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Research Progress on Mechanisms in Regulating Anxiety-Related Neural Circuits

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Abstract: Anxiety is a common disease in the modern society which significantly affects people's daily lives and function, thus it has become an increasingly highlighted issue. Anxiety is regulated by neural circuits in the brain. Therefore, the basal mechanism of anxiety has been studied, especially research based on the related neural circuits. For a long time, due to the limitations of science and technology, there was no breakthrough in research regarding anxiety. However, in recent years, due to the progress of technology, the research on anxiety neural circuits has made great progress. For example, the interaction among various brain regions, such as the central nucleus of the amygdala (CeA), the ventral tegmental area (VTA), the ventral hippocampus (vHPC), and so on. This article focuses on three brain regions: including BLA, BNST, and VTA, and illustrate their different roles and mechanisms in regulating anxiety. On this basis, this intensive study of anxiety will further promote the progress of anxiety research and provide therapeutic targets for the related treatment.

Keywords: Anxiety; Basal lateral amygdala (BLA); Bed nucleus of stria terminalis (BNST); Ventral tegmental area (VTA); Brain

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1. Introduction

Anxiety is a kind of negative human emotion which has an impact on both the physical and mental health. It can cause a range of symptoms, such as mood instability, irritability, fatigue, and lack of concentration. The Royal College of Psychiatrists said that anxiety disorders such as separation anxiety disorder, post-traumatic stress disorder and social phobia affect 1 in 10 people [1]. Anxiety disorders affect up to 33.7% of the population according to large population-based surveys [2]. Comorbid depression and anxiety disorders occur in up to 25% of general practice patients. About 85% of patients with depression have severe anxiety, and 90% of patients with anxiety disorders have depression [3]. With the increasing emphasis on mental and spiritual health, anxiety and related disorders have received increasing attention.

The whole fear emotion is based on Pavlovian reflex, which provides a research idea for the transition from normal fear to abnormal fear. Recent studies have used advanced technologies such as optogenetics, behavioral neuroscience, and electrophysiology to examine the causal relationship between anxiety and various brain regions and neural circuits. According to previous studies, some of the most important brain regions include basal lateral amygdala (BLA), bed nucleus of stria terminalis (BNST), medial prefrontal cortex (mPFC), ventral tegmental area (VTA), ventral hippocampus (vHPC) and so on. One of the key parts of the brain involved in fear and anxiety is the amygdala which is the hub of anxiety regulation. Studies have found the effect of bidirectional reverse regulation pathway activity between BLA and mPFC on anxiety. The results show that stimulation of BLA projections to the mPFC promotes anxiety response [4].

Research has observed the activation of BLA projections to the central nucleus of the amygdala (CeA) had the effect of relieving anxiety, and inhibition of this pathway can promote anxiety. Another BLA output that has been recently examined is the vHPC. While photoactivation of the BLA-vHPC inputs produced anxiogenic effects, photoinhibition had the opposite effects. The BLA inputs to the anterodorsal BNST promote mental and physical anxiolysis, and the anterodorsal BNST causes these responses on the innate anxiety state and mediated via projections from itself the ventral tegmental area (VTA). The BNST modulates fear and anxiety, amBNST afferents also can activate VTA dopamine (DA) neurons. Its regulatory mechanism are two different reward and aversion mechanisms that work together to regulate stress centers. At the same time, BNST's projection to BLA alleviates anxiety, and CeA and BNST have complementary effects, and they regulate the anxiety behavioral response together.

In this paper, through the investigation of several relevant papers on neural circuits and anxiety, the mechanism of action of neural circuits related to anxiety of anxiety are elaborated with aims to provide further guidance and exploration for the clinical research progress of anxiety.

2. The function of BLA in anxiety

Multiple brain regions are involved in the anxiety-related circuits, including BLA, BNST, VTA mPFC, HPC, and so on. In previous studies, multiple technologies such as optogenetics, electrophysiology, are used to study the relationship between neural circuits and anxiety. These circuits are modulated by neural circuits, which then determine whether the external environment is threatening. The body's defense mechanisms are then mobilized to perform different tasks, such as physiological activities and responses [4]. Among them, BLA is the center of regulation of fear and anxiety. When a sensation is stimulated, the amygdala collects and processes information which is then projected to the downstream to further regulate neuroendocrine activity and cognitive behaviors. BLA receives the afferent input from BNST, and the projection from BNST to the VTA can lead to anxiety. By using retrograde labeling of mPFC projections to the BLA, research found in response to a social signal, the activation of BLA-projecting neurons in the infralimbic cortex (IL) is preferred compared to BLA-projecting neurons in the prelimbic cortex (PL). Chemogenetic study of these sub-circuits shows that activation of PL-BLA or inhibition of IL-BLA circuits influences social behavior.

When the threat response stimulates the microcircuits in the CeA, the BLA receives the corresponding stimulus. Among them, BLA and mPFC have dense reciprocal connections which regulate anxiety. The mPFC is a cortical structure that is important for assessing sources of threat. It usually plays an important role in modulating subcortical stimuli to threats. When the BLA projects to the mPFC, it creates anxiety. According to the previous report, the light stimulation of the projection from BLA to mPFC has anxiety-promoting effects. However, the projection from mPFC to BLA inhibits anxiety, and the light stimulation of mPFC to BLA alleviates depression, thus reducing the corresponding social behavior [5]. Therefore, it can be concluded that when the projection from BLA to mPFC is inhibited, an anti-anxiety effect can be achieved. Besides, the BLA-CeA projection, including CeL and CeM, responses to anxiety, and in this circuit, glutamate signals from the BLA are transmitted to CeL, where they stimulate two groups of GABAergic neurons, including protein kinase c-δ (pkcδ)-negative CeLON cell 77 and pkcδ-positive CeLOFF cell 73. The inhibition of CeLON cell 77 or CeLOFF cell 73 results in a reduction of the inhibitory effect of CeM on neurons, leading to a corresponding change in heart rate. It can be concluded that the projection from BLA to CeM will lead to the learning and increase of fear [6]. In general, the amygdala is a very important part of the neural regulatory circuit. It's made up of a lot of mixed and different types of cells that express different kinds of proteins. The amygdala itself is not only a center for fear or anxiety, but also it plays an important role in response to threats. In addition, the function of highly reciprocal limbic circuits is to connect a chain of signals received by an individual, including psychological threats,

environments, and learned associations based on past experiences, and to consolidate them into a specific experience.

3. The function of BNST in anxiety

Regarding the neural circuitry of BNST, BNST projections to BLA have anxiety-relieving effects. The projections from BLA to BNST always have interaction, they interact with each other. At the same time, BNST also regulates anxiety by dominating VTA, and BNST projects glutamatergic neurons to VTA, and then produces corresponding anxiety-related emotions and behaviors. BNST also alleviates anxiety by releasing GABA neurons in a parallel pathway. Therefore, BNST plays an important regulatory role in the relief of anxiety when there is a threat stimulus in the external environment. At the same time, as the regulatory hub of the circuit, BNST participates in the regulation of risk assessment and defensive response when there is uncertainty in the external threat stimulus. The stimulus will also be passed on to the ventral striatum to initiate defensive behaviors like avoidance and evasion. CeA and BNST have complementary effects in the neural circuits. Anxiety stimulation is transmitted to the basal lateral amygdala and BNST via optogenetic transmission of CeA. Fear reflex induces increased conditioned stimulus-off neurons, which overlap with the PKCδ-positive neurons of CeA. Pkcδ-positive neurons are involved not only in the regulation of fear, but also in the generalization of fear, that is, in continuous response state of fear and anxiety. Pkcδ-positive neurons provide bidirectional control of anxiety-related behavior. Furthermore, spontaneous activity of PKCδ-positive neurons is correlated with generalization of fear and anxious behavior without photogenetic projections. This suggests that PKCδ-positive neurons may be regulated by endogenous mechanisms, providing further evidence that the inhibition of endogenous α5GABAAR-mediated controls spontaneous activity of CeA neurons *in vivo*. It is concluded that PKCδ-positive neurons are central channels for control of the fear response circuit, as well as for control of continuous anxiety. Rodent studies shows that BNST plays an important role in sustained threat monitoring, a form of adaptive anxiety, and also plays a key role in the withdrawal and relapse of an addiction. BNST is closely connected to the paraventricular nucleus of the hypothalamus and is also the node of the hypothalamic-pituitary adrenal endocrine regulation that triggers the cortisol response [6]. Related studies have shown that BNST damage alters cortisol release, which is involved in stress regulation. This suggests that BNST may play an important role in diseases triggered by stress responses [7]. Through the analysis of behavior, *in vivo* and *in vitro* electrophysiology, respiratory physiology, and optogenetics, research found that two subregions in BNST had opposite effects on anxiety states: the features of anxiety promoted by elliptical BNST are independent of each other, whereas the neural activity associated with dorsal BNST showed the same characteristics. They also found three different dorsal BNST output projections — to lateral hypothalamus, parbrachial nucleus, and ventral tegmental area — each achieved an independent anxiety decomposition feature: reduced risk avoidance, reduced respiratory rate, and increased positive valence, respectively. This suggests that different subregions of BNST play different roles in the regulation of anxiety [8].

4. The function of VTA in anxiety

In the nervous system of whole anxiety adjustment, which in turn order is divided into detection, interpretation, evaluation, and response initiation. The hypothalamus, sensory cortex and superior and inferior colliculi are responsible for the detection of sensory stimuli. BNST, BLA, CeA, CeL, CeM, and vHPC are responsible for interpretation. The VTA is the hub of evaluation. VTA generates anxiety by receiving the projections from BNST, and BLA also regulates VTA. LH has both excitatory and inhibitory projections over VTA. VTA exerts modulatory projection on the medial prefrontal cortex (mPFC) and the nucleus acumens (NAc), which regulates and triggers a cascade of anxiety-related responses, resulting in rising heart rate, freezing, increased breathing, and so on. The most important of these circuits is the

relationship between VTA and BLA. Recent research shows that the anxiety-like behaviors influence VTA → BLA dopamine neuron related activity. The system of the midbrain dopamine originating from the VTA is crucial and it can play a role in reward processing and enhancement effect, and it is also helps in learning adaptive behaviors in order to better cope with acute and chronic stress environment [9]. A chronic stress response will lead to neurological dysfunction of projection from VTA to mPFC and projection from VTA to NAc, resulting in depressive behavior. The dopamine (DA) neurons of VTA aimed to control anxiety-liked behaviors. VTA DA neuron hyperactivity induced by chronic emotional stress (CES) is involved in the anxiety-like behavior in the innate anxiogenic environment. Chemogenic activation by DA neurons in the VTA directly triggers anxiety-like behaviors. In addition, the projection pathway from NAc to VTA dopaminergic neurons is activated. Bidirectional modulation of the NAc-VTA circuit can promote or inhibit CES-induced anxiety-like behavior. Thus, we propose that the NAc-VTA circuit plays a key role in establishing and regulating CES-induced anxiety-like behavior [10]. Another research found that optogenetic activation of VTA DA neurons promote anxiety-related behaviors due to chronic stress, and when these neurons are suppressed, similar behaviors are produced. This indicates that DA release purposefully in the NAc is prepared for the anti-depressant outcomes of VTA DA neuron activation [11]. At the same time, VTA is not just made up of DA and GABA neurons. These neurons have dual functions, for example, the VTA GABA neurons have a dual inhibitory effect on VTA DA neurons and it also has a long-term inhibitory effect on other parts of the brain. The VTA GABA neuronal circuit has been proved to be a very important key point in the study of depression and anxiety. As effective regulators of VTA DA neurons, VTA GABA neurons are the key centers of reward-related behaviors by projecting to distal brain regions [12]. GABA neurons have local inhibitory effects on DA neurons as well as long-term inhibitory effects on projection areas, including NAc. The GABA neurons of the VTA can also regulate reward and aversion-related learning. GABA neurons include two types of neurons, which are interneurons and local inhibitory and projection neurons that provide DA neurons, providing long-term inhibition of multiple brain regions, including NAc, which is involved in reward-related learning. Inhibition of VTA GABA cells results in the release of the inhibitory effects onto DA neurons, such reduction of inhibition promotes the release of DA in brain and regulate subsequent synaptic transmission, and finally regulate some specific behaviors on this basis. There is an example of reward schemes, the oral-self administration of benzodiazepines (BDZs). DA cell neurons in the VTA and GABA neurons co-regulate this behavior, where GABA neurons are locally connected to DA neurons and send long-range projections to brain regions innervated by DA neurons in the VTA. With continuous research, the role of these inhibitory neurons in the mesolimbic reward system has been gradually affirmed [13].

In gaining insight into the mechanisms underlying the corresponding responses to native anxiety and antianxiety, these results suggest that anxiety in the amygdala is continually regulated by equilibrium antagonistic pathways and illustrate the importance of projection in studying the function of anxiety-related neural circuits. Among them, the mutual projection relationship between BLA and vHPC is vital, making it a hot topic for research. Relevant experimental results show that BLA projection to vHPC plays a key role in bidirectional regulation of social interaction. The extending findings are showing that BLA projections to the vHPC not only modulate anxiety-related behaviors but also modulate social behaviors. Moreover, activation of this pathway increases sad emotions and decreases social interaction. These findings make broad influence on the involvement of this pathway in behaviors associated with ASD, obsessive-compulsive disorder, and social anxiety, and provide potential new targets for treatment development [14].

The BNST is a region of the brain that processes both anxiety and reward. It is a highly fragmented structure composed of multiple subnuclei and cells with different neural functions. Different subregions in BNST play different roles. Most CRF neurons are located in the lateral region, which induces anxiety, while

those in the medial region fights anxiety. Studies on complex neurochemistry and neural circuitry of BNST helps in formulating targeted treatments based on the connectivity, neurochemical phenotype, and electrophysiology associated with BNST neuroplasticity and stress and reward-seeking behaviors. In order to gain a deeper understanding of the complex structure of BNST, further studies on the functional roles of different cell types, morphological organization, and neuronal populations in BNST will be necessary [15].

Through the use of circuit detection technology and other relevant behavioral models, experimental results show that the dysfunction of dopamine neurons in VTA and BNST can produce abnormal anxious behavior, but this disorder is not associated with similar depressive behavior. Using real-time VTA BLA fiber photometric recordings, it can be concluded that the neuronal activity of VTA and BLA is related to the level of anxiety and stress, and the former may have an inhibitory effect on the latter two. Previous experiments have shown that VTA → NAc nucleus hyperactivity is somewhat related to depressive-like behaviors observed in mice with Alzheimer disease [16]. One thing to note when we talk about VTA is that it plays a key role in motivation and reward. It further suggests that DA plays a very important role in dealing with the corresponding aversion and reward mechanisms. These results further illuminate the critical role of the midbrain and dopamine system in regulating the brain, and demonstrate the interplay between chronic social stress and depression-related abnormal behaviors and VTA subcircuits in differential and reverse control [11].

5. Summary

This article mainly elaborated about the anxiety regulation mechanism of the brain. Potential, indirect and expected threats from the external environment can cause anxiety, and neural circuits in brain also regulate anxiety. There are many brain regions involved in regulating anxiety. Specifically, BLA, BNST and VTA, were discussed in this article. The most important research on BLA is the bidirectional projection relationship between BLA and mPFC. Besides, BNST plays a very important role in reducing anxiety. There are many studies that are specific to neurons, along with associated chemical reactions and associated hormonal regulation, such as noradrenaline. By studying their neural circuits and projection effects on each other, it provides a new therapeutic target for studying the formation and treatment of anxiety, which makes treatment more tractable.

The treatments for anxiety are also an important topic. Anxiety can be treated in various ways, often using a combination of medication and psychotherapy. The most important therapy is cognitive-behavioral therapy (CBT), and it includes exposure and cognitive therapy. Exposure therapy is based on emotional processing, it is based on emotional processing theory, association means fear. It facilitates the reception of relevant fear information and processing of fear responses. It can be used in post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD) and so on. CBT targets the interaction among thoughts, behaviors, and physiology through cognitive and behavioral strategies. The treatment effect is enhanced when it is designed according to the patient's condition. The medicine often used for most anxiety disorders is benzodiazepines, which are compounds that act on the GABAA receptors. Benzodiazepines are effective at suppressing the amygdala [17]. Overall, observations from these experiments provide research targets for the treatment of anxiety. Treatment strategies for improvement and prevention were established and formulated accordingly.

Despite some progress in the study of anxiety, the brain is still a very complex system. Therefore, further experiments are needed to understand the details of the brain's structure. There are evidence that suggests that the central mechanisms underlying states of fear and anxiety are similar in animals and humans. Optogenetics has been used to study anxiety-like behaviors and specific circuits in the anxious state of rodents. These studies provide biological insights into the phenomenon of anxiety-like behaviors. Hence, a challenge for future research would be to use the function and anatomy of these circuits in the

brain for analysis and to use the data to make calculations. Future research needs to address how stimulus representation, association, and behavioral output programs are encoded in the circuitry of brain neurons. This will require the realization of integrated electrophysiological and optical recordings in deep brain regions to further understand the mechanisms of anxiety formation. The study of circuit organization and function in anxiety will provide new lines of inquiry into brain functions that translate sensory inputs into specific behavioral outputs.

Disclosure statement

The author declares no conflict of interest.

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