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Review Article

Persistent Stress-Induced Neuroplastic Changes in the Locus Coeruleus/Norepinephrine System

Olga Borodovitsyna, Neal Joshi, and Daniel Chandler

Department of Cell Biology and Neuroscience, Rowan University School of Osteopathic Medicine, Stratford, NJ 08084, USA

Correspondence should be addressed to Daniel Chandler; chandlerd@rowan.edu

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Neural plasticity plays a critical role in mediating short- and long-term brain responses to environmental stimuli. A major effector of plasticity throughout many regions of the brain is stress. Activation of the locus coeruleus (LC) is a critical step in mediating the neuroendocrine and behavioral limbs of the stress response. During stressor exposure, activation of the hypothalamic-pituitary-adrenal axis promotes release of corticotropin-releasing factor in LC, where its signaling promotes a number of physiological and cellular changes. While the acute effects of stress on LC physiology have been described, its long-term effects are less clear. This review will describe how stress changes LC neuronal physiology, function, and morphology from a genetic, cellular, and neuronal circuitry/transmission perspective. Specifically, we describe morphological changes of LC neurons in response to stressful stimuli and signal transduction pathways underlying them. Also, we will review changes in excitatory glutamatergic synaptic transmission in LC neurons and possible stress-induced modifications of AMPA receptors. This review will also address stress-related behavioral adaptations and specific noradrenergic receptors responsible for them. Finally, we summarize the results of several human studies which suggest a link between stress, altered LC function, and pathogenesis of posttraumatic stress disorder.

1. Introduction

Stressful stimuli and events engage a number of brain circuits that ultimately activate the hypothalamic-pituitary-adrenal (HPA) axis. During periods of stress, the paraventricular nucleus of the hypothalamus (PVN) releases the stress peptide corticotropin-releasing factor (CRF), which stimulates both direct central and indirect peripheral effects, activating signal transduction pathways that enhance catabolism of energy stores and mobilize physiological and psychological resources of the organism to permit an appropriate behavioral response to the stressor. These pathways become dysregulated following chronic or traumatic stress, which leads to destabilization of homeostasis and impaired immune, cardiovascular, and gastrointestinal functions, and promoting central nervous system (CNS) changes associated with depressive and anxiety-like behaviors that contribute to the diagnosis of stress-associated disorders [1–10]. The ability to mobilize CNS function to respond to stressful stimuli and ensure survival is explained in part by changes in neuroplastic adaptations. Several CNS structures have been demonstrated to undergo neuroplastic changes following stress [2, 11–24] which may contribute to stress-associated anxiety and mood disorders [12, 14, 19, 25, 26]. Chronically altered noradrenergic transmission is a characteristic of many neuropsychiatric and neurodegenerative disorders [12, 27–34], and therefore, short- and long-term stress-induced adaptations in norepinephrine- (NE-) containing cell bodies may contribute to these conditions. For the purposes of this review, we consider short-term effects to refer to the immediate and primary action CRF signaling during stressor exposure and the stress response on electrophysiological properties such as membrane depolarization and action potential generation that result from the opening of channels already inserted in the membrane. Long-term effects on the other hand include persistent changes that continue long after the stress response and CRF signaling have ceased and resulted from intracellular signaling cascades that promote receptor and channel trafficking, altered gene expression, and neurite outgrowth.

A major node in the stress response that promotes noradrenergic signaling in the CNS is the brain stem nucleus locus coeruleus (LC). The LC and other smaller noradrenergic brainstem nuclei, such as A1/C2 region in the solitary tract, are activated by CRF and reciprocally communicate with the HPA axis. Activation of A1/C2 promotes a positive feedback loop in stress circuitry by releasing NE in the PVN which stimulates CRF production and release by engaging α_1-adrenoreceptors (α_1AR) [35, 36]. The LC is the primary source of NE to the forebrain [37–45], where its actions affect sleep/wake cycles, sensory signal discrimination and detection, and cognition [2, 37, 46, 47]. It is innervated by a number of stress-responsive CRF-containing brain regions which when released, acts on CRF receptor 1 (CRFR1) receptor to produce acute changes in LC physiology and responsiveness to synaptically released transmitters [48–51]. Additionally, activation of CRFR1 stimulates Gs proteins and cAMP production [48, 52], which promotes numerous genetic and cellular effects [28, 50, 53–57]. These observations suggest that LC neurons may undergo many long-lasting stress-induced adaptations (Figure 1). These changes include receptor trafficking [58–60], altered expression of genes necessary for transmitter synthesis and release [28, 54–56, 61], protein kinases that activate transcription factors [57] and growth factors [18], electrophysiological properties [53, 62], and morphological changes [50, 53, 63], all of which would directly impact LC function at both immediate and chronic time point poststress.

While most investigations have focused on the transient effects of stress and CRF on LC function [48, 49, 51, 64–66], some have examined their lasting impact [28, 50, 52–54, 56, 57, 62]. This review will summarize how stress and CRF signaling persistently modify morphological and physiological features of the locus coeruleus/norepinephrine (LC/NE) system and its associated behaviors from a genetic, cellular, and neuronal circuitry/transmission perspective. While the stress-induced plastic changes that occur in LC and other brain regions during disease pathogenesis are not entirely clear, identifying how stress can chronically alter the function of this broadly projecting brainstem nucleus across multiple levels of regulation represents an important step forward in clarifying the mechanisms of conditions characterized by hyperactive noradrenergic transmission.

2. LC/NE Synaptic Plasticity Changes during Stress

2.1. Adaptive Functional and Anatomical Changes of LC after Stress. HPA axis activation is pivotal for mediating the central stress response. Through the release of peripheral and central neurohormones, it mobilizes various body tissues and brain areas to orchestrate an appropriate physiological and behavioral response. Importantly, during stressor exposure, CRF is released onto the LC by the PVN and other CRF-containing stress-responsive structures, such as the bed nucleus of the stria terminalis, Barrington's nucleus, and the central nucleus of the amygdala [67–73] which increase its tonic discharge [51, 62, 65, 66]. LC activity correlates highly with an animal's behavioral state: during quiet rest, LC discharges slowly in a highly regular fashion. During periods of focused attention, a phasic mode of operation dominates such that LC responds to salient stimuli with high-frequency bursts of action potentials that facilitate orientation and sustained attention towards behaviorally relevant stimuli [74]. During stress, CRF causes increased tonic discharge which compromises the ability of LC to respond to salient sensory stimuli with phasic bursts. This leads to impairments in sensory signal discrimination, several aspects of cognition, and a generally anxious state [2, 37, 74–77]. While this might seem generally maladaptive, a consequence of short-term stress-induced LC activation is to promote behaviors that increase the likelihood of survival in a threatening situation [2, 66]. By increasing LC discharge [51, 62, 65, 66] and therefore forebrain NE release [78–82], prefrontal cortical operations are inhibited [3, 78], promoting a behavioral phenotype characterized by broad scanning attention and vigilance [2, 66, 81, 83], which facilitates escape from a threatening situation.

The role of LC in stress has been the subject of study since 1970, when karyometric studies of sleep-resistant rabbits demonstrated an increase in nuclear size during stress [84]. Subsequently, an extensive body of literature has shown that LC is critical for mediating stress-induced behavioral and neuroendocrine responses. The electrophysiological effects of stress and CRF on LC have been well characterized in a number of *in vivo* and ex vivo studies [48, 49, 51, 53, 62, 65, 85]. *In vivo*, CRF increases tonic/spontaneous LC discharge [65, 86, 87] through a cyclic AMP (cAMP)/protein kinase A-dependent mechanism that depolarizes the membrane by decreasing potassium conductance [48]. Additionally, CRF has been demonstrated to decrease sensory-evoked phasic responses by LC [65, 86]. This effect could partially be explained by recent findings from our laboratory that show that a high concentration of bath-applied CRF [49] and preexposure to acute stress [62] both diminish excitatory glutamatergic synaptic transmission in LC. We found that these electrophysiological effects persist for at least a week poststress in adolescent rats. Moreover, electrophysiological changes which were absent immediately after stressor exposure develop over seven days, including increased intrinsic excitability and a hyperpolarized threshold for action potential generation [62]. These findings suggest that LC cells in adolescent rat brain undergo long-lasting changes following even short-term acute stressor exposure and lead to chronically increased forebrain NE concentration and behavioral changes.

2.2. CRF and Morphological Changes. CRF orchestrates a series of neuroplastic changes in LC neurons and LC-derived cell cultures [50, 52, 53, 58, 63]. Specifically, CRF triggers morphological changes in immortalized catecholaminergic neurons, such as the formation of long neurites with prominent growth cones [52]. Similarly, another study demonstrated the ability of CRF to promote neuronal outgrowth in organotypic slice cultures of rat LC [50]. In this study, it was found that 12 hours of CRF exposure increased

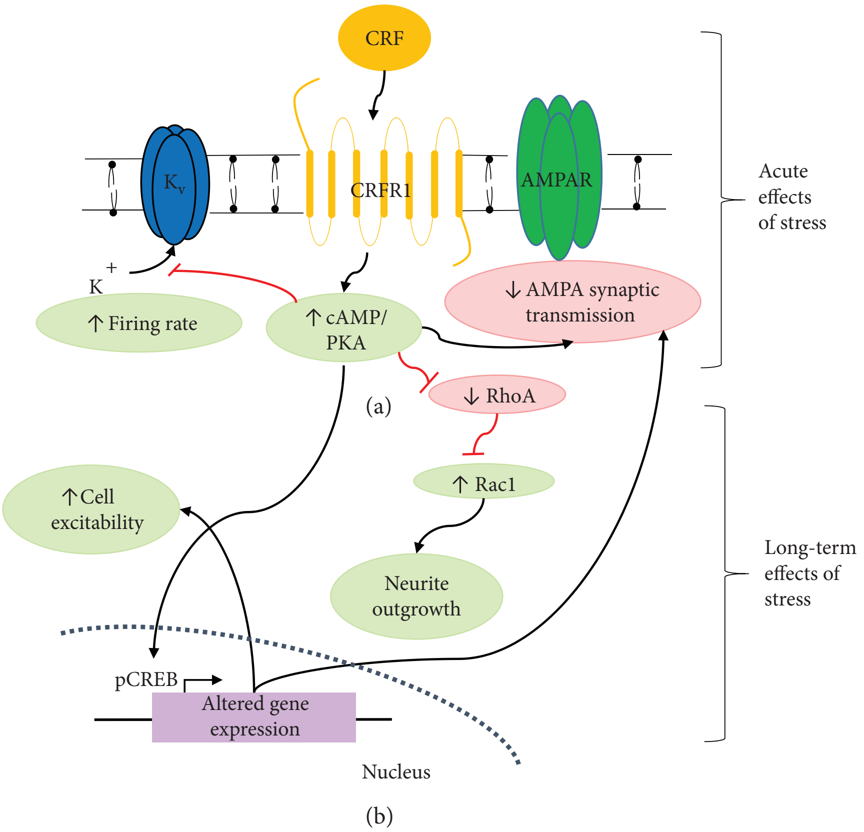

Figure 1: Model of signal transduction pathways induced by stress in LC neurons. (a) Pathways which mediate short-term effects of stressor exposure. CRF interacts with CRFR1, which through Gs-coupled receptor mechanisms increases intracellular cAMP levels, reducing potassium conductance resulting in cell depolarization. Through unknown mechanisms, CRF decreases glutamatergic synaptic transmission through AMPARs. (b) Pathways which mediate long-term effects of stressor. Initial CRF activation of Gs-coupled CRFR1 increases PKA activity, which phosphorylates CREB to initiate expression of stress-induced genes. These could potentially include genes regulating AMPAR and voltage-gated ion channel expression. Inactivation of RhoA by PKA phosphorylation disinhibits Rac1 to increase neurite outgrowth via actin remodeling and microtubule stabilization.

the number of primary processes and branching pattern of neurites. Mechanisms of dendritic growth regulation by CRF have been proposed to occur through Rac and RhoA GTPases (Figure 1), which regulate intracellular actin dynamics and spine length [88]. Elsewhere in the brain, inhibition of Rac1 has been shown to promote strong effects on dendritic spines from apical and basal dendrites on pyramidal neurons with relative absence of branching effects [89].

Additional unpublished observations from our laboratory also suggest that in animals subjected to acute intense stressor exposure, LC cells might undergo morphological changes. We have previously shown that fifteen minutes of combined physical restraint and exposure to predator odor induces a number of long-lasting changes in LC function that are accompanied by chronically increased anxiety-like behavior [62]. During whole-cell patch clamp electrophysiological recordings, some neurons were filled with biocytin so their morphology could be recovered. Preliminary findings show that LC cells from stressed animals have larger and more complex dendritic arbors than those from control rats. Additionally, using RNA-Seq, we identified that expression of Ntf3, the gene for neurotrophin 3, which promotes neuronal survival, differentiation, and neurite outgrowth [18, 90], was approximately twice as high in rats one week after stressor exposure than in their control counterparts (Figure 2). These observations, in combination with earlier reports of stress-induced morphological alterations in LC neurons [50, 52, 53, 75, 91–93], suggest that stress may cause long-lasting changes in noradrenergic transmission throughout the CNS in response to even acute stressor exposure. Such an effect on CNS noradrenergic transmission might be achieved through morphological plasticity because as LC dendrites and axons proliferate, there would be more sites of afferent input to excite LC neurons and a greater density of release points from which NE efflux could occur upon this enhanced excitation, respectively. Such findings could have important implications for posttraumatic stress disorder (PTSD), a condition in which evidence suggests that NE transmission is impaired [12, 31, 79, 94].

It is interesting to note that rodent LC neurons are sexually dimorphic with respect to their morphological characteristics and response to stress/CRF exposure. Female LC dendritic arbors have been reported to extend further into the peri-LC region where synaptic contacts with CRF-positive afferents are made [71, 95, 96] and are larger with more branching points than those of males [68, 97]. This

Figure 2: LC neurons from stressor-exposed animals show a trend for increased dendritic complexity. Representative traced neurons from control (top) and stressor exposed (bottom) animals filled with biocytin reveal a tendency for LC cells from stressed rats to possess larger and more complex dendritic arbors a week after stressor exposure. Additionally, neurotrophin 3, which promotes neurite outgrowth and dendritic proliferation, is upregulated in LC one week after stressor exposure. $^*p < 0.05$ versus control.

suggests that the female LC might be subjected to greater afferent regulation by CRF and therefore more stress-responsive. This sexual dimorphism might provide a structural basis for differences in emotional arousal between sexes and the greater increased susceptibility of females to anxiety disorders [98]. Interestingly, in mice that genetically overexpress CRF, the complexity of male dendritic morphology increases to resemble the morphology of wild-type and CRF-overexpressing females. This further suggests that enhanced CRF signaling produces neurite proliferation and extension in LC [58]. Such observations provide further evidence for stress and CRF-induced central noradrenergic reorganization.

2.3. CRF and Modified AMPA Receptor-Dependent Synaptic Transmission. Plasticity is highly dependent on the AMPA receptor (AMPAR), an ionotropic glutamate receptor, permeable to Na^+ and Ca^{2+} ions. It is composed of four subunits: GluA1, GluA2, GluA3, and GluA4, which form a heterotetramer. [99–103]. We have previously shown that both stressor exposure *in vivo* [62] and CRF exposure ex vivo [49] alter LC AMPAR signaling. Given that stress and CRF can alter AMPAR-dependent transmission, this receptor might play a critical role in stress-induced neural plasticity. Several mechanisms could account for altered AMPAR functioning in LC following CRF exposure. CRF signaling in LC causes internalization of its own receptor [59, 60, 63], and thus, if CRF and AMPARs are in close apposition to one another on postsynaptic LC membranes, CRF receptor trafficking might inadvertently induce AMPAR internalization as well. This is particularly important with respect to some of the intracellular proteins that AMPARs interact with. AMPARs interact directly and indirectly with kinases and GTPases that regulate actin cytoskeletal dynamics [50, 53, 99–101, 104, 105]. In particular, Rho GTPase activity is modulated by guanine nucleotide exchange factors (GEFs), which are known to interact with *surface-expressed* AMPARs and promote synaptic plasticity [104]. Thus, if CRF causes shuttling of vesicular AMPARs to the cell membrane, which, based on our prior observations, might occur during high concentrations of CRF exposure [49], their association with GEFs could promote structural plasticity in LC neurons through interaction with Rho GTPases and modulation of cytoskeletal structure. Identifying the mechanisms that link CRF and AMPA receptor function and trafficking could be informative of how LC cells adapt morphologically following stress, thus providing insights to a number of disease states in which LC plasticity is perturbed [29, 50, 53, 106, 107]. In addition to receptor trafficking and altered gene expression, there are other posttranslational modifications that can be made to the AMPAR and its subunits which could promote plastic changes to LC neurons. Using data from both LC and non-LC studies of AMPAR function and modification, we will review possible mechanisms for AMPAR regulation.

There are multiple mechanisms of posttranslational regulation of AMPAR function, which include reversible phosphorylation, ubiquitination, and palmitoylation [108–110]. CRF stimulates cAMP synthesis and PKA activity [48, 50, 52], and therefore, stress could potentially alter AMPAR phosphorylation states. The GluA1 subunit is phosphorylated at different positions at the C-terminal end. For example, phosphorylation at Ser-845 by PKA [101] and Ser-831 by PKC and CaMKII [111, 112] increase single channel conductance. Phosphorylation of Ser-818 and Thr–840 by PKC increases the mean channel conductance [113]. Importantly, mechanisms that increase channel conductance have been shown to promote activity-dependent plasticity [99, 114]. PKCλ was found to phosphorylate Ser-818 on the GluA1 subunit which mediates PI3K-induced AMPAR insertion [115]. GluR2 can also regulate synaptic plasticity through Ser-880 phosphorylation-dependent interactions with PDZ domain-containing proteins, which regulate receptor internalization in the hippocampus [116] and cerebellum [117].

Thus, due to the actions of CRF on cAMP production and PKA activity, stress could potentially impact LC plasticity through modulation of AMPAR function which we have demonstrated in the past [49, 62].

Another modification of AMPARs is ubiquitination, which promotes endocytosis and degradation [108, 109, 118–120] and can occur at multiple places across the subunits. One effect of stress on AMPAR ubiquitination is to decrease glutamatergic synaptic transmission in the prefrontal cortex (PFC), which requires specific ubiquitin ligases Nedd4-1 and Fbx2, an effect which can be blocked by a proteasome inhibitor [121]. Identification of LC-specific ubiquitin ligases would help to find a precise target for stress response control and intervention. In contrast to ubiquitination, AMPAR C-terminal cysteine residue palmitoylation protects from degradation [122] and regulates its internalization [123]. Palmitoylation of the transmembrane domain promotes accumulation of AMPAR in the Golgi, possibly performing a quality control step for proper folding, while depalmitoylation stimulates membrane insertion of AMPAR [123–125]. Identifying any potential mechanisms linking CRF signaling to AMPAR ubiquitination in LC or elsewhere would be informative of means of promoting or inhibiting stress-induced plasticity within the nucleus.

2.4. CRF and Intracellular Signal Transduction. CRF mediates its action through CRFR1, which through Gs-coupled mechanisms increases the concentration of cAMP that phosphorylates PKA [52]. However, there is another mechanism caused by CRFR1 activation which acts through a MAPK cascade, in which a Gq-coupled mechanism increases concentration of phospholipase C (PLC), which activates metabolites which phosphorylate PKC, which in turn phosphorylates ERK1/2 [50, 126]. CRF has been shown to cause an increase in LC neurite length, an effect that is abolished by specific inhibition of PKA or MAPK, but not PKC [50]. PKC appears to also trigger a RhoA-activating cascade through downstream Rho-associated protein kinase (ROCK), which subsequently phosphorylates the collapsin response mediator protein 2 (CRMP-2) and causes growth cone collapse [127] (Figure 2).

Such receptor-mediated acute cellular changes could occur through the aforementioned mechanisms, but long-term changes could also potentially occur through regulation of gene expression. A study of single and repeated restraint stress demonstrated an increase in immunoreactivity of c-Fos, pERK, pCaMKII, and pCREB in the LC two hours following the stressor [128]. The same study also showed that pERK and pCREB had the same expression pattern and were colocalized to the same neurons, suggesting that activation of the MAPK/ERK pathways with CREB phosphorylation promote changes in gene expression. The exact mechanism of transcriptional changes following CRF expression in the LC is not clear. However, another study demonstrated increased c-Fos expression and CREB phosphorylation after acute immobilization stress, while repeated stress increased phosphorylation of p38, cJun N-teminal kinase (JNK 1/2/3), and ERK1/2 [129]. CREB is a transcriptional factor which regulates transcription of multiple downstream genes including c-Fos, brain-derived neurotrophic factor (BDNF), tyrosine hydroxylase (TH), and neuropeptides [130, 131]. These observations corroborate other studies that have shown altered expression of trophic factors and NE synthetic enzymes [18, 28, 54–57, 61].

BDNF stimulates dendritic outgrowth and increased synaptic connectivity. Mice genetically overexpressing the receptor for neurotrophin 3, TrkC, show increased anxiety-like behavior, as well as increased LC neuronal density [132], suggesting that some degree of positive feedback might exist between stress, neurotrophin 3 signaling, and LC plasticity. This is particularly interesting in light of preliminary observations by our laboratory that show that one week after acute stressor exposure, neurotrophin mRNA is increased, an effect accompanied by a trend for increased LC dendritic length and complexity (Figure 2). Others have also reported increased neurotrophin 3 expression in LC following stress, which can be normalized with antidepressant treatment [18]. Interestingly, in addition to sexual dimorphism of LC morphology and stress responsiveness, there are also sex differences in LC intracellular signaling induced by CRF: specifically, CRFR1 is more strongly coupled to β-arrestin in males, promoting receptor internalization and potentially blunted responsiveness to CRF in the future. In females, however, CRFR1 is more strongly coupled to Gs signaling pathways, which promotes increased LC discharge and dendritic proliferation, potentially increasing future sensitivity to stress by providing more space for synaptic contacts with CRF-positive afferents [63, 133]. In this way, the male and female LC may be differentially aligned to respond to stress with specific neuroplastic adaptations that promote disease.

3. CNS Neural Plasticity Changes in Response to NE Volume Transmission Changes

LC contributes to major CNS functions such as waking, arousal, attention, sensory discrimination, and cognition. Because stress promotes both short- and long-term functional and neuroplastic changes in LC, some of these functions might also be impacted by stressor exposure, either directly or indirectly. Through modulation of intrinsic and synaptic features of LC neurons, stress likely modifies noradrenergic volume transmission in target brain areas such as the amygdala, hippocampus, and PFC, where it potently modulates neural plasticity [134–138]. Because stress acutely and chronically alters LC discharge [53, 62, 66, 86] and NE release [78–82], different adrenergic receptors might become engaged during and after stressor exposure. The adrenergic receptors vary in their affinity for NE [3, 78, 139, 140], and different receptors promote different forms of plasticity and learning [134, 135, 137, 141]. Low concentrations of NE engage the high-affinity α_1 receptor, particularly in the prefrontal cortex, which promotes working memory, sustained attention, and other cognitive functions [3, 142, 143].

Conversely, high NE concentration which occurs in response to stress causes engagement of the α_1 and β adrenergic receptors. The α_1 receptor promotes LTD of prefrontal synapses [137] and inhibition of prefrontal-dependent cognitive functions such as working memory and sustained attention [2, 83]. Indeed, enhanced α_1 signaling in PFC is associated with increased behavioral flexibility [144]. Furthermore, stressor exposure has been shown to increase tonic LC discharge and promote scanning attention and behavioral flexibility [65, 66]. It has been proposed that such a change would permit lower-order sensorimotor regions to guide behavior with little modulation by prefrontal circuitry, allowing disengagement from specific stimuli and goal-oriented behaviors to instead promote rapid impulsive responses [2]. Such a stress-induced shift might be beneficial when an animal is faced with a threatening stimulus and a quick escape must be made. Additionally, engagement of the β receptor promotes hippocampal plasticity and encoding and recall of contextual fear memory [141, 145, 146]. Therefore, persistent stress-induced changes in LC function would elevate NE concentration in prefrontal cortex and hippocampus enhancing plasticity in both areas through signaling at α_1 and β receptors to synergistically promote encoding and recall of fear memories, impaired cognition, hypervigilance, and behaviors that allow an appropriate behavioral response to be generated. Therefore, an inverted U relationship between LC firing and arousal/behavioral performance model has been proposed [2, 37, 139], with maximal cognitive function corresponding to “ideal” levels of LC tonic firing [147] and hyperarousal and vigilance corresponding with excessive levels of discharge. During stress, increased tonic LC firing is enhanced, which leads to increased levels of NE in LC projection fields, promoting broad scanning attention, hyperarousal, hypervigilance, and other anxiety-like behavioral symptoms in stressed subjects.

4. Role of Stress-Induced LC/NE Changes in PTSD

Chronic stress-induced alterations in LC structure and function that lead to behavioral impairments might contribute to disease pathogenesis and symptomatology. Many studies show the involvement or potential involvement of the LC in stress-related disease states, particularly PTSD. Both peripheral and central measures of NE activity are increased in PTSD patient populations, including enhanced sympathetic nervous system function [148–151], and increased functional connectivity between LC and the basolateral amygdala during conscious processing of threatening stimuli [152]. This enhanced connectivity is particularly important because of the role that the basolateral amygdala and its noradrenergic inputs in particular [153–157] play in fear conditioning. Furthermore, PTSD patients frequently show disturbances in sleep patterns [158–160], which may be related to chronically elevated LC discharge due to its well-established role in mediating arousal and a forebrain EEG associated with waking [161]. Such an effect could potentially be related to dysregulation of other stress-sensitive systems, such as the HPA axis which releases CRF. LC is potently activated by CRF, and increased levels of the peptide have been found in the cerebrospinal fluid of combat veterans afflicted with PTSD [162, 163], providing a potential means for maintaining LC hyperactivity even in the absence of a stressor. More recently, an fMRI study showed that PTSD patients showed exaggerated behavioral and autonomic responses to loud sounds, suggesting sensitized phasic responses of LC neurons [34]. Evidence for LC as a central mediator of PTSD-like symptoms comes from observations that yohimbine, an α_{2A} receptor antagonist which disinhibits LC neurons, produces panic attacks in up to 70% of PTSD patients and in 89% of patients with comorbid PTSD and panic disorder, but not in control subjects. Additionally, plasma levels of a NE metabolite postyohimbine administration were twice as high in PTSD patients [163]. These findings suggest that NE release is altered presynaptically at the level of the LC in PTSD patients, which may affect many downstream targets [164].

In contrast to the actions of yohimbine, clonidine, a presynaptic α_{2A} receptor agonist which limits noradrenergic transmission in the forebrain, has been shown to have beneficial effects on hyperarousal, hypervigilance, sleep disruption, exaggerated startle responses, and nightmares in veterans with PTSD [31]. The notion that increased NE release promotes some behaviors associated with PTSD and anxiety is further supported by observations that the β-receptor antagonist propranolol attenuates PTSD symptoms, possibly due to the actions that the β receptor plays in fear memory consolidation and emotion [31, 134, 135, 165–167]. Prazosin, an α_1-adrenergic antagonist, has also been shown to be beneficial for alleviating nightmares and sleep disturbances in both veteran [168] and children PTSD patients [169], as well as for improving symptoms of hyperarousal, avoidance/numbing, and traumatic recall of past events [170]. It is also interesting to note that an *in vivo* PET study that the availability of the NE transporter in the LC is decreased in PTSD patients [171]. This could be indicative of elevated extracellular NE concentration and would be consistent with other reports of LC hyperactivity in this population. Thus, due to the well-documented ability of stress to promote forebrain NE release through short-term physiological activation and enduring molecular and cellular changes in the LC, stress-induced neuroplastic adaptations in the LC likely contribute to disease pathogenesis. This could occur at the level of the LC as a primary site of stress-induced plasticity or in downstream targets of the LC due to the well-established role of NE in mediating neuroplastic changes throughout the brain: fMRI studies have also shown changes in hippocampal volume and altered function in the amygdala, hippocampus, mPFC, orbitofrontal cortex, anterior cingulate, and insular cortex in PTSD patients [172], all of which may be related to maladaptive plastic changes in the LC or the plastic changes promoted by it [134, 135, 137, 165].

Based on these clinical reports, there is clear evidence that LC hyperfunction is at least characteristic of, if not causal to, PTSD symptomatology. However, some clinical observations suggest a more complicated relationship that exists between LC function and PTSD disease progression and treatment. As mentioned above, there is clinical evidence for decreased NE transporter availability in the LC of PTSD patients. This could be explained by elevated extracellular NE concentration; another potential explanation could be LC neuronal loss. Indeed, a postmortem neuromorphometric analysis of veterans with probable or possible war-related PTSD showed a lower LC cell count compared to controls [173], suggesting that the LC plays in the role in the pathophysiology of PTSD, or that a lower LC cell count may predispose individuals to PTSD. While decreased LC cell numbers would suggest reduced forebrain NE levels, in other pathologies in which LC cell counts are decreased such as Alzheimer's disease, the surviving neurons show evidence for hyperactivity [174] and dendritic sprouting and remodeling [107]. Additionally, recent clinical trials using 3,4-methylenedioxymethamphetamine (MDMA) have shown promising results in reduction or remission of PTSD symptoms: specifically, six phase II clinical trials have shown that combined MDMA and psychotherapy are safe and efficacious such that 52.7% of patients receiving active drug no longer meet PTSD criteria [175]. Despite a wealth of evidence showing that enhanced noradrenergic transmission contributes to PTSD etiology, MDMA increases release of catecholamines, including NE. One potential explanation for MDMA's somewhat paradoxical efficacy is that memory reconsolidation is enhanced via plastic changes in the hippocampus due to elevated NE levels [141, 145]. MDMA also facilitates fear extinction learning [176], and thus, enhanced NE efflux following MDMA administration might also promote plastic changes within the amygdala [12]. Additionally, because NE is generally increased in PTSD patients, the benefits of MDMA on symptom improvement are likely due to the drug complex polypharmacological interactions and its effects on brainwide neurotransmission. It is hypothesized that in addition to enhanced plasticity and memory reconsolidation, heightened monoaminergic neurotransmission following MDMA administration promotes a number of subjective psychological effects such as increased introspection and receptiveness for psychotherapy that lead to improved outcomes in PTSD patients [175]. Collectively, however, many clinical observations strongly suggest that hyperactive noradrenergic transmission contributes to PTSD symptomology and anxiety-like behavior.

5. Conclusions

Stressor exposure induces a series of neuroendocrine, physiological, and behavioral adaptations that promote an appropriate response to the stressor. Central to these diverse functions is CRF signaling which in a number of brain regions promotes a number of immediate [48, 49, 51, 177–184] and persistent [50, 52, 60, 121, 185–187] cellular changes. These effects are of particular interest in LC, where the interaction of CRF with its receptor CRFR1 activates cAMP-dependent intracellular signaling cascades, increasing tonic discharge and promoting anxiety-like behavior [64, 77, 188, 189]. Evidence suggests that chronic stressor exposure is able to alter LC gene expression [18, 28, 54–57, 61], promote long-term changes in synaptic transmission and excitability [53, 62] and receptor trafficking [58–60, 185], and, importantly, induce morphological changes and dendritic remodeling (Figure 1) [50, 52, 53, 57, 190]. These actions appear to be dependent on a number of kinases and GTPases and their associated signaling pathways [50, 52, 57] and potentially on AMPAR function [191, 192] which is modulated by CRF in the short term [49] and stressor exposure in the long term [62]. Through its complex signaling cascades, CRFR1 activation in LC induces a number of long-lasting cellular effects which ultimately impact the function of the nucleus itself as well as other target brain regions which are heavily innervated by LC and modulated by noradrenergic transmission. Critically, the LC promotes plasticity in other structures including the PFC, amygdala, and hippocampus by promoting noradrenergic transmission at α_1 and β receptors [137, 141, 145, 146]. Therefore, stress and CRF can induce neuroplastic changes in LC, which can lead to subsequent neuroplastic changes elsewhere, ultimately promoting causing chronic anxiety-like behavior. Specifically, increased tonic discharge in the short term will drive an animal to display such behavior [62, 64, 77]. Maintenance of increased LC discharge in the long term [62] along with enhanced expression of genes necessary for NE synthesis and release [54–56] will lead to chronically elevated forebrain NE levels. This promotes network adaptations and plasticity in target regions which facilitate fear memory encoding and drive an animal towards a behavioral state characterized by vigilance, impulsivity, and impaired cognition [3, 78, 83, 193]. Meanwhile, morphological plasticity and dendritic outgrowth into the peri-LC area [50, 52, 53, 68, 194] will make LC subject to greater afferent regulation by stress-responsive structures such as PVN and CeA [58, 63, 194]. Through these mechanisms, chronic or traumatic stress could permanently alter forebrain noradrenergic transmission to promote long-lasting changes in behavior, manifesting in humans as mood and anxiety disorders such as depression and posttraumatic stress disorder. Thus, identifying how stress and CRF promote synaptic and morphological plasticity in LC to chronically elevate forebrain NE concentration represents an important step in understanding disease pathogenesis and symptomatology for mood, anxiety, and other neuropsychiatric disorders.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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