FOCUS: PSYCHIATRY AND PSYCHOLOGY

A Neuroplasticity Hypothesis of Chronic Stress in the Basolateral Amygdala

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Chronic stress plays a role in the etiology of several affective and anxiety-related disorders. Despite this, its mechanistic effects on the brain are still unclear. Of particular interest is the effect of chronic stress on the amygdala, which plays a key role in the regulation of emotional responses and memory consolidation. This review proposes a neuroplasticity model for the effects of chronic stress in this region, emphasizing the roles of glutamate and BDNF signaling. This model provides a review of recent discoveries of the effects of chronic stress in the amygdala and reveals pathways for future research.

INTRODUCTION

Deep in the medial temporal lobes of the brain, two small, almond-shaped nuclei called the amygdalae play critical roles in the establishment of the human emotional experience [1,2] and memory consolidation [3,4,5]. When rodents [6,7] or humans [8,9,10] are exposed to chronic stress, defined as a prolonged period of exposure to

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potentially threatening or emotionally challenging stimuli, changes in behavior and morphology of the amygdala occur.

Chronic stress and its effects on the amygdala both contribute to the formation of affective and anxiety disorders [11], which represent some of the foremost causes of disability worldwide [12]. Furthermore, studies have demonstrated that amygdalar activity is increased in patients suffering from anxiety and affective disorders [13,14]. While existing treatments benefit a large percentage of the population, there is still a significant need to develop better drug and behavioral therapies [15]. Due to the relationship between chronic stress, amygdalar activity, and the formation of affective and anxiety disorders, it is important to characterize the effects of chronic stress in this region.

This paper will examine the biological basis for chronic-stress induced changes in the amygdala and the hippocampus (HC†), as well as illuminate potential targets for future studies. In particular, the basolateral amygdala (BLA), which is critical in anxiety and memory consolidation [1,2,4,5], will be explored. The activity of the HC, a key structure for memory processes, also changes following a period of chronic stress [6,16] and will serve as a point of comparison for the effects on chronic stress in the brain.

These observations will be used to form a "neuroplasticity hypothesis" of the effects of chronic stress in the amygdala. It will be shown that stress increases glutamatergic signaling in the BLA, resulting in enhanced brain-deprived neurotrophic factor (BDNF) expression and dendritic outgrowth. In contrast, chronic stress-induced increases in glutamatergic signaling in the hippocampus are accompanied by decreased BDNF signaling. These changes contribute to changes in BLA and HC morphology and activity, which then result in an enhanced stress response. By contributing to the understanding of chronic stress in the BLA, this hypothesis should aid in the search for better treatments of affective and anxiety disorders.

CHRONIC STRESS ALTERS SYNAPTIC PLASTICITY AND AMYGDALA-DEPENDENT LEARNING

When vertebrates are exposed to chronic stress for prolonged periods of time, a dichotomy appears in the morphology of different brain regions. In the rodent amygdala, chronic restraint stress (CRS) increases dendritic arborization in spiny pyramidal and stellate neurons [6]. In contrast, chronic stress leads to a loss of spines and dendritic branch points in the HC [6,16]. While the morphological changes in the hippocampus CA3 area are reversed within 21 days of the end of chronic stress [7], the changes in the BLA persist during this time.

These changes are important because the hippocampus and amygdala play key roles in regulating the hypothalamic-pituitary-adrenal (HPA) axis [17]. The HPA axis controls the stress response through interactions between the hypothalamus, pituitary gland, and the adrenal gland. These responses regulate body processes such as digestion, the immune system, and mood. Inhibitory inputs from the amygdala and excitatory connections from the hippocampus project to inhibitory neurons in the paraventricular nucleus (PVN) and hypothalamus [18,19]. This implies that increasing input from the amygdala or decreasing input from the hippocampus (as occurs during chronic stress) enhances the net activity of the HPA axis. This dysregulation of the HPA axis is responsible for many of the negative effects of chronic stress on brain functioning and behavior [20,21].

In addition to changes in the HPA axis, chronic stress enhances the consolidation of memories in auditory fear conditioning [1,7], a task that depends on amygdala activity. This is supported by evidence that damage or inactivation of the amygdala impairs fear learning [3,4,5]. This result opposes that for hippocampal-dependent learning, where chronic stress impairs contextual memory in rats [22,23] and declarative memory in humans [24,25,26]. Chronic stress additionally leads to increased anxiety in rats, which has been as-

sociated with activity of the basolateral amygdala [1,2].

CHRONIC STRESS ENHANCES GLUTAMATERGIC SIGNALING

Despite the fact that the morphology of the hippocampus and basolateral amygdala are regulated in opposite ways following chronic stress, glutamate transmission is enhanced in both regions [27,28,29]. Studies of the hippocampus reveal chronic stress or treatment with glucocorticoids up-regulates glutamate transporter expression hippocampal CA3 region glia [30,31]. Furthermore, antidepressant treatment minimizes the transmission of glutamate in the hippocampus [32]. In the BLA, studies have found that repeated activation of the corticotropin releasing factor (CRF) receptor occurs during periods of chronic stress and results in an increased N-methyl-D-aspartate (NMDA) glutamate receptor-mediated calcium influx [33].

The role of glutamate is complicated by its implication in the inhibition of dendritic growth cones in a Ca^{2+}-dependent manner [34,35]. Ca^{2+} influx through NMDA receptors inhibits the polymerization of the tubulin dimers responsible for microtubule and neurite elongation [36,37,38]. Ca^{2+} simultaneously triggers the local polymerization of actin that forms filopodial extensions of growth cones [39]. If Ca^{2+} is sustained at high levels, microtubules and microfilaments are depolymerized to trigger dendritic regression [39,40]. Thus, while the calcium activity from NMDA receptor activation can explain the dendritic atrophy of the hippocampus, some other mechanism must explain the dendritic hypertrophy of the basolateral amygdala.

This does not mean that glutamate does not play a critical role in the morphological changes that occur in the basolateral amygdala. NMDA receptor antagonists in the amygdala reduce anxiety-like behavior [41], and mice with decreased expression of the NR2A subunit of the NMDA receptor have reduced pyramidal dendritic spines in the BLA [42]. The reasons for this ap-

parent discrepancy will be explored in the next section.

## THE ROLE OF NEUROTROPHIC FACTORS IN THE BLA

Calcium release in the cell has a multitude of effects, including triggering mitogen-activated protein kinases (MAPK) such as the extracellular signal-related kinases (ERK) 1 and 2 at the point of calcium entry [43,44], as well as activating protein kinase A (PKA) through the cAMP signaling pathway [45]. These kinases translocate to the nucleus, where they activate the protein cAMP response element-binding protein (CREB), which regulates the expression of proteins including BDNF [46]. Glutamate, through its action at NMDA and non-NMDA receptors, stimulates the expression of BDNF [47].

BDNF and other neurotrophic factors typically increase axonal and dendritic outgrowth [48,49]. It has been hypothesized that this action occurs in a Ca^{2+}-dependent manner through changes in local cytoskeletal dynamics, along with increases in cytoskeletal protein and cell adhesion molecule gene expression [35,50]. Growth factors, therefore, alter the effects of glutamate in the cell and inhibit glutamate-induced dendritic atrophy. BDNF is released from the postsynaptic terminal and binds to TrkB channels in a retrograde fashion on the presynaptic cell, activating intracellular signaling pathways including phospholipase C-γ (PLCγ) and ERK signaling [51,52,53].

BDNF also increases postsynaptic responses to glutamate by triggering NMDA receptor phosphorylation and the rapid delivery of NR2B-containing NMDA receptors to the membrane [54]. This is supported by studies showing inhibition of NMDA receptors containing NR2B results in the loss of BDNF enhancement of glutamatergic transmission in the hippocampus [55]. While glutamate enhances BDNF, it can also shut off CREB expression through the action of glutamate at extrasynaptic NMDA receptors [56]. Glutamate and neurotrophic factors therefore work together to control neurite outgrowth and synaptogenesis.

Figure 1. The effect of chronic stress on glutamate synapses and neurotransmission in the amygdala. (1) Repeated activation of the CRF receptor following chronic stress increases NMDA receptor-mediated calcium influx. (2) FAAH activity increases during chronic stress, thereby decreasing AEA levels and increasing the release of glutamate from the presynaptic terminal. (3) Through the activity of FAAH and other factors, glutamate release increases following chronic stress along with NMDAR activity. (4) Increased calcium influx activates intracellular pathways that in turn activate CREB, which results in an up-regulation of BDNF. (5) BDNF increases axonal and dendritic outgrowth in the amygdala, acting retrogradely to activate intracellular pathways and postsynaptically increasing NMDAR activity. Notably, in the hippocampus BDNF levels are decreased and dendritic atrophy occurs. (6) Norepinephrine release is increased following stress, and its binding to β1-adrenoceptors triggers the cAMP and PKA signaling pathways. These pathways, in turn, disrupt the constitutive cycling of SK channels from the membrane and enhance excitatory neurotransmission in the amygdala.
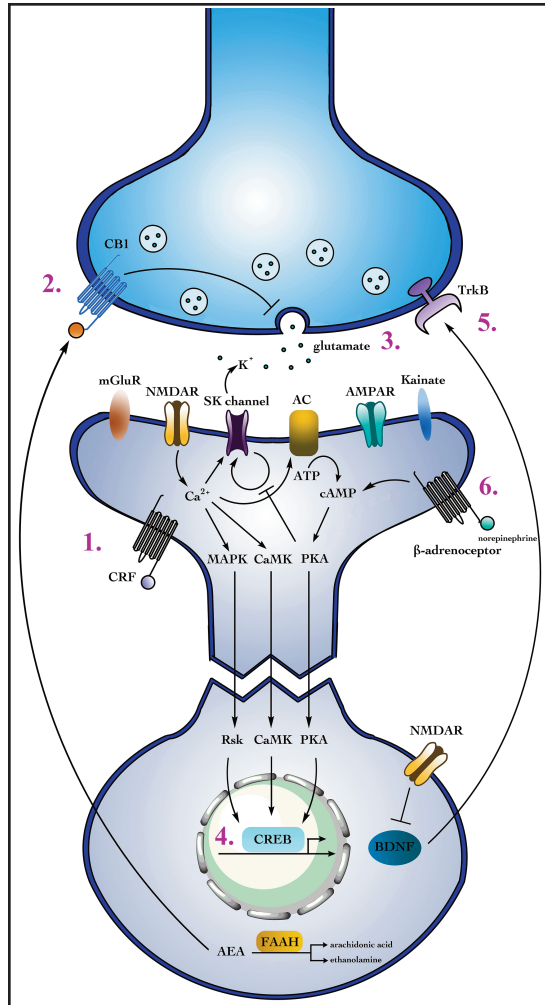
Chronic stress has been shown to significantly alter BDNF expression in vertebrates. In the basolateral amygdala, chronic stress triggers increased expression of BDNF, while in the hippocampus, BDNF levels are significantly decreased [57]. The duration of BDNF expression in each of these areas mimics the duration of morphological changes, with BDNF returning to baseline in 21 days in the hippocampus but not the amygdala [57]. Furthermore, BDNF heterozygous deletion mutant mice have less dendritic branching in the hippocampus [58]. In clinical populations, atrophy in the hippocampus is associated with a variety of affective and anxiety disorders [59,60,61].

Based on this data, I propose a neuroplasticity hypothesis of chronic stress in which stress leads to increases in gluta-matergic signaling in the amygdala, resulting in enhanced BDNF expression and dendritic outgrowth (Figure 1). In contrast, in the hippocampus, a signaling mechanism downstream from the glutamate and upstream of BDNF results in decreased BDNF signaling. This allows glutamate to inhibit microtubule and neurite elongation and trigger dendritic retraction [34,36,37,38,40]. These changes in morphology result in abnormal HPA axis signaling and an enhanced stress response.

This model would also suggest that drugs altering BDNF expression nonspecifically in the brain may be ineffective at treating pathologies caused by chronic stress because of the dichotomy between the hippocampus and amygdala. This is supported by recent studies showing transgenic overexpression of BDNF

in mice prevents the hippocampal atrophy caused by chronic stress but increases spinogenesis in the BLA [62]. There is, therefore, a need to develop drugs with regional specificity that have BDNF as a molecular target.

THE ROLE OF NOREPINEPHRINE AND SK CHANNELS DURING CHRONIC STRESS

Along with the morphological changes to the BLA, treatment with glucocorticoids increases the activity of principal glutamatergic neurons at least partially through the altered activity of small-conductance Ca^{2+}-activated K^+ channels (SK channels) [63,64]. The compound 1-EBIO, which increases SK channel activity, diminishes excitability of neurons in the lateral amygdala (LA) following chronic stress [63]. Similarly, overexpression of the type-2 SK channel (SK2) causes dendritic retraction in the BLA and reduces anxiety-like behavior [65].

The biological action of the SK channels has now been established. Activation of postsynaptic NMDA receptors results in the opening of SK channels, which are positioned in close proximity to NMDA receptors in the cell membrane [64]. These channels can be activated by release of intracellular Ca^{2+} stores through metabotropic glutamate receptors activity [64]. SK channels are stabilized by the actin cytoskeleton of the cell and constitutively removed from the membrane through a dynamin-dependent mechanism. The channels are then replaced through actin cytoskeleton-mediated transport [66].

Following a stressful stimuli, release of norepinephrine is increased in the basolateral amygdala [67]. Norepinephrine binds to β adrenoceptors within the basolateral amygdala, and β1 adrenoceptors trigger activation of the cAMP signaling pathway and PKA. PKA then alters the recycling of SK channels in the cell membrane, reducing the number of postsynaptic SK channels [66]. Furthermore, SK channels have been shown to regulate anxiety-like behavior and the secretion of corticosterone, a glucocorticoid involved in the stress response [65]. This

theory is supported by studies showing disruption of the actin cytoskeleton results in loss of SK channels and β adrenoceptor-mediated action [66]. Chronic stress thus results in loss of SK channels and enhanced excitatory synaptic transmission in the amygdala.

ENDOCANNABINOIDS AND GLUTAMATERGIC TRANSMISSION

Endocannabinoids (eCBs) are atypical neurotransmitters in that they are not released vesicularly but are instead synthesized in response to increases in neuronal excitation or intracellular calcium [68]. eCBs act retroactively, binding to cannabinoid type one (CB1) receptors to inhibit neurotransmitter release [69,70,71]. Of the endocannabinoids, anandamide (AEA) is particularly active in the amygdala. AEA activation inhibits the release of glutamate and GABA in the BLA, with evidence that this signaling preferentially targets CB1 receptors on glutamatergic terminals [71]. Fatty acid amide hydrolase (FAAH), localized on pyramidal neurons [72], regulates AEA activity.

A recent study found FAAH activity increases during chronic stress [73], therefore decreasing levels of AEA and modulating the release of glutamate from the presynaptic terminal. It has been suggested that chronic stress, through an increase in FAAH activity, reduces the AEA activation of excitatory inputs to the pyramidal neurons of the BLA and results in abnormal glutamate release. Recent studies indicate that a similar mechanism occurs in the hippocampus [74].

CONCLUSIONS AND IMPLICATIONS FOR TREATMENT

Chronic stress results in persistent and significant changes in brain morphology and functioning and is associated with the formation of a variety of affective and anxiety disorders. In this review, I have proposed the following neuroplasticity-related model (Figure 1): Chronic stress enhances glutamatergic signaling in the amygdala and hippocampus through repeated activation of the

CRF receptor and increased FAAH activity. Low BDNF levels indicate that this abnormal glutamate transmission results in dendritic atrophy in the hippocampus [75], while in the amygdale, high BDNF levels alter glutamate signaling to increase synaptogenesis and dendritic outgrowth. Differences in BDNF are caused by a yet-unknown pathway downstream from glucocorticoids and glutamate. Chronic stress also increases the action of norepinephrine, which enhances excitatory transmission in the amygdala by facilitating the removal of SK channels from the membrane.

This model affords many potential therapeutic targets for chronic stress-related disorders. Studies indicate that current antidepressant treatments increase BDNF expression in the hippocampus [76,77], although there is currently no consensus on the actions of antidepressants on BDNF expression in the amygdala [78,79,80,81]. As discussed, returning BDNF expression to normal levels in the brain is complicated by differential expression of BDNF in the amygdala and hippocampus.

Glutamate is another target for drug development. Ketamine, a non-competitive NMDA receptor antagonist, triggers persistent and rapid antidepressant effects [82,83]. A recent study demonstrated that ketamine exerts its influence at least in part by increasing BDNF expression in the hippocampus and deactivating eEF2 kinase [84]. In the hippocampus CA3 region, mice lacking the NMDA receptor did not show evidence of chronic stress-induced dendritic atrophy [85], and co-treatment with the antidepressant fluoxetine or imipramine and the NMDA antagonist amantadine increases BDNF protein levels in the rat hippocampus [86,87]. In the amygdala, blockade of NMDA receptors prevents stress-induced anxiety-like behavior [41].

Finally, SK channels and FAAH represent additional molecular targets. Overexpression of SK2 has been shown to reduce anxiety-like behavior and trigger dendritic retraction in the BLA [65]. Similarly, mice deficient in FAAH or treated with an FAAH inhibitor do not have stress-induced changes in the structure of the amygdala and lack chronic-stress induced anxiety-like behavior [74].

These targets and their associated pathways all represent promising future routes in drug development for chronic stress-induced affective and anxiety disorders. While many studies have focused on the role of the hippocampus, only a fraction has targeted the amygdala. Because of its key role in regulating the HPA axis and its regulation of emotional responses, the amygdala and its role in the neuroplasticity model of stress must be considered in the development of future treatments for affective and anxiety disorders.

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