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Glucocorticoid-mediated mechanisms of hippocampal damage: contribution of subgranular neurogenesis

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Abstract.

A comprehensive overview of the interplay between glucocorticoids (GCs) and adult hippocampal neurogenesis (AHN) is presented, particularly, in the context of a diseased brain. The effectors of GCs in the dentate gyrus neurogenic niche of the hippocampal are reviewed, and the consequences of the GC signaling on the generation and integration of new neurons are discussed. Recent findings demonstrating how GC signaling mediates impairments of the AHN in various brain pathologies are overviewed. GC-mediated effects on the generation and integration of adult-born neurons in the hippocampal dentate gyrus depend on the nature, severity, and duration of the acting stress factor. GCs realize their effects on the AHN primarily via specific glucocorticoid and mineralocorticoid receptors. Disruption of the reciprocal regulation between the hypothalamic–pituitary–adrenal (HPA) axis and the generation of the adult-born granular neurons is currently considered to be a key mechanism implicating the AHN into the pathogenesis of numerous brain diseases, including those without a direct hippocampal damage. These alterations vary from reduced proliferation of stem and progenitor cells to increased cell death and abnormalities in morphology, connectivity, and localization of young neurons. Although the involvement of the mutual regulation between the HPA axis and the AHN in the pathogenesis of cognitive deficits and mood impairments is evident, several unresolved critical issues are stated. Understanding the details of GC-mediated mechanisms involved in the alterations of AHN could enable the identification of molecular targets for ameliorating pathology-induced imbalance in the HPA axis/AHN mutual regulation to conquer cognitive and psychiatric disturbances.

Keywords: adult hippocampal neurogenesis, glucocorticoid(s), stress, corticosterone, radial glia-like stem cells, proliferation, differentiation.

Abbreviations.

AHN -- adult hippocampal neurogenesis
BDNF -- brain-derived neurotrophic factor
BrdU -- 5-Bromo-2'-deoxyuridine
CNS -- central nervous system
DG -- dentate gyrus (DG)
ECS -- electroconvulsive seizures
FGF2 -- fibroblast growth factor 2
GABA -- γ-aminobutyric acid
GC(s) -- glucocorticoid(s)
GR -- glucocorticoid receptor
HPA -- hypothalamic–pituitary–adrenal

MR -- mineralcorticoid receptor

RGLs -- radial glia-like stem cells

1. Introduction.

Generation of new granular neurons and their functional integration into the existing hippocampal neuronal circuits continue over the lifespan (Gould *et al.* 1999b; Kuhn *et al.* 1996; van Praag *et al.* 2002; Imayoshi *et al.* 2008). This process is referred to as adult hippocampal neurogenesis (AHN) and is considered to represent an extraordinary form of the structural plasticity unique for the hippocampal neuronal network and essential for learning, memory, and mood (Gonçalves *et al.* 2016; Cameron and Glover 2015; Toda *et al.* 2019; Braun and Jessberger 2014; Anacker and Hen 2017). Various abnormalities in the generation of new granular neurons have been demonstrated to accompany numerous congenital and acquired brain diseases when the hippocampus is not affected by the initial pathology. This can explain, at least partially, cognitive deficits and mood impairments observed in different brain diseases.

The AHN is responsive to diverse physiological and pathological stimuli. Stress and stress hormones, glucocorticoids (GCs), have been identified as major negative regulators of the AHN. A tight reciprocal link between stress, GCs, and hippocampal neurogenesis is well documented and has been described in a number of outstanding reviews (Kino 2015; Fitzsimons *et al.* 2016; Saaltink and Vreugdenhil 2014; Numakawa *et al.* 2017; Anacker 2014; Gould and Tanapat 1999; Mirescu and Gould 2006). Here, we present a comprehensive overview of the interplay between stress, GCs, and AHN in the context of injured and aged brain. In this review, we will briefly describe key features and functional significance of the AHN and basic aspects of the GC-mediated stress response. Then, we will discuss the effectors of GCs in the neurogenic niche of the hippocampal dentate gyrus (DG) and the impact of the GC signaling activity regulate the generation and integration of new neurons. Finally, we will review recent findings demonstrating how the GC signaling mediates chronic stress-induced impairments of the AHN in different brain pathologies.

It should be noted that we will primarily focus on the studies using animal models to explore how GCs and/or activation of their receptors are involved on different stages of the AHN. As a rule, neural progenitor cell cultures fail to reproduce some unique features of the AHN, such as predominant quiescent state of the hippocampal stem cells, division-coupled depletion of their pool, and well-organized interactions between undifferentiated and mature cells in the neurogenic niche. Moreover, an increased mitogen control of neural progenitor cell cultures can interfere with GC signaling, thus complicating the interpretation of the results.

2. Adult hippocampal neurogenesis: a significance for normal brain function and an involvement in the pathogenesis of brain diseases.

2.1. A functional significance of the adult hippocampal neurogenesis

Continuous addition of new granular neurons in the neuronal network of the DG is believed to be essential for learning and memory (Gonçalves *et al.* 2016; Cameron and Glover 2015; Toda *et al.* 2019; Braun and Jessberger 2014). This belief relies on the observations that animals exhibiting improved performance in hippocampus-dependent learning and memory tasks have elevated levels of the AHN (van Praag *et al.* 1999; Gould *et al.* 1999a; Garthe *et al.* 2016). Moreover, experiments with selective genetic ablation or enhancement of the newborn neuron generation unambiguously demonstrated the importance of the AHN for basic hippocampus-dependent brain functions, such as pattern separation, spatial navigation, object recognition, and contextual learning (Berdugo-Vega *et al.* 2020; Jessberger *et al.* 2009; Saxe *et al.* 2006; Sahay *et al.* 2011; Nakashiba *et al.* 2012). During a period of maturation and integration into the neuronal network (between 1 and 1.5 months upon last mitotic division), young granular neurons exhibit remarkable structural and synaptic plasticity and are more excitable than mature ones (Li *et al.* 2012; Ge *et al.* 2007). It is supposed that, within this period, young granular neurons are able to rearrange the pattern of their synaptic connections in response to external stimuli, thus "remembering" the experience (Bergami *et al.* 2015; Zhao 2006; Piatti *et al.* 2011; Marín-Burgin *et al.* 2012). Computational modeling supports a demand of new neuron integration into the existing neuronal networks for episodic memory retrieval (Weisz and Argibay 2009; Fang *et al.* 2018; Aimone and Gage 2011). The AHN was found to be essential for mood as well. The existence of the relationship between neurogenesis, depression, and antidepressants is currently well documented (reviewed in (Anacker and Hen 2017; Miller and Hen 2015; Hanson *et al.* 2011; Taupin 2006; Dranovsky and Hen 2006; Gould and Tanapat 1999)). Furthermore, direct evidence that the AHN contributes to the regulation of mood and stress response were obtained when depressive-like behaviors were evaluated after genetic ablation or enhancement of the newborn neuron production and chemogenetic suppression or activation of young neurons (Tunc-Ozcan *et al.* 2019; Hill *et al.* 2015; Snyder *et al.* 2011). Hence, the AHN is currently considered to be one of the mechanisms underlying the adaptive response of the brain to changing external circumstances.

2.2. The neurogenic cascade.

New granular neurons are generated from Radial Glia-Like stem cells (RGLs) inhabiting the subgranular zone of the DG (Seri *et al.* 2001; Suh *et al.* 2007; Bonaguidi *et al.* 2011; Encinas *et al.* 2011; Gebara *et al.*

2016). A vast majority of RGLs reside in a non-proliferative, quiescent state, while only a bit of them undergoes divisions at a time. These dividing RGLs undergo self-renewal and generate transient progenitor cells that, in turn, divide to expand their own pool. A portion of the transient progenitor cells disappear via apoptotic cell death or are eliminated by microglia (Encinas *et al.* 2011; Sierra *et al.* 2010). The remaining viable transient progenitor cells migrate into granular cell layer and differentiate into functionally integrated granular neurons via sequential maturation stages (van Praag *et al.* 2002; Seri *et al.* 2001; Bonaguidi *et al.* 2011; Pilz *et al.* 2018; Urbán *et al.* 2016; Laplagne *et al.* 2006; Toni *et al.* 2008) (Figure 1). Several scenarios have been proposed to explain how RGLs maintain through the lifespan and how they convert into mature neurons and glial cells (reviewed in (Lazutkin *et al.* 2019)). These scenarios vary in describing modes of stem cell maintenance and division, while generally coinciding in depicting the later stages of the AHN. Particularly, some of them suggest that RGLs either undergo a limited number of consecutive asymmetric neurogenic divisions with subsequent irreversible differentiation into astrocytes (Encinas *et al.* 2011) or form a temporary-existing pool of the proliferating RGLs, which subsequently eliminate via conversion into neurons, return to a quiescent state, or death (Urbán *et al.* 2016). Other scenarios argue unlimited self-renewal of RGLs via symmetric divisions. However, experimental evidence regarding capability of RGLs to expand their pool under normal conditions via symmetric divisions remain controversial (Bonaguidi *et al.* 2011; Encinas *et al.* 2011; Mineyeva *et al.* 2018). Currently, mostly prevailing view is that the age-related decrease in the AHP is explained by division-coupled depletion of the RGLs pool (Encinas *et al.* 2011; Urbán *et al.* 2016). It seems, however, that symmetric divisions may be induced by physiological or pathological stimuli. Expansion of the RGLs pool via symmetric divisions was observed in case of neuronal hyperactivity or upon the administration of pro-neurogenic drug memantine (Sierra *et al.* 2015; Namba *et al.* 2009). However, these symmetric divisions were found to produce RGLs with aberrant morphological and molecular characteristics.

2.3. The adult hippocampal neurogenesis in the human brain: current state

The ongoing AHN has been documented for most mammalian species examined. Experimental evidence regarding the continuation of the hippocampal neurogenesis in the adult and aging human brain remain ambiguous. One line of observations supports the existence of high levels of the hippocampal neurogenesis in the adult and aging human brain (Eriksson *et al.* 1998; Spalding *et al.* 2013; Boldrini *et al.* 2014; Boldrini *et al.* 2018; Boldrini *et al.* 2012; Knoth *et al.* 2010; Roy *et al.* 2000; Moreno-Jiménez *et al.* 2019; Mathews *et al.* 2017). Furthermore, these observations revealed that neurogenesis in the adult human hippocampus possess multiple attributes characteristic for the rodent AHN. Particularly, neurogenesis in the adult human hippocampus was found to be responsive to antidepressant treatment

(Boldrini *et al.* 2012, 2014), and a considerable impairment of the AHN was identified in patients with Alzheimer's disease (Moreno-Jiménez *et al.* 2019) similar to findings reported earlier in various rodent models of Alzheimer's disease (reviewed in (Lazarov *et al.* 2010)). At the same time, a recent study by Sorrels at al. (Sorrells *et al.* 2018) has reported that the hippocampal neurogenesis declines rapidly in childhood, becoming undetectable in the adult and aging human brain. This study revived debates on the existence of neurogenesis in the adult and aging human hippocampus (Kempermann *et al.* 2018; Lucassen *et al.* 2020a; Lucassen *et al.* 2020b). The controversy in the experimental evidence primarily originates from the technical challenges. Firstly, postmortem brain tissues are collected from individuals that, in most cases, died from a severe disease and, therefore, might have sufficiently decreased hippocampal neurogenesis. Secondly, basic methodological approaches based on tracing dividing cells labeled by nucleotide analogs or viral constructs are not available in human studies. Thirdly, the immunohistochemical detection of the AHN in the human brain may be drastically affected by the following. True markers of human adult neurogenesis may remain unknown (Kempermann *et al.* 2018), and destructive processes that occur in brain tissues during the course of the agonal stage and the postmortem time period prior to fixation worsen the subsequent revealing of the neurogenesis markers known from rodent studies (Lucassen *et al.* 2020b). Both these issues can lead to underestimation of numbers of neuroblasts and immature neurons in postmortem human hippocampus. Therefore, the careful selection of subjects with known health history and the standardization of the tissue preparation procedures will further enable resolving a question regarding the existence and true levels of the hippocampal neurogenesis in the healthy, aging, and diseased human brain.

2.4. Impaired adult hippocampal neurogenesis as a pathogenetic cofactor in diverse brain disorders.

The hippocampus, being a part of the limbic system, receives and processes a wide variety of information about the organism's internal state and external circumstances to generate appropriate behaviors. Therefore, tiny alterations in the hippocampus may elicit marked manifestations primarily in cognitive capabilities and mood. Structural and functional alterations in the hippocampus were found to accompany diverse brain diseases independently on whether this brain structure has been implicated in the initial pathology or not. Furthermore, a growing body of experimental evidence shows that the AHN is in some way implicated in the pathogenesis of different brain disorders too. Decreased proliferation of stem and progenitor cells and/or reduced survival of newborn cells and/or abnormal morphology and localization of new neurons is observed in major depression, bipolar disorder, schizophrenia, Parkinson's disease, and Huntington's disease both in human individuals and rodent models (Berger *et al.* 2020; Kang *et al.* 2016; Marxreiter *et al.* 2013; Aniol and Gulyaeva 2015; Gil-Mohapel *et al.* 2011). In most diseases,

the AHN is generally reduced. More complex alterations in the AHN accompany seizures in animal models of epilepsy (Sierra *et al.* 2015; Jessberger and Parent 2015; Hattiangady *et al.* 2004; Kralic *et al.* 2005; Huttmann *et al.* 2003; Fu *et al.* 2019). A seizure episode quickly elevates proliferation in the subgranular zone, predominantly stimulating the division of RGLs. However, seizure-stimulated neurogenesis is accompanied by aberrant localization and wiring of newborn neurons. Overstimulation of the quiescent RGLs accelerates the depletion of their pool through symmetric divisions and subsequent conversion of daughter cells into reactive astrocytes, eventually leading to a profound decline in the generation of new neurons later after seizures. Perturbations of the AHN are also considered to be a involved in the cognitive decline observed after ischemic stroke and brain trauma (Gao *et al.* 2009; Zhang *et al.* 2020; Kathner-Schaffert *et al.* 2019; Niv *et al.* 2012). A picture of ischemic stroke- or brain trauma-induced alterations of neurogenesis closely resembles that observed after seizures: a transient enhancement of the AHN accompanied by abnormal localization and morphology of newborn neurons followed by a significant decrease in production of new neurons later. However, whether this decrease is due to division-coupled exhaustion of quiescent RGLs activated by ischemic stroke or brain trauma, remains obscure.

Impaired AHN seems to be associated with most brain diseases accompanied by cognitive deficit and/or mood disorders, however, clinical observations in humans have not yet identified a brain disease associated with the impairment of the AHN solely (Gonçalves *et al.* 2016). If a brain disorder has somehow affected the AHN, the impaired AHN subsequently becomes a part of the pathogenetic process and aggravate a previously formed pathological state, accelerating the disorder progression, and enhancing signs of cognitive and mood deficit. Therefore, securing the AHN during the course of a brain disorder progression might have beneficial effects on the integrity of the hippocampal functions, thus preserving cognitive capacities and preventing mood decline. Although impairments of the AHN are well-documented in many animal models of brain disorders and, for some of them, the affected neurogenic stages were identified, little is known on exact mechanisms delivering a pathological stimulus to cells of the neurogenic cascade. Among numerous signal transduction pathways regulating the AHN, an interplay between the AHN and the stress response control system, the hypothalamic–pituitary–adrenal (HPA) axis, via the glucocorticoid-mediated signaling seems to play a leading role in transferring a pathological stimulus into the neurogenic niche. This thought is based on two facts. First, many brain pathologies are transiently or permanently accompanied by the deregulation of the HPA axis. Second, stress and glucocorticoids are strong regulators of the AHN. Therefore, the integrity of the AHN is highly dependent

on proper regulation of stress response, while the deregulated the HPA activity may transiently or permanently impair the AHN via injurious GCs action.

3. GC-related regulation of stress response and complex mechanisms of the GCs action.

Stress response is a reaction of body's systems to intrinsic or environmental challenges. Stress response primarily aims to reimburse basal functional state of body's systems disturbed by the challenges (reviewed in (Denver 2009; Herman *et al.* 2016)). The HPA axis regulates stress response via a multilevel negative feedback. When an organism is stressed, neurosecretory neurons of the hypothalamic paraventricular nucleus release corticotropin-releasing hormone, which induces secretion of adrenocorticotropic hormone from the anterior part of the pituitary gland into general circulation system. Adrenocorticotropic hormone, in turn, acts on the adrenal cortex, stimulating synthesis and release of GCs, mineralcorticoids, and androgens from zona glomerulosa, zona fasciculata, and zona reticularis, respectively. Released GCs cortisol in humans or corticosterone in rodents) act on virtually all cells of an organism primarily via up- or down-regulation of genes involved in multiple cellular functions. In parallel, GCs suppress the HPA axis activity at different levels by repressing transcription of genes encoding corticotropin-releasing hormone, the corticotropin-releasing hormone receptor, and the precursor of adrenocorticotropic hormone (Timmermans *et al.* 2019).

GCs, being the cell membrane-penetrating compounds, act on cells primarily via their interaction with two types of cytoplasmic receptors: low-affinity glucocorticoid receptor (GR) NR3C1 (nuclear receptor subfamily 3, group C, member 1) (Vandevyver *et al.* 2014) and high-affinity mineralcorticoid receptor (MR) NR3C2 (nuclear receptor subfamily 3, group C, member 2) (ter Heegde *et al.* 2015). MR also able to bind another ligand, a mineralcorticoid aldosterone (Lombes *et al.* 1994). GRs and MRs belong to a superfamily of ligand-inducible transcription factors that exist in the cell cytoplasm in the form multiprotein complexes with accessory chaperone proteins (Hsp90, Hsp70, and others) (Kirschke *et al.* 2014; Echeverria and Picard 2010). When GCs bind to their receptors, they exert release of GRs or MRs from chaperone-receptor complexes. The released GC-receptor complexes are translocated into the cell nucleus where they repress or enhance gene expression via binding to GC response elements in the DNA (Kadmiel and Cidlowski 2013; Ayroldi *et al.* 2012). (Schiller *et al.* 2014; Yudt and Cidlowski 2002; Weikum *et al.* 2017; Kadmiel and Cidlowski 2013; Meijer *et al.* 2019; Trapp *et al.* 1994). They are also able to directly interact with some transcription factors (for instance, AP-1, NF-κB, and STAT3), modulating their binding to the respective regulatory sequences in the DNA and thus repressing or enhancing gene expression (De Bosscher *et al.* 2003; McKay and Cidlowski 1999; Ramamoorthy and Cidlowski 2016; Timmermans *et al.* 2019). It is believed that, acting via their receptors, GCs control the expression of thousands of genes

(Oakley and Cidlowski 2013). Interaction of GCs with their receptors may also exert profound epigenetic modifications via changes in the methylation state at specific sites in the genomic DNA (Zannas and Chrousos 2017). This mode of GCs action seems to underlie the long-lasting effects of stress or contribute to cumulative life stress.

GCs exhibit multiple effects on virtually all organism's systems. Since the GCs action is cell type-specific and context-dependent, they are able to orchestrate cellular responses to diverse forms of stress. How can a single molecule exert all these effects? The divergent and even opposite effects of GCs are explained by the existence of numerous molecular mechanisms modulating the activity of GR and MR in the cell (Meijer *et al.* 2019). Due to alternative splicing and translation initiation, numerous isoforms of GR and MR exist. These isoforms are expressed in a cell-type-specific manner and primarily differ each other by their ligand affinity, by a repertoire of interactions with other proteins, and by a set of target genes (Ramamoorthy and Cidlowski 2016; Oakley and Cidlowski 2013). GR and MR also undergo posttranslational modifications, primarily phosphorylation, at multiple sites. These modifications modulate the activity of GR and MR, thus making effects of GCs to be context-dependent.

In addition, GCs exhibit non-genomic action on cell functions. This type of action is independent on the transcription of genes and synthesis of proteins. GCs are able to display rapid effects (within seconds to minutes) via interaction with plasma membrane-associated isoforms of GR and MR (Timmermans *et al.* 2019; Groeneweg *et al.* 2012). The existence of these isoforms has been confirmed in several regions of the limbic system, including the hippocampus (Evans *et al.* 2000; Liposits and Bohn 1993; Johnson *et al.* 2005; Karst *et al.* 2005). Moreover, these isoforms were found to locate in dendritic spines and pre- and post-synapses (Prager *et al.* 2010; Yoshiya *et al.* 2013). Such localization of membrane-associated isoforms of GR and MR in nerve cells allows to consider direct modulation of synaptic transmission and dendritic spine formation by GCs. Similarly, GCs may modulate synaptic transmission in exciting and inhibiting neurons via unidentified G protein-coupled membrane receptors activating multiple downstream signaling pathways mediated by nitric oxide, cAMP, ERK1/2, JNK, p38, protein kinase A (PKA), and protein kinase C (PKC) (Zhang *et al.* 2012; Di *et al.* 2009; Groeneweg *et al.* 2012). GCs accumulated within the cell plasma membrane are able to modulate the activity of cation pumps via the reduction of spontaneous ion flux into the cell (Schmid *et al.* 2000). GC-GR complexes are also able to translocate into mitochondria where they modulate mitochondrial gene expression, calcium accumulating and oxidation capacities, as well as membrane potential (Du *et al.* 2009; Psarra and Sekeris 2011).

Under physiological conditions, GCs serve as major regulators of the stress response, retrieving organism's systems to their normal state. However, repeated or severe stressors (repeated or acute psychological

stress, chronic disease or a severe injury) may disturb fine-tuned GC control of stress response, leading to situations making GCs injurious (de Kloet *et al.* 2005; Gulyaeva 2019a). Imbalance in GCs-related signaling exerts a deregulation of the organism's systems resulting in a loss of the ability to resist internal and external challenges and thus enhancing vulnerability to diseases or aggravating existing pathologies.

4. Cross-talk between the HPA axis and the AHN: functional and translational relevance.

The hippocampal DG where neurogenesis occurs over the lifespan is the brain area with one of the highest abundances of both GRs and MRs (Reul and Kloet 1985; Herman and Spencer 1998; Han *et al.* 2005). Structural integrity and functions of the DG are highly susceptible to various types of stress and activity of GC-mediated signaling via both genomic and non-genomic pathways at all stages of life (Gould *et al.* 1990; Sloviter *et al.* 1989; Stienstra *et al.* 1998; Krugers *et al.* 2007; Dahlin *et al.* 2019; Datson *et al.* 2012; Woolley *et al.* 1991; Sapolsky *et al.* 1991). Most, if not all effects of GCs on the AHN depend on the interaction of GCs with their receptors. The implication of GRs and MRs in the regulation of the AHN represents a key link necessary to understand mechanisms of GCs-mediated control of hippocampal structural plasticity. MR is abundant in neurons of the hippocampus (DG in particular) and mostly absent in other regions, opposite to ubiquitously expressed GR. Since the MR has a ten-fold higher affinity for GCs than the GR, the MR appears to be fully occupied even at low physiological GCs levels while the GR can be activated only at high GCs concentrations (at the peak of the circadian rhythm or under stress). Therefore, the balance between occupancies of the GR and MR seems to play a central role in modulation of various brain functions, including the AHN (Wong and Herbert 2005; Le Menuet and Lombès 2014).

GCs are central to hypotheses regarding AHN involvement in age-related and psychiatric disturbances associated with altered hippocampal plasticity, particularly dementia and major depression. In this respect, GCs are some of the most potent and relevant factors. Numerous reports show that high vulnerability to stress and elevated corticosterone are injurious to the AHN and contribute to neuronal loss. These features are common for some forms of depression, diabetes, cognitive disturbances, and aging, suggesting their involvement in the hippocampal abnormalities revealed in these situations. Stress factors are critical links of various pathological states, including emotional disturbances, cognitive and metabolic disorders. Indeed, a number of studies demonstrated that the AHN is decreased in rodent models for stress-related disorders, and in many cases, high levels of GCs accompanied this phenomenon. Fitzsimons and co-authors (Fitzsimons *et al.* 2016) have reviewed the literature on the evidence for the direct and indirect effects of GCs on neural stem/progenitor cell proliferation and the AHN. The available data suggest that GCs rhythmicity and oscillations originating from the activity of the HPA axis may be

crucial for the regulation of neural stem/progenitor cells in the hippocampus, both in normal conditions and in pathologies associated with modifications of GCs oscillations.

GCs target certain cell types in the neurogenic niche of the DG. Their receptors, GR and MR, are differentially expressed in sequential stages of the neurogenic cascade (Garcia *et al.* 2004) (1). Analysis of GR and MR expression in the mouse DG at different time points (4 h, 1, 3, 7 days, 4 weeks) after a single pulse administration of 5-Bromo-2'-deoxyuridine (BrdU) revealed that there were no cells expressing only MR at any time points. Cells expressing MR appeared at 3 days after a single BrdU injection, and all of them were positive for GR. The portion of MR and GR double-positive cells progressively grew with time reaching approximately 90% at 4 weeks. At all time points tested, only a small portion of GR-positive cells incorporated BrdU. These observations indicated that the vast majority of cells undergoing divisions (up to 3 days after a single BrdU injection) in the DG do not express either GR or MR, and, therefore, are not responsive to GCs at least via the genomic mechanism of action. Combining the use of transgenic nestin-GFP mouse strain (Yamaguchi *et al.* 2000) with the cell phenotyping, Garcia and co-authors revealed that approximately a half of the early precursors, RGLs and transient progenitor cells expressing the transgene nestin-GFP, had only GR (Garcia *et al.* 2004). Late proliferating precursors expressing the transgene nestin-GFP and doublecortin had neither GR nor MR. A half of doublecortin-positive postmitotic neuroblasts expressed only GRs. The next stage, when differentiating newborn neurons express calretinin, is characterized by the absence of both GR and MR. All fully differentiated calbindin-positive neurons expressed both MRs and GRs. Interestingly, the pattern of GR and MR expression through the neurogenic stages differed in young and aged animals. Particularly, in aged mice, the proportion of the early GR-positive precursors (RGLs and transient amplifying cells) was increased, and calretinin-positive differentiating newborn neurons acquired expression of both MR and GR. These age-related changes in the expression of the receptors of GCs in early neural precursors and maturating neurons may explain, at least in part, reduced precursor cell proliferation (Garcia *et al.* 2004; Cameron and McKay 1999) and delayed maturation of newborn neurons (Rao *et al.* 2005) in the aged DG. In general, these observations reveal a higher significance of GC signaling for the hippocampal neurogenesis in the aged brain.

Similarly, single-cell transcriptomic analysis revealed that expression of the *NR3C1* gene encoding GR is downregulated when quiescent RGLs become activated and enter the cell cycle, and is no longer detected in early transient progenitor cells (Shin *et al.* 2015). Clonal analysis of single precursor cells purified by fluorescence-activated cell sorting from the mouse DG indicated that neurosphere-forming cells comprise of two populations, one of them decreasing proliferative activity in response to corticosterone treatment

(Jhaveri *et al.* 2015). In general, these findings are in agreement with observations by Garcia and co-authors (Garcia *et al.* 2004). Additionally, most recent findings have demonstrated the involvement of the GC-dependent signaling in the maintenance of RGLs in the quiescent state. Schouten and co-authors (Schouten *et al.* 2019) revealed differences in the time course of age-related exhaustion of GR-negative and GR-positive subpopulations of the RGLs in the mouse DG. The GR-negative subpopulation exhibited more rapid, exponential depletion with age, whereas GR-positive one exhausted linearly during aging and became predominant at 6 months of age. Circadian oscillations of the blood plasma corticosterone, especially in the aged animals, were found to be crucial for the maintenance of the GR-positive RGLs in the quiescent state and to preserve the RGL pool from premature exhaustion. In the cultured hippocampal neural precursors, oscillations of corticosterone were shown to exert long-lasting alterations in the methylation state of promotors of numerous genes involved in governing the cell cycle. These findings allowed for establishing relationships between the GC-dependent signaling and the regulation of the RGL quiescence/division balance and explaining the mechanism of RGLs maintaining across the life span (Figure 1).

The generation of new neurons in the DG is not an isolated process; at each stage of the AHN, they are surrounded by multiple cell types such as exciting and inhibiting neurons, astrocytes, and microglia. The neurogenic niche is also rich in exciting and inhibiting afferent neuronal projections from the entorhinal cortex, medial septum, contralateral hilus, and the brainstem raphe nuclei (Bao *et al.* 2017; Yeh *et al.* 2018; Moore and Halaris 1975; Ino *et al.* 1998) and is closely associated with blood vessels (Palmer *et al.* 2000). All these components of the neurogenic niche modulate stem cell life cycle, progenitor cell proliferation, and maturation and integration of newborn neurons via contact interactions (Notch) and the release of soluble factors such as neurotransmitters (glutamate, GABA, serotonin), neurotrophic factors (BDNF), growth factors [vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2)], morphogens [Wnt ligands, Sonic Hedgehog, bone morphogenic protein (BMP), etc]. Since virtually all these components of the neurogenic niche are responsive to GCs, they serve as indirect mediators of GC action on different stages of the AHN. For instance, stress and GCs were demonstrated to perturb BDNF-, FGF2-, VEGF-, and glutamate-dependent signaling pathways, reduce expression of the serotonin 5-HT_{1A} receptor, and activate Dickkopf-1 (an inhibitor of the canonical Wnt pathway) in the neurogenic niche of the DG (Suri and Vaidya 2013; Numakawa *et al.* 2017; López *et al.* 1998; Meijer and Kloet 1995; Lowy *et al.* 1993; Moghaddam *et al.* 1994; Hansson *et al.* 2000; Mocchetti *et al.* 1996; Kirby *et al.* 2013; Heine *et al.* 2005; Matrisciano *et al.* 2011; Joëls 2007). It is believed that, due to this divergence of the pathways mediating the GC action on the neurogenic cascade, different levels of stress and activity

of the GC-dependent signaling exert diverse and even opposite effects on the rate of newborn neuron production and on their maturation and integration in the existing neuronal circuits (Saaltink and Vreugdenhil 2014) (Figure 1).

Although rapid non-genomic effects of GCs, primarily associated with the GC binding to the membrane-associated GRs and MRs, on the synaptic transmission in the hippocampus are well documented, it remains obscure whether non-genomic effects of GCs are important for the AHN. This uncertainty is primarily linked to the fact that noticeable changes in the rate of proliferation in the DG and in the maturation and integration of newborn neurons appear, at least, hours after exposure to any stimulus. This complicates the unambiguous separation between rapid non-genomic and transcription-dependent effects of GCs on the AHN. A potent role of non-genomic effects of GCs on proliferation of neural progenitor cells has been demonstrated in the neurosphere cultures from embryonic mouse brain (Samarasinghe *et al.* 2011). It was found that gap junction intercellular communication is rapidly inhibited when cells are treated with a cell-impermeable conjugate of dexamethasone bound to bovine serum albumin for 1 h. This transient inhibition is mediated by the membrane GR and MAPK-dependent phosphorylation of the gap junction protein Connexin43. Pharmacological suppression of the gap junction intercellular communication was shown to shorten the duration of the S-phase of the cell cycle, thus linking non-genomic action of GCs with division kinetics of the neural progenitor cells. In light of recent evidence indicating that deletion of Connexin43 in astrocytes and RGLs induces their uncoupling accompanied by decreased proliferation in the DG (Liebmann *et al.* 2013; Zhang *et al.* 2018), non-genomic effects of GCs on gap junction intercellular communication seem valid for the AHN as well.

The effects of corticosterone on immature neurons are more prominent in the ventral hippocampus. high corticosterone decreased immature neuron activation; high corticosterone exposure may have enduring consequences on the integration or function of cells (workman *et al.* 2015). an in vitro study demonstrated dose- and time-dependent suppressive effects of the long-term cortisol treatment on the growth rate and proliferation of the neural stem/precursor cells derived from subventricular and subgranular zones (abdanipour *et al.* 2015). in human hippocampal progenitor cells, cortisol at a low concentration (100 nM) augmented proliferation, reduced differentiation into microtubule-associated protein 2 (MAP2)-positive neurons and doublecortin (Dcx)-positive neuroblasts, and increased differentiation into S100β-positive astrocytes (Anacker *et al.* 2013). These effects were eliminated by spironolactone, the MR antagonist, and mimicked by aldosterone, the MR-agonist. On the contrary, cortisol at a high concentration (100 μM) reduced proliferation and differentiation into MAP2-positive neurons and into Dcx-positive neuroblasts, but did not regulate astrogliogenesis. These effects were

blocked by RU486, the GR antagonist, and mimicked by dexamethasone, the GR agonist,. It should be noted that the interpretation of these data is limited by the understanding that cell cultures do not reproduce some essential specific features of in vivo AHN.

Two decades ago a significant body of evidence was collected that the proliferation of granule cell precursors, and eventually the production of new granule cells, are dependent on the levels of circulating GCs, excessive GCs inhibiting cell proliferation in the DG during the early postnatal period and in adulthood (Gould and Tanapat 1999). It has been proposed that the suppressive action of GCs on cell proliferation is not direct but occurs through an NMDA receptor-dependent excitatory pathway. Stressful experiences elevating circulating levels of GCs and stimulating hippocampal glutamate release, inhibit the proliferation of granule cell precursors (Gould and Tanapat 1999). Later a number of other mechanisms have been suggested. Since GCs also change expression and signaling of BDNF, the neurotrophin supporting neuroplasticity, enhancing cell survival, augmenting hippocampal neurogenesis, and cellular excitability, it has been suggested that definite adverse effects of GCs may be mediated by decreased BDNF expression and signaling (Suri and Vaidya 2013). Gene expression microarray and pathway analysis have shown that cortisol at a low concentration augments Notch/Hes-signaling, at a high concentration it reduces TGFβ-SMAD2/3-signaling, and at both concentrations it slows down Hedgehog signaling, reduced Hedgehog signaling significantly contributing to the cortisol-induced reduction in neuronal differentiation (Anacker *et al.* 2013). Epigenetic mechanisms may be involved in GCs-mediated modulation of neurogenesis, though so far this suggestion is confirmed mostly by in vitro data. Exposure to GCs during hippocampal neurogenesis primes future stress response by inducing changes in DNA methylation in a human hippocampal progenitor cell (HPC) line (Provençal *et al.* 2019). It is proposed that early exposure to GCs can change the setpoint of future transcriptional responses to stress by inducing lasting DNA methylation changes, such altered setpoints being probably related to differential vulnerability to stress exposure later in life.

Yu and co-authors (Yu *et al.* 2004) have reported about differential effects of corticosterone and a GR specific agonist dexamethasone on hippocampal neurogenesis in vitro suggesting that corticosterone elicits its effects on neurogenesis including proliferation and differentiation while stimulation of the GR is sufficient to decrease only. While corticosterone significantly decreased the number of BrdU-labeled cells, caused the dendritic atrophy in MAP2-labeled cells and dose-dependently decreased expressions of NeuroD, BDNF, and NR1 mRNA levels as well as protein levels of p-ERK and p-CREB, dexamethasone had an inhibitory effect on proliferation, but not differentiation. Like other in vitro data, the validity of these results for in vivo situation is debatable. Fitzsimons and co-authors (Fitzsimons *et al.* 2013) showed a

primary role of the GR in newborn hippocampal cells; the GR are involved in establishing their synaptic connectivity, and as well as functional and structural integration into mature hippocampal circuits mediating fear memory consolidation. Selective GR knockdown in newborn cells of the hippocampal neurogenic niche, accelerated their neuronal differentiation and migration. Remarkably, GR knockdown resulted in ectopic localization of a subset of the new granule cells, modified their dendritic complexity, and augmented the number of mature dendritic spines and mossy fiber boutons. Functionally, cells with GR knockdown possessed increased basal excitability parallel to impaired contextual freezing during fear conditioning. Corticosterone treatment attenuated the proliferation of cells which subsequently developed into neurons, but administration of mifepristone, the gr antagonist, during the final 4 days of a 21 days period of corticosterone treatment completely normalized the reduced number of newborn cells (Hu *et al.* 2012). Despite the continuous corticosterone exposure, on following days, corticosterone effects on neurogenesis could be fully reversed by a single-day treatment with mifepristone on day 18.

Genetic disruption of MR leads to impaired neurogenesis and granule cell degeneration in the hippocampus of adult mice. Gass and co-authors (Gass *et al.* 2000) compared MR-/- mice (with salt loss syndrome corrected by exogenous NaCl), with GR-/- mice with a brain-specific deletion of the GR gene generated by the Cre/loxP-recombination system. A decreased density of granule cells was revealed in the hippocampus of adult MR-/- mice but not in GR-/- mice. Adult MR-/- mice had elevated corticosterone plasma levels and showed a significant reduction of granule cell neurogenesis, possibly mediated by GR. These data suggest the involvement of MR in long-term trophic effects of GCs on dentate granule cells, these MR-related alterations potentially participating in the pathogenesis of hippocampal changes observed in aging, chronic stress, and affective disorders. Some remarkable data have been received in in vitro experiments, though not confirmed in in vivo studies. The MR agonist fludrocortisone promoted the survival and proliferation of adult hippocampal progenitors (Gesmundo *et al.* 2016). It attenuated the detrimental effects of amyloid-β peptide 1-42 (Aβ1-42) on cell survival, proliferation, and apoptosis in adult rat hippocampal progenitor cells, and increased the phosphorylation of both PI3K/Akt and GSK-3β, which was reduced by Aβ1-42. Fludro blocked Aβ1-42-induced hyperphosphorylation of Tau protein, suggesting the potential therapeutic importance of targeting MR for increasing hippocampal neurogenesis and for treating neurodegenerative diseases. In cultured hippocampal neurons it has been shown that MR mediates augmentation of neurogenesis and differentiation of processes, whereas GR is involved in the suppression of their morphology (Fujioka *et al.* 2006). Interestingly, the administration of GCs decreased polysialylated neural cell adhesion molecule expression in the adult rat DG (Nacher *et al.* 2004). Montaron and co-authors (Montaron *et al.* 2003) demonstrated that stimulation of the MR was sufficient to mediate

the effects of corticosterone on neurogenesis and to protect mature cells from cell death whereas stimulation of the GR was necessary to modulate PSA-NCAM expression. Chronic corticosterone administration reduced dendritic complexity in mature, but not young granule cells in the rat DG. Yau and co-authors (Yau *et al.* 2016) showed a progressive increase in the protein levels of GR in the cultured primary hippocampal neurons during neuronal maturation suggesting that mature neurons are likely more vulnerable to chronic exposure to corticosterone due to their higher expression of GR. Thus, a number of studies show inter-reliant involvement of MR and GR in the regulation of hippocampal neurogenesis by GCs.

Though the evidence of the control of the AHN by GCs is quite strong, however, during more than two decades of studies within this field a number of contradictory data have been reported and the situation with the cross-talk between GCs and hippocampal neurogenesis does not appear that straightforward anymore. For example, Martínez-Claros and co-authors (Martínez-Claros *et al.* 2013) showed that moderate corticosterone replacement resulted in significantly more surviving new cells in the DG of the adult rat hippocampus when compared to sham controls. Dominance hierarchy influenced adult neurogenesis in the DG (Kozorovitskiy and Gould 2004), though dominant and subordinate animals showed similar basal, stress, and recovery from stress levels of corticosterone, suggesting that other variables could be responsible for the observed changes. The substantial adolescent-related change in cellular proliferation in the DG was largely unaffected by chronic oral corticosterone exposure in males and females (Shome *et al.* 2018). A prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging DG was demonstrated in the absence of an age-related HPA axis activation (Heine *et al.* 2005). Proliferation, migration, and differentiation of new cells into a neuronal or glial phenotype were strongly reduced from 6 weeks of age onwards and hardly present in middle-aged and old rats as confirmed by confocal microscopy analysis. Unexpectedly, no relationships between cell birth and corticosterone levels or stress response parameters were found by these authors in any age group. Cell proliferation in the adult hippocampus decreased as a result of inescapable stress and this effect was reversed by treatment with fluoxetine, both effects being apparently not dependent on blood corticosterone levels (Malberg and Duman 2003).

5. GC-mediated alterations of the AHN in diseased and aged brain.

5.1. Interplay between stress, GCs and hippocampal neurogenesis.

Exposure to stress remains one of the most recognized negative regulators of the AHN, though now there is plenty of evidence for differential effect of stress. In many studies, indeed, stress has been shown to

reduce cell proliferation and, eventually, the AHN. This effect is common across mammalian species, life stages, and most types of stressors. As mentioned above, although most evidence point to a modulatory role for GCs in mediating this effect, contradictory data exist (Mirescu and Gould 2006). We suggest that these contradictions are related to the variety of stress models and rodent strains used in the experimental studies. The stress factors are diverse with respect to their nature, severity, and action period/chronicity; on the other hand, their effects depend on the stress reactivity/resilience of the organism in general and of the hippocampus in particular. Therefore, the diversity of the results reported by different groups using various models and experimental animals is not really unexpected reflecting differential effects of stress and GCs on the AHN. The effects of acute and mild stress on the AHN are generally believed to be brief and easily conquerable, while chronic or severe forms of stress can provoke long-lasting decline in the AHN (Lucassen *et al.* 2015). Notably, restraint stress for 2 h can have positive but short-term effects on granule cell survival, showing a transient increase in survival of 14-day-old granule cells, which was not evident 7 days later (Snyder *et al.* 2009). A related point deserving a special analysis elsewhere is possible involvement of a mild stress component in well documented stimulating effects of learning on the AHN. Morris water maze, quite a stressful learning paradigm, was used for the first evidence that learning enhances adult neurogenesis in the hippocampal formation (Gould *et al.* 1999a). Interestingly, the situation appears even more complicated: in rats, spatial learning in the Morris water maze shapes the network by regulating the number and dendritic development of new neurons (Lemaire *et al.* 2012), while in mice, learning in this test does not modify cell proliferation, survival, death, neuronal phenotype, and dendritic morphology (Trinchero *et al.* 2015). Taking into account that both rodent species show learning and memory in this task, these data may at least partially reflect differences in their stress response with respect to the AHN.

As mentioned above, the effects of acute stress on the AHN are mediated by different signal transduction systems (Chapter 4); many of them are induced by GCs and some may be specific with respect to the nature of the stressogenic factor. For example, acute infectious stress upregulates COX-2-related signaling in the DG neurons; this may play a protective role in neurogenesis at least partially through the EP2 receptor. GCs suppressed this COX-2-related signaling, resulting in decreased neurogenesis (Ma *et al.* 2017).

Chronic stress often impairs the activity of the HPA axis, the capability of the hippocampus to change downstream brain structures involved in the stress response, the sensitivity of the hippocampal granule cell network to the effects of novelty/GCs, and the hippocampus-dependent HPA axis negative feedback (Figure 1). According to the majority of the data published, chronic stress results in a significant decrease

in the number of dividing cells, and exogenous corticosterone administration produces a similar effect. Conversely, the removal of circulating GCs via adrenalectomy was shown to dramatically increase cell proliferation in rodent DG. Although cell proliferation Ki67 labeling was initially enhanced by adrenalectomy in rats, the increase was transient and no longer apparent by 4 weeks after adrenalectomy (Spanswick *et al.* 2011). Importantly, cell death continued from day 3 after adrenalectomy for at least 23 weeks. Chronic but not acute foot-shock stress in rat lead to a temporary containment of cell proliferation in the hippocampus (Dagyte *et al.* 2009). Even a strong activation of the HPA axis during acute foot-shock stress was not sufficient to reduce hippocampal cell proliferation, but repeated exposure to stressful stimuli for a prolonged period of time ultimately resulted in deregulated AHN. These data suggest that chronic stress may induce cumulative changes in the brain increasing vulnerability to neuropathology. However, unlike unpredictable chronic stress, believed to decline hippocampal neurogenesis and memory, predictable chronic mild stress (5 min of daily restraint stress for 28 days) decreased depressive- and anxiety-like behaviors and enhanced cognitive function (Parihar *et al.* 2011). This effect was accompanied by a prominent increase in the generation and development of new neurons in the hippocampus. Thus, the chronicity of the stress factor *per se* does not predict negative effects on AHN, the nature of the factor being potentially very important.

Chronic restraint stress decreased the AHN in mice, leading to an impairment of hippocampus-dependent fear memory; corticosterone-induced down-regulation of the brain-specific transcription factor Npas4 expression may be involved in the stress-induced impairment of the hippocampal function (Yun *et al.* 2010). The autophagic death of neural stem cells mediates chronic stress-induced decline of the AHN and cognitive deficits. Chronic restraint stress suppressed the AHN in mice by inducing autophagic cell death (ACD) of hippocampal neural stem cells (Jung *et al.* 2020). NSC-specific, inducible Atg7 conditional knockout mice had an intact number of neural stem cells and neurogenesis level under chronic restraint stress and were resilient to stress- or corticosterone-induced cognitive and mood deficits. Corticosterone treatment of adult hippocampal NSC cultures induced autophagic cell death via serum/GC regulated kinase 3 (SGK3).

Chronic mild stress exposure-induced impairment of cognitive behaviors in Swiss albino mice was accompanied by changes in the neuroimmune (increase in proinflammatory interleukins) and neuroendocrine systems (increased corticosterone and adrenocorticotropic hormone) as well as in neurogenesis (Li *et al.* 2008). Stress by noise (24 h) produced differential corticosterone-dependent effects increasing the proliferation rate of radial astrocytes and decreasing survival of neuroblasts in the adult subgranular zone of mice (Gonzalez-Perez *et al.* 2011). Repeated UV exposure through the skin

harmfully affected the AHN and synaptic plasticity together with the activation of the HPA axis (Han *et al.* 2017). However, Grégoire and co-authors (Grégoire *et al.* 2014) failed to demonstrate a prolonged impact on the AHN of either group housing, social isolation, or chronic increase in plasma corticosterone levels.

Alves and co-authors (Alves *et al.* 2018) described proliferation and survival of adult-born neural cells along the transverse axis of the rat dorsal DG, both basal and stress-related. Normally, proliferating cells, newborn neurons and glial cells were preferentially located at the subgranular zone and suprapyramidal blade. Exposure to chronic stress associated with the HPA axis activation induced a general decrease in the generation of adult-born neural cells and a regional-specific decline in the survival of adult-born neurons at the suprapyramidal blade.

Suppression of neurogenesis results in a potentiated HPA axis response after an exposure to a mild stressor indicating that suppressed neurogenesis regulates the HPA axis response (Schloesser *et al.* 2009). Ablation of hippocampal neurogenesis in mice impaired the response to stress suggesting that newborn neurons in the hippocampus were involved in sensing and eliciting an appropriate response to stress (Tsai *et al.* 2015). Obviously, the molecular mechanisms of stress-associated alterations in neurogenesis need more extensive investigation, however, the involvement of GRs is undoubted. Brief treatment with the GR antagonist mifepristone normalized the corticosterone-induced reduction of the ahn (mayer *et al.* 2006). However, in adult male mice implanted subcutaneously with pellets providing 21-day slow-release of corticosterone, cell proliferation was associated with reduced MR, but unchanged GR mRNA expression (Robinson *et al.* 2016).

The data on the sex differences in the effects of GCs on basal as well as on stress-induced hippocampal neurogenesis are highly contradictory. Indeed, there are very few studies in rodents including both sexes in the same experiment. In adult male and female rats, chronic high corticosterone decreased both cell proliferation and immature neuron density in the DG (Brummelte and Galea 2010). Furthermore, high corticosterone males demonstrated the reduced density in immature neurons in the ventral and dorsal regions of the dg, whereas high corticosterone females only demonstrated the reduced density of immature neurons in the ventral hippocampus. Despite male-female differences in the HPA axis activity, higher levels of GCs and elevated stress responses in female rats, both sexes exhibited similar stress-induced alterations in AHN (Hulshof *et al.* 2012). As a rule, constant GCs elevations correspond with hippocampus-dependent learning deficits, while acute or cyclic GC rises are associated with an improved initial acquisition, the sensitivity being greater for males than for female rats (Claflin *et al.* 2017). Importantly, changes in the AHN paralleled some but not all effects. Hillerer and co-authors (Hillerer *et al.* 2013) found that under baseline conditions, only the number of immature neurons within the

hippocampal DG was higher in males as compared with females. Chronic restraint stress resulted in a number of sex-specific alterations, reducing cell proliferation in males with a concurrent increase in stem cell quiescence, while it did not alter either parameter in females but decreased cell survival. Chronic stress exposure did not affect corticosterone levels in either sex across the initial stress period. chronic administration of corticosterone to female mice (a procedure enhancing behavioral emotionality in male mice) failed to potentiate the behavioral effects of corticosterone and did not affect the AHN (Mekiri *et al.* 2017).

Sleep deprivation is a clinically relevant situation which can be regarded as a specific form of stress. Deprivation or fragmentation of sleep for longer than 2 days significantly inhibited cell proliferation and neurogenesis in the hippocampus of adult rats and mice. Impaired AHN is believed to cause some of the effects un memory and mood inducted by acute and chronic sleep disruptions. The mechanisms of this phenomenon remain obscure, though some experimental data are available. Some authors show that sleep deprivation inhibits the AHN in the hippocampus by elevating GCs through its compensatory aftereffects, though GCs-independent factors may be also involved (Mirescu *et al.* 2006). Other groups suggest that sleep deprivation can inhibit the AHN most probably independently of GCs (Mueller *et al.* 2008). As a rule sleep disruption procedures are regarded as stressful, surprisingly, elevated corticosterone was not essential for this effect. nevertheless, procedures preventing both increased corticosterone and interleukin 1β signaling appear to block the influence of sleep deprivation on cell proliferation (Mueller *et al.* 2015). The inhibitory effect of sleep deprivation on cell proliferation in the hippocampus of adult mice was eliminated by corticosterone clamp combined with interleukin-1 receptor 1 knockout (Mueller *et al.* 2014). Although deprivation procedures can stimulate adrenal corticosterone release, suppression of cell proliferation by sleep deprivation may not require elevated corticosterone. Rat AHN was reduced by sleep fragmentation, but elevated GCs did not account for most of the reduction in cell proliferation (Guzman-Marin *et al.* 2007).

Decreased AHN following prolonged stress may have a cumulative impact of stress-induced structural plasticity in aging (Radley and Morrison 2005). Aging is accompanied by alterations of spatial memory, a decline in the AHN, and a dysregulation of the HPA axis leading to elevated levels of circulating cortisol/corticosterone. Montaron and co-authors (Montaron *et al.* 2006) showed that suppression of GCs secretion in rats from midlife to the rest of the life increased neurogenesis in old animals and prevented the appearance of age-related memory disorders. Reciprocally, aged rats with a chronic upregulation of the HPA axis demonstrated spatial memory impairments associated with low levels of hippocampal cell proliferation and survival. These data suggest that the extent of lifetime exposure to GCs can determine

the degree of age-related decline in hippocampal neurogenesis and as a result age-related cognitive dysfunctions.

In conclusion, effects of stress-factors on GC-mediated changes in AHN cannot be described with dominating simple picture "impairment in severe and chronic stress, stimulation in mild acute stress". They are much more intricate; depend on the species, sex and age of animals as well as on specific features of the stress factor.

5.2. Early life stress, depression, antidepressants

GCs as regulators of the AHN are considered as an essential link in the hypotheses regarding altered hippocampal plasticity related to the AHN as central in the pathogenesis of in age-related and psychiatric disturbances. The suggestion that impaired neurogenesis is important to the affective symptoms of depression is being discussed for more than two decades (Sapolsky 2004). Using either transgenic or radiation approaches to supress AHN specifically, Snyder et al. (2011) found that GC levels recovered slower after moderate stress and were less inhibited by dexamethasone in neurogenesis-deficient mice as compare with intact animals. Neurogenesis-deficient mice also demonstrated elevated food avoidance in a novel environment after acute stress, augmented behavioural despair in the forced swim test, and reduced sucrose preference. These data support a direct role for the AHN in depressive illness and suggest that a small subset of neurons within the DG is critical for a hippocampal negative control of the HPA axis and mediates the central role for the AHN in depression (Snyder *et al.* 2011).

Adverse juvenile experiences have negative health consequences later in life. During the sensitive period of early life, stress may reprogram brain plasticity, particularly, in the hippocampus. It is believed that early life experience may alter the response of the AHN to stress and inhibit structural plasticity via hypersensitivity to GCs thus diminishing the ability of the hippocampus to effectively respond to stress in adulthood (Mirescu *et al.* 2004). One of the most popular approaches to confirm this is modeling early life stress inducing the development of depressive-like and anxiety-like behavior. Indeed, animals subjected to early life stress show an early onset of age-induced alterations on depression and metabolic risk, and these effects relate to alterations in the AHN (Ruiz *et al.* 2018). In general, stress in early life inhibits the AHN. Adverse experience limited to early life, specifically the removal of rat pups from their mothers for three hours each day, decreased production of new granule neurons in adulthood through a corticosterone-dependent mechanism (Karten *et al.* 2005). However, Lajud and co-authors (Lajud *et al.* 2012) suggested that the decrease in hippocampal neurogenesis is an early onset phenomenon and that adverse experiences alter hippocampal ontogeny without chronic elevation of GCs levels. Though periodic

maternal separation decreased hippocampal neurogenesis without affecting basal corticosterone during the stress hyporesponsive period, it altered the HPA axis and coping behavior in adulthood. The early rise of GCs occurring after exposure to adverse early life experiences may affect hippocampal ontogeny by altering the hippocampal negative feedback on the adult HPA axis. Activation of GR during the key period of postnatal NSC generation has a profound impact on both the AHN and behavior (Ortega-Martínez and Trejo 2015).

Intrauterine exposure to stress or high levels of GCs, endogenous or synthetic, has a molecular and structural impact on brain development and appears to impair cognition and increase anxiety and reactivity to stress. The hippocampus and amygdala are particularly sensitive to this type of stress (Miranda and Sousa 2018). Prenatal stress modifies the morphological development of the hippocampus, the effects of stress being intensity-dependent. Short and mild prenatal stress increased neonatal neurogenesis and differentiation of of hippocampal neuronal processes, however, long and severe stress had harmful influence on their morphology, alterations in MR and GR contributing to stress-induced morphological changes (Fujioka *et al.* 2006). Leuner and co-authors (Leuner *et al.* 2007) reported that maternal experience inhibited the production of immature neurons in the hippocampus during the postpartum period through elevations in GCs. The mechanisms of early life stress influence on the AHN in rodent models are the focus of many studies. Many of them show the involvement of neuroinflammatory cytokines. In particular, in mice brain interleukin-1 was shown to mediate chronic stress-induced depressive behavior associated with adrenocortical activation and the AHN repression (Goshen *et al.* 2008). GRs are discussed as key players in the cytokine-induced signaling mechanisms involved in regulating neurogenesis (O'Léime *et al.* 2017). Stress-induced placental 11beta-hydroxysteroid dehydrogenase type 2 expression (an enzyme preventing GC-mediated over-stimulation of the MR by converting the biologically active cortisol/corticosterone to the inactive cortisone) may be critical in protecting the fetal brain from maternal stress-induced effects on the AHN (Lucassen *et al.* 2009).

Effects of early life stress on neurogenesis are age- and sex-dependent. Loi and co-authors (Loi *et al.* 2014) suggested that normalization can be expected during critical stages of brain development. In male rats, postnatal stress to some extent augmented neurogenesis until the onset of puberty; neurogenesis was diminished when rats reached adulthood. However, female rats demonstrated a significant reduction in neurogenesis prior to the onset of puberty, while this effect subsided when animals reached young adulthood. Transient treatment with a GR antagonist normalized cell proliferation in maternally deprived female rats. Chronic restraint stress in adolescence differentially influenced functioning of the HPA axis and the AHN in male and female rats (Barha *et al.* 2011). Males and females differently responded to

chronic stress during adolescence; and only adult females demonstrated higher basal corticosterone levels as compared to nonstressed controls. Stressed females showed a reduced number of proliferating and surviving BrdU-labeled cells co-labeled with NeuN cells in the DG in adulthood as compared to non-stressed same-sex controls. Adolescent male rats appeared more reactive to chronic stress; they had higher corticosterone levels and lower body weight. however, in adulthood, they demonstrated a small raise in cell survival and no influence of adolescent stress on basal corticosterone. Prolonged maternal postpartum corticosterone increase (a model of postpartum stress/depression) in rats blunted negative feedback in the HPA axis in males and tended to augment the density of immature neurons in males, however, but reduced it in female offsprings (Gobinath *et al.* 2016). Concurrent maternal postpartum antidepressant fluoxetine raised the density of doublecortin-expressing immature neurons in the hippocampus of adult male offsprings, though diminished the density of immature neurons in adult female offsprings.

The complex interplay between stress and the AHN includes the involvement of the GR, the key mediator of the stress response of AHN, including the proliferation, differentiation, migration, and functional integration of newborn neurons. Many mechanisms regulating GR activity in relation to the AHN have been discussed by Saaltink & Vreugdenhil (Saaltink and Vreugdenhil 2014). They have postulated a novel concept: the intensity of GR expression can directly regulate the excitation-inhibition balance, essential for appropriate neurogenesis. The authors suggest that an excitation-inhibition disbalance may cause aberrant functional integration of newborn neurons associated with psychiatric and paroxysmal brain diseases. Kronenberg and co-authors (Kronenberg *et al.* 2009) reported that hippocampal neurogenesis was reduced in the GR(+/-) genetic mouse model of depression. These mice showed a depression-like phenotype including augmented learned helplessness on the behavioral level and neuroendocrine changes with the HPA axis overdrive characteristics of depression as well as reduced BDNF levels. Neurogenesis in GR(+/-) mice was additionally inhibited by restraint stress. Social defeat stress exposure of juveniles induced social avoidances more persistent as compared to adults, these social avoidances being accompanied by GR-mediated inhibition of hippocampal neurogenesis (Mouri *et al.* 2018). Chen and co-authors (Chen *et al.* 2019) showed that MR-dependent neurogenesis may be closely related to anxiety-like behavior. Exposure to chronic stress either early in life or in adulthood reduces the expression of GR through epigenetic mechanisms. Stress exposure up-regulates the expression of the co-chaperone gene FKBP5 and controls the activity of GR by regulating the translocation of the receptor complex to the nucleus (Cattaneo and Riva 2016). Another mechanism contributing to alterations in responsiveness of the GR is its state of phosphorylation controlling its activation, subcellular localization and transcriptional

activity. Furthermore, phosphorylation of the GR may represent an essential mechanism for the cross-talk between GR-dependent and transcription neurotrophic signaling, two key actors involved in mood disorders. Serum GC kinase-1 (SGK1) is a gene downstream from GR, potentially contributing to stress-related alterations. SGK1 expression is considerably augmented after chronic stress exposure in rodents and in the blood of drug-free patients with depression. SGK1 up-regulation may eventually decrease the AHN and add to the structural abnormalities occurring in these patients (Cattaneo and Riva 2016).

The effects of GCs and the GR are believed to be a central mechanism by which stress and antidepressants may exert their contrasting effects on the AHN, and finally, on mood and behavior. In patients with depression, hyperactivity of the HPA axis and increased blood levels of GCs are found indicative of impaired feedback regulation of the HPA axis mediated by altered function of the GR and excessive GCs signaling. As a consequence, AHN is reduced and neuroplasticity impaired (Anacker *et al.* 2011a). Integrating existing data from clinical studies, animal work, and cellular models suggest a that neurogenesis may be a neurobiological mechanism for continuous reduction of depression symptoms (Anacker 2014).

It has been proposed that antidepressants recruit new neurons to improve stress response regulation. Indeed, in animal models, antidepressants increase the AHN, reversing the loss of adult neural stem cells after chronic stress. Hitoshi and co-authors (Hitoshi *et al.* 2007) used a forced-swim model of stress in mice and showed that chronic stress reduced the number of neural stem cells in the subventricular zone. The effect of of NSC number reduction persisted for several weeks after the termination of stress and could be reversed by treatment with fluoxetine and imipramine, the antidepressant drugs. Using in vitro colony-forming neurosphere assay these authors demonstrated that corticosterone attenuated neurosphere formation by adult neural stem cells. In mice, unpredictable chronic mild stress not only reduced the AHN but also dampened the relationship between the hippocampus and the HPA axis. This relationship was restored by treatment with the antidepressant fluoxetine in a neurogenesis-dependent manner (Surget *et al.* 2011). Although ablation of hippocampal neurogenesis alone did not damage the activity of the HPA axis, fluoxetine could restore regulation of the HPA axis by the hippocampal under chronic stress conditions only if the neurogenic niche remained intact. It has been concluded that newly generated neurons may help stress integration. Increasing neurogenesis during chronic stress or depression allows a dysfunctional hippocampus to re-establish the central control over stress response systems and thus promote recovery.

Anacker and co-authors (Anacker *et al.* 2011b), using progenitor cells of human hippocampus, explored the molecular pathways mediating the antidepressant-stimulated neurogenesis modulation.

Augmentation of neuronal differentiation by antidepressant sertraline involved a GR-dependent mechanism: both immature, doublecortin-positive neuroblasts and mature, (MAP2)-positive neurons were elevated. GR-antagonist, RU486T, abolished this effect. The increase in proliferation of progenitor cells studied by BrdU incorporation could be detected only after co-treatment of the cells with sertraline and dexamethasone, the GR-agonist. Mechanisms induced by sertraline were dependent on PKA-mediated signaling, phosphorylation of GR, and activation of a specific set of genes. GCs and lithium reciprocally regulated the proliferation of adult DG-derived neural precursor cells through the GSK-3beta and beta-catenin/TCF pathway (Boku *et al.* 2009).

5.3. Diabetes/metabolic disturbances

As mentioned above, high susceptibility to stress and increased corticosterone levels are harmful to neurogenesis and induce neuronal cell loss. This is common for some forms of depressive disturbances, diabetes, and aging and suggests the involvement of GCs in hippocampal abnormalities reported in these situations.

Diabetes mellitus is related to unfavorable changes in different organs, in particular, the brain. Diabetic circumstances alter hippocampal plasticity: in both insulin-deficient rats and insulin-resistant mice, diabetes impaired hippocampus-dependent memory, perforant path synaptic plasticity and the AHN (Stranahan *et al.* 2008). These adverse effects were mediated by corticosterone. Rats treated with streptozocin had hyperglycemia induced by reduced insulin as well as increased corticosterone, impairments in the AHN, synaptic plasticity and learning. The mouse strain db/db with insulin resistance and obesity demonstrated similar effects. Importantly, changes in hippocampal plasticity and function in both models could be reversed by restoring and maintaining normal physiological levels of corticosterone. These data suggest that GCs-mediated deficits in neurogenesis and synaptic plasticity can underlie cognitive impairment in diabetes. In two different experimental mouse models of Type 1 diabetes (induced by streptozotocin and the spontaneous non-obese diabetic mice (NOD) with hyperactivity of the HPA axis), Beauquis and co-authors (Beauquis *et al.* 2008) showed effects on the DG neurogenesis, in particular, significant reduction of proliferation and differentiation measured by BrdU immunodetection. Using non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice and C57BL/6 mice once injected with streptozotocin intraperitoneally, Guo and co-authors (Guo *et al.* 2010), demonstrated that diabetes inhibited proliferation of cells both in the hippocampus and in the subventricular zone, this inhibition being accompanied by increased GCs levels and decreased BDNF expression. However, in Goto-Kakizaki rats, a spontaneous model of type 2 diabetes, decreased GR immunolabeling in hippocampal CA1, associated with hypercorticosteronemia, increased proliferation of cells cell, and neuronal

differentiation was detected without associated modification of survival (Beauquis *et al.* 2010). The authors interpret a high rate of proliferation as a "compensatory mechanism for neuronal suffering", however, these data do not confirm the unambiguous decrease of neurogenesis by GCs overload.

Metabolic disturbances of other types associated with the HPA axis dysfunction also affect the AHN. High dietary fat intake can disrupt hippocampal neurogenesis in rodents, probably through an increase in serum corticosterone levels, males being more susceptible than females (Lindqvist *et al.* 2006). Huntington's disease is a fatal genetic neurological disorder caused by a mutation in the human Huntingtin (HTT) gene. Along with a widespread neuropathology and progressive motor, cognitive, psychiatric, and metabolic symptoms, Huntington's disease patients also show neuroendocrine changes including a robust, significant elevation in circulating cortisol levels. HTT mutation confers a toxic gain of function of the encoded mutant huntingtin (mHTT) protein, leading to the formation of mHTT-positive inclusion bodies, gene deregulation, reduced levels of the AHN and neuronal loss throughout many regions of the brain. Importantly, normalizing GCs levels attenuated metabolic and neuropathological symptoms in the R6/2 mouse model of Huntington's disease (Dufour and McBride 2019).

5.4. Brain injury

Brain injuries can have negative effects on neural stem cells and the following neurogenic cascade in the hippocampus, resulting in the induction of aberrant neurogenesis, which is believed to compromise hippocampal network function deterring hippocampus-dependent behavior (Bielefeld *et al.* 2019). Stroke, traumatic brain injury, and other focal brain injuries may induce the development of postponed (months, years) cognitive and depressive disturbances, often comorbid. In spite of the lack of a primary hippocampal injury, these delayed disturbances are associated with functional and structural hippocampal alterations. These facts, together with the lack of an apparent association between the chance of cognitive and depressive disorders development and the severity and localization of primary focal cerebral damage, formed the basis for a novel hypothesis considering distant hippocampal damage as an essential link in the development of cognitive and psychiatric disturbances (Gulyaeva 2019b). The GCs excessively secreted after brain damage, interact with hippocampal receptors of GCs and stimulate signaling pathways inducing neuroinflammation and consequent events, ultimately resulting in AHN disturbances hippocampal neurodegeneration. These events are most possible in patients with HPA axis dysfunction underlying abnormal stress-response (Gulyaeva 2019a). The problem of injury-induced neurogenesis is one of most clinically relevant growing points in the field. Though it is believed that injury increases proliferation of quiescent stem and progenitor cells in neurogenic niches of the brain, specific mechanisms of partial recovery from brain injury induced by trauma, hypoxia, or stroke remain obscure

and the data on a potential contribution of this injury-induced neurogenesis to recovery after brain injury remain controversial. However, current data show that the activation of hippocampal neural stem/precursor cell and following neurogenesis are involved in spontaneous recovery following brain injury (Yu *et al.* 2016). The contribution of AHN in unfavorable events, such as seizures, and other aspects of injury-induced neurogenesis, are still being explored, and the involvement of GCs-induced signaling is one of the putative mechanisms. The polyphenol resveratrol showed regulatory effects on the AHN, significantly attenuating ischemia-induced DCX/PSA-NCAM expression (Girbovan *et al.* 2016). Resveratrol attenuated corticosterone levels 3 days post-ischemia and a trend toward attenuating corticosterone secretion in response to a 15 min restraint stress and demonstrated beneficial effects on spatial memory retention.

5.5. Seizures

Though the complicated and often contradictory influence of neuronal hyperexcitation/ seizures/ epilepsy on the AHN has been well documented (reviewed in (Parent and Murphy 2008; Parent and Kron 2012; Bielefeld *et al.* 2014; Jessberger and Parent 2015; Pineda and Encinas 2016)), the involvement of GCs in these effects remains obscure. Notably, recurrent seizures and epilepsy are often accompanied by a raise in cortisol/corticosterone levels. In rodents, suppression of hippocampal neurogenesis is associated with developmental stage, the number of perinatal seizure episodes, and GCs level (Liu *et al.* 2003). Importantly, a history of only one or two perinatal seizure(s) can suppress neurogenesis if a second or third seizure recurs after a critical developmental period associated with a marked flash in corticosterone. During the first 2 postnatal weeks, constant augmentation in postictal circulating corticosterone levels but not the duration or intensity of ictal activity affected neurogenesis. The increased proportion of immature granule cells and putative stem cells with irregular morphology suggested that progenitors may not differentiate properly and remain in an immature state.

High levels of GCs often reduce the AHN, but electroconvulsive seizures (ECS) have opposite effects in the presence of elevated levels of GCs (Hellsten *et al.* 2002). ECS induced an increase in neuronal precursor proliferation in the subgranular zone, this increase being not inhibited by elevated levels of corticosterone although corticosterone strongly inhibited ECS-induced endothelial cell proliferation. Despite common factors regulating neurogenesis and angiogenesis, ECS-induced proliferation of neuronal precursors can take place even if the angiogenic response is blunted (Ekstrand *et al.* 2008). ECS increased both the number and dendritic complexity of adult-born migrating neuroblasts and ECS were able to prevent corticosterone -induced anxiety- and depressive-like behaviors. The ability of ECS to promote antidepressant-like behavior was blocked in mice lacking the AHN demonstrating possible association of

corticosterone-induced behavioral deficits with neurogenesis (Schloesser *et al.* 2015). Using rapid amygdala kindling, Kumar and co-authors (Kumar *et al.* 2011) demonstrated that early life stress resulted in continuing augmentation of the responses of the HPA axis to limbic seizures, accompanied by more expressed cell loss in hippocampal CA3 and increased neurogenesis, all these effects being a sex-dependent.

In conclusion, the existing data on the involvement of GCs in the alteration of the AHN induced by seizures do not yet allow creating an unambiguous concept, though the nature of seizures may be an essential issue.

5.6. GCs-mediated up-regulation of hippocampal neurogenesis.

The above-mentioned data show that impairments of the AHN are not always clearly mediated by GCs. However, GCs orchestrate divergent effects on mood through the AHN. Despite the well-described negative consequences of stress hormones on progenitor cell proliferation in the hippocampus, some experiences producing strong increases in GCs levels in fact promote neuronal growth (Schoenfeld and Gould 2013). In these circumstances, the factors that buffer against the suppressive influence of elevated GCs remain unknown; their discovery may provide clues to reversing pathological processes arising from chronic exposure to aversive stress (Schoenfeld and Gould 2012). Importantly, increasing AHN is believed to be sufficient for reducing anxiety- and depression-like behavior (Hill *et al.* 2015). Overall, the recent findings suggest that rewarding experiences buffer progenitor cells in the DG from the harmful effects of elevated GCs. Experiences up-regulating the AHN include running, mating, living in an enriched environment, and intracranial self-stimulation; they all share in common a strong hedonic component. For example, sexual experience promotes the AHN despite an initial elevation in corticosterone (Leuner *et al.* 2010). While GCs-dependent declines in neurogenesis drive changes in mood after social defeat, GCs secreted during enrichment promote neurogenesis and restore normal behavior after the defeat (Lehmann *et al.* 2013).

Physical exercise is one of the striking examples of GCs mediated increase in the AHN. There are numerous confirmations that physical activity is beneficial for the AHN. Running has strong effects on AHN, including proliferation, survival and maturation of young granule cells. Snyder et al. (Snyder *et al.* 2009) found a significant increase in granule cell survival in the adult DG of mice subjected to voluntary running in the wheel. Okamoto and co-authors (Okamoto *et al.* 2015) reported that mild exercise augmented the AHN without increasing corticosterone blood levels, while both MR and GR antagonists eliminated mild-exercise-induced AHN, but did not influence it during intense exercise. The authors

discuss a permissive, facilitative role of GR and MR in the AHN during mild exercise. In aged mice, running lessened stress and enhanced cell genesis (Kannangara *et al.* 2011). Proliferation of cells and neurogenesis were decreased in the subventricular zone of aging C57Bl/6 mice (17-18 months old). Irrespective of individual or social housing, aged mice had similar basal levels of cell proliferation and demonstrated augmented neurogenesis induced by running. Neither physical activity nor housing conditions no affected corticosterone levels were observed in young mice. Notably, at the onset of the dark cycle a considerable corticosterone elevation was shown in aged sedentary animals in the condition of social housing. Additionally, the increased expression of the *NR3C1* gene encoding GR in the hippocampal tissue was observed in single-housed mice that exercised (Pan-Vazquez *et al.* 2015). This observation indicates that physical activity may increase GC-dependent signaling in the hippocampus, thus promoting enhanced resilience to stress (Pan-Vazquez *et al.* 2015).

Long-term mild, rather than intense, exercise enhanced the AHN and greatly changed the transcriptomic profile of the hippocampus (Inoue *et al.* 2015). Voluntary wheel running reversed the decrease in the neurogenesis (cell proliferation and differentiation) caused by the chronic injection of corticosterone (Lee *et al.* 2016). In young mice, regular treadmill running improved spatial learning and memory, most probably through augmented hippocampal neurogenesis and reduced stress by decreasing the corticosterone level (Li *et al.* 2013). Prolonged treatment of rats with corticosterone (40 mg/kg) suppressed the AHN, decreased hippocampal BDNF levels, and impaired spatial learning; these changes could be prevented by voluntary wheel running (Yau *et al.* 2012). Social isolation stress delayed the positive effects of running on the AHN (Stranahan *et al.* 2006). Individual housing prevented the positive effects of short-term running on the AHN in the hippocampus of rats and inhibited the generation of new neurons, in case of additional stress. Isolation also affected corticosterone levels; irrespective of housing conditions, runners had elevated corticosterone during the active phase, while individually housed runners had higher levels of corticosterone in response to stress. Furthermore, lowering corticosterone levels changed the effect of short-term running on neurogenesis in individually housed rats from negative to positive. These data suggest that a normally beneficial experience can exert a potentially deleterious influence on the brain when social interaction are absent (Stranahan *et al.* 2006).

6. Concluding remarks.

GC-mediated effects on the generation and integration of adult-born neurons in the hippocampal DG heavily depend on the nature, severity, and duration of the acting stress factor. GCs exhibit their effects on the AHN primarily via activation of GR and MR, though, non-genomic effects seem to take place as well. Various brain pathologies and aging are accompanied by a deregulation of the HPA axis and changed

GC-mediated signaling in the brain that in turn cause a wide range of injurious alterations in the AHN (Figure 1). These alterations vary from reduced proliferation of stem and progenitor cells to increased cell death and abnormalities in morphology, connectivity, and localization of young neurons. The lack of normal young granular neurons exerts loss of plasticity of the hippocampal neuronal circuitry, leading to cognitive deficits and mood impairments. In parallel, this insufficiency disrupts hippocampal control of the HPA axis, thus deteriorating resilience to stress and accelerating disease progression. Disruption of the reciprocal regulation between the HPA axis and the generation of the adult-born granular neurons is currently considered to be a key mechanism implicating the AHN into the pathogenesis of numerous brain diseases, including those without a direct robust damage of the hippocampus.

Frequently, though not always, recovering normal levels of the GCs is beneficial for the restoration of the AHN rate and subsequent improvement of cognition and mood impaired by brain pathology. Additionally, temporal deregulation of GC-mediated signaling may have delayed deleterious effects on the AHN. Recent findings have revealed the importance of the proper GC signaling for maintenance of the RGLs in the quiescent state and preserving the RGL pool from exhaustion in the aged brain (Schouten *et al.* 2019; Garcia *et al.* 2004). Thus, a pathology-induced deregulation of GC signaling, apart from other negative effects on the generation of newborn neurons, can exert irreversible premature depletion of the RGL pool, resulting in decreased neurogenesis at later stages of life.

Although the involvement of the reciprocal regulation between the HPA axis and the AHN in the pathogenesis of cognitive deficits and mood impairments appears to be obvious, several critical issues remain unresolved. For instance, what is the contribution of direct and indirect (via niche cells) GC action on the distinct stages of the neurogenic cascade under pathologic conditions? Do non-genomic effects of GCs significantly contribute to the GC-mediated impairments of the AHN in the diseased brain? Are there specific GC-dependent signaling pathways implicated in the pathogenesis of definite brain diseases, or do different brain pathologies share same GC-dependent pathogenetic mechanisms? Resolving these questions could enable identification of molecular targets for ameliorating pathology-induced imbalance in the HPA axis/AHN mutual regulation to conquer cognitive deficits and mood impairments.

--Human subjects --
Involves human subjects:
If yes: Informed consent & ethics approval achieved:

=> if yes, please ensure that the info "Informed consent was achieved for all subjects, and the experiments were approved by the local ethics committee." is included in the Methods.
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Conflicts of interest: Natalia Gulyaeva is a Deputy Chief Editor for the Journal of Neurochemistry.
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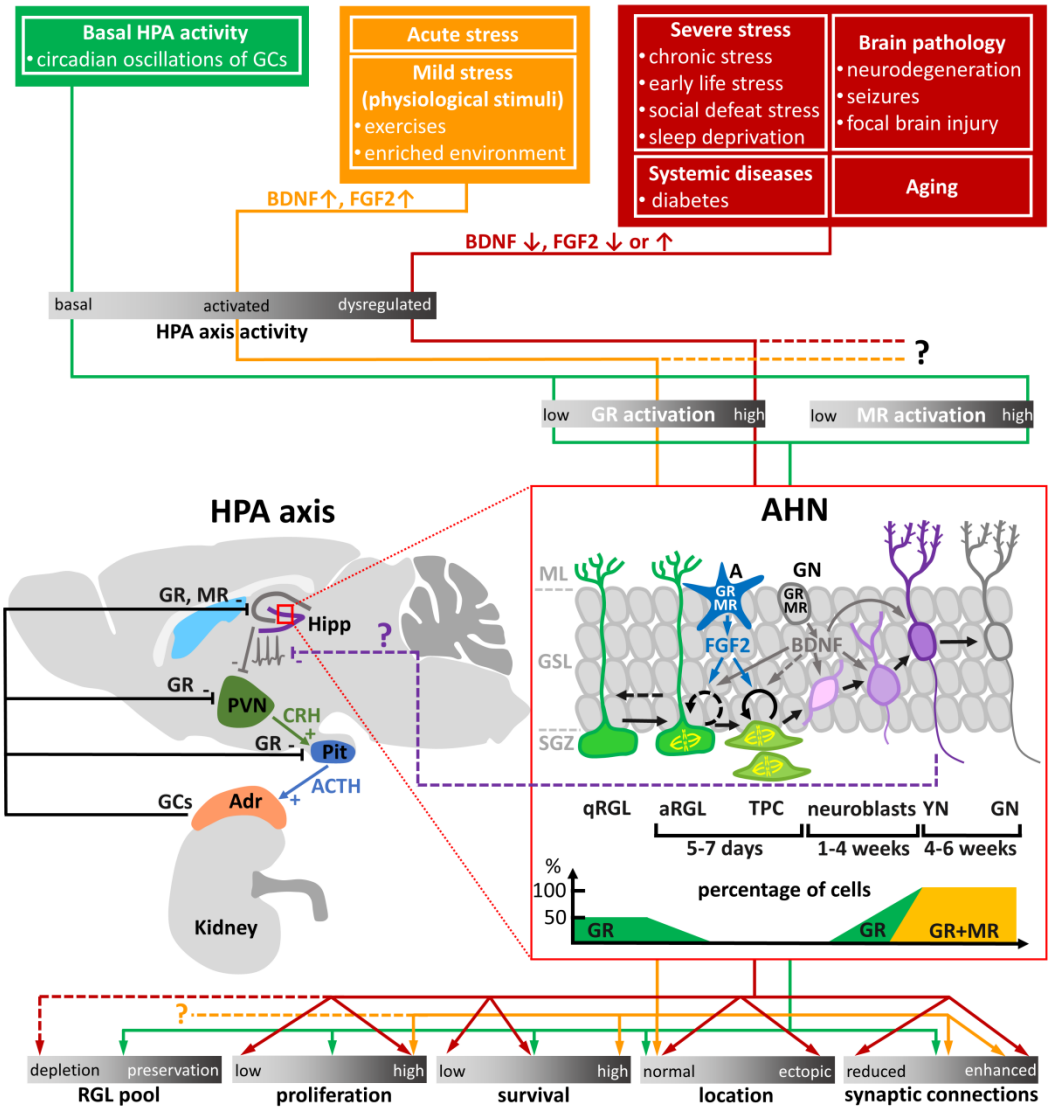
Figure caption

Figure 1. A cross-talk between the HPA axis and the AHN in various contexts and the influence of the glucocorticoid-related signaling activation in the DG on the AHN. Normal functioning of HPA axis (GCs: glucocorticoids, PVN: hypothalamic paraventricular nucleus, Pit: pituitary, Adr: adrenal gland, CRH: corticotropin-releasing hormone, ACTH: adrenocorticotropic hormone) is crucial for stress resilience and for maintaining appropriate levels of the AHN (qRGL: quiescent radial glia-like cell, aRGL: activated radial glia-like cell, TPC: transient progenitor cells). The balanced activation of glucocorticoid (GR) and mineralcorticoid (MR) receptors in the neurogenic cascade and in surrounding cells is necessary for supporting appropriate rates of generation of young neurons (YN) with proper location and synaptic connections. The actions of GCs on the AHN under physiological conditions is coordinated by BDNF and FGF2 produced by surrounding astrocytes (A) and mature granular neurons (GN). The HPA axis deregulation in severe stress conditions, brain pathologies, and aging reduces stress resilience and exerts different impairments of the AHN ranging from the premature depletion of RGLs to abnormal location and wiring of newborn granular neurons.



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