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Invited review

Long-term effects of early life stress exposure: Role of epigenetic mechanisms

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ABSTRACT

Stress is an adaptive response to demands of the environment and thus essential for survival. Exposure to stress during the first years of life has been shown to have profound effects on the growth and development of an adult individual. There are evidences demonstrating that stressful experiences during gestation or in early life can lead to enhanced susceptibility to mental disorders. Early-life stress triggers hypothalamic-pituitary-adrenocortical (HPA) axis activation and the associated neurochemical reactions following glucocorticoid release are accompanied by a rapid physiological response. An excessive response may affect the developing brain resulting in neurobehavioral and neurochemical changes later in life. This article reviews the data from experimental studies aimed to investigate hormonal, functional, molecular and epigenetic mechanisms involved in the stress response during early-life programming. We think these studies might prove useful for the identification of novel pharmacological targets for more effective treatments of mental disorders.

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Contents

Abbreviations: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type-2; CNS, central nervous system; CRH, corticotropin-releasing hormone; DHA, docosahexaenoic acid; FC, frontal cortex; GABA, gamma-aminobutyric acid; GC, glucocorticoid hormone; GR, glucocorticoid receptor; 5-HT, serotonine; HDACi, HDAC inhibitors; Hic, hippocampus; HPA, hypothalamic–pituitary–adrenal; MR, mineralocorticoid receptor; MS, maternal separation; NA, noradrenaline; NMDA, N-methyl-D-Aspartate; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotrophin-3; NT4, neurotrophin-4; OXT, oxytocin; PCMS, prenatal chronic mild stress; PD, postnatal day; PFC, prefrontal cortex; PS, prenatal stress; PVN, paraventricular nucleus.

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1. Introduction

Until recent years, it was falsely believed that brain and body were shaped by experiences only when the child became able to respond rationally to the social environment without taking into account early life events. However, it is now accepted that both the embryo and the fetus are highly responsive to the gestational environment and in deed, several animal studies have described that pre and postnatal exposure to adverse events like stress can influence the offspring's neurodevelopment. Moreover, the neuroendocrine and the immune systems have also been described to be altered by stress inducing behavioral changes and thus affecting neuroplasticity [1–5]. Additionally, several reports indicate that stress plays a fundamental role in the etiology and evolution of many diseases including neuropsychiatric disorders like depression, autism and bipolar disorder [6,7].

Interpretation of retrospective studies from the 1960's suggests that exposure to prolonged stress during pregnancy cause developmental and behavioral disorders of the descendants. The brain is particularly susceptible to early-life programming by deregulation of the HPA axis and this can be manifested as stress hyper-reactivity and increased susceptibility to affective disorders like anxiety, depression and schizophrenia in childhood or adulthood [8–12]. Alteration of the circadian rhythm, imbalance of neurotransmitters in the brain and impaired immune function has also been described as consequences of perinatal stress exposure [10,13,14].

The term neuroplasticity refers to the potential of the brain to reorganize by creating new neural pathways to adapt, as it needs. This phenomenon requires the stable modulation of gene expression, which is mediated at least in part, by epigenetic processes such as DNA methylation and histone modifications. The sensitivity of the mature phenotype to environmental factors and the subsequent risk of disease are determined by the interactive influence of both genome and epigenome [15]. Although the link between prenatal exposure to stress and altered postnatal behavior is not fully understood, emerging evidences indicate that epigenetic regulation prior to birth, can exert profound effects on the development and functioning of the brain and over many neurodevelopmental syndromes [16].

The aim of this article is to overview the current state of knowledge in the field describing different animal models of pre and postnatal stress and discussing the epigenetic mechanisms involved in the modulation of the physiological response.

2. HPA axis response to stress

The physiological response to a stressful event involves the activation of the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system and the immune system whose physiological mediators are glucocorticoids (GCs), catecholamines and cytokines respectively [17]. The neuroendocrine stress response plays a key role in the adaptation to the environment, however, excessive or chronic stress exposure may lead to persistent maladaptation of neuronal circuits and may promote the development of psychiatric pathologies, such as mood or anxiety disorders [18] that often arise in adolescence [19,20].

The HPA axis is an adaptive and plastic system and is characterized by inter- and intra- individual variability. A stressful experience triggers the activation of the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These hormones bind to their specific receptors (CRHR1 and V1b) in the anterior pituitary stimulating the release of adrenocorticotropic hormone (ACTH). ACTH stimulates glucocorticoid synthesis (cortisol in human, corticosterone in rodents), which regulate different processes [21,22]. The biological effects of GCs are usually adaptive; however, inadequate or excessive activation of the HPA axis may contribute to the development of pathologies [23,24].

Glucocorticoids bind to two types of receptors: mineralocorticoid (MR) and glucocorticoid receptors (GR). Upon binding to GRs, glucocorticoids modulate the transcription of HPA components creating a regulatory negative feedback loop [25–27]. Given the distinctive pharmacology of GRs and MRs, it has been suggested that while MRs regulate basal HPA tone, GRs mediate the glucocorticoid negative feedback following stress [28].

Interestingly, the effects of long-term changes in the function of the HPA axis observed as a consequence of developmental adversities (e.g., pre or postnatal stress exposure) exhibit similarities with psychiatric disorders characterized by abnormalities in the HPA axis function and in the stress response [29].

3. Early life stress

The pre and postnatal periods are critical for the development of the nervous system. Exposure to adverse events early in life may profoundly affect brain development leading to long-lasting effects on neuronal structure and behavior playing a key role in the etiology of mood and anxiety disorders [30]. The interactions between the genome and the environment during the perinatal interval generate windows of vulnerability in which interference by a stressor could lead to abnormalities at birth (low weight), to growth retardation, or structural and functional changes that remain in adulthood [31].

Animal models are useful tools that help us understand how genetic vulnerability factors can modulate responses to early environmental experiences. By controlling environmental exposure to different stressors and following animals prospectively from or before birth, these models provide insights about behavioral and physiological mechanisms involved in the pathways through which early stress might produce long-term effects. In this review we will focus on models of pre and postnatal stress.

3.1. Prenatal stress (PS)

During the gestational period animals are susceptible to factors that can disrupt the homeostasis and therefore development is affected. In humans, psychosocial work stress during pregnancy has been related to postnatal consequences such us reduction in birth weight and time of gestation [32]. Numerous animal models of prenatal stress (PS) are conceived to mimic suboptimal womb environments. Different paradigms have been used in order to study the effects of stress exposure over development and predisposition to lifelong health problems including immobilization [33], exposure

to noise, sleep deprivation, nutrient restriction, overfeeding during pregnancy, and exogenously administered glucocorticoids [11].

Several animal and preliminary human studies have linked PS exposure to deficiency in development and behavioral disorders suggesting that the effects of PS can have long-lasting effects on the offspring's immune system and on neurocognitive functions [34–36]. These studies suggest that PS could predispose rats to behavioral abnormalities such as increased anxiety, greater tendency to drug addiction and depressive-like behavior [11,13,32,37,38]. Furthermore, behavioral studies have shown that PS offspring exhibited increased exploratory behavior and increased locomotor activity [31,36] as well as impairment in learning and memory performance [39,40]. These findings are in agreement with deficits in social behavior found in several neuropsychiatric disorders with a presumed developmental origin [40]. Likewise, Zorrilla Zubilete and colleagues demonstrated that offspring from Wistar rats subjected to a daily immobilization stress protocol during pregnancy showed impairment in spatial memory and territory discrimination [40].

Different effects of prenatal stress exposure have been described for males and females [41,42]. This gender variance may have a physiological basis which is probably determined throughout intrauterine development. During this period, sexual hormones play an important role in determining different brain regions which accounts for the neuronal differentiation characteristic of each sex. Since glucocorticoids exert a regulatory effect on the gonads it is likely that intrauterine stress response would be involved in this process.

Environmental stimulation is critical for neural circuit formation and functioning. It is accepted that favorable conditions such as environmental enrichment (EE) exposure increase brain plasticity and represent a significant advantage for the psychological and behavioral response [43,44]. Several animal studies have demonstrated that pre- or postnatal EE housing enhanced behavioral performance suggesting that EE exposure would counteract the cognitive deficits induced by adverse early life experiences [45]. Additionally, reversal of abnormal behaviors such as emotional reactivity, motor skills and spatial learning induced by prenatal stress were observed upon EE exposure [46]. Furthermore, early postnatal EE treatment was shown to neutralize prenatal stress-induced deficits in hippocampal neurogenesis [47].

Some studies suggest that resilience to stress exposure during development may be mediated, at least in part, via nitric oxide and neurotrophins among other intracellular signaling cascades [48]. As mentioned, prenatal stress is associated with behavioral effects in the offspring. For these reasons, further studies are necessary to understand the pathways involved in these processes in order to provide prospective targets for novel antidepressant and mood stabilizing treatments, including epigenetic modulators.

3.2. Postnatal stress

The effects of early postnatal adversities in adulthood have been explored through a variety of experimental animal models. Different types of alterations in maternal care are used as models to approximate childhood adversity in humans. The most commonly used is the so-called Maternal Separation (MS) which involves temporarily separating or isolating litters or individual pups from the dam daily during the early postnatal life [49]. This procedure is performed between birth and weaning for different periods of time and allows a set of experimental designs, which differ in the frequency, duration and age at which maternal separation occur.

Other model consists on a brief separation (generally 15 min) of the pups from the dam to mimic a physiological maternal absence. Levine et al. [50] developed this procedure named "early handling" and found that the long-term consequences of it have opposite effects than maternal separation since the former has a positive impact for stress coping later in life, whereas the latter appears to be detrimental [51].

Different protocols of MS in rats have shown alterations in the functioning of the CNS evidenced by learning disabilities, increase of self-administration drugs abuse and behavioral changes, which demonstrates the importance of early maternal care and the long-term impact on many biological and behavioral processes [52,53].

Early life stress events in humans such as physical, sexual and emotional abuse is associated with increased risk of psychopathology in childhood and adulthood, as well as social and health problems [54–56]. Natural disasters, wars and terrorism-related events should also be considered as adverse experiences that correlate with the development of mood and anxiety disorders in adulthood [56]. Moreover, abuse in childhood has been described as a risk factor for depression, post-traumatic stress disorder, idiopathic chronic pain disorders, substance abuse, antisocial behavior, as well as obesity, diabetes, and cardiovascular disease partly due to a sensitization of the neurobiological systems involved in the stress response [57–60].

4. Neurobiological responses to early life stress

4.1. Glucocorticoids and oxytocin response

Epidemiological, clinical and experimental studies have shown that stress exposure during early life periods, along with genetic predisposing factors, may exert prolonged impact on the HPA axis function and on subsequent neurochemical and behavioral responses in adulthood. Many studies have shown the impact of stress exposure during development on the HPA axis activity and on psycho-emotional disorders during adulthood [61,62]. In the rat, the HPA axis completes its development between postnatal days (PD) 5–7, so this period becomes highly vulnerable to the action of some type of stressor [63]. In fact, one of the proposed explanations of how maternal stress affects the developing fetus involves the increased levels of glucocorticoids that can pass through the placenta [13]. Nevertheless, the role of maternal GCs in transmitting the effects of maternal stress to the fetus is not clear-cut. The first physiological control is exerted by the placenta which expresses 11β-hydroxysteroid dehydrogenase type-2 (11β-HSD2). This enzyme metabolizes corticosterone into inactive 11-dehydrocorticosterone serving to limit fetal exposure to maternal GCs [64]. However, repeated stress exposure during pregnancy significantly reduces the activity and the placental gene expression of 11β-HSD2 [65,66], potentially enlarging the exposure of the fetus to maternal glucocorticoids. Another line of control involves the maternal HPA axis that dramatically reduces its response to stress during the late pregnancy, thus minimizing fetal exposure to maternal GCs [67]. Actually, the long-term effects of prenatal stress as the result of excessive exposure of the fetus to maternal corticosterone were shown to be prevented in rodents by surgical removal of the adrenal glands from the mother [13,68]. Furthermore, inhibition of 11β-HSD2 was shown to produce permanent alterations of the HPA axis and anxiety-like behavior in the offspring suggesting that fetal overexposure to endogenous GCs may represent a common link between the prenatal environment and disorders linked to adult HPA axis dysfunction [69,70]. In addition, elevated maternal glucocorticoids were shown to stimulate the production of placental CRH affecting the fetus's HPA axis [71,72] and a 30-min restraint stress protocol applied to the mother during gestational day 15–17 was found to increase the expression of CRH mRNA in the fetal PVN [73].

Exposure to high levels of glucocorticoids, both in the prenatal and postnatal environments, has been linked to the development

of adult pathologies, including heart disease, diabetes mellitus, depression and anxiety disorders [69,70]. In this context, many studies indicate that MS may permanently disrupt the ability of hippocampal GRs to negatively regulate the HPA axis [74–77] and that pups exposed to a brief separation from the dam tended to be less responsive (more resistant) in terms of HPA activity than control littermates as adults [78]. Moreover, the decreased expression of MR/GR receptors in the Hic and the consequent increase in plasma glucocorticoids has also been documented in PS animals [79,80].

Other hormone that is a potent modulator of HPA axis activity both in animals and humans is the neuropeptide oxytocin (OXT). Central OXT has been described as an important regulator of the stress response and is believed to attenuate the response of the HPA axis. Accordingly, increased levels of OXT, both in the central and the peripheral nervous system, have been associated with stressful events [81–83]. Moreover, evidences from rodent models suggest that both acute and chronic administration of OXT reduces physiological and behavioral stress response [84–87]. Additionally, human studies revealed that intranasal OXT administration attenuate cortisol and behavioral responses to psychosocial stress [88–91]. Furthermore, it has been demonstrated that OXT receptor expression in Hic is modulated by stress and GCs [92]. Ultimately, alterations of the OXT system as a consequence of early experiences may contribute to individual vulnerability related to the pathological effects of stress in humans.

4.2. Effects of perinatal stress on the Brain-Derived Neurotrophic Factor (BDNF)

Neurotrophic factors are peptides that promote neuronal development and differentiation, and are expressed in a particular region during a defined period of time [83]. They are involved in remodeling processes, adaptation and neuronal plasticity acting in an autocrine or a paracrine manner [93]. Neurotrophins are the best-characterized family of neurotrophic factors and they comprise the Nerve Growth Factor (NGF), the Brain-Derived Neurotrophic Factor (BDNF), Neurotrophins 3 and 4 (NT3, NT4) among others.

Deregulation of neurotrophins is associated with various pathologies of the nervous system and it was suggested that during gestation, these factors may play numerous roles in angiogenesis, energy homoeostasis, regulation of growth factors and development and maturation of the fetus-placental unit [94]. For instance, BDNF, the most abundant and widely expressed neurotrophin in the brain, was shown to potentiate the placental development playing a critical role in cytotrophoblast differentiation, proliferation and survival [95,96]. Other studies reported that maternal BDNF could circumvent the utero-placental barrier influencing the fetal brain and contributing to its development [97]. BDNF, by binding to its receptor TrkB (tyrosine kinase), exerts its biological function initiating many signaling cascades that have been implicated in neurological disorders like schizophrenia [98,99].

Numerous neuropsychiatric disorders, including depression, autism, bipolar disorder and schizophrenia were associated with the neurotrophin *bdnf* gene [100–102]. It has been demonstrated that BDNF induces the survival [103], development and function [104] of selected neuronal populations of the peripheral and the central nervous systems and participate in the modulation of dendritic growth and morphology [105,106]. In the later stages of the CNS development and in the adult brain, BDNF regulates synaptic transmission, acts as a central modulator of pain [107] and modulates plasticity of neuronal networks involved in depressive behaviors [108,109]. Regulation of BDNF may reverse stress-induced deficits in the adult brain, resulting in cognitive flexibility and, subsequently, in increased ability to cope with environmental challenges that may precipitate or exacerbate depressive episodes [110]. Notably, in humans, reduced BDNF levels associated to significant memory impairment were reported in adult women with childhood sexual abuse history and posttraumatic stress disorder [111,112].

A differential expression pattern of BDNF was described in the Hic in a rodent model of maternal separation. While increased levels of BDNF were found in the CA1 and the dentate gyrus (DG) of adolescent rats as well as in the DG of young adult rats, the expression was decreased in the medial prefrontal cortex (mPFC) [113]. Moreover, the offspring of mothers that showed high frequency of maternal licking/grooming and arched-back nursing levels revealed augmented expression of BDNF mRNA and NMDA receptor subunit, in addition to increased cholinergic innervation of the hippocampus and improved spatial learning and memory [114].

Genetic studies demonstrated that transgenic mice carrying the Val66Met polymorphism in the *bdnf* gene exhibited increased anxiety-related behaviors under stress conditions [115], as well as decreased BDNF levels in the hippocampus [116]. Interestingly, in humans the met allele was related with poorer episodic memory and atypical hippocampal activation [117].

Since BDNF is an important intracellular mediator that can exert neurotoxic and/or neuroprotective effects in different processes induced by pre and postnatal stress, it would be of paramount importance to fully characterize its role in these processes for the development of new therapeutic approaches.

4.3. Neurochemical response

Different neurotransmitters such as noradrenaline (NA), serotonine (5-HT), glutamate, gamma-aminobutyric acid (GABA) and neuromodulators such as a gaseous molecule, nitric oxide (NO), have been implicated in the pathogenesis of stress-dependent disorders in early stages of life [118–121].

Several hippocampal alterations have been described to be induced by PS including decreased neurogenesis [122], reduction of long term potentiation (LTP) accompanied by a decline of NR1 and NR2B subunits of the NMDA type glutamate receptor in the post-sinapsis [123], a decrease in the number of GABA and serotonin 5-HT1A receptors [124,125], a decreased expression of PKCβ1 [39,126], an increase in the NA turnover [127] and altered levels of metabolites of DA and 5-HT [128].

Altered glutamate receptor (GluR) expression has been implicated in the pathogenesis of stress-induced disorders. Wang et al. [129] has shown that prenatal chronic mild stress exposure (PCMS) induced behavioral dimorphism response associated with a regional change in the expression of GluR concluding that PCMS increased the vulnerability to depressive disorders in males. Moreover, Adrover et al. [130] have shown that glutamate neurotransmission might be impaired in the brain of prenatally stressed rats. They observed an increased uptake capacity for glutamate in the PFC of PS males while no such changes were observed in the Hic. These results led to the conclusion that PS produced long-term changes in the glutamatergic system modulating the expression of glutamate transporters and altering synaptic transmission in the adult brain. Additionally, Acosta et al. studied the effects of chronic postnatal stress (CPS) exposure on alcohol intake and found an increased in voluntary consumption, accompanied by augmented glutamate uptake in Hic and decreased protein levels of the glial glutamate transporter-1 (GLT-1), the glutamate aspartate transporter (GLAST) and the excitatory amino-acid transporter-3 (EAAT-3) in Hic and FC. They propose that CPS-induced decreases in GLT-1 and EAAT-3 may be compensatory mechanism to prevent excitotoxicity [131].

Interestingly, prenatal stress has been demonstrated to result in a reduction in the density of paravalbumin-positive GABAer-

gic interneurons in the medial prefrontal cortex and Hic [132,133] and the number of GABAA receptors was found to be significantly reduced in the hippocampus and the central amygdala of PS rats [124]. Similarly, the group led by Acosta has shown that both CPS and acute maternal separation (AMS) affect the expression of the GABA transporter GAT1 [134].

Nitric oxide is an endogenous modulator of the neuronal function acting as an important brain messenger released upon stimulation of the glutamate *N*-methyl-D-aspartate (NMDA) receptor and the consequent Ca2+ -dependent activation of the neuronal NO synthase (nNOS) [135,136]. It has been demonstrated that NO plays an important role in LTP in the hippocampus [136] and in Long Term Depression (LTD) in the cerebellum [137] and participates in multiple interactions between the neuroendocrine and the neuroimmune systems both under physiological and pathological conditions. In the CNS, neuronal nNOS, the enzyme responsible of catalyzing NO formation, modulates learning and memory processes and is involved in the development of neuropsychiatric diseases, including depression. Maur and colleagues showed an increase cerebellar in calcium-dependent NOS activity in prenatally stressed animals, suggesting that an increment in NO might drive to neurotoxic mechanisms in the cerebellum, inducing long-term alterations in the circuits involved in memory processes [40].

Diet composition during pregnancy is also an influencing factor on the nitric oxide system. Accordingly, recent studies showed that zinc insufficiency during fetal life and lactation induced a decrease in nitric oxide renal activity and an increase in oxidative stress which would contribute to augmented arterial blood pressure and renal dysfunction in adulthood [138]. Moreover, maternal feeding of docosahexaenoic acid (DHA), known to play a critical role in postnatal brain development, significantly prevented prenatal stress-induced impairment of learning and memory and enhanced the expression of nitric oxide synthase [139,140]. Additionally, recent findings from human studies revealed that the levels of global arginine bioavailability, a marker of NO synthetic capacity in vivo, were diminished in veterans with PTSD [141]. The multiple effects of stress exposure on the HPA axis are summarize in Fig. 1.

5. Epigenetic mechanisms

Control of gene expression in mammals, in addition of being modulated by transcriptional and translational initiation, can also be controlled epigenetically. Epigenetics refers to mechanisms in which the environment interacts with the genotype to produce a variety of phenotypes by either modification of chromatin structure or control of mRNA translation without affecting the nucleotide composition of the genome [141]. These epigenetic modifications are stable, yet reversible. DNA methylation, post-translational histone modifications (methylation, phosphorylation, acetylation) and noncoding RNA activity are among the most studied epigenetic mechanisms that regulate gene expression.

Emerging evidences indicate that epigenetic regulation prior to birth can exert a profound influence on the development and functioning of the brain and over many neurodevelopmental syndromes. However, the link between perinatal exposure to stress and altered postnatal behavior is far from being fully understood. Epigenetic information can be transmitted on to subsequent generations through fetal programming, behavioral intervention or germline transmission [142] and stress may influence each of these types of inheritance. Understanding the epigenetic mechanisms involved in stress response regulation could help explain the developmental and transgenerational programming of the HPA axis.

Epigenetic mechanisms have been described to regulate synaptic plasticity in the hippocampus by modulating neurotrophic factors [143,144]. Methylation of exon IV was postulated as a possible mechanism in mediating *bdnf* gene expression during development and is, consequently, predisposed to environmental insults [145]. Moreover, early experiences of maltreatment were shown to cause an increase of *bdnf* DNA methylation at exons IV and IX within the prefrontal cortex of offspring exposed to a stressed-abusive mother [146]. Conversely, decreased DNA methylation in *bdnf* exon IV was found in the hippocampus of adult female offspring of predator odor exposed mothers [147]. A recent paper reports that early life stress affect DNA methylation of the *Crf* gene promoter correlating with CRF mRNA levels in the central amygdala in a learned helplessness paradigm [148].

Several studies have shown that exposure to adverse environment during pregnancy induces differential methylation of genes coding for adhesion molecules and neurotransmitter receptors and decreased expression levels of glutamatergic receptors (PGluR1) and glutamate transporters (glial EAAT2 and neuronal EAAT3) in hippocampus, frontal cortex frontal and striatum [149,150]. Furthermore, changes in the methylation status of the neuronal membrane glycoprotein gene (gpm6a) and an impaired hippocampal neurogenesis have been described in rats subjected to prenatal stress [151–153]. Moreover, McGowan and collaborators demonstrated that variations in maternal care (low licking and grooming) in the rat produce differential methylation of the neuron-specific glucocorticoid receptor NR3C1 promoter, which regulates hippocampal glucocorticoid receptor expression and HPA responses to stress [153]. Similarly, early-life stress in mice was described to cause sustained DNA hypomethylation of an important regulatory region of the arginine vasopressin gene [154–156]. Other studies in human adults showed hypermethylation of the GR promoter in individuals that had experienced childhood trauma [152]. However, this epigenetic mark was not found in individuals with depression but not history of child abuse [156,155,157].

5.1. Epigenetic pharmacology

The fact that epigenetic states might be reversible even in the adult brain has extremely important implications on the potential of pharmacological intervention. Histone deacetylases (HDACs), by removing acetyl groups from histones, can regulate gene expression by making chromatin less accessible to transcription factors [158]. The opposite action is exerted by histone acetyltransferases (HATs). Genetic or pharmacological modulation of HDACs or HATs could account for gene expression regulation. Since histone acetylation is associated with active gene transcription, HDAC inhibition is related to gene up-regulation. In this context, epigenetic pharmacology has brought interest into the development of HDACs modulators [159].

According to structure the HDAC inhibitors (HDACi) can be categorized into different groups, including short- chain fatty acids, hydroxamic acids, epoxyketones, and benzamides [160]. While hydroxamic acid inhibitors like suberanilohydroxamic acid (SAHA; comercial name Vorinostat), that target Class I and II HDACs, have emerged as promising and potent treatments for cancers other HDAC inhibitors have shown great potential for the treatment of neurodegenerative and psychiatric diseases. Several drugs, including valproic acid (VPA), vorinostat, MS-275, sodium butyrate, and phenyl butyrate have been shown to cross the blood-brain barrier making these compounds suitable candidates to be tested in treating brain disorders [159]. Clinical evidences showed that VPA can reduce brain inflammation by inducing microglia apoptosis [161–163] and promote neurotrophin production by astrocytes [164,165] suggesting a potential therapeutic relevance of HDAC inhibitors in CNS pathologies [159]. Accordingly, in a mouse model of Alzheimer's disease (AD), injections of the inhibitors sodium valproate, sodium butyrate, or vorinostat completely restored contextual memory indicating that targeted inhibition of class I HDAC

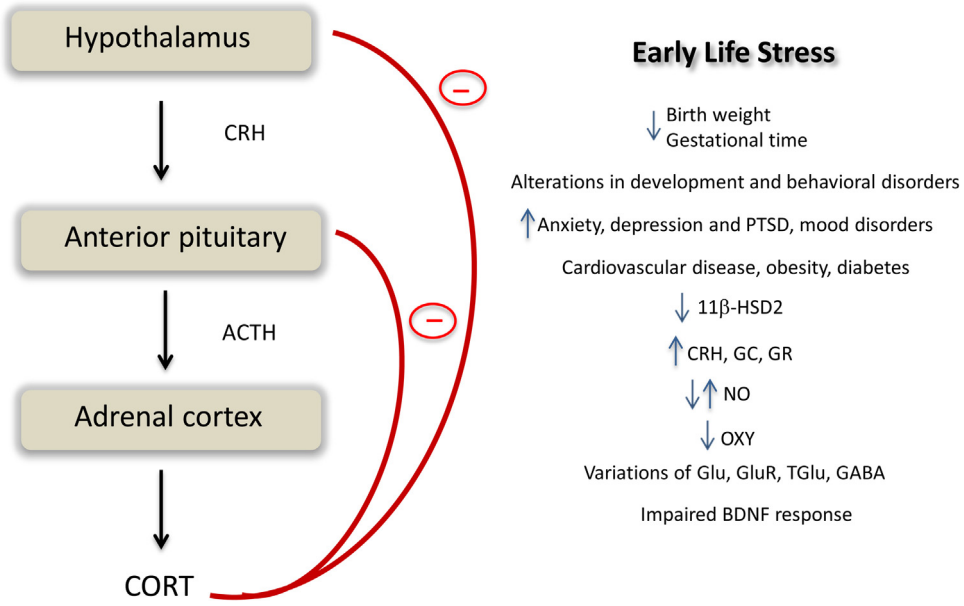

Fig. 1. Effects of stress exposure on the HPA axis activity. Early life adverse events may disrupt the HPA axis response at many levels thus affecting several systems. Alterations in the CNS development and the neurochemical response may contribute to the onset or development of long-last neurobehavioral and neurochemical changes later in life.

isoforms would be promising for treating the cognitive deficits associated with early stage AD [166]. Similarly, in Huntington's disease, a late-onset progressive neurodegenerative disorder, it has been demonstrated that the mutant huntingtin protein enters the nucleus where it binds and inhibits HATs, leading to a decrease in H3 and H4 histone acetylation and causing a global silencing of neuronal genes [167,168]. Hence, drugs proficient in correcting the epigenetic imbalances in these disorders represent auspicious possible treatments for such diseases in the future.

The commonly used HDAC inhibitor valproic acid, usually known for its function as an anticonvulsant mood-stabilizing drug, has been shown to have roles in up-regulation and down-regulation of genes [169,170]. Interestingly, an increasing number of women of reproductive age are taking VPA for the treatment of bipolar disorder [171]; however, significant caution should be taken when prescribed since children exposed to VPA *in utero* exhibit increased risk of congenital spina bifida and neurodevelopmental disorders [172,173] including reduced cognitive function, attention-deficit disorder, learning difficulties, and autistic spectrum disorder [174]. Another HDACi, sodium butyrate, when administered intraperitoneally, alone or in combination with fluoxetine, was shown to have antidepressant-like effects [175–177] and, in high doses appears to act as a pharmacological stressor increasing the peripheral levels of HPA hormones [178]. Similarly, L-acetyl carnitin (LAC), another potent HDAC inhibitor, has been shown to exert a rapid anti-depressant effect through epigenetic modulation of the type 2 glutamate metabotropic receptor (mGlu2) [179].

Since HDAC inhibitors have pleiotropic actions in different cell types, many aspects should be taken into account when considering a pharmacological approach using these molecules. Chronic versus acute treatment, knowledge of the regional brain distribution of individual HDAC enzymes, systemic or region-specific delivery represent some of them. Moreover, since HDACs also deacetylate other non-histone proteins, HDACi may influence several processes, including cell cycle arrest, angiogenesis, immune modulation, and apoptosis [180] disrupting numerous pathways and adding an additional complication to rational drug design.

Identification of the signaling pathways that influence fetal programming is key to harnessing the potential of regulating epigenetic mechanisms to modulate the stress response and becomes essential for the development of more efficient new therapeutic strategies.

6. Discussion

A growing body of evidence points to a tight relationship between perinatal stress exposure and development of short- and long-term health disorders. Stressful events that occur during the perinatal period may have an impact on several aspects of the neuroendocrine programming, subsequently modifying the offspring's growth, metabolism, sexual maturation, stress responses, and immune system ultimately resulting in the development of long-term diseases, such us metabolic syndromes and psychiatric disorders. Deciphering the link between early life adverse events (*in utero* stress exposure, maternal separation, maltreatment) and the behavioral, cognitive, emotional, and physiological reactivity of the progeny has brought a lot of interest in the past decade. However, the mechanisms underlying these processes remain to be fully understood.

The variability in the response to stress depends on both genetic and epigenetic background. Epigenetic mechanisms (DNA methylation, histone modification and microRNA) play a key role in many processes in the nervous system, such as neurodevelopment and neural function, neuroplasticity and memory formation. All these mechanisms are affected by stress. The role of epigenetics in guiding the mechanisms by which the brain adapts to stress is a field of growing interest. The involvement of epigenetics processes that would modulate the onset of psychiatric and neurological disorders manifested later in life but that may partly have developmental origins has extremely important implications on the potential of pharmacological intervention to reverse the effects of early life adversity. However, the lack of specificity of current pharmacological treatments that are unable to target specific genomic sites makes uncertain whether the manipulation of single components of the epigenome will provide successful therapeutic outcomes. Further studies using class and subtype-specific HDAC inhibitors, as well as methylation and phosphorylation modulators, alone and also in combination, are necessary to provide greater specificity of

action and to produce better therapeutic options with reduced side effects.

A better understanding of the mechanisms underlying the stress response and the windows of opportunities during early development would allow to design new drugs and treatments that would modulate epigenetic processes improving or reversing deficits in adult health generating new therapeutic strategies.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the manuscript.

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References

[1] E. Llorente, M.L. Brito, P. Machado, M.C. González, Effect of prenatal stress on the hormonal response to acute and chronic stress and on immune parameters in the offspring, J. Physiol. Biochem. 58 (2002) 143–149.
[2] G. Kay, N. Tarcic, T. Poltyrev, M. Weinstock, Prenatal stress depresses immune function in rats, Physiol. Behav. 63 (1998) 397–402.
[3] C.C. Vanbesien-Mailliot, I. Wolowczuk, J. Mairesse, O. Viltart, M. Delacre, J. Khalife, M.C. Chartier-Harlin, S. Maccari, Prentral stress has pro-inflammatory consequences on the immune system in adult rats, Psychoneuroendocrinology 32 (2007) (2007) 114–124.
[4] S. Maccari, S. Morley-Fletcher, Effects of prenatal restraint stress on the hypothalamus-pituitary-adrenal axis and related behavioural and neurobiological alterations, Psychoneuroendocrinology 32 (Suppl. 1) (2007) S10–15.
[5] Y. Diz-Chaves, M. Astiz, M.J. Bellini, L.M. Garcia-Segura, Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice, Brain Behav. Immun. 28 (2013) 196–206.
[6] B.S. McEwen, P.J. Gianaros, Stress- and allostasis-induced brain plasticity, Annu. Rev. Med. 62 (2011) 431–445.
[7] J.E. Grant, N. Fineberg, M. van Ameringen, D. Cath, H. Visser, L. Carmi, S. Pallanti, E. Hollander, A.J. van Balkom, New treatment models for compulsive disorders, Eur. Neuropsychopharmacol. 15 (2015) 358–362.
[8] J.I. Koenig, B. Kirkpatrick, P. Lee, Glucocorticoid hormones and early brain developmentin schizophrenia, Neuropsychopharmacology 27 (2002) 309–318.
[9] O. Kofman, The role of prenatal stress in the etiology of developmental behavioural disorders, Neurosci. Biobehav. Rev. 26 (2002) 457–470.
[10] M. Weinstock, Does prenatal stress impair coping and regulation of hypothalamic–pituitary–adrenal axis? Neurosci. Biobehav. Rev. 21 (1997) 1–10.
[11] M. Weinstock, Alterations induced by gestational stress in brain morphology and behaviour of the offspring, Prog. Neurobiol. 65 (2001) 427–451.
[12] M. Weinstock, The long-term behavioural consequences of prenatal stress, Neurosci. Biobehav. Rev. 32 (2008) 1073–1086.
[13] S. Maccari, M. Darnaudery, S. Morley-Fletcher, A.R. Zuena, C. Cinque, O. Van Reeth, Prenatal stress and longterm consequences: implications of glucocorticoid hormones, Neurosci. Biobehav. Rev. 27 (2003) 119–127.
[14] M. Darnaudéry, S. Maccari, Epigenetic programming of the stress response in male and female rats by prenatal restraint stress, Brain Res. Rev. 2 (2008) 571–585.
[15] P.D. Gluckman, M.A. Hanson, C. Cooper, K.L. Thornburg, Effect of in utero and early-life conditions on adult health and disease, N. Engl. J. Med. 3 (2008) 61–73.
[16] T.Y. Zhang, M.J. Meaney, Epigenetics and the environmental regulation of the genome and its function, Annu. Rev. Psychol. 61 (2010) 439–466.
[17] A.C. Foster, R. Gill, J.A. Kemp, G.N. Woodruff, Systemic administration of MK-801 prevents *N*-methyl-D-aspartate-induced neuronal degeneration in rat brain, Neurosci. Lett. 76 (1987) 307–311.
[18] S.J. Lupien, B.S. McEwen, M.R. Gunnar, C. Heim, Effects of stress throughout the lifespan on the brain, behaviour and cognition, Nat. Rev. Neurosci. 10 (2009) 434–445.
[19] R.C. Kessler, S. Avenevoli, K. RiesMerikangas, Mood disorders in children and adolescents: an epidemiologic perspective, Biol. Psychiatry 49 (2001) 1002–1014.
[20] M. King, P. Bearman, Diagnostic change and the increased prevalence of autism, Int. J. Epidemiol. 38 (2009) 1224–1234.
[21] R.M. Sapolsky, L.M. Romero, A.U. Munck, How do glucocorticoids influence stress responses? Integrating permissive suppressive, stimulatory and preparative actions, Endocr. Rev. 21 (2000) 55–89.
[22] E. Charmandari, C. Tsigos, G. Chrousos, Endocrinology of the stress response, Annu. Rev. Physiol. 67 (2005) 259–284.
[23] C.M. Bamberger, H.M. Schulte, G.P. Chrousos, Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids, Endocr. Rev. 17 (1996) 245–261.
[24] S.M. Smith, W.W. Vale, The role of the hypothalamic–pituitary–adrenal axis in neuroendocrine responses to stress, Dialogues Clin. Neurosci. 8 (2006) 383–395.
[25] P.E. Sawchenko, Evidence for a local site of action for glucocorticoids in inhibiting CRF and vasopressin expression in the paraventricular nucleus, Brain Res. 437 (1987) 253–263.
[26] L. Jacobson, R. Sapolsky, The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis, Endocr. Rev. 12 (1991) 118–134.
[27] S. Deppermann, H. Storchak, A.J. Fallgatter, A.-C. EhliS, Stress-induced neuroplasticity: (mal)adaptation to adverse life events in patients with PTSD—a critical overview, Neuroscience 283 (2014) 166–177.
[28] A. Ratka, W. Sutanto, M. Bloemers, E.R. de Kloet, On the role of brain mineralocorticoid (type I) and glucocorticoid (type II) receptors in neuroendocrine regulation, Neuroendocrinology 50 (1989) 117–123.
[29] L. Arborelius, M.J. Owens, P.M. Plotsky, C.B. Nemeroff, The role of corticotropin-releasing factor in depression and anxiety disorders, J. Endocrinol. 160 (1999) 1–12.
[30] M.N. de Lima, J. Presti-Torres, G. Vedana, L.A. Alcalde, L. Stertz, G.R. Fries, R. Roesler, M.L. Andersen, J. Quevedo, F. Kapczinski, N. Schröder, Early life stress decreases hippocampal BDNF content and exacerbates recognition memory deficits induced by repeated D-amphetamine exposure, Behav. Brain Res. 224 (2011) 100–106.
[31] P. Smirnaki, M.A. Magiakou, Pregnancy- maternal and perinatal stress-effects of. (2007) Encyclopedia of Stress, George Fink, 2 da ed., vol. 3: 165-73.
[32] B.E. Lee, M. Ha, H. Park, Y.C. Hong, Y. Kim, Y.J. Kim, E.H. Ha, Psychosocial work stress during pregnancy and birth weight, Paediatr. Perinat. Epidemiol. 25 (2011) 246–254.
[33] S. Maccari, M. Vallée, V. Mayo, M. Le Moal, Prenatal stress during pregnancy and metabolic consequences in adult rats, Arch. Pediatr. 4 (2 Suppl. (2)) (1997) 138s–140s.
[34] M. Vallée, W. Mayo, F. Dellu, M. Le Moal, H. Simon, S. Maccari, Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion, J. Neurosci. 17 (1997) 2626–2636.
[35] A.R. Zuena, J. Mairesse, P. Casolini, C. Cinque, G.S. Alemà, S. Morley-Fletcher, V. Chiodi, L.G. Spagnoli, R. Gradini, A. Catalani, F. Nicoletti, S. Maccari, Prenatal restraint stress generates two distinct behavioral and neurochemical profiles in male and female rats, PLoS One 3 (2008) e2170.
[36] R. Ruiz, C. Avant, Effects of maternal prenatal stress on infant outcomes, ANS Adv. Nurs. Sci. 28 (2005) 345–355.
[37] B.R. Mueller, T.L. Bale, Impact of prenatal stress on long term body weight is dependent on timing and maternal sensitivity, Physiol. Behav. 88 (2006) 605–614.
[38] D.L. Van den Hove, H. Steinbusch, A. Scheepens, B.W. Vande, L. Kooiman, B. Boosten, J. Prickaerts, C. Blanco, Prenatal stress and neonatal rat brain development, Dev. Neurosci. 27 (2005) 313–320.
[39] J. Wu, T.B. Song, Y.J. Li, H.S. He, L. Ge, L.R. Wang, Prenatal restraint stress impairs learning and memory and hippocampal PKCbeta1 expression and translocation in offspring rats, Brain Res. 13 (2007) 205–213.
[40] D.G. Maur, C.B. Romero, B. Burdet, M.L. Palumbo, M.A. Zorrilla-Zubilete, Prenatal stress induces alterations in cerebellar nitric oxide that are correlated with deficits in spatial memory in rat's offspring, Neurochem. Int. 61 (2012) 1294–1301.
[41] V. Patin, B. Lordi, A. Vincent, J. Caston, Effects of prenatal stress on anxiety and social inter-actions in adult rats, Brain Res. Dev. Brain Res. 160 (2005) 265–274.
[42] S. Maccari, H.J. Krugers, S. Morley-Fletcher, M. Szyf, P.J. Brunton, The consequences of early-life adversity: neurobiological: behavioural and epigenetic adaptations, J. Neuroendocrinol. 26 (2014) 707–723.
[43] M. Solinas, N. Thiriet, R. El Rawas, V. Lardeux, M. Jaber, Environmental enrichment during early stages of life reduces the behavioral, neurochemical, and molecular effects of cocaine, Neuropsychopharmacology 34 (2009) 1102–1111.
[44] M.J. Eckert, W.C. Abraham, Effects of environmental enrichment exposure on synaptic transmission and plasticity in the hippocampus, Curr. Top. Behav. Neurosci. 15 (2013) 165–187.
[45] T.R. Guilarte, C.D. Toscano, J.L. Mcglothan, S.A. Weaver, Environmental enrichment reverses cognitive and molecular deficits induced by developmental lead exposure, Ann. Neurol. 53 (2003) 50–56.
[46] P. Chapillon, V. Patin, V. Roy, A. Vincent, J. Caston, Effects of pre- and postnatal stimulation on developmental, emotional, and cognitive aspects in rodents: a review, Dev. Psychobiol. 41 (2002) 373–387.

[47] V. Lemaire, S. Lamarque, M. Le Moal, P.V. Piazza, D.N. Abrous, Postnatal stimulation of the pups counteracts prenatal stressinduced deficits in hippocampal neurogenesis, Biol. Psychiatry 59 (2006) 786–792.
[48] K.J. O'Donnell, V. Glover, J.D. Holbrook, T.G. O'Connor, Maternal prenatal anxiety and child brain-derived neurotrophic factor (BDNF) genotype: effects on internalizing symptoms from 4 to 15 years of age, Dev. Psychopathol. 26 (2014) 1255–1266.
[49] J. Lehmann, C.R. Pryce, A.L. Jongen-Relo, T. Stohr, H.H. Pothuizen, J. Feldon, Comparison of maternal separation and early handlingin terms of their neurobehavioral effects in aged rats, Neurobiol. Aging 23 (2002) 457–466.
[50] S. Levine, J.A. Chevalier, S.J. Korchin, The effects of early shock andhandling on later avoidance learning, J. Pers. 24 (1956) 475–493.
[51] F.S. Hall, Social deprivation of neonatal adolescent, and adult rats hasdistinct neurochemical and behavioral consequences, Crit. Rev. Neurobiol. 12 (1998) 129–162.
[52] E. Roman, L. Gustafsson, M. Berg, I. Nylander, Behavioral profiles and stress-induced corticosteroid secretion in male Wistar rats subjected to short and prolonged periods of maternal separation, Horm. Behav. 50 (2006) 736–747.
[53] A. Anisman, K. Matheson, Stress, depression, and anhedonia: caveats concerning animal models, Neurosci. Biobehav. Rev. 29 (2005) 525–546.
[54] C. Heim, G. Meinlschmidt, C.B. Nemeroff, Neurobiology of early-life stress, Psych. Ann. 33 (2003) 1–10.
[55] R. Gilbert, A. Kemp, J. Thoburn, P. Sidebotham, L. Radford, D. Glaser, H.L. Macmillan, Recognising and responding to child maltreatment, Lancet 373 (2009) 167–180.
[56] E. McCrory, S.A. De Brito, E. Viding, The impact of childhood maltreatment: a review of neurobiological and genetic factors, Front. Psychiatry 2 (2011) 48.
[57] R.F. Anda, V.J. Felitti, J.D. Bremner, J.D. Walker, C. Whitfield, B.D. Perry, S.R. Dube, W.H. Giles, The enduring effects of abuse and related adverse experiences in childhood, Eur. Arch. Psychiat. Clin. Neurosci. 256 (2006) 174–186.
[58] V.J. Felitti, R.F. Anda, D. Nordenberg, D.F. Williamson, A.M. Spitz, V. Edwards, M.P. Koss, J.S. Marks, Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study, Am. J. Prev. Med. 14 (1998) 245–258.
[59] C. Heim, C.B. Nemeroff, The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies, Biol. Psychiatry 49 (2001) 1023–1039.
[60] C. Heim, T. Mletzko, D. Purselle, D.L. Musselman, C.B. Nemeroff, The dexamethasone/corticotropinreleasing factor test in men with major depression: role of childhood trauma, Biol. Psychiatry 63 (2008) 398–405.
[61] C. Heim, P.M. Plotsky, C.B. Nemeroff, Importance of studying the contributions of early adverse experience to neurobiological findings in depression, Neuropsychopharmacology 29 (2004) 641–648.
[62] J.W. Jahng, An animal model of eating disorders associated with stressful experience in early life, Horm. Behav. 59 (2011) 213–220.
[63] D.A. Gutman, C.B. Nemeroff, Neurobiology of early life stress: rodent studies, Semin. Clin. Neuropsychiatry 7 (2002) 89–95.
[64] R. Benediktsson, A.A. Calder, C.R. Edwards, J.R. Seckl, Placental 11 beta-hy-droxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure, Clin. Endocrinol. (Oxf.) 46 (1997) 161–166.
[65] L.A. Welberg, L.V. Thrivikraman, P.M. Plotsky, Chronic maternal stress inhibits the capacity to up-regulate placental 11 beta-hydroxysteroid dehydrogenase type 2 activity, J. Endocrinol. 186 (2005) R7–R12.
[66] J. Mairesse, J. Lesage, C. Breton, B. Breant, T. Hahn, M. Darnaudery, S.L. Dickson, J. Seckl, B. Blondeau, D. Vieau, S. Maccari, O. Viltart, Maternal stress alters endocrine function of the feto-placental unit in rats, Am. J. Physiol. Endocrinol. Metab. 292 (2007) E1526–E1533.
[67] P.J. Brunton, J.A. Russell, A.J. Douglas, Adaptive responses of the maternal hypothalamic–pituitary–adrenal axis during pregnancy and lactation, J. Neuroendocrinol. 20 (2008) 764–776.
[68] A. Barbazanges, P.V. Piazza, M. Le Moal, S. Maccari, Maternal glucocorticoid secretion mediates long-term effects of prenatal stress, J. Neurosci. 16 (1996) 3943–3949.
[69] L.A. Welberg, J.R. Seckl, M.C. Holmes, Inhibition of 11beta-hydroxysteroid dehydrogenase, the foeto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring, Eur. J. Neurosci. 12 (2000) 1047–1054.
[70] F. Fumagalli, R. Molteni, G. Racagni, M.A. Riva, Stress during development: impact on neuroplasticity and relevance to psychopathology, Prog. Neurobiol. 81 (2007) 197–217.
[71] C.A. Sandman, P.D. Wadhwa, A. Chicz-Demet, C. Dunkel-Schetter, M. Porto, Maternal stress, HPA activity, and fetal/infant outcome, Ann. N. Y. Acad. Sci. 814 (1997) 266–275.
[72] B.G. Robinson, R.L. Emanuel, D.M. Frim, J.A. Majzoub, Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 5244–5248.
[73] T. Fujioka, Y. Sakata, K. Yamaguchi, T. Shibasaki, H. Kato, S. Nakamura, The effects of prenatal stress on the development of hypothalamic paraventricular neurons in fetal rats, Neuroscience 92 (1999) 1079–1088.
[74] R.L. Huot, M.E. Gonzalez, C.O. Ladd, K.V. Thrivikraman, P.M. Plotsky, Foster litters prevent hypothalamic–pituitary–adrenal axis sensitization mediated by neonatal maternal separation, Psychoneuroendocrinology 29 (2004) 279–289.
[75] E. Kitraki, O. Kremmyda, D. Youlatos, M.N. Alexis, C. Kittas, Gender-dependent alterations in corticosteroid receptor status and spatial performance following 21 days of restraint stress, Neuroscience 125 (2004) 47–55.
[76] W. Sutanto, P. Rosenfeld, E.R. de Kloet, S. Levine, Long term effects of neonatal maternal deprivation and ACTH on hippocampal mineralocorticoid and glucocorticoid receptors, Brain Res. Dev. Brain Res. 92 (1996) 156–163.
[77] R.M. Vázquez, H. Van Oers, S. Levine, H. Akil, Regulation of glucocorticoid and mineralocorticoid receptor mRNAs in the hippocampus of the maternally deprived infant rat, Brain Res. 731 (1996) 79–90.
[78] M.J. Meaney, S. Bhatnagar, J. Diorio, S. Larocque, D. Francis, D. O'Donnell, N. Shanks, S. Sharma, J. Smythe, V. Viau, Molecular basis for the development of individual differences in the hypothalamic–pituitary–adrenal stress response, Cell Mol. Neurobiol. (1993).
[79] A. Kapoor, S.G. Matthews, Prenatal stress modifies behavior and hypothalamic–pituitary–adrenal function in female guinea pig offspring: effects of timing of prenatal stress and stage of reproductive cycle, Endocrinology 149 (2008) 6406–6415.
[80] S. Maccari, P.V. Piazza, M. Kabbaj, A. Barbazanges, H. Simon, M. Le Moal, Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress, J. Neurosci. 15 (1995) 110–116.
[81] A.J. Grippo, T.G. Beltz, R.M. Weiss, A.K. Johnson, The effects of chronic fluoxetine treatment on chronic mild stress induced cardiovascular changes and anhedonia, Biol. Psychiatry 59 (2006) 309–316.
[82] T. Nishioka, J.A. Anselmo-Franci, P. Li, M.F. Callahan, M. Morris, Stress increases oxytocin release within thehypothalamicparaventricular nucleus, Brain Res. 781 (1998) 56–60.
[83] S.E. Taylor, G.C. Gonzaga, L.C. Klein, P. Hu, G.A. Greendale, T.E. Seeman, Relation of oxytocin to psychological stress responses and hypothalamic–pituitary–adrenocortical axis activity in older women, Psychosom. Med. 68 (2006) 238–245.
[84] R.J. Windle, Y.M. Kershaw, N. Shanks, S.A. Wood, S.L. Lightman, C.D. Ingram, Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity, J. Neurosci. 24 (2004) 2974–2982.
[85] R.J. Windle, L.E. Gamble, Y.M. Kershaw, S.A. Wood, S.L. Lightman, C.D. Ingram, Gonadal steroid modulation of stress-induced hypothalamo-pituitary-adrenal activity and anxiety behavior: role of central oxytocin, Endocrinology 147 (2006) 2423–2431.
[86] D.A. Slattery, I.D. Neumann, Chronic icv oxytocin attenuates the pathological high anxiety state of selectively bred Wistar rats, Neuropharmacology 58 (2010) 56–61.
[87] M. Lukas, I. Toth, S.O. Reber, D.A. Slattery, A.H. Veenema, I.D. Neumann, The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice, Neuropsychopharmacology 36 (2011) 2159–2168.
[88] M. Heinrichs, T. Baumgartner, C. Kirschbaum, U. Ehlert, Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress, Biol. Psychiatry 54 (2003) 1389–1398.
[89] B. Ditzen, M. Schaer, B. Gabriel, G. Bodenmann, U. Ehlert, M. Heinrichs, Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict, Biol. Psychiatry 65 (2009) 728–731.
[90] M. Quirin, J. Kuhl, R. Dusing, Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities, Psychoneuroendocrinology 36 (2011) 898–904.
[91] A.M. Linnen, M.A. Ellenbogen, C. Cardoso, R. Joober, R, Intranasal oxytocin and salivary cortisol concentrations during social rejection in university students, Stress 15 (2012) 393–402.
[92] I. Liberzon, E.A. Young, Effects of stress and glucocorticoids on CNS oxytocin receptor binding, Psychoneuroendocrinology 22 (1997) 411–422.
[93] S. Korsching, The neurotrophic factor concept: a reexamination, J. Neurosci. 13 (1993) 2739–2748.
[94] S. Mayeur, M.A. Lukaszewski, C. Breton, L. Storme, C. Junien, D. Vieau, J. Lesage, BDNF in feto-placental development, Med. Sci. (Paris) 27 (2011) 251–252.
[95] K. Kawamura, N. Kawamura, W. Sato, J. Fukuda, J. Kumagai, T. Tanaka, Brain-derivedneurotrophic factor promotes implantation and subsequent placental development by stimulating trophoblast cell growth and survival, Endocrinology 150 (2009) 3774–3782.
[96] K. Kawamura, N. Kawamura, Y. Kumazawa, J. Kumagai, T. Fujimoto, T. Tanaka, Brain-derived neurotrophic factor/tyrosine kinase B signaling regulates human trophoblast growth in an in vivo animal model of ectopic pregnancy, Endocrinology 152 (2011) 1090–1100.
[97] I. Kodomari, E. Wada, S. Nakamura, K. Wada, Maternal supply of BDNF to mouse fetal brain through the placenta, Neurochem. Int. 54 (2009) 95–98.
[98] K. Hashimoto, H. Koizumi, M. Nakazato, E. Shimizu, M. Iyo, Role of brain-derived neurotrophic factor in eating disorders: recent findings and its pathophysiological implications, Prog. Neuropsychopharmacol. Biol. Psychiatry 29 (2005) 499–504.
[99] T. Numakawa, E. Kumamaru, N. Adachi, Y. Yagasaki, A. Izumi, H. Kunugi, Glucocorticoid receptor interaction with TrkB promotes BDNF-triggered PLC-gamma signaling for glutamate release via a glutamate transporter, Proc. Natl. Acad. Sci. U. S. A. 106 (2010) 647–652.
[100] C.T. Correia, A.M. Coutinho, A.F. Sequeira, I.G. Sousa, L.L.O. Venda, J.P. Almeida, R.L. Abreu, C. Lobo, T.S. Miguel, J. Conroy, L. Cochrane, L. Gallagher, M. Gill, S. Ennis, G.G. Oliveira, A.M. Vicente, Increased BDNF levels and

NTRK2 gene association suggest a disruption of BDNF/TrkB signaling in autism, Genes Brain Behav. 9 (2010) 841–848.
[101] P.F. Buckley, S. Mahadik, A. Pillai, A. JrTerry, Neurotrophins and schizophrenia, Schizophr. Res. 94 (2007) 1–11.
[102] F. Angelucci, S. Brene, A.A. Mathe, BDNF in schizophrenia, depression and corresponding animal models, Mol. Psychiatry 10 (2005) 345–352.
[103] B.L. Hempstead, Dissecting the diverse actions of pro- and mature neurotrophins, Curr. Alzheimer Res. 3 (2006) 19–24.
[104] L.F. Reichardt, Neurotrophin-regulated signalling pathways, Philos. Trans. R. Soc. Lond. B Biol. Sci. 361 (2006) 1545–1546.
[105] D.K. Binder, H.E. Scharfman, Brain-derived neurotrophic factor, Growth Factors 22 (2004) 123–131.
[106] M. Bibel, Y.A. Barde, Neurotrophins: key regulators of cell fate and cell shape in the vertebrate nervous system, Genes Dev. 14 (2000) 2919–2937.
[107] S. Pezet, S.B. McMahon, Neurotrophins: mediators and modulators of pain, Annu. Rev. Neurosci. 29 (2006) 507–538.
[108] C. Pittenger, R.S. Duman, Stress, depression, and neuroplasticity: a convergence of mechanisms, Neuropsychopharmacology 33 (2008) 88–109.
[109] A.F. Schinder, M. Poo, The neurotrophin hypothesis for synaptic plasticity, Trends Neurosci. 23 (2000) 639–645.
[110] H.D. Schmidt, R.C. Shelton, R.S. Duman, Functional biomarkers of depression: diagnosis, treatment, and pathophysiology, Neuropsychopharmacology 36 (2011) 2375–2394.
[111] J.D. Bremner, M. Vythilingam, E. Vermetten, S.M. Southwick, T. McGlashan, A. Nazeer, S. Khan, L.V. Vaccarino, R. Soufer, P.K. Garg, C.K. Ng, L.H. Staib, J.S. Duncan, D.S. Charney, MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder, Am. J. Psychiatry 160 (2003) 924–932.
[112] R. Grassi-Oliveira, L.M. Stein, R.P. Lopes, A.L. Teixeira, M.E. Bauer, Low plasma brain-derived neurotrophic factor and childhood physical neglect are associated with verbal memory impairment in major depression–a preliminary report, Biol. Psychiatry 64 (2008) 281–285.
[113] Q. Wang, F. Shao, W. Wang, Maternal separation produces alterations of forebrain brain-derived neurotrophic factor expression in differently aged rats, Front. Mol. Neurosci. 8 (2015) 49.
[114] D. Liu, J. Diorio, J.C. Day, D.D. Francis, M.J. Meaney, Maternal care, hippocampal synaptogenesis and cognitive development in rats, Nat. Neurosci. 3 (2000) 799–806.
[115] Z.Y. Chen, D. Jing, K.G. Bath, A. Ieraci, T. Khan, C.J. Siao, D.G. Herrera, M. Toth, C. Yang, B.S. McEwen, B.L. Hempstead, F.S. Lee, Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior, Science 314 (2006) 140–143.
[116] S. Murakami, H. Imbe, Y. Morikawa, C. Kubo, E. Senba, Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly, Neurosci. Res. 53 (2005) 129–139.
[117] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell 112 (2003) 257–269.
[118] V.G. Barros, M.A. Berger, I.D. Martijena, M.I. Sarchi, A.A. Perez, V.A. Molina, F.I. Tarazi, M.C. Antonelli, Early adoption modifies the effects of prenatal stress on dopamine and glutamate receptors in adult rat brain, J. Neurosci. Res. 76 (2004) 488–496.
[119] C.H. Vinkers, R.S. Oosting, M.J. van Bogaert, B. Olivier, L. Groenink, Early-life blockade of 5-HT(1A) receptors alters adult anxiety behavior and benzodiazepine sensitivity, Biol. Psychiatry 67 (2010) 309–316.
[120] M. Popoli, Z. Yan, B.S. McEwen, G. Sanacora, The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission, Nat. Rev. Neurosci. 13 (2013) 22–37.
[121] C.J. Huppertz-Kessler, J. Poeschl, R. Hertel, K. Unsicker, J. Schenkel, Effects of a new postnatal stress model on monoaminergic neurotransmitters in rat brains, Brain Dev. 34 (2012) 274–279.
[122] V. Lemaire, M. Koehl, M. Le Moal, D.N. Abrous, Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 11032–11037.
[123] G.H. Son, D. Geum, S. Chung, E.J. Kim, J.H. Jo, C.M. Kim, K.H. Lee, H. Kim, S. Choi, H.T. Kim, C.J. Lee, K. Kim, Maternal stress produces learning deficits associated with impairment of NMDA receptor-mediated synaptic plasticity, J. Neurosci. 26 (2006) 3309–3318.
[124] E. Fride, Y. Dan, M. Gavish, M. Weinstock, Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors, Life Sci. 36 (1985) 2103–2109.
[125] D.L. Van den Hove, H.W. Steinbusch, A. Scheepens, W.D. Van de Berg, L.A. Kooiman, B.J. Boosten, J. Prickaerts, C.E. Blanco, Prenatal stress and neonatal rat brain development, Neuroscience 137 (2006) 145–155.
[126] L.P. Chandravanshi, R.S. Yadav, R.K. Shukla, A. Singh, A. Sultana, A.B. Pant, D. Parmar, V.K. Khanna, Reversibility of changes in brain cholinergic receptors and acetylcholinesterase activity in rats following early life arsenic exposure, Int. J. Dev. Neurosci. 34 (2014) 60–75.
[127] P. Huttunen, Microdialysis of extracellular noradrenaline in the hippocampus of the rat after long-term alcohol intake, Brain Res. 560 (1991) 225–228.
[128] R.E. Bowman, N.J. MacLusky, Y. Sarmiento, M. Frankfurt, M. Gordon, V.N. Luine, Sexually dimorphic effects of prenatal stress on cognition, hormonal responses, and central neurotransmitters, Endocrinology 145 (2004) 3778–3787.
[129] Y. Wang, Y. Ma, J. Hu, W. Cheng, H. Jiang, X. Zhang, M. Li, J. Ren, X. Li, Prenatal chronic mild stress induces depression-like behavior and sex-specific changes in regional glutamate receptor expression patterns in adult rats, Neuroscience 301 (2015) 363–374.
[130] E. Adrover, M.E. Pallarés, C.J. Baier, M.C. Monteleone, F.A. Giuliani, H.S. Waagepetersen, M.A. Brocco, R. Cabrera, U. Sonnewald, A. Schousboe, M.C. Antonelli, Glutamate neurotransmission is affected in prenatally stressed offspring, Neurochem. Int. 88 (2015) 73–87.
[131] M.M. Odeon, M. Andreu, L. Yamauchi, M. Grosman, G.B. Acosta, Chronic postnatal stress induces voluntary alcohol intake and modifies glutamate transporters in adolescent rats, Stresss 18 (2015) 427–434.
[132] T. Uchida, T. Furukawa, S. Iwata, Y. Yanagawa, A. Fukuda, Selective loss of parvalbumin-positiveGABAergic interneurons in the cerebral cortex of maternally stressed Gad1-heterozygousmouse offspring, Transl. Psychiatry 4 (2014) e371.
[133] S. Giovanoli, L. Weber, U. Meyer, Single and combined effects of prenatal immune activationand peripubertal stress on parvalbumin and reelin expression in the hippocampal formation, Brain Behav. Immun. 40 (2014) 48–54.
[134] M.M. Odeon, A.E. Salatino, G.B. Acosta, Consequences of early adverse life events on GABAergic neurons produce long term changes in brain function, Trends Comp. Biochem. Physiol. 15 (2011) 67–72.
[135] J.P. Kiss, E.S. Vizi, Nitric oxide: a novel link between synaptic and nonsynaptic transmission, Trends Neurosci. 24 (2001) 211–215.
[136] R.D. Hawkins, H. Son, O. Arancio, Nitric oxide as a retrograde messenger during long-term potentiation in hippocampus, Prog. Brain Res. 118 (1998) 155–172.
[137] V. Lev-Ram, T. Jiang, J. Wood, D.S. Lawrence, R.Y. Tsien, Synergies and coincidence requirements between NO, cGMP, and Ca^{2+} in the induction of cerebellar long-term depression, Neuron 18 (1997) 1025–1038.
[138] A.L. Tomat, L.C. Veiras, S. Aguirre, H. Fasoli, R. Elesgaray, C. Caniffi, M.A. Costa, C.T. Arranz, Mild zinc deficiency in male and female rats: early postnatal alterations in renal nitric oxide system and morphology, Nutrition 29 (2013) 568–573.
[139] Z. Feng, X. Zou, H. Jia, X. Li, Z. Zhu, X. Liu, P. Bucheli, O. Ballevre, Y. Hou, W. Zhang, J. Wang, Y. Chen, J. Liu, Maternal docosahexaenoic acid feeding protects against impairment of learning and memory and oxidative stress in prenatally stressed rats: possible role of neuronal mitochondria metabolism, Antioxid. Redox Signal. 16 (2012) 275–289.
[140] F.S. Bersani, O.M. Wolkowitz, D. Lindqvist, R. Yehuda, J. Flory, L.M. Bierer, I. Makotine, D. Abu-Amara, M. Coy, V.I. Reus, E.S. Epel, C. Marmar, S.H. Mellon, Global arginine bioavailability a marker of nitric oxide synthetic capacity, is decreased in PTSD and correlated with symptom severity and markers of inflammation, Brain Behav. Immun. 1591 (2015) 30041–30046.
[141] A. Bird, Perceptions of epigenetics, Nature 447 (2007) 396–398.
[142] J. Bohacek, I.M. Mansuy, Epigenetic inheritance of disease and disease risk, Neuropsychopharmacology 38 (2013) 220–236.
[143] J.M. Levenson, K.J. O'Riordan, K.D. Brown, M.A. Trinh, D.L. Molfese, J.D. Sweatt, Regulation of histone acetylation during memory formation in the hippocampus, J. Biol. Chem. 279 (2004) 40545–40559.
[144] I. Branchi, N. Francia, E. Alleva, Epigenetic control of neurobehavioural plasticity: the role of neurotrophins, Behav. Pharmacol. 15 (2004) 353–362.
[145] K.E. Dennis, P. Levitt, Regional expression of brain derived neurotrophic factor (BDNF) is correlated with dynamic patterns of promoter methylation in the developing mouse forebrain, Brain Res. Mol. Brain Res. 140 (2005) 1–9.
[146] T.L. Roth, F.D. Lubin, A.J. Funk, J.D. Sweatt, Lasting epigenetic influence of early-life adversity on the BDNF gene, Biol. Psychiatry 65 (2009) 760–769.
[147] S. St Cyr, P.O. MacGowan, Programming of stress-related behavior and epigenetic neural gene regulation in mice offspring through maternal exposure to predator odor, Front. Behav. Neurosci. 9 (2015) 145.
[148] R.H. van der Doelen, I.A. Arnoldussen, H. Ghareh, L. van Och, J.R. Homberg, T. Kozicz, Early life adversity and serotonin transporter gene variation interact to affect DNA methylation of the corticotropin-releasing factor gene promoter region in the adult rat brain, Dev. Psychopathol. 27 (2015) 123–135.
[149] J.E. Oh, N. Chambwe, S. Klein, J. Gal, S. Andrews, G. Gleason, R. Shaknovich, A. Melnick, F. Campagne, M. Toth, Differential gene body methylation and reduced expression of cell adhesion and neurotransmitter receptor genes in adverse maternal environment, Transl. Psychiatry (2013) 3.
[150] X.H. Zhang, N. Jia, X.Y. Zhao, G.K. Tang, L.X. Guan, D. Wang, H.L. Sun, H. Li, Z.L. Zhu, Involvement of pGluR1, EAAT2 and EAAT3 in offspring depression induced by prenatal stress, Neuroscience 250 (2013) 333–341.
[151] M.C. Monteleone, E. Adrover, M.E. Pallarés, M.C. Antonelli, A.C. Frasch, M.A. Brocco, Prenatal stress changes the glycoprotein GPM6A gene expression and induces epigenetic changes in rat offspring brain, Epigenetics 19 (2013) 152–160.
[152] L. Belnoue, N. Grosjean, E. Ladevèze, D.N. Abrous, M. Koehl, Prenatal stress inhibits hippocampal neurogenesis but spares olfactory bulb neurogenesis, PLoS One 8 (2013) e72972.
[153] P.O. McGowan, A. Sasaki, A.C. D'Alessio, S. Dymov, B. Labonté, M. Szyf, G. Turecki, M.J. Meaney, Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse, Nat.Neurosci. 12 (2009) 342–348.

[154] C. Murgatroyd, A.V. Patchev, Y. Wu, V. Micale, Y. Bockmuhl, D. Fischer, F. Holsboer, C.T. Wotjak, O.F. Almeida, D. Spengler, Dynamic DNA methylation programs persistent adverse effects of early-life stress, Nat. Neurosci. 12 (2009) 1559–1566.
[155] A.R. Tyrka, J.K. Lee, J.A. Graber, A.M. Clement, M.M. Kelly, L. DeRose, M.P. Warren, J. Brooks-Gunn, Neuroendocrine predictors of emotional and behavioral adjustment in boys: longitudinal follow-up of a community sample, Psychoneuroendocrinology 37 (2012) 2042–2046.
[156] S.R. Alt, J.D. Turner, M.D. Klok, O.C. Meijer, E.A. Lakke, R.H. Derijk, C.P. Muller, Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed, Psychoneuroendocrinology 35 (2010) 544–556.
[157] B. Labonte, M. Suderman, G. Maussion, L. Navaro, V. Yerko, I. Mahar, A. Bureau, N. Mechawar, M. Szyf, M.J. Meaney, G. Turecki, Genome-wide epigenetic regulation by early-life trauma, Arch. Gen. Psychiatry 69 (2012) 722–731.
[158] W.S. Xu, R.B. Parmigiani, P.A. Marks, Histone deacetylase inhibitors: molecular mechanisms of action, Oncogene 26 (2007) 5541–5552.
[159] A.G. Kazantsev, L.M. Thompson, Therapeutic application of histone deacetylase inhibitors for central nervous system disorders, Nat. Rev. Drug Discov. 7 (2008) 854–868.
[160] M. Dokmanovic, C. Clarke, P.A. Marks, Histone deacetylase inhibitors: overview and perspectives, Mol. Cancer Res. 5 (2007) 981–989.
[161] M. Dragunow, J.M. Greenwood, R.E. Cameron, P.J. Narayan, S.J. O'Carroll, A.G. Pearson, H.M. Gibbons, Valproic acid induces caspase 3-mediated apoptosis in microglial cells, Neuroscience 140 (2006) 1149–1156.
[162] P.S. Chen, C.C. Wang, C.D. Bortner, G.S. Peng, X. Wu, H. Pang, R.B. Lu, P.W. Gean, D.M. Chuang, J.S. Hong, Valproic acid and other histone deacetylase inhibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity, Neuroscience 149 (2007) 203–212.
[163] H.J. Kim, M. Rowe, M. Ren, J.S. Hong, P.S. Chen, D.M. Chuang, Histone deacetylase inhibitors exhibit anti-inflammatory and neuroprotective effects in a rat permanent ischemic model of stroke: multiple mechanisms of action, J. Pharmacol. Exp. Ther. 321 (2007) 892–901.
[164] P.S. Chen, G.S. Peng, G. Li, S. Yang, X. Wu, C.C. Wang, B. Wilson, R.B. Lu, P.W. Gean, D.M. Chuang, J.S. Hong, Valproate protects dopaminergic neurons in midbrain neuron/glia cultures by stimulating the release of neurotrophic factors from astrocytes, Mol. Psychiatry 11 (2006) 1116–11125.
[165] X. Wu, P.S. Chen, S. Dallas, B. Wilson, M.L. Block, C.C. Wang, H. Kinyamu, N. Lu, X. Gao, Y. Leng, D.M. Chuang, W. Zhang, R.B. Lu, J.S. Hong, Histone deacetylase inhibitors up-regulate astrocyte GDNF and BDNF gene transcription and protect dopaminergic neurons, Int. J. Neuropsychopharmacol. 11 (2008) 1123–1134.
[166] M. Kilgore, C.A. Miller, D.M. Fass, K.M. Hennig, S.J. Haggarty, J.D. Sweatt, G. Rumbaugh, Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease, Neuropsychopharmacology 35 (2010) 870–880.
[167] S.Y. Cong, B.A. Pepers, B.O. Evert, D.C. Rubinsztein, R.A. Roos, G.J. van Ommen, J.C. Dorsman, Mutant huntingtin represses CBP but not p300, by binding and protein degradation, Mol. Cell Neurosci. 30 (2005) 12–23.
[168] R.N. Saha, K. Pahan, HATs and HDACs in neurodegeneration: a tale of disconcerted acetylation homeostasis, Cell Death Differ. 13 (2005) 539–550.
[169] D.C. Lagace, M.W. Nachtigal, Inhibition of histone deacetylase activity by valproic acid blocks adipogenesis, J. Biol. Chem. 279 (2004) 18851–18860.
[170] R.A. Blaheta, M. Michaelis, P.H. Driever, J. Cinatl Jr., Evolving anticancer drug valproic acid: insights into the mechanism and clinical studies, Med. Res. Rev. 25 (2005) 383–397.
[171] G. Koren, A.A. Nava-Ocampo, M.E. Moretti, R. Sussman, I. Nulman, Major malformations with valproic acid, Can. Fam. Phys. 52 (2006) 444–447.
[172] J. Koch, S. Gärtner, C.M. Li, L.E. Quintern, K. Bernardo, O. Levran, D. Schnabel, R.J. Desnick, E.H. Schuchman, K. Sandhoff, Molecular cloning and characterization of a full-length complementary DNA encoding human acid ceramidase. Identification ofthe first molecular lesion causing Farber disease, J. Biol. Chem. 271 (1996) 33110–33115.
[173] P.G. Williams, J.H. Hersh, A male with fetal valproate syndrome and autism, Dev. Med. Child. Neurol. 39 (1997) 632–634.
[174] A.D. Rasalam, H. Hailey, J.H. Williams, S.J. Moore, P.D. Turnpenny, D.J. Lloyd, J.C. Dean, Characteristics of fetal anticonvulsant syndrome associated autistic disorder, Dev. Med. Child. Neurol. 47 (2005) 551–555.
[175] N. Carey, N.B. La Thangue, Histone deacetylase inhibitors: gathering pace, Curr. Opin. Pharmacol. 6 (2006) 369–375.
[176] M. Minamiyama, M. Katsuno, H. Adachi, M. Waza, C. Sang, Y. Kobayashi, F. Tanaka, M. Doyu, A. Inukai, G. Sobue, Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy, Hum. Mol. Genet. 13 (2004) 1183–1192.
[177] F.A. Schroeder, C.L. Lin, W.E. Crusio, S. Akbarian, Antidepressant-like effects of the histone deacetylase inhibitor sodium butyrate, in the mouse, Biol. Psychiatry 62 (2007) 55–64.
[178] H. Gagliano, R. Delgado-Morales, A. Sanz-Garcia, A. Armario, High doses of the histone deacetylase inhibitor sodium butyrate trigger a stress-like response, Neuropharmacology 79 (2014) 75–82.
[179] C. Nasca, D. Xenos, Y. Barone, A. Caruso, S. Scaccianoce, F. Matrisciano, G. Battaglia, A.A. Mathé, A. Pittaluga, L. Lionetto, M. Simmaco, F. Nicoletti, L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 4804–4809.
[180] J.E. Bolden, M.J. Peart, R.W. Johnstone, Anticancer activities of histone deacetylase inhibitors, Nat. Rev. Drug Discov. 5 (2006) 769–784.