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Chapter 15

GLUCOCORTICOIDS AND NEURODEGENERATION

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ABSTRACT

Glucocorticoids (GCs) exert wide-spread actions in central nervous system ranging from gene transcription, cellular signaling, modulation of synaptic structure and transmission, glial responses to altered neuronal circuitry and behavior through the activation of two steroid hormone receptors, glucocorticoid receptor (*NR3C1*, GR) and mineralocorticoid receptor (*NR3C2*, MR). These highly-related receptors exert both genomic and non-genomic actions in the brain, which are context-dependent and essential for adaptive responses to stress resulting in modulations of behavior, learning and memory processes. Thus, GCs through their receptors are implicated in neural plasticity as they modulate the dendritic and synaptic structure of neurons as well as the survival and fate of newly-generated cells (neuro- and glio-genesis) in adult brain. GCs are also important in fetal brain programming as inappropriate variations in their levels during critical developmental periods are suggested to be casually related to the development of brain pathologies and maladaptive responses of hypothalamic-pituitary adrenal (HPA) axis to stress during adulthood. They regulate immune responses in brain, which have important consequences for neuronal survival. In situations of chronic stress and HPA axis dysfunction resulting in chronically high or low GCs levels, a multitude of molecular, structural and functional changes occur in the brain, eventually leading to

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maladaptive behavior. In fact, clinical studies suggest a causal relation of deregulated GC responses with development of neurodegenerative disorders such as Alzheimer´s (AD) and Parkinson's (PD) diseases. AD and PD patients have high levels of circulating cortisol while animal studies suggest that this chronic GC elevation participates in neurodegenerative processes in both AD and PD pathologies. This chapter will focus on the role of HPA axis and GCs on neurodegenerative processes involved in AD and PD pathogenesis.

Keywords: glucocorticoids, neurodegeneration, Alzheimer's disease, Parkinson's disease, epigenetics

INTRODUCTION

Glucocorticoid (GC) hormone is synthesized and released into systemic circulation from adrenal glands following activation of hypothalamic-pituitary-adrenal (HPA) axis, which entails synthesis of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by paraventricular neurons (PVN) of hypothalamus and their release from median eminence into portal blood. These hormones stimulate the synthesis of adrenocorticotropic hormone (ACTH) in the anterior pituitary, which when released into general circulation binds to ACTH receptor (melanocortin type II receptor) in adrenal glands promoting GC synthesis from cholesterol. GC release by HPA axis is under circadian control and occurs in an oscillatory pattern or ultradian rhythm that varies in amplitude according to the time of day (peak in the morning and trough in the evening/night in diurnal animals including humans and vice versa in nocturnal animals, e.g., rodents). In addition, there is a surge of GC release in response to a stress stimulus, which can be either psychogenic (e.g., fear) or physical (e.g., cellular lesion or pathogen invasion). In response to stress, GCs exert critical adaptive functions by modulating most biological processes (e.g., metabolism, cardiovascular and immune systems as well as behavior); and through feedback inhibition of HPA axis they play a role in terminating the stress response as well as facilitating the restoration of physiological homeostasis [1]. In addition to their role in stress response, appropriate GCs levels are important during development, for example in cell maturation, and in the differentiation of lungs, kidneys and brain [2-4].

It is now thoroughly established that GCs have the capacity to profoundly modulate different brain functions, as well, increasing evidence points to their role in brain development. The appreciation that brain is a key target of this circulating adrenal steroid hormone emerged from the pioneering work, principally by the laboratories of McEwen and de Kloet, on identification and biochemical characterization of two receptors in the hippocampus to which GCs bind - the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) [5, 6]. Since then, GR presence in brain was observed to be widespread with every cell type expressing this receptor in contrast to MR expression, which is more restricted. MR is expressed by the neurons of the limbic system, i.e., hippocampus, locus coeruleus, amygdala, prefrontal cortex and nucleus of the solitary tract, as well as neurons of hypothalamus. MR is also present in non-neuronal cells, namely in glia and in epithelial cells of choroid plexus and ependyma [7]. In brain, ^{3}[H] corticosterone binding assays showed that MR has 10-fold higher affinity (K_d= 0.5 nM) for GCs compared to GR (K_d= 5 nM), which

means that at basal GC levels, MR is occupied and activated [8] whereas GR is only activated when GC levels reach a certain level as it happens in circadian peak and during stress [9]. GC actions are pleiotropic, the principle factors determining their functions are: a) circulating levels with accessibility to each cell type and b) context in which the receptors are activated. GC levels are tightly regulated at each level of HPA axis and this is important in ensuring that stress response is correctly executed. Deregulated HPA axis resulting in sustained high or low GC levels are implicated in different diseases, for example disorders of metabolism (e.g., diabetes, obesity), immune (e.g., rheumatoid arthritis) and nervous systems (e.g., depression) [10-12].

Synthetic GCs (e.g., dexamethasone, methylprednisolone) are routinely used in clinical situations, particularly in disorders with an inflammatory component such as rheumatoid arthritis or brain edema as they exert powerful anti-inflammatory and immunosuppressive actions. However, prolonged GC use suppresses HPA axis resulting in harmful side effects such as increased risk of infection, hyperglycemia, weight gain, behavioral or cognitive problems. Interestingly, GCs are now also used clinically in neonates, as endogenous GCs are required for fetal lung maturation as they promote the production of lung surfactant. This could affect the programming or subsequent responsiveness of HPA axis particularly with regards to stress responses in adults [13]. Thus prolonged GC exposure or exposure to high levels of GC in specific developmental windows such as the prenatal and perinatal period can impair the HPA axis negative feedback, increasing the propensity for developing neuropsychiatric and metabolic disorders [14].

Glucocorticoid actions through MR and GR in brain have been particularly studied in relation to glutamatergic as well as monoaminergic (e.g., dopaminergic and serotonergic) systems, which have wide-range consequences from mood behaviors to cognition. Several excellent reviews already exist on our current understanding of neuronal functions of GCsin brain via these two receptors [15-19]. Our aim in this chapter is to describe how their actions in neurons and glia impact the neurodegenerative processes, emphasizing on Alzheimer (AD) and Parkinson diseases (PD). One of the arguments for their implication relates to GC functions being exquisitely dependent on environmental changes, and in this regard, both genetic susceptibility and environmental factors are believed to play key roles in the etiology of these neurodegenerative diseases. Most of our current understanding of GCs involvement in brain disorders relates to the functions of GR as this receptor plays a major role in stress responses. Thus, before describing our current knowledge of GCs in neurodegeneration, we reiterate the regulation of GC release by HPA axis and functional activity of GR as both are likely affected in AD and PD as discussed below.

REGULATION OF GC RELEASE AND AVAILABILITY

Paraventricular nucleus (PVN) of hypothalamus receives integrated information from suprachiasmatic nucleus for circadian control of GCs and from the limbic system for psychogenic stress-induced GC release [20, 21]. In stress-induced GC release, limbic structures such as amygdala are involved in stimulating PVN neurons to synthesize CRH whilst hippocampus plays a crucial role in negative feedback inhibition of the HPA axis [22]. The fast feedback inhibition of HPA axis following acute stress is important to prevent

depletion of GC needed for both successive stress and ultradian release, which interestingly is impaired in aging as well as in patients suffering from depression. Both MR and GR at hypothalamic and hippocampal levels play an important role in regulating the activity of PVN neurons. In addition GR in anterior pituitary was found to regulate pulsatile ACTH release [23]. HPA axis is also activated in response to cellular lesion or pathogen invasion by pro-inflammatory cytokines such as IL-1β, IL-6 or TNF-α released by either peripheral immune cells or microglia [24]. IL-6 through activation of its receptor can also stimulate ACTH release from anterior pituitary and GC from adrenal glands [25].

The availability of GCs to neurons and non-neuronal cells in brain is controlled in two ways. Firstly, in the blood, most GCc are bound to corticosteroid binding globulin (CBG) whose levels are down regulated by stress thereby increasing free-circulating GC levels [26]. Secondly, once inside the cells, the availability of GC for GR activation is controlled by GC-metabolizing enzymes: 11-β-hydroxysteroid dehydrogenase type I (HSD11β1), which regenerates active glucocorticoids (e.g., cortisol from cortisone) thus amplifying GR activation. In addition, 11-β-hydroxysteroid dehydrogenase type II (HSD11β2) has an opposite function, i.e., increasing the inactive form of GC. Using mice deficient for HSD11β1, previous studies have shown that these mice are protected from hippocampal memory impairments associated with aging. However, cognitive problems arise normally because GR activity predominates due to high GC levels catalyzed by this enzyme [27, 28].

GENOMIC AND NON-GENOMIC ACTIONS OF GLUCOCORTICOID RECEPTOR (GR)

GR exerts both genomic and non-genomic actions in brain. The genomic actions of GR pertain to its ligand-activated transcriptional activity. Non-liganded GR in the cytoplasm is normally in complex with chaperone proteins such as heat shock proteins 90, 70, 40, 23 as well as immunophilins such as FKBP51 and 52. Upon GC binding, the conformational change of the complex results in exposure of nuclear localization signal of GR, which allows importin-mediated translocation of GR into the nucleus. Recent studies highlight the importance of correlation between GR transcriptional activity and ultradian pulsatile nature of GCs for generation of appropriate response to stress stimulus [29, 30].

GR protein is comprised of N-terminal transactivation domain which is important site for GR co-regulatory binding proteins such as cAMP-response-element binding protein binding protein (CBP), it also contains phosphorylation sites, e.g., serine 203, serine221 and serine 226. The central zinc-finger DNA-binding domain is important for the GR binding to the so-called Glucocorticoid Response Elements (GREs), which are present in promoters of GR target genes. The carboxy-terminal domain is the site of GC binding to GR as well as co-activators such as histone acetylases or co-repressors. The transcriptional regulation by GR is both cell-type and context-dependent. GR can regulate transcription by: a) direct binding as homo-dimers to GRE DNA sequences to stimulate transcription, e.g., *mitogen-activated protein kinase phosphatase-1* gene; b) direct binding to negative GRE elements to repress transcription, e.g., *CRH* or *ACTH receptor* genes; c) trans-repression or "tethering" i.e., association with other transcriptional factors to inhibit their transcriptional activity. This mechanism is by far the most notable in immune cells where GR regulates transcription of

nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein-1 (AP-1) and members of interferon regulatory transcription factors (IRFs). In brain, identification of GR-modulated genes is difficult due to anatomical complexity and cellular heterogeneity. Nevertheless, transcriptomic studies in the hippocampus have identified functional classes of genes modulated by GR which include genes coding for neurotransmitter catabolism, neurotrophic factors and their receptors, signal transduction, energy metabolism and cell adhesion [31].

The genomic actions of GR are slow in onset and long lasting. In contrast, GR exerts non-genomic actions at plasma membrane of neurons, which are rapid (seconds to minutes), involve alterations in neuronal excitability and are dependent on the context of the signal. The non-genomic actions of GR at the membranes also involve activation of down-stream signaling pathways involving kinases such as ERK, AKT, PKC and PKA [32]. Altogether, this provides a surprising diversity and complexity of GC modulation of gene expression and cellular signaling.

EPIGENETIC REGULATION OF GR

Animal studies confirm earlier anecdotal observations in humans indicating that early life adverse experience has a profound impact on adult behavior. Early life stress or exposure to GC (endogenous or exogenous) may induce neuroendocrine programming, subsequently altering offspring's growth, metabolism, immune system and even the stress response as previously mentioned. These observations derive from both animal and human studies, where an alteration in the activity of the HPA axis was found [14, 33, 34]. Such prenatal *programing* may be an evolutionary mode of shaping internal characteristics of the developing organisms in order to adapt to the environment. However, such modifications might ultimately result in the development of long-term diseases, from metabolic syndromes to psychiatric disorders [35-39].

This long-lasting effect of early life experiences in brain function and behavior appears to be mediated (at least partially) by epigenetic mechanisms [14, 34, 40]. In the last years, considerable progress has been made in untangling the epigenetic alterations induced by stress/GC. However, most of the studies are merely correlative and the mechanism through which stress/GC induce epigenetic programing remains completely unkown.

One way of buffering the impact of maternal GC exposure in the developing fetus is by converting cortisol/corticosterone into inactive metabolites through the action of placental HSD11β2. However, some studies indicate that maternal adversity can increase the methylation at specific CpG sites within the HSD11β2 gene promoter and lead to a down-regulation of this enzyme [41, 42], which may allow excessive levels of GC to reach the fetus and program different organs and systems. The first evidence of brain epigenetic programing induced by early life adversity was reported by Meaney and colleagues, which showed that natural variations in maternal behavior were correlated with DNA methylation levels of a neuron-specific exon 1_7 promoter of the GR gene.

Briefly, male rats reared by “good dams” (i.e., those that presented high pup licking and grooming) demonstrated lower levels of stress response, greater performance on cognitive tasks and larger exploratory activity in a novel environment, compared to the offspring of

"bad dams"; this was associated with a differential methylation of this specific region of the GR promoter [43, 44]. Importantly, these results were later replicated in humans showing individuals with childhood stressful experiences (abuse during childhood), presented hypermethylation of this region, in comparison to non-abused individuals [45].

Later studies revealed an increased methylation of a CpG-rich region in the promoter and exon1F of the GR gene in the cord blood of newborns of mothers with depressed mood during the third trimester of gestation [46]. Importantly, this pattern on methylation of the GR gene occurred only in the offspring (and not the mothers), correlated with levels of response to stress in infants at 3 months of age, and persisted beyond infancy. Similarly, pregnancy-related anxiety is associated with the methylation state of the GR gene in the child [47]. These findings suggest a common effect of parental care in both rodents and humans on the epigenetic regulation of hippocampal GR expression. One question that still remains is whether these epigenetic changes are the cause of maladaptive behaviors or a mere adaptation, in the light of evidence showing that healthy individuals with a history of childhood adversity can also present increased GR methylation and an attenuated cortisol response to the dexamethasone test [48]. In this perspective, such adversity-induced epigenetic changes may predispose the individual to disease (in combination with other genetic or extrinsic factors) but are not the cause *per se*.

In addition, other pivotal stress players are also affected by early life stress/GC exposure. For example, mice, in a model of early-life stress present hypersecretion of corticosterone, alterations in passive stress coping and memory followed by a persistent increase in arginine vasopressin expression in neurons of the hypothalamic PVN due to sustained DNA hypomethylation of CpG residues that serve as DNA-binding sites for the methyl CpG-binding protein 2 (MeCP2) [49]. In addition, stress/GC exposure early in life may induce long-lasting epigenetic changes in neurotransmission-related genes. For example, animal studies demonstrated that prenatal GC exposure leads to differential methylation of dopamine receptor D2 [50]. In humans, depressed mood during pregnancy leads to decreased levels of methylation in the promoter of the *SLC6A4* gene, encoding the serotonin transporter, in maternal peripheral leukocytes and in umbilical cord leukocytes collected from their infants at birth [51]. Such changes may affect how the individual senses/processes/responds to environmental stimuli and may explain, in part, the increased vulnerability for neuropsychiatric disorders later in life.

In addition to particular gene epigenetic changes, stress/GC have a strong impact in the epigenome (elegantly reviewed in [52]. Human studies on different cohorts have shown that early life maltreatment induces long-lasting methylation changes in the genome [53-55] while recent animal-based evidence suggest that the epigenomic landscape is also strongly correlated with gestational maternal adversity [56] and even with natural variations in maternal care [57]. In addition to methylation, gene expression can be further controlled by hydroxymethylation and diverse histone modifications, adding additional layers of complexity to the GC-driven changes that may predispose individuals to the development of brain pathologies.

SUSTAINED GR ACTIVATION AND NEURODEGENERATION IN AD

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by slow and progressive dementia while the major histopathological hallmarks are senile plaques containing amyloid beta (Aβ) deposits and intracellular neurofibrillary tangles (NFT) made of hyperphosphorylated forms of the cytoskeletal protein Tau [58-60]. Aβ is the proteolytic product of the bigger transmembrane protein called amyloid precursor protein (APP), which is sequentially cleaved by β-secretase (BACE-1) and γ-secretase (enzymatic complex of proteins) resulting in the production of Aβ; this cellular pathway is often called APP misprocessing. Many studies have demonstrated that APP misprocessing and Aβ trigger AD neuropathological processes such as synaptic malfunction (impairing mechanisms of synaptic plasticity, e.g., LTP), neuronal atrophy and synaptic loss as well as mitochondrial dysfunction, oxidative stress and glial activation.

While still debated, it is suggested that Aβ also triggers abnormal Tau hyperphosphorylation leading to the formation of NFTs and neuronal loss in AD brain. Indeed, accumulating data suggest the involvement of Tau protein in the detrimental effects of Aβ as use of Tau-KO blocked the Aβ neurotoxic effects [61-64]. Further support of the essential role of Tau in the establishment of AD pathology is based on the clinical findings that have consistently shown that the cognitive deficits in AD patients correlate with NFTs rather with Aβ deposition. Indeed, hyperphosphorylated and aggregated Tau resulting in NFTs is associated with neuronal loss. Gomez-Isla et al. [65] demonstrated that strong correlation of neuronal loss in cerebral cortex and increased NFT burden with disease progression; no such correlation was found with Aβ. Furthermore, reduction of hippocampal volume in AD patients was associated with phosphorylated Tau, but not Aβ levels in cerebral spinal fluid (CSF) [66].

Several risk factors have been suggested for AD while recent evidence supports an etiopathogenic role of chronic stress and glucocorticoid hormones in the establishment and development of AD pathology [67, 68]. Clinical studies report high cortisol levels, measured in plasma, saliva or CSF, of AD patients indicative of altered HPA axis [69-73] while the increase of cortisol levels is negatively associated with memory scores in AD patients [74, 75]. Furthermore, Hartman et al. [76] monitored the 24hr secretory pattern of plasma cortisol in AD patients finding a higher mass of cortisol release; however, the diurnal changes in cortisol levels were not altered. Since chronic elevation of GC levels is known to impair memory and cognitive performance, it is speculated that GCs play a role in progressive cognitive decline in AD. Indeed, it is unclear whether high GCs are a cause or a consequence of the disease as one of the explanations of high GC levels in AD patients is the deregulation of feedback inhibition of the HPA axis, particularly in relation to psychogenic stressors, occurring at the level of the hippocampus, a region significantly damaged in AD brains.

It is noteworthy that many clinical and experimental reports suggest a reduction of adult neurogenesis in AD hippocampus while the same is true for chronic stress conditions [77-79]. Reduction of hippocampal adult neurogenesis was shown to increase HPA activity implying that this region is involved in hippocampal feedback regulation of HPA axis during stress [80]. Thus, high GCs can aggravate hippocampal memory processes in AD by having a

negative effect on hippocampal neurogenesis, which may, in turn, contribute to maintenance of deregulated HPA axis.

GC IMPACT ON AD NEURODEGENERATIVE MECHANISMS

Clinical studies show that chronic stress is a risk factor in AD pathogenesis and it also lowers the age of onset of the familial form of AD [67, 68]. Indeed, it has been evoked that chronic stress is among the principal factors that contributes to development of AD [77]. A principal target of GCs is hippocampus, which is a main target area for AD pathology and chronic stress (Figure 1). The hippocampal dysfunction in AD has significant detrimental consequences on declarative, spatial and contextual memory processes. As hippocampal neurons have very strong GR expression and are intimately involved in regulation of HPA axis, there has been a great deal of interest in how high cortisol levels and stress impact the deterioration of hippocampal functions caused by toxic Aβ and Tau hyperphosphorylation in AD.

Previous studies show that elevated GC levels and exposure to chronic stress increase Aβ production in AD transgenic mouse models exacerbating their memory deficits [81, 82], Specifically, chronic immobilization stress in amyloid precursor protein (APP)V717ICT-100 transgenic mice (this APP mutation is known for aggressive early onset AD) evoked acceleration and greater severity of memory deficits and increased extracellular Aβ deposits. Similarly, Green at al [81] showed that prolonged treatment with the synthetic GC, dexamethasone, triggers APP misprocessing resulting in increased Aβ levels using both *in vitro* and *in vivo* approaches (neuronal N2A cell line and pre-pathological 3xTg-AD young mice). In addition, the same study also demonstrated transcriptional up-regulation of APP and β-secretase expression by GR (both contain GRE in their promoter region).

Similarly, other *in vitro* studies have confirmed that GCs trigger APP misprocessing without influencing the non-amyloidogenic pathway, i.e., the other cellular cascade of APP cleavage/processing [83]. Similar observations were made in middle-aged rats in which the amyloidogenic potential of chronic stress (chronic unpredictable stress paradigm) and prolonged GC treatment was demonstrated insofar that both treatments were found to drive APP processing towards the generation of Aβ and its precursor molecule (C99), both of which have neurotoxic and cognition-impairing properties [84]. This study also showed that GC/stress increased β-secretase (BACE-1) levels as well members of γ-secretase complex (Nicastrin). Given that stressful stimuli occur intermittently over the lifetime, and that their effects may be cumulative, an important finding by Catania et al., [84] was that GC potentiate the APP misprocessing pathway in previously stressed animals of AD model (Aβ-infused rats).

Interestingly, clinical studies suggested that the stress-related neuropsychiatric disorder, depression, is a risk factor for the development of AD pathology as the history of depression is correlated with increases of amyloid plaques and NFT [85]. In addition, other studies suggested the utility of measurements of the various APP cleavage products as biomarkers to discriminate between subjects undergoing normal aging from those suffering from depression or AD [86-89]. Interestingly, more recently, some studies report the influence of anti-depressant drugs on the proteolytic cleavage of APP suggesting its anti-amyloidogenic role

[89, 90] while many antidepressants are shown to normalize the HPA axis and the resulting GC levels which are increased in many depressed patients and models of stress-driven depression.

Besides APP misprocessing, high levels of GC trigger the other main AD neurodegenerative pathway, the aberrant hyperphosphorylation of Tau protein. Among the first reports suggesting a potential connection between GC and Tau was the study by Stein-Behrens et al. which demostrated high GC levels exacerbated neuronal loss induced by kainic acid injection in hippocampus while in parallel increased Tau immunoreactivity. Later on, it was shown that treatment with synthetic dexamethasone for 7 days in 3xTg AD mouse model resulted in Tau accumulation in somatodendritic compartment of neurons in hippocampus, amygdala and cortex [81].

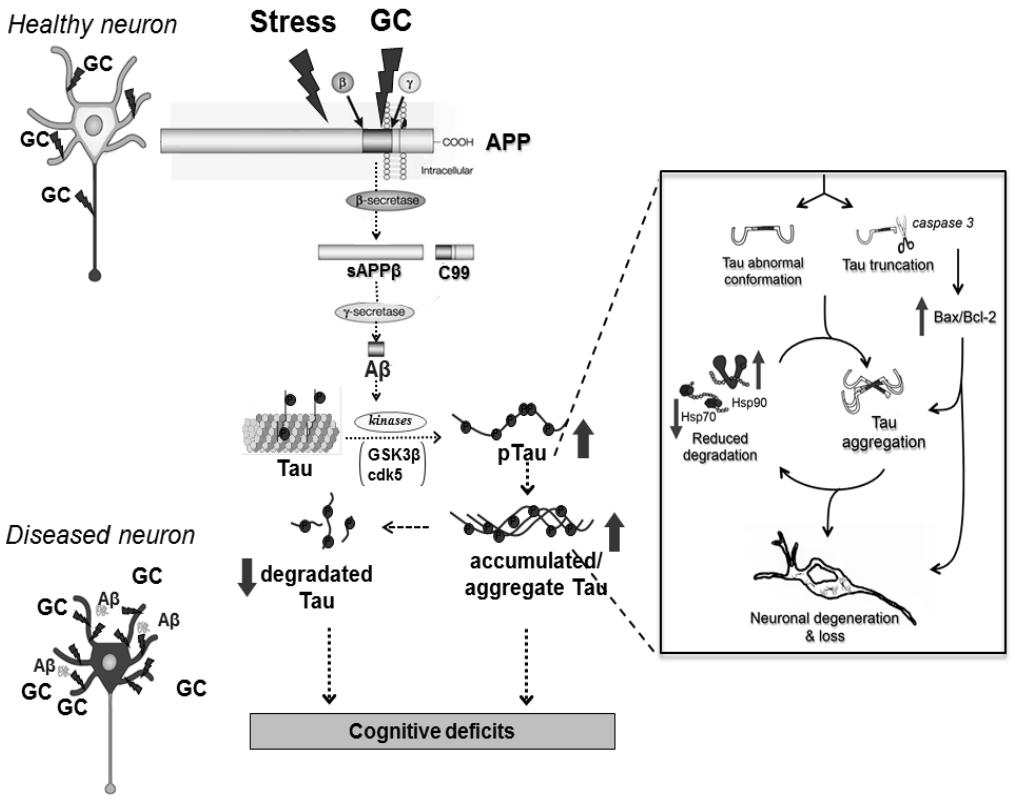

Figure 1. Glucocorticoids (GCs) and Stress impact on AD neurodegenerative mechanisms. The schematic presentation reflects the triggering role of high GC levels and chronic stress on AD cellular mechanisms based on experimental evidence using animal and cellular AD models. Prolong exposure to GC and/or stress activates amyloidogenic cellular pathway resulting in the sequential cleavage of APP by β- and γ-secretase which produces Aβ. Next, the cytoskeletal protein Tau, mainly found at neuronal axon (rdown (dark) part in the healthy neuron scheme), is aberrantly hypersphosphorylated through the activation of different kinases (e.g., GSK3-β and cdk5) which results in Tau somatodendritic accumulation (upper (dark) part in in diseased neuron scheme). In addition, abnormal conformation and caspase 3-mediated truncation of Tau occurs together with a parallel dysregulation of the molecular chaperones (e.g., Hsp90 and Hsp70) facilitating reduced Tau degradation and increased Tau oligomerization and ultimately, aggregation (see panel on the right). The above cellular cascades result in neuronal atrophy and loss leading to the establishment of cognitive impairment.

In addition, Sotiropoulos et al., [91] showed that chronic stress or GC treatment triggers Tau hyperphosphorylation in different epitopes implicated in cytoskeletal pathology and synaptic loss in AD patients (e.g., pSer262) [92, 93]; note that these epitopes are correlated with hippocampal atrophy in AD patients (e.g., pThr231) [94]. Indeed, clinical studies report a strong correlation between the extent of Tau hyperphosphorylation (e.g., Thr231 and Ser262 residues) and severity of impairments of memory, speed of mental processing, and executive functions [95-97].. Futhermore Tau hyperphosphorylation is associated with synaptic loss and memory impairment in experimental animals [98] that could be also related with the stress-induced synaptic and memory loss.

Albeit specific Tau phosphoepitopes maybe differentially regulated by chronic stress and prolonged GC treatment, the overall *in vitro* and *in vivo* evidence [83] clearly implicates GCs as a key mediator of the cellular response to stress. Nevertheless, other studies have also suggested the contribution of other stress-related molecules, e.g., corticotrophin-releasing hormone [99, 100]. Furthermore, *in vitro* studies suggest the mediation of glycogen synthase kinase 3 (GSK3) or CDK5 in the above GC- and stress-triggered Tau hyperphosphorylation, both known to lead to microtubule disruption as well as formation of NFTs [83]. In parallel, GC were also shown to increased Tau accumulation by affecting turnover of the protein [83], which may involve reduced degradation through dysregulation of molecular chaperones responsible for Tau proteostasis (e.g., Hsp90, Hsp70 [101]). Interestingly, Hsp90 and Hsp70 serve to maintain the glucocorticoid receptor (GR) in a high affinity state (as previously discussed) and thus, offering a clear cross-point between GC/GR cellular signaling and Tau degradation machinery. This reduced degradation could facilitate the increased aggregation of Tau into insoluble forms triggered by stress in P301L-Tau Tg mice [mice expressing human Tau carrying the most common Tau mutation (P301L-Tau)]. In addition, chronic stress also promotes C-terminal truncation of Tau by caspase-3 and, abnormal conformation of Tau in the hippocampus of the same animals. Indeed, both truncation and abnormal conformation of Tau precede its aggregation and formation of neurofibrillary tangles [99, 102, 103] thus serving as early markers of disease. The Tau-C3 species have been suggested to contribute to misfolding of Tau into a conformation that can nucleate and recruit other Tau molecules into aggregates [99, 103, 104], which are shown to be neurotoxic and related to neuronal loss [105].

GLUCOCORTICOID ROLE IN THE ONSET AND PROGRESSION OF PARKINSON'S DISEASE

Parkinson's disease (PD), the most common neurodegenerative movement disorder, is characterized by preferential loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and dopamine depletion in striatum that underlies the appearance of motor symptoms such as akinesia, resting tremor, rigidity and postural instability. The main histopathological characteristic in PD brain is Lewy bodies (LBs), which are proteinaceous inclusions containing the presynaptic protein, alpha-synuclein, and are found in many different brain regions far beyond SN and striatum; e.g., cerebral cortex, limbic system, hypothalamus as well as the autonomic nervous system that are also affected in PD brain [106-108]. Thus, in addition to motor symptoms due to SN and striatum neurodegeneration

and lessions, PD patients with cortical LBs also suffer from dementia and visual hallucinations [109].

While several gene mutations have been identified in the familial forms of PD, the majority of PD cases are sporadic with unknown etiology. Different cellular mechanisms have been suggested to be involved in PD neurodegeneration and dopaminergic neuronal loss such as oxidative and nitrative stress, mitochondrial dysfunction and deregulated intracellular calcium levels, damaged proteostasis related to alpha-synuclein aggregation [110]. Like in AD, deregulated HPA activity is also reported in PD patients. Specifically, previous studies [76, 111-113] including our work [114] show that plasma cortisol levels are significantly higher in idiopathic PD patients compared to control subjects; however the cortisol levels are not related to disease duration or to L-3,4-dihydroxyphenylalanine (L-DOPA) treatment. Interestingly, the diurnal mode of cortisol secretion in PD patients, in particular the normally quiescent nocturnal cortisol secretory pattern, is affected [76].

Furthermore, monoaminergic neurotransmission in hypothalamus, the first compartment of HPA axis, is also affected in PD patients who exhibit reduced levels of dopamine, serotonin and noradrenaline in this brain area [115, 116] followed by reduced density of dopamine receptors [117]. Notably, this reduction was not altered by dopamine medication, which is often used in PD patients. Future studies are necessary to clarify whether the deregulation of HPA axis in PD patients is situated at the hypothalamic and/or the adrenal level as Lewy body pathology is observed in both regions.

THE NEURODEGENERATIVE POTENTIAL OF GC IN PD PATHOLOGY

The deregulated HPA axis and the subsequent elevated GC levels in PD patients reflects the role of stress which was suggested as one of the earliest proposed causes of PD. Although it may not be a major etiological factor, there are clinical reports showing that chronic stress triggers the appearance of PD symptoms or exacerbates the motor symptoms [118, 119]. Furthermore, experimental studies demonstrate that stressors such as food deprivation or tailshock aggravate motor deficits in the 6-hydroxydopamine (6-OHDA) PD model (6-hydroxydopamine local injections lesions the nigrostriatal pathway) [120]. Using the same model, Smith et al. [118] showed that chronic stress exposure (restraint) before the 6-OHDA injection worsened the 6-OHDA-driven motor deficits, aggravated the neurodegeneration of nigrostriatal system and completely blocked compensatory recovery of motor tasks.

How does high stress level of GC-GR exacerbate motor impairments following nigrostriatal lesions? GCs are known to profoundly shape the dopaminergic neurotransmitter system, exerting differential or heterogeneous effects depending on whether the dopaminergic projections arise from the ventral tegmentum area (VTA) or the SNpc. While plethora of studies have monitored the impact of GC on the limbic arm of dopamine neuronal circuitry related to behavioral changes as well as neuropsychiatric diseases, our knowledge about the exact GC influence on motor-related dopamine neuronal networks is very limited. There is lack of evidence about the impact of chronic GC elevation on nigral and striatal neurons or glia and how this contributes to nigrostriatal degeneration and motor impairments. Analysis of GR in PD brain revealed that global GR levels were lower in SNpc and higher in putamen

compared to control subjects and these results were recapitulated in MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine)-treated mice [114].

However, the cell types in which GR changes occur have not been identified. Interestingly, high GR levels in putamen of PD patients raises the possibility that dopaminergic nerve terminal degeneration induces upregulation of GR in striatal neurons and/or glia. In a study by Barrot et al. [121], GCs in SNpc or in dorsolateral striatum were found not to modify either tyrosine hydroxylase levels or dopamine transporter activity. On the contrary, adrenalectomy and the subsequent loss of corticosterone resulted in reduced D1 dopamine receptor in dorsolateral striatum suggesting that neurons expressing dopamine receptors may represent a target of GC-GR actions for basal ganglion regulation of movement. While the molecular mechanisms by which high GC through GR activity exacerbate motor deficits are not well understood, it is possible that they alter glutamatergic synapses in striatum that are under dopamine regulation.

ROLE OF GLUCOCORTICOID RECEPTOR IN REGULATION OF INFLAMMATION IN PARKINSON'S DISEASE

Chronic inflammation mediated principally by activated microglia, astrocytes and infiltrating T cells is a major neuropathological characteristic of PD. Evidence from recent genome-wide studies point to involvement of the immune system in the etiology of idiopathic PD. A number of susceptibility loci identified relate to genes expressed in immune cells such as HLA-DQB1, LRRK2 or BST-1 [122, 123]. In addition, identified PD risk factors [such as age, environmental toxins (e.g., heavy metals or pesticides,) traumatic brain injury, bacterial or viral infections] activate immune responses in periphery and brain.

Using radiolabelled ligand ^{11}C-PK-11195 for translocator protein, Positron Emission Tomography (PET) studies in PD patients revealed an early activation of microglia in many brain regions including basal ganglia and substantia nigra [124, 125]. Furthermore, post-mortem studies as well as analyses of serum and cerebrospinal fluid from PD showed high levels of pro-inflammatory mediators such as TNF-α, IL-1β, iNOS, IFN-γ and COX-2 [126]. In line with observations in PD patients, presence of inflammatory mediators and glial reactivity in striatum and substantia nigra is a key feature in many of the experimental animal models of PD. For example, treatment of mice or monkeys with neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which selectively induces degeneration of nigrostriatal pathway, 6-hydroxydopamine lesion of nigro-striatal pathway in rodents or toxicity induced by alpha-synuclein injection [126, 127].

Among all the brain regions, substantia nigra has one of highest density of microglia. Activated microglia functioning as innate-immune competent cells are likely involved in releasing the above inflammatory molecules, thereby inducing dopamine neurodegeneration. Indeed the important role of these pro-inflammatory mediators in promoting degeneration of dopaminergic neurons of substantia nigra was demonstrated using mice with specific knockout of these genes [128-131]. Many of the pro-inflammatory mediators found in PD patients are transcriptional targets of GR. The synthetic analogue of GCs, dexamethasone, was shown to attenuate dopamine neuronal loss by precluding activated microglia from releasing toxic inflammatory molecules [132, 133]. In adrenalectomized mice (lacking

endogenous production of GCs), dopamine neuronal loss was augmented following MPTP intoxication indicating that endogenous GCs do play a role in protecting dopamine neurons [134] Examination of GR in microglia revealed an increase in nuclear localization of GR following MPTP treatment in mice, which coincided with rise in systemic corticosterone levels indicating that GR is activated in microglia during degeneration of dopamine neurons [114]. The unequivocal evidence that GR in microglia normally protects dopamine neurons appeared in a study using mice in which GR gene is deleted in microglia/macrophages. MPTP treatment in these mice resulted in increased dopamine neuronal loss as well as increased microglial activation and expression of pro-inflammatory mediators [114]. Indeed, the absence of GR in microglia resulted in sustained activation of NF-κB as was shown in these microglial GR mutants. The above finding has a significant relevance for PD pathogenesis as nuclear expression of p65 subunit of NF-κB, indicative of transcriptional activity, was found in substantia nigra microglia of PD post-mortem [135].

Chronic inflammation and sustained activation of glia in PD suggests that processes involved in regulation of glial activation and expression/secretion of inflammatory mediators are likely compromised. Chronic inflammation, an important component of pathology in neurodegenerative diseases, is suggested to be a maladaptive response of homeostasis as successful inflammatory response has a resolution phase which is an active process that enables restoration of homeostatic set points [136, 137]. Inflammation mediated by immune-competent cells including microglia is normally a very tightly regulated process. The immune-regulatory processes are affected in aging leading to increased susceptibility to infections and immune activation. Thus in aging, microglia show enhanced sensitivity to inflammatory stimuli - a process called “priming” which could be also induced by chronic stress and deregulated HPA axis. In this regard, there are several studies showing that chronically elevated GC levels in response to different stressors cause pro-inflammatory cytokine production and sensitization or “priming” of microglia. Importantly, subsequent inflammatory or toxic stimulus results in aggravatation of neuronal injury [138-140]. Aging is associated with chronically high GC levels and immuno-senescence exemplified by a sustained low production of pro-inflammatory molecules [141]. Thus, in contrast to their well-known anti-inflammatory actions, in fact high and sustained GCs can exacerbate inflammation. However, it is currently not known whether GR transcriptional activity regulating inflammatory response of microglia is compromised in AD and PD pathological conditions where deregulated HPA axis and sustained high GC levels of are found.

GC-DRIVEN BRAIN PROGRAMMING AND NEURODEGENERATIVE PATHOLOGIES

Although Alzheimer’s disease (AD) is often seen as an age-related neurodegenerative disorder, recent evidence suggests that early life events may play a role in the onset of the disorder (Borenstein, A.R.; Early-life risk factors for Alzheimer disease. Alzheimer Dis. Assoc. Disord., 2006). In this perspective, AD is probably not determined by a single etiologic factor, but results from the interplay between genetic and environmental factors throughout life, being a possible explanation why monozygous twins can be discordant for AD.

Albeit there is still controversy and the literature is sparse, it has been suggested that early life adverse events such as maternal stress, intrauterine infections, poor maternal and perinatal nutrition can potentially predispose to AD eventually by epigenetic programing of specific genes/pathways related to AD neurodegeneration. For example, early-life lead exposure of older rats and primates induces overexpression of the amyloid precursor protein and its amyloid beta (Aβ) product, both characteristically found in AD brain as will be discussed later in this chapter. One interesting finding was that cognitive impairment was only observed in mice exposed to lead [142], highlighting the relevance of the "window of opportunity" for some environmental factors to trigger the disease.

Similarly, Tau hyperphosphorylation and accumulation, the other main histopathological characteristic of AD pathology) was elevated in both aging rodents and primates previously exposed to lead at younger age, [143] suggesting the potential impact of early-life stress exposure to the precipitation of AD neurodegeneration later in life. Interestingly, a recent study has also highlighted the GC-related epigenetic drive in the establishment of AD pathology in the brain of CK-p25 AD mouse model (exhibiting Tau pathology). These Tg mice exhibit increased levels of HDAC2 associated with cognitive impairment, which seems to be mediated through glucocorticoid receptor induced HDAC2 transcription [144].

Furthermore, the role of early life stressful events in the etiopathogenesis of another neurodegenerative disorder, Parkinson's disease (PD) has emerged in the last years. In an interesting study, pups of female animals exposed to lipopolysaccharide (LPS), a bacterial endotoxin, during pregnancy, showed loss of dopaminergic neurons. This suggests that high LPS levels in mothers might interfere with the dopaminergic neurons in the fetus enhancing the susceptibility to PD [145].

Accordingly, different stressful stimuli could act cumulatively with the developmental stress exposure representing the first imprint in the developing brain, determining the PD phenotype characterized at the pathological level by a deficient substantia nigra with a low burden of DA neurons at birth corresponding to a limited nigro-striatal neurochemical reserve [146]. The low number of DA neurons in the substantia nigra reflecting the developmental damage may remain subclinical during life. Thus, later exposure to the same or other DA neuron-targeted toxicants might attack the few residual neurons leading to insurgence of PD.

CONCLUSION

Accumulating evidence suggests the neurodegenerative potential of chronic stress and elevated GC levels in triggering clinical symptoms and participating in neuropathological mechanisms and processes in AD and PD, two devastating age-related neurodegenerative disorders. High circulating GC (cortisol) levels and deregulated HPA axis observed in patients of both disorders imply that GR activity in the affected regions is most likely compromised but the cause-consequence interrelationship between elevated GC levels and development of neurodegenerative pathology remains unclear. While the ramifications of prolonged exposure to GC stress are many, being causally implicated in immunosuppression, metabolic syndrome, diabetes and others, our current understanding of the exact actions of GC on these neurodegenerative diseases, although limited, opens a window of opportunities to identify the various parameters that contributes to stress/GC-driven brain pathology. As

both context and cell type determine GR functions, future works using, e.g., cell-specific mouse models of GR activation/inactivation should shed light on their roles in pathological brain aging and onset of neurodegenerative disorders such as AD and PD.

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