Trends in Neurosciences

CellPress

Review

The multiple roles of chronic stress and glucocorticoids in Alzheimer's disease pathogenesis

Mia R. Burke[1,2], Ioannis Sotiropoulos[3], and Clarissa L. Waites[1,4,*]

Chronic stress and the accompanying long-term elevation of glucocorticoids (GCs), the stress hormones of the body, increase the risk and accelerate the progression of Alzheimer's disease (AD). Signatures of AD include intracellular tau (MAPT) tangles, extracellular amyloid β (Aβ) plaques, and neuroinflammation. A growing body of work indicates that stress and GCs initiate cellular processes underlying these pathologies through dysregulation of protein homeostasis and trafficking, mitochondrial bioenergetics, and response to damage-associated stimuli. In this review, we integrate findings from mechanistic studies in rodent and cellular models, wherein defined chronic stress protocols or GC administration have been shown to elicit AD-related pathology. We specifically discuss the effects of chronic stress and GCs on tau pathogenesis, including hyperphosphorylation, aggregation, and spreading, amyloid precursor protein (APP) processing and trafficking culminating in Aβ production, immune priming by proinflammatory cytokines and disease-associated molecular patterns, and alterations to glial cell and blood–brain barrier (BBB) function.

Highlights

Chronic stress and glucocorticoids (GCs, the stress hormones of the body) are implicated in the tau, amyloid β (Aβ), and neuroinflammatory pathology that is characteristic of Alzheimer's disease.

Stress and GCs activate kinases and inhibit proteostasis mechanisms, thus driving tau hyperphosphorylation, aggregation, and secretion/spreading through the brain.

Stress and GCs promote Aβ pathology by increasing the expression and amyloidogenic processing of amyloid precursor protein (APP) and by impairing APP and Aβ clearance mechanisms.

Stress and GCs stimulate neuroinflammation through upregulation of the inflammasome and damage-associated molecular pattern (DAMP) receptors, thereby promoting the secretion of proinflammatory cytokines.

Stress and GCs induce aberrant glial cell functioning, leading to over-pruning of synapses, glutamate excitotoxicity, and decreased integrity of the blood–brain barrier (BBB) and glymphatic clearance systems.

Stress and GC signaling in the brain

During exposure to stressful stimuli, nuclei in the locus coeruleus of the brainstem release norepinephrine, coinciding with activation of the hypothalamic–pituitary–adrenal (HPA) axis [1,2]. The HPA axis initiates a cascade of hormones, culminating in the release of GCs – the primary stress hormones – from the adrenal glands into the systemic circulation [2,3]. GCs in turn induce physiological changes, including alterations to neuronal communication and energy mobilization, that enable organisms to cope with the initiating stressor and enhance their chance of survival in threatening situations; thus, strong selective pressure has maintained the HPA axis and stress/GC signaling throughout evolution. However, prolonged exposure to stressors and persistent elevation of GCs, manifesting as chronic stress, have profoundly negative consequences on organismal physiology [4,5]. The brain is particularly sensitive to changes in energy production that occur during sustained stress signaling because it has the highest energy demand of any organ. This sensitivity is due in part to the polarized morphology of neurons, wherein energy-intensive protein/organelle transport and clearance pathways are necessary to maintain the function of neuronal synapses [6,7]. Accumulating evidence suggests that dysregulation of these pathways during chronic stress signaling mimics changes to neurons and glia observed early in neurodegeneration; indeed, chronic stress is now a well-documented risk factor for AD [4,8–10].

GCs signal through mineralocorticoid receptors and GC receptors (GRs). Although GCs have high affinity for mineralocorticoid receptors, these receptors are typically saturated by basal GC levels, whereas stress and elevated GC levels facilitate GR-mediated effects. GRs are expressed

[1]Department of Pathology and Cell Biology, Taub Institute for Research on Alzheimer's Disease and Aging Brain, Columbia University Irving Medical Center, New York, NY, USA
[2]Pathobiology and Mechanisms of Disease Graduate Program, Columbia University Irving Medical Center, New York, NY, USA
[3]Institute of Biosciences and Applications, National Centre for Scientific Research (NCSR) Demokritos, Agia Paraskevi, Greece

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[4]Department of Neuroscience, Columbia University Irving Medical Center, New York, NY, USA

*Correspondence:
cw2622@cumc.columbia.edu
(C.L. Waites).

ubiquitously throughout the brain [11] but are particularly enriched in the hypothalamus (for feedback to the HPA axis), hippocampus [12], and prefrontal cortex, where GCs have wide-ranging effects on learning, memory, and neuronal morphology [11]. GRs localize not only to the plasma membrane, like conventional ligand-binding receptors, but also to the cytosol and to membranes of subcellular organelles such as mitochondria. Cytosolic GRs facilitate the genomic effects of GCs on gene expression. In the absence of GCs, cytosolic GRs are bound to an inhibitory complex, comprising HSP70, HSP90, FKBP51, FKBP52, and BAG1, that conceals the GR nuclear localization signal [11]. This complex is displaced upon GC binding, facilitating nuclear translocation of GC-bound GRs and their indispensable function as transcription factors that regulate a large set of steroid hormone-responsive genes via GC response elements in the genome [11]. GC/GR complexes directly regulate multiple genes relevant to protein homeostasis and mitochondrial quality control (biogenesis, fission/fusion, mitophagy) [13], and can physically interact with nearly 300 other transcription factors to achieve context-specific, tunable gene regulation [11,14]. In contrast to their cytosolic counterparts, GRs associated with plasma and mitochondrial membranes typically facilitate the non-genomic effects of GCs. At the plasma membrane, GC-bound GRs interact with phosphatases, kinases, the membrane-trafficking machinery, and receptors for neurotransmitters, thereby orchestrating changes in synaptic strength that facilitate responsiveness/adaptation to stress-provoking stimuli. Mitochondria-associated GRs stimulate mitochondrial Ca^{2+} buffering [15,16] and oxidative phosphorylation [17], while inhibiting autophagy via phosphorylation and activation of the kinase mTOR [16,18]. These and other actions facilitate rapid energy production and utilization that enable organisms to escape from acute stressors. By contrast, sustained GC exposure causes decreased mitochondrial ATP production [15], long-term inhibition of autophagy, and dysregulation of organelle and protein trafficking [16], all of which are pathogenic mechanisms implicated in AD [19,20].

Indeed, clinical and epidemiological studies implicate chronic stress as a risk factor for AD, which the World Health Organization credits as the cause of ~70% of dementia in individuals over age 65 [21]. The dual observations that AD patients exhibit hypercortisolemia [22,23], and that AD subjects treated daily with prednisone (a synthetic GC) experience significantly greater cognitive decline than those who do not receive this treatment [24], support the hypothesis of stress as a risk factor or accelerant of AD pathogenesis. In addition, a recent cohort study of >1 million individuals revealed that a diagnosis of chronic stress-induced exhaustion disorder confers an odds ratio for Alzheimer disease of 2.45 [9], greater than the odds ratios for all other modifiable AD risk factors.

This review aims to discuss recent work linking chronic stress and high GC levels to AD pathogenesis, as well as the molecular and cellular mechanisms through which stress/GCs precipitate or accelerate AD. We focus primarily on stress as modeled through well-documented paradigms in rodents (e.g., chronic unpredictable stress, chronic social defeat stress [25,26]) and exogenous GC administration, although we acknowledge that other hormones and neurotransmitters [e.g., norepinephrine, corticotrophin-releasing hormone (CRH), and aldosterone] contribute to the physiological effects of stress, and that these animal model studies incompletely recapitulate the experience of chronic psychological stress in humans. In the following sections we specifically highlight the impacts of chronic stress and high GC levels on three hallmark features of AD: tau pathogenesis, Aβ production, and neuroinflammation.

Chronic stress and GCs induce intracellular tau pathology

Tau is a microtubule-associated protein that has crucial roles in the assembly, stability, and spatial organization of microtubules in neurons [27,28]. As such, tau is essential for normal axonal and nucleocytoplasmic transport; its aberrant hyperphosphorylation, aggregation, and incorporation

into neurofibrillary tangles disrupt these processes and are hallmarks of AD [29]. Considerable evidence implicates chronic stress/GC-induced tau pathogenesis (hyperphosphorylation, accumulation, aggregation, transcellular spreading) as a key mechanism through which stress precipitates brain pathology and accelerates AD progression [4]. Tau is phosphorylated by multiple kinases, including glycogen synthase kinase 3β (GSK3β), cyclin-dependent kinase 5 (CDK5), SRC kinases, p38 mitogen-activated protein kinase (MAPK), and microtubule affinity regulating kinase 4 (MARK4) [30], and stress/GCs are reported to activate several of these. For instance, increased GC signaling via the expression of a constitutively active GR was shown to promote MAPK signaling [31], whereas knockout of neuronal GRs conversely led to downregulation of MAPK pathway components [RAS, RAF1, extracellular signaling-regulated kinase 1 (ERK1), ERK2, and EGR-1] in mouse hippocampus. In addition, GCs were found to induce tau hyperphosphorylation in primary neuronal cultures [32] and rodent brain [33–35] through phosphorylation/ activation of GSK3β, CDK5, and ERK1/2, kinases that are also implicated in tau pathogenesis in AD (Figure 1) [30]. Chronic unpredictable stress paradigms involving daily exposure to randomly selected stressors (e.g., white noise, restraint, damp bedding, overcrowding, tilted cage) similarly upregulate CDK5 and GSK3β phosphorylation in mouse anterior cingulate cortex [36], an area associated with development of negative mood and depression. Such hyperphosphorylation promotes tau detachment from microtubules and its mis-sorting to synapses, where it has been shown to impair presynaptic neurotransmitter release via interactions with

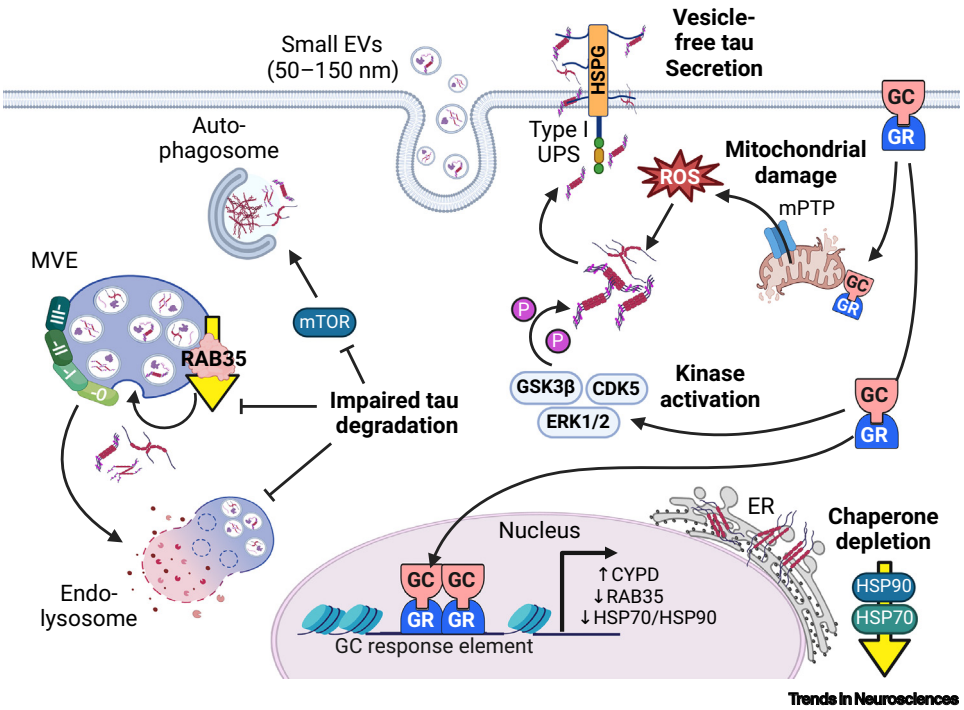


Figure 1. Glucocorticoids (GCs) stimulate tau pathology through multiple mechanisms. GCs (top right) activate kinases and deplete protein chaperones, which can lead to tau hyperphosphorylation, misfolding, and aggregation. GCs also induce mitochondrial damage (e.g., by activating the mitochondrial permeability transition pore, mPTP), thereby increasing the production of reactive oxygen species (ROS) that in turn promote tau pathogenesis. Tau oligomers and aggregates accumulate in cells because GCs impair their clearance via inhibition of autophagy and RAB35-mediated endolysosomal sorting. Finally, GCs promote tau secretion through type I unconventional protein secretion (UPS), which requires interactions between phospho-tau and plasma membrane heparin sulfate proteoglycans (HSPGs), and likely through the release of small extracellular vesicles (sEVs) upon multivesicular endosome (MVE) fusion with the plasma membrane. Abbreviations: ER, endoplasmic reticulum; GR, glucocorticoid receptor; P, phosphorylation. Figure created with BioRender.

the synaptic vesicle-associated protein synaptogyrin 3 [37], and to stimulate postsynaptic *N*-methyl-D-aspartic acid receptor (NMDAR)-mediated excitotoxicity via interactions with FYN kinase [38,39]. Indeed, exposure to chronic unpredictable stress was found to increase NMDAR/FYN-driven synaptic signaling in the hippocampus of wild-type mice, but did not alter this signaling pathway in tau (*Mapt)* knockout mice, demonstrating the tau-dependence of this synaptic effect [39]. Hyperphosphorylation of tau also facilitates its intracellular aggregation into neurofibrillary tangles and its secretion from neurons [30,40,41], thereby contributing to the transcellular spreading of pathogenic tau species (discussed in the next section).

Another mechanism by which stress/GCs contribute to tau aggregation is through the downregulation of molecular chaperones. One of these is heat-shock protein HSP70, which mediates the folding and trafficking of newly synthesized proteins and is particularly crucial for regulating the interactions of aggregation-prone proteins such as tau (Figure 1) [42]. Although HSP70 is upregulated in multiple cell types during acute stress [43], it is significantly downregulated under chronic stress or GC administration via downregulation of its transcription factor heat-shock factor 1 (HSF1) [42]. This reduction of HSP70 likely precipitates tau misfolding, leading to exposure of its intrinsically disordered regions which in turn drives aggregation of tau monomers into oligomers and ultimately neurofibrillary tangles [44,45].

In addition to promoting tau phosphorylation and aggregation, stress/GCs inhibit autophagy and endolysosomal protein degradation, allowing hyperphosphorylated and aggregated tau to accumulate in cells over time. High GC levels in cultured neuronal cells and the chronic unpredictable stress paradigm *in vivo* were shown to induce phosphorylation and activation of mTOR, thereby inhibiting autophagy and promoting the accumulation of tau aggregates, leading to cell death (Figure 1) [18]. Inhibition of mTOR with the rapamycin analog CCI-779 attenuated these GC-driven phenotypes *in vitro* [18], demonstrating the importance of autophagy for tau aggregate clearance in cells and its impairment by GCs. High GC levels also inhibit tau degradation via the endolysosomal pathway through transcriptional downregulation of the small GTPase RAB35 [46], a master regulator of endosomal protein trafficking. RAB35 was shown to mediate tau sorting into the endolysosomal pathway by promoting interactions between ubiquitinated tau and the early endosome-associated protein HRS [46], the first component of the ESCRT (endosomal sorting complex required for transport) pathway (Figure 1). Notably, adeno-associated virus (AAV)-mediated expression of recombinant RAB35 in rat hippocampus prevented GC-induced tau accumulation and downstream tau-dependent loss of dendrites and synapses in CA1 pyramidal neurons. These findings demonstrate that GC-mediated disruption of tau proteostasis precipitates tau-driven synaptic and neuronal toxicity (Figure 1), which can be rescued by stimulating tau degradation.

Our group has recently uncovered another mechanism by which GCs contribute to tau pathogenesis through the regulation of mitochondrial health [47]. As discussed in the preceding text, prolonged GC exposure impairs mitochondrial function, and decreases ATP production and energy availability while increasing the production of cytotoxic reactive oxygen species (ROS) [13]. GCs also promote mitochondrial ROS production via transcriptional downregulation of the mitophagy adaptor NIX [48], leading to the accumulation of damaged mitochondria. ROS are highly toxic to cells and have been shown to induce tau hyperphosphorylation and aggregation through mechanisms that are poorly understood [49]. Our recent work shows that GCs damage mitochondria via a further mechanism, the transcriptional upregulation of cyclophilin D (CYPD) [47]. CYPD is an activator of the mitochondrial permeability transition pore (mPTP) that forms in the inner mitochondrial membrane upon CYPD binding to ATP synthase [50]. GC-induced mPTP opening was found to promote mitochondrial depolarization and ROS production, as well as

the accumulation of oligomeric tau adjacent to damaged mitochondria, in hippocampal neurons *in vitro* and *in vivo* (Figure 1) [47]. Both mitochondrial damage and tau oligomerization were prevented by administration of the CYPD inhibitor cyclosporin A or by CYPD knockdown. Intriguingly, administration of mito-apocynin, a mitochondria-targeted compound that inhibits mPTP opening and ROS production, prevented GC-induced mitochondrial damage, tau phosphorylation/oligomerization, and downstream synapse and dendrite loss in the hippocampus and cortex of mice [47]. It is notable that CYPD protein levels are also elevated in AD post-mortem brain tissue [51] and in an *ex vivo* model of AD mitochondrial dysfunction, SH-SY5Y cytoplasmic hybrid (cybrid) cells, wherein endogenous mitochondria are replaced by mitochondria from AD patients [52]. Cybrid cells recapitulate key changes observed in the AD brain, including increased expression of markers associated with oxidative stress, inflammation, and apoptosis, and higher levels of oligomeric tau [52]. We and others have found that treatment of AD cybrid cells with CYPD/mPTP inhibitors [47,53] or with the GR antagonist mifepristone [47] effectively normalizes mitochondrial function and associated tau pathology to the level of non-AD control cybrids, demonstrating that mitochondrial damage, and mPTP opening in particular, can induce tau pathogenesis in the context of both AD and GR signaling.

Chronic stress and GCs induce pathogenic tau spreading

Another feature of tau pathology in AD is its stereotypical propagation between brain regions, beginning as pre-tangle structures in the locus coeruleus, then spreading through the entorhinal cortex, hippocampus, and finally the neocortex [54]. The identification of early tau pathology in the locus coeruleus provides compelling evidence for stress as an initiator of AD pathology because the locus coeruleus is implicated in arousal and the detection of stressful stimuli and feeds into the HPA axis [55]. The locus coeruleus is also the main source of norepinephrine in the brain; it is therefore likely that the interactions between GCs and norepinephrine that occur as a result of dysregulated feedback between the HPA and locus coeruleus underlie some of the earliest features of tau pathology resulting from stress [56]. Tau spreading is highly correlated with cognitive decline [57] and is thus regarded as a key driver of AD progression, leading many researchers to study the mechanisms of tau secretion and propagation with the hope of slowing or halting the disease. Tau release occurs through both vesicle- and non-vesicle-based mechanisms [58], and emerging work from our laboratories indicates that chronic stress and elevated GC levels stimulate tau secretion through both pathways. In a recent study, we showed that GC exposure promotes the secretion and spreading of vesicle-free tau in murine hippocampal neurons *in vitro* and *in vivo* [59]. This mode of secretion requires GSK3β-mediated tau phosphorylation and likely occurs through type 1 unconventional protein secretion (UPS), wherein phosphorylated/oligomeric tau is directly translocated across the plasma membrane via interactions with lipids and heparin sulfate proteoglycans (Figure 1) [60,61]. Intriguingly, GC-induced tau spreading *in vivo* was strongly attenuated by epigallocatechin gallate (EGCG) [59], a polyphenol component of green tea that inhibits tau oligomerization and secretion via type 1 UPS [60]. These findings provide compelling evidence that type 1 UPS plays an important role in GC-mediated tau propagation *in vivo*.

Tau is also secreted in small extracellular vesicles (sEVs), 50–150 nm diameter vesicles that carry diverse biomolecules (i.e., RNAs, proteins, metabolites, lipids) and mediate intercellular communication [62]. Proteomic analyses of sEVs isolated from AD patient blood and cerebrospinal fluid (CSF) have revealed that they carry phosphorylated tau [63] and Aβ oligomers [64], and can be used to diagnose AD up to 10 years before clinical onset [65,66]. Importantly, sEVs have also been shown to mediate pathogenic tau spreading in AD mouse models, and drugs that inhibit sEV release attenuate the development of tau-related pathology and cognitive impairment in these animals [67–69]. Our recent work demonstrates that the chronic unpredictable stress

paradigm promotes a dramatic increase in sEV secretion from murine hippocampal and cortical tissue [70]. Together with previous studies showing that stress-induced tau pathology is detected across connected areas of hippocampus and cortex [39,71], these findings provide evidence that stress and GCs stimulate tau spreading through sEVs. Although it remains unclear how stress/GCs induce sEV release, one potential mechanism is via activation of the neutral sphingomyelinase 2 (nSMase2/SMPD3) and ceramide synthesis pathway [62,72,73], one of the major sEV biogenesis pathways (Box 1).

Chronic stress and GCs stimulate Aβ production

In addition to tau tangles, another main neuropathological hallmark of AD is extracellular plaques composed of Aβ peptides. Pathogenic Aβ is formed through the proteolytic cleavage of amyloid precursor protein (APP), a member of the APP family that have roles in *trans*-synaptic adhesion, dendritic spine complexity, and synaptic plasticity [74]. Non-amyloidogenic cleavage of APP by α-secretase produces sAPPα, a secreted fragment that promotes prosurvival mechanisms in neurons, whereas amyloidogenic cleavage by β-secretase (BACE1) produces sAPPβ and is the rate-limiting step in Aβ peptide production. As with tau pathology, stress and GCs have been shown to increase Aβ pathogenesis through several mechanisms. For instance, GCs are reported to stimulate Aβ production and processing via transcriptional upregulation of *APP*, *BACE1* [75,76], and nicastrin (*NCSTN*), a component of the γ-secretase proteolytic complex that is responsible for the final cleavage of the C-terminal C99 fragment of APP into Aβ [77]. GCs also increase APP and BACE1 expression in non-neuronal cells, including astrocytes [78]. Because astrocytes are recruited to the borders of Aβ plaques and have been shown to phagocytose and degrade extracellular Aβ, it is also notable that GCs decrease this capacity by downregulating their expression of Aβ-degrading proteases (e.g., IDE, MMP9). Interestingly, treatment with a selective GR antagonist was sufficient to normalize the levels of APP, BACE1, C99, presenilin 1 subunit of γ-secretase (PSEN1), and IDE to levels observed in age-matched controls in rats with amyloid pathology induced via intracerebroventricular injection of Aβ [76]. These findings suggest that GCs can drive amyloidogenic processing and block Aβ degradation in the rodent brain even at physiological levels.

GCs, in addition to their transcriptional regulation of *APP* and its processing enzymes, also promote Aβ formation through alterations to mitochondria–endoplasmic reticulum (ER) contact sites (MERCS), which are enriched in the APP processing enzymes BACE1 and PSEN1. In the human neuroblastoma cell line SH-SY5Y, GCs promote the formation of MERCS through upregulation of BCL2, leading to BCL2 complex formation with mitochondrial GRs and BCL2-mediated

Box 1. Chronic stress/GCs may induce the release of small extracellular vesicles (sEVs) by activating the nSMase2/ceramide synthesis pathway, thus contributing to the propagation of AD pathology

sEVs originate as intraluminal vesicles that are released from multivesicular endosomes (MVEs) upon fusion with the plasma membrane (Figure 1). MVE formation typically occurs through two pathways: the endosomal sorting complex required for transport (ESCRT), which captures cargo and induces intraluminal vesicle formation through the sequential recruitment of protein complexes (ESCRT-0, -I, -II, -III), and the neutral sphingomyelinase (nSMase2)/ceramide synthesis pathway, which induces intraluminal vesicle formation through synthesis of the sphingolipid ceramide. This latter pathway is activated by the proinflammatory cytokines TNF-α [148,149] and IL-1β [150], as well as by several AD-associated DAMPs including Aβ [151,152], extracellular ATP [153], and reactive oxygen species [154]. Because stress and GCs induce proinflammatory cytokine release and augment cellular responses to DAMPs, it is highly likely that nSMase2/ceramide-driven MVE/sEV biogenesis and secretion are amplified by stress/GCs, and thereby contribute to disease spread. Supporting this concept, ceramide levels are increased in sEVs purified from the blood of patients with depression, and ceramide-containing sEVs can drive depressive behaviors in mice [155,156]. Furthermore, chronic unpredictable stress increases the secretion of sEVs from mouse brain tissue [70], suggesting that GCs serve as a direct [157] or indirect stimulus driving sEV secretion and sEV-mediated spreading of pathology in AD. Multiple nSMase2 inhibitors are under development [158] and have shown promise in reducing sEV release, as well as amyloid- and tau-related pathology, in AD mouse models [67,69,159].

interactions between the ER and the mitochondrial proteins PACS2 and mitofusin 2, respectively [16]. GCs further promote amyloidogenic processing at MERCs through downregulation of RER1, which facilitates local accumulation of PSEN1 and γ-secretase assembly. GC-induced MERCS thus serve as sites of APP misprocessing where Aβ peptides are generated and subsequently translocated to the mitochondrial matrix, a common site of Aβ accumulation in the early phases of AD [79] (Figure 2).

Another mechanism by which GCs impact APP processing is through the regulation of APP and BACE1 subcellular trafficking. Crucial to this process is the GTPase RAB35, a key regulator of endosomal trafficking that is transcriptionally downregulated by GCs and implicated in tau degradation (discussed in the preceding text) [75]. RAB35 regulates the trafficking of APP and BACE1 out of the endosomal network to distinct subcellular regions (plasma membrane and *trans*-Golgi network, respectively) through its effector proteins OCRL and ACAP2 [75]. GC-mediated downregulation of RAB35 thus leads to increased accumulation and interaction of BACE1 and APP within endosomes, thereby facilitating APP cleavage into Aβ (Figure 2). RAB35 levels are also downregulated during aging [75], indicating a point of mechanistic convergence between stress and aging, two important AD risk factors.

Finally, as previously mentioned, GCs inhibit both autophagy and endolysosomal protein degradation, further contributing to elevated APP and Aβ levels because both molecules are degraded

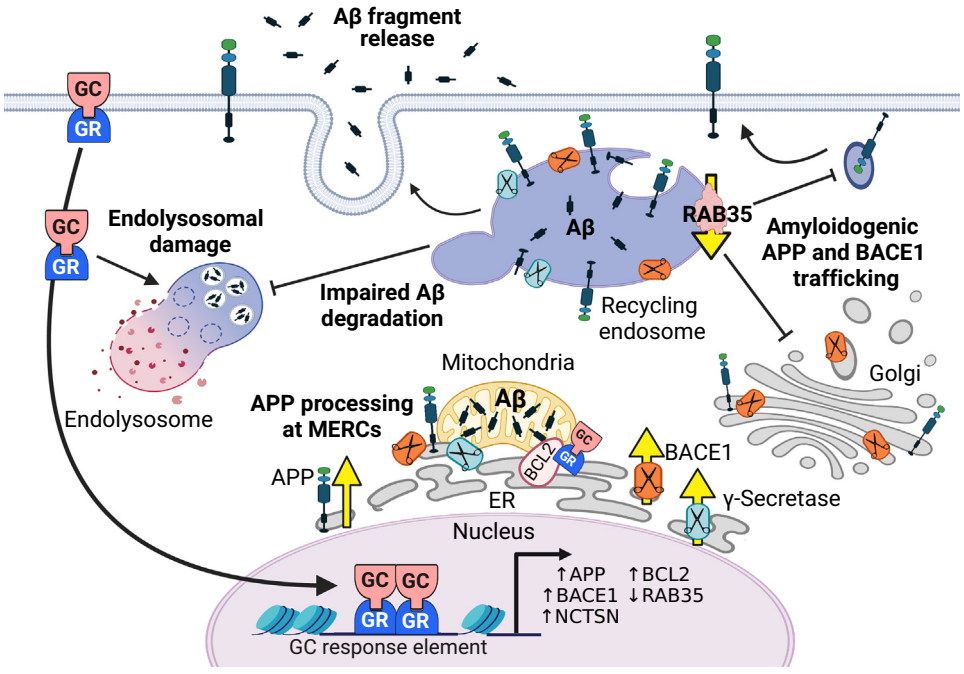


Figure 2. Glucocorticoids (GCs) promote amyloid β (Aβ) production via regulation of APP expression, processing, and trafficking. GCs (top left) transcriptionally upregulate *APP*, *BACE1*, and the nicastrin (*NCTSN*) subunit of γ-secretase, thereby promoting APP cleavage into Aβ. GCs increase mitochondria–endoplasmic reticulum (ER) contact sites (MERCS), that are enriched in BACE1 and γ-secretase, to promote Aβ formation and accumulation in mitochondria – a hallmark of early AD. GC-mediated downregulation of RAB35 inhibits sorting of APP and BACE1 to the plasma membrane and *trans*-Golgi network, respectively, thereby promoting their accumulation within endosomes and facilitating amyloidogenic APP processing and Aβ production. Widespread endolysosomal defects similarly impair the ability of the cells to degrade APP and Aβ. Abbreviation: GR, glucocorticoid receptor. Figure created with BioRender.

in part through these pathways [80]. Interestingly, GC-treated microglia, the resident immune phagocytes of the brain, appear to exhibit intact abilities to phagocytose extracellular Aβ. However, GC-driven endolysosomal trafficking and degradation defects may underlie the decreased capacity of these microglia to degrade plaques once they are internalized [81].

As expected based on these cellular impacts, chronic stress paradigms and GC administration have been found to stimulate Aβ secretion and accelerate the onset of Aβ plaque formation and cognitive deficits in mouse models of AD-related amyloidogenesis [82–85]. In several of these models, tau pathology and neuroinflammation were observed concomitantly with amyloid deposition, providing further evidence that stress and GCs are drivers of these multiple intertwined pathogenic mechanisms.

Chronic stress and GCs amplify neuroinflammation

Activation of proinflammatory signaling pathways accompanies Aβ and tau pathology as cardinal features of AD [86]. Neuroinflammation has a central role in AD pathophysiology, underscored by genome-wide association studies that identified the innate immune genes *TREM2* [87] and *CD33* [88] as risk genes for AD. Paradoxically, although GCs are commonly prescribed for their potent anti-inflammatory effects [89], demonstrated by the widespread use of synthetic corticosteroids such as prednisone to treat autoimmune disorders, accumulating evidence suggests that chronic elevation of GCs potentiates inflammatory signaling and that neuroinflammation is a key feature of stress-related brain pathology [90–92]. Proponents of the 'glucocorticoid resistance model' discount the role of GCs in driving proinflammatory pathways [93], and instead suggest that activation of these pathways reflects insufficient GC signaling through GR downregulation. However, emerging evidence [94,95] indicates that GR expression levels and/or activation do not necessarily correlate with proinflammatory gene expression, suggesting that inflammation is not simply a consequence of GC resistance.

Chronic stress and GCs prime brain cell sensitivity to AD-associated damage-associated molecular patterns (DAMPs)

Ongoing research efforts are directed towards identifying the mechanisms by which stress/GCs promote neuroinflammation, and the role of such inflammatory signaling in AD development and progression. Multiple studies demonstrate that GCs 'prime' brain cells for proinflammatory signaling and synergize with other stimuli to activate these signaling pathways. For example, GCs have been shown to upregulate Toll-like receptor 2 (TLR2) [96,97], which initiates inflammatory signaling in response to DAMPS and pathogen-associated molecule patterns (PAMPs) and is activated by Aβ peptides, tau fibrils, and extracellular ATP in mouse models of AD [98,99]. Several studies have also demonstrated GC-mediated upregulation of the NLRP3 (nucleotide-binding, leucine-rich repeat, pyrin domain-containing protein 3) inflammasome [100–102], an intracellular signaling complex activated by pathogens and other harmful endogenous/exogenous stimuli, including Aβ and tau fibrils [103]. GCs have also been shown to augment the expression of P2Y2R, a purinergic receptor that activates p38 MAPK signaling upon detection of damage-associated extracellular ATP, thereby promoting proinflammatory gene expression [104]. It is thus probable that stress/GC-mediated upregulation of TLR2, the NLRP3 inflammasome, and P2Y2R primes neurons and glia for activation by Aβ, tau, and other AD-associated DAMPs, thereby amplifying AD-related neuroinflammation (Figure 3). Supporting this concept, GCs were found to augment the effects of another inflammatory agent, lipopolysaccharide (LPS), on activation of the MAPK/NF-κB proinflammatory pathway in the rat brain [94,105]. Interestingly, a different study found that administration of a selective NLRP3 inhibitor rescued GC-induced impairment of long-term potentiation (LTP), a form of synaptic strengthening that underlies learning and memory, in both wild-type rats and an AD transgenic rat model (McGill-R-Thy1-APP) [106]. Given that learning

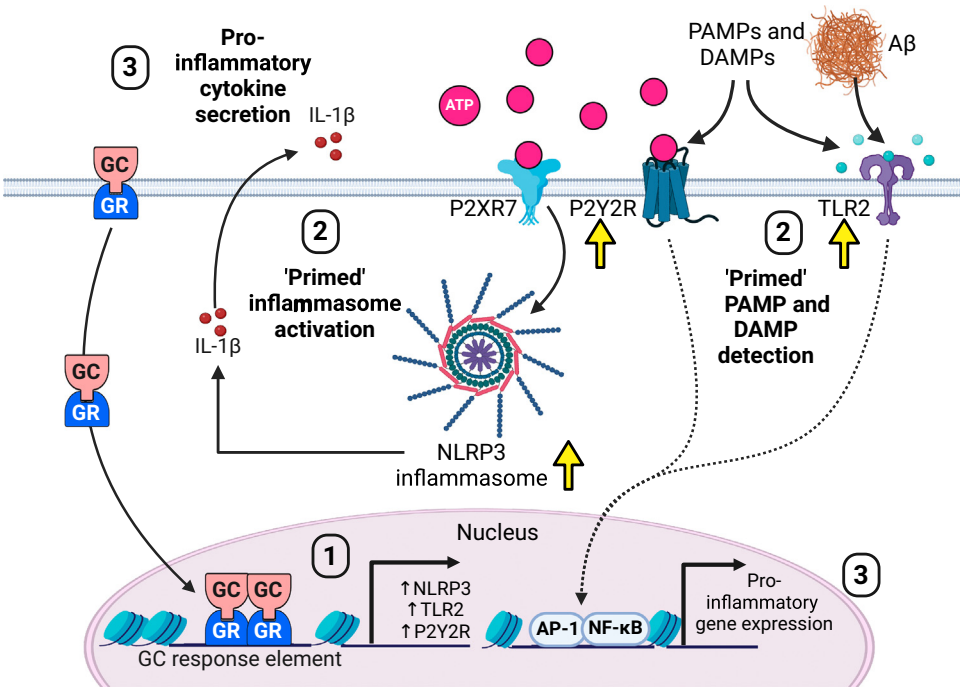


Figure 3. Chronic stress/glucocorticoid (GC) exposure primes brain cell sensitivity to Alzheimer's disease (AD)-associated damage-associated molecular patterns (DAMPs), thereby driving neuroinflammation. (1) The GC/GR complex transcriptionally upregulates the DAMP-sensing receptors *TLR2* and *P2Y2R* and the *NLRP3* inflammasome. (2) Primed brain cells rapidly recognize AD-associated DAMPs [e.g., amyloid β (Aβ) and extracellular ATP] via TLR2, P2Y2R, and P2XR7. P2XR7 activates primed NLRP3 inflammasome, facilitating the cleavage and secretion of proinflammatory cytokines. (3) Signaling through TLR2 and P2Y2R drives proinflammatory gene expression programs. Autocrine and paracrine signaling by proinflammatory cytokines potentiates AD-associated neuroinflammation and glial activation. Abbreviations: GR, glucocorticoid receptor; PAMP, pathogen-associated molecular pattern. Figure created with BioRender.

and memory deficits are early clinical features of AD, these findings offer insight into how inflammatory signaling may contribute to stress/GC-induced cognitive decline in AD.

Chronic stress and GCs induce glial dysfunction

Glia play diverse roles in the central nervous system (CNS), including contributing to immune responses crucial for the maintenance of health and homeostasis in the brain. Microglia are the resident immune cells of the brain and have important roles in immune surveillance, including cytokine production as well as phagocytosis of pathogens, dead cells, debris, and neuronal synapses, among other roles [107,108]. In constantly surveilling the environment for PAMPs and DAMPs, microglia undergo rapid cellular expansion and phenotypic changes, and adopt an ameboid-like morphology to phagocytose material upon PAMP/DAMP recognition. Chronic stress and GC exposure can induce these morphological changes, thereby increasing microglia number (identified by IBA1$^+$, CD11b, or CX3CR1$^+$ immunoreactivity) and soma size, and decreasing branch complexity [107,109–111]. For instance, in mouse studies, in response to chronic social defeat stress (i.e., repeat exposure to aggressor conspecifics) and chronic unpredictable stress, microglia were found to upregulate markers associated with microglial activation (IBA1, CD11b, CD68, CD86, TLR4, and CD14) [111–113] in various brain areas including the amygdala, prefrontal cortex, and hippocampus. In response to chronic unpredictable stress, microglia in the rat hippocampus upregulate HMGB1, a DAMP recognized by TLRs that propagate

immune activation [114]. Microglia also secrete inflammatory cytokines that amplify neuroinflammation through crosstalk with other immune-responsive cells in the brain and periphery. In particular, repeated social defeat stress has been shown to stimulate microglial release of the cytokines IL-1β and CCL2, leading to CNS recruitment of monocytes from peripheral circulation (Figure 4) [108,115]. Paradigms for chronic stress (e.g., social defeat stress, sleep deprivation) and GC elevation have also been shown to increase microglial synaptic pruning in rodent medial prefrontal cortex and hippocampus, resulting in decreased brain volume [109,116]. Notably, pruning by microglia is implicated in synaptic loss in AD, and this represents another potential mechanism through which stress/GCs may promote AD pathogenesis. It remains to be examined whether chronic stress induces a similar profile of microglial gene expression changes as reported for other drivers of neuroinflammation in AD, such as amyloid plaques (e.g., upregulation of *Apoe*,

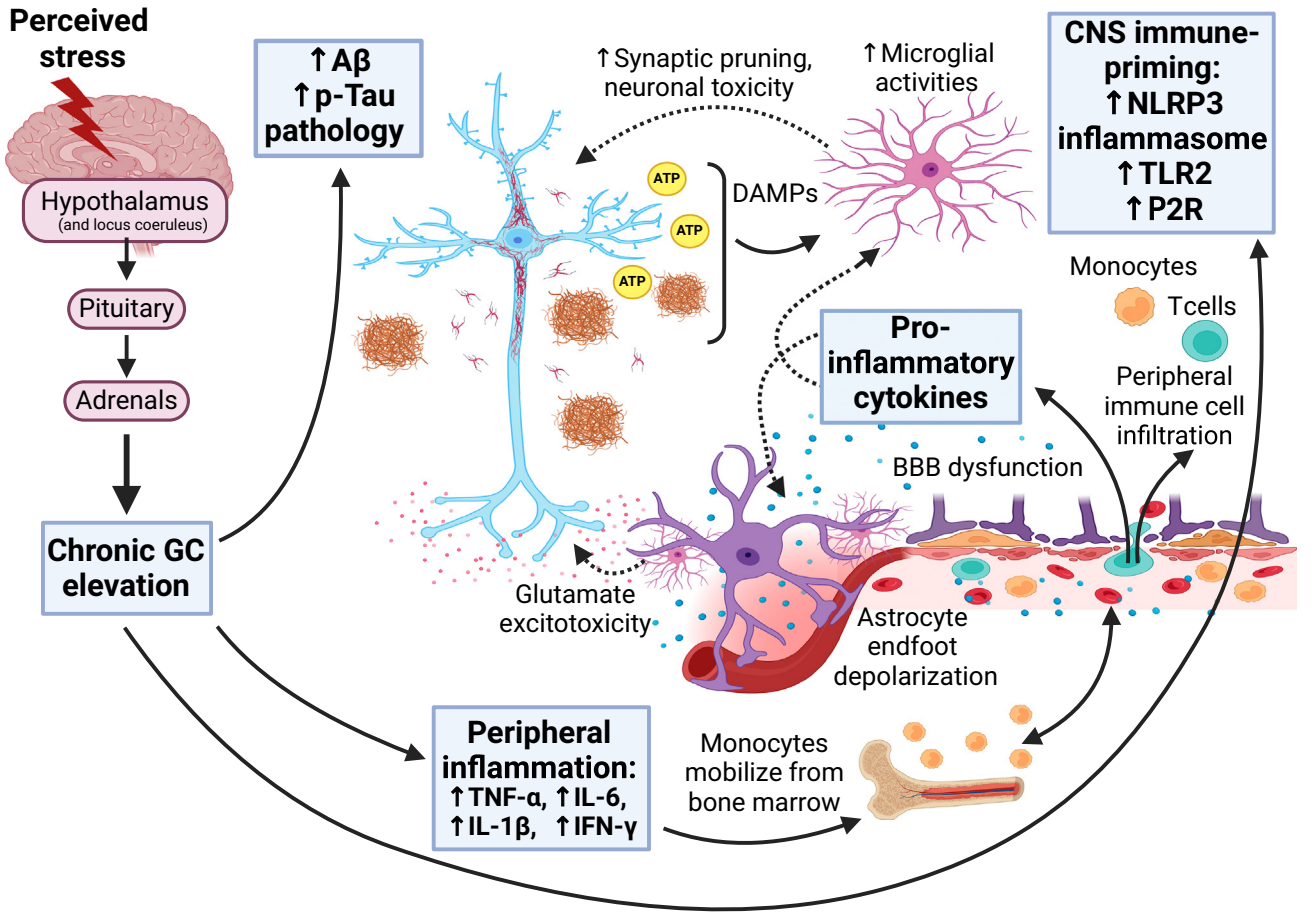


Figure 4. Chronic stress and glucocorticoid (GC) elevation drive neuroinflammation through immune priming, glial activation, and blood–brain barrier (BBB) breakdown. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to chronic elevation of GCs, has broad neuroinflammatory consequences. Immune priming heightens cellular sensitivity to damage-associated molecular patterns (DAMPs), such as extracellular amyloid β (Aβ) and ATP, that are produced during Alzheimer's disease (AD) pathogenesis, and potentiates neuroinflammatory signaling through activation of the NLRP3 inflammasome and upregulation of proinflammatory cytokines and transcriptional programs. Prolonged, maladaptive glial activation contributes to loss of microglial phagocytic function (including inability to phagocytose Aβ) and loss of synaptic and BBB maintenance by astrocytes. Widespread neuroinflammation has deleterious effects on neurons and glia alike, and contributes to aberrant synaptic pruning, neuronal cell death, dysfunction of glutamate release and uptake at the synapse, loss of BBB integrity, and defects in glymphatic clearance. Central nervous system (CNS)-derived cytokines and chemokines, together with BBB dysfunction, permit infiltration of peripheral immune cells into the CNS, with varied disease-promoting consequences. Abbreviation: p-Tau, phosphorylated tau. Figure created with BioRender.

Axl, *Clec7a*, *Itgax*, and *Lgals3* [117]). Moreover, because microglia are highly sensitive and responsive cells, additional studies will be necessary to understand how other stress-associated hormones and neurotransmitters impact the activation of these cells. Further information about microglial responses to chronic stress can be found in earlier reviews [118,119].

In contrast to microglia, which undergo amplification and activation in response to chronic stress paradigms and GC elevation, astrocytes undergo atrophy and reduced functionality [120,121]. Among the astrocytic functions inhibited by stress/GCs are synaptic glutamate clearance, glutamate metabolism, and gap junction-mediated astrocytic signaling [121–123]. Together, these functions regulate glutamatergic synaptic transmission, and their impairment may contribute to the enhanced excitotoxicity seen in the hippocampus and cortex during chronic stress/GC elevation (Figure 4) [121,124], as well as in the early stages of AD [125,126]. Astrocytes also secrete inflammatory cytokines and represent a key source of stress-induced cytokine secretion in numerous brain regions, including the hippocampus [127,128]. Indeed, astrocytes appear highly sensitive to inflammatory signaling in this context and were found to undergo NLRP3-mediated pyroptotic death in the mouse hippocampus following the chronic unpredictable stress paradigm [129]. Decreased astrocyte density and size are also observed in the hippocampi of patients who receive chronic corticosteroid treatment as well as in late-stage AD brain tissue, implicating GC-mediated astrocyte dysfunction as a potential contributing factor to brain atrophy in AD.

Chronic stress and GCs compromise BBB and glymphatic integrity

Breakdown of the BBB is thought to occur during prodromal AD [130], enabling the infiltration of peripheral immune cells and cytokines into the brain [131] as cells in the neurovascular unit degenerate and endothelial tight junctions and adherens junctions are lost [132]. Likewise, several studies indicate that chronic stress may contribute to loss of BBB integrity. For example, in mice, chronic restraint stress in the form of prolonged housing in a confined space was found to decrease the expression of the adherens junctions protein VE-cadherin in the amygdala, whereas chronic social stress led to decreased expression of the tight junction component claudin-5 in the nucleus accumbens and prefrontal cortex [133,134]. Another investigation of BBB function in a murine chronic restraint stress model, using real-time two-photon imaging, revealed a decrease in BBB integrity based on permeability to dextran and decreased claudin-5 tight junctions [135]. Stress and GCs also contribute to BBB disruption by stimulating the recruitment of peripheral immune cells into the brain. For instance, chronic restraint stress was demonstrated to facilitate the infiltration of $CD4^+$ type 17 T helper (Th17)-type T cells into the brain, which in turn disrupted BBB integrity via secretion of the cytokine IL-17A [136]. Peripheral monocyte recruitment is also facilitated by high GC levels, which promote bone marrow monocyte mobilization into the blood, thereby expanding the pool available for recruitment into the brain parenchyma (Figure 4) [137]. BBB disruption and infiltration of peripheral immune cells, including neutrophils and both $CD4^+$ and $CD8^+$ (i.e., cytotoxic) T cells, have also been observed in postmortem AD brain [127]. Moreover, Th17 T cells and IL-17A are implicated in AD [138] pathophysiology, with the former inducing neuronal death and the latter impairing BBB tight junctions and recruiting peripheral lymphocytes to the brain [139].

Finally, dysregulation of the glymphatic flux system, resulting in impairment of brain interstitial fluid drainage, occurs following chronic unpredictable stress and treatment with high GC levels [140]. Mechanistically, this impairment is proposed to occur through the loss of aquaporin channels on astrocytic endfeet, which facilitate water transport across the BBB (Figure 4). Disruption of the glymphatic system has also been reported in AD, and likely contributes to impaired clearance of Aβ oligomers and other protein aggregates from the brain [141,142].

Concluding remarks and future perspectives

Clinical and epidemiological studies implicate chronic stress and high GC levels in accelerating the onset and progression of AD, and experiments in animal and cell culture models demonstrate that stress and GCs drive molecular/cellular processes underlying tau, Aβ, and neuroinflammatory pathologies. Stress/GCs promote tau pathology by activating kinases and inhibiting molecular chaperones, degradative pathways, and mitochondrial function. In parallel, stress/GC-mediated transcriptional upregulation of *APP* and genes encoding APP processing enzymes, together with the impairment of endosomal trafficking, contribute to increased Aβ production. Chronic stress and GCs also drive neuroinflammation, in particular by priming cells to AD-associated DAMPs, thereby impacting glial function and permeability of the BBB and the blood–CSF barrier to peripheral immune cells. Although age is the strongest risk factor for AD [143], the ability of stress/GCs to synergize with other disease-associated stimuli to exacerbate AD pathogenic mechanisms underscores why chronic stress and elevated GCs are factors that accelerate AD pathology.

Current FDA-approved AD therapeutics target the accumulation of Aβ in the brain [144,145]; however, the modest symptomatic improvement offered by these treatments may reflect persistent galvanization of other features of the disease and their amplification by chronic elevation of the human GC, cortisol. The increasing awareness of the medical research community that AD onset occurs decades before clinical symptoms, and that adverse life events can promote CNS degeneration, should fuel the expansion of early and mid-life interventions for stress, including lifestyle modification, and of therapeutics for treatment-resistant depression. Because the incidence of AD is higher in females than males [21,146,147], additional research on the crosstalk between estrogens and GCs will be necessary to understand the relationship between stress and AD pathogenesis in post-menopausal females (Box 2). Moreover, given the common misconception that synthetic GCs have predominantly anti-inflammatory properties, it is imperative that future studies define the specific contexts in which GCs drive proinflammatory priming and neuroinflammation (see Outstanding questions). Exploration of the proinflammatory

Box 2. The interplay of estrogens and GCs in sex-specific vulnerability to Alzheimer's disease

Females have a significantly higher incidence of AD than males [21,146]. Although psychosocial and lifestyle factors likely contribute to this difference, evidence suggests that intrinsic biological factors play a larger role. In particular, the age-dependent loss of the gonadal hormone estrogen, which confers protection against neurodegeneration, appears to be a major factor in the increased vulnerability of females to AD [147,160]. In contrast to GCs, estrogen and estrogen-like compounds have been demonstrated to reduce GSK-3β kinase activation and tau phosphorylation in rats [161] and promote non-amyloidogenic trafficking of APP in neuronal cell lines and primary cultures from mice, rats, and humans [162]. In addition, loss of estrogen through ovariectomy in mice impairs the dynamic functions of neuronal mitochondria, and decreases the levels of proteins necessary for biogenesis, fusion, and mitophagy [163]. Findings in humans further support protection from age-related bioenergetic changes by estrogen [164,165], which regulates gene expression programs underlying increased oxidative phosphorylation in female peripheral blood mononuclear cells [166] and decreased ROS production by human brain endothelial cells [167]. These benefits are reversed in post-menopausal women lacking estrogen [168], potentially increasing their susceptibility to GCs thereafter. There is also broad consensus that estrogens promote immune function and homeostasis [164], and that loss of estrogens contributes to age-related maladaptive immune responses associated with neurodegeneration [169]. For example, studies in aged mice demonstrate an age-dependent increase in the expression of proinflammatory and chemotactic gene programs in the hippocampus, accompanied by findings that proinflammatory cytokine release in response to lipopolysaccharide (LPS) is more dramatically elevated in ovariectomized mice [170]. This finding has been replicated in primary microglia treated with LPS in the presence of selective estrogen-receptor modulators [171]. How the loss of estrogen interacts with GC-mediated neuroimmune priming in the aged brain is unclear and will require further investigation. Estrogen may counteract GC-mediated immune priming through transcriptional repression or may synergize with GCs to coactivate anti-inflammatory gene programs in the brain [172,173]. In either case, the loss of estrogen could amplify GC-driven augmentation of AD neuroinflammatory pathology. The loss of estrogen in post-menopausal females may thus increase susceptibility to GC signaling to promote tau and Aβ pathology as well as the neuroinflammatory signatures of AD, and these mechanisms may combine additively with other modalities of female sex vulnerability, including genetic sex differences [174–176], differential sensitivity to HPA axis-activating stimuli [147,177], and myriad environmental factors and societal biases experienced by women [178,179].

Outstanding questions

AD-associated tau pathology typically appears first in the locus coeruleus, the nucleus of the brainstem that initiates the stress response. What is the timecourse of tau, Aβ, and neuroinflammatory pathologies induced by stress/GCs, and how are they causally related?

How do stress/GC-induced mitochondrial dysfunction and ROS production stimulate tau pathogenesis and other AD-related pathologies, and how do these pathologies in turn impact on mitochondrial function and brain energy metabolism?

Through what mechanisms do stress/GCs promote the spreading of AD pathology through the brain (e.g., extracellular vesicles, unconventional secretory pathways)?

GCs, inflammatory cytokines, and sex hormones all regulate distinct gene expression programs and have distinct impacts on AD pathogenesis. How do these hormones and cytokines interact to regulate the gene expression changes underlying AD, and in particular how does the loss of estrogen in post-menopausal women alter stress susceptibility and AD risk?

How does chronic stress alter microglia and astrocyte function and gene expression throughout the course of AD (e.g., prodromal, early, late-stage)?

Chronic stress and GCs regulate the infiltration of peripheral monocytes and T cells into the brain. Do other subtypes of peripheral immune cells enter the CNS during chronic stress/GC elevation, and, if so, what functions do they carry out?

Do GR antagonists have therapeutic efficacy in either early or late-stage AD?

How do AD risk alleles (e.g., *APOE ε4*) and other environmental factors (e.g., diet, air pollution) interact with chronic stress to impact on the onset and progression of AD?

consequences of chronic GC elevation will have therapeutic relevance not only for AD but also for other GC-sensitive conditions and diseases.

Acknowledgements

M.R.B., C.L.W., and I.S. are supported by National Institutes of Health (NIH) grant RF1AG069941.

Declaration of interests

The authors declare no competing interests.

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