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Adverse Stress, Hippocampal Networks, and Alzheimer's Disease

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Abstract

Recent clinical data have implicated chronic adverse stress as a potential risk factor in the development of Alzheimer's disease (AD) and data also suggest that normal, physiological stress responses may be impaired in AD. It is possible that pathology associated with AD causes aberrant responses to chronic stress, due to potential alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Recent work in rodent models of AD suggests that chronic adverse stress exacerbates the cognitive deficits and hippocampal pathology that are present in the AD brain. This review summarizes recent findings obtained in experimental AD models regarding the influence of chronic adverse stress on the underlying cellular and molecular disease processes including the potential role of glucocorticoids. Emerging findings suggest that both AD and chronic adverse stress affect hippocampal neural networks in a similar fashion. We describe alterations in hippocampal plasticity that occur in both chronic stress and AD including dendritic remodeling, neurogenesis and long-term potentiation. Finally, we outline potential roles for oxidative stress and neurotrophic factor signaling as key determinants of the impact of chronic stress on the plasticity of neural networks and AD pathogenesis.

Keywords

Alzheimer's disease; chronic stress; glucocorticoids; hippocampal plasticitiy

Introduction

A majority of AD cases are sporadic and do not have a genetic component (Mattson, 2004); environmental and social factors that can increase the risk of AD include incidence of head trauma, overeating, a sedentary lifestyle and severe adverse stress (Mejia et al., 2003). Chronic stresses such as loss of a spouse or sleep deprivation, may cause memory impairments and increase susceptibility to AD. The occurrence of a major stressful event seems to lower the age of onset of familial AD (Mejia et al., 2003). People vary greatly in their response to stressful events, and those most vulnerable to adverse outcomes exhibit a trait that can be described as negative affectivity, neuroticism or distress proneness (Watson and Clark, 1984; Lockenhoff et al., 2009; Weiss et al., 2009). Patients with a high level of distress proneness are 2.7 times more likely to develop AD than those not prone to distress, and the trait is also associated with a more rapid progression of the disease (Wilson et al., 2006, 2007).

It is widely accepted that in the normal central nervous system (CNS), stress induces activation of the hypothalamic-pituitary-adrenocorticol (HPA) axis which leads to increased release of steroid hormones known as glucocorticoids from the adrenal cortex (cortisol in humans, corticosterone in rodents) (Nelson, 1972; Munck and Guyre, 1986). Chronic stress and elevated glucocorticoids are associated with mood disorders such as depression (deKloet and Derijk, 2004; Sotiropoulos et al., 2008). Recent data shows efficacy for anti-depressant therapy in ameliorating deficits in spatial navigation and reducing the levels of Aβ in a transgenic model of AD, which supports a connection between depression and AD (Nelson et al., 2007). Patients

with the AD type of dementia also exhibit an increase in circulating cortisol, which could indicate a dysregulation of the HPA-axis in AD, the potential for an altered stress-response in patients with AD, and a physiological connection between pathways in chronic stress, AD and depression (Davis et al., 1986; Umegaki et al., 2000; Rasmuson et al., 2001; Csernansky et al., 2006). A basal dysregulation of the HPA axis could contribute to abnormal cognitive and pathological responses to adverse environmental stress in AD patients. Even in neurologically normal subjects, excessive adverse stress can lead to cognitive impairment (Wolf, 2009), an effect that is mimicked in experimental rodent models of stress which demonstrate impairments in spatial memory, contextual memory and object recognition in response to psychosocial or environmental stress (Krugers et al., 1997; Li et al., 2008). Interestingly, in models of chronic adverse stress, the hippocampus, a region of the brain considered critical for learning and memory, appears to be extremely vulnerable, which is also the case in AD (Cequeira et al., 2007). Further, adverse stress drastically alters hippocampal neuronal circuitry, a phenomenon that manifests as remodeling of dendrties, decreases in neurogenesis and alterations in long-term potentiation (LTP) (Fuchs and Flugge, 1998; deKloet et al., 1999; McEwen, 2001; Fuchs et al., 2006). In AD, hippocampal neuronal networks are similarly altered, making the hippocampus particularly vulnerable to the effects of exposure to chronic stress.

Finally, it is noteworthy in the context of this review that not all stressful events are considered adverse. For example, exercise, dietary energy restriction and environmental enrichment can be considered mild stresses that have beneficial effects on cognitive function and may potentially increase an organism's resistance to further stress (Stranahan and Mattson, 2008; van Praag, 2009). Although the HPA axis is activated transiently during exercise and chronically during dietary energy restriction (Patel and Finch, 2002; Droste et al., 2009), these mild stressors confer numerous health benefits. Interestingly, beneficial and adverse stressors may differentially affect the ways in which neurons respond to elevated glucocorticoids. As evidence, adverse stressors (psychosocial stress and sleep deprivation, for example) decrease the expression of mineralocorticoid receptors (MR) whereas beneficial stressors such as dietary energy deprivation decrease the expression of glucocorticoid receptors (GR) in hippocampal neurons (Lee et al., 2000). For the purposes of this review, ‘stress’ should be considered ‘adverse stress’.

Chronic stress exacerbates cognitive deficits and amyloidogenesis in experimental models of AD

Despite the clinical connections between adverse stress, depression and the onset and progression of AD, few studies to date have utilized adverse behavioral stress paradigms in experimental models of AD (Table 1). Repeated adverse stress or chronic corticosterone administration are widely used to induce symptoms of clinical depression in laboratory rodents (Malberg and Duman 2003;David et al., 2009;Hajszan et al., 2009). Recent data obtained from a limited number of *in vivo* AD models demonstrate further declines in cognitive function after the application of adverse stress compared to the cognitive decline of AD alone (Dong et al., 2004;Jeong et al., 2006;Catania et al., 2009;Srivareerat et al., 2009). Chronic psychosocial stress induced by an intruder paradigm significantly exacerbated learning impairments in rats directly exposed to amyloid β-peptides (Aβs) $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$, two cleavage products of the amyloid precursor protein (APP) that are believed to be neurotoxic in AD (Butterfield and Boyd-Kimball, 2004;Irie et al., 2007;Catania et al., 2009;Srivareerat et al., 2009). Similarly, in a transgenic model of AD, 6 months of intermittent immobilization stress worsened learning deficits as measured by both passive avoidance and olfaction tests (Jeong et al., 2006). Further, 6 months of social isolation in a transgenic model of AD accelerated the onset of impairments in contextual, but not cued memory in a fear conditioning test (Dong et al., 2004). Although these above-mentioned studies are the only to our knowledge (Table 1), to measure the cognitive effects of adverse stress in AD, many experimental models of stress demonstrate

decreases in cognitive function following a wide range of stressors such as chronic stress paradigms consisting of unpredictable periods of individual housing, tilted cage, food and water deprivation, and wet cage, as well as prolonged subordination and sleep deprivation (Smith and Kelly, 1988;Krugers et al., 1997;Youngblood et al., 1997;Park et al., 2001;Graves et al., 2003;Yap et al., 2006;Li et al., 2008). Chronic administration of dexamethasone, a GR agonist, caused learning and memory impairments in a passive avoidance test for aged, but not young, mice suggesting an increased susceptibility to elevated glucocorticoids with age (Yao et al., 2007).

In addition to cognitive deficits measured after adverse stress in both AD and normal animals, several key pathological hallmarks of AD pathology are accelerated in response to adverse stress (Wisor et al., 2005; Green et al., 2006; Jeong et al., 2006; Catania et al., 2009; Lee et al., 2009) (Table 1). AD is characterized by extracellular deposits of Aβ which form 'plaques' and intracellular aggregates of the microtubule-associated protein tau which form neurofibrillary 'tangles' (Mattson, 2004). The number of Aβ immunoreactive plaques was increased in the cortex and hippocampus in a transgenic AD model after 6 months of social isolation (Dong et al., 2008). A similar increase in extracellular and neuronal Aβ as well as an increase in phosphorylated tau was noted in the hippocampus in a transgenic model of AD following long-term immobilization stress (Jeong et al., 2006). In fact, in a separate study with a similar transgenic mouse model of AD, only 16 days of immobilization stress accelerated Aβ plaque formation and tau phosphorylation implying that even short-term stress will alter amyloid processing in AD (Lee et al., 2009). Because adverse stress causes activation of the HPA axis and increases levels of circulating glucocorticoids, direct administration of glucocorticoids is often used to model chronic stress (Nelson, 1972; Munck and Guyre, 1986; Green et al., 2006; David et al., 2009). In a triple-transgenic model of AD, application of dexamethasone accelerated increases in intraneuronal $A\beta_{40}$ and $A\beta_{42}$ levels as well as increasing levels of tau (Green et al., 2006). In fact, corticosterone and dexamethasone increase levels of secreted $A\beta_{40}$ and $A\beta_{42}$ *in vitro*, implying that corticosterone can directly affect APP processing (Green et al., 2006). In the normal non-AD brain, exposure to chronic adverse stress modulates amyloid protein processing; 4 weeks of chronic unpredictable stress caused an increase in cleavage products of APP as well as an increase in amyloidogenic β-secretase cleavage of APP in the hippocampus, indicating a shift towards amyloidogenesis for the application of chronic stress (Sayer et al., 2008; Catania et al., 2009). Exposure to corticosterone or dexamethasone causes increased vulnerability to the neurotoxic effects of Aβ *in vitro*, potentially via increased intracellular calcium (Goodman et al., 1996; Yao et al., 2007). Collectively, this work strongly implicates adverse stress in exacerbating the cognitive and biochemical hallmarks of AD. Experimental results are beginning to show that the AD brain is particularly susceptible to challenges posed by adverse environmental stressors potentially due to dysregulation of the HPA axis and results seem to indicate that chronic stress and AD cause similar cognitive impairments and pathological hallmarks, specifically in the hippocampus (Table 1). Yet the pathways through which adverse stress promote AD pathogenesis are unknown.

Regulation of glucocorticoids and the HPA axis

Increased levels of glucocorticoids, associated with chronic stress and activation of the HPA axis, are linked with impaired memory function and endogenous cortisol levels are elevated in patients with AD leading to the hypothesis that AD causes dysregulation of the HPA axis leading to increased cortisol release and impairment of memory (Davis et al., 1986; Umegaki et al., 2000; McEwen, 2001 Rasmuson et al., 2001; Csernansky et al., 2006). Further support for this hypothesis comes from studies showing that the basal and stress-induced corticosterone levels are elevated in several transgenic rodent models of AD (Pedersen et al., 1999; Touma et al., 2004; Green et al., 2006; Pedersen et al., 2006; Dong et al., 2008). Interestingly, accumulations in Aβ in the hippocampus precede elevations in basal levels of plasma

corticosterone in a triple-transgenic model of AD, implying that the observed alteration in the HPA axis in AD may be due to AD neuropathology (Green et al., 2006).

The hippocampus directly regulates the HPA axis, as demonstrated by studies that show that hippocampal CA3 lesions cause increases in corticosterone levels (Herman et al., 1989; Jacobson and Sapolsky, 1991; Roozendaal et al., 2001) (Fig. 1A). It has therefore been hypothesized that in AD, an increase in Aβ plaques in the hippocampus causes disinhibition of the HPA axis which then leads to an increase in basal glucocorticoid levels (Kulstad et al., 2005; Breyhan et al., 2009; Nuntagij et al., 2009). As mentioned above, increases in glucocorticoid levels may promote accelerated Aβ production and a decrease in Aβ degradation in AD (Green et al., 2006). The early progression of AD pathology could be leading to the initiation of a powerful positive-feedback loop that exacerbates AD pathology via dis-inhibition of the HPA axis and production of glucocorticoids (Fig. 1A). Indeed, elevated basal levels of corticosterone are further increased in AD animal models with the application of adverse stress implying an elevated stress response in AD which may lead to exacerbated AD pathology and, potentially, a worsening of cognitive deficits (Green et al., 2006; Jeong et al., 2006; Dong et al., 2008; Lee et al., 2009). A one-time administration of metyrapone, a corticosterone synthesis inhibitor, to un-stressed mice in a transgenic model of AD attenuated losses in spatial working and reference memory implying that production of corticosterone leads to these cognitive deficits (Pedersen et al., 2006). Further, in a transgenic model of AD, chronic restraint stress caused an increase in Aβ plaques, yet this effect was reversed by pharmacologically blocking the restraint-induced surge in plasma corticosterone, which could indicate that elevated corticosterone directly mediates accelerated plaque formation after chronic stress in AD (Lee et al., 2009).

Glucocorticoids exert their biological effects via two receptors, the high affinity MR, and the GR which has roughly one-tenth of the affinity of MR receptors (Reul and de Kloet, 1985; de Kloet et al., 1999). MRs are predominantly expressed in the hippocampus and GRs, while expressed throughout the brain, are most densely present in the CA1 region of the hippocampus (Nishi et al., 2007; Patel et al., 2008; Romeo et al., 2008). In the resting state, when glucocorticoid levels are low, high affinity MR receptors are occupied, whereas GR are relatively unoccupied. When glucocorticoid levels rise, such as in cases of chronic adverse stress, GR receptors begin to become activated, suggesting that the adverse affects of glucocorticoids may be mediated mainly through GR rather than MR (Conrad et al., 1999; Pavlides et al., 2002; deKloet and Kerijk, 2004). As we will discuss later, the relative activation of these receptors may help explain how glucocorticoids regulate long-term potentiation (LTP), the increase in synaptic strength that is thought to underlie learning and memory function (Martin and Clark, 2007; Raymond, 2007). Both clinical and experimental studies of AD show that neurons in the CA1 region of the hippocampus, which express very high levels of GR receptors, are particularly prone to dysfunction and degeneration (Fig. 1B) (Bobinksi et al., 1998; West et al., 1994, 2000; Casas et al., 2004). It is possible that in AD, increased levels of circulating glucocorticoids are related to a loss of GR-expressing neurons. In the normal hippocampus, the expression of GRs is usually decreased in response to adverse stress, perhaps as an attempt to limit glucocorticoid-mediated damage (Sapolsky et al., 1986; McEwen, 2006). However, in a transgenic model of AD, chronic isolation stress caused an increase in GR expression in the hippocampus (Dong et al., 2008). The increase in GR expression in the hippocampus after the application of stress in AD could indicate an aberrant response of dying or degenerating CA1 neurons and could explain the altered reaction to adverse stress in AD.

AD, stress and hippocampal plasticity

Both adverse stress and AD cause alterations in hippocampal plasticity, including shortening and remodeling of dendrites, altered patterns of neurogenesis and impairments in LTP and

learning and memory. Although no study to date has established changes in hippocampal plasticity in AD after chronic stress, it is noteworthy that the changes in plasticity in AD and adverse stress paradigms share several common features.

Dendritic remodeling

Cognitive deficits resulting from chronic adverse stress and hyperactivation of the HPA axis, are likely mediated through alterations in hippocampal networks. The hippocampus plays a critical role in learning and memory processes, and alterations in hippocampal neuronal network function and plasticity are detected after corticosterone administration and chronic adverse stress and in models of AD (Jacobsen et al., 2006; Shankar et al., 2008; Aisa et al., 2009). Dendritic remodeling, in the form of reduced/retracted dendtritic spines, occurs in the CA3 region of the hippocampus after chronic psychosocial stress, chronic mild unpredictable stress or corticosterone administration (Fig. 1B) (Magariños, 1996; Sousa, 2000). Shortening of dendrites appears to also be connected to an overall decrease in the number of synapses in the hippocampus after chronic stress (Magariños et al., 1998; Sousa et al., 2000). This affect is noted *in vivo* after a wide range of chronic stress paradigms as well as after corticosterone administration (Woolley et al., 1990; Watanabe et al., 1992; Magariños et al, 1998). A similar reduction in dendritic spine density is observed in AD (Jacobsen, 2006). Clinical postmortem studies of AD determined that the overall number of synapses is decreased in both the dentate gyrus and the CA1 region, even in cases of mild AD (Selkoe, 2002; Scheff et al., 2006, 2007).

Several studies show that deposits of Aβ can lead to alterations in dendritic spines and a decrease in the number of synapses in AD. Oligomers of Aβ isolated from AD brains attach selectively to dendrites *in vitro* implying that Aβ directly influences alterations in dendritic morphology in AD (Gong, 2003; Lacor, 2004). Application of Aβ oligomers to normal organotypic hippocampal slice cultures induces reductions in spine density (Selkoe, 2008). Notably, electrophysiologic studies demonstrate that decreased spine density is manifest as a loss of excitatory synapses (Selkoe, 2008). Synaptic degeneration in the hippocampus in a transgenic model of AD was ameliorated by lowering of Aβ levels using Aβ immunotheraphy, further implicating Aβ in mediating synaptic alterations in AD (Buttini, 2005). It is also possible that basal increases in glucocorticoids in AD are responsible for dendritic alterations in the hippocampus, particularly considering that corticosterone administration alone is sufficient to induce a decrease in dendritic spines and the number of synapses in the hippocampus (Magariños et al., 1998).

Neurogenesis

Although it was previously thought that the birth of new neurons in the brain did not occur beyond development, it is now widely accepted that adult neurogenesis occurs in both the subventricular zone/olfactory bulb and the hippocampus. In the subgranular zone of the hippocampal dentate gyrus the newly generated cells become incorporated into the granule cell layer and become morphologically and biochemically neuronal in nature (Fig. 1B) (Cameron et al., 1993;Eriksson et al., 1998;van Praag et al., 2002). The production of new cells is believed to be one mechanism through which the hippocampus exerts plasticity and alters neural networks in response to external stimuli. While the exact mechanisms through which memory function and neurogenesis are linked are not yet known, inhibition of neurogenesis causes impairments in spatial and contextual memory, which could indicate a direct role for adult neurogenesis in maintaining normal memory function (Fig. 2) (Snyder et al., 2005;Saxe et al., 2006;Imayoshi et al., 2009). Neurogenesis is regulated by many environmental factors, including both adverse and beneficial stresses. Chronic stresses such as exposure to predator odor, psychosocial stress and restraint, as well as direct corticosterone administration all cause decreases in adult neurogenesis in the hippocampus (Gould et al., 1997;Czeh et al.,

2003;Malberg and Duman, 2003;David et al., 2009). Further, the effect of chronic stress on newly generated neurons in the dentate gyrus, as measured by BrdU, is age-dependent with older animals showing greater vulnerability to stress (Simon et al., 2005). Chronic adverse stress may also lead to increased apoptosis of newly generated neurons in the hippocampus (Lucassen et al., 2006). Both clinical and experimental studies show that overall hippocampal volume is decreased following chronic stress, in depression and in AD, which could indicate that a decrease in neurogenesis and an increase in cell loss in the hippocampus contributes to the cognitive deficits noted in these three neurological conditions (Sheline et al., 1996, 2003;Donohue et al., 2006;Breyhan et al., 2009;Henneman et al., 2009).

Neurogenesis can be enhanced by stressors known to improve overall health including regular exercise (van Praag, 2009), dietary energy restriction (Lee et al., 2002a, 2002b) and environmental/social enrichment (Kempermann et al., 2002). The proliferation of the neural progenitor cells may be increased and/or the survival of newly generated neurons (many of which normally undergo apoptosis) may be enhanced by beneficial types of stress.

While the loss of hippocampal CA1 neurons is accepted as pathological characteristic of AD, the influence of the AD process on hippocampal neurogenesis is currently under debate. A clinical post-mortem study of AD patients indicated an increased expression of some markers of immature neurons in the hippocampus, such as doublecourtin and TUC-4, which could indicate increased neurogenesis in AD. However, several experimental studies in transgenic mouse models have detected a decrease in neurogenesis using markers of dividing cells as well as markers of immature neurons (Haughey et al., 2002; Jin et al., 2004; Zhang et al., 2007; Rodriguez et al., 2008). It is likely that confounding factors in the clinical setting, such as a history of head trauma or other brain damage, could be causing the appearance of mitotic cells in AD. Further, it is possible that cell loss in the CA1 region coupled with a decrease in neurogenesis in the dentate gyrus causes the reduction in the overall volume of the hippocampus that is noted in AD, resulting in an artifactual appearance of increased density of proliferative cells (Fig. 1B). Potentially, basal levels of neurogenesis remain normal in AD, but survival and differentiation of newly generated neurons is impaired. Coupling AD and chronic stress, which is proven to reduce neurogenesis, would then certainly cause a reduction in the birth of new neurons in the hippocampus. Although no study to date has evaluated neurogenesis in the hippocampus after chronic stress in AD animal models, it is likely that stress exacerbates any reductions in neurogenesis in AD, since both AD and stress alone cause decreases in neurogenesis in the hippocampus.

Long-term potentiation

Long-term potentiation (LTP), a persistent increase in synaptic strength, is considered a likely candidate to be the neuronal mechanism that underlies learning and memory and is consequently of considerable interest in the study of AD as well as stress-induced impairments in memory function. Conversely, long-term depression is the weakening of synapses likely due to persistent weak synaptic stimulation (Sheng and Kim, 2002). Adverse stress reduces LTP in the hippocampus, a phenomenon that was initially demonstrated in models of inescapable foot shock and has since been replicated for exposure to predators, psychosocial stress, chronic mild unpredictable stress and sleep deprivation (Shors et al., 1989; Holderbach et al., 2007; Aleisa et al., 2006; Tadavarty et al., 2009). This effect is likely mediated through release of glucocorticoids; both *in vitro* and *in vivo* studies show that LTP is impaired in hippocampal neurons after exposure to high doses of corticosterone (Zhou et al., 2000, Alfarez et al., 2002; Joels and Krugers, 2007). Alterations in hippocampal plasticity from chronic stress appear to be longer-lasting than from acute stress paradigms; hippocampal slices taken from rats after 21 days of chronic mild stress did not respond to synaptic stimulation by corticosterone implying that the induction of LTP was severely impaired (Alfarez et al.,

2003). The relationship between corticosterone levels and LTP follows a well-characterized 'inverted U-shape' pattern; extremely low levels of corticosterone will reduce LTP, intermediate levels of glucocorticoids are required for normal LTP, and higher levels that occur in stress paradigms impair LTP (Diamond et al., 1992). It is noteworthy that this inverted U-shape is similar to the relationship between chronic stress and cognitive function, with a lack of stimulation having an adverse affect on cognitive function, small stimulations such as exercise and environmental enrichment having a positive effect on memory function, and adverse stressful stimulations such as psychosocial stresses or chronic restraint having an adverse effect on cognitive function (Smith and Kelly, 1988; Youngblood et al., 1997; Park et al., 2001; Graves et al., 2003; van Praag et al., 2005; Yap et al., 2006; Ibi et al., 2008; Li et al., 2008).

In some transgenic models of AD, impairment of LTP begins early in the progression of the disease, before significant accumulation of insoluble plaque depositions (Jacobsen et al., 2006; Liu et al., 2008). Evidence implicates soluble pre-plaque Aβ oligomers in these alterations in LTP; LTP deficits are induced in rats as well as in hippocampal slices after exposure to Aβ and these deficits are alleviated by Aβ immunotherapy or pretreatment of Aβ solutions with proteolytic agents that hydrolyze Aβ (Walsh et al., 2002; Shankar et al., 2008). In a rat model of AD, both chronic infusion of Aβ and chronic psychosocial stress caused impairments in the early phase of LTP *in vivo*, and the combination of the two worsened these impairments and also impaired activation of calcium-calmodulin kinase II (CaMKII) after *in vivo* LTP induction (Srivareerat, 2009). Although infusion of Aβ does not represent the most relevant model of AD, the latter findings do provide compelling evidence that Aβ-induced alterations in LTP can be exacerbated by chronic mild stress, which could explain the worsening of cognitive symptoms in this and other AD models when chronic stress is also present.

Cellular and Molecular Mechanisms of Stress-Induced Neuronal Dysfunction and Degeneration

Adverse stressors have been shown to increase oxidative and metabolic stress in neurons on the one hand, while impairing adaptive cellular stress response pathways, on the other hand. A better understanding of the molecular alterations responsible for the neuronal degeneration-promoting and repair-inhibiting effects of adverse stress is leading to novel therapeutic interventions designed to preserve and restore functional neuronal circuits.

Oxidative stress

In addition to similar alterations in hippocampal plasticity, chronic stress and AD are both associated with oxidative stress. In AD, increased oxidative stress is closely linked to Aβ accumulation and neurofibrillary tangle pathology (Butterfield et al., 2001) (Fig. 2). Aβ induces the formation of reactive oxygen species which can then cause lipid peroxidation and protein oxidation (Hensley et al., 2004; Goodman and Mattson, 1994; Yatin et al., 1999; Butterfield et al., 2001; Matsuoka et al., 2001). When Aβ aggregates at the synapse, it induces lipid peroxidation and oxidation of membrane proteins (Keller et al., 1997; Mark et al., 1997). Data indicate the presence of oxidative stress in the brain in AD, including increases in reactive oxygen species, lipid peroxidation products and protein oxidation (Butterfield et al., 2001). Chronic restraint stress, sleep deprivation and social isolation cause increases in markers of oxidative stress in the brain, including lipid peroxidation, protein carbonyls and nitrite levels (Pajovic et al., 2006; Atif et al., 2008; Singh and Kumar, 2008; Zafir and Banu, 2009). Corticosterone may promote oxidative stress, since exogenous administration of corticosterone causes an increase in oxidative stress in the brain (Zafir and Banu, 2009).

Chronic restraint induced a significant increase in lipid peroxidation in the hippocampus in both wild-type mice and in a transgenic mouse model of AD. However, increases in lipid peroxidation were three-fold greater in AD mice subjected to chronic restraint stress compared to unstressed controls (Lee et al., 2009) implying that the AD hippocampus is vulnerable to oxidative stress induced by adverse stress. The increases in lipid peroxidation products after restraint stress were reduced by a pharmacologic block of corticosterone release, implying that this effect is mediated by corticosterone (Lee et al., 2009). It is possible that early increases in Aβ in AD, as well as elevated corticosterone levels cause oxidative stress in the brain. The addition of chronic stress further increases corticosterone levels and exacerbates oxidative damage to neurons (Fig. 2).

Metabolic Stress

Brain imaging studies in which cerebral blood flow or glucose utilization were evaluated demonstrated that cellular energy metabolism is decreased in patients with mild cognitive impairment, and to an even greater extent in AD patients, in brain regions involved in cognition including the hippocampus and associated structures (Friedland et al., 1989; Johnson et al., 2005; Perneczky et al., 2007). While cell loss likely contributes to the deficits in regional brain energy metabolism detected by brain imaging methods, increasing evidence suggests that the ability of neurons to generate energy (ATP and NAD^+) efficiently is impaired in neurons well prior to cell death and the onset of cognitive symptoms. In particular, mitochondrial function is compromised (see Mattson et al., 2008 for review). For example, the activities of the α-ketoglutarate dehydrogenase complex, the pyruvate dehydrogenase complex and isocitrate dehydrogenase are decreased in brain regions most affected in AD (Bubber et al., 2005). In addition, oxidative damage to mitochondrial DNA is greater in brain tissue samples from patients with mild cognitive impairment and AD compared to samples from age-matched control subjects (Shao et al., 2008). Other studies have documented mitochondrial deficits in peripheral cells from patients with mild cognitive impairment or AD, including platelets (Trimmer et al., 2004; Valla et al., 2006). Finally, studies of cell culture and animal models have documented multiple adverse effects of genetic factors and stressors relevant to aging and AD (oxidative stress, Aβ and others) on neuronal energy metabolism (Mark et al., 1997; Begley et al., 1999; Hauptmann et al., 2008; Reddy and Beal, 2008).

Adverse stressors may endanger neurons, in part, by impairing energy metabolism in neurons themselves, as well in peripheral cells. Levels of glucocorticoids achieved during chronic stress can inhibit glucose transport in neurons (Horner et al., 1990), a process which may contribute to energy deficits that increase the vulnerability of neurons to aging and AD. Indeed, the damaging effects of levels of glucocorticoids that occur during exposures to adverse stress can be prevented by administering “brain fuels” including ketone bodies (Sapolsky, 1986). Interestingly, low doses of glucocorticoids enhance, whereas high doses impair, mitochondrial function in neural cells (Du et al., 2009). Increasing evidence suggests that impaired peripheral energy (glucose) metabolism (insulin resistance and diabetes) is a risk factor for cognitive impairment (Stranahan et al., 2008a; Craft, 2009), and adverse stress can impair peripheral glucose metabolism by reducing the insulin sensitivity of muscle, liver and other cells (Fu et al., 2009). Treatments that improve glucose metabolism, including dietary energy restriction (Bruce-Keller et al., 1999; Stranahan et al., 2009), exercise (Radak et al., 2001; Stranahan et al., 2008b, 2009) and insulin administration (Bohringer et al., 2008) can enhance cognitive function in animal models. Analysis of the effects of exercise on hippocampal gene expression suggest that this anti-diabetic factor upregulates genes associated with synaptic plasticity, mitochondrial function, energy metabolism, and insulin, MAP kinase and Wnt signaling; genes associated with oxidative stress and infl ammation were downregulated by exercise (Stranahan et al., 2008b). It has been known for several decades that the hypothalamic/sympathetic neural network that regulates energy balance responds to stress and glucocorticoids on the one hand,

and that energy intake and output influence HPA stress responses, on the other hand (Dallman, 1995). More recent findings, such as those described above, reveal a much larger neural network (that includes the hippocampus and associated structures) which integrates cognitive responses to stress that may be adaptive or maladaptive depending upon the nature, frequency and intensity of the stressor.

Neurotrophic Factors

Studies show that the normal nervous system responds to a moderate level of stress by enhancing its ability to withstand more severe stress, a phenomenon that is termed 'neurohormesis' (Mattson, 2008). An important class of adaptive stress response proteins upregulated by beneficial stressors is the neurotrophic factors. For example, exercise and cognitive stimulation activate an adaptive stress response pathway in neurons involving the transcription factor CREB (cyclic AMP response element-binding protein) which induces the expression of brain-derived neurotrophic factor (BDNF) (see Mattson et al., 2004 for review). Similarly, the expression of fibroblast growth factor 2 (FGF2) is increased in the hippocampus in response to exercise and cognitive stimulation (Gomez-Pinilla et al., 1997). In contrast, to upregulation in response to beneficial stressors, neurotrophic factor expression is suppressed under conditions of chronic adverse stress. BDNF is normally produced in the entorhinal cortex where it is anterogradely transported to the hippocampus, however in AD, BDNF levels are reduced in both the entorhinal cortex and hippocampus, suggesting that production and transport of the neurotrophin is decreased in AD (Connor et al., 1997; Hock et al., 2000). Reductions in BDNF in AD may have wide-reaching effects since this neurotrophin is involved in a wide range of processes that govern neural networks. Moreover, BDNF protects neurons against damage caused by oxidative, metabolic and excitotoxic stress (Mattson, 2004a; Marini, 2007; Nagahara, 2009).

Adverse stress and aging have been consistently shown to reduce the expression of neurotrophic factors. For example, BDNF levels in the hippocampus are decreased in animals subjected to chronic immobilization stress (Smith et al., 1995). Interestingly, chronic social stress during adolescence in mice results in reduced hippocampal BDNF levels and cognitive impairment when the animals are older (Sterlemann et al., 2009) suggesting that adverse stress during early life can endanger the brain during aging. Acute stress enhances, whereas chronic stress inhibits, cocaine-induced bFGF production in a brain region-specific manner (Fumagalli et al., 2008). It is possible that changes in basal BDNF expression that occur in the hippocampus in normal aging and AD render brain cells vulnerable to the adverse effects of chronic stress on neuroprotective signaling pathways. Specifically, BDNF mediates the formation of memories via long-term potentiation (LTP). Animals subjected to exercise demonstrate increased neurogenesis and acquisition and memory retention, effects that are mediated by increases in BDNF in response to exercise (van Praag et al., 2005; Gomez-Pinilla et al., 2008; Stranahan et al., 2009). In contrast, animals subjected to chronic adverse stress exhibit reduces levels of BDNF in hippocampal neurons (Li et al., 2008), suggesting an adverse effect chronic stress on the ability of neurons to protect themselves against injury and disease. Although no research to date has quantified how BDNF regulation in AD affects the response to chronic stress, it is likely that administration of BDNF would improve the stress response, considering that recent work has shown that overexpression of BDNF increases cognitive performance in mice and administration of BDNF reverses synapse loss and restores learning and memory in rodent and primate models of AD (Nakajo et al., 2008; Nagahara et al. 2009).

Finally, it should be noted that although recent data have begun to identify the mechanisms underlying the vulnerability of the hippocampus to chronic stress and AD, it is likely that the type and intensity of the stressful stimulus greatly affects cognitive and pathological outcomes. At least one recent study found no affect of chronic social isolation on Aβ deposits and only a

limited affect of social isolation on cognitive measures (Pietropaolo et al., 2009). In a study using chronic restraint stress, levels of Aβ were increased and this effect was blocked by corticotrophic hormone receptor antagonists implying that regulation of the HPA axis was involved (Lee et al., 2009). However in a study of sleep deprivation-induced memory impairment in normal mice, the deficits were not abolished by a corticosterone synthesis inhibitor indicating that restraint stress and sleep deprivation potentially induce varying pathological outcomes even if cognitive deficits are similar (Tiba et al., 2008).

Implications for Therapeutic Interventions to Preserve and Restore Cognitive Function

Several approaches to preserving cognitive function during aging and preventing or delaying the onset of AD are suggested by the findings described above. Lifestyles that incorporate mild intermittent beneficial stressors (exercise, dietary energy restriction and cognitive challenges) and minimize adverse chronic stressors (psychosocial stress, sleep deprivation and the like) provide the first line of defense. Improving peripheral and brain cell energy metabolism through dietary supplementation (with creatine, for example) or drugs (exendin-4, for example) is another approach that may be used in individuals at risk (Sullivan et al., 2000; Pan et al., 2007; Li et al., 2009; Martin et al., 2009). Suppressing glucocorticoid production pharmacologically would be expected to counteract the adverse effects of chronic stress on neural networks in the brain (Smith-Swintosky et al., 1996), although such drugs may compromise the beneficial effects of glucocorticoids in acute stress conditions. Upregulation of the expression of neurotrophic factors using drugs that increase serotonergic and/or noradrenergic signaling is another approach for combating the potentially damaging effects of adverse stress on the integrity and plasticity of nerve cell circuits involved in learning and memory (Mowla et al., 2007; Nelson et al., 2007). Further interrogation of the signaling pathways involved in adaptive and maladaptive responses of neural circuits to stress will likely lead to additional preventative and therapeutic approaches for optimizing cognitive performance throughout the lifespan.

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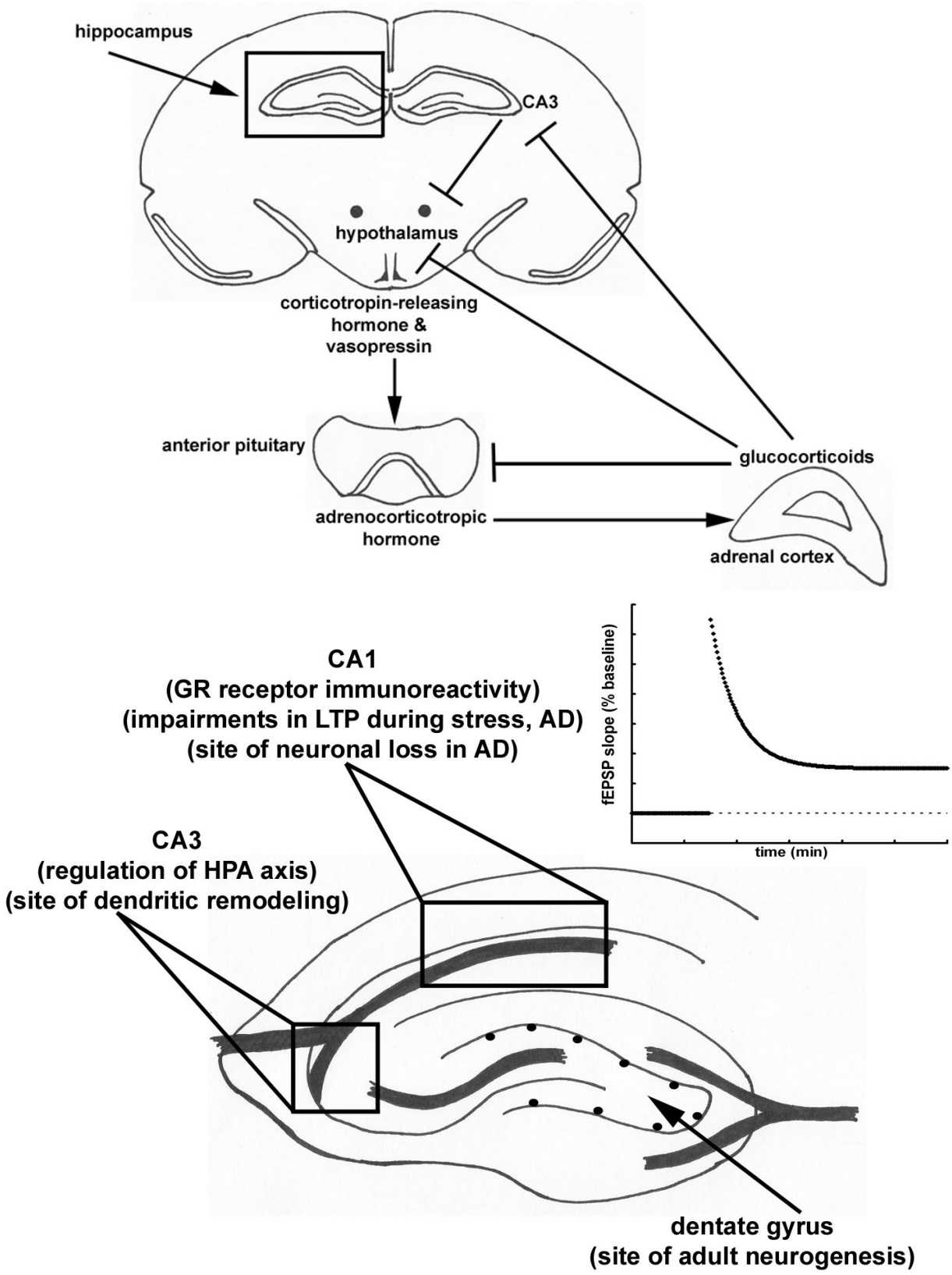

Figure 1.

Schematic showing the components of the HPA axis **(A).** Activation of the HPA axis results in release of glucocorticoids (corticosterone in rodents, cortisol in humans). The CA3 region of the hippocampus inhibits activation of the HPA axis. Schematic of the hippocampus showing areas CA1, CA3 and the dentate gyrus **(B).** Specific sites of hippocampal plasticity as well as control of the HPA axis and the site of glucocorticoid receptors (GR) are noted.

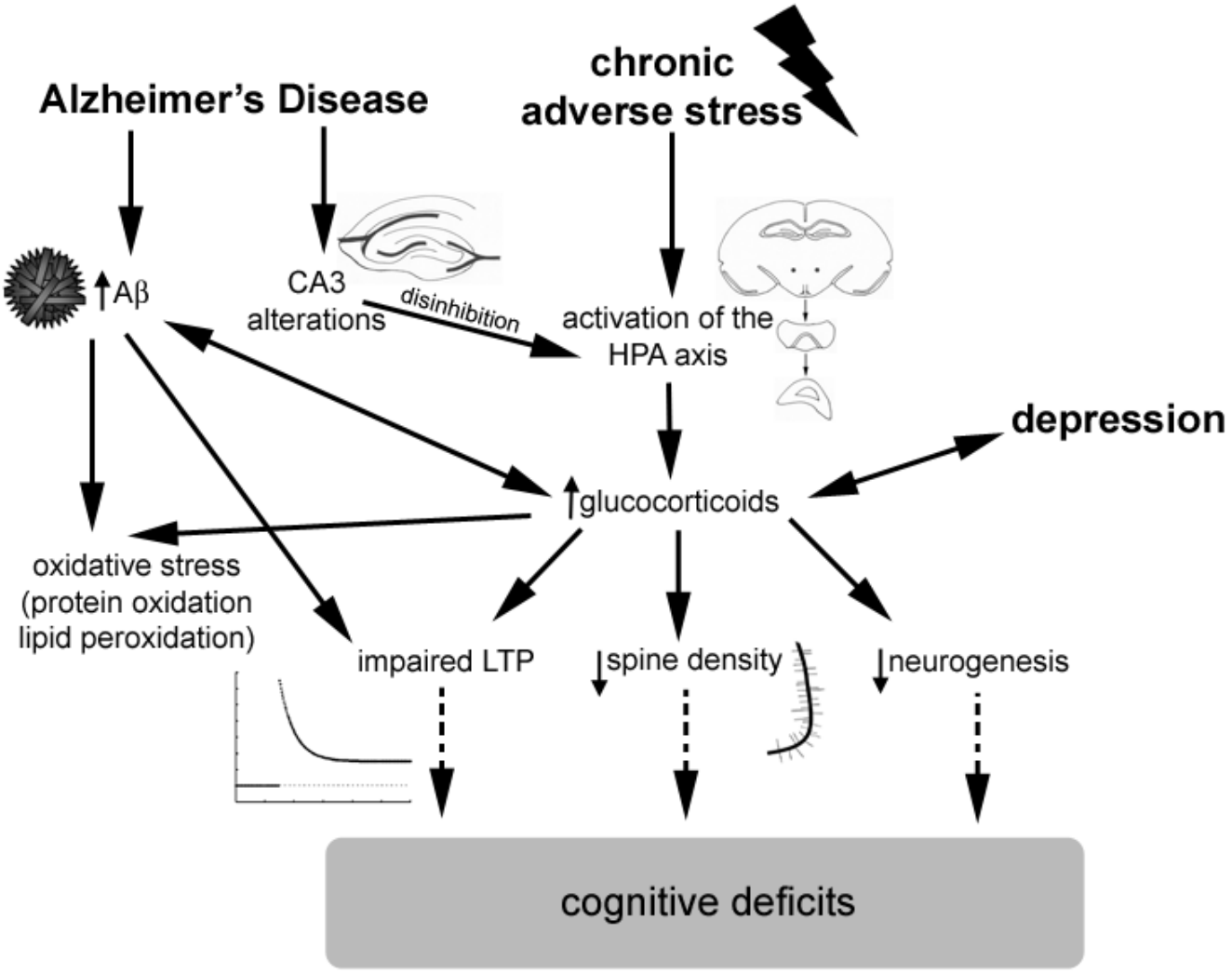

Figure 2.
Pathways through which AD and chronic adverse stress potentially lead to cognitive impairments. Chronic stress and AD share similar pathways via increased release of glucocorticoids. Dashed arrows indicate that impairments in LTP, alterations in dendritic morphology and decreases in neurogenesis are all thought to lead to cognitive impairments although the exact mechanisms are not entirely known.

Table 1

Summary of current research on the effects of chronic stress in various models of AD.

		Outcome		
AD model	**Environmental Stress**	**Behavioral**	**Biochemical & Physiological**	**Reference**
infusion of Aβ (rat)	• intruder psychosocial stress model (6 weeks)	• chronic stress worsens Aβ-induced deficits in spatial learning	• stress exacerbates impairment of early phase LTP in Aβ treated rats	Srivareerat et al., Biol Psychiat 2009
			• stress reduces basal levels of phosphorylated calcium/calmodulin dependent protein kinase II and increases basal calcineurin after Aβ infusion	
infusion of Aβ (rat)	• chronic unpredictable stress (4 weeks) • dex administration	• chronic stress and dex both exacerbate Aβ-induced deficits in spatial learning	• stress and dex magnify increases in C99, BACE-1 and nicastrin induced by Aβ in the hippocampus and cortex	Catania et al., Mol Psychiat 2009
	• chronic stress and dex administration	• Aβ, stress and dex all induce anxiety but the effect is not compounded by their combination		
APP_{V717I}-CT100 (mouse)	• immobilization stress (6 or 8 months)	• stress accelerates learning and memory impairments in a passive avoidance paradigm and social transfer of food preference test	• stress increases extracellular amyloid plaques and intraneuronal Aβ deposition in the hippocampus	Jeong et al., FASEB 2006
Tg 2576 (mouse)			• stress increases tau phosphorylation in the hippocampus and cortex	
Tg 2576 (mouse)	• social isolation (6 months)	• social isolation accelerates the onset of memory impairments in contextual, but not cued, fear conditioning	• social isolation accelerates deposition of Aβ plaques in the hippocampus	Dong et al., Neuroscience 2004
			• social isolation exacerbates the decrease in hippocampal neurogenesis in AD	
Tg 2576 (mouse)	• social isolation (6 months)		• social isolation increases basal cort	Dong et al., Neuroscience 2008
			• social isolation increases expression of GR in the cortex and CRF1 in the cortex and hippocampus	
			• social isolation increases Aβ plaque deposition	
Tg 2576 (mouse)	• restraint stress (16 days)		• restraint increases plasma cort	Lee et al., J Neurochem 2009
			• chronic restraint increases Aβ plaque deposition in the cortex, tau hyperphosphorylation and metabolic oxidative stress	
			• chronic restraint downregulates expression of MMP-2	
3xTgAD (mouse)	• dex administration (7 days)		• basal plasma corticosterone is elevated in 3xTgAD mice	Green et al., J Neurosci 2006
			• dex increases intraneuronal Aβ, total APP, C99 and BACE	
			• dex accelerates accumulation of tau in dendrites	

Abbreviations: AD (Alzheimer's Disease); dex (dexamethasone); LTP (long term potentiation); C99 (C-terminal fragment 99); BACE-1 (β-site APP-cleaving enzyme) cort (corticosterone); CRF1 (corticotropin releasing factor); MMP2 (matrix metalloproteinase 2); APP (amyloid precursor protein); GR (glucocorticoid receptor)