Research Progress on Neural Circuit Mechanisms of Depression

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Abstract: Depression is one of the most prevailing neurological and psychotic disorders with a high rate of mental disability. The depression is closely related to the abnormality of neural circuits in brain. As a result, it is of great significance to make a profound study of the neural circuit of depression for revealing new clinical therapies of depression. Currently, neural circuits about depression have not been fully understood and there are still many difficulties puzzling researchers. While with the processing effort of neuroscientists and the development of electrophysiology, epigenetics or neuroimmunology, great progresses have been made in studies about neuronal circuits in depression to some extent. In this paper, we discuss various brain areas those are related to depression including the ventral tegmental area (VTA), nucleus accumbens (NAc) and dorsal raphe nucleus (DRN), and then put emphasis on their local function with different neurotransmitters and abnormality of neural circuits of depression by reviewing previous studies. In a way, figuring out the mechanism of depression can improve the cure rate, and reduce the economic loss due to depression around the world.

1. INTRODUCTION

Depression is one of the most prevailing neurological and psychotic disorders with a high rate of mental disability. Many concurrent biotypes may underlie depression, like rumination, anxious avoidance, negative bias, threat dysregulation, anhedonia, context insensitivity, cognitive dyscontrol, and inattention (Williams, 2016). Currently, more than 300 million individuals have suffered depression, and it has brought increasingly serious burdens and incalculable losses to the global economy (Gururajan, 2019). To deal with the crisis resulted by this disorder, researchers have investigated the mechanism of depression with pre-clinical models like chronic unpredictable mild stress (CUMS), chronic social defeat stress (CSCD), and focused on the brain regions and related neural circuits. The brain regions related to depression mainly include the ventral tegmental area (VTA), medial prefrontal cortex (mPFC), nucleus accumbens (NAc), dorsal raphe nucleus (DRN), ventral hippocampus (vHPC), lateral habenula, ventral pallidum (VP), amygdala and so on (Knowland, 2017; Kumar, 2018; Knowland, 2018).

VTA is mainly composed of dopaminergic neuros (60%), glutamatergic neurons (10%) and GABAergic neurons (30%) (Oliva, 2016). On one hand, it outputs to the PFC through dopaminergic projections with decreased level of neural activity in depression models. On the other hand, VTA also projects to the NAc with hyperactivity dopaminergic neurons in susceptible mice (Fox, 2019). In addition, it sends dopaminergic projection to hippocampus as well (Heshmati, 2015). According to previous report, the activity of dopamine neurons decreased in CUMS, and the activity of DA neurons increased in CSCD (Fox, 2019). Besides, cholinergic neurons also exist in VTA, and improving VTA cholinergic tone can produce depression-like behaviors (Small, 2016). The firing frequency and burst potential of VTA dopamine neurons in susceptible mice were increased and mainly projected to NAc (Han, 2017), resulting in depression like manifestations.

The NAc is a part of the ventral striatum and is the main cortical receiving area constituting the basal ganglia marginal subcircuits (Islam, 2015). It mainly includes D1 neurons and D2 neurons. D1 neurons are related to antidepressant function, and D2 neurons may be involved in the expression of depressive state (Francis, 2017). NAc D1 neurons project back to the VTA, ventral pallidum (VP), and the substantia nigra, while D2 neurons only send projection to the VP. There is a decrease of GABAergic neuron excitability from NAc in CUMS depression mice, and in resilient mice the excitability of GABAergic neuron increased in CUMS depression mice adversely (Zhu, 2017).

DRN is the primary site for serotonin synthesis (Dean, 2017), and mainly contains both serotoninergic neurons and GABAergic neurons (Xiao, 2017). The DRN is situated on the midline of the brainstem and beneath the aqueduct of the midbrain. Its brain area includes the most serotonergic neuron and mainly projects to the forebrain, including the limbic system regulating emotions and the hypothalamus controlling energy balance with different neurochemical substances (Xiu, 2021). In animal depression models, there is a reduction of function of 5-HT projection in DRN (Prakash, 2020). Through the inhibition of DRN 5-HT neurons, depression behaviors could be induced by GABA injections (Beier, 2015). Most importantly, 5-HTergic projections from

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DRN to the LHb, which suppress the excitability of LHb, suppresses depressive behaviors (Bruchim-Samuel, 2016).

In this paper, we investigated the effect of different neural circuits of depression by reviewing previous studies, and VTA, NAc, DRN have been highlighted, and their different mechanisms in correlation to depression have been discussed.

2 THE NEUROMODULATION MECHANISM OF VTA IN DEPRESSION

The ventral tegmental area (VTA) contains many various groups of cells locating in the interior of the brainstem and together next to the midline on the bottom of the midbrain. And it is an important brain area to depression which consists of dopaminergic, glutamatergic, and GABAergic neurons (Settell, 2017). In addition, there is also serotonin in connection with glutamate and dopamine that elicits precise and complex neural modulation, and it may be a supplement for transmission of VTA activity in depression (Prakash, 2020). VTA is the origin of dopaminergic cell bodies in the mesolimbic or mesocortical systems and has an interrelationship with electrical stimulation treatment of depression (Bruchim-Samuel, 2016). A long-term stimulation effect of VTA can cause a significant increase in protein levels of dentate gyrus (DG) brain-derived neurotrophic factor (BDNF), which is a highly reliable factor that is associated with depression (Bruchim-Samuel, 2016). The VTA plays a critical role in the increase of BDNF. The change of BNDF correlates to the increasing firing rate of VTA dopaminergic neuron activity in depression models. To be specific, the increase can be the improvement of baseline firing rate and phasic firing properties of VTA dopamine neurons in susceptible mice (Han, 2017). Besides, with the effect of DA and GABA neurons, VTA may be an intermediary that controls both reward and punishment learning, which may lead to anhedonia and negative bias respectively that are the core features of depression. In major depression disorder (MDD) patients, dopaminergic neurons, which response to unpredicted reward and anticipation of impending reward and reward learning in the VTA fire, is impaired. In impaired reward learning models, which may lead to depression, there is disrupted reward prediction error (RPE) signaling in the striatum as well as reduced VTA-striatal connectivity in MDD. And there is strengthened VTA-habenula connectivity during punishment owing to the impaired punishment learning with blunted RPE signaling. In some instances, increased VTA activity can elicit depression, while in others, decreased VTA activity is also required. To be specific, chronic physical or psychosocial social defeat stressors increase the activity of VTA dopamine neuron to elicit depression-like behavior. However, chronic unpredicted mild stress, chronic cold stress as well as learned helpless, reduced VTA dopaminergic population activity instead of promoting, resulting in behavioral deficits like depression (Fox, 2019). Moreover, from previous studies, enhanced VTA cholinergic activity increases anhedonia and other stress behaviors through mAChRs and promotes pro-depressive, which demonstrates that specific activation of VTA muscarinic receptors can induce pro-depressive and is in relation to depression responses (Small, 2016).

Complex functional connections exist between the VTA and many subcortical and cortical structures, and these functional connections have also been of interest in MDD research. First and foremost, the projections of VTA dopaminergic neurons are mainly to the NAc, the amygdala, the hippocampus, the bed nucleus of the stria terminalis (BNST), the lateral septal area, the lateral hypothalamus, and to cortical structures such as the medial prefrontal cortex(mPFC) and insular cortex, and so on (Figure1) (Kaufling, 2019). It is an emerging evident that where the outputs of VTA dopaminergic projection go is becoming more and more important. For instance, the projection from VTA to NAc is essential in MDD research since the neurons can modulate the excitatory effect of glutamate afferents that come from the limbic. Indeed, according to previous study, a hyperactivity in susceptible mice can be displayed in VTA dopaminergic outputs sending to NAc (Han, 2017). Besides, another mechanism resulting in depression-like behaviors may be more active BDNF signaling in VTA-NAc circuit after chronic stress like CSCD (Han, 2017). Excitatory projections from the PFC to the VTA play an important role in regulating the activity of VTA neurons. On the contrary, it is illustrated that VTA dopamine neurons projecting to the mPFC display hypoactivity in susceptible mice and improve electrical event in mPFC could attenuate or reverse depressive behaviors (Han, 2017).

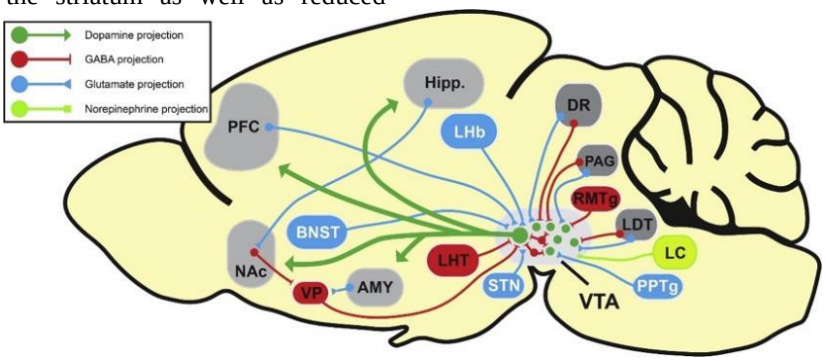

Figure1. Efferent projection of VTA (Knowland, 2018)

Despite it is of importance in efferent neurons of VTA in depression, the afferent projections of VTA occupy a great position in the aspect of depression mechanism as well. The inputs include GABAergic afferents from the VP or the tail of the VTA (tVTA) and glutamatergic projections from the medial prefrontal cortex, the bed nucleus of the stria terminalis, or the pedunculopontine nucleus (PPN). Cholinergic projections from the laterodorsal tegmentum nucleus (LDTg) and noradrenergic inputs from the locus coeruleus (LC) are the supplement pathways (Scheler, 2000). To be specific, the projections from LC to VTA increased the level of its activity selectively in resilient mice and improved the depressive-behaviors in susceptible mice 10. Then the excitation of GABAergic neurons in tVTA, which has also named as the rostromedial tegmental nucleus (RMTg)), decreased DA levels in the striatum, and finally induced depression 4. What is more, increased activity of cholinergic projections from LDT to VTA in the development of dopaminergic behavioral and cellular aspects of the depressive-like phenotype can be induced by chronic social defeat (Scheler, 2000). The PPN projects to VTA indirectly and have both glutamatergic neurons and cholinergic neurons. Glutamatergic neurotransmitter is accepted by receptors from DA neurons, and possibly GABA neurons in VTA, causing both sleep disorders and affective disorders like depression (Rye, 1997; Baek, 2022). Electrical stimulation of the PFC can also produce burst events in VTA dopaminergic neurons and lead to improvement in depressive like behavior (Kaufling, 2019). Furthermore, the deep cerebellar nuclei (DCN), which is the major cerebellar output, projects to VTA. Previous research of neural circuits showed that cerebellar neurons play a crucial role of in the development of chronic stress-dependent depressive behavioral changes in mice (Nauczyciel, 2013).

3 THE NEUROMODULATION MECHANISM OF NAC IN DEPRESSION

Nucleus accumbens (NAc) is another important area with the effect of complicated interaction between depression and itself. It belongs to the basal ganglia, where is located beneath the anterior limb of the internal capsule and occupies a wide range of the basal forebrain rostral to the anterior commissure (Liu, 2021). There are two parts in NAc, including central core and peripheral shell, which participate in cognitive system and the limbic system respectively. Signals are projected from the shell to the core within NAc (Liu, 2021). Moreover, NAc has broad interaction with other brain areas of the limbic system and the prefrontal cortex. NAc is consist of dopaminergic, serotoninergic and glutamatergic neurons (Xu, 2020). Depression is negatively related to NAc volume in general. However, the specific mechanism of depression in the NAc are obscured due to the complex connection and neuron types. The NAc contains amounts of neuro-subtypes, in which the predominant type of them is GABAergic medium spiny neurons with two subpopulations, dopamine receptor 1 positive medium spiny neurons (D1 neurons) and dopamine receptor 2 positive medium spiny neurons (D2-neurons) (Francis, 2017). The rest few numbers of the neurotype in NAc are tonically active neurons, which function in regulating the MSN activity (Abdallah, 2017). Both cell types contribute to depressive-like behavior.

After chronic stress resulting in depression, NAc MSNs appear many anatomical and physiological changes (Fox, 2019). In stress-induced depression models, decreased mEPSC frequency can be observed in D1 neurons but there is increased mEPSC frequency in D2 neurons (Francis, 2017). And stress-induced depression can trigger NAc hypertrophy, which to a large extent depends on the abnormal monoamine like dopamine (Correia, 2022). D1 neurons can set up a remedy for depression-like behavior and finally lead to resilience outcomes, whereas abnormal D2 neurons activity may induce depression state (Fox, 2019). Besides, depression may be caused by chronic stress that can alter the excitation of MSN input neurons. In chronically stressed mice, the excitatory input of D1 neurons is weakened and of D2 neurons are enhanced (Fox, 2019). Most importantly, D1 neurons promote reward-related behavior and D2 neurons induce aversive behavior (Abdallah, 2017). For instance, stimulation of D1 neurons may remove social avoidance and improve sucrose preference, while improving D2 neurons electrical activity can strengthen stress behaviors like learning helplessness. According to previous research on the mechanism of depression in NAc, glutamatergic projection onto D1 neurons is enhanced and can improve the resilience to depression and reduction in D1 neurons may play a role for inducing social avoidance (Fox, 2019). On the contrary, glutamate signaling strengthens the excitatory input in D2 neurons and then drives susceptibility of depression generally. Also, dopamine in NAc is completely in the reward circuit that has a connection with depression, and adjustment of reward-related behavior can also attribute to DA system in the NAc. To be specific, dopamine can improve the associative learning and the sensitivity of reward (Abdallah, 2017), which may reverse depressive-behaviors. Plus, there are expansive distribution of GABAergic neurons in the core and shell of NAc, and down-regulated GABAergic neurons in the NAc is observed from depression-like mice, but not resilience (Zhu, 2017).

The function, structure and pathological changes of neuron circuit in NAc is also of vital importance for depression. To begin with, VTA and the thalamus, PFC, hippocampus mediodorsal thalamus (MDT), LH and amygdala all project blended dopaminergic and glutamatergic neurons to NAc (Correia, 2022; Hoflich, 2019). And excitation of those transmission can be altered by stress, especially in the thalamus, mPFC and hippocampus. Dopaminergic, glutaminergic, and GABAergic projections are complementary to affect the function of neural circuits. The VTA sends dense dopaminergic projections to the NAc. Social isolation can induce a raise of NAc dopamine release and absorb speed, leading to anhedonia, loss of motivation and even depression. Then, in the aspect of glutamatergic

transmission, intralaminar thalamus sends increased glutamatergic projections to NAc synapses in CSDS models. Additionally, mPFC projects decreased glutamatergic neurons to NAc synapses in susceptible mice, which means that inputs from mPFC or amygdala to NAc can reverse depressive-like behaviors. Besides, stress-induced depression may enhance the projections between ventral hippocampus (vHip) and NAc synapses (Fox, 2019). The neurons of NAc are almost MSNs, and efferent neurons which are GABAergic, project to the VP, VTA, LH and BLA, respectively. They cover from the mediodorsal thalamus to the cortex (Hoflich, 2019). NAc D1 neurons project backward to the VTA, as well as the substantia nigra and VP, while projections of D2 neurons sent exclusively to the VP and then back to VTA (Fox, 2019). According to optogenetic research studying, activation of D1 neurons to VP or VTA does not induce obvious depressive-like behaviors. However, increased excitation of D2-neurons-VP projections significantly triggered depression-like behavior by optical activation (Correia, 2022). Most importantly, GABA stabilizing modulator on D2 MSN -VP projection can stop the optically-triggered depression-like behavior, and the neuronal activity changes more in the VP than the activation of D 1 MSN-VP (Correia, 2022), which makes sense that VP plays an important role as a intermediation in depression through GABAergic neurons in NAc MSNs.

4 THE NEUROMODULATION MECHANISM OF DRN IN DEPRESSION

The raphe nucleus also plays a crucial role in depression as a multifunctional and multitransmitter nucleus. The raphe nucleus is divided into dorsal and medial nuclei (DRN, MRN). DRN is a heterogeneous brainstem nucleus, lying in the lateral and ventral periaqueductal gray matter (PAG) of the midbrain (Hornung, 2012). The median raphe nucleus (MRN) extends from the decussation of the superior cerebellar peduncles to the middle pons at the level of the trigeminal motor nucleus. Dorsally, the MRN ends below the medial longitudinal fasciculus and ventrally at the bottom of the midline tegmental region (Hornung, 2012). The DRN is the largest serotonergic nucleus and the MRN is the secondary large one. In addition to serotonin, the DRN and MRN also contains GABA, glutamate, DA and a variety of peptides. The 5-HT is related to stress, reward and emotional systems in response to acute and chronic stress, which may lead to behaviors like anhedonia or even depression in both DRN and MRN (Jahanshahi, 2011). Stress-induced depression can eventually upregulate the uptake efficiency of 5-HT on the post-synapses of neurons in DRN, which finally results in the deficits of 5-HT in intercellular space and cerebrospinal fluid. Therefore, it is evident that the reduction of neurotransmission mediated by serotonin can induce depression (Prakash, 2020). In addition, The DRN includes both 5-HT neurons and GABAergic neurons. Abnormal GABAnerigc injection into the DRN induces depression-like behavior as well. In susceptible models, the GABA inhibited serotoninergic neurons expression in DRN and finally incurred depression (Xiao, 2017). Galanin is another factor that may trigger depression (de Souza, 2018). Galanin is a neuropeptide distributed in mammal brain regions related to depression like hippocampus, BNST and DRN. Galanin and serotonin occupies overlapped in nearly 40% of DRN neurons and the function of galanin in DRN is the same as GABA neurons, which reduce the firing rate of 5-HT (de Souza, 2018). Moreover, in stress-induced depression models, there is a reduction of glutamatergic neurons in ventral DRN which is modulated by the central amygdala. Besides, melanocortin signaling like MC4R in the DRN affects depressive-like behavior by modulating the serotonergic system. MC4R is preferentially enriched in DRN GABAergic neurons, and it is of vital importance for regulating depression-like behavior. To be specific, the inhibition of MC4R can also down-regulate the emission of 5-HT and lead to depression. What's more, energy consumption is modulated by GABAergic neurons and MC4R in DRN has an influence on the regulation of feeding. The feeding effect of melanocortin signaling may also be one of vital causes of depression (Bruschetta, 2020).

The DRN can be divided into the ventral subnucleus, the caudal subnucleus, ventrolateral subnucleus, interfascicular subnucleus. The ventral part of DRN receives afferent projections from the LH, central amygdala, OFC, and sends efferent projections to LHb, OFC and other cortical areas and the VTA 16. The DRN is a critical hub that may modulate stress and reward systems, of which part is involved all those areas referred above (Prakash, 2020). The neurons projecting from CeA to DRN is consist of GABA and corticotropin releasing hormone (CRH) neurotransmission, which regulate the activity of both 5-HT and non-5-HT neuron in DRN. According to previous study, the CRH neurons in the CeA send strong output to the DRN which has been involved in the development of depression-like phenotypes in response to uncontrollable stressors (Prakash, 2020). Also, the circuit between DRN and LHb is a critical mediator of 5-HT, which is associated with depression. The activity of 5-HT transmitting from the DRN to the LHb can be down-regulated by injection of GABA into DRN. The LHb sends GABAergic projections to the DRN and the activation of GABAergic projections can inhibit the activity of 5-HT in DRN. Besides, serotoninergic projection from the DRN to the LHb also activates GABA neurons in LHb. When the LHb is actived, it not only leads to the inhibition of DRN 5-HT neurons, but activity of it is also restricted by hypoactivity of DRN 5-HT neurons. This is to say that input of GABA to the DRN may reduce the activity of LHb neurons due to the inactivation of LHb when DRN 5-HT neurons are inhibited. And it is the maintenance of homeostasis in the LHb-DRN circuit. Furthermore, there may be the polysynaptic effect of 5-HT in the DRN-LHb by changing the activity of downstream brain areas, except for direct injection within DRN. As a result, the down-regulated activity of 5-HT from DRN to LHb inducing depressive behaviors may also trigger its downstream abnormality in other brain areas (Xiao,

2017).

5 DISCUSSION

Depression is a mental disease which is associated with different areas. In this review, we focus on VTA, NAc and DRN, and explain functions and pathologic changes of their local activities and their neural circuits in depression. VTA has many outputs and inputs mainly including dopaminergic, GABAergic and glutamatergic neurotransmitters, and activity of DA neurons in VTA is the dominant among them. VTA-NAc neural circuit plays a significant role in depression by BDNF signaling and dopaminergic transmission which activates glutamate efferent from the limbic. In depression, NAc is also a crucial area which can be divided into D1 and D2 neurons. D1 neurons and D2 neurons have opposite function in regulating depression, which means that activity of D1 neurons is reduced in depression and the stimulation of D1 neurons can ameliorate depression-like behaviors, while D2 neurons are vice versa. DRN is another critical area and is highly associated with the serotonin. Depression is always accompanied by down-regulate of 5-HT.

Except those areas mentioned above, other circuits participate in the depression as well. Firstly, electrical stimulation of the PFC can promote acute electrical excitation events in VTA dopaminergic neurons. The VTA also send projections to the PFC, and the projections to the reward system can be more active, which lead to resilience of depression. LHb not only sends projections to DRN, but also connect with VTA and the entopeduncular nucleus. The circuits elicit negative emotional behaviors like aversion or depression likewise (Knowland, 2018). The VP is supposed to be an intersection of the motivational and reward circuitry implicated in depression. Parvalbumin-positive (PV) is a special cell type in VP which projects to LHb and VTA respectively. Increased activity of VP PV neurons is a salient mark of depression, and projections from VP PV to the LHb and VTA induce distinct depressive behaviors including behavioral despair and social withdrawal (Knowland, 2017). Plus, the basolateral amygdala (BLA) also has many projections to different targets, of which functions are highly associated with depression. For instance, BLA outputs densely to the NAc and it is investigated that social avoidance behavior can be reversed promptly by optogenetic stimulation of amygdalar projections to NAc in susceptible animals (Knowland, 2018).

Look into the future, a variety of unknown circuits and effects of distinct neuromolecular in different local brain areas need to be investigated further to figure out the depression clearly. What's more, except for strengthening basic research, drug development and clinical research should also be carried out to find new therapeutic targets for depression. It is believed that with the development of neuroscience and genomics, and the deepening research on the pathogenesis of depression, new progress will be made in the prevention and treatment of depression.

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