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Review

Repeated stress and structural plasticity in the brain

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Abstract

Although adrenal steroid receptors are distributed widely throughout the central nervous system, specific limbic and cortical regions targeted by stress hormones play a key role in integrating behavioral and physiological responses during stress and adaptation to subsequent stressors. When the stressor is of a sufficient magnitude or prolonged, it may result in abnormal changes in brain plasticity that, paradoxically, may impair the ability of the brain to appropriately regulate and respond to subsequent stressors. Here we review how repeated stress produces alterations in brain plasticity in animal models, and discuss its relevance to behavioral changes associated with these regions. Interestingly, prolonged stress produces opposing effects on structural plasticity, notably dendritic atrophy and excitatory synapse loss in the hippocampus and prefrontal cortex, and growth of dendrites and spines in the amygdala. The granule cells of the dentate gyrus are also significantly affected through a decrease in the rate neurogenesis following prolonged stress. How functional impairments in these brain regions play a role in stress-related mental illnesses is discussed in this context. Finally, we discuss the cumulative impact of stress-induced structural plasticity in aging.

1. Introduction

Stress may be defined as any type of threat, either real or perceived, that requires compensatory responses for the maintenance of homeostasis. The stress response consists a rapid component, also referred to as the ‘‘fight or flight’’ response, that involves the activation of the sympatho-adrenal system and catecholamine release, mobilizing energy reserves, increasing cardiovascular output, redirecting blood flow from the viscera to peripheral muscles, and enhancing cognition and attention. The slower acting

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hypothalamo-pituitary-adrenal (HPA) system results in glucocorticoid release, thereby assisting the sympatho-adrenal response, while also having a negative feedback regulatory function following the cessation of stress. In this regard, glucocorticoids exert their effects throughout the brain during stress that alter cognition and behavior in an adaptive manner, and also play a key role in the termination of HPA responses to stress.

Despite these benefits of the stress response, stressors that are either prolonged or extreme, may result in abnormal changes in brain plasticity that, paradoxically, may impair the ability of the brain to appropriately regulate and respond to subsequent stressors. Similar to the glucocorticoid hypothesis proposed by Sapolsky et al. (1986), if brain regions that are critical in regulating HPA responses to stress become susceptible to the effects of glucocorticoids (GCs), then their ability to regulate the response to subsequent stressors may become compromised. At least in general terms, this would readily account for how the maladaptive effects of repeated stress may enhance susceptibility for depression, increased anxiety, or posttraumatic stress disorder (PTSD). However, it may also be the case that dysregulation of the HPA axis gives rise to a host of adverse systemic effects on the body known to result from chronic stress, such as myopathy, fatigue, hypertension, ulcers, impotency, amenorrhea, and immunosuppression. Indeed, chronic stress has been linked to heart disease and depression-illnesses which collectively have a prevalence of almost 15% in the adult population in the US (Lethbridge-Çejku et al., 2004).

Insofar as it is plausible to reduce all of the health consequences of chronic stress to a dysegulation of HPA axis negative feedback at key regulatory sites in the brain, it is nonetheless useful to examine how prolonged stress may alter neuronal plasticity. In this review, we will examine the relationship between repeated stress and neuronal plasticity in the hippocampus, medial prefrontal cortex, and amygdala, with specific attention focused on changes observed in animal models and their relationship to human stress-related mental illnesses such as depression and PTSD. The study of repeated stress in animals has been demonstrated to recapitulate the constellation of behavioral abnormalities in, and has proven to be a reliable model for, stress-related mental illnesses in humans (Ottenweller et al., 1989; Willner, 1997). The relative contributions of elevated GCs and excitatory amino acids (EAAs) levels will be considered accordingly. Last, we will discuss how stress-induced effects on the brain are recapitulated during the aging process.

2. Hippocampal formation

2.1. Dendritic plasticity

Since the discovery that the hippocampus has a significant representation of GC receptors it is now appreciated that GCs exert effects throughout the brain (McEwen et al., 1968). The hippocampus is also one of the key limbic structures shown to be important for the termination of HPA activation following stress (Sapolsky et al., 1984). In this regard, the hippocampus is a target to the effects of GCs and stress, which in turn, may affect its regulation of the HPA axis. Chronic GC administration to artificially high levels induces apical dendritic retraction and debranching (∼20%) in rat CA3c pyramidal neurons (Watanabe et al., 1992b; Woolley et al., 1990b), while longer durations of GC

administration result in more substantial hippocampal damage, such as neuron death, gliosis, and atrophied perikarya in principal layers, most notably in the CA3c region (Sapolsky et al., 1985).

Repeated stress exerts similar effects as GCs on dendritic remodeling in CA3. Three weeks of daily restraint stress results in a 20% reduction in apical dendritic length and branch number in rat CA3c pyramidal neurons (Watanabe et al., 1992b,c). Other repeated stress paradigms, such as repeated variable stress, social dominance stress (Magariños and McEwen, 1995a; Sousa et al., 2000; McKittrick et al., 2000), and in tree shrews, psychosocial stress (Magariños et al., 1996), all result in a similar type of dendritic remodeling in the CA3 region. Repeated stress-induced dendritic remodeling may also be prevented by GC antagonist administration (Magariños and McEwen, 1995b).

Although the effects of stress on the hippocampus are GC-dependent, excitatory amino acids (EAAs) play an important role downstream to GCs as mediators of dendritic remodeling (Reagan and McEwen, 1997). For instance, in the 3-week repeated restraint stress paradigm, plasma GCs return to basal levels within 14 days, and longer durations of repeated restraint (e.g., 5 weeks) do not result in any further dendritic atrophy in CA3 from that which is observed after 3 weeks (Magariños and McEwen, 1995a; Magariños et al., 1999). Despite the ebbing of plasma GCs, repeated stress-induced dendritic remodeling in CA3 is only reversible after a stress-free recovery period of at least 10 days (Conrad et al., 1999). Stress-induced elevations in GCs result in an increase in extracellular levels of glutamate in the hippocampus (Abraham et al., 1998; Lowy et al., 1995). Phenytoin administration, a drug that interferes with EAA release and transmission, prevents repeated stress-induced dendritic atrophy in CA3 (Watanabe et al., 1992a). The vulnerability of hippocampal neurons following GC exposure has been shown to be dependent on *N*-methyl-D-aspartate (NMDA) activation, and similarly, NMDA receptor antagonist treatment prevents repeated stress-induced dendritic atrophy (Armanini et al., 1990; Magariños and McEwen, 1995b). The glial glutamate reuptake transporter (GLT-1) is upregulated in expression in CA3 following repeated restraint stress, which may also help to ameliorate the excitotoxic effects of prolonged glutamatergic stimulation (Reagan et al., 2004). Tianeptine is an antidepressant drug that increases the neuronal uptake of serotonin that is effective in preventing or reversing the effects of stress on dendritic remodeling in the hippocampus (Magariños et al., 1999; McEwen and Chattarji, 2004). Although, the antidepressant effects of tianeptine are not well understood, the observation by Kole et al. (2002) that tianeptine modulates NMDA receptor-mediated currents in the hippocampus suggests this as a potential mechanism for the prevention of dendritic atrophy in CA3.

Although, the downstream events that link the stress-induced effects of GCs and EAAs to dendritic plasticity in the hippocampus involve changes in gene expression, post-translational modifications play a significant role as well. After 3 weeks of repeated restraint stress, there was not any significant change in neurotrophin expression, such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), or basic fibroblast growth factor (bFGF; Kuroda and McEwen, 1998). In contrast, shorter-term stressors have been shown to reduce BDNF levels (Smith et al., 1995; Ueyama et al., 1997). One possibility is that the maintenance of hippocampal neurotrophin levels throughout prolonged stress could account for why these neurons are resistant to neuronal damage. Another possibility is that elevated GCs during repeated stress are accompanied by reduced

trophic support, such that the return of GCs to basal levels results in the restoration of neurotrophic influence that has mitigating effects on hippocampal dendritic atrophy and neuronal damage. In this regard, that repeated variable stress produces a more pronounced and extensive dendritic atrophy in the hippocampus may be the result of a more sustained elevation of GCs and reduction in neurotrophic support, accordingly (Sousa et al., 2000).

The rise in intracellular calcium may play an important role in stress-induced hippocampal plasticity, since it occurs prior to the onset of CA3 dendritic retraction, and is capable of exerting genomic and non-genomic effects as a second messenger. Homeostatic dysregulation of intracellular calcium may be enhanced by elevated EAAs, and may become neurotoxic (Arundine and Tymianski, 2003). At shorter-term intervals of immobilization stress (1 day and 4 day, but not after 2 weeks) an increase in phosphorylated calcium/calmodulin-dependent protein kinase (CaMK) II was evident in the hippocampus, which is induced by an increase in intracellular calcium (Suenaga et al., 2004). GC administration enhances the effects, and the duration, of calcium conductances in neurons (Joels and de Kloet, 1994).

The cytoskeletal network undergoes alterations following repeated stress that may promote structural stability. Alpha-tubulin is the major isoform of microtubules that comprise the neuronal cytoskeleton, and can be post-translationally modified to a highly dynamic tyrosinated form (Gundersen et al., 1987), or acetylated stable form (Contin and Arce, 2000). Repeated stress results in an increase in hippocampal acetylated-tubulin and decrease in tyrosinated tubulin, suggesting that the cytoskeletal network undergoes stabilization as an adaptive response that may be protective (Bianchi et al., 2003; McCall et al., 2004). The microtubule associated protein, MAP-1, which may also be important for stabilizing microtubules (Tucker et al., 1989), was increased in the hippocampus following repeated stress (Xu et al., 2004). In addition, the non-phosphorylated form of neurofilament proteins are increased in dentate granule cells following social deprivation in prepubescent rhesus monkeys (Siegel et al., 1993). However, under more extreme conditions of stress or GC administration, evidence of cytoskeletal destabilization is manifest by increased tau phosphorylation and spectrin proteolysis (Okawa et al., 2003; Stein-Behrens et al., 1994). Although more work is needed to understand the cytoskeletal changes that underlie dendritic remodeling following prolonged stress, the emerging view is that these post-translational changes may not only protect hippocampal neurons, but also allow for their rapid reversibility following the termination of stress.

Repeated stress impairs several forms of spatial learning that correlate with dendritic remodeling in the rat CA3 (Conrad et al., 1996; Luine et al., 1994; Sunanda et al., 2000), which has also been demonstrated to be reversible after the cessation of stress (Luine et al., 1994). Contextual fear conditioning is one example of hippocampal-dependent learning that is enhanced following repeated restraint stress, and is not dependent on dendritic remodeling in CA3 (Conrad et al., 1999). The latter finding suggests that these structural changes in hippocampus may not globally affect all hippocampal-dependent behaviors, or that stress-induced alterations in amygdala function may play a modulatory role in this type of learning (Huff and Rudy, 2004). Although beyond the scope of this review, the effect of stress on hippocampal-dependent forms of learning may vary according to the duration of the stressor, and may also be sexually dimorphic (Shors, 2004; Luine, 2002).

2.2. Neuronal toxicity

If repeated stress persists over a long period of time, neuronal damage and death will ultimately ensue in vulnerable cell populations. Whereas 1 month of social stress is not sufficient to induce neuron loss in tree shrews, longer periods of stress result in increased cell death in the hilus of the dentate gyrus, a reduction in overall hippocampal volume, and substantial neuronal damage throughout the hippocampal formation (Vollmann-Honsdorf et al., 1997; Lucassen et al., 2001; Czeh et al., 2001; Uno et al., 1989). Therefore, during prolonged stress, CA3 apical dendrites seem to be most susceptible to atrophy, and increasing the duration of stress may result in a more widespread dendritic atrophy throughout the hippocampal formation, eventual neuronal damage, and neuron death.

Stress-induced neuronal damage in the hippocampus may be mediated through alterations in neuronal energetics. For instance, the diversion of energy and metabolic resources to muscles is part of the adaptation to an acute stressor, such as ''fight or flight'' responses. However, part of this adaptation also involves the inhibition of energy uptake and storage, especially in the brain and hippocampus (for review, see Sapolsky, 1996). GCs may damage hippocampal neurons through the inhibition of glucose transport by neurons and glia (Horner et al., 1990; Virgin et al., 1991). Nonenergetic mechanism may also account from hippocampal damage that results from prolonged stress. Accumulating evidence also shows that prolonged stress and elevated GCs may damage neurons through glutamate excitotoxicty and elevated levels of intracellular calcium (for review, see Reagan and McEwen, 1997). As it will be discussed below, one key feature of prolonged stress is the alteration in dendritic spine number and morphology in the hippocampal formation and (medial prefrontal cortex). Such structural synaptic changes may be compensatory to glutamatergic and calcium-induced toxicity in these neurons during prolonged periods of stress.

2.3. Axospinous synaptic plasticity

Since repeated stress induces apical dendritic retraction in CA3, this may have significant consequences for the total synaptic population. Considering that 3 weeks of repeated restraint stress produces a 20% decrease in the amount of dendritic material, if spine density remained constant, one might expect a similar overall 20% decrease in excitatory synapse number. However, synapse density is likely to vary as a function of dendritic length (Peters and Jones, 1984), and may undergo further modifications following stress. This issue is further complicated by the lack of detailed phenotypic description of apical dendritic retraction, whether it is occurring throughout the arbor, in proximal, or distal dendrites. The first study to address this question found that 3 weeks of repeated restraint stress actually increased spine density on apical and basal dendrites, and density of thorny excresescences, in Golgi-impregnated CA3c pyramidal neurons (Sunanda et al., 1995). This suggests that increasing the density of spines may be compensatory to the extensive loss of dendritic material (Sorensen and Zimmer, 1988). Another group found that 3 weeks of repeated stress did not affect number or total area occupied by complex spines (Magariños et al., 1997). Instead, they reported changes in the packing density, and a net depletion, of synaptic vesicles, and increased area of the terminal occupied by

mitochondrial profiles, all of which are consistent with the interpretation that mossy fiber synapses are functionally enhanced for more efficient glutamate release (Magariños et al., 1997).

Subsequent studies that have employed stereological methods involving 3-D reconstructions through dendritic spines have shown that repeated stress results in a reversible decrease in dendritic spine density and synapse number (Sandi et al., 2003; Sousa et al., 2000; Stewart et al., 2005). However, consistent with (Magariños et al., 1997), the effects of stress on spines were not inclusive of thorny excrescenses, suggesting that these complex spines may be regulated and maintained independently of their terminal input from mossy fibers (Frotscher and Ghwiler, 1988; Madeira and Paula-Barbosa, 1993; Sousa et al., 2000).

2.4. Neurogenesis in the dentate gyrus

One unique feature of the hippocampal formation is its ability to undergo neuronal replacement throughout the lifespan of rodents and primates (Eriksson et al., 1998; Gould et al., 1999b; Kaplan and Bell, 1983). Neurogenesis is decreased by exposure to GCs and NMDA receptor agonist administration. Various types of stressors, including repeated restraint stress, maternal separation, psychosocial stress, and exposure to predator odor (Gould et al., 1992, 1997; Pham et al., 2003; Mirescu et al., 2004; Tanapat et al., 2001), all result in a decrease in granule neuron production. Although their functional ramifications have yet to be determined, these newly-generated neurons are known to migrate into the granule cell layer, extend axons to their appropriate targets in CA3, and become functionally integrated into the hippocampal network. In fact, there is evidence that links neurogenesis to certain forms of hippocampal-dependent learning (Cameron et al., 1993; Hastings and Gould, 1999; Markakis and Gage, 1999; van Praag et al., 2002; Gould et al., 1999a; Shors et al., 2001, 2002). Repeated stress also seems to impact the total granule neuron population and granule cell layer volume, which was not affected after 3 weeks, but decreased by 13% after 6 weeks of repeated restraint stress (Pham et al., 2003). Since plasma GCs return to basal levels by the third week of repeated restraint (Magariños and McEwen, 1995a), the continued and cumulative effect of stress on neurogenesis more likely results from the effects of EAAs. It is likely that the decrease observed in neurogenesis in these studies accounts for at least some of the reduction in total cell numbers. However, that longer intervals of stress result in the hippocampal cell death may also account for these observed decreases (Uno et al., 1989).

2.5. Clinical relevance

The most compelling similarities between repeated stress in animals and human clinical data are hipocampal atrophy and metabolic abnormalities. This was initially demonstrated in Cushing's disease, characterized by GC hypersecretion, where substantital hippocampal volume loss is evident (Starkman et al., 1992). Hippocampal atrophy has also been shown to correlate with depression and is reversible with antidepressant treatment (Sheline, 1996, 2003). In addition, alterations in cerebral blood flow and metabolism are evident in the hippocampal formation of depressed patients (for review see Czeh et al., 2001; Drevets,

2000a,b), similar to changes observed after repeated stress (Czeh et al., 2001). Whether stress-induced alterations in dentate gyrus neurogenesis and dendritic atrophy in CA3 characterize the structural alterations that underlie depression remains to be shown. Nonetheless, it is promising that both the decrease in neurogenesis and dendritic atrophy the result from repeated stress may be prevented by antidepressant therapies (Czeh et al., 2001; Malberg and Duman, 2003; Watanabe et al., 1992b).

3. Medial prefrontal cortex

The medial prefrontal cortex (PFC) plays an important role in the integration of higher cognitive and emotionally relevant information (Bush et al., 2000). Similar to the hippocampus, the medial PFC provides an interface between limbic and cortical structures (Groenewegen and Uylings, 2000), and regulates stress-induced HPA activity (Diorio et al., 1993; Spencer et al., 2005). The available evidence suggests that repeated stress produces a phenotypically conserved pattern of structural changes in the medial PFC relative to its effects in CA3c pyramidal neurons. Three weeks of repeated restraint stress produces apical dendritic retraction in layer II/III pyramidal neurons in the rat anterior cingulate and prelimbic cortices (Cook and Wellman, 2004; Radley et al., 2004), and 3 weeks of daily GC administration also induced dendritic reorganization in these same regions of the medial PFC (Wellman, 2001). Similar to CA3, dendritic atrophy in medial PFC is reversible following a stress-free recovery period (Radley et al., 2005a). In addition to the known effects of GCs, the structural changes in the medial PFC may also result from the prolonged elevation of EAAs. Numerous studies have shown that repeated stress activates PFC glutamate neurotransmission (for review, see Moghaddam, 2002). Prolonged exposure of cortical neurons to glutamate may result in excitotoxic degeneration through the persistent activation of extracellular-regulated kinase (ERK; Stanciu et al., 2000). Abnormalities in ERK signaling are also associated with cytoskeletal destabilization and neuronal dysfunction (Runden et al., 1998; Stanciu et al., 2000; Vaillant et al., 2002). That phosphorylated ERK1/2 is expressed in high levels in distal dendrites pyramidal neurons in medial PFC following repeated footshock stress (Kuipers et al., 2003; Trentani et al., 2002), supports the possibility that this stress-induced dendritic remodeling is mediated through an ERK-dependent mechanism.

Additionally, prolonged stress affects excitatory synaptic input into the medial PFC. Repeated restraint stress (Radley et al., 2005b), and postweaning social isolation stress (Silva-Gomez et al., 2003) led to a reduction of dendritic spine density in the medial PFC. After 3 weeks of restraint stress, there was an overall 16% decrease in apical dendritic spine density, with terminal branches and large diameter branch segments revealing the largest spine loss (Radley et al., 2005b). In this same study, stressed animals also revealed a 20% decrease in total apical dendritic length, which suggests that prolonged stress may substantially impact the axospinous synaptic input into the medial PFC. Interestingly, these effects were limited to apical dendrites, which is similar to the previously described effects of stress on CA3 pyramidal neurons.

Dendritic spine morphology may also be altered by prolonged stress. Following 3 weeks of repeated stress, fewer long, thin spines and a greater number of short, stubby and

mushroom-shaped spines were evident (Radley, unpublished observations). In addition to providing a postsynaptic target, spines are responsible for the sequestration of calcium, because the spine neck prevents its exchange between the spine head and dendrite (Nimchinsky et al., 2002). This barrier to calcium exchange, along with the compartmentalization of molecules associated with the postsynaptic density and spine apparatus, is important for the regulation of synaptic transmission. Calcium sequestration by spines also may be neuroprotective, preventing excitotoxicity to the dendrite and neuron by restricting excessive influxes of calcium within the synaptic region (Segal, 1995), and may be important in preventing the neurotoxic effects that result from the stress-induced disruption in calcium homeostasis. Calcium influx has also been linked with BDNF expression via activation of a cyclic AMP response element binding (CREB) family protein (Tao et al., 1998), and phosphorylation of CREB regulates the transcription of genes important for synaptic plasticity (Nguyen and Woo, 2003). In this regard, phosphorylated CREB has been reported to be significantly reduced in medial PFC pyramidal neurons following repeated footshock stress (Kuipers et al., 2003). Thus, repeated stress may alter spine shape and induce spine loss, rendering these neurons more resistant to excitotoxicity from excessive calcium influx. Under this scenario, the excitotoxic effects of stress would be ameliorated at the cost of a functionally compromised PFC. For example, stress impairs PFC cognitive functions, such as working memory (Arnsten, 2000; Arnsten and Goldman-Rakic, 1998; Mizoguchi et al., 2000). Nonetheless, it remains to be shown whether these signaling molecules are the cause or consequence of stress-induced structural plasticity in the medial PFC.

Recently, numerous studies have demonstrated a relationship between functional changes in the PFC and depression (Botteron et al., 2002; Drevets, 2000a). PTSD is associated with impaired cerebral blood flow and volume reduction in the medial PFC (Rauch et al., 2003; Yamasue et al., 2003). Despite the similarities observed in PFC in depression and PTSD, it is interesting to note that cortisol levels seem to be dramatically reduced in PTSD patients. This suggests that PTSD patients may have an exaggerated HPA axis negative feedback, and increased sensitivity in response to stressors, whereas in depression the HPA response is generally attenuated (for review, see Newport and Nemeroff, 2000). This is perhaps surprising, given the relevance of animal models of stress to depression and PTSD, and their underlying similarities in brain plasticity relative to human depression and PTSD (Ottenweller et al., 1989; Willner, 1997). These differences underscore the importance in reconciling functional alterations with their respective circuitry, and how these circuits regulate the HPA axis.

4. Extended amygdala/bed nucleus of the stria terminalis

The amygdala is another region that undergoes structural plasticity in response to repeated stress. However, in contrast to the cortical regions, amygdala neurons undergo hypertrophy following repeated stress. After 10 days of immobilization stress, a paradigm that is similar to repeated restraint stress, pyramidal-like and stellate neurons of the basolateral nucleus of the amygdala (BLA) undergo increases in dendritic length and branching patterns (Vyas et al., 2002). Pyramidal-like neurons are very spiny and have a

branching pattern similar to pyramidal neurons, however, they do not exhibit any clear polarity or laminar organization (McDonald and Culberson, 1981). As such, their dendritic hypertrophy following repeated stress is not limited along the same lines as is the case for pyramidal neurons of CA3c and the medial PFC. Neurons also increase dendritic spine density (S. Chattarji, personal communication), which suggests that the total axospinous synaptic population is substantially increased in response to repeated stress. The structural changes in BLA following repeated stress are further distinguishable from hippocampus and medial PFC by their permanence, since even after a stress-free recovery period of 3 weeks, increased dendritic arborization still persists (Vyas et al., 2004). Interestingly, medium spiny stellate neurons in the central nucleus of the amygdala were not observed to undergo any morphologic alterations in response to repeated stress, whereas neurons in the bed nucleus of the stria terminalis underwent a hypertrophy reminiscent of BLA neurons (Vyas et al., 2003).

Stress-induced structural plasticity in the BLA may also be associated with an increase in anxiety-like behaviors. Fear conditioning, a form of amygdala-dependent Pavlovian learning, is enhanced following 3 weeks of repeated restraint stress (Conrad et al., 1999). Open-field exploration (Conrad et al., 1999), and elevated plus maze performance (Vyas et al., 2004), two measures of anxiety-like behavior in rodents, were impaired following repeated stress. Finally, the latter study verified that neither dendritic hypertrophy in the BLA nor the enhancement in anxiety were abated following a stress free recovery period (Vyas et al., 2004). The amygdala is also critical in the development of fear-potentiated startle and other forms of fear learning which are similar to the hyperarousal phenomenon observed in PTSD (Davis et al., 1993; LeDoux, 2000). In this regard, combat veterans with PTSD showed amygdala activation following exposure to combat sounds. In another fMRI study conducted in humans, fear conditioning was shown to involve the selective activation of the amygdala and related structures (LaBar et al., 1998). Collectively, these data implicate the stress-induced structural changes in the BLA with the enhancement of fear and anxiety, and more generally, might play a role in the re-experiencing of traumatic memories and the hyperarousal symptoms in PTSD.

Several important questions remain with regard to the exclusivity of the BLA in stress-related fear and anxiety. The first is that the BLA, unlike hippocampus and medial PFC, is not directly activated by stressful and anxiety-like events (Campeau et al., 1997; Cullinan et al., 1995; Dayas et al., 2001; Li and Sawchenko, 1998; Sullivan et al., 2003). The BLA does not share any direct connections with the paraventricular nucleus of the hypothalamus (PVH), the key structure that induces HPA activity and GC release during the stress response (Antoni, 1986; Sawchenko and Swanson, 1989). Finally, the medial PFC is extensively interconnected with the amygdala (Krettek and Price, 1977; McDonald, 1987; McDonald et al., 1996; Petrovich et al., 1996), and certain aspects of fear learning, such as the extinction of fear conditioning, seem to be contingent on medial PFC as well as amygdala (Morgan and LeDoux, 1995; Quirk et al., 2003).

At present, it is unresolved whether the stress-induced enhancement of fear and anxiety is mediated exclusively through structural plasticity in the amygdala or medial PFC. It may be that a combination of changes throughout this circuit are important in generating the stress-induced changes in emotionality. Structural changes in the BLA may be involved in encoding the salience and behavioral output derived from emotionally significant events, as

it may stem from certain types of stress (especially laboratory-induced). The medial PFC may play a regulatory role in stress-induced fear and anxiety-like behaviors through inhibitory effects on amygdala processing and output. Indeed, extensive evidence supports the notion that the BLA is a site of plasticity for fear conditioning (Blair et al., 2001; LeDoux, 2000), and the BLA is extensively connected with the central nucleus of the amygdala (Pitkanen et al., 1995, 1997). In turn, the central nucleus of the amygdala does have direct and indirect projections to the PVH (Gray et al., 1989; Prewitt and Herman, 1998; van der Kooy et al., 1984), thereby providing the most likely route for any BLA-dependent effects on stress-induced HPA output. Clinically relevant data also support the notion that the medial PFC regulates amygdala-dependent emotional behaviors. In a recent human fMRI study, the ventromedial PFC was shown to be selectively activated during the extinction fear learning (Phelps et al., 2004). Moreover, amygdala activation occurred reciprocally with decreases in PFC activity in a positron emission tomography study in PTSD patients during the recollection of traumatic events (Shin et al., 2004).

5. Relevance to aging

There is a fairly large literature dealing with the impact of chronic or prolonged stress on the organism's ability to age successfully, (for reviews, see McEwen, 2002; Sapolsky et al., 1986), with one conclusion being that the neuronal damage that accumulates from chronic stress throughout life leaves the organism at a disadvantage to deal with the age-associated decrease in neuronal function and viability. The neurobiological data reveal some cell populations where such interactive effects might play out, but the overlap between neurons vulnerable to stress and those vulnerable to aging is incomplete, and there are few data available that experimentally combine stress and aging effects. For example, both stress and aging decrease neurogenesis in the dentate gyrus (Cameron and McKay, 1999; Gould et al., 1997; Pham et al., 2003), thus prolonged inhibition of neurogenesis throughout life due to stress that is then impacted further by aging could leave the dentate gyrus and associated circuits highly vulnerable. In the case of aging, the perforant path input from entorhinal cortex to the dentate gyrus is highly vulnerable (Morrison and Hof, 1997; Smith et al., 2000), such that stress could leave the granule cell targets with a heightened vulnerability to aging. CA3 pyramidal cells display dendritic atrophy and in extreme cases death in response to chronic stress, which would exacerbate a compromised mossy fiber projection to CA3. Similarly, CA1 is vulnerable to aging (Barnes et al., 2000; Morrison and Hof, 1997), which would be exacerbated by a stress-induced compromised projection to CA1 from CA3. Thus, while the cellular targets of stress and aging are not completely overlapping, the combined effects would lead to the entire trisynaptic loop being damaged far more extensively than either influence in isolation.

A similar scenario is likely in the medial PFC, though the data are far less well-developed. Pyramidal neurons in medial PFC of rat are vulnerable to stress in that they lose a considerable percentage of their excitatory axospinous inputs (Radley et al., 2004, 2005b). Non-human primate studies show a similar loss of spines with aging in the prefrontal cortex. Behavioral studies of non-human primates have shown that both age (Arnsten, 1999) and stress (Arnsten, 2000) compromise prefrontal function, with each

impairment involving the catecholamine innervation and their receptors in prefrontal cortex. These shared catecholamine mechanisms provide an opportunity for augmentation of age-induced cognitive decline by stress.

Although while data are still missing from primate models, if one looks at the emerging data across species, both stress and aging lead to a loss of spines in frontal and/or medial association areas, which would decrease axospinous synapse density and NMDA receptor-mediated transmission in prefrontal cortex. The functional impact of such a change on prefrontal functions such as learning, planning, working memory, executive function and attentional processing are hard to predict without knowing the extent of synaptic compromise and likely would only become manifest as a threshold of synapse loss was approached. The aging literature has made clear that such synaptic compromise can impact cortical function, even in the absence of any neuronal death (Hof and Morrison, 2004). Thus, the interactive effects of stress and aging would likely lead to synaptic compromise that is more extensive than either alone and that would likely reach a threshold for functional decline more readily, and perhaps at an earlier age than the effects of aging alone. Endocrine senescence regarding sex steroids such as estrogen would likely contribute to the same vulnerability, since in the absence of estrogen hippocampal spine loss occurs in female rats and monkeys as well as in monkey prefrontal cortex (Woolley et al., 1990a; Hao et al., 2003; Tang et al., 2004). Interestingly, an interaction between vulnerability to aging and estrogen loss has already been demonstrated in female rats, in that the estrogen-induced spine increase seen in CA1 of young female rats does not occur in response to estrogen in aged rats (Adams et al., 2001). Thus, there may be multiple interactions between sex steroids, stress steroids and aging that lead to heightened vulnerability of certain hippocampal and neocortical circuits when the system is subject to combined effects. The combined effects could lead to fairly dramatic synaptic compromise and associated functional loss, even in the absence of neuron death.

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