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Glucocorticoid induced leucine zipper in central nervous system health and disease

Mythily Srinivasan* and Debomoy K. Lahiri@

*School of Dentistry, Indiana University–Purdue University Indianapolis

@Institute of Psychiatry Research, Department of Psychiatry and Medical & Molecular Genetics, School of Medicine, Indiana University–Purdue University Indianapolis

Abstract

The central nervous system (CNS) is a large network of intercommunicating cells that function to maintain tissue health and homeostasis. Considerable evidence suggests that glucocorticoids exert both neuroprotective and neurodegenerative effects in the CNS. Glucocorticoids act by binding two related receptors in the cytoplasm, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The glucocorticoid:receptor complex then mediate cellular responses by transactivating target genes or via protein:protein interactions. The paradoxical effects of glucocorticoids in mediating survival and death of neurons have been attributed to the concentration and the ratio of mineralocorticoid to glucocorticoid receptor activation. Glucocorticoid induced leucine zipper (GILZ) is a recently identified protein transcriptionally upregulated by glucocorticoids. It is constitutively expressed in many tissues including brain. Functionally while GILZ mimics many of the beneficial effects of glucocorticoids including the anti-inflammatory and anti-proliferative potential, it suppresses the adverse effects of glucocorticoids presumably by exerting differential effects on lineage development by pluripotent cells. As opposed to glucocorticoids, GILZ downregulates the adipogenic transcription factor peroxisome proliferator-activated receptor (PPAR)- γ and upregulates runt-related transcription factor 2 (RUNX2) widely implicated in osteogenesis and more recently in neurogenesis as well. Further, data on GILZ expression and effects following induced stress or spinal cord injury suggest potential roles in CNS diseases. Here we provide a short overview of GILZ expression in CNS health and discuss three potential rationales for its role in the pathogenesis of Alzheimer's disease, a common neurodegenerative pathology.

Keywords

GILZ; Alzheimer's disease

Address Correspondence to: Mythily Srinivasan, MS, PhD., Associate Professor, Oral Pathology, Radiology and Medicine, Indiana University School of Dentistry, Tel: 317 278 9686, FAX: 317-278-3018, mysriniv@iupui.edu.
Debomoy K. Lahiri, Ph.D., Professor of Neurosciences, Departments of Psychiatry, and of Medical & Molecular Genetics, Indiana University School of Medicine, Core-leader, Indiana Alzheimer Disease Center (IADC), Neuroscience Research Center, 320 West 15th Street, NB 200C, Indianapolis, IN 46202-2266 USA, Tel: (317) 274-2706; Fax: (317) 231-0200, dlahiri@iupui.edu

Introduction

I. Glucocorticoids in the central nervous system (CNS)

Glucocorticoids (corticosterone in rodents and cortisol in humans) secreted in response to stress induced activation of the hypothalamo-pituitary-adrenal (HPA) axis exert a wide range of actions on most cell types including the cells of the central nervous system (CNS) [1, 2]. Upon binding the mineralocorticoid receptor (MR) or the glucocorticoid receptor (GR) in the cytoplasm, the glucocorticoid:receptor complex translocate to the nucleus and mediate cellular responses by genomic mechanisms via specific glucocorticoid response elements (GRE) in the DNA or by non-genomic protein:protein interactions. The receptors shuttle between the cytoplasm and the nucleus; their subcellular localization being determined by the equilibrium between nuclear import and export [3]. The negative feedback and circadian rhythmicity of circulating glucocorticoids are critical for maintaining the basal HPA axis activity and facilitate the termination of HPA activation [3, 4].

Glucocorticoids exhibit ten-fold higher affinity for MR than GR [5, 6]. This one ligand/two receptor system works in balance, modulating a large spectrum of actions in the CNS. While MR is highly expressed in limbic areas such as the hippocampus and amygdala; GR is ubiquitously expressed throughout the brain [7, 8]. Sensitivity to glucocorticoids depends on the concentration and duration of exposure, bioavailability and the density of receptors. In physiological conditions and during circadian trough the high affinity MR is preferably occupied with less than 10% GR occupancy to help maintain low basal glucocorticoid levels [3, 9]. Several studies suggest that the MR functionality is important for maintaining the basal HPA activity and preserving the normal metabolism of the neurons [10, 11]. Pathological effects of glucocorticoids are largely mediated by GR. While both receptors can modulate transcription of the same target genes, microarray studies suggest that approximately 20% of the expression profiles are uniquely modulated by GR [12]. This is largely attributed to the non-genomic functions, wherein nuclear GR tethers to and interferes with the functioning of other transcription factors such as nuclear factor-kappa B (NF- κ B) and activator protein 1 (AP-1) [8, 13].

I. a: Glucocorticoids in Alzheimer's disease—Both lack and overexposure of glucocorticoids increases the risk for neurodegenerative diseases. Excessive glucocorticoid alters MR/GR ratio, disrupts nucleocytoplasmic shuttling of the receptors and dysregulates HPA activity [1, 4]. Clinical observations of elevated plasma cortisol and/or changes in circadian rhythm of glucocorticoid release in Alzheimer's disease (AD) and Parkinson's disease (PD) support a role for high glucocorticoids in neurodegenerative pathologies [14–16]. In AD patients, the higher plasma glucocorticoids correlated with decreased hippocampal volume, a region of the brain critical for learning and memory [15, 16]. Mechanistically, highly elevated glucocorticoids have been shown to accelerate the beta amyloid (A β) plaque formation and tau phosphorylation, two major pathological hallmarks of AD, and thereby enhance the vulnerability of neuronal cells to toxic stimuli [17]. In triple transgenic mouse model of AD which develops both A β and tau pathologies in a progressive and region-specific manner, dexamethasone treatment upregulated steady state levels of amyloid precursor protein (APP), β -site APP cleaving enzyme (BACE-1) and enhanced A β

generation [18, 19]. Blockade of glucocorticoid:GR but not glucocorticoid:MR interaction abrogated the dexamethasone mediated upregulation of A β secretion [20].

Both stress and A β aggregates precipitate oxidative stress, considered as one of the early events in AD pathology as evidenced by the increased presence of reactive oxygen species in vulnerable neurons [21, 22]. Chronic stress has been shown to increase lipid peroxidation in the hippocampus in normal and AD mice with three fold higher upregulation in the diseased animals [23]. It has been observed that the oxidative stress mediate negative regulation of GR and allow retention of the glucocorticoid:GR complex in the cytoplasm [23, 24]. This reduces the ability of glucocorticoids to repress transcription factors NF- κ B and AP-1 leading to inflammatory distress. Increased oxidative stress further enhances A β accumulation initiating a vicious cycle [21]. In AD mice, the A β induced oxidative stress could be suppressed by pharmacological blockade of corticosterone release suggesting that the elevated glucocorticoids and A β act synergistically to enhance the vulnerability of neurons to apoptosis [20].

II. Glucocorticoid induced leucine zipper (GILZ)

GILZ is a recently identified protein that has been shown to mediate many of the cellular effects of glucocorticoids. It is a member of the TSC22D (transforming growth factor β 1-stimulated clone 22 domain) family of proteins that potentially impact multiple biological processes [25, 26]. Four different isoforms have been identified arising as splice variants from a single gene [27]. Structurally, the GILZ protein has an amino terminal leucine zipper motif for dimerizing and a carboxy terminal proline rich region for protein-protein interactions [25, 26]. Constitutive expression of GILZ has been reported in many cell types and multiple organs including skeletal muscle, lungs, intestine, kidney and brain [27]. With six GRE in its promoter region, GILZ is strongly induced by glucocorticoids [25]. Much like other glucocorticoid responsive genes such as the tyrosine aminotransferase, glutamine synthetase, cholesterol-7 α -hydroxylase and the glucocorticoid receptor, GILZ exhibits circadian rhythm of expression in response to the rhythmic release of endogenous glucocorticoid [27].

II. a. GILZ in the CNS—Endogenous GILZ is widely expressed throughout the brain and spinal cord suggesting a physiological role in the CNS [27]. In mice exposed to water immersion restraint stress, activation of HPA activity and increased glucocorticoid secretion correlated with elevated GILZ expression in medial pre-frontal cortex and hippocampal neurons [28, 29]. The stress induced GILZ upregulation was abrogated in adrenalectomized mice attributing the response to the increase in glucocorticoid:GR mediated transactivation [29]. Constitutive expression of GILZ has been observed in murine microglial cells. Further, similar to the observations in macrophages and lymphocytes, microglial GILZ expression correlated negatively with inflammatory cytokines and was downregulated following induced anxiety [28, 30].

III. Plausible roles of GILZ in AD

Three distinct rationales are postulated for potential roles of GILZ in AD pathogenesis. 1) A role in A β regulation supported by the ubiquitous expression of GILZ in neurons and glia

[27, 29]; 2) GILZ as an anti-inflammatory molecule that modulates the processes of neuroinflammation and neurodegeneration in AD [31, 32] and 3) a role in neurogenesis based on potential cross-talk between GILZ and other nuclear transcriptional hormone receptors such as peroxisome proliferator-activated receptor (PPAR)- γ and CCAAT/enhancer-binding protein (C/EBP)- δ [33].

Hypothesis 1: Constitutive GILZ regulates physiological A β in CNS health—

Normal brain contains both soluble and neuronal A β . Picomolar concentration of A β exhibit neurotrophic properties, promote neurogenesis and contribute to normal synaptic activity and memory [34]. Mechanistically physiological A β has been shown to mediate tyrosine phosphorylation and increase phosphatidylinositol-3-kinases (PI3K) activity in neuronal cells [22, 35, 36]. The PI3K pathway has been implicated in modulating autophagy, neuronal survival, neurite extension and synaptic plasticity in the brain. Blockade of this pathway has been shown to increase apoptosis in A β exposed neuronal cells [37, 38].

As stated above, considerable data suggest essential roles for MR, the high affinity receptor for glucocorticoids, in neuronal survival and neurogenesis [10]. In health under low GC conditions, ligand activated MR not only induces BACE-1 transcription and inflammatory cytokines that facilitate A β production, but also upregulates many neuroprotective molecules [4, 39]. In PC12 neuronal cells overexpression of MR has been shown to enhance neuron specific genes such as microtubule associated protein-2 (MAP2) and β -tubulin III, increase the ratio of anti-apoptotic (Bcl2 and Bcl_{xL}) to pro-apoptotic (Bax and Bak) proteins and diminish caspase 3 cleavage [40, 41]. While exposure to A β reduced MR and increased nuclear GR in cultured rat hippocampal and cortical neurons with consequent increase in cell death, activation of MR reduced the vulnerability of the cultured neurons to apoptosis [41, 42]. Tauroursodeoxycholic acid (TUDCA), a cholesterol derived endogenous molecule, has been shown to exhibit neuroprotective effects by selectively binding MR and increasing its nuclear translocation with subsequent transactivation of Bcl-2 and other anti-apoptotic genes [43]. It has been suggested that an optimal balance between MR and GR activation with MR predominating in the hippocampus is necessary for best emotional and cognitive function [1, 10, 11].

GILZ is one of the transcripts upregulated by both MR and GR [31, 44]. Mechanistically much like glucocorticoids, GILZ has been shown to enhance expressions of anti-apoptotic molecules such as Bcl-2 and Bcl_{xL} in different cell types including cardiomyocytes, epithelial cells and many human cancer cells [31, 45–47]. GILZ has also been shown to modulate the PI3K pathway, suppress cytokines and inhibit inflammation in activated lymphocytes and epithelial cells [48, 49]. Taken together it is plausible that the constitutive GILZ induced in neuronal cells under low GC conditions may act in concert with picomolar A β in regulating autophagy and neuronal survival by increasing anti-apoptotic factors and suppressing excessive cytokines. Furthermore, since PI3K signaling has been shown to play critical roles in regulating survival of A β exposed neurons, it is tempting to speculate that the regulation of PI3K signaling by constitutive GILZ in neurons may indirectly control the threshold of A β accumulation and CNS health.

Hypothesis 2: Exogenous GILZ is an attractive strategy to suppress

neuroinflammation—Neuroinflammation plays critical roles in the initiation and/or progression of most neurodegenerative diseases including AD [50–52]. Aging and chronic stress are significant risk factors. In addition, persistent stress mediated increase in glucocorticoids enhances the neuronal cell vulnerability to glutamate, the excitatory neurotransmitter and A β induced neurotoxicity [1, 19]. A β exposure activates the p65:p50 NF- κ B dimers in glia and post-mitotic neurons and enhance transactivation of inflammatory and apoptotic genes [53]. Elevated Bax (pro-apoptotic) to Bcl-2 (anti-apoptotic) ratio has been observed in A β stimulated neuronal cells [54–56]. Increased presence of IL-1 β , IL-6, and TNF- α has been reported in the affected tissues, serum and cerebrospinal fluid of AD patients [57]. However, exogenous glucocorticoids, the prototype anti-inflammatory agents have been largely ineffective and even counter-productive in the treatment of AD. The low therapeutic efficacy of glucocorticoids is correlated with a disproportionate increase in the glucocorticoid:GR complex with enhanced susceptibility to apoptosis [58].

GILZ represents a potentially efficacious alternative anti-inflammatory molecule to suppress neuroinflammation. Mechanistically the anti-inflammatory and anti-apoptotic effects of both glucocorticoids and GILZ are largely attributed to the suppression of NF- κ B mediated transactivation [59, 60]. While the glucocorticoid:GR complex tether to and interfere with NF- κ B-DNA binding, GILZ binds to and sequesters the p65 subunit of NF- κ B in the cytoplasm, thereby preventing nuclear translocation and transactivation of pathological mediators [7, 26, 61]. Overexpression of GILZ has been shown to suppress inflammatory cytokines and ameliorate pathology in models of colitis, multiple sclerosis and spinal cord injury [32, 62, 63]. We observed that selective blockade of activated p65 by a synthetic peptide mimic of the p65 binding domain of GILZ suppressed A β mediated toxicity in neuroblastoma cells and in primary human neuronal cells [64, 65]. Taken together, it is hypothesized that by virtue of binding the transactivation domain of p65 exposed only in activated cells, exogenous GILZ represents an attractive strategy to suppress neuroinflammatory-neurodegenerative diseases including AD (Fig 2).

Hypothesis 3: GILZ plays a role in neurogenesis—Neurogenesis involves

proliferation, survival, migration and lineage differentiation of neural stem/progenitor cells. Continuous stimulation including cognitive functions elicits protective responses that avoid tissue damage, promote neurogenesis and maintain homeostasis in the CNS. This involves complex signaling pathways that are interlinked and tightly regulated [66]. Glucocorticoid and NF- κ B signaling are two cross-talking pathways shown to play crucial roles in adult neurogenesis [67, 68]. In health, stimulation of NF- κ B signaling by low concentrations of proinflammatory cytokines such as TNF- α or the excitatory neurotransmitter glutamate has been shown to increase proliferation and differentiation of neural stem cells and promote neuronal survival [67, 69]. It has been suggested that neuroprotection is largely attributed to the activation of NF- κ B C-rel dimers [70]. Similarly at physiological concentrations, glucocorticoids signaling via MR increased the proliferation and differentiation of human hippocampus-derived stem cells. However, excessive inflammation or high glucocorticoids largely inhibited neuronal stem cells [68, 71]. GILZ as an interface molecule that connects

glucocorticoid and NF- κ B pathways could potentially play a role in modulating the neural stem cell responses and hence neurogenesis [59].

In addition to NF- κ B, the GILZ also interacts with other transcription factors implicated in adult neurogenesis, the PPAR- γ and C/EBP- δ [72, 73]. The basal expression of both C/EBP δ and PPAR- γ in the adult CNS is relatively low [74, 75]. While NF- κ B activation and cytokines such as TNF- α enhance C/EBP δ expression, sustained elevation of inflammatory cytokines suppress its transcription [76]. Glucocorticoids enhance the transcription of both C/EBP δ and PPAR- γ [77, 78]. Further, C/EBP δ has also been shown to bind the C/EBP binding elements in PPAR- γ promoter and upregulate its transcription [75, 76]. Several reports substantiate a neurogenic role for PPAR- γ . Activation of PPAR- γ in neural stem cells has been shown to promote differentiation to mature neurons, astrocytes and oligodendrocytes [74]. Treatment with PPAR- γ agonists has been shown to induce neurite outgrowth and increased axonal length in hippocampal neurons [79].

GILZ has been shown to bind a tandem repeat of C/EBP binding sites and act as a sequence-specific trans-repressor of PPAR- γ in pluripotent mouse mesenchymal stem cells [33]. In human bone marrow derived stem cells dexamethasone induced GILZ has been shown to suppress PPAR- γ 2 and upregulate RUNX-2 transcription factor [73, 80]. Although a plethora of studies substantiate the critical involvement of RUNX2 in osteogenesis, recent reports suggest a potential role for the molecule in neuronal development [81]. Adult human hippocampus and cultured rat astrocytes have been shown to express RUNX2 transcript [82, 83]. In human astroglioma cells RUNX2 is significantly elevated and regulates the expression of galectin 3, a β galactoside-binding lectin that has been shown to promote neural cell adhesion and neurite growth [83].

Collectively, the physical interactions of GILZ with multiple transcription factors greatly enhances the number of potentially regulated genes or post-translational modifications that could crucially affect molecular mechanisms involved in the dynamic process of adult neurogenesis. It is postulated that under low glucocorticoid and inflammatory conditions, GILZ could facilitate neuronal differentiation of stem cells and promote hippocampal neurogenesis by upregulating RUNX-2 transcription. This is supported by the observations of inverse relationship between NF- κ B and RUNX-2 transcription factors and elevated RUNX-2 in adult hippocampus [83, 84].

IV. Conclusion

The effects of endogenous and exogenous glucocorticoids in neurogenesis, neuroinflammation and neurodegeneration in the CNS have been extensively investigated with some mechanistic elucidations, some contradictory findings and some as yet unanswered questions. It is tempting to speculate that some of the contradictory or unknown glucocorticoids effects could be attributed to the GILZ expression. The uneven distribution and upregulated expression following HPA activation suggests multiple roles for GILZ in the CNS. Much like its effects on osteogenic differentiation, GILZ could potentially play a role in neuronal differentiation and development. In microglial cells a tightly controlled and coordinated action of MR and GR has been shown to regulate NF- κ B functions [8]. At low ligand concentration or at early time points following activation, the effects of MR mediated

transactivation of neurotrophic factors and anti-inflammatory GILZ could potentially supersede that of BACE1 and pro-inflammatory cytokines. In conditions of chronic stress and/or A β toxicity inflammatory mediators suppress GILZ. In this context, exogenous GILZ could represent an attractive strategy to suppress neuroinflammation. In conclusion, elucidation of the physiological role of GILZ in the CNS, its induction by other factors including microbial agents or free radicals, role in BACE-1 activity and A β homeostasis will enhance our understanding of the glucocorticoid signaling in the CNS and help in the identification of alternative therapeutic strategies to target neuroinflammation and neurodegeneration.

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Fig. 1.

Schematic representation of potential role of GILZ in regulating physiological amyloid beta in CNS health. Low glucocorticoid (GC) and picomolar concentration of amyloid beta ($A\beta$) are features of healthy CNS. Signaling via phosphatidylinositol-3-kinases (PI3 K) has been shown to critical for neurotrophic and anti-apoptotic effects of picomolar $A\beta$. Blockade of PI3 K has been shown to abrogate such effects. Under low GC conditions, MR is preferentially occupied and mediates GILZ expression. In lymphocytes and epithelial cells, GILZ overexpression has been shown to suppress PI3 kinase activity and inhibit inflammatory responses. Micromolar concentration of $A\beta$ is associated with enhanced production of anti-apoptotic factors via increased PI3 kinase signaling. This figure speculates that constitutive GILZ expression plays a role in modulating PI3 K signaling thereby regulating indirectly the physiological $A\beta$.

Fig. 2.

Schematic representation of exogenous GILZ as a potential therapeutic agent for AD. Aging, chronic stress, amyloid b aggregates or other factors mediated oxidative stress activate NF-κB p65 which in turn induces activation of pro-inflammatory (cytokines, glutamate) and proapoptotic factors that ultimately lead to cell death. Exogenous GILZ will bind p65 and prevent activation of deleterious mediators.

Fig. 3.

Potential role of GILZ adult neurogenesis: Schematic representation of some of the factors involved in adult neurogenesis. Toll like receptor (TLR) stimulation and cytokines such as TNF- α activate NF- κ B transcription factor in adult hippocampal neural stem cells. While NF- κ B C-rel containing dimers are predominantly neuroprotective, p65 containing dimers promote transactivation of inflammatory cytokines that upregulate C/EBP δ transcription factor which in turn induces PPAR- γ . However, inflammatory cytokines can also downregulate both C/EBP δ and PPAR- γ . Glucocorticoids induced GILZ expression in neural stem cells can modulate this process at two steps (inhibitory actions shown in red): 1) blockade of NF- κ B p65 and 2) suppression of PPAR- γ and transactivation of RUNX-2.