroendocrinol. 8(7):501-6.
62. Geoffroy, M.C., Cote, S.M., Parent, S., Seguin, J.R. (2006). Daycare attendance, stress, and mental health. Can J Psychiatry. 51(9):607-15.
63. Gunnar, M.R., Donzella, B. (2002). Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology. 27(1-2):199-220.
64. Meijer, A. (1985). Child psychiatric sequelae of maternal war stress. Acta Psychiatr Scand. 72(6):505-11.
65. Huttunen, M.O., Niskanen, P. (1978). Prenatal loss of father and psychiatric disorders. Arch Gen Psychiatry. 35(4):429-31.
66. Meaney, M.J., Brake, W., Gratton, A. (2002). Environmental regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse? Psychoneuroendocrinology. 27(1-2):127-38.
67. Cabib, S., Puglisi-Allegra, S., D'Amato, F.R. (1993). Effects of postnatal stress on dopamine mesolimbic system responses to aversive experiences in adult life. Brain Res. 26;604(1-2):232-9.
68. Tidey, J.W., Miczek, K.A. (1996). Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Res. 20;721(1-2):140-9.
69. Copeland, B.J., Neff, N.H., Hadjiconstantinou, M. (2005). Enhanced dopamine uptake in the striatum following repeated restraint stress. Synapse. 1;57(3):167-74.
70. Lodge, D.J. (2005). Acute and chronic corticotropin-releasing factor 1 receptor blockade inhibits cocaine-induced dopamine release: correlation with dopamine neuron activity. J Pharmacol Exp Ther. 314:201-6.
71. Bekris, S., Antoniou, K., Daskas, S., Papadopoulou-Daifoti, Z. (2005). Behavioural and neurochemical effects induced by chronic mild stress applied to two different rat strains. Behav Brain Res. 3;161(1):45-59.
72. Kalivas, P.W., Duffy, P. (1995). Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. Brain Res. 27;675(1-2):325-8.
73. Morrow, B.A., Redmond, A.J., Roth, R.H., Elsworth, J.D. T(2000). The predator odor, TMT, displays a unique, stress-like pattern of dopaminergic and endocrinological activation in the rat. Brain Res. 2;864(1):146-51.
74. Imperato, A., Angelucci, L., Casolini, P., Zocchi, A., Puglisi-Allegra, S. (1992). Repeated stressful experiences differently affect limbic dopamine release during and following stress. Brain Res. 17;577(2):194-9.
75. Louilot, A., Simon, H. (1986). Differential reactivity of dopamine neurons in the nucleus accumbens in response to different behavioral situations: an in vivo voltametric study in freely moving rats. Brain Res Dev Brain Res. 397:395–400.
76. Puglisi-Allegra, S., Kempf, E., Cabib, S. (1990). Role of genotype in the adaptation of the brain dopamine system to stress. Neurosci Biobehav Rev. 14(4):523-8.
77. Imperato, A., Puglisi-Allegra, S., Casolini, P., Angelucci, L. (1991). Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. Brain Res. 1 4;538(1):111-7.
78. Dietz, D.M., Dietz, K.C., Nestler, E.J., Russo, S.J. (2009). Molecular mechanisms of psychostimulant-induced structural plasticity. Pharmacopsychiatry. 42 (1): 69-78.
79. King, K.M. C.L. (2008). Adolescent stressors, psychopathology, and young adult substance depenence: a prospective study. J Stud Alcohol Drugs. 69:629–38.
80. McCormick, C.M. (2010). An animal model of social instability stress in adolescence and risk for drugs of abuse. Physiol Behav. 9;99(2):194-203.
81. Gatzke-Kopp, L.M. (2010). The canary in the coalmine: the sensitivity of mesolimbic dopamine to environmental adversity during development. Neurosci Biobehav Rev. 35(3):794-803.
82. Lorberbaum, J.P., Kose, S., Johnson, M.R., Arana, G.W., Sullivan, L.K., Hamner, M.B. (2004). Neural correlates of speech anticipatory anxiety in generalized social phobia. Neuroreport. 22;15(18):2701-5.
83. Schneier, F.R., Liebowitz, M.R., Abi-Dargham, A., Zea-Ponce, Y., Lin, S.H., Laruelle, M. (2000). Low dopamine D(2) receptor binding potential in social phobia. Am J Psychiatry. 157(3):457-9.

84. Pani, L., Porcella, A., Gessa, G.L. (2000). The role of stress in the pathophysiology of the dopaminergic system. Mol Psychiatry. 5(1):14-21.
85. Francis, D., Diorio, J., Liu, D., Meaney, M.J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science. 5;286(5442):1155-8.
86. Parent, C.I., Del Corpo, A., Cameron, N.M., Meaney, M.J. (2013). Maternal care associates with play dominance rank among adult female rats. Dev Psychobiol. 55(7):745-56.
87. Matthews, S., Phillips, D. (2012). Transgenerational inheritance of stress pathology. Exp Neurol. 233(1):95-101.
88. Crewsa, D., Gillettea, R., Samuel, V., Marina, I., Savenkovab, Skinner, M.K. (2012). Epigenetic transgenerational inheritance of altered stress responses. Proc Natl Acad Sci U S A. 2012;109:9143-8.
89. Anway, M.D., Cupp, A.S., Uzumcu, M., Skinner, M.K. (2005).Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 308(5727):1466-9.
90. Franklin, T.B., Russig, H., Weiss, I.C., Graff, J., Linder, N., Michalon, A. (2010). Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry. 68(5):408-15.
91. Saavedra-Rodriguez, L,, Feig, L.A. (2013). Chronic social instability induces anxiety and defective social interactions across generations. Biol Psychiatry. 73(1):44-53. PubMed PMID: 22906514.
92. Weaver, I.C., Champagne, F.A. (2004). Epigenetic programming by maternal behavior. Nature Neurosci. 7:847-54.
93. Champagne, F.A., Curley, J.P. (2005). How social experiences influence the brain. Curr Opin Neurobiol. 15(6):704-9.
94. Whishaw, I.Q., Kolb, B., Pellis, S.M. (2001). Accelerated nervous system development contributes to behavioral efficiency in the laboratory mouse: a behavioral review and theoretical proposal. Dev Psychobiol. 39:151-70.
95. Piazza, P.V., Deroche, V., Maccari, S., Abrous, D.N., Simon, H., Le Moal, M. (1993). Suppression of glucocorticoid secretion and antipsychotic drugs have similar effects on the mesolimbic dopaminergic transmission. Pro Natl Acad Sci USA 1993;93:8716-20.
96. Harris, A., Seckl, J. (2011). Glucocorticoids, prenatal stress and the programming of disease. Horm Behav. 59(3):279-89.
97. Paris, J.J., Frye, C.A. (2011). Juvenile offspring of rats exposed to restraint stress in late gestation have impaired cognitive performance and dysregulated progestogen formation. Stress. 14(1):23-32.
98. Skinner, M.K., Guerrero-Bosagna, C. (2011). Epigenetic transgenerational actions of endocrine disruptors. ReprodToxi- col 2011;31:337–43.
99. Bridge, E.S., Schoech, S.J., Bowman, R., Wingfield, J.C. (2008). Temporal predictability in food availability: effects upon the reproductive axis in Scrub-Jays. J Exp Zool A Ecol Genet Physiol. 311(1):35-44.
100. Griesemer, J. (2003). What is "epi" about epigenetics? Ann N Y Acad Sci. 981:97-110.
101. Veldic, M., Guidotti, A., Maloku, E., Davis, J.M., Costa, E. (2005). In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. Proc Natl Acad Sci U S A. 102(6):2152-7.
102. Tamara, B., Franklin, H.R., Isabelle, C., Weiss J., Gräff, J. (2010). Epigenetic Transmission of the Impact of Early Stress Across Generations. Biol psychiatry. 68:408–15.
103. Ladd, C.O., Huot, R.L., Thrivikraman, K.V., Nemeroff, C.B., Plotsky, P.M. (2004). Long-term adaptations in glucocorticoid receptor and mineralocorticoid receptor mRNA and negative feedback on the hypothalamo-pituitary-adrenal axis following neonatal maternal separation. Biol Psychiatry. 15;55(4):367-75.
104. Fabricius, K., Wortwein, G., Pakkenberg, B. (2008). The impact of maternal separation on adult mouse behaviour and on the total neuron number in the mouse hippocampus. Brain Struct Funct. 212(5):403-16.
105. Plotsky, P.M., Meaney, M.J. (1993). Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Brain Res Mol Brain Res. 18(3):195-200.
106. Cottrell, E.C., Seckl, J.R. (2009). Prenatal stress, glucocorticoids and the programming of adult disease. Front Behav Neurosci. 3:19.
107. Caspi, A., Sugden, K., Terrie, E., Taylor, A., Craig, I.W., Harrington, H. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 301:386-9.
108. Jeon, J.T., Carlborg, O., Tornsten, A., Giuffra, E., Amarger, V., Chardon, P. (1999). A paternally expressed QTL affecting skeletal and cardiac muscle mass in pigs maps to the IGF2 locus. Nature genetics. 21(2):157-8.
109. Turner, B. (2008). Chromatin and Gene Regulation. . Blackwell Science Ltd, Oxford.
110. Franklin, T.B., Mansuy, I.M. (2011). The involvement of epigenetic defects in mental retardation. Neurobiol Learn Mem. 96(1):61-7.
111. Elliott, E., Ezra-Nevo, G., Regev, L., Neufeld-Cohen, A., Chen, A. (2010). Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. Nat Neurosci. 13(11):1351-3.
112. Dietz, D.M., Laplant, Q., Watts, E.L., Hodes, G.E., Russo, S.J., Feng, J. (2011). Paternal transmission of stress-induced pathologies. Biol Psychiatry. 70(5):408-14.
113. Champagne, F.A., Curley, J.P., Keverne, E.B., Bateson, P.P. (2007). Natural variations in postpartum maternal care in inbred and outbred mice. Physiol Behav. 8;91(2-3):325-34.
114. Oberlander, T.F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., Devlin, A.M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics. 3(2):97-106.
115. Champagne, F.A.(2008). Epigenetic mechanisms and the transgenerational effects of maternal care. Front Neuroendocrinol. 29:386-97.

116. LaPlant, Q., Vialou, V., Covington, H.E., Dumitriu, D., Feng, J., Warren, B.L. (2010). Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens. Nat Neurosci. 213(9):1137-43.