Stress and the Etiopathogenesis of Alzheimer's Disease and Depression

20

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Introduction

The brain is the most adaptive of all organs. It has a remarkable capacity to respond to a variety of internal and environmental stimuli and to mount pro-survival behavioral responses by orchestrating multiple molecular and biochemical cascades. The latter changes are embraced by the term neural plasticity, the cornerstone of learning and memory [1]. Impairments in neuroplastic mechanisms are commonly found during aging, the primary risk factor for Alzheimer's disease (AD), a disorder characterized by memory deficits. Over their lifetime, individuals experience both good and adverse (stressful) events and notably, stressful events appear to accelerate brain aging [2]. Accumulating clinical and experimental evidence suggests a causal role of lifetime stress in AD. This chapter summarizes current knowledge about how chronic stress and its accompanying high levels of glucocorticoid (GC) secretion, trigger the two main pathomechanisms of AD: (i) misprocessing of amyloid precursor protein (APP) and the generation of amyloid beta (Aβ) and (ii) Tau hyperphosphorylation and aggregation. Given that depression is a well-known stress-related illness, and the evidence that depression may precede AD, this chapter also explores neurobiological mechanisms that may be common to depressive and AD pathologies. This review also discusses emerging insights into the role of Tau and its malfunction in disrupting neuronal cascades and neuroplasticity and, thus triggering brain pathology.

Stress: A Physiological Tug-of-War – From Adaptive to Maladaptive Responses

Stress is defined as a challenge to homeostasis (physiological and behavioral equilibrium) by physical or psychological events [3]. When challenged by endogenous or exogenous aversive or threatening stimuli (stressors), a series of defensive systems and processes become activated; these include the release of monoamines and GC that initially promote a return to the homeostatic state [4, 5]. The "stress response" normally terminates once homeostasis has been restored, but when the organism is faced with an insurmountable stress (high intensity, contextually inappropriate and/or chronic), it may take

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inappropriate – maladaptive – actions that result in chronically elevated GC secretion. Besides interfering with normal structural and plastic arrangements within the brain, such inadequate responses can have negative consequences for the immune and visceral systems that may ultimately lead to multiple disorders, including neuropsychiatric and neurological diseases [6–9].

The endocrine response to stress is orchestrated within the so-called hypothalamo–pituitary–adrenal (HPA) axis (Fig. 20.1). Stress, perceived by cortical areas of the brain, triggers the release of corticotropin-releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PVN) which, in turn, induces the secretion of adrenocorticotropic hormone (ACTH) release from the pituitary and GC (cortisol in humans and corticosterone in rodents) from the adrenal glands. This sequence of events is normally curtailed by negative feedback of GC at central sites; however, the nature of the stressor and/or impairments in negative feedback mechanisms (e.g. during aging) may block this crucial feedback loop, resulting in supraphysiological exposure to GC. A key area among the brain regions involved in the regulation of the HPA axis is the hippocampus; this area, which also plays a pivotal role in learning and memory, sends inhibitory projections to the PVN (and other hypothalamic nuclei). Similarly, the frontal cortex mediates GC negative feedback effects on the HPA axis, whereas the GC activation of the amygdala results in a positive drive on this axis (see Fig. 20.1).

Mechanisms and Consequences of GC Action in the Brain

Corticosteroid actions in the brain are mediated by glucocorticoid (GR) and mineralocorticoid (MR) receptors. The previously-referred feedback effects of GC during stressful experiences primarily depend on activation of GR, expressed throughout the brain, but at highest density in the hippocampus [10]. Indeed, almost all we know about GC actions in the brain are GR-mediated. Less is known about the role of MR, although, they have a ten-fold higher affinity for GC compared to GR and are believed to play an important role in GC feedback under physiological (non-stressful) conditions [11]. In addition, MR have been implicated in "protecting" the brain against GR-mediated cytotoxicity [12, 13] and behavioral maladaptation [14]. Interestingly, the central expression of GR and MR is subject to regulation by stress and age [15, 16].

While GC have been shown to modulate synaptic activity through non-genomic mechanisms [17–19], GR and MR are better known as potent ligand-dependent transcriptional regulators, i.e. control gene expression/repression [20–23]. The unliganded receptors are located in the cytoplasm in association with chaperone proteins (e.g. the heat shock proteins Hsp90 and 70 and the immunophilins FKBP51 and 52) [24]. Ligand binding results in conformational change of the GR-chaperone complex and subsequently, receptor translocation to the nucleus and binding to specific regions of DNA containing glucocorticoid response elements (GRE) within the promoters of target genes [25]. Gene transcription or repression is then determined by the recruitment of co-activators and repressors [26] as well as by post-translational modifications of the receptor [27–29].

In the brain, MR and GR differentially regulate the expression of genes, in a site-specific manner; these include genes responsible for the regulation of the HPA axis (*CRH* and *CRH receptors* and *pro-opiomelanocortin [POMC],* from whose gene product ACTH is cleaved) as well as pro- and anti-apoptotic genes [13] and, importantly, genes with roles in neural energy metabolism, structure and synaptic transmission, the synthesis of rate-limiting neurotransmitter enzymes and receptors as well of various neuropeptide, growth factors and cell adhesion molecule [30–34]. While all of these GC-initiated transcriptional events contribute to neural plasticity, stress and GC result in the manifestation of visualizable effects, namely, alterations in neuronal morphology. As reviewed by Lucassen [35], stress and GC lead to changes in the rate of neurogenesis, cell death, and neuronal connectivity as well as astroglia-neuronal interactions. In particular, numerous studies have highlighted how

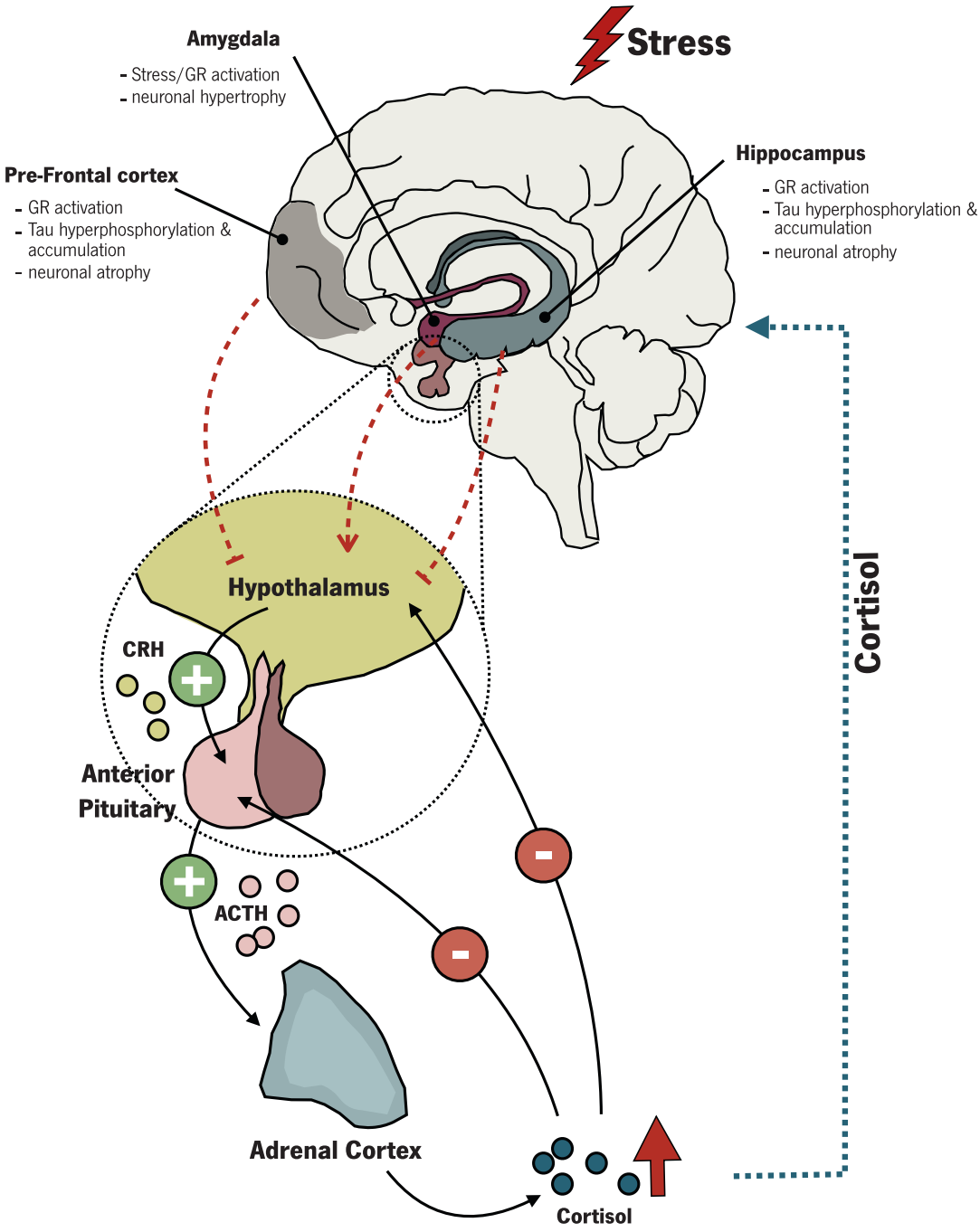

Fig. 20.1 The hypothalamo-pituitary-adrenal (HPA) axis and the response to stress in the healthy state. Stressors perceived in higher brain centers trigger the release of corticotropin-releasing hormone (CRH) from neurons in the paraventricular nucleus (PVN). Carried via a portal vein system, CRH reaches the anterior pituitary where it stimulates the secretion of adrenocorticotropin hormone (ACTH) which, in turn, stimulates the production and release of glucocorticoids (GC) [cortisol in humans and corticosterone in rodents] from the adrenal cortex. The secreted GC access peripheral and central tissues via the general circulation where they serve to mount adaptive responses to the initiating stimulus (stress) after binding to glucocorticoid receptors (GR). Eventually, GC secretion and action is restrained by inhibitory feedback of GC on central (chiefly, the frontal cortex, hippocampus, hypothalamus and pituitary) components of the HPA axis

stress, acting through GC, impacts on dendritic arborization and synaptic number; this aspect of GC actions is considered in the following section. First, in the context of AD as a disease that develops as age progresses, it is important to briefly mention the growing view that stress and GC leave long-lasting "memories" of past experiences via epigenetic mechanisms; these are thought to contribute importantly to the organism's physical and mental health trajectory [36–39]. Notably, epigenetic mechanisms have recently been implicated in the lasting effects of lifetime adversity in humans [40, 41].

Stress, Glucocorticoids and Neural Plasticity

Functional plasticity in the brain is generally preceded by structural plasticity, typically, dendritic and synaptic remodeling. Basal levels of GC are crucial for maintaining synaptic plasticity in the hippocampus in the form of long-term potentiation (LTP) [42], a well-documented mechanism involved in memory formation [43]. On the other hand, high levels of GC such as those experienced during stress impair LTP induction and facilitate long-term depression (LTD) [44]. An important role for *N*-methyl-d-aspartate (NMDA) receptors and shifts in calcium flux has been suggested in both, LTP and LTD modulation by stress/GC [45–48].

One of the best-described forms of stress-evoked structural plasticity is dendritic retraction, with a pioneering study revealing that chronic stress interrupts connectivity between hippocampal CA1 neurons and neurons in the medial prefrontal cortex (PFC) [49, 50]. The latter work followed previous demonstrations that chronic stress causes atrophy of apical (but not basal) dendritic complexity in CA3 pyramidal neurons [51]. Meanwhile, other studies have reported that stress can also increase dendritic length in certain brain regions such as the orbitofrontal cortex, amygdala and bed nucleus of the stria terminalis (BNST, also known as the "extended amygdala") [52, 53]. Interestingly, chronic stress has also been associated with a loss of mossy fiber synapses, increased surface area of the post-synaptic density, and rearrangements of synaptic mitochondria and vesicles at the presynaptic terminals [54]. Further, dendritic spines, which have an important role in information storage, are severely reduced by stress [55] but can mostly be rapidly reversed after a recovery period or subsequent training ([56, 57]; but see [58] for exceptions).

New work from our labs indicates that Tau, a key factor in AD pathology, is essential for chronic stress to disrupt neuroplasticity. Briefly, we showed that mice in which *Tau* has been deleted are spared from the deleterious behavioral (e.g. deficits in learning and memory, depressive-like behavior and anxiety) and neurostructural (namely, dendritic atrophy disconnection of the hippocampal-prefrontocortical pathway) of chronic stress and GC [59, 60].

As already alluded to, stress and GC also influence neuroplasticity by modulating the production of new neurons in adult brain [61]. Several studies indicate that stress/GC related effects on neurogenesis have the potential to affect mental health, including susceptibility to depression [62, 63] and AD [64, 65].

Chronic Stress: Etiopathogenic Role and Mechanisms in AD

A sizeable literature suggests that elevated GC and chronic stress – a state that an increasing proportion of the population finds itself in today – may increase the risk for developing AD pathology and related dementias [66, 67] and may even advance the age of onset of the familial form of AD [68–70]. Indirect support for the link between high GC exposure and AD includes reports that AD patients produce and secrete higher-than-normal levels of cortisol [67, 71–74]. Interestingly, transgenic mouse models of AD also display high levels of GC [75, 76]. Nevertheless, while the direction of the cause-effect relationship between AD-like pathology and hypercorticalism remains unclear, it is worth recalling (see previous section) that the hippocampus is responsible for mediating the negative

feedback effects of GC on the HPA axis; thus, any damage to this brain region is likely to uncouple this control mechanism and unleash unrestrained GC secretion.

To put these findings into context, it is worth noting that there is evidence that GC levels correlate with the rate of cognitive decline [35, 77] and the extent of neuronal remodeling in AD subjects [78]. Such remodeling is especially marked in the hippocampus, the area in which most studies on stress/GC effects on neuroplasticity have been conducted in rodents, and the brain area which clearly displays the first signs of AD neuropathology – deposits of amyloid β (Aβ) and accumulation and aggregation of hyperphosphorylated Tau [79–81]. The hippocampal lesions induced by these deposits correlate with the extent of deficits in declarative, spatial and contextual memory [82].

Consideration Regarding How Chronic Stress and High GC Levels May Contribute to AD Pathology

In this section, we will review some of the evidence for a link between GC/stress and AD and consider some of the possible underlying mechanisms. After briefly considering stress/GC effects on amyloidogenesis, our attention will focus on how chronic exposure to stress or high levels of GC influence Tau biology, culminating in its malfunction and dendro-synaptic toxicity.

As noted earlier, AD neuropathology is characterized by overproduction of Aβ that forms deposits into senile (amyloid) plaques, and by accumulation of hyperphosphorylated forms of Tau protein that becomes insoluble, aggregates and forms neurofibrillary tangles (NFT) [79–81]. Aβ is the proteolytic product of amyloid precursor protein (APP), a large transmembrane protein called, that is sequentially cleaved by β-secretase (BACE-1) and γ-secretase (a complex of enzymes, including presenilin) to yield Aβ; this post-translational pathway is often called APP misprocessing. Studies have shown that extended exposure to immobilization stress increases the load of extracellular Aβ deposits and exacerbates memory deficits in mice expressing an aggressive (human) mutant form of APP V717ICT-100 [76, 83]. Similar observations were made when young 3xTg-AD mice (expressing APP Swedish, P301L-Tau, and PSEN1 M146V mutations) were treated with the synthetic GC, dexamethasone [76]. That the effects of stress are most likely transduced by GC was demonstrated by experiments on dexamethasone-treated neural cell lines (N2A [76] and differentiated PC12 cells [84]). Consistent with these reports, our own studies in wildtype rats demonstrated that chronic stress and/or treated with GC increases APP misprocessing along the amyloidogenic pathway by upregulating BACE-1 and Nicastrin (a component of the γ-secretase complex) to produce neurotoxic and cognition-impairing effects [85]; in this regard, it is worth noting that high exogenous levels of GC upregulate the transcription of *APP* and *βACE-1*, the promoters of which contain a glucocorticoid response element (GRE) [76]. Lastly, experiments that attempted to mimic intermittent stressful events (the effects of which may be cumulative over the lifetime) showed that GC potentiate the APP misprocessing pathway [85].

In recent years, an increasing amount of attention has turned to Tau pathology, especially its hyperphosphorylated forms, in a range of neurodegenerative diseases. Among the first reports to indicate a relationship between stress/GC and Tau was a study by Stein-Behrens et al. [86] who found that GC exacerbate kainic acid-induced hippocampal neuronal loss with a contemporaneous increase in Tau immunoreactivity. A later study showed that chronic treatment of 3xTg AD mice with dexamethasone leads to the somatodendritic accumulation of Tau in the hippocampus, amygdala and cortex [76]. Our own *in vivo* studies demonstrated that chronic stress or GC increase the levels of aberrantly hyperphosphorylated Tau in the rat hippocampus and PFC, both in the presence and absence of exogenous Aβ [87]. Importantly, the hyperphosphorylation occurred at certain Tau epitopes that are strongly implicated in cytoskeletal dysfunction and synaptic loss (e.g., pSer262) [88, 89] and hippocampal atrophy (e.g., pThr231) [90] in AD patients.

Here, it is pertinent to note that the extent of phosphorylation at Thr231- and Ser262-Tau correlates strongly with severity of memory impairment, speed of mental processing, and executive functioning in AD patients [91–93]. Although chronic stress and GC treatment exert similar, but not identical, effects on individual Tau phosphoepitopes *in vivo* and *in vitro* [84], the overall evidence points to GC as the key mediator of the AD-like pathology induced by stress. On the other hand, some studies have suggested a role for at least one other stress-related molecule, namely, corticotrophin-releasing hormone (CRH) as deletion of the *CRH receptor 1* gene in mice prevents the detrimental effects of stress on Tau phosphorylation [94, 95]. Supporting these links, are the results from *in vitro* experiments which indicate that the GC effects on Tau involve activation of glycogen synthase kinase 3 (GSK3) and cyclin-dependent kinase 5 (CDK5), two principal Tau kinases [84].

Transgenic mice expressing human P301L-Tau (the most common Tau mutation), also helped strengthen the evidence that chronic stress can exacerbate Tau pathology. Briefly, we found that stress stimulates the aberrant hyperphosphorylation and aggregation of insoluble Tau [96]. Further, we demonstrated in the latter work that chronic stress enhances caspase 3-mediated truncation of Tau at its C-terminal in the hippocampus, with the protein misfolding and adopting a conformation [96] that facilitates its nucleation and recruitment of other Tau molecules into neurotoxic, pre-tangle aggregates of Tau (see [97–100]. Importantly, experiments also showed that GC contribute to AD pathology by reducing the degradation of Tau, thereby increasing its accumulation [84]. The latter is likely to result from dysregulation of molecular chaperones (e.g. Hsp90 and Hsp70) that are responsible for Tau proteostasis [96]. As noted previously, these same heat shock proteins serve to maintain GR in a high affinity state; thus, they may represent a point at which GC signaling intersects with the cellular machinery that regulates Tau degradation.

While Kobayashi et al. [101] showed Tau may be synthesized *de novo* in the somato-dendritic compartment, earlier work by Ittner and colleagues [102] demonstrated that hyperphosphorylated Tau is missorted to synapses which subsequently become dysfunctional. The missorting of Tau to synapses is now acknowledged as an early event in AD, preceding the manifestation of detectable neurodegenerative processes [102–104]. It is important to note that this series of events depend on Tau hyperphosphorylation [103, 105, 106] and results in the targeting of Fyn (a member of the Src kinase family) to postsynaptic sites [102] where it selectively modulates the function of GluN2B-containing NMDAR (GluN2BR), by phosphorylation of the GluN2B at the Y1472 epitope [102, 107]. The latter stabilizes GluN2B at postsynaptic sites, thus increasing the risk for excitotoxicity [102, 107].

Since NMDAR are known to mediate stress- and GC-driven neurotoxicity [108] and neuronal remodeling [109], we were prompted to examine whether the mechanistic scenario just described also applies to the actions of stress and GC. Indeed, we found that chronic stress and GC also trigger Tau accumulation at synapses with subsequent increases of Fyn at postsynaptic sites [59, 110] (see also Fig. 20.2).

Other mechanisms that may underlie the ability of stress/GC to contribute to AD pathology have been coming to light in the last few years. One of these is autophagy. As the guardian of cellular homeostasis, autophagy is now seen to play a pivotal role in the pathology of a number of neurodegenerative disorders [111, 112]. Briefly, autophagic mechanisms are responsible for the degradation of misfolded proteins and aggregates such as Tau aggregates; interruption of autophagy leads to the accumulation of protein aggregates, a pathological features shared by a range of neurodegenerative disorders [113, 114]. Our investigations demonstrated (summarized in Fig. 20.3), for the first time, that both, chronic stress and high GC levels inhibit autophagic process, thus explaining how these conditions contribute to the accumulation and

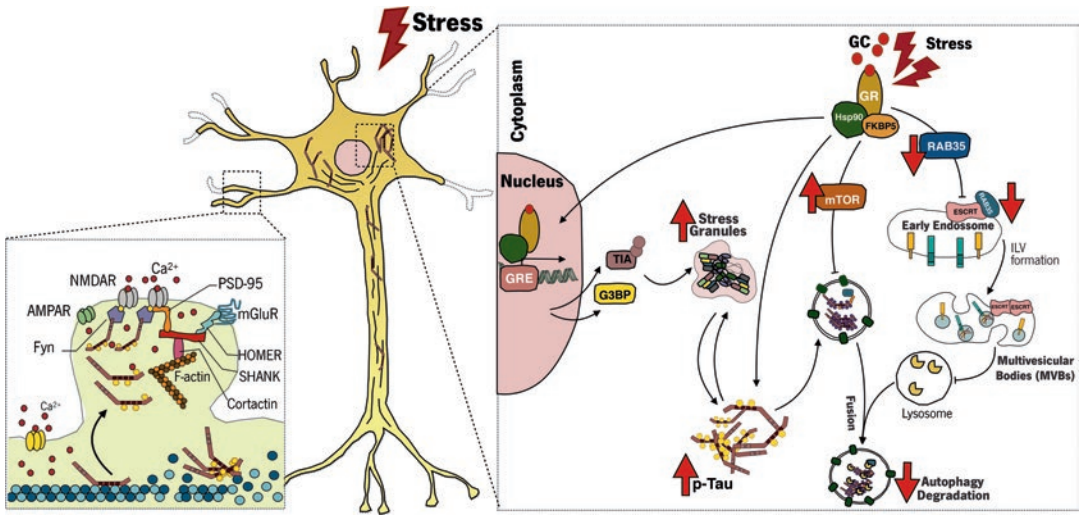

Fig. 20.2 Multiple mechanisms contribute to the induction of Tau pathology and AD by chronic stress. The scheme summarizes the potential mechanisms through which chronic stress and GC activate processes that result Tau accumulation, aggregation and neurotoxicity. Stress leads to increased activation of glucocorticoid receptors (GR) by GC; GR transcriptional activity depends on an interplay of a variety of molecular chaperones (e.g. Hsp90, Hsp70, FKBP51) and HDAC6, a protein that may lead to cytoskeletal instability by reducing the acetylation of tubulin and cortactin. As described in the text, GC induce hyperphosphorylation of Tau and its consequent detachment from microtubules, leading to microtubule destabilization and cytoskeletal disturbances that, together with HDAC6, may contribute to: (i) the formation of stress granules (SG) that promote Tau aggregation and (ii) the inhibition of autophagic process that also contribute to Tau accumulation and aggregation. Interestingly, stress/GC inhibit mTOR, a crucial signaling molecule in the initial phases of autophagy

aggregation of Tau [115]. In fact, defective autophagy is suggested to be major player in AD pathology [116–118]; although Tau itself is a proteosomal substrate [119, 120], it is thought that Tau inclusions and aggregates may be inaccessible to the ubiquitin-proteasome system [121, 122]. Our results showing that chronic stress and GC increase mTOR signaling and reduces the ratio of the autophagic markers LC3II:LC3I and accumulation of p62 [115], indicate that chronic stress inhibits the autophagic process by activating the mTOR pathway; these findings are in line with previous reports that chronic stress stimulates mTOR activity in the hippocampus [123], an event associated with increased total Tau levels in the brains of AD subjects [124, 125]. In addition, support for our interpretation comes from the finding that inhibition of mTOR signaling ameliorates Tau pathology [126, 127] while we demonstrated that inhibition of mTOR blocked the GC-triggered Tau accumulation and aggregation [115].

New research has implicated the endolysosomal pathway in neurodegenerative diseases such as AD and Parkinson's disease in which Tau accumulation is a pathological feature [128–130]. As shown in Fig. 20.2, Tau has been identified as a substrate of the endolysosomal degradation pathway [131]. We demonstrated that *in vitro* or *in vivo* exposure to elevated GC levels block this pathway, accompanied by increases in the build-up of Tau, including that of specific phospho-Tau species. Further, we showed that the involvement of the small GTPase Rab35 and the endosomal sorting complexes required for *transport* (*ESCRT*) machinery that delivers Tau to lysosomes via early endosomes and multivesicular bodies (MVBs). The ESCRT system mediates the degradation of membrane-associated proteins such as epidermal growth factor receptor [132],

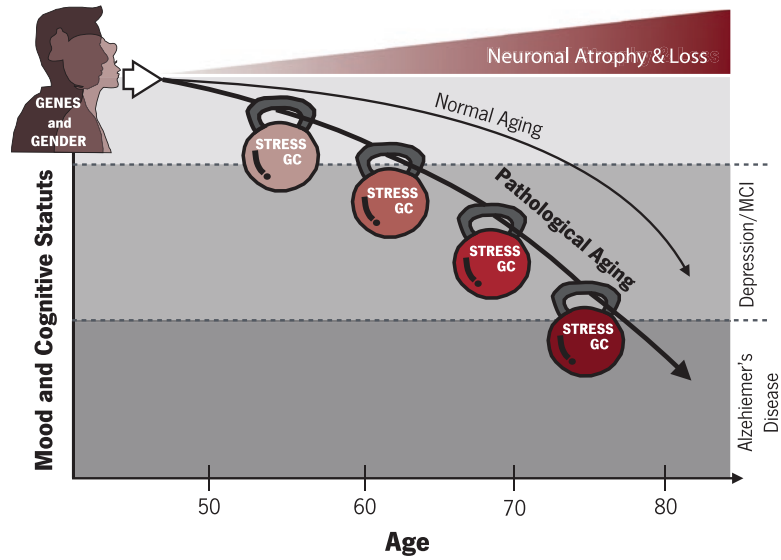

Fig. 20.3 Cumulative effects of stress and glucocorticoids on normal and pathological aging. In this hypothetical representation of brain aging, cognitive and mood status may decline over time. Chronic exposure to stressful conditions, associated with higher exposure to GC, lead to cumulative effects that accelerate brain aging by imposing an increasing allostatic load on brain function by causing neuronal atrophy and synaptic loss, modified by other factors such as genetics and sex – the latter also influence the magnitude of the stress load by modulating the activity of the hypothalamo-pituitary-adrenal (HPA) axis. The model assumes that elements of the HPA axis serve as part of a threshold-regulator mechanism (represented by thick line). Note that brain areas important for regulation of HPA axis (e.g. hippocampus, prefrontal cortex) also appear to be subject to impairments triggered by presymptomatic AD pathology (e.g. mild cognitive impairment, depression), thus feeding into a vicious cycle that further drives GC secretion and neuronal damage. The shaded grey area represents the threshold-transition area where a subject may progress from depression (with or without MCI symptoms) to Alzheimer's disease (AD)

but is also implicated in the degradation of cytosolic proteins GAPDH and aldolase [133]; these findings are of particular relevance for Tau, which has both cytosolic and membrane-associated pools [134, 135], and has been shown to localize to different neuronal sub-compartments, depending on its phosphorylation state [103, 110]. Interestingly, not all phosphorylated Tau species are equally susceptible to degradation in the Rab35/ESCRT pathway. In particular, we found that pSer396/404 and pSer262, but not pSer202, phospho-Tau species undergo Rab35-mediated degradation, indicative of preferential sorting of specific phospho-Tau proteins into the Rab35/ESCRT pathway [131]. Importantly, we demonstrated that high GC levels suppress *Rab35* transcription, and thus, result in an accumulation of Tau due impaired degradation of the protein (Fig. 20.2). Further, overexpression of Rab35 reverses GC-induced Tau accumulation and rescues hippocampal neurons from the dystrophic actions of chronic stress [131].

RNA-Binding Proteins and Stress Granules Facilitate Stress-Induced Tau Pathology

Stress granules (SG) have been recently implicated in the Tau pathology that accompanies AD and fronto-temporal dementia with parkinsonism-17 (FTDP-17) in humans as well as in various transgenic mouse models of Tau-related disorders [136]. The eukaryotic stress response involves translational suppression of non-housekeeping proteins and the sequestration of

unnecessary mRNA transcripts by RNA-binding proteins (RBP) into SG. These macromolecular complexes constitute a protective mechanism against cellular stress (e.g. oxidative stress) that help protect mRNA species and enable the fast production of cytoprotective proteins [136–138]. However, prolonged SG induction can become pathological and neurotoxic; in neurodegenerative diseases such as AD, SG promote the accumulation of Tau aggregates [139–142]. In fact, SG are suggested to accelerate Tau aggregation in a vicious cycle wherein Tau stimulates SG formation, with the RNA binding protein TIA1 playing a lead role in Tau misfolding and aggregation [143]. Notably, while hyperphosphorylation and aggregation-prone mutations of Tau can enhance SG formation, they are not essential for this event [143].

We recently showed that chronic stress and high GC upregulate various RBP and SG markers in soluble and insoluble fractions in the hippocampus of P301L-Tau Tg animals and primary neuron cultures. Specifically, tissues from animals exposed to chronic stress displayed increased cytoplasmic (soluble and insoluble) levels of several RBPs and SG-associated markers (e.g. TIA-1, PABP, G3BP, FUS, DDX5) that contributed to the formation of insoluble Tau inclusions and Tau accumulation. As noted above, TIA-1 plays a prominent role in Tau aggregation: under stressful conditions, TIA-1 is trafficked the nucleus to the cytospasm where it interacts directly with Tau (and other RBP such as PABP and EWSR1) to stimulate its aggregation and accumulation [143–145].

In other recent work, we showed that Tau missorting and accumulation in the dendritic compartment, such as is found in AD pathology [102], is also triggered by chronic stress/GC exposure [59, 110]. This is interesting because Tau missorting is hypothesized to facilitate formation of SG as part of the translational stress response [143]. While the temporal profile and precise mechanisms underlying stress/GC-evoked dysregulation of RBPs and the associated SG cascade remain to be elucidated, Fig. 20.2 illustrates our current working model, designed to explore more about the biology of RNA-protein interactions in stress-related pathologies.

Tau and Its Malfunction in Stress-Related Brain Pathology: Beyond Alzheimer's Disease

Stress pervades all our lives and most of us will respond to daily life stressors in an adaptive manner. However, as noted by Selye as early as 1936, mounting a transient and adaptive response may not be possible in all circumstances and the stressful experience may become chronic and maladaptive. The negative impact of chronic stress (and the associated rise in circulating GC levels) on brain structure and function (e.g. cognition, mood, emotion) is now well recognized. In addition to the role of chronic stress/GC in the development of AD pathology, chronic stress is causally related to major depression which, as in AD, may reflect defects in neuroplastic mechanisms [1, 5, 146]. As briefly mentioned above, major depressive disorder appears to predispose to AD [147]. The body of evidence supporting the latter clinical observation includes findings of potentially common neurobiological mechanisms in the two disorders [84, 85, 148, 149]. Given this, it is interesting that epidemiological studies implicate depression as a risk factor for the development of AD [5], with support for this coming from the observation that previously depressed subjects have increased amyloid plaque and neurofibrillary tangles (NFT) loads [150]. Indeed, since clinicians are sometimes faced with the challenge of distinguishing between patients suffering from depression and AD, several authors have attempted to develop assays based on the detection of various APP cleavage products that might help such distinction [151–154], albeit with little success.

We previously referred to neurogenesis as a phenomenon that contributes neuroplasticity, with impaired neurogenesis being implicated in the pathogenesis of depression [155] as well as

AD [156]. Neurogenesis declines with age (also in humans [156]) and is disrupted by stress and high GC levels [62]. In light of the previously-referred interactions between stress/GC and Tau, it is therefore interesting that our recent research suggests that Tau plays an essential role in stress-driven suppression of birth of neurons (but not astrocytes) in the adult dentate gyrus (DG, a hippocampal subfield) [62]; specifically, chronic stress is unable to impair the propliferation of neuroblasts and newborn neurons in the DG of mice in which the *tau* gene is deleted. Interestingly, *tau* ablation does not interfere with stress-induced suppression of astrocyte proliferation. This finding is likely related to the differential expression of Tau in neuronal *vs.* astrocytic precursor cells – Tau is expressed in neurons at much higher levels than in astrocytes [157]. These observations suggest a novel mechanism through which stress can remodel the adult brain. Interestingly, our investigations also showed that chronic stress increases the 4R-Tau:3R-Tau isoform ratio in the DG. Given that 3R-Tau has a lower affinity for MT than 4R-tau, neuroblasts may be endowed with greater cytoskeletal plasticity than mature neurons since 3R-Tau is more abundant in the former. Here, it is also relevant to note that it was recently shown that higher levels of 4R-Tau are associated with increased Tau phosphorylation and brain pathology [158]. Moreover, an increased 4R/3R-Tau ratio is associated with cytoskeletal disturbances and tauopathies such as AD [64].

Summary/Conclusions

The evidence reviewed in this chapter suggest that deficits in Tau function and Tau proteostasis may be critical and cooperative mechanisms through which stress (whose actions are executed by GC) remodels neural circuits (cell birth and death, dendritic and synaptic atrophy/connectivity), thus inducing impairments mood and cognition. Importantly, we suggest that Tau lies at the core of a set of common neurobiological mechanisms that link stress with AD and other brain pathologies such as depression.

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