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Stress-Induced Deficits in Cognition and Emotionality: A Role for Glutamate

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Abstract

Stress is associated with a number of neuropsychiatric disorders, many of which are characterized by altered cognition and emotionality. Rodent models of stress have shown parallel behavioral changes such as impaired working memory, cognitive flexibility and fear extinction. This coincides with morphological changes to pyramidal neurons in the prefrontal cortex, hippocampus and amygdala, key cortical regions mediating these behaviors. Increasing evidence suggests that alteration in the function of the glutamatergic system may contribute to the pathology seen in neuropsychiatric disorders. Stress can alter glutamate transmission in the prefrontal cortex, hippocampus and amygdala and altered glutamate transmission has been linked to neuronal morphological changes. More recently, genetic manipulations in rodent models have allowed for subunit-specific analysis of the role of AMPA and NMDA receptors as well as glutamate transporters in behaviors shown to be altered by stress. Together these data point to a role for glutamate in mediating the cognitive and emotional changes observed in neuropsychiatric disorders. Furthering our understanding of how stress affects glutamate receptors and related signaling pathways will ultimately contribute to the development of improved therapeutics for individuals suffering from neuropsychiatric disorders.

Keywords

Glutamate; Stress; Emotionality; Cognition

1 Introduction

Stress is associated with a number of neuropsychiatric disorders either as a trigger, as with post-traumatic stress disorder (PTSD), or a risk factor, as with drug addiction or depression. Thus understanding the neurobiological consequences of stress is critical to treating these diseases. The first part of this chapter focuses on behavioral changes in animal models of stress and structural changes in key cortical regions mediating these behaviors. The second part focuses on the role of the glutamatergic system in mediating these changes and, through

genetic approaches, some of the advances made in our understanding of the molecular underpinning of stress and mental disorders.

2 Stress-Induced Executive Dysfunction in Humans and Rodents

Stress is a known risk factor of a number of neuropsychiatric disorders such as depression, PTSD and addiction (Hammen 2005; Lupien et al. 2009; Schneiderman et al. 2005; Sinha 2008). Stress can be defined as the expense or “allostatic load” on the organism’s homeostatic regulating system (McEwen 2000a). When faced with a stressor, the hypothalamic-pituitary-adrenal (HPA) axis is activated, resulting in the release of corticosteroids (de Kloet et al. 2005; Joels et al. 2007; McEwen 2000b). Though short bouts of stress can be tolerated or even be beneficial, prolonged exposure to stress can be detrimental (McEwen 2000a). Early life stress, such as an unstable childhood, is a strong predictor for the development of depression or addictive behavior in adulthood (Lupien et al. 2009). A stressful life event, a death in the family or chronic stress such as poverty is strongly linked with the development of PTSD, depression and alcoholism (Hammen 2005; Schneiderman et al. 2005; Sinha 2008).

Characteristic of these stress-related neuropsychiatric disorders are deficits in emotional regulation and cognition (Ferreri et al. 2011). Patients with panic disorder or PTSD are unable to normally regulate their emotions. These individuals express greater aversive feelings toward negative stimuli, find themselves preoccupied with worry and are impaired in their ability to suppress feelings of fear (Blecher et al. 2007; Michael et al. 2007). Individuals with attention deficit hyperactivity disorder (ADHD), depression or schizophrenia have deficits in certain learning and memory functions such as spatial working memory and cognitive flexibility (McLean et al. 2004; Murphy et al. 2003; Murray et al. 2008; Rogers et al. 2004; Waltz and Gold 2007). Using various stress paradigms, animal models have begun to show evidence for a direct link between stress and emotional or cognitive dysfunction.

In rodents, exposure to stress can result in increased anxiety- and depression-related behaviors (Sterner and Kalynchuk 2010). Adult rodents that experienced maternal separation as pups, a model of early life stress, have heightened corticosterone secretion following stress and show greater anxiety in the elevated plus-maze (e.g. Eiland and McEwen 2012; Holmes et al. 2005; Huot et al. 2001). Rodents exposed to chronic unpredictable stress (CUS) or repeated restraint stress, or simply injected with corticosterone, show elevated anxiety- like behaviors in the light/dark exploration and the elevated plus-maze test, and a heightened startle response relative to non-stressed controls (e.g. Mozhui et al. 2010; Pego et al. 2008). Cross-strain comparisons indicate the effect of stress is more pronounced in mouse strains with greater trait anxiety-like behavior, suggesting genetic background influences stress susceptibility (Mizoguchi et al. 2000). In addition to heightened anxiety, stress can evoke a behavioral profile reminiscent of depression. Rodents exposed to a stressor or those that received corticosterone orally or systemically show reduced social interaction and increased behavioral despair (e.g. Berton et al. 2006; Gourley et al. 2008; Shirayama et al. 2002; Wood et al. 2008). History of maternal separation or oral

corticosterone delivery can decrease sucrose consumption or responding in an appetitive progressive ratio test, measures of anhedonia (Gourley et al. 2009, 2008; Huot et al. 2001).

Also sensitive to stress are fear conditioning and extinction, measures of emotional learning and regulation (Rodrigues et al. 2009). Stress prior to conditioning has a potentiating effect on fear learning resulting in greater freezing during fear conditioning and post-conditioning fear recall tests (Rau et al. 2005; Sandi et al. 2001; Wood et al. 2008; Yamamoto et al. 2009). A series of experiments examining the effect of footshock stress prior to fear conditioning found that stressed rats showed enhanced fear recall when tested the following day (Rau et al. 2005). Using variants of this basic design, fear generalization and reinstatement were ruled out as alternate explanations for the increase in fear. Rather it appears that stress strengthens the fear memory, which may explain the impairing effects of stress on fear extinction, the learned suppression and the fear response (Corcoran and Quirk 2007; Quirk and Mueller 2008). Rats exposed to restraint stress or given oral corticosterone fail to extinguish the fear response, retaining a greater level of freezing after extinction training as compared to non-stressed subjects (Baran et al. 2009; Gourley et al. 2009; Miracle et al. 2006). In mice, a mere three days of 10 min forced swim stress was sufficient to impair fear extinction (Izquierdo et al. 2006). Stress does not have to immediately precede fear conditioning to affect learning. Rat pups exposed to five days of footshock stress and then tested on fear conditioning as adults fail to extinguish the fear response showing that stress can have long-lasting repercussions on cognition (Judo et al. 2010).

The effects of stress are not limited to cognitive processes associated with emotionality (Arnsten 2009; Holmes and Wellman 2009; Sterner and Kalynchuk 2010). Working memory, the ability to transiently store, recall and utilize recently learned information is vulnerable to stress. Mice exposed to four weeks of cold water submersion are impaired in a delayed alternation T-maze task (Mizoguchi et al. 2000). In rats, four weeks or merely six days of CUS result in impaired spatial working memory in the Morris water maze (MWM) (Cerqueira et al. 2005). This deficit is replicated by four weeks of daily injections of dexamethasone, an agonist of the glucocorticoid receptor, one of the two main corticosterone receptors, suggesting that the effects of stress are mediated at least in part by glucocorticoid receptor activity (Cerqueira et al. 2005).

Spatial learning itself is disrupted by stress. Rats that experienced maternal separation were impaired in an object placement task which examines the ability to discriminate between objects placed in the same or a novel location (Eiland and McEwen 2012). A single session of restraint stress or a corticosterone injection resulted in mice having longer escape latencies in circular hole board maze (Schwabe et al. 2010). In the hidden platform version of the MWM, tail shock stressed rats had greater escape latencies than non-stressed rats (Kim et al. 2001). Predator stress, where the rodent is exposed to either the odor of or an actual predator, impairs spatial working memory in the radial arm version of the MWM (RAWM) (Diamond et al. 1999; Park et al. 2008). In the RAWM, up to six swim paths are available from a center start point, one of which leads to the escape platform. An effect of stress was not present when just four arms were available. However, increasing the difficulty of the task by presenting six arms reveals an effect of stress, suggesting that observable effects of stress may be dependent on task demands (Diamond et al. 1999). Pretreatment

with the antidepressants ago-melatine or tianeptine can rescue this effect (Campbell et al. 2008; Conboy et al. 2009).

Stress also interferes with cognitive flexibility, the ability to adjust previously learned behavior in response to changing task demands. Rats subjected to either four weeks of CUS or dexamethasone injections or six just days of CUS were impaired on a spatial reversal variant of the MWM, where the escape platform is switched to the quadrant opposite from where it was located during training (Cerqueira et al. 2007; Cerqueira et al. 2005). Two weeks of CUS impaired reversal and extra-dimension set shifting in a texture-odor attention set-shifting task (Bondi et al. 2008). In this rodent adaptation of human cognitive flexibility tasks, the rodent learns to discriminate between digging textures or odors to locate a hidden reward. This stress-induced set-shifting impairment is robust, having been replicated with a number of different stress protocols (Bondi et al. 2008; Lapiz-Bluhm et al. 2009; Liston et al. 2006) and has been shown to be rescued with the antidepressants desipramine and citalopram (Bondi et al. 2008; Lapiz-Bluhm et al. 2009).

From the subset of work highlighted here, there is strong evidence to support the link between stress exposure and altered emotionality and cognitive function. Similar to what is seen in clinical populations, in rodent models stress increases anxiety- and depression-like behaviors, and facilitates the acquisition of fear while impairing control over fear expression. Stress also impairs certain cognitive functions such as spatial learning, working memory and cognitive flexibility. How stress may be affecting these changes via morphological and molecular alterations will be discussed in the following sections.

3 Structural Changes in Response to Stress

Key substrates mediating emotionality and cognition include the prefrontal cortex, hippocampus and amygdala. Changes in cortical volume have been recorded in these regions in human neuropsychiatric patients suggesting possible loci for the behavioral and cognitive pathologies (Sterner and Kalynchuk 2010; van Harmelen et al. 2010). These regions are anatomically interconnected, often working in concert to mediate emotional regulation and cognition (Thierry et al. 2000). Preclinical studies in rodents have not only shown parallel changes but have provided more precise information on morphological changes in these areas.

Loss of prefrontal cortex (PFC) function can impair working memory and cognitive flexibility as well as other higher-order cognitive functions (Chudasama and Robbins 2006; Dalley et al. 2004; Robbins 2007). In rodents, the prelimbic and infralimbic cortices are subregions of the PFC thought to mediate fear expression and fear extinction, respectively (Corcoran and Quirk 2007; Myers and Davis 2007; Quirk and Mueller 2008). Four weeks of CUS result in neuronal atrophy, specifically reduced volume, neuron number and apical dendritic length in layers I–III in both these regions (Cerqueira et al. 2005; Dias-Ferreira et al. 2009). This stress effect is replicated pharmacologically with four weeks of corticosterone or dexamethasone, a corticosterone-receptor agonist, injections (Cerqueira et al. 2005). In addition to neuronal atrophy, decreases in spine density and spine surface area have been observed in the medial PFC following exposure to three weeks of restraint stress

(Liston et al. 2006; Radley et al. 2004, 2006, 2008). Interestingly, while restraint stress reduced apical dendritic length in the medial PFC, there was a corresponding increase in the orbitofrontal cortex, suggesting that subregions of the PFC may respond differently to stress (Liston et al. 2006). Shorter stress exposures have highlighted the potential sensitivity of the PFC to stress. A reduced restraint stress paradigm, ten days of two-hour restraint stress, reduced apical dendritic length in rat infralimbic cortex (Shansky and Morrison 2009). Seven days of only ten-minute daily restraint stress was effective in reducing apical branch number and length in layer II/III of the cingulate cortex (Brown et al. 2005). Even more limited, one bout of ten-minute forced swim stress was sufficient to reduce apical dendritic length in layer II/III of the mouse infralimbic cortex though no change was seen in the prelimbic cortex (Izquierdo et al. 2006).

Also key in the fear learning circuitry are the hippocampus and amygdala (Maren and Quirk 2004). The hippocampus has a well-established role in learning and memory and is particularly important for spatial learning, as in the MWM or with contextual fear learning (Bird and Burgess 2008; Ji and Maren 2007; Maren and Holt 2000). Stress has a similar effect on morphology in the hippocampus as it does in the PFC (Joels et al. 2004; McEwen 2001). Five weeks of social conflict decreased cell proliferation and survival in the rat dentate gyrus, an effect rescued by concomitant fluoxetine treatment (Czeh et al. 2007). Rats exposed to either a brief (two days) or chronic (21 days) social stressor induced morphology changes, though changes were more robust following chronic stress (Kole et al. 2004). Four weeks of CUS or pharmacological stress by corticosterone or dexamethasone injections resulted in reduced CA3 and DG volume and decreased dendritic length of granule cells, CA3 and CA1 pyramidal cells (Cerqueira et al. 2007; Sousa et al. 2000). Shorter durations of stress, 21 days of restraint stress or ten days of CUS, also results in hippocampal dendritic retraction which was reversed when tianeptine was given in conjunction with stress (Vyas et al. 2002; Watanabe et al. 1992b).

In contrast to the PFC and hippocampus, stress induces neuronal hypertrophy in the amygdala, a region essential for the acquisition and consolidation of aversive memories (Maren and Quirk 2004; Pare et al. 2004; Roozendaal et al. 2009). While 21 days of restraint stress decreased hippocampal dendritic length, this same stressor increased dendritic length and branching in neurons of the basolateral amygdala (BLA) as well as the bed nucleus of stria terminalis (Vyas et al. 2002, 2003). This effect has been replicated with either CUS or corticosterone injections which lead to increases in dendritic length and spine density in the BLA and bed nucleus of stria terminalis (Pego et al. 2008). Stress-induced changes appear to be longer lasting in the amygdala than in the hippocampus or PFC. Following 21 days of recovery from stress, BLA pyramidal cells of stressed rats were still longer than controls, whereas CA3 hippocampal neurons were no different and overextension was seen in proximal dendritic arbors of IL neurons (Goldwater et al. 2009; Vyas et al. 2004).

As with behavior, stress results in different changes in neuronal structure in the PFC, hippocampus and amygdala. Generally, stress-induced dendritic retraction in the PFC and hippocampus but induced extension in the amygdala. This appears to align with the differing effects of stress on behavior, with impairments in largely PFC and hippocampus-associated behaviors and enhancements in amygdala-associated behaviors. However, it is unlikely that

structural changes alone are the cause of stress-induced behavioral changes. More likely stress results in a cascade of changes on a molecular level of which modification to structure is an observable consequence.

4 Molecular Mechanisms of Structural Changes: Focus on Glutamate

It is clear that exposure to stress can alter neuronal morphology in regions associated with the emotional and cognitive changes seen with psychiatric disorders. Stress can alter multiple molecular signaling cascades that could explain the observed structural changes (a subset of these are reviewed in Pittenger and Duman (2008)). Here, we focus on evidence for the role of the glutamatergic system in mediating stress-induced changes because of its known role in mechanisms of plasticity, cognition, and increasingly, emotional and psychiatric disorders.

Glutamate is the main excitatory neurotransmitter in the CNS and binds to multiple metabotropic receptors and three families of ionotropic receptors: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, kainate receptors and *N*-methyl-D-aspartate (NMDA) receptors. Activity-dependent alterations in glutamate transmission are a key mechanism of synaptic plasticity that in turn influences multiple downstream signaling pathways, including those activating neurotrophic factors involved in cell growth. Activation of synaptic NMDA receptors appears to be crucial for activity-dependent changes in synapses and even neuronal survival (Hardingham and Bading 2003). Changes in synaptic plasticity have been shown to influence spine morphology, as LTP-inducing protocols can lead to new dendritic spines (Engert and Bonhoeffer 1999; Matsuzaki et al. 2004). Conversely, elevated glutamate levels and excessive activation of NMDA receptors can lead to cell damage and even death in many neuropathological conditions, (Dirnagl et al. 1999; Lipton and Rosenberg 1994; Olney et al. 1986; Sapolsky 2000a, 2000b). The opposing effects of glutamate transmission most likely depend on the pattern of NMDA receptor activation and have been reviewed in (Hardingham and Bading 2003). Variations in the pattern of glutamate receptor activation could in part explain a shift in the activation of cell growth versus cell death pathways that influence the observed morphological changes.

Stress is known to lead to changes in glutamate transmission in the same regions showing stress-induced morphological changes. Various forms of stress as well as acute injections of corticosterone lead to a rapid and transient increase in extracellular glutamate in the hippocampus and PFC (Moghaddam 1993; Venero and Borrell 1999). Interference with glutamate signaling using glutamatergic receptor antagonists can attenuate the dendritic atrophy observed after chronic restraint stress. The anti-epileptic drug phenytoin is known to reduce excitatory amino acid release including glutamate and injections of phenytoin block stress-induced atrophy of the CA3 hippocampal neurons (Watanabe et al. 1992a). More specifically, blocking NMDA but not AMPA receptors attenuates CA3 dendritic atrophy suggesting that the NMDA receptor has a particular role in mediating the morphological changes seen with stress (Magarinos and McEwen 1995).

In the PFC, less is understood about how NMDA receptor antagonists alter stress-induced atrophy. However, lesions resulting in cholinergic deafferentation lead to dendritic

remodeling and increased spine density in the PFC, an effect shown to be dependent on NMDA receptors (Garrett et al. 2006). Interestingly, systemic administration of the NMDAR antagonist CPP during chronic restraint stress not only blocks dendritic atrophy in the mPFC, but actually induces dendritic hypertrophy in this region, an effect not observed in unstressed control rats (Martin and Wellman 2011). Most recently, the NMDA receptor antagonist ketamine was found to block the loss of synaptic proteins in the PFC after stress induced by the learned helplessness paradigm (Li et al. 2010). NMDA receptor antagonists not only block stress-induced atrophy but have also been found to increase spine density in medial PFC pyramidal cells 24 h after administration in the absence of stress (Li et al. 2010). While additional data directly studying the role of glutamate transmission in each region showing stress-induced structural changes is sparse, much is known about the effects of glutamate transmission in cognitive and emotional behavioral paradigms mediated by these regions.

5 Glutamate in Rodent Behavioral Correlates of Emotion and Cognition

The NMDA receptors are heteromeric assemblies composed of an obligatory NR1 subunit and one or more NR2 (NR2A-NR2D) (Rosenmund et al. 1998) or NR3 subunits (Ciabarra et al. 1995). *Postmortem* studies of the brains of depressed patients have found reduced NR1 mRNA in the hippocampus (Law and Deakin 2001) and decreased NR2A and NR2B protein levels in the PFC (Feyissa et al. 2009). In rodent models, a single exposure to forced swim stress leads to increases in surface (but not total) NR1, NR2A, NR2B and AMPA receptor subunits in the PFC (Yuen et al. 2009). As mentioned earlier, NMDA, but not AMPA receptor antagonism, attenuates dendritic atrophy resulting from chronic stress or glucocorticoid injections (Magarinos and McEwen 1995). Similarly, NMDA receptor antagonists block stress-induced alterations in long-term potentiation and long-term depression in hippocampal CA1 neurons (Kim et al. 1996). Together, NMDA receptors appear to be modulated by stress and necessary for some stress-induced morphological changes. Further evidence has demonstrated that NMDA receptors are also involved in the cognitive and emotion-related paradigms affected by stress.

Genetic manipulations in rodent models have allowed for a subunit-specific analysis of the NMDA receptor's role in behaviors shown to be altered by stress. While there are no NR2A subunit-specific antagonists, a mutant mouse line lacking this subunit has been developed and displays decreased anxiety- and depression-related behaviors (Boyce-Rustay and Holmes 2006). While wild-type mice normally show restraint stress-induced changes in the light/dark exploration task, this effect was blocked or even reversed in NR2A knockout mice, highlighting the importance of NR2A in behavioral changes consequential to stress (Mozhui et al. 2010). Supporting the importance of NMDA receptors in morphology, these knockout mice also demonstrated decreased spine density on pyramidal neurons of the BLA (Mozhui et al. 2010). As mentioned earlier, stress-induced increases in anxiety-like behavior are often paralleled by increases in BLA spine density. The loss of spine density in the BLA NR2A KO mice could in part explain their reduced anxiety-like behavior. Future studies could evaluate if the increase of spines after stress is also blocked in these mice, and if local NR2A knockdown in the BLA still blocks the stress-induced behavioral changes in the light/dark exploration task.

Prenatal deletion of the NR1 or NR2B subunit is lethal. However, several genetic models with reduced NR1 or NR2B levels have been successfully used. With the development of a floxed NR1 mouse line, it has been possible to study the effects of NR1 deletion in specific regions of the brain. One such model limited NR1 deletion to hippocampal CA1 pyramidal cells and found a deficit in trace, but not delay, fear conditioning and impaired spatial (MWM, T-maze), but not non-spatial memory (Huerta et al. 2000; Tonegawa et al. 1996; Tsien et al. 1996a, 1996b). Mice with a deletion of NR1 restricted to hippocampal CA3 pyramidal cells are impaired in retention of one-trial context discrimination at three h, but not 24 h after avoidance training (Cravens et al. 2006). Similar results were found in mice with the NR2B subunit deleted in CA1 and cortical pyramidal cells (Brigman et al. 2010). Mice lacking the NR2B subunit on pyramidal cells of the cortex and CA1 also showed multiple learning and memory deficits, including in the MWM, T-maze and trace, but not delay fear conditioning. These same mice additionally showed decreased spine density in pyramidal cells of the CA1. While they demonstrated normal depressive-like behavior in the six-minute forced swim test, these mice developed less depressive-like behavior over the course of a novel 10 day swim stress paradigm, indicating a phenotype specific to repeated stress (Kiselycznyk et al. 2011).

Ketamine and other NMDA receptor antagonists have acute behavioral effects in humans and rodent models that appear to resemble many of the symptoms of schizophrenia. This has in part led to the NMDA receptor hypofunction hypothesis, suggesting that NMDA receptor hypofunction on inhibitory neurons in the PFC is responsible for excessive neuronal excitability in this region thus disrupting executive functions. Mice that are viable with only 5–10% of the normal NR1 levels have been used to test the relationship between NR1 subunits and schizophrenia. These mice have decreased prepulse inhibition, sociability and anxiety-like behavior but increased locomotion, a constellation of behaviors similar to those seen in patients (Halene et al. 2009). A recent study found that deletion of NR1 on interneurons during early postnatal development resulted in schizophrenia-like phenotypes in mice. This included novelty-induced hyperlocomotion, impaired nest building and mating, increased anxiety- and anhedonia-like behaviors, behaviors that were exacerbated by social isolation stress (Belforte et al. 2010). The schizophrenia-like behavior was selective to mice with early postnatal deletion (approximately equivalent to late gestation to age 2 in humans) and was not observed in mice with post-adolescence NR1 deletion. This is consistent with hypotheses proposing a developmental cause in schizophrenia, with stress exacerbating deficits in cortical development.

An additional post-synaptic receptor of glutamate, the AMPA receptor, is also essential for synaptic plasticity. The AMPA receptor is a heteromeric receptor composed of a combination of four subunits: GluR1–GluR4. Various anti-depressants with diverse structures have been found to alter the phosphorylation of GluR1 receptors, therefore altering glutamatergic synaptic transmission (Svenningsson et al. 2007). In schizophrenia, studies have found decreased GluR1 expression in the hippocampus, striatum and PFC that is reversed by treatment with neuroleptics (Sokolov 1998). Mice lacking the GluR1 subunit display novelty-induced hyperlocomotion that is reversed by the antipsychotic haloperidol (Wiedholz et al. 2008). These mice also demonstrated altered social behavior and deficits in prepulse inhibition and impairments in a spatial reversal learning task. In additional studies,

GluR1 KO mice were found to demonstrate behaviors indicative of mania-related phenotypes as they also showed stress-induced hyperactivity, reduced immobility in the forced swim test, and alterations in approach/avoid conflict tests. Treatment with lithium reversed the KO's anxiety-like phenotype and partially reversed their stress-induced hyperlocomotion (Fitzgerald et al. 2010). However, deletion of GluR1 did not affect the stress-induced changes in light/dark exploration, as was observed in NR2A knockout mice (Mozhui et al. 2010). As mentioned earlier, AMPA receptor antagonists alone do not block stress-induced changes in morphology as with the NMDA antagonists (Magarinos and McEwen 1995). While this appears contradictory, it is likely that activation of these two types of glutamatergic receptors activate a different collection of downstream signaling pathways (such as calcium-activated pathways), and there are some pathways specific to NMDA receptors that explain stress-induced changes.

The amount of glutamate available to NMDA and AMPA receptors is partially regulated by reuptake with glutamate transporters (EAAT1-5 in humans) located both on neurons and neighboring glial cells (Anderson and Swanson 2000). Postmortem studies of schizophrenic patients have found elevated expression of mRNA but decreased protein expression of EAAT1 in the dorsolateral PFC and anterior cingulate cortex (Bauer et al. 2008) and increased thalamic EAAT1 and EAAT2 (Smith et al. 2001). Similarly, variants of the EAAT1 gene (SLC1A3) have been linked with schizophrenia (Walsh et al. 2008). Conversely, microarrays of postmortem samples of depressed patients found a decrease of EAAT1 and EAAT2 mRNA in the frontal cortex (Choudary et al. 2005) and decreases in EAAT3 and EAAT4 mRNA in the striatum (McCullumsmith and Meador-Woodruff 2002). The antidepressant riluzole has been found to enhance glutamate transporter activity (Fumagalli et al. 2008), and the mood stabilizer valproate has been shown to increase EAAT1 but decrease EAAT2 levels in the hippocampus (Hassel et al. 2001; Ueda and Willmore 2000).

Human EAAT1-4 corresponds to the rodent GLAST, GLT-1, EAAC1 and EAAT4, respectively, (Arriza et al. 1994), with GLT-1 (human EAAT2) responsible for the majority of extracellular glutamate regulation (Arriza et al. 1994; Shigeri et al. 2004; Zarate et al. 2002). Complete GLT-1 knockout results in hippocampal damage and spontaneous epileptic seizures and is often lethal. To avoid these effects, antisense knockdown of GLAST, GLT-1 and EAAC1 have been used and revealed that GLAST and GLT-1 knockdown cause an elevation in extracellular glutamate, neurodegeneration and paralysis while EAAC1 knockdown does not elevate extracellular glutamate and produces only mild neurotoxicity (Rao et al. 2001a, 2001b; Rothstein et al. 1996). GLAST knockout mice are viable and have a phenotype resembling the positive and negative symptoms of schizophrenia, including increased novelty-induced hyperlocomotion that is reversed by the antipsychotic haloperidol, abnormal sociability, reduced acoustic startle response and impaired visual discrimination (Karlsson et al. 2008, 2009). It is not known, however, how a deficit in glutamate transporters affects depression-related behaviors or response to stress. Future studies could investigate the role of glutamate transporters in buffering pyramidal cells to the increased glutamate release during stress.

Because of their role in synaptic plasticity, these glutamatergic receptors have been extensively studied in animal models of cognition. Animals lacking these receptors often show deficits in cognitive-related tasks that overlap those seen in models of neuropsychiatric disorders. Their role in emotional-related behaviors and stress response, however, has not been systematically studied and still remains untested in many of these mutant models. There have been examples of baseline alterations in emotionality (as with the NR2A mice) and schizophrenia-related behaviors, suggesting that dysfunction of the glutamatergic system alone can result in pathology. A more nuanced approach, however, is seen in those studies analyzing changes in the normal stress response in animals with alterations in the glutamatergic system. As mentioned earlier, stress can act as a predisposing factor for many neuropsychiatric illnesses and it is important to see how stress can lead to a disruption in cognition and emotional regulation. Here, we briefly discussed the dysregulated stress response in NMDA, but not AMPA, receptor-related manipulations. In the future, it will be interesting to see studies of stress response applied to more models of glutamatergic function.

6 Conclusions

Stressful experiences are often reported in the life histories of neuropsychiatric patients and it is well established that stress can be a risk factor for the development of neuropsychiatric disorders. Typical to this clinical population are deficits in emotional regulation and cognitive function. Preclinical data showing parallel behavioral and structural changes in the PFC, hippocampus and amygdala following stress support a direct role for stress modifying these emotional and cognitive functions. Multiple molecular mechanisms could explain these stress evoked changes. Here, we have shown how the glutamate system can be linked to the structural and ultimately behavioral changes seen in neuropsychiatric disorders.

Glutamatergic transmission is integral to multiple levels of neural function. At one level, alterations in glutamate transmission can influence downstream signaling pathways involved in cell death or cell growth. Changes in glutamate transmission during stress could lead to differential activation of these signaling pathways, possibly explaining the morphological changes observed. One such signaling pathway of interest involves brain-derived neurotrophic factor (BDNF). In its mature form, BDNF promotes neuronal growth and survival and its release is dependent on glutamatergic synaptic activity (Carvalho et al. 2008; Lu 2003). BDNF itself also influences glutamatergic transmission, altering the release of glutamate, glutamate receptor composition and synaptic plasticity (Carvalho et al. 2008; Kuczewski et al. 2009; Lu 2003). BDNF expression is reduced with stress, an effect reversed by antidepressants, and has itself been shown to be reduced in depression-like behaviors (Gourley et al. 2009; Nibuya et al. 1995; Shirayama et al. 2002; Siuciak et al. 1997). Thus far few studies have collectively examined the effects of stress, morphology and behavior in relation to BDNF. Preliminary work has shown that genetically induced BDNF overexpression can prevent stress-induced hippocampal dendritic retraction and reduced learned helplessness, making BDNF a particularly relevant molecule in the study of stress and cognition (Govindarajan et al. 2006). The contributions of BDNF and other downstream signaling pathways will be important targets elucidating the mechanisms of stress-induced morphological changes.

In addition, many studies have used genetic techniques to understand the contribution of glutamate receptors in emotional and cognitive behavioral tasks. These studies have shown that changes in activity and composition of glutamate receptors can lead to changes in emotional regulation and cognitive deficits. However, few studies have used these models to directly investigate the role of receptors in the context of stress. These receptors are integrally involved in synaptic plasticity mechanisms, thus examining the effects of stress on these receptors could help explain why stress is a precursor to the development of neuropsychiatric disorders.

Furthering our understanding of how stress affects glutamate receptors and alters downstream signaling pathways will ultimately contribute to the development of improved therapeutics for individuals suffering from neuropsychiatric disorders.

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