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Dual Effect: The Locus Coeruleus's Function in Chronic Pain and Coexisting Depression or Anxiety

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Abstract. The locus coeruleus (LC), nestled within the dorsal pontine tegmentum, stands as a pivotal hub in the brain's intricate network, exerting a profound influence over the modulation of pain perception and the emotional turbulences that often accompany it, notably depression and anxiety. Although a wealth of research has been dedicated to unraveling the LC's enigmatic operations, its intricate mechanisms continue to elude full comprehension. Nevertheless, the advent of sophisticated animal models and state-of-the-art investigative tools, exemplified by DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) and optogenetics, has catalyzed a deeper foray into the LC's role in chronic pain and its comorbid psychiatric manifestations. This comprehensive review endeavors to dissect a decade's worth of clinical and preclinical inquiries, spotlighting the intricate neuronal dynamics within the LC and its associated neural circuit for chronic pain and its affective sequelae. Furthermore, the review delves into the pivotal role of neurotransmitters—such as noradrenaline (NA), glutamate, histamine, and others—alongside their hormonal counterparts, in orchestrating the LC's regulatory ballet. These neurochemical envoys are instrumental in mediating the nuanced interplay within the LC, thereby sculpting its reactivity to noxious stimuli. By shedding light on potential therapeutic strategies that home in on the LC, this review uncovers fertile ground for innovative therapeutic modalities, paving the way for efficacious clinical interventions that could transform the landscape of pain management and mental health treatment.

Keywords: Locus Coeruleus; Depression; Anxiety; Neurotransmitters; Hormone.

1. Introduction

Pain is a complex and multifaceted sensory and emotional phenomenon that acts as a crucial alarm system, signaling the presence of actual or potential tissue damage to the body. An effective pain response is characterized by its ability to elicit aversion and induce stress, which are essential for activating the body's protective mechanisms and preventing further injury. However, in instances of chronic pain, the discomfort endures beyond the period when normal healing would have been expected to take place, thereby diminishing its original role as a safeguard against harm [1]. Chronic pain not only causes physical discomfort but also extends its influence to multiple dimensions of a patient's well-being and daily life, specifically impacting mood, sleep quality, and cognitive functions. Among patients who endure such persistent pain, mood disturbances, particularly depression and anxiety, are often observed. Epidemiological research has consistently demonstrated that a significant proportion—approximately half—of individuals afflicted with chronic pain concurrently contend with major depressive disorder. This percentage is around 30% for those experiencing neuropathic pain and can rise to approximately 80% for patients with fibromyalgia [2]. Despite advancements in pain modulation research, our understanding of the complex mechanisms that underlie chronic pain conditions remains limited. These knowledge gaps can hinder the development of effective therapeutic approaches to pain relief. As a result, unmanaged severe chronic pain often leads to the emergence of comorbid disorders such as depression and anxiety, significantly complicating the diagnosis and treatment of chronic pain patients. This, in turn, perpetuates a vicious cycle of

symptoms [3,4]. To shatter this pernicious cycle, it is imperative that we delve deeper into the research, aiming to elucidate the foundational mechanisms that underpin chronic pain and its concurrent disorders. Such an endeavor is essential for crafting more efficacious treatment strategies that can offer respite to those afflicted and potentially revolutionize our approach to pain management and psychiatric care.

With the development of animal models and research techniques, it is found that a distinct biological basis exists for this comorbidity, as both sensory regions and neural circuits linked to stress become activated under these circumstances. Given that NA is pivotal in modulating a range of critical functions, including arousal, attention, cognitive processes, stress responses, and pain perception, and considering the LC as the brain's principal source of NA, it is reasonable to deduce that the noradrenergic system centered in the LC, situated in the pons, plays a significant role in the intricate interplay of sensory and emotional aspects of pain processing. Certainly, although the inhibitory effect of the LC on acute pain has been firmly established, recent studies over the past ten years have revealed its role in either promoting or suppressing chronic pain. Additionally, despite numerous reported alterations in LC activity in animal models and individuals with depression or anxiety, as well as its pivotal function in the mechanism of antidepressants, the specific role of LC circuits in depression or anxiety remains enigmatic.

Consequently, our investigation will extend to scrutinize the regulatory function of the LC within the spectrum of chronic pain, and how its intricate operations contribute to the emergence of comorbidities that frequently accompany this condition, such as anxiety and depression. This exploration is poised to yield insights that could be pivotal in the development of targeted interventions and a more holistic understanding of the interplay between chronic pain and its associated emotional disturbances (Figure 1).

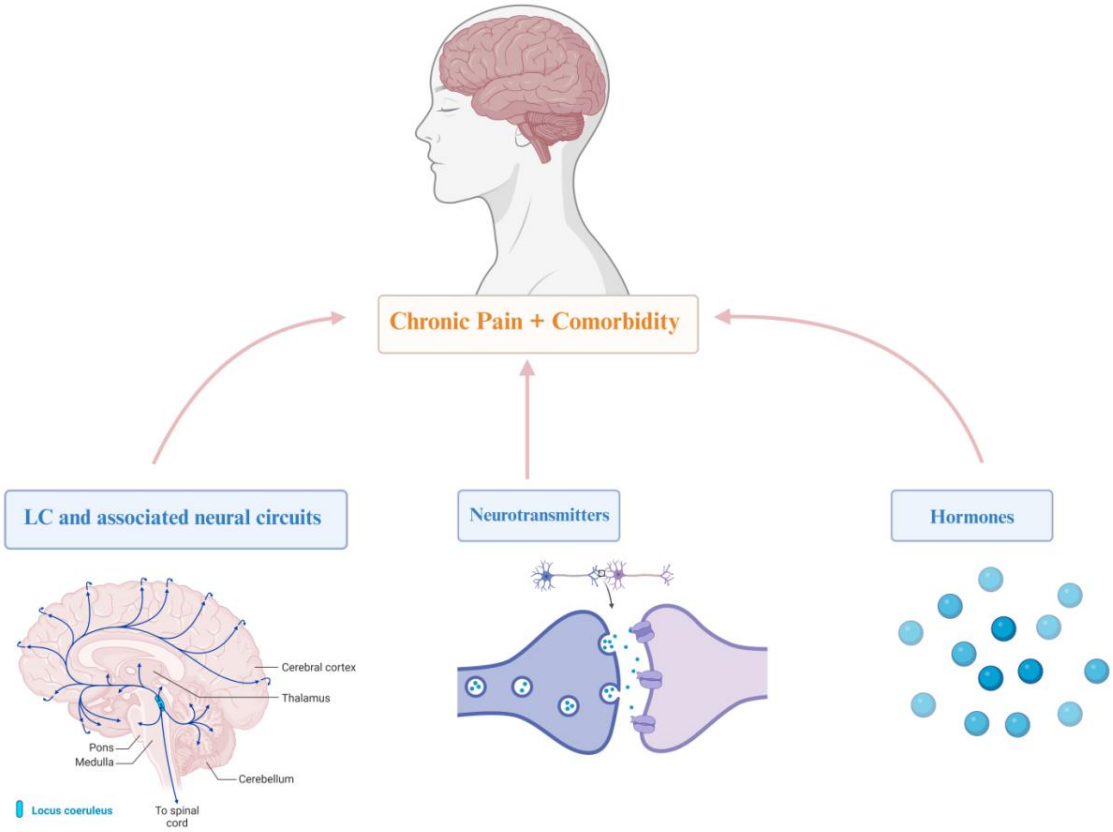

Figure 1. The overview of the role of the LC in chronic pain and comorbid depression or anxiety.
Notes: This legend highlights the complex neuronal interactions within the LC and its related neural circuitry in chronic pain and emotional consequences, emphasizing the crucial role of neurotransmitters and their hormonal counterparts in coordinating the LC's regulatory functions.

2. The Neuroregulatory Functions of the LC in Pain and Emotion

In the span of the past two decades, a multitude of scholars has delved into the hypothesis that the brain's plasticity, encompassing both architectural flexibility and cellular reorganization, may significantly influence the etiology and therapeutic approaches for mood disorders. This theory could potentially extend to mood disturbances triggered by pain, given that chronic pain has been associated with modifications in both the function and structure of cortical and subcortical neural plasticity [6]. The LC has traditionally been regarded as a single, compact neuromodulatory nucleus. Its extensive noradrenergic projections within the central nervous system (CNS) have made it a significant aspect of various theories on brain function. However, recent advancements in technology have revealed that the LC is actually composed of multiple modules, each responsible for specific neuromodulation tasks [5]. This new understanding represents a paradigm shift in our comprehension of the LC. Furthermore, as neuropathy progresses, it becomes apparent that the modules of the LC contribute asymmetrically to its function.

Existing research has shown that as pain transitions from acute to chronic, there are plastic changes in the noradrenergic-LC system that occur over time, and these alterations are linked to behavioral despair. After nerve injury, endogenous LC experiences asymmetric activation in the short term, as evidenced by c-Fo's activity. Immunohistochemistry has uncovered an elevation in c-Fo's expression following nerve damage, both in the immediate and extended periods. Nevertheless, in the short term, c-Fo's expression is notably higher on the ipsilateral side of the LC compared to the contralateral side, whereas in CCI-LT animals, the bilateral increase in the LC is of comparable magnitude. These findings demonstrate that the LC alterations provoked by nerve injury differ depending on the side of the body and the duration of the injury. The application of chemogenetic suppression to LC activity has uncovered that ipsilateral LC neuron activity is associated with a reduced pain phenotype, but this effect is limited to the initial phases of nerve damage. In contrast, inhibiting contralateral LC neurons did not alter pain sensation at any given time. This suggests that the ipsilateral LC plays a significant role in regulating and alleviating pain caused by nerve damage, whereas the contralateral LC may have a smaller or even negligible effect in relieving neuropathic pain. Surprisingly, in contrast to its influence on sensory sensitivity, the blockage of either ipsilateral or contralateral LC neurons fully abolished the depressive phenotype noticed in CCI-LT [2]. Overall, asymmetric LC activation contributes to early analgesia and later depression-like behavior in chronic pain and depression comorbidity [11]. It is intriguing to note that the suppression of LC activity via hM4D(Gi)-DREADD did not alter sensory exploration or induce a depressive-like phenotype in sham animals, indicating a relatively low baseline activity of the LC in the absence of injury [7]. Such observations are invaluable for elucidating the functional shifts that occur within the LC as it transitions between states of health and injury.

Unlike acute pain, the LC changes in chronic pain are harder to define, one reason being that the temporal dynamics of neural plasticity vary among different animal models of pain [8]. After 28 days of chronic constriction injury (CCI) of the sciatic nerve, both spontaneous discharge activity and nocuous stimulus-induced responses in the LC increased, manifesting as an increase in burst discharge frequency and irregular discharge patterns. This coincides with the timing of the development of depressive and anxiety-like behaviors [10]. This experiment demonstrates that neuropathic pain can cause anxiety and depression in rodents, with alterations in the activity of LC noradrenergic neurons potentially contributing to these behavioral changes. Research indicates that rats with sciatic nerve injury display anxious and depressive-like behaviors, concurrent with an enhanced firing rate of LC neurons and upregulated expression of α2-AR, NA transporter, and tyrosine hydroxylase [9]. In a separate study, it was observed that neuropathic pain, triggered by streptozotocin-induced (STZ) diabetes, also led to anxiety-like behaviors in rodents. In contrast to CCI rats, STZ rats showed reduced levels of LC discharge activity, tyrosine hydroxylase, phosphorylated cAMP-response element-binding protein (CREB), and NA transporter, but both models exhibited enhanced LC α2-adrenergic receptor sensitivity at the same time point. Diabetes induced anxiety-like behavior with LC impairment long-term, but nociceptive sensitivity and LC

functions differed from CCI, indicating that although various neuropathic pain types may all trigger anxiety-like behavior in rodents, the diverse impacts of neuropathic pain on noradrenergic activity in the LC could originate from distinct etiologies of neuropathic pain (Figure 2) [12].

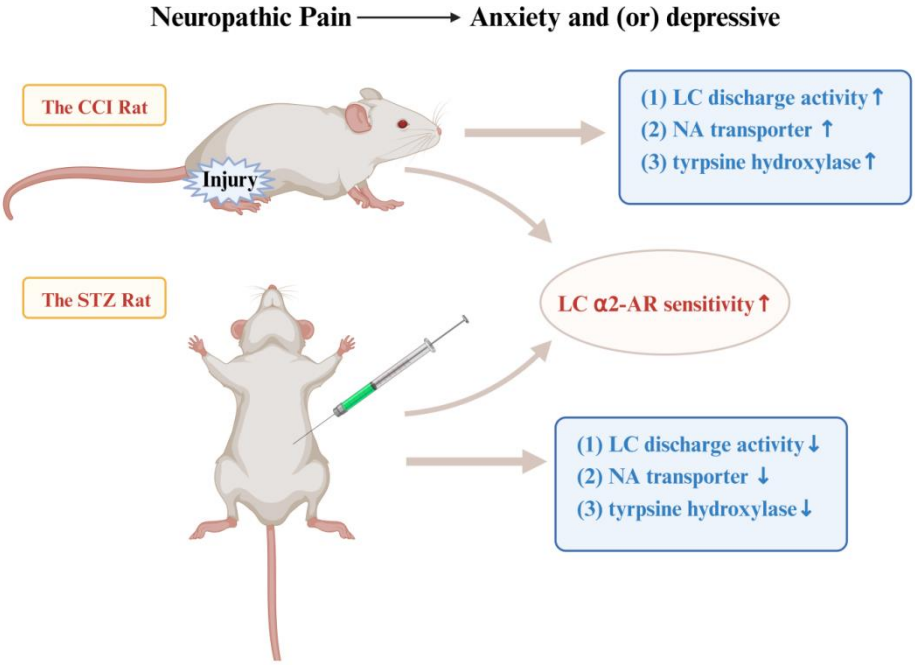

Figure 2. The influence of different neuropathic pain models on noradrenergic activity in the LC
Notes: The legend shows that chronic pain in rats leads to anxious and depressive behaviors, altered LC neuron activity, and changes in related biochemical markers. However, different neuropathic pain models can lead to different changes in the noradrenergic system of the LC. In CCI rats, the discharge activity of the LC increases (↑), and the levels of tyrosine hydroxylase and NA transporter increase (↑), while in STZ rats, the discharge activity of the LC as well as the levels of tyrosine hydroxylase and NA transporter decrease (↓). However, both conditions lead to increased (↑) sensitivity of α2-adrenergic receptors in the locus coeruleus.

Notably, the LC, a sexually dimorphic noradrenergic nucleus, integrates signals linked to emotions, cognition, and pain. Significant sex disparities were observed in the LC, where female mice had fewer noradrenergic cells but larger dendritic volumes and heightened cell excitability. Given the LC's crucial role in stress and pain regulation, these findings could offer insights into the higher incidence of stress-related disorders, including anxiety and depression, as well as chronic pain among women. Consequently, it is imperative to take into account sex differences in preclinical and clinical research studies aimed at elucidating pathologies linked to these phenomena [13].

3. LC associated neural circuits

Increasing evidence has shown that LC neurons are involved in extensive projection networks across the central nervous system, with clearly identifiable subsets of these neurons capable of encoding specific processes [17,18]. Therefore, LC is considered to be involved in both pain facilitation and pain relief through distinct circuits [19]. Understanding structural connectivity of brainstem nuclei with limbic cortices is vital for neuromodulation in depression, pain, addiction, and anxiety [14].

3.1. LC-dorsal reticular neural (DRt) circuit

In a groundbreaking study utilizing the chronic constriction injury of the sciatic nerve in male Sprague-Dawley rats—a well-established model for neuropathic pain—researchers have observed prolonged pain enhances the expression of phosphorylated cAMP-response element binding protein (p-CREB) within the contralateral dorsal reticular nucleus (DRtcontra), a phenomenon not mirrored in the ipsilateral dorsal reticular nucleus (DRtipsi). This discovery underscores the lateralized

response within the central nervous system to neuropathic pain stimuli. Employing a dual viral-mediated gene transfer technique, the targeted inactivation of the LCcontra→DRtcontra neural circuit was achieved by introducing a designer receptor that is uniquely responsive to designer drugs. This precise intervention has been shown to elicit consistent and significant pain relief for both evoked and spontaneous pain modalities, with the therapeutic effects enduring for a substantial period of 30 days post-injury. Moreover, microinjection of an α1 adrenoceptor antagonist, but not an α2 adrenoceptor antagonist, dampened nerve injury-induced hypersensitivity. Hence, the LC could potentially have an indirect nociceptive influence as a result of its connections to the DRt, which interact with α1 adrenoceptors [16]. Chemogenetic inactivation of the LCcontra→DRtcontra circuit elicited depressive-like behavior in naïve animals, while leaving long-term pain-induced depression unaffected. In summary, nerve damage initially activates ipsilateral LC (as previously mentioned), temporarily mitigating neuropathic symptoms. Nevertheless, the subsequent activation of the contralateral LC to dorsal reticular nucleus (LC→DRt) facilitatory pain projection pathway has been implicated in the perpetuation of chronic pain states. In contrast, the global bilateral activation of the LC is thought to contribute to the depressive-like phenotype often observed in conjunction with chronic pain conditions [15].

3.2. LC -the rostral ventromedial medulla (RVM) circuit

Since the early 1980s, the RVM has been acknowledged as a crucial pain-gating nucleus that oversees the integration of pain inhibition and facilitation processes [20]. Chemogenetic LC-RVM activation induced colorectal visceral hyperalgesia and anxiety in mice. In a DSS-induced pain model, LC-RVM hyperactivity correlated with pain and anxiety, which were alleviated by LC-RVM inhibition. CRS-induced anxiety and visceral hyperalgesia were also reduced by LC-RVM inhibition. LC-RVM circuitry may be critical for comorbidity of visceral pain and stress-related disorders [21]. The rearrangement of the LC's functional structure during times of stress may triggers the activation of the LC→RVM circuit, which enhances colorectal visceral pain. Conversely, suppressing this circuit can significantly reduce stress-induced colorectal visceral pain. It is probable that the LC functions as an intermediary hub, facilitating the exchange of information between stress-related mental health disorders and visceral pain. These revelations offer a fresh viewpoint for exploring neural circuit changes associated with stress-induced pain sensation and suggest a potential new therapeutic target for treating stress-induced colorectal visceral hyperalgesia.

3.3. LC-basolateral amygdala (BLA) circuit

It has been shown that the LC- BLA circuit contributes to the anxiety-like behavior seen after prolonged neuropathic pain. This is evidenced by the fact that inhibiting LC neurons projecting to the BLA reversed anxiety symptoms in rats with CCI of the sciatic nerve, without affecting sham-treated controls [9,22]. It has been demonstrated that activating the noradrenergic projections from the LC to the BLA through optogenetics leads to the release of NA in the BLA, inducing anxiety-like behavior that is mediated by β-adrenergic receptors (β-ARs) [9,23]. The chemogenetic blockade of the LC/BLA circuit or the intra-BLA administration of a beta-adrenergic receptor antagonist has been found to eliminate both long-term pain-induced anxiety and enhanced fear learning. Similarly, the administration of beta blockers systemically also produced this beneficial effect, potentially paving the way for new treatment options for comorbid pain and anxiety. Therefore, pain would increase the level of NA in the BLA, thereby strengthening the memory of adverse occurrences. Then, It is intriguing to observe that the activation of neural projections from the LC to the BLA has been linked to the encoding of traumatic memories, indicating a possible similar dysregulation in posttraumatic stress disorder and persistent pain conditions [25]. Additionally, a neuroimaging study has revealed reduced gray matter volume in corticolimbic brain areas, including the BLA, in patients suffering from trigeminal neuralgia (TN) [24].

3.4. LC-anterior cingulate cortex (ACC) circuit

The ACC is one of the LC-associated networks that plays a role in the affective dimensions and emotional expressions related to pain [26]. Consequently, individuals suffering from depression exhibit hyperactivity in the ACC, and this hyperactivity leads to antidepressive-like outcomes caused by chronic neuropathic pain. Aligned with this, long-term neuropathic pain (six weeks post nerve injury) has been linked to a bilateral elevation of NA levels in the prefrontal cortex, indicating an excessive activation of the noradrenergic system in persistent pain conditions. Furthermore, in vitro experiments have demonstrated that optogenetic activation of the LC-ACC circuit significantly enhances excitatory neurotransmission, as reported in the literature. The depressive symptoms induced by long-term pain were effectively alleviated through two distinct approaches: bilateral chemogenetic deactivation of the LC-rostral ACC circuit, and intra-rostral ACC administration of antagonists targeting both alpha1- and alpha2-adrenoceptors [11]. From this, we can infer that after nerve injury, over time, the restorative analgesia provided by the LC loses its effectiveness due to the bilateral activation of the LC and its projections to the rACC and the activity of α1- and α2-adrenoceptors mediates the long-term contribution of these projections to depression.

3.5. LC-prefrontal cortex (PFC) circuit

Studies have shown that the chemical activation of LC-norepinephrine neurons, which govern PFC, increases anxiety-like behavior in rats [27].

3.6. LC-dentate gyrus of hippocampus (DG) circuit

A recent investigation revealed that the application of chemogenetic inhibition on the LC projections targeting the DG, lasting for 15 days, led to the emergence of anxiety-like conduct and a decrease in hippocampal neurogenesis among female sham rodents. Conversely, prolonged chemogenetic stimulation of these projections was found to alleviate anxiety and enhance hippocampal neurogenesis in neuropathic male rodents. Therefore, it is plausible to infer that a reduction in LC activity directed towards the hippocampus could potentially induce anxiety caused by pain in male rodents [28].

Table 1. LC associated neural curcuits contributes to pain and its coexisting Depression or Anxiety

(-) LCcontra→DRtcontra	evoked and spontaneous pain ↓ induced depressive-like behavior in naïve animals
(+) LC→RVM	visceral hyperalgesia↑ anxiety↑
(-) LC→BLA	anxiety↓ adverse learning and memory↑
(-) LC→ACC	depression↓
(+) LC→PFC	anxiety↑
(-) LC→DG	anxiety↑ in male rodents

Notes: (+) indicates activation, (-) indicates inhibition; (↑) represents increase, (↓) represents decrease

4. The Role of Neurotransmitters in Pain and Emotion Modulation by the LC

A fundamental mechanism by which the LC exerts its influence involves the release of neurotransmitters, which serve as chemical mediators facilitating interneuronal communication. Various neurotransmitters, notably NA, Glutamate, histamine, and Gamma-aminobutyric acid, have been delineated as pivotal in modulating pain and emotional processes. These neurotransmitters

interact with diverse receptors dispersed across the brain and spinal cord, thereby modulating pain perception and emotional states, including fear, anxiety, and depression.

4.1. Glutamate

Although the regulation of glutamate release, the archetypal excitatory neurotransmitter, has undergone extensive investigation in the spinal cord and brain, its exploration in the LC remains relatively limited. Glutamate is distinguished as the principal excitatory modulator within the spectrum of neurotransmitters that govern neuronal activity in the LC. It predominantly mediates its excitatory influence through the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Additionally, glutamate exerts an inhibitory effect on its own release by presynaptic group II/III metabotropic glutamate receptors (mGluRs) [29]. Recent scholarly investigations within the LC of rats have underscored the pivotal role of astroglial glutamate transporter-1 (GLT-1) in keeping the levels of extracellular glutamate low. This discovery highlights the critical function of GLT-1 in modulating neurotransmission and sustaining the homeostatic balance of glutamate in the synaptic cleft. These studies also indicate that peripheral nerve damage can lead to a decrease in GLT-1 expression, resulting in elevated basal extracellular glutamate concentrations, ultimately leading to a reduction in evoked glutamate release through presynaptic mGluRs [30]. Previous research conducted on rats exhibiting chronic neuropathic hypersensitivity has shown that peripheral nerve damage causes a downregulation of GLT-1, leading to elevated basal extracellular glutamate levels in the LC, which consequently increases the basal activity of the noradrenergic neurons. Nonetheless, the surge in baseline extracellular glutamate also triggers the LC's noxious stimulation-induced glutamate release to diminish, which in turn causes a decline in spinal NA release and LC neuronal activity. It eventually compromises pain-induced endogenous analgesia.

These findings align with clinical observations indicating a diminished capacity for patients with established neuropathic pain to physiologically engage descending inhibition [31,32].

4.2. NA

The projections of the LC to the spinal cord, which involve noradrenergic neurons, are essential in modulating the inherent analgesic processes of the human body. These projections can be stimulated by glutamate signaling within the LC. Recent scholarly research has expanded our comprehension of chronic neuropathic pain, elucidating that the tonic inhibition of basal glutamate release within the LC is not exclusively governed by glutamate itself. Instead, it is significantly modulated by NA. This finding underscores the complex interplay between neurotransmitters in the regulation of pain pathways and highlights the multifaceted nature of neural modulation within the LC [31]. Within the LC, NA not only auto-inhibits LC neurons by stimulating α2 adrenergic receptors but also reduces presynaptic glutamate release via the same receptor subtype in the central nervous system [33,34]. Despite peripheral nerve injury possibly having no direct impact on the basal release of NA in the LC, it does elevate the levels of dopamine-β-hydroxylase, the key enzyme in NA synthesis, along with heightening the expression of α2 adrenergic receptors in the LC [35]. This leads to an enhancement of the inhibitory effect of α2 adrenergic receptor agonists on LC neuronal firing. Stimulation of α2 adenosine receptors causes membrane depolarization, thereby decreasing the firing of NA neurons in brainstem nuclei and inhibiting the release of NA. Experiments have demonstrated that blocking α2 adrenoceptors within the LC can induce glutamate release specifically in the LC six weeks after spinal nerve ligation (SNL) injury, but not in a normal LC. Furthermore, blocking AMPA receptors within the LC and α2 adrenoceptors in the spinal cord can inhibit the antihypersensitivity effect observed in SNL rats [36]. These findings suggest that in chronic neuropathic hypersensitivity, descending noradrenergic circuits are subject to tonic inhibitory control. This control arises not only from the auto-inhibition of noradrenergic neurons but also from the inhibition of continuous glutamate release in the LC through the activation of α2 adrenoceptors by NA.

Overall, blocking α2-adrenergic or metabotropic glutamate receptors can induce glutamate release in the LC, activating descending inhibition in rats with chronic neuropathic hypersensitivity, which can reduce hypersensitivity following nerve injury.

4.3. Gamma-aminobutyric acid (GABA)

Unlike glutamate, GABA serves as the main inhibitory neurotransmitter for LC neurons by acting on GABA-A and GABA-B receptors. And, it suppresses evoked glutamate release through presynaptic GABA-B receptors in the LC. Previous studies in rats have shown that spinal nerve ligation (SNL) elevates basal GABA release and the immunoreactivity of the GABA-synthesizing enzyme glutamate decarboxylase in the LC, suggesting an increased GABA tone following nerve injury. Five weeks after chronic constriction injury of the infraorbital nerve, bilateral injections of bicuculline (a GABA receptor antagonist, 200 ng per site) into the LC can inhibit hypersensitivity [37].

4.4. Serotonin

The LC also receives serotonergic inhibitory inputs from the DRt nucleus, and serotonin has been demonstrated to attenuate both the responses evoked by sensory stimuli in the LC and the excitation of LC neurons induced by glutamate [38].

4.5. Histamine

The pontine LC, which is engaged in descending noradrenergic pain control, is one of the brain structures that get efferent projections from the histaminergic tuberomammillary nucleus [39]. Histamine promotes the inhibition of neuropathic hypersensitivity in the descending spinal circuit via histamine H2 receptors on noradrenergic cell bodies. Blocking the autoregulatory histamine H3 receptors on histaminergic nerve terminals in the LC enhances histamine release, which in turn strengthens the descending noradrenergic pain inhibition, thereby enhancing antihypersensitivity effects [40]. At the spinal cord level, NA released from coeruleospinal axons, stimulated by histamine in the LC, suppresses nociception. This suppression occurs through the activation of inhibitory interneurons via α1-adrenoceptors, as well as through both postsynaptic and presynaptic inhibition of spinal pain-relay neurons mediated by α2-adrenoceptors.

The above content indicates that excitatory and inhibitory inputs regulate the firing activity of noradrenergic neurons in the LC, which are involved in descending noradrenergic analgesia.

5. Hormonal Influences

The LC is not an isolated entity, it is intricately linked with a variety of hormonal systems throughout the body. This interconnectedness allows the LC to engage in a nuanced dialogue with these systems, enabling it to adjust its responses to a wide array of stimuli with precision and adaptability. This complex interaction serves as crucial to the LC's function to control pain and the emotional problems that go along with it.

5.1. Stress hormones

One of the principal endocrine systems that interfaces with the LC is the hypothalamic-pituitary-adrenal (HPA) axis, tasked with orchestrating the body's stress response regulation. Corticotropin-releasing factor (CRF), released from neurons in the paraventricular nucleus (PVN) of the hypothalamus, is a stress-related hormone that regulates the activity of the LC. CRF exerts its effects on various key sites within crucial pain regulatory structures, thereby directly involving this molecule in the modulation of pain. Specifically, the LC, which serves as the primary source of NA in the brain, stands out as a significant target for CRF neurotransmission. Complete Freund's adjuvant-induced monoarthritic served as the inflammatory chronic pain model, and in this context, four-week-old monoarthritic animals received a microinjection of α-helical corticotropin-releasing factor receptor antagonist into the contralateral LC. Subsequent assessments quantified nociceptive and anxiety-like

behaviors, as well as the expression of phosphorylated extracellular signal-regulated kinases 1/2 and corticotropin-releasing factor receptors in the paraventricular nucleus and LC. The results indicated that monoarthritic rats exhibited anxiety and elevated phosphorylated extracellular signal-regulated kinases 1/2 levels in both the LC and paraventricular nucleus, while the expression of corticotropin-releasing factor receptors remained unchanged. Importantly, the administration of the α-helical corticotropin-releasing factor antagonist effectively reversed both the anxiety-like behavior and normalized the phosphorylated extracellular signal-regulated kinases 1/2 levels specifically in the LC [41]. In summary, CRF signaling, mediated through the ERK1/2 cascade in the LC, emerges as a crucial mechanism that is strongly associated with anxious behavior resulting from chronic inflammatory conditions.

5.2. Sex hormones

Research on rodents has revealed that sex hormones influence the analgesic effects produced by α2-AR. Specifically, in female rats, the presence of estrogen diminishes the analgesic response triggered by α2-AR activation in the trigeminal region. Conversely, in male rats, the analgesic effect is dependent on the presence of testosterone. The administration of the α2-AR agonist clonidine demonstrates analgesic properties in male rats, testosterone-treated castrated male rats, and ovariectomized female rats. However, the analgesic effects can be abrogated by the α2-AR antagonist yohimbine [42]. In essence, the differential modulation of α2-AR-mediated inhibition based on sex may offer insights into why females are more susceptible to trigeminal neuralgia (TN). This understanding contributes to elucidating the sex- and age-related variations observed in pain regulation, potentially aiding in the creation of improved analgesics specifically designed for each sex.

6. Therapeutic Strategies

6.1. Antidepressants

Depression and pain frequently coexist, with over 75% of depressed individuals reporting painful symptoms. Moreover, patients suffering from chronic pain face a fourfold increased risk of depression. Serotonergic and noradrenergic neurons regulate mood, movement, cognition, and emotions. They also project to the spinal cord, inhibiting painful stimuli input. Dysfunction of these neurons affects ascending and descending pathways, causing depression and somatic pain.

Traditional antidepressants typically exert their effects by elevating the concentrations of monoamine neurotransmitters, such as serotonin and dopamine, within the synaptic cleft. Among these antidepressants, selective serotonin reuptake inhibitors (SSRIs) are less effective in treating pain. However, antidepressants with dual actions, such as venlafaxine, milnacipran, and duloxetine, which are selective serotonin and norepinephrine reuptake inhibitors, may be more effective in relieving pain and better tolerated. They may modulate neurogenesis and neuroplasticity, leading to more complete recovery in patients with depression and chronic pain [43].

In contrast, ketamine nasal spray, the sole medication approved in Europe for the targeted treatment of treatment-resistant depression, operates on a distinct mechanism. It facilitates the release of glutamate—through the blockade of N-methyl-D-aspartic acid receptors (NMDA), a subtype of ionotropic glutamate receptors. This action initiates a cascade of reactions that foster neuroplasticity and the establishment of new neural connections. The expedited therapeutic response of esketamine positions it as a promising agent for the management of patients presenting with acute suicidal ideation or behavior. Extended-release quetiapine, endorsed by clinical guidelines as an antipsychotic augmentation strategy, is frequently utilized in the therapeutic armamentarium against treatment-resistant depression. Its mechanism of action encompasses a complex interplay with a spectrum of brain receptors. As an antagonist of serotonin 5-HT2 and dopamine D2 receptors, quetiapine's antipsychotic properties are attributed to the intricate dynamics of these receptor interactions. Recent studies illuminate a higher remission rate at the eight-week mark for patients administered esketamine

nasal spray in conjunction with selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs), surpassing the outcomes achieved with extended-release quetiapine combined with SSRIs or SNRIs [47].

Moreover, Studies have demonstrated the efficacy of the tricyclic antidepressant desipramine (DMI), a norepinephrine reuptake inhibitor, in preventing or alleviating noradrenergic damage caused by neuropathic pain. Electrophysiological and Western blot analyses show dysfunction in the LC of rats with chronic sciatic nerve ligation. Desipramine effectively alleviates pain and despair-like behavior, reduces burst rate, and decreases tyrosine hydroxylase expression. Surprisingly, early DMI treatment did not alter anxiety caused by pain but did reduce pain aversion, although these effects were abolished when treatment began after the establishment of noradrenergic damage. Therefore, DMI appears to produce different outcomes depending on the timing of treatment, suggesting that the balance between the benefits and adverse effects of DMI treatment may shift as neuropathy progresses [44].

In summary, research on the role of LC in pain combined with depression has provided us with promising research directions and treatment strategies：(1) Further investigation into how NA and other neurotransmitters like glutamate interact in LC, as well as how these interactions affect pain perception and emotional states, may reveal new therapeutic targets (2) Exploring how neuroplasticity changes in LC correlate with the development of chronic pain and depression could potentially aid in the development of treatments that promote neural recovery. (3) Studying the role of non-pharmacological treatments, such as neuromodulation techniques (deep brain stimulation, transcranial magnetic stimulation, etc.), in regulating LC activity and improving pain combined with depression.

6.2. Acupuncture treatment

Visceral pain (VP) is a complex pain condition linked to negative emotions like anxiety and depression. Acupuncture relieves pain by integrating signals from acupoints and pain sites in the CNS. Key brain nuclei are LC, RVM, ACC, and amygdala. Neural circuits like PBN-amygdala, LC-RVM, amygdala-insula, ACC-amygdala, etc., are involved. Acupuncture modulates central structures and neural circuits in medulla oblongata, cortex, thalamus, and hypothalamus. Neurotransmitters like serotonin, glutamate, and enkephalin are also involved. However, brain mechanisms of acupuncture for VP relief are still limited. Further animal and clinical studies are needed [45].

6.3. CRF receptor 1 antagonist

Irritable Bowel Syndrome (IBS) is a prevalent gastrointestinal disorder linked to chronic abdominal pain, irregular bowel movements, heightened anxiety, and heightened sensitivity to stress. A growing body of preclinical and clinical evidence underscores the significant involvement of the CRF/CRF receptor 1 signaling pathway in the pathophysiology of IBS. Studies in rodent models have demonstrated that CRF can induce anxiety-like behaviors and modulate colonic functions, implicating its role in the disorder. In clinical studies, the administration of CRF to IBS patients has been shown to enhance gastrointestinal motility and increase visceral pain sensitivity, effects that are effectively mitigated by treatment with a non-selective CRF receptor antagonist [46].

7. Conclusion

In conclusion, the LC is a key player in both pain processing and emotional regulation, highlighting its potential as a therapeutic target for conditions like depression and anxiety that frequently accompany chronic pain. Unraveling the neuroregulatory mechanisms and the LC's interactions with neural networks and neurotransmitters can pave the way for innovative treatment approaches. Additionally, examining the hormonal influences on LC function may yield promising insights. Future research should aim to translate these findings into effective clinical interventions to enhance the management of both pain and associated mood disorders.

The LC has risen as a promising target for treating pain and comorbid emotional disorders such as depression and anxiety. This brain region is pivotal in modulating the body's stress and pain responses, positioning it as an ideal target for therapeutic interventions. By focusing on the LC, researchers and clinicians aim to alleviate not only the symptoms of pain but also address the emotional aspects that are often intertwined with chronic pain conditions.

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