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Review

Stress, depression, and hippocampus: from biochemistry to electrophysiology

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Abstract. Major depressive disorder is a very common serious mental illness with increasing prevalence in the population. Its pathology includes biochemical, morphological, and electrophysiological changes in various brain areas. In spite of decades of extensive research pathophysiology of depression is still not sufficiently understood. When depression occurs just before or during pregnancy, it may have a detrimental effect on perinatal and/or postnatal brain development, affecting the offspring's behavior. An important role in the pathology of depression is the hippocampus as a center for cognition and memory. Here we review changes in morphology, biochemical, and electrical signaling caused by depression in first and second generation identified in various animal models.

Key words: Depression — Excitability — Hippocampus — Neurogenesis — Offspring

Abbreviations: ACTH, adrenocorticotropic hormone; AP, action potential; BDNF, brain-derived neurotrophic factor; CA, *cornu ammonis;* CRH, corticotropin-releasing hormone; CRH-R, corticotropin-releasing hormone receptor; DH, dorsal hippocampus; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; GD, *gyrus dentatus;* HCN, hyperpolarization-activated cyclic nucleotide-gated channels; HPA, hypothalamic-pituitary-adrenal; 5-HT, 5-hydroxytryptamine (serotonin); I_h, hyperpolarization-activated current; IL, interleukin; LTP, long-term potentiation; MPF, maternal-placental-fetal; mTOR, mammalian target of rapamycin; NE, norepinephrine; pCRH, placental CRH; PS, prenatal stress; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; TNF, tumor necrosis factor; VH, ventral hippocampus; V_{rest}, resting membrane potential.

Introduction

Depression is a common mental disorder that affects more than 280 million people worldwide. It is characterized by persistent low mood and loss of interest in activities we once enjoyed (Diseases and Injuries Collaborators 2020). Depression significantly limits psychosocial functioning and reduces the quality of life. It is also one of the most common complications during pregnancy, with a prevalence of around 20%. Anxiety is a common symptom of depression. However, clinical anxiety is also present in nearly two-thirds of individuals with major depressive disorder (Goldberg and Fawcett 2012). Anxiety symptoms often appear 1 or 2 years before the onset of major depression (Malhi et al. 2002).

While the underlying mechanisms are not well understood, some reviews and meta-analyses have demonstrated the impact of maternal depression symptoms on child development in cognitive, behavioral, social, mood, language, and "attachment" manifestations (Kingston et al. 2018; Ahun and Cote 2019; Rogers et al. 2020). Maternal depression is a known risk factor and has adverse consequences for the offspring, such as preterm birth, low birth weight, and intrauterine growth restriction (Accortt et al. 2015; Gelaye et al. 2016). Complications of low birth weight and preterm birth are reported as the leading cause of death in children

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under five years of age (Eshete et al. 2019; Silveira et al. 2019). Children of depressed mothers also have higher rates of cognitive, social, and mood disorders later in childhood and adolescence (Grundwald and Brunton 2015; Braun et al. 2020).

Depression is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the abnormal release of the stress hormone cortisol (Seth et al. 2016). Cortisol can disrupt the flow of oxygen and nutrients, predisposing the fetus to intrauterine growth restriction, low birth weight, and preterm birth (Meltzer-Brody 2011). Antenatal depression can disrupt the immune system, leaving the mother vulnerable to various infections that can affect fetal growth and cause premature birth and other congenital defects. In addition, depression can affect the mother's appetite, which affects the mother's nutritional status. This causes poor fetal development, leading to low birth weight and intrauterine growth restriction (Grote et al. 2010). Ghimire et al. (2021) demonstrated that there is a significant risk of preterm birth (35%), low birth weight (86%), and a fourfold increase in the risk of intrauterine growth restriction due to antenatal depression.

Changes in fetal response to vibroacoustic stimulation, fetal heart rate variability, altered motor activity, and altered behavioral reactivity and development have been observed in prenatal stress and depression (Hanley and Oberlander 2012; Graignic-Philippe et al. 2014). Effects of prenatal depression observed in infants included altered neonatal behavior scores, reduced vagal tone, altered cortisol reactivity, altered reactivity to pain or stress, altered temperament, increased irritability, altered attention, sleep problems, and delayed neuromotor development (Hanley and Oberlander 2012; Suri et al. 2014).

An important role in stress-induced depression is the hippocampal-prefrontal pathway, representing a unidirectional projection (Godsil et al. 2013). Hippocampus is a brain region essential for learning and memory, abilities known to be impaired during the depression. It is also unique in its capacity to generate new neurons from neural stem cells (Eriksson et al. 1998; van Praag et al. 2002). Defects in hippocampal neurogenesis were identified in animal models of depression and patients suffering from a depressive disorder. Therefore, the hippocampus is emerging as a brain structure significantly contributing to the development of the depressive disorder.

Neurogenesis and neuroplasticity in stress and depression

One of the most important neuroscience discoveries of the last century was the identification of pluripotent stem cells in the adult brain from which new neurons can be generated. This process is called neurogenesis. Growth and adaptability at the level of neurons are more commonly called neuroplasticity. Neuroplasticity at the cellular level is likely altered by inflammation and HPA axis dysfunction caused by environmental stress (Egeland et al. 2015). The process of neurogenesis is managed by regulatory proteins such as brain-derived neurotrophic factor (BDNF), which is reduced in the serum of patients with major depressive disorder (Singh et al. 2022). Abnormally low serum BDNF concentrations in depressed patients can be restored by antidepressant therapy, either pharmacotherapy or psychological interventions (Molendijk et al. 2014; Zhou et al. 2017).

Numerous clinical studies demonstrated lowered serum BDNF level during pregnancy (Singh et al. 2022). BDNF serum concentration decreased significantly from 1st to 2nd trimester, then from 2nd to 3rd trimester, and this decrease was fully reversed during weeks 4–11 postpartum (Lommatzsch et al. 2006; Christian et al. 2016). Participants in clinical studies were also tested for depression symptoms using standardized tests. Most studies demonstrated a negative correlation between BDNF serum concentration and depression scores (Gazal et al. 2012; Pinheiro et al. 2012; Dhiman et al. 2014; Fung et al. 2015; Gao et al. 2016). However, other authors reported only a weak correlation (Lommatzsch et al. 2006) or no association (Akbaba et al. 2018).

A possible association between BDNF level and depression-like behavior was also found in animal models. Prolonged but not short repeated restrain stress during the last week of pregnancy significantly decreased BDNF expression in rat hippocampi (Maghsoudi et al. 2014). BDNF expression in the prefrontal cortex was significantly reduced in the estrogen withdrawal rat model of postpartum depression (Li et al. 2018). In the mouse model exposed to stress during the first week of gestation, hippocampal BDNF expression was significantly lowered at day 28 postpartum (Vanmierlo et al. 2018).

Animal studies report that limiting neurogenesis prevents the action of antidepressants and has been shown to lead to depression-like symptoms, particularly in stressful situations. Therefore, neurogenesis is thought to facilitate resistance to stress, which could underlie the clinical effects of antidepressants (Kraus et al. 2017). Postmortem studies of depressed patients show a deficit of granule neurons in the *gyrus dentatus* (GD) in untreated subjects compared to non-depressed and treated groups. Patients treated for depression have significantly more dividing neural progenitor cells compared to the untreated depressed group and even the non-depressed group (Gururajan et al. 2016). These findings are consistent with mouse studies showing that antidepressants can act by increasing neurogenesis in the adult brain.

Several animal models of maternal depression have been designed and developed in recent decades. Models of maternal depression are based on prenatal and/or early life

stress (Pereira-Figueiredo et al. 2017). Prenatal stress (PS) has direct effects on the processes of neurogenesis, neuronal migration, cellular differentiation, and synaptic refinement that occur during the prenatal period. The results of maternal stress coincide with significant neurodevelopmental changes in the fetus. Low to moderate levels of PS can enhance fetal maturation and have an adaptive role, but higher persistent stress can lead to adverse neurodevelopmental outcomes (DiPietro et al. 2006). Evidence of neurodevelopmental deficits was observed in rats exposed to maternal PS from G14 (14^{th} day of gestation), with developmental differences in the amygdala nuclei suggesting that fear-related behaviors elicited anxiety-like symptoms (Kraszpulski et al. 2006). PS also causes learning deficits associated with inhibiting neurogenesis (Lemaire et al. 2000) and expression of the neural cell adhesion molecule PSA-NCAM, which is involved in the migration of new neurons (Morley-Fletcher et al. 2011).

Structure of hippocampus

The hippocampus, a paired functional system located within the temporal lobe, is a phylogenetically old cortical structure ("archicortex") (Vida 2010). It consists of anatomically distinct subregions: GD and *cornu ammonis* (CA). The interface between them is a region called the hilus (El Falougy et al. 2008). The CA region consists of three subregions (CA1, CA2, CA3) divided according to the density, size, and branching of pyramidal cell axons and dendrites (Vida 2010; Witter 2010). Currently, the existence of a fourth area, CA4, is still debatable. Some studies report this area as a separate part between the CA3 and GD areas (Zaidel et al. 1997). In others, it is mentioned only as another name for the hilus area (Scharfman and Myers 2012). A common feature of all hippocampus regions, except for the hilum, is a highly laminar structure. The principal cells of the CA regions form a layer called the *stratum pyramidale*. In GD, this layer is called the granular cell layer. Other areas are *stratum lucidum* (only in the CA3 area), *stratum radiatum*, and *stratum lacunosum*, which is often connected to the *stratum moleculare* and thus forms the *stratum lacunosum-moleculare* (Spruston and McBain 2007). The primary cells forming the hippocampus are the pyramidal neurons of the CA regions, granular neurons of the dentate gyrus, and the mossy fibers of the hilum, each group forming a largely homogeneous population. Pyramidal neurons of the CA1 region are some of the best-studied neurons in the brain. A pyramidal or elliptical shape of the soma, a large apical dendrite and several small basal dendrites characterize them. Pyramidal cell axons usually originate from the base of the soma but may also originate from the proximal basal or apical dendrite (Maccaferri et al. 2000). Altered hippocampal CA1 is an emerging marker of depression (Zierhut et al. 2013; Roddy et al. 2019). A global study has found that the hippocampus, the brain region responsible for memory and emotion, shrinks in people with recurrent and poorly treated depression.

Hippocampal neurogenesis

The hippocampus is one of the brain structures that is highly vulnerable to early-life stress (Hoeijmakers et al. 2017). Animal studies pointed out that neurogenesis, in which new neurons are generated in the hippocampal GD throughout life, occurs more during early life and adolescence than in adulthood (Kozareva et al. 2019; Moreno-Jimenez et al. 2019). Hippocampal neurogenesis is essential in learning and spatial memory (Terranova et al. 2019) and is involved in anxiety, forgetting stress response, and antidepressant effects (Santarelli et al. 2003; David et al. 2009). Accumulating evidence suggests that the hippocampus is functionally segregated along its longitudinal axis into dorsal and ventral regions, with the dorsal region playing a more dominant role in spatial learning and memory. In contrast, the ventral region is more dominant in regulating anxiety and stress response (Bannerman et al. 2004; Fanselow and Dong 2010). There is also emerging evidence that neurogenesis in the ventral hippocampus (VH) is more sensitive to stress regulation than neurogenesis in the dorsal hippocampus (DH) (O'Leary and Cryan 2014; Levone et al. 2021) . In a study by Coe et al. (2003), pregnant rhesus macaque monkeys were exposed to PS (during early and late pregnancy) by being moved to a dark room for 90 min for five days *per* week and intermittently awakened by an acoustic startle protocol. This reduced hippocampal volume and inhibition of maternal hippocampal neurogenesis in the GD. In addition, it was proven that prenatally stressed mothers showed impaired long-term potentiation (LTP). This was demonstrated in the Morris water maze (MWM) and facilitated long-term depression in the CA1 hippocampal region (Yang et al. 2006). Based on the fact that the transition to motherhood itself in the absence of stress affects hippocampal plasticity (Kinsley et al. 2006; Leuner et al. 2007; Pawluski and Galea 2007; Pawluski et al. 2010), neurogenesis was observed depending on the number of litters. During the post-pregnancy period, primiparous rats had reduced dendritic complexity in CA1 and CA3 pyramidal neurons and lower levels of hippocampal neurogenesis compared to nulliparous or multiparous females (Pawluski and Galea 2007). Van den Hove et al. (2005) failed to find a relationship between PS and neurogenesis in the GD of stressed rats, but cell proliferation measurements concerning PS differed. They suggested that the neurodevelopmental variability in rats in response to maternal stress is due to genetic influences that explain why some individuals are negatively affected by PS and others remain resistant or even benefit from it.

Animal structural studies confirmed in depressed humans found that hippocampal volume diminishes in severely de-

pressed compared to non-depressed humans (Schmaal et al. 2017). Some studies have linked the degree of hippocampal volume loss to the duration of untreated lifetime depression (Cole et al. 2011; Kempton et al. 2011). Postmortem studies have shown that the GD volume in untreated depressed patients is approximately half that of non-depressed controls and treated depressed patients (Boldrini et al. 2013, 2018). The therapeutic effect of antidepressants in rodent animal models was directly related to increased neurogenesis (Santarelli et al. 2003; Hill et al. 2015). Antidepressants like fluoxetine, imipramine (Santarelli et al. 2003) and lithium (Chen et al. 2000) were shown to increase adult neurogenesis in rodents GD, each acting by a different mechanism. Adult hippocampal neurogenesis was also demonstrated in young to adult humans (Boldrini et al. 2018). Whether the depression-dependent reduction of hippocampal volume can be reversed by pharmacological treatment and whether this is necessary for antidepressant response in humans remains to be seen in further clinical trials.

Functional neuroimaging provides information on brain networks involved in critical processes such as emotion regulation, rumination (lack of sleep), inability to experience the pleasure of reward, and self-awareness. Studies examining these networks in depressive disorders have found that the amygdala generally has increased activity and connectivity. Other structures, such as the subgenual anterior cingulate, are hyperactive. The insula and dorsal lateral prefrontal cortex are hypoactive in depressed individuals (Hamilton et al. 2012; Pizzagalli 2014). Different types of treatment, such as drugs, psychotherapies, and stimulation therapies, have different effects. Research linking pre-existing brain abnormalities to the selection of optimal therapies is an area of current research.

HPA axis in stress and pregnancy

Long-term or chronic exposure to stress can have adverse effects and lead to dysregulation of the HPA axis (Tsigos and Chrousos 2002). The coordinated action of hormones produced by the mother, the placenta, and the fetus regulates the neurodevelopmental processes of the fetus and helps the formation of the brain (Baud and Berkane 2019).

An essential role play steroid hormone from the glucocorticoid group, cortisol in humans and/or corticosterone in rodents. A negative feedback loop mechanism controls the cortisol synthesis and secretion. After stimulation, the hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to synthesize and secrete adrenocorticotropic hormone (ACTH). The latter stimulates the adrenal glands to synthesize and secrete cortisol, inhibiting the secretion of both CRH and ACTH. Cortisol secretion increases during stress (De Kloet et al. 1998).

Effects of stress-induced increases in cortisol include activation and regulation of the cardiovascular and immune systems, utilization of energy stores and gluconeogenesis, inhibition of reproductive and growth functions, and enhancement of memory and attention processes (de Kloet et al. 1998, 2005; Xiong and Zhang 2013). High levels of circulating cortisol inhibit further HPA activity at the level of the hypothalamus, pituitary gland, and hippocampus (De Kloet et al. 1998; Smith and Vale 2006). Under normal conditions, this negative feedback loop terminates the stress response. Increased maternal cortisol is beneficial in the short term because it promotes the maturation of fetal organs and improves neurodevelopment. However, excessive maternal cortisol during early to mid-gestation negatively affects the fetus (Davis et al. 2005, 2007; Davis and Sandman 2010).

The primary regulator of the HPA axis is CRH. HPA responses during pregnancy are characterized by the placenta, which synthesizes placental CRH (pCRH) as early as seven weeks of gestation. pCRH exhibits distinct responses to glucocorticoids and is bidirectionally released into the maternal and fetal compartments during pregnancy (Smith and Vale 2006).

CRH is a key modulator of neurogenesis, and genetic disruption of CRH/CRH-R (R-receptor) impairs hippocampal neurogenesis. CRH has a neuroprotective role (Koutmani et al. 2013, 2019). However, intrauterine exposure to excessive CRH can affect fetal neurodevelopment and lead to brain changes such as reductions in cortical volume, neuronal density in limbic brain regions, and changes in neuronal circuits, synaptic plasticity, neurotransmission, and in GPCR (G protein-coupled receptors) signaling (Fig. 1). This leads to cognitive and emotional deficits that persist into later life (Curran et al. 2017; Sandman et al. 2018).

Full-term infants of mothers with lower levels of CRH at 25 weeks of gestation showed lower levels of childhood anxiety compared to infants exposed to elevated levels of the stress hormone (Davis et al. 2005). Experimental animal models have demonstrated in offspring CRH-induced changes in dendritic branching, specifically reduced branching of cortical neurons (Curran et al. 2017); altered synaptic plasticity, impaired myelin formation, and reduced density of dendritic processes in the hippocampal region (Hermes et al. 2020; Shang et al. 2021).

The hippocampus and the HPA are functionally linked. Therefore stress-induced changes in the HPA axis could mediate changes in the developing hippocampus in the offspring (Pervanidou and Chrousos 2018). Recent studies have shown that maternal adversity causes, among other things, the activation of brain CRH-R1 and the regulation of neuronal connectivity and developmental trajectories of the immature hippocampus (Chen et al. 2004). This leads to the structural remodeling of hippocampal CA3 neurons with a significant reduction in apical dendrite complexity

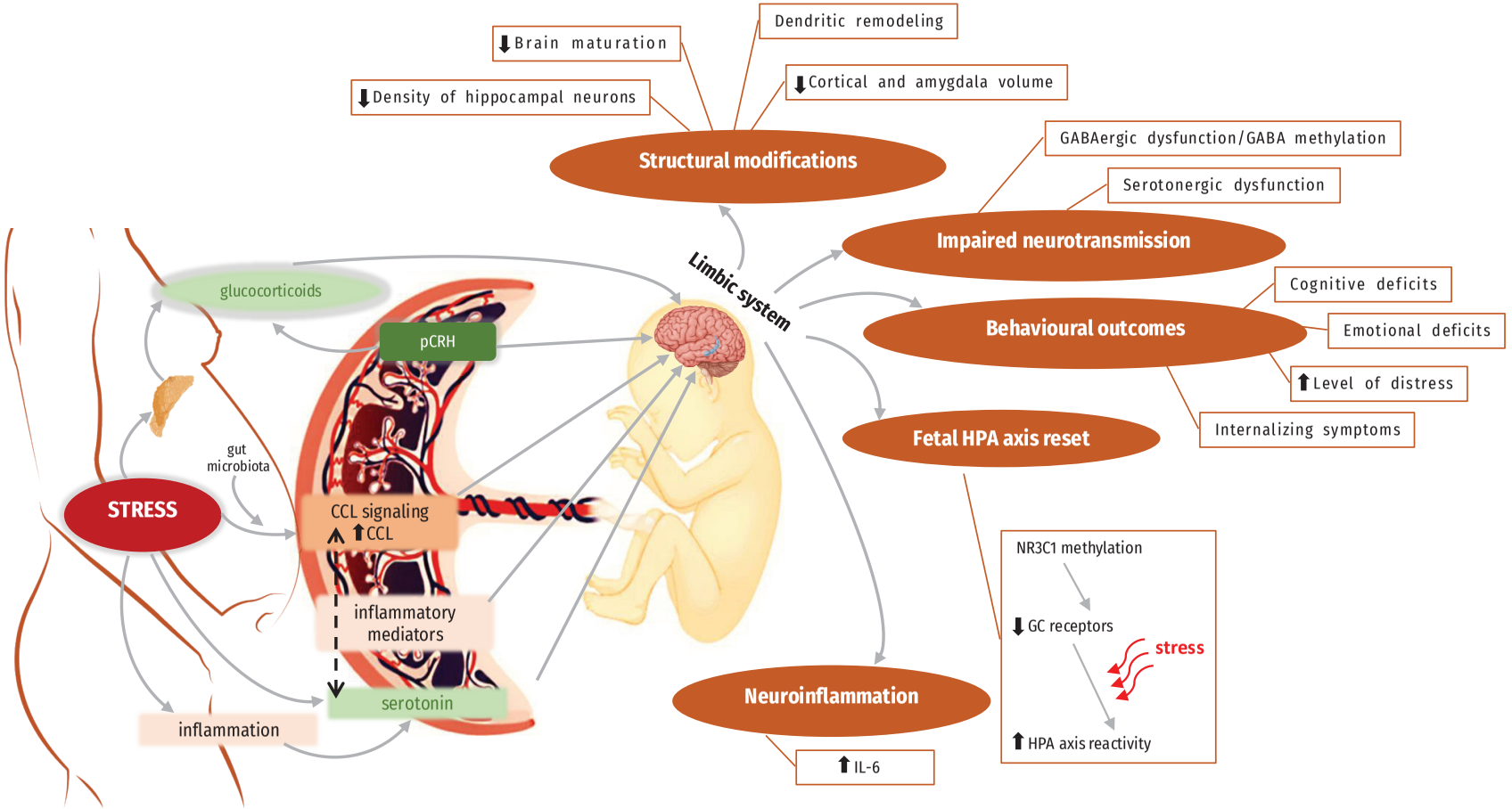

Figure 1. Possible pathophysiological mechanisms linking prenatal maternal adversity to fetal brain programming disruptions. Maternal stress can activate the production of adrenal glucocorticoids (GCs), which can cross the placenta and regulate neurogenesis of fetal brain. GCs also promote the production and release of placental CRH (pCRH) into the fetal compartment, which is a neuropeptide that produces both a neuroprotection and a neuroimpairment. Excessive levels of GCs and pCRH are associated with structural changes in the fetal brain, impaired neurological transmission and impaired fetal hypothalamic-pituitary-adrenal (HPA) axis programming, which involves epigenetic modification of the glucocorticoid receptor (GR) gene and increased reactivity of HPA axis of neonate and this mechanism is associated with adverse behavioral and emotional outcomes later in life. In addition, maternal stress or inflammatory conditions can increase delivery of serotonin (5-HT) from the placenta to the fetal brain, leading to loss of serotonergic function. Excessive maternal stress can affect signals from intestinal microbiota and can influence placenta CC chemokine ligand (CCL) signals. Interactions between placental 5-HT, CCL-2 and other inflammatory mediators ultimately lead to fetal neuroinflammation and elevated IL-6 in the fetal brain (modified according to Kassotaki et al. 2021; Langel et al. 2020).

and spine density (Wang et al. 2011; Liao et al. 2014; Liu et al. 2016).

Increased inflammation as an effect of maternal depression

Several forms of psychological stress are associated with increased inflammatory processes during pregnancy. Depression may aggravate the proinflammatory state in pregnancy (Leff-Gelman et al. 2016) and link maternal depression with child development (Glover 2015; Van den Bergh et al. 2020). Preclinical studies show the effects of these maternal processes on offspring neurobehavioral development, and increasing evidence also shows effects on neural and behavioral phenotypes relevant to psychiatric disorders in humans. Many other aspects of stress-sensitive maternal-placental-fetal (MPF) biology, including the HPA, oxidative stress, serotonin signaling, and epigenetic mechanisms, also affect fetal brain development (Buss et al. 2012; Entringer et al. 2015). Significantly, the inflammatory process interacts with other aspects of MPF biology through multiple mechanisms. Knowing the mechanisms of the inflammatory processes is very important for a better understanding of the potentially harmful effects of maternal psychological stress during pregnancy on the brain development of the offspring.

Increased inflammation is a key pathway through which increased maternal psychological stress during pregnancy affects fetal brain development and the risk of adverse neurodevelopmental outcomes. Maternal inflammation during pregnancy is associated with an increased risk of mental disorders in the offspring, including schizophrenia, autism, and attention-deficit/hyperactivity disorder (Instanes et al. 2017; Meyer 2019). Stress-induced changes in immune functioning are thought to occur through interactions between the immune system and the HPA axis. Cortisol, the end product of the HPA axis, regulates immune function (Cohen et al. 2012). However, chronic activation of the HPA axis in response to stress can lead to impaired glucocorticoid regulation of immune function, and thereby contribute to increased inflammation (Cohen et al. 2012).

Cytokines are essential for fetal brain development, including signaling cell differentiation, axonal growth and synaptogenesis (Boulanger 2009; Deverman and Patterson 2009). An increase in proinflammatory cytokines in maternal blood is accompanied by increased levels in placental tissues, amniotic fluid, and the fetal brain (Gayle et al. 2004; Meyer et al. 2006). This demonstrates that maternal inflammation influences the inflammatory environment of the fetus. The effects of increased maternal inflammation during pregnancy on the neurodevelopment of the offspring include altered gene expression in the fetal brain (Garbett et al. 2012), reduced total brain volume (da Silveira et al. 2017), reduced volume of the prefrontal cortex, hippocampus (Piontkewitz et al. 2012; Crum et al. 2017), anterior cingulate cortex, amygdala, striatum, nucleus accumbens, and lateral ventricles, and increased volume of thalamus, ventral mesencephalon, and brainstem (Crum et al. 2017). Persistent effects on offspring behavior consistent with human psychopathology are also observed (Martin et al. 2008; Sullivan et al. 2011; Sasaki et al. 2013). The effects can be eliminated by antibodies that inactivate specific proinflammatory cytokines (Smith et al. 2007; Wu et al. 2017).

Preclinical models provide evidence that inflammatory factors influence the development of fetal neurotransmitter systems critical for behavioral regulation, including serotonergic (Hsueh et al. 2017), dopaminergic (Bronson and Bale 2014; Luchicchi et al. 2016), and glutamatergic (Rahman et al. 2017) systems. In addition to directly affecting fetal brain development, exposure to inflammation *in utero* is thought to trigger an inflammatory process in the fetal brain (Manjeese et al. 2021; Singh et al. 2021), which can alter brain development through the activation of glial cells (Reus et al. 2015), increased oxidative stress (Hassan et al. 2016), and aberrant neuronal development.

Neuroinflammation may cause defects in the expression of ion channels in the hippocampus, thus causing defective synaptic plasticity related to memory and/or emotional deficits. Intravenous injection of proinflammatory cytokine interleukine-1β (IL-1β) induced depression-like behavior in rats (Gui et al. 2016), while intracerebroventricular application of IL-1 receptor agonist relieved it (Norman et al. 2010). Overproduction of IL-1β and/or another proinflammatory cytokine, tumor necrosis factor (TNF-α) were shown to impair long-term potentiation in the hippocampus (Katsuki et al. 1990; Pickering et al. 2005). Upregulation of TNF-α reduced dendritic length and spine densities in CA1 pyramidal neurons in mice hippocampus (Liu et al. 2017), thus contributing to attenuated hippocampal excitability.

Stress, depression, and neuronal excitability

While extensive research has focused on understanding the behavioral correlates of stress during pregnancy, little has focused on neuronal excitability. Behavioral and biochemical changes in the brain are manifested, among other things, by changes in excitability in relevant brain areas. Therefore, a detailed analysis of neuronal excitability is of great importance when investigating the effects of stress and/or depression in both the first and second generations. Experimental objects such as the primary hippocampal neuron culture and/or the acute hippocampal slices allow this investigation. Acute hippocampal slices are most often obtained from the brains of young or adult rodents and will enable the analy-

sis of alteration in excitability in both stressed animals and their offspring. Primary cultures of hippocampal neurons are prepared from the brain of late embryonic or newborn rodents and can be maintained *in vitro* for 2–3 weeks (Nagerl et al. 2004; Galimberti et al. 2006), allowing analysis of early changes in offspring brains.

Resting membrane potential and voltage-dependent potassium channels

The resting membrane potential of an excitable cell (V_{rest}) is its basic property and facilitates or attenuates the propagation of action potentials (APs) in excitable tissues. A major determinant of V_{rest} is potassium conductance. Several types of potassium channels contribute to setting V_{rest}, along with nonspecific cation channels that can transport both K^+ and Na^+ ions (Nishitani et al. 2019). These channels also contribute to the membrane repolarization required for firing the recurrent AP, so their altered function may underlie changes in both V_{rest} and activation of the depolarization-activated AP. It has been shown that stress can change the activity of Kv7 (KCNQ) and Kv1 potassium channels. Acute restraint stress reduced the activity of Kv7 channels (Zhou et al. 2017) and increased the firing activity of neurons in the hypothalamic paraventricular nucleus of rats. Chronic stress associated with the onset of major depressive disorder altered the expression of Kv1 channels in mice (Miyata et al. 2016). The possible alteration of resting membrane potential was not investigated in these experiments.

Hippocampal HCN channels in stress and depression

Other channels highly expressed in the hippocampus and contributing to V_{rest} maintenance are hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Monteggia et al. 2000), permeable to both K^+ and Na^+ ions. In the hippocampal CA1 region, HCN1 is the primary type of HCN channels expressed with a gradient of increasing channel density along the CA1 somatodendritic region (Lorincz et al. 2002; Notomi and Shigemoto 2004). As they are active at a resting membrane potential, they contribute to the electrical properties of the neuronal membrane, such as input resistance (R_{inp}), AP generation, and resonance frequency (Hu et al. 2002; Shah et al. 2004; Narayanan and Johnston 2007). Several studies suggest that HCN channels play a role in depression and contribute to the mechanism of antidepressant effects (Fig. 2). Reduction of the functional I_h current mediated by HCN channels in the brain produces antidepressant-like effects (Lewis et al. 2011). Mice in which the pore-forming or accessory subunits of HCN chan-

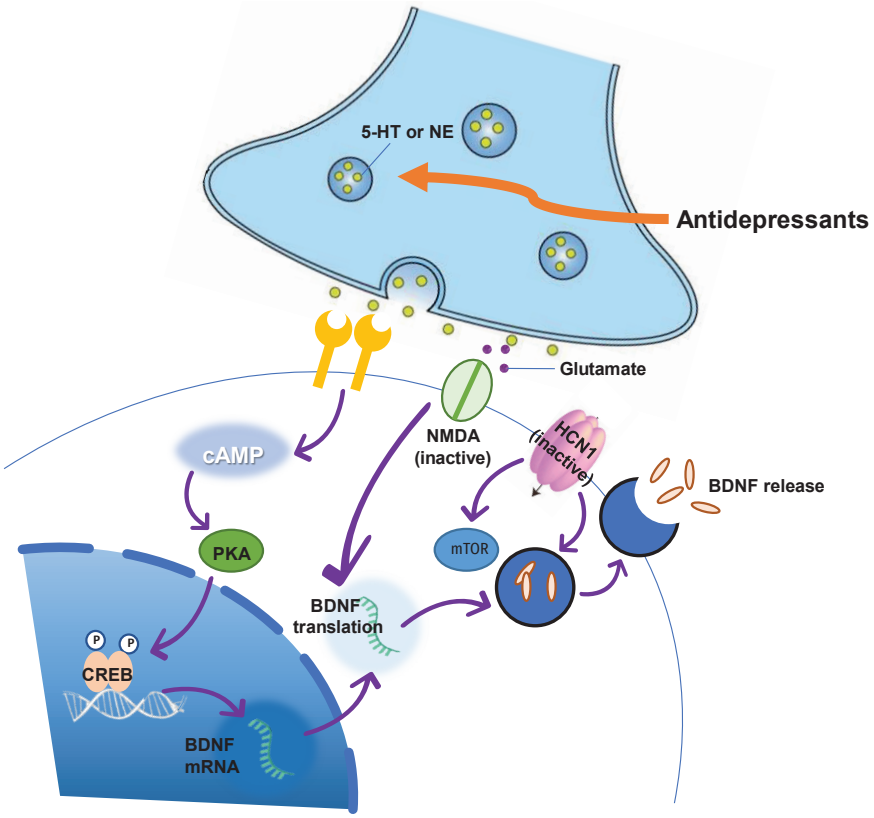

Figure 2. Cellular pathways connecting antidepressant effect, BDNF synthesis, and HCN activation in the hippocampus. Antidepressants increase the levels of monoamines such as serotonin (5-HT) and norepinephrine (NE) in the synaptic cleft. They act on their respective receptors to stimulate cAMP and protein kinase A (PKA), resulting in cAMP response element binding (CREB), transcription factor phosphorylation, and higher BDNF production. The production of BDNF will be enhanced by the pharmacological inhibition of N-methyl-aspartate (NMDA) receptors or the reduction of HCN channels activity. The reduction of HCN channels activity also stimulates the kinase mTOR. Molecular mechanisms by which the reduced function of HCN channel enhances BDNF synthesis and phosphorylation of mTOR remain to be elucidated.

nels (HCN1, HCN2, and TRIP8b) were deleted exhibited antidepressant-like behavior (Lewis et al. 2011; Kim et al. 2012). However, the physiological role of HCN channels in the hippocampus in developing anxiety and depression is not clarified in detail. Kim and collaborators (Kim et al. 2012, 2018) found that chronic, but not acute stress, leads to increases in the expression of perisomatic HCN1 channels and the amplitude of I_h currents, that correlates temporally with the development of depression- and anxiety-like symptoms in rats. Furthermore, these changes were restricted to the dorsal hippocampus region only. Interestingly, the expression of the HCN1 channel is negatively correlated with the expression of BDNF (Hou et al. 2018). In line with this finding, chronic stress causing depression-like behavior also decreased BDNF expression in the hippocampus (Gronli et al. 2006) and, *vice versa*, knock-down of expression of BDNF in the hippocampus induced depression-like behavior (Taliaz et al. 2010).

Regulation of Ca^{2+} fluxes in depression

Abnormal increases in intracellular calcium levels were found in platelets and lymphocytes from depressed patients (Dubovsky et al. 1992; Emamghoreishi et al. 1997). Several pathways lead to an increased intracellular calcium concentration. Chronic stress induces hypersecretion of glucocorticoids, resulting in an increased calcium current through L-type voltage-gated Ca^{2+} channels (Karst et al. 2000; Zhao et al. 2009). Chronic restraint stress-induced depressive-like behavior was accompanied by an enhanced $Ca_V1.2$ channel expression (Moreno et al. 2020). The increase in mRNA and protein levels in the hippocampus and L-type calcium current amplitude in CA1 neurons was observed. Calcium influx through L-type calcium channels may activate several intracellular signaling pathways. In an investigated depression model, enhanced activity of the L-type calcium channel selectively activates the calmodulin-NFAT axis, leading to enhanced Fas ligand expression, which may lead to apoptotic neuronal death (Moreno et al. 2020).

Activation of calcium release from intracellular stores and/or inhibition of calcium reuptake by the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) also increases intracellular calcium concentration. Elevated intracellular calcium level induces a perisomatic increase in I_h current in CA1 neurons previously observed in the animal depression model (Narayanan et al. 2010; Clemens and Johnston 2014). This perisomatic increase in I_h current was partially mediated by an increase in intracellular calcium and activation of inositol 1,4,5-triphosphate receptors (IP3Rs) and store-operated channels (SOC) (Narayanan et al. 2010; Ashhad et al. 2015). *Vice versa*, inhibition of SERCA induced depression-like behavior in rats (Kim et al. 2018).

Early changes in hippocampal excitability caused by prenatal stress

Prolonged exposure to stress before or during pregnancy is a well-established model for studying the effects of maternal depression on the offspring. Primary culture of hippocampal neurons prepared from late embryonic or newborn pups enables investigation of alterations developed *in utero*.

In the primary culture of hippocampal neurons prepared from offspring of rats exposed to pregestational stress resulting in depression-like behavior, depolarization of the V_{rest} was found in the early days of neuronal culture. Still, it did disappear as neurons gradually matured (Bogi et al. 2019). In the same model, suppressed depolarization-activated AP firing and increased spontaneous hippocampal cell activity were found in newborns exposed to pregestational stress.

Cultured hippocampal neurons from pups born to mothers exposed to stress during pregnancy did not differ in V_{rest}, R_{inp}, and AP properties like the AP threshold, overshoot, duration, or after-potentials compared to cultures from non-stressed mothers (Grigoryan and Segal 2013a). While there was no difference in the excitatory postsynaptic currents, the rate of spontaneous miniature inhibitory postsynaptic current was lowered in prenatally stressed pups (Grigoryan and Segal 2013a). Further, these authors also reported more developed dendritic networks in cultured neurons from prenatally stressed pups.

Later changes in the excitability of hippocampal neurons caused by prenatal stress

Acutely prepared slices from the hippocampus allow us to analyze neuronal excitability at the age of several days to several weeks. The significant advantage is the possibility of precise visual identification of individual types of hippocampal neurons.

Reduction of inhibitory tone caused by prenatal stress observed in the primary culture of neonatal hippocampal neurons was confirmed in slices prepared from 2–3 weeks old male offspring by measurement of population spikes in the CA1 region (Grigoryan and Segal 2013a). In 4-5 weeks old rats, exposure to prenatal stress did not affect pair-pulse facilitation of field excitatory postsynaptic potentials (fEPSPs) but significantly reduced long-term potentiation (LTP) (Yaka et al. 2007). A similar reduction of LTP, accompained by promoted induction of long-term depression (LTD), was observed by Yeh and colleagues (Yeh et al. 2012) in 5-week-old rats exposed to prenatal stress, but the effect disappeared at eight weeks of age. In a different prenatal stress model, the impairments of hippocampal LTP persisted up to 8 weeks of age (Yang et al. 2007). Reduced NMDA-dependent hippocampal LTP was also reported for 7–8-week-old prenatally stressed male mice (Son et al. 2006).

It is well known that noradrenergic stimulation plays a key role in the regulation of excitability, attention, cognitive function, and stress responses. One of the underlying regulatory pathways involves the facilitation of LTP *via* adrenergic receptors in the hippocampus (Izumi and Zorumski 1999). This mechanism is specific to the dorsal (DH) and ventral (VH) sections of the hippocampus (Grigoryan and Segal 2016). In control rats 4–5 weeks of age isoproterenol activated LTP in DH but not in VH. The effect was the opposite in prenatally stressed rats: isoproterenol activated LTP in VH but not in DH (Grigoryan and Segal 2013b).

Another signaling pathway affected by prenatal stress is the BDNF pathway. Conversion from pro-BDNF to mature BDNF is impaired in prenatally stressed rats (Yeh et al. 2012), and BDNF signaling is reduced in these animals (Neeley et al. 2011). This can affect the maturation of GABAergic neurons. It has been reported that the expression of GABAergic neurons is reduced in the hippocampus of prenatally stressed rats (Vaid et al. 1997). This reduction in inhibition was manifested as a reduction in the spike population during the paired-pulse depression, which could be distinct from a similarly insignificant change in EPSP slope, an indicator of excitatory synaptic function. A reduction in inhibition may underlie the increased efficacy of isoproterenol in VH in prenatally stressed rats reported by Grigoryan and Segal (2013b).

Conclusion

The hippocampus is a region of the brain that has recently received much attention in research on mood disorders and may play a central role in depressive disorders. Animal models of depression allow us to analyze the underlying organic changes in detail. In addition to pathological changes in biochemical and electrical signaling underlying behavioral changes in animal models of depression, maternal depression models allow investigation of altered offspring brain activity at multiple systemic levels. The behavioral changes observed in the offspring may not only be caused by the depression of the mother's altered behavior but also by biochemical changes in the offspring's brain that occur during pregnancy and are also manifested by altered neuronal excitability in the hippocampus. These changes are extremely complex, as demonstrated by the altered expression of 6.1% of 9505 valid genes, including those encoding for voltage- and ligand-gated ion channels, in prenatally stressed rats (Bogoch et al. 2007). A detailed description of modified pathways may offer useful hints for the design of improved therapeutic strategies.

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