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Mechanisms underlying brain programming by early-life adversity and nutrition

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CHAPTER 1

1

Stress and its main target system: role of the HPA axis

Stress and its effects on neurons and glia with a focus on the glucocorticoid signaling

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Abstract

Exposure to adversity throughout life, especially when in a chronic fashion, is one of the key risk factors for the development of psychopathologies such as depression. One hallmark of such stress-related pathologies is a dysregulated hypothalamic-pituitary-adrenal axis. Therefore, massive research has been aimed at understanding the neurobiology of stress response, and the adaptation and maladaptation that take place in the brain in response to stress exposure. Historically, the impact of glucocorticoids on brain tissues has been examined on neurons. There is however increasing evidence that glucocorticoid receptor-dependent signaling relies on the cell type and that glucocorticoids can also impact glial cells such as microglia and astrocytes. In this chapter, we describe the glucocorticoid receptors expression both on neurons and glia, and that glucocorticoids exposure can affect both neurons and glial cells morphology and functionality. We argue that the stress signal, mediated by glucocorticoids and their receptors, is integrated and fine-tuned with the signaling on neurons, microglia and astrocytes, which all together contribute to the ultimate effects of glucocorticoids exposure on brain plasticity and function. We highlight the need for further studies on the converging effects of glucocorticoids on both neurons and glial cells.

Glossary

Glial cells: Non-neuronal cell types of the brain, fundamental for neuronal and immune support within the brain. These include microglia, astroglia and oligodendrocytes.
Glucocorticoids: Steroid hormones released by the adrenal gland
Hypothalamic-pituitary-adrenal (HPA) axis: The neuroendocrine stress response system of the body. When stress is perceived, corticotropin releasing factor (CRF) is released from the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary, which finally triggers production and release of glucocorticoids from the adrenal glands.
Neurons: Cell types of the brain that receives and sends signals throughout the body.

Keywords

Microglia; Astrocytes; Chronic stress; Glucocorticoid receptor; Mental health; Neurons; Hypothalamic-pituitary-adrenal axis; Brain; Glucocorticoids; Glia

Stress and the Hypothalamic-Pituitary-Adrenal Axis

About one billion people worldwide suffer from mental disorders, causing a considerable social and financial burden (Rehm and Shield, 2019). Besides genetic factors, one of the key systems that has been a focus of attention in understanding the origin of mental disorders has been a dysregulated stress-response. Indeed, exposure to environmental challenges of various nature may have deleterious effects on brain health, resulting in the onset of a range of brain disorders. Accordingly, chronic exposure to adversity and stressful experiences throughout life play a key role in the vulnerability to several psychiatric conditions (McEwen and Akil, 2020).

Although many questions still remain open, the research that has been conducted over the last 50 years allowed to unravel the underlying systems that regulate our body's stress response as well as which dysregulations are key in the development of stress-related psychopathologies, delineating a major role for the neuroendocrine stress axis, the hypothalamic-pituitary-adrenal (HPA) axis.

When stress is perceived the HPA axis is activated (Sapolsky et al., 2000). The threatening stimulus triggers the firing of neurons in the medial parvocellular region of the paraventricular nucleus of the hypothalamus (PVN) leading to the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH in turn triggers the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which eventually leads to the production of glucocorticoids by the adrenal cortex. In addition, CRH, next to being released in the portal circulation and stimulating the pituitary gland, is also released within the brain, in for example the hypothalamus, amygdala, hippocampus and locus coeruleus, where it acts on CRH receptors 1 and/or 2 (CRHR1 and CRHR2), modulates neuronal firing and gene expression, thereby influencing functional behaviors (Joëls and Baram, 2009).

The ultimate signal of stressful events on the brain and body is mediated by glucocorticoids binding to the glucocorticoid and mineralocorticoid receptors (GRs and MRs). GR and MR act via a genomic pathway and, as ligand-activated transcription factors, positively or negatively regulate gene expression (Weikum et al., 2017). Thereby, glucocorticoids and their receptors can modulate several different processes including metabolism, immune and cardiovascular functions, cognition and emotions (Oakley and Cidlowski, 2013). In the brain, the binding of corticosteroid hormones enables cytosolic GR to translocate to the nucleus and interact with the promoter region of responsive genes as well as with other transcription factors, leading to long-lasting transcriptional activation or repression. In addition, GR also acts through rapid nongenomic pathways that do not require transcriptional changes (Oakley and Cidlowski, 2013). Rapid effects of glucocorticoids are mediated by membrane-associated GRs coupled to downstream G protein-dependent

signaling cascades that can modulate short-lasting glutamate, gamma aminobutyric acid (GABA) and endocannabinoid release (McEwen et al., 2016; Tasker et al., 2006). GRs are expressed in several interconnected regions involved in cognition and emotion such as the hippocampus, prefrontal cortex (PFC), amygdala, lateral septum and PVN (Joëls and Baram, 2009). Due to its ubiquitous expression, GR regulates transcription as a function of cell type within networks comprising thousands of genes, determining distinct context-driven transcriptional outputs (Weikum et al., 2017). On the contrary, MRs are highly distributed in the hippocampus and lateral septum, and to a lesser extent in the amygdala, PVN and locus coeruleus (Joëls and Baram, 2009). Furthermore, since MRs have higher affinity for glucocorticoids than GRs, MRs are mostly occupied by the hormones at basal conditions, while the increase of circulating glucocorticoids (i.e. after stress) mostly involves GRs (De Kloet et al., 2005).

Importantly, under basal (non stressed induced) circumstances glucocorticoids release is characterized by a prominent and robust circadian rhythm. At physiological levels, glucocorticoids are secreted over a 24-h period with a daily peak in the morning and minimal levels in the evening. The circadian rhythm is strongly regulated by endogenous central and peripheral clock mechanisms in the suprachiasmatic nuclei, PVN, pituitary and adrenal glands (Oster et al., 2017). Moreover, further ultradian rhythm confers a high frequency pulsatile secretion of glucocorticoids, with inter-peak intervals of approximately 1 h (Gjerstad et al., 2018). When individuals are exposed to stress, glucocorticoids will be released in a dynamic fashion, comprising an initial rise of hormones followed by their decline 60-90 min later thanks to the internal feedback loop of the HPA axis (De Kloet et al., 2005). All together these physiological homeostatic waves imply that the response to stressful situations is efficiently activated and terminated. However, when exposure to stress becomes chronic, this affects these processes leading to an exaggerated activation of the HPA axis (De Kloet et al., 2005; McEwen, 2003). Chronic stress can be considered as a cumulative process triggering a continuous activation of the HPA axis occurring at each individual stimulus. This amplified activation of the HPA axis thus leads to an increased glucocorticoids release associated with ultimately a loss of negative feedback control of the HPA axis (Herman et al., 2016). It is thought that such a dysregulated HPA axis is one of the key bases of stress-related psychiatric diseases such as depression (Lupien et al., 2009) and therefore ample research has been dedicated to understanding the effects of stress on the brain.

Concerning the glucocorticoid actions on the brain up to date most focus has been given to their effects on neurons. Nevertheless, both human and rodent brains display different cell populations that can be broadly classified into neurons and non-neuronal glial cells which are sensitive to stress hormones as well, as will be explained in more detail.

Therefore, in the next sections we will highlight the glucocorticoid-induced modulations on neuronal as well as glial cells, focusing on GRs in both cell types **(Fig. 1)**.

Glial and Neuronal Glucocorticoid Receptors

Brain activity depends on both neurons and glia, that each amount to about 50% of all cells in the brain (Azevedo et al., 2009; Herculano-Houzel, 2009; Pelvig et al., 2008). Glial cells can be divided into macroglia, including astrocytes and oligodendrocytes, and microglia. Microglia, accounting for about 5-10% of the cells within the brain, are the primary immune cells of the brain, responsible for the inflammatory response of the central nervous system. Furthermore, microglia are involved in synapse formation and elimination, regulating synaptic plasticity. Astrocytes, the most abundant glial cells within the brain (10-20% of all cells), exert several physiological functions including myelin genesis, synaptogenesis, regulation of neuronal excitability and energy supply to neurons. Oligodendrocytes (10% of all cell types) synthesize myelin sheaths to wrap and insulate axons, ensuring rapid action potential propagation. Thus, neuronal and glial functions are closely interrelated, and it is their integrated modulation that will ultimately lead to changes in behavior, emotional and cognitive functions and dysfunctions.

Indeed, in the last decade there have been tremendous advances in the field of neuroimmunology and several studies showed that the neuron-glia cross talk is crucial for synapse development, maturation, and plasticity. Indeed, the number of neuronal synapses is highly regulated by glial cells that, through an array of secreted and contact-dependent signals, lead to an increase of mature and functional synapses necessary to maintain proper plasticity (Reemst et al., 2016; Ullian et al., 2001). In line, an ablation of glia determines neuronal loss associated with a reduction of dendritic spine formation and altered synaptogenesis (Schreiner et al., 2015). Moreover, glia is involved in synapse pruning and refinement required for normal brain development and homeostasis (Chung et al., 2015; Reemst et al., 2016). At the same time, glia activity is regulated by neuronal signals and synaptic activity (Stogsdill and Eroglu, 2017).

The findings that glial cells impact neurons at physiological levels suggests that impaired neuron-glia interactions, besides purely neuronal defects, may contribute to stress related brain disorders. On these bases, in this chapter we aim at unraveling how stress inputs are integrated across multiple cell types in different brain regions to ultimately modulate adaptive and maladaptive behaviors. We will start by describing GR expression in both neuronal and glial populations and thereafter how stress modulates the function of these cells **(Fig. 1)**.

GR is expressed in neurons in a brain region specific fashion. For example, hippocampal CA1 and dentate gyrus neurons display high levels of GR (Madalena and Lerch, 2017; Mahfouz et al., 2016). Similarly, GR has been found highly expressed in cortex and to a lesser extent also in thalamus (Mahfouz et al., 2016). As explained above, in neurons, GRs can exert both delayed gene-mediated and rapid non-genomic actions on brain function (Joëls et al., 2006).

In addition there is evidence that GR is also expressed on microglia (Sierra et al., 2008). In detail, cytoplasmic and nuclear localization of GR in hippocampal microglial processes has been reported (Jenkins et al., 2014; Sierra et al., 2008). Furthermore, it is interesting to notice that GRs are the most abundant steroid hormone receptors in microglia, showing higher mRNA levels than MRs and estrogen receptors (Madalena and Lerch, 2017). This evidence would suggest that microglia may be uniquely sensitive to glucocorticoids through GR.

In addition to microglia, both astrocytes and oligodendrocytes express GRs. The expression of GR has been detected in astrocytes within the hippocampal CA1 region as well as in the dentate gyrus and the PVN of the hypothalamus (Kasckow et al., 2009). Moreover, GR has been found to be expressed on astrocytes within the striatum, where GR-transcriptional targets relate to cellular metabolism and differentiation as well as to circadian homeostasis (Slezak et al., 2013). GRs have been found also in astrocytes of the rat lateral amygdala (Johnson et al., 2005). Astrocyte cultures allowed to specifically detect cytoplasmic and nuclear GR expression (Jenkins et al., 2014). Interestingly, GR mRNA levels appear higher in ex vivo astrocyte cultures than in cultured neurons (Piechota et al., 2017), and astrocytes are transcriptionally more responsive to a GR-agonist when compared to neurons (Piechota et al., 2017).

There is evidence for the presence of GR in oligodendrocytes in various brain regions of adult mice including hippocampal CA1 and CA3 regions, dentate gyrus, cortex and amygdala (Johnson et al., 2005; Matsusue et al., 2014). In vitro studies confirmed GR localization both in the cytosol and in the nucleus of oligodendrocytes (Jenkins et al., 2014). However, GR expression in oligodendrocytes is lower than in microglia and astrocytes and the treatment with a GR agonist revealed that ligand-induced transcriptional effects are more pronounced in astrocytes and microglia than in oligodendrocytes (Jenkins et al., 2014). This evidence suggests that microglia and astrocytes might have a more prominent role in contributing to the brain stress response.

Lastly, it is important to remember that glucocorticoids can exert their functions via binding not only to GRs but also to MRs. However, the ratio of GRs/MRs in neurons and

glia is different. Indeed, despite MRs are highly expressed in neurons, their localization on microglia, astrocytes and oligodendrocytes is nearly absent (Madalena and Lerch, 2017).

Altogether, this evidence suggests that glia, next to neurons, may be a direct target of stress-induced glucocorticoids and that for a better understanding of the neurobiology of stress it is key to focus, next to the effects of glucocorticoids on neurons, also on their effects on glial cells and on the integration of their effects on these different cell types.

On this basis, in the upcoming sections we will describe the stress-induced effects of glucocorticoids on neurons and glial cells focusing on microglia and astrocytes due to the more prominent presence of GRs in these cell types.

Stress and the effects of HPA axis activation on neurons

The effects of glucocorticoids and the consequent activation of GR pathways on neurons have been studied at multiple levels including the effects on adult hippocampal neurogenesis (AHN) and modulation of excitatory/inhibitory neuronal activity.

AHN is a unique form of brain plasticity consisting of the generation of new neurons in adult life. This form of plasticity is present only in two brain regions in the rodent brain namely the dentate gyrus of the hippocampus and the olfactory bulb. Particularly interesting in the context of stress neurobiology is the hippocampus as this brain region is rich in GR and critically involved in the modulation of stress response. Multiple studies reported that glucocorticoid levels modulate AHN (Anacker et al., 2013; Lucassen et al., 2015). For example, overactivation of the HPA axis following chronic stress reduces cell proliferation, neuronal differentiation and cell survival (Saaltink and Vreugdenhil, 2014; Schoenfeld and Gould, 2013). Furthermore, it has been recently shown that the disruption of glucocorticoids rhythms extensively impairs neuronal proliferation (Schouten et al., 2020). Accordingly, aberrant neurogenesis has been implicated in psychiatric diseases (De Kloet et al., 2005). In addition, the expression of GR has been detected in progenitor cells and immature neurons (Saaltink and Vreugdenhil, 2014) and GR inhibition following chronic stress exposure was able to block the stress-induced inhibition of hippocampal neurogenesis (Anacker et al., 2013; Horchar and Wohleb, 2019), suggesting a direct effect of stress hormones on adult neurogenesis.

There are several lines of evidence that stress-induced glucocorticoid exposure impacts on the balance of excitatory/inhibitory neuronal activity. For example chronic stress has been shown to enhance excitatory synaptic inputs by reducing GABAergic extrasynaptic receptors and consequently inhibitory GABAergic transmission in PVN neurons (Herman

and Tasker, 2016). Similarly, prenatal exposure to stressors can determine an over-exposure of the fetus to maternal glucocorticoids, associated with a disbalance in glutamatergic and GABAergic neurons (Lu et al., 2018). In detail, stress-induced hippocampal GR activation is responsible for the demethylation of the glutamate decarboxylase (GAD67) promoter and consequent upregulation of GAD67 expression, eventually altering the balance of excitatory/inhibitory neuronal activity (Lu et al., 2018). It has also been reported that chronic stress specifically decreases GR expression in inhibitory GABAergic GAD67-positive neurons and parvalbumin (PV)-positive interneurons of the PFC, suggesting that it might lead to an enhanced GABAergic inhibition onto prefrontal glutamatergic output neurons (McKlveen et al., 2016). This evidence pointed out the role of GR also in cortical interneurons. In line, targeted GR deletion in forebrain GABAergic neurons causes a loss of GR in interneurons of the PFC and hippocampus, associated with an elevated responsiveness to acute stress and impaired retention of passive avoidance learning (Scheimann et al., 2018).

In addition, other neuronal populations are affected by glucocorticoids exposure. Elevated circulating glucocorticoid levels has been shown to lead to impairments in dopaminergic cells in the ventral tegmental area (VTA), with a decrease of dopamine levels, tyrosine hydroxylase and dopamine D1 receptor expression (Niwa et al., 2013). These effects were mediated by GR as the concomitant administration of a GR antagonist was able to block these abnormalities (Niwa et al., 2013).

Lastly, several studies show that glucocorticoids exposure can eventually affect GR expression, downregulating its levels in specific subsets of neuronal populations (Herman and Tasker, 2016; McKlveen et al., 2016). Altogether, these examples confirm that neurons are highly sensitive to glucocorticoids and that they modulate them on multiple levels.

We will next evaluate the impact of the glucocorticoid signaling on glial cells, focusing on microglia and astrocytes.

Stress and the effects of HPA axis activation on microglia

In the last few years, microglia have been proven to be highly sensitive to glucocorticoid's and HPA axis overactivation.

Under basal conditions, microglia display a ramified morphology and constitutive expression of cluster of differentiation 11b (CD11b) and ionized calcium-binding adaptor molecule-1 (Iba-1) (Frank et al., 2007). On the contrary, upon aversive stimuli, microglia exhibit shorter and thick processes and gradually become amoeboid, displaying a so called "activated"

hypertrophic phenotype, characterized by increases of colony-stimulating factor 1 receptor (Csf1r) mRNA levels, essential for microglia survival (Elmore et al., 2014), associated with an up-regulation of Iba1 and CD11b expression (Horchar and Wohleb, 2019).

Activated microglia have been detected in the PFC, nucleus accumbens, CA3 region of the hippocampus, and dorsal bed nucleus of the stria terminalis as a consequence of chronic physical stress exposure (Hinwood et al., 2012; Tynan et al., 2010). Similarly, chronic social stress induces hypertrophy of microglia in the medial amygdala, PFC, hippocampus, and PVN (Wohleb et al., 2011). Interestingly, the treatment with minocycline, that inhibits microglia proliferation and activation by specifically inhibiting the p38 MAPK pathway in microglia cells, reduces these effects both in the prelimbic and infralimbic regions of the PFC (Hinwood et al., 2012).

Considering that microglia contribute to the regulation of neuronal activity and connectivity (Graeber, 2010), glucocorticoids-induced activation of microglia may in turn cause neuronal damage. Indeed, the morphological alterations induced by glucocorticoids exposure on microglia are paralleled by reduced dendritic spine density on apical dendrites of pyramidal neurons and changes in neuronal activation within the PFC (Hinwood et al., 2012; Horchar and Wohleb, 2019; Tynan et al., 2010).

Lastly, highlighting a role for glucocorticoid signaling in the stress-induced pathological outcome in microglia, GR inhibition prevents the functional alterations in microglia. Indeed the treatment with a glucocorticoid antagonist suppresses the stress-induced up-regulation of *Csf1r* mRNA levels on cortical microglia as well as the increase of Iba1 positive microglia in the PFC (Horchar and Wohleb, 2019). However, underlining the necessary contribution of microglia on neuronal functionality, the inactivation of GR gene expression on microglia induces a substantial neuronal degeneration associated with a significant rise of pro-inflammatory markers following chronic stress exposure (Carrillo-De Sauvage et al., 2013).

Overall, we can conclude that a rise of glucocorticoids can negatively impact microglia and that these effects seem to be mediated by GR. Furthermore, given the crosstalk between neurons and microglia, it is evident that microglia impairments in turn affect neuronal activity.

Stress and the effects of HPA axis activation on astrocytes

Contrary to microglia, the contribution of astrocytes to the effects of glucocorticoids in the brain is still in its infancy. There is initial evidence that the astrocytic morphological status

is affected by glucocorticoids exposure (Abbink et al., 2019). Few morphological changes in astrocytes were detected as a result of glucocorticoids increase such as a reduction of the number, soma volume and protrusion length of astrocytes (Gong et al., 2012; Zhang et al., 2015). In the adult brain, astrocytes express the glial fibrillary acidic protein (GFAP) in their filaments and this is generally used as astrocyte marker. The impairments driven by glucocorticoids are usually associated with a down regulation of GFAP mRNA expression itself (Banasr et al., 2010) and can last long after glucocorticoids exposure (Abbink et al., 2019; Gong et al., 2012). Indeed, since the peak of astrogenesis occurs early in life, the exposure to glucocorticoids during this sensitive period may have deleterious effects.
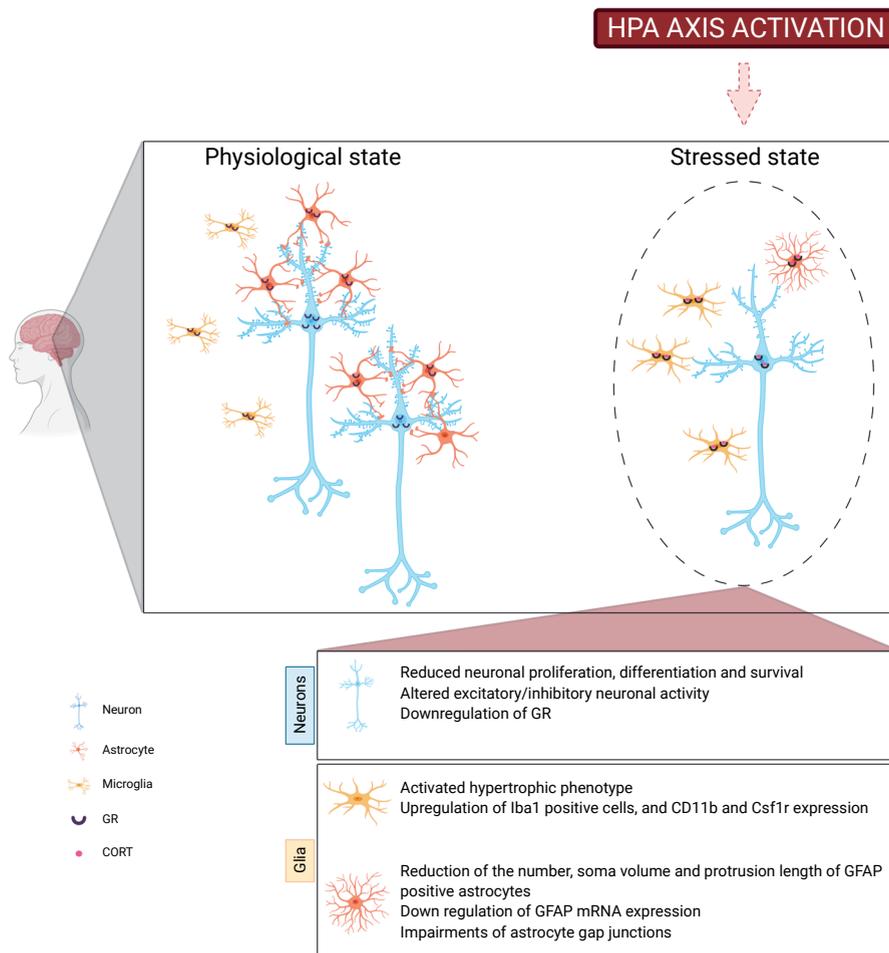
Figure 1: Integrated effects of stress and HPA axis activation on neurons, microglia and astrocytes morphology and functionality (Created with BioRender.com).

Besides a loss of astrocytes, chronic stress exposure has been shown to impair astrocyte gap junctions, main determinants of astrocyte communication and function, within the PFC (Lou et al., 2018). Interestingly, the treatment with a GR antagonist prevents both the astrocyte loss and the gap junction dysfunction, highlighting a role for GR activation on astrocytes (Lou et al., 2018; Sun et al., 2012).

Furthermore, it seems that losing astrocytes or pharmacologically blocking gap junctions on astrocytes can itself induce depressive-like phenotypes similarly to chronic stress exposure, suggesting that cellular alterations on astrocytes drive the functional effects of stress exposure (Banasr and Duman, 2008; Sun et al., 2012).

Altogether, emerging evidence suggests the role of astrocytes in the functional effects of glucocorticoids exposure, although most studies selectively focused on structural changes and how these relate to functional changes in astrocytes still remains understudied.

Conclusions

Despite the historical view of glucocorticoids as stress hormones acting only on neurons and neuronal physiology, emerging evidence points out their direct effects on glial cells as well. In this chapter, we delineated the changes induced by glucocorticoids exposure on both neurons and glial cells with a focus on microglia and astrocytes (Figure 1). Neuronal populations throughout the brain mainly undergo inhibition of cell proliferation and differentiation, associated with impaired excitation-inhibition balance in response to stress. On the other side, microglia face morphological changes that lead to an overactivated state. Similarly, astrocytes experience structural alterations and also reduce in numbers. The main conclusion that we can draw is that there might be synchronized and integrated contribution of both neurons and glia in the behavioral and molecular alterations induced by glucocorticoids exposure (Wohleb et al., 2018) and that GR signaling may represent the converging mechanism that is able to drive the stress-induced neurobiological and functional changes observed in both cell types. Whether these effects might be the result of a convergent action of glucocorticoids on both cell types or whether glucocorticoids primary act on selective cells within the brain, and a dysfunction in one cell population may drive the impairments in the other cells, is still unclear. Considering the crucial role of microglia and astrocytes in neuronal functioning, it may be argued that stress experience, next to directly impacting on neurons, also leads to glia-mediated GR signaling, that consequently converts into glial (over)activation and eventually to neuron degeneration, which might in turn also contribute to the observed functional deficits. Nevertheless, the extent of glucocorticoids effects on glial cells, mostly astrocytes and oligodendrocytes,

under basal conditions and following a chronic stress exposure as well as their functional consequences still remains not well-understood and requires further investigations.

Acknowledgement

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