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REVIEW

Hippocampus: Molecular, Cellular, and Circuit Features in Anxiety

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Abstract Anxiety disorders are currently a major psychiatric and social problem, the mechanisms of which have been only partially elucidated. The hippocampus serves as a major target of stress mediators and is closely related to anxiety modulation. Yet so far, its complex anatomy has been a challenge for research on the mechanisms of anxiety regulation. Recent advances in imaging, virus tracking, and optogenetics/chemogenetics have permitted elucidation of the activity, connectivity, and function of specific cell types within the hippocampus and its connected brain regions, providing mechanistic insights into the elaborate organization of the hippocampal circuitry underlying anxiety. Studies of hippocampal neurotransmitter systems, including glutamatergic, GABAergic, cholinergic, dopaminergic, and serotonergic systems, have contributed to the interpretation of the underlying neural mechanisms of anxiety. Neuropeptides and neuroinflammatory factors are also involved in anxiety modulation. This review comprehensively summarizes the hippocampal mechanisms associated with anxiety modulation, based on molecular, cellular, and circuit properties, to provide tailored targets for future anxiety treatment.

Keywords Anxiety · Hippocampus · Excitatory neurons · Interneurons · Neural circuit

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Introduction

The hippocampus is a major target of stress mediators which lead to multiple psychiatric disorders, especially anxiety disorders. Several studies have shown that the hippocampus is structurally and functionally differentiated between the dorsal and ventral portions [1–4]. The ventral hippocampus (vHPC) is closely related to emotion, and its injury particularly impacts anxiety-related functions, whereas the dorsal hippocampus (dHPC) plays a preferred role in learning and spatial memory [1, 5, 6]. Despite many animal and clinical studies suggesting that aberrant hippocampal activity is associated with anxiety disorders, the underlying mechanism is far from being conclusive. Intrahippocampal infusion studies have suggested that different neurotransmitter systems and receptor sub-types are responsible for anxiety or memory functions in the hippocampus [7]. In addition, hippocampal excitatory and inhibitory neurons have been described as targets of anxiety modulation. Many studies using optogenetics and chemogenetics have shown that the connection of neural circuits in the hippocampus and related brain regions is the physiological basis of the regulation of anxiety behavior. Therefore, revealing the molecular, cellular, and neural circuit underpinnings of anxiety would provide answers regarding the functions of the hippocampus in modulating anxiety.

In this review, we summarize the molecular features and cell types of the hippocampal sub-regions, as well as the intra-hippocampus network and connections made by the hippocampus and extra-hippocampus regions, and discuss the recent evidence on the molecular, cellular, and neural circuit mechanisms of anxiety.

Anxiety Disorders

Anxiety arises from a highly alert state in the unambiguous presence of immediate threats and consists of trait and state components [8–10]. Trait anxiety is an individual predisposition that is considered a stable long-term feature in daily life [11–13]. In comparison, state anxiety refers to an acute and transitory response to external stimuli [11, 13], and is usually a context-dependent behavior. State anxiety has evolved as an adaptive avoidance of potential dangers, while extensive and prolonged trait anxiety responses are considered to be pathological phenomena [11]. Anxiety disorders, including generalized anxiety disorder, social phobia, specific phobias, separation anxiety disorder, and panic disorder with or without agoraphobia, are among the most prevalent psychiatric disorders and social problems [14, 15]. The etiology of anxiety disorders is an interaction of genetic vulnerability and psychosocial stress factors, such as adversity in childhood and adolescence, or stressful life events [14–16]. At present, antidepressants are the primary therapeutics for most anxiety disorders, and among these drugs, selective serotonin re-uptake inhibitors and selective serotonin-norepinephrine re-uptake inhibitors are the first-line anxiolytic treatments [17]. However, these agents are not effective in relieving anxiety symptoms for all patients; the harmful side effects and delayed action onset also limit their use. A thorough understanding of the mechanisms underlying anxiety regulation, at the molecular, cellular, and neural circuit levels, will provide a conceptual framework for improving anxiety treatment strategies.

The classic idea that the hippocampus is associated with learning and memory began with the study of Henry Molaison who exhibited severe memory deficits after bilateral medial temporal lobectomy to alleviate drug-resistant seizures [18]. In recent years, the role of the hippocampus in emotion regulation has received more attention, and exciting progress has been made in understanding the mechanism of the hippocampus in anxiety.

Hippocampus

The hippocampus is a complex structure located in the medial temporal lobe, which is implicated in extensive cognitive functions, including declarative memory [19] and spatial navigation [20], as well as emotional responses, such as emotional memory and adaptation [21, 22], and is a model system for structure and function research in animals. Many studies on the anatomy and circuitry of the hippocampus have been done in rodents and primates. Current studies indicate that the extensive role of the hippocampus in cognition and emotion stems from its position in the center of the cerebral cortex and its special internal anatomical structure [23, 24].

Anatomical Features

Anatomically, the rodent hippocampal formation is mainly subdivided into three distinct divisions: the dentate gyrus (DG), the hippocampus (cornu ammonis, CA3, CA2, and CA1), and the subiculum (SUB) [25] (Fig. 1A), which correspond to human hippocampus DG, CA4, CA3, CA2, CA1, and SUB; the human CA4 subregion contains cells within the hilus of the DG [26, 27]. Neuronal somata, dendrites, and axons in all subfields are distributed into specific layers: the stratum pyramidale (SP), alveus, stratum moleculare (SM), stratum oriens (SO), stratum radiatum (SR), and stratum lacunosum (SL) [28].

The DG subdivision is divided into five layers involving the outer SM (SMo), the middle SM (SMm), the inner SM (SMi), the stratum granulosum (SG), and the hilus. The principal glutamatergic neurons are granule cells (GCs) in the SG and mossy cells (MCs) in the hilus. The dendrites and axons of the GCs are located in the SO and hilus, respectively. The two types of glutamatergic neurons have distinct transcriptional characteristics. GCs have specific gene expression including *Prox1, Stxbp6, Ctip2, Maml2,* and *Dock10* [29, 30], while MCs specifically express *Calb2, Gria2/3, Cntn6, Drd2, Ociad2,* and *Nmb* [31–33].

The hippocampus properly refers to three CA fields: CA3, CA2, and CA1. CA3 has a five-layered appearance which comprises the stratum lacunosum moleculare (SLM), SR, SL, SP, and SO. The laminar organization of CA1 and CA2 is similar to that of CA3 except for the absence of SL. The excitatory neurons within CA subdivisions are predominantly pyramidal neurons expressing the broad marker *Sv2b* [33–35]. The apical dendrites of pyramidal neurons are present in the SLM and SR, while their basal dendrites are ramified in the SO, and the axons enter the alveus.

In situ hybridization and next-generation sequencing have demonstrated that CA2 has unique molecular markers (*Rgs14, Step, Pcp4,* and *Vcan*) [33, 36–40], distinct from those of CA3 (*Socs2, Cpne4, Tyro3, Lyd,* and *Coch*) [33, 41] and those of CA1 (*Satb2* and *Wfs1*) [33, 35].

The inside-to-outside anatomical structure of the SUB comprises three layers: the SM, SP, and polymorphic layer. The SP in the SUB is thicker than in CA3, CA2, and CA1; its principal cell type is pyramidal cells expressing the unique molecular marker *Fn1* [29]. The SUB receives substantial projections from CA1 and other subfields of the hippocampus [42, 43], and outputs to multiple brain regions. Hence the SUB is the hub of information processing between the hippocampus and other brain regions through this different interconnectivity [44].

All hippocampal subregions have highly heterogeneous inhibitory interneurons, which can be categorized by molecular markers, electrophysiological properties, and morphological characteristics; they are further

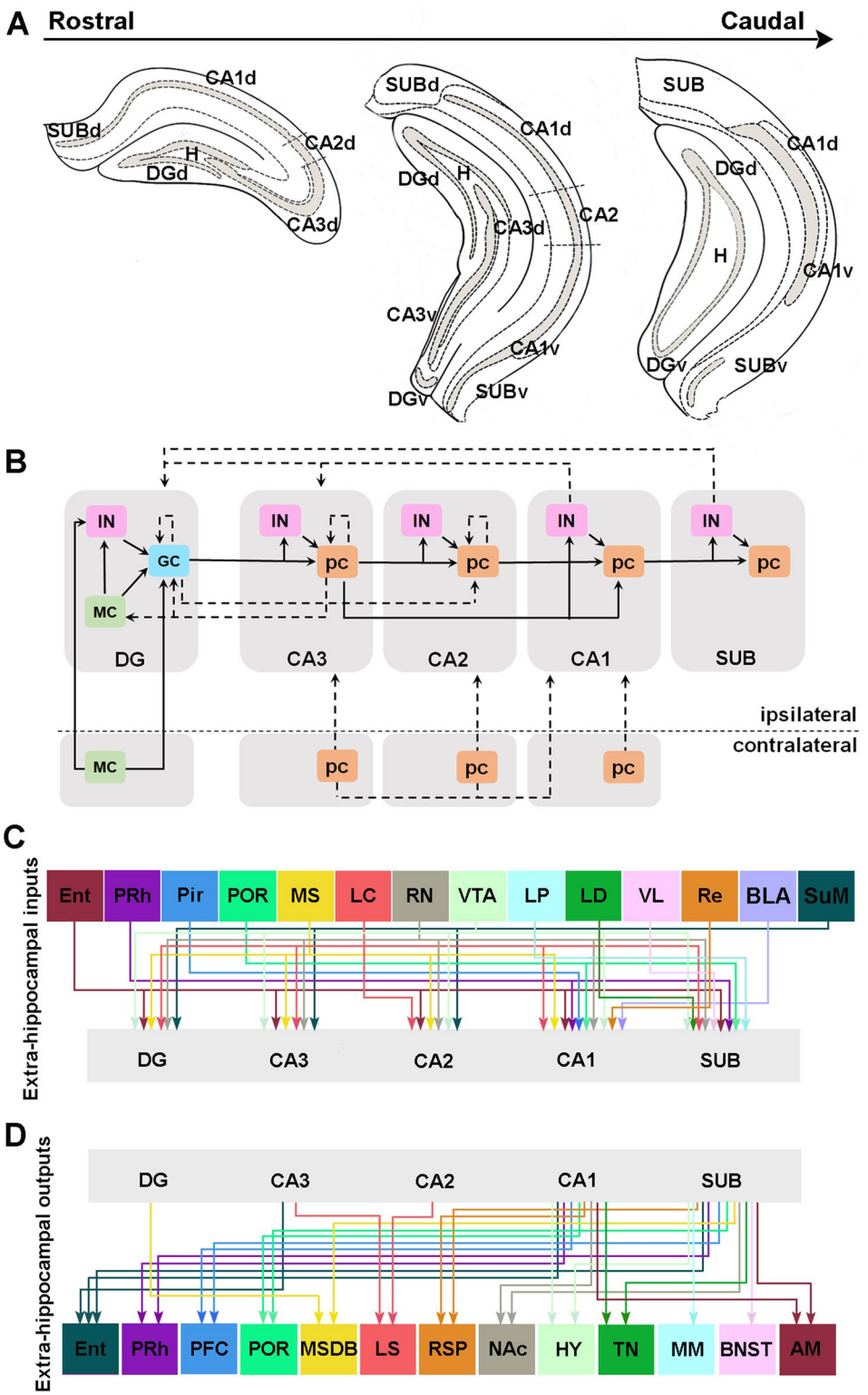

Fig. 1 Anatomical features of the hippocampus. **A** Simplified diagram depicting the distribution of different subfields of the dorsal and ventral parts of the hippocampus from rostral to caudal. **B** The projected connections between different neuron types in subregions of the hippocampus, including ipsilateral and contralateral connections. Dashed arrows represent weak projections, solid arrows represent strong projections. **C**, **D** Hippocampal external input (**C**) and output (**D**) connectivity networks. DG, dentate gyrus; H, hilus; CA1-3, cornu ammonis 1-3; SUB, subiculum; d, dorsal; v, ventral; i, intermediate; GC, granule cell; MC, mossy cell; pc, pyramidal cell; IN, interneuron; EC, entorhinal cortex; PRh, perirhinal cortex; Pir, piriform cortex; POR, postrhinal cortex; MS, medial septum; LC, locus coeruleus; RN, raphe nuclei; VTA, ventral tegmental area; LP, lateral posterior thalamic nucleus; LD, laterodosal thalamic nucleus; VL, ventrolateral thalamic nucleus; Re, reuniens nucleus; SuM, supramammillary nucleus; BLA, basolateral amygdala; PFC, prefrontal cortex; DB, diagonal band; LS, lateral septum; RSP, retrosplenial cortex; NAc, nucleus accumbens; HY, hypothalamic nuclei; TN, thalamic nucleus; MM, mammillary bodies; BNST, bed nucleus of stria terminalis; AM, amygdala.

differentiated into at least eight defined GABAergic interneuron populations: positively stained for parvalbumin (PV^+), neuropeptide Y (NPY^+), somatostatin (SOM^+), calbindin (CB^+), calretinin (CR^+), cholecystokinin (CCK^+), vasoactive intestinal peptide (VIP^+), and neuronal nitric oxide synthase ($nNOS^+$) [28].

Hippocampal Intrinsic Circuitry

The anatomical connectivity of the hippocampus is described as a 'tri-synaptic loop'. Neurons in the lateral and medial entorhinal cortex (LEC/MEC) provide primary cortical inputs to the dendrites of the GCs in the SMo and SMm of the DG *via* the perforant path, respectively [45]. GCs project to the SL apical dendrites of the CA3 pyramidal cells *via* the mossy fiber (MF) pathway [46]. CA3 pyramidal cells project to the proximal apical dendrites of the CA1 pyramidal cells in the SR *via* the Schaffer collateral (SC) pathway [47, 48]. Finally, CA1 projects to the SUB and back to the deep layers of the EC region, completing a processing loop. Neurons in the DG and CA3 also project to CA2 [49, 50]. In addition to the classical tri-synaptic circuit, the actual microcircuit connections within the hippocampus are quite complex (Fig. 1B).

Commissural systems connect ipsilateral and contralateral structures in the hippocampus. Contralaterally-projecting neurons mainly consist of glutamatergic cells in the dHPC; however, SOM^+ and PV^+ GABAergic interneurons also innervate the contralateral hippocampus, but with a lower density [51]. The hilar mossy cells project to the SMi of the contralateral DG [52, 53]. The CA3 pyramidal cells send commissural projections onto synapses in the SO of the contralateral CA3 [54]. CA1 pyramidal neurons receive contralateral CA3 or CA2 inputs in the SR, and contralateral CA1 inputs to the SO *via* commissural projections [40, 55].

In the ipsilateral hippocampus, the DG mainly receives excitatory inputs from MCs and CA3, and inhibitory inputs within the DG, plus a small number of long-distance inhibitory inputs from CA1 and the SUB [53]. In addition, GCs mainly interact indirectly with each other through interneurons or MCs, but there are still a few local direct projections between GCs [53]. Hilar MCs receive a large number of hippocampal inputs, mainly excitatory and inhibitory inputs from the DG and CA3 [56]. GC projections account for 57% of MC inputs. Excitatory inputs of pyramidal neurons from proximal CA3 (CA3c) and intermediate CA3 (CA3b) account for 4.9% and 1.5% of MC inputs [53]. Studies have shown that CA3c indirectly regulates DG GCs through their inputs to MCs [57]. Inhibitory inputs from the DG and CA3 non-pyramidal layers account for 3.7% and 2.5% of MCs presynaptic inputs, respectively [53]. CA3 pyramidal cells (CA3pcs) not only receive EC and DG excitatory inputs but also receives indirect inhibitory inputs from CA3 interneurons and extensive excitatory interconnection between CA3pcs [50, 58, 59]. Recently, retrovirus tracing has shown many direct projections of CA3 pyramidal neurons and inhibitory neurons in DG GCs, where they are distributed in CA3a, CA3b, and CA3c, the distal CA3a input being the strongest [53].

In CA2, the apical dendrites of pyramidal cells receive CA3 Schaffer collateral inputs in the SR [50], while the axons target the basal and apical dendrites of CA1pcs through SO and SR, respectively [60]. Studies have shown that both the basal and apical dendrites of CA2pcs receive projections from ipsilateral CA2 neurons [61] and that DG GCs send functional monosynaptic outputs to pyramidal cells of CA2 through longitudinal projections [37]. CA1 SO has a class of long-distance projection interneurons ("back projection cells"), whose axons project backward through the fissure to other hippocampal subfields, including CA3 and DG [62].

The Extra-hippocampal Connection Network

The hippocampal circuit is mainly modulated by extrinsic inputs, including various cortical areas, the medial septal region, the thalamus, the amygdaloid complex, the supramammillary nucleus, and monoaminergic brainstem nuclei (Fig. 1C).

The EC consists of two subregions with different cytoarchitectures and connectivity (LEC and MEC). The projection is strong to all subfields of the hippocampus, where the superficial cells (layer II) directly project to the DG and CA3, and the deeper cells (layer III) directly project to CA1 and the SUB [63]. There are differences in their direct projections to CA1, as the LEC projects to the region closer to the SUB, whereas the MEC innervates the region closer to CA3 [64]. In addition, hippocampal CA2 receives direct inputs from LEC and MEC [65, 66]. The perirhinal and postrhinal cortices project weakly and only to CA1 and the SUB. The perirhinal cortex preferentially projects to the ventral SUB, whereas the postrhinal cortex targets mainly the dorsal CA1 and SUB [67]. The piriform cortex also weakly contacts vCA1 [68].

The medial septal GABAergic neurons with low-rhythmic firing innervate the DG and CA3, and the connection between these neurons and CA1 regulates contextual memory retrieval [69, 70]. Meanwhile, the septal glutamatergic projections mainly contact interneurons in the alveus/oriens of CA1 [71]. The medial septal nucleus sends cholinergic outputs to CA2 and CA1 [72, 73]. Septo-hippocampal glutamatergic and GABAergic projections terminate predominantly on GABAergic neurons in the hippocampus [74, 75]. Conversely, the septal cholinergic projections primarily target the pyramidal neurons in the hippocampus [75].

The lateral posterior, laterodorsal, and ventrolateral thalamic nuclei send monosynaptic outputs to the SUB [76]. Moreover, the thalamic midline nucleus reuniens afferent inputs in the hippocampus modulate CA1 network activity *via* direct excitation and indirect inhibition [77]. Major inputs to the hippocampal formation also come from the amygdala. The basolateral amygdala

(BLA) establishes monosynaptic and glutamatergic outputs to CA1 of the vHPC [78]. Under physiological conditions, the posterior BLA-vCA1 connection is more prominent than the anterior BLA-vCA1 connection [79].

The hippocampal formation also receives inputs from the hypothalamic supramammillary nucleus [80]. This supramammillary projection terminates in all hippocampal subfields *via* the fornix but is more prominent in the DG, CA2, and CA3. The hippocampus also receives projections from brainstem nuclei, including a major noradrenergic input from the locus coeruleus [81, 82], dopaminergic projections from the ventral tegmental area [83, 84], and serotonergic innervation from the raphe nuclei [85, 86] to all subfields of the hippocampus. A study suggests that the locus coeruleus also releases dopamine in the dorsal hippocampus [87].

In addition to the inputs from many regions, the hippocampus forms network connections through outputs to other regions outside the hippocampus, which affects overall brain network activity (Fig 1D). The DG, CA3, and CA2 subregions contribute relatively little to extra-hippocampal outputs; the DG provides GABAergic outputs to the medial septum [88], while CA3 and CA2 mainly project to the dorsolateral septum [89, 90]. Agster and colleagues first found a direct projection from ventral CA3 to the entorhinal cortex [67]. In contrast, the CA1 and SUB regional projections constitute the main network of extra-hippocampal connections. The SUB and CA1 project to the postrhinal, perirhinal, entorhinal, prefrontal, and retrosplenial cortices, as well as to the nucleus accumbens, amygdala, hypothalamic nuclei, and various midline thalamic nuclei [67, 91–95]. The SUB also projects to the septum and diagonal band [89], the bed nucleus of the stria terminalis [96], mammillary bodies, and anterior thalamic nuclei along with the postsubiculum [97].

The Hippocampus in the Pathophysiology of Anxiety

Studies have suggested that the hippocampus is closely involved in cognitive learning and the pathogenesis of mood and anxiety disorders, which may be mediated by the functional heterogeneity of its dorsoventral axis, with the dHPC mediating cognitive learning and the vHPC contributing to emotional regulation, especially in regulating anxiety [5, 98–102]. Moreover, some studies have also shown that dorsal hippocampal neurons are involved in anxiety regulation [103–105]. Here, we review the identified cell types, molecules, and projections in the hippocampus, especially the vHPC, that modulate anxiety-related behaviors.

Cellular Mechanisms of the Hippocampus During Anxiety

The hippocampus is extremely responsive to chronic stress and anxiety-inducing stimuli. In almost all hippocampal subregions, excitatory and inhibitory neurons provide a cellular substrate for anxiety modulation. Chronic stress causes changes in synaptic plasticity, including dendritic shortening and the debranching and spine loss of excitatory neurons, which further impacts excitability in the MF-CA3 and CA3-CA1 synapses. Chronic stress also causes a reduction in dendritic branches and the number of interneurons, thus affecting the excitation-inhibition balance in the hippocampus.

DG Granule Cells in Anxiety In adult rodents and humans, the subgranular zone (SGZ) of the DG continuously generates new GCs [106–109]. Recently, several findings have demonstrated the important role of adult-born and mature GCs in influencing stress response and anxiety regulation. Increased neurogenesis in the DG reduces corticosteroid-induced anxiety-like behaviors [110], whereas inhibition of hippocampal neurogenesis increases anxiety-related behaviors [111]. Several important studies have proposed that adult-born GCs in the vDG, but not in the dDG, are key factors in mediating stress-induced anxiety-related behaviors. In mice, increasing neurogenesis in the vDG prevents the social defeat of stress-induced anxiety-like behaviors by inhibiting the activity of mature GCs [112]. Conversely, chemogenetic silencing of adult-born GCs induces an increased activity in mature GCs, leading to avoidance behavior in the social interaction test and a decrease in center exploration in the open field test [112]. However, another study from the same group found that optogenetic activation of mature vDG GCs contributes to the anxiolytic effects in mice [113]. In addition, chemogenetic activation of tactile experience-induced vDG GCs relieves anxiety [100]. Recently, with the application of single-cell sequencing and transcriptomics, heterogeneous cell populations with different molecular or functional characteristics have been found in different subregions of the hippocampus. Therefore, the above contradictory conclusions may be due to the different functions of GC subsets. In addition, a recent study indicates that activating osteocalcin-positive dDG GCs decreases anxiety-like behaviors by promoting adult DG neurogenesis [103].

GABAergic Interneurons in Anxiety Besides the principal excitatory neurons, the hippocampus is also under the inhibitory control of diverse GABAergic interneurons, which are susceptible to chronic stress and play important roles in modulating anxiety-related behaviors. Disturbances in GABAergic neurotransmission are considered to be the pathological basis of anxiety disorders, as studies in patients and animal models suggest that an imbalance of excitatory

Table 1 Effects of chronic stress on the number and expression of marker protein in hippocampal interneurons.

	Chronic stress response	References
PV-Parvalbumin		
	Reduced in vCA1 - Chronic mild stress	[115]
Number	Loss of PV^+ interneurons in vHPC results in anxiety-like behavior in 5xFAD mice	[121]
Activity	Activation of PV^+ interneurons in vDG produced significant anxiolytic-like effects	[120]
	Reduced intensity of PV in the vHPC - maternal separation with early weaning	[123]
Expression	Reduced in dHPC - Chronic mild stress	[119]
CR-Calretinin/CB-Calbindin		
Number	Reduced in vCA1- Chronic mild stress	[115]
	Increased in dCA1- Maternal separation	[125]
Expression	Increased in CR and CB expression in vDG - Chronic social defeat	[131]
NPY-Neuropeptide Y		
Number	Reduced in vCA1-3 - Chronic mild stress	[115]
Expression	Reduced in dCA1, dCA3 - Chronic restrain stress	[128]
	Reduced in dDG - Chronic mild stress	[127]
SOM - Somatostatin		
Number	Reduced in vDG and vCA1 - Chronic mild stress	[115]
Expression	Reduced in all vHPC - Chronic mild stress	[119]
CCK - Cholecystokinin		
Number	No effects on vHPC - Chronic mild stress	[115]
	No effects on vHPC - Chronic restrain stress	[122]
Expression	Reduced in dCA1-3 - Chronic restrain stress	[133]

dDG, dorsal dentate gyrus; dCA1-3, dorsal cornu ammonis 1-3; dHPC, dorsal hippocampus; vCA1, ventral CA1; vDG, ventral dentate gyrus; dCA3, dorsal CA3; vHPC, ventral hippocampus.

and inhibitory neurotransmitters is the primary cause of anxiety disorders (Table 1).

PV^+ interneurons are particularly susceptible to chronic stress [114]. Studies indicate that exposure to multiple chronic stress significantly reduces the number of PV^+ interneurons in vCA1 [115–118], and a decreased expression of PV has been reported in the dorsal hippocampus [119]. Moreover, activation of PV^+ interneurons in the vDG produces significant anxiolytic-like effects [120], and loss of SST^+ and PV^+ interneurons in the vHPC leads to anxiety-like behavior in 5xFAD mice [121]. These changes may also relate to functional deficits like failure to generate the rhythmic spontaneous inhibitory postsynaptic currents recorded after chronic stress [122] and disruption of the balance between excitation and inhibition. Recently, a study has suggested that maternal separation with early weaning reduces the level of parvalbumin (PV) and increases the density of perineuronal nets around PV^+ interneurons in the vHPC, as well as increasing theta power and enhancing theta-gamma coupling in the vHPC [123]. Contradictory results suggest that no changes in the number or expression of PV occur after chronic unpredictable stress or maternal separation [124, 125], and may be due to different types of stressors or stress times.

NPY^+ interneurons, as endogenous 'stress-resistant molecules', have marked anxiolytic and anti-epilepsy effects [120, 126]. Evidence suggests that the number of NPY^+ interneurons decreases in vCA1-3 of the hippocampus after chronic maternal stress (CMS) [115] and that CMS, as well as chronic restraint stress (CRS), reduce NPY expression in the dDG and dCA1-3 respectively [127, 128]. Early life stress events can lead to a reduction in the number of NPY^+ interneurons in the hilus, which leads to overexcitation of the DG-CA3 circuit [129]. Anxiety-like behaviors induced by predator odor stress are due to reduced NPY release from CA1 NPY^+ neurons [130]. The impairment of NPY release promotes glutamate release onto the CA1 pyramidal cells, thus increasing synaptic short-term facilitation [130].

CR^+ interneurons are also reduced in vCA1 after CMS exposure [115], while chronic social defeat increases the CR and CB expression in the vDG [131]. CMS exposure significantly reduces the SOM^+ interneurons in the vDG and vCA1 [115] and decreases the expression of SOM in the vHPC [119]. The hyperexcitability of SOM^+ neurons leads

to an enhancement of the inhibitory synaptic output onto the dendrites of CA1 pyramidal neurons and anxiolytic phenotypes [132]. In addition, although chronic stresses have no effect on the number of CCK^+ interneurons [115, 122], CRS exposure reduces the CCK mRNA [133].

In addition, hippocampal vCA1 oriens-lacunosum moleculare (OLM) interneurons, which specifically express the nicotinic acetylcholine receptor α2 subunit, drive type 2 theta and are associated with increased risk-taking behavior in response to predator odor [98].

Chronic stress leads to changes in the number of inhibitory neurons or the expression of inhibitory neurotransmitters in the hippocampus, and affects the release of glutamate from excitatory neurons, supporting the role of excitation-inhibition imbalance in the pathology of anxiety disorders. Further research into the structural and functional connectivity between glutamatergic and GABAergic neurons in orchestrating hippocampal excitation-inhibition balance may provide a theoretical basis for anxiolytic therapy.

Stress-induced Hippocampal Plasticity in Anxiety The precise pattern of dendrites is the major factor affecting the formation and function of neural circuits, and its morphology also affects the strength of synaptic connections [134]. Stress-induced changes in structural plasticity may lead to the expression of anxiety-related behaviors.

Many studies using magnetic resonance imaging have shown a lower hippocampal volume in patients suffering from anxiety disorders, and antidepressant treatments normalize it [135, 136]. Hippocampal volume loss has also been reported in individuals with adverse life events and chronic glucocorticoid treatment [137–139]. In rodent model studies, exposure to chronic stress and corticosterone also reduces hippocampal volume, which may be due to many cellular changes, including decreased glial number, inhibition of adult neurogenesis, and dendritic atrophy, particularly in the CA3 and CA1 pyramidal cells, as well as DG GCs [136]. Dendritic atrophy is considered to be a reversible loss of the total dendritic length, branching density of apical dendrites, and dendritic spines [140]. For example, it has been shown that CRS causes a significant reduction in branch points and length of the apical and basal dendrites in CA3 [141, 142]. Chronic immobilization stress (CIS) elicits an anxiety response accompanied by a pronounced shortening and debranching of the apical and basal dendrites of the CA3 pyramidal cells and the apical dendrites of CA1 pyramidal cells [143, 144].

Dendritic spines (small protrusions on dendrites) are crucial components in mediating the stress-induced structural plasticity of neurons. Both CRS and maternal separation (MS) stress significantly reduce the mature dendritic spine density of CA1 pyramidal cells [145, 146]. The neurotrophin brain-derived neurotrophic factor (BDNF) promotes the growth of dendrites and spines [147]. Both CIS and CRS decrease BDNF levels [147, 148], suggesting that BDNF is linked to the stress-induced alterations of dendrites and spines in the hippocampus [149].

Stress-induced abnormal long-term potentiation (LTP) in the MF-CA3 and SC-CA1 synapses is another cellular mechanism that may cause anxiety behaviors [150–152]. A study found that early deprivation induces anxiolytic behaviors by decreasing the threshold of LTP induction in the CA3-CA1 pathway [153]. In contrast, CRS increases anxiogenic behaviors due to the impairment of LTP in the SC-CA1 synapses [154]. These findings reveal that enhanced LTP in the SC synapses may be correlated with anxiolytic-like symptoms. Furthermore, another study showed that MS stress may induce anxiety-like behaviors through decreasing LTP and increasing paired-pulse facilitation ratios in the MF-CA3 pathway [152].

Hippocampus-related Molecular Mechanisms of Anxiety

Mounting evidence reveals that a diversity of molecules in the hippocampus are involved in anxiety modulation: channel proteins, receptors, neurotransmitters, neuropeptides, neuroinflammatory factors, and compounds associated with oxidative stress. These provide significant clues to hippocampus-related molecular mechanisms of anxiety (Table 2).

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel family governs hippocampal neuronal excitability. Among these, HCN1 is the predominant isoform, while the HCN4 expression level is much lower in CA1 pyramidal neurons [104]. Although both isoforms have been shown to regulate hippocampus-related anxiety-like behaviors, the two proteins exert opposing functions. Knockdown of the HCN1 channel protein in the dCA1 enhances dCA1 activity, upregulates BDNF-mTOR signaling, and produces anxiolytic-like behaviors [105]. Conversely, the shRNA-mediated knockdown of HCN4 in the dHPC generates an anxiogenic effect [104]. A recent study found that HCN channel proteins participate in regulating synaptic transmission and glutamate release [155], suggesting that HCN deficiency might impair glutamatergic transmission.

The glutamatergic and GABAergic systems have crucial roles in the modulation of anxiety [156, 157]. Infusion of N-methyl-D-aspartate receptor (NMDAR) agonists and antagonists into the vHPC induces anxiogenic and anxiolytic responses, respectively [158]. In contrast, the direct injection of gamma amino butyric acid A receptor ($GABA_AR$) agonists and antagonists into the vHPC have effects opposite to those of NMDAR agonists and antagonists [158]. Moreover, maintaining the excitation-inhibition balance might have a significant effect on regulating glutamate release from hippocampal pyramidal cells.

Table 2 Summary of hippocampal molecules involved in anxiety modulation.

Examples	Subfields	Anxiety-regulating functions	References
Channel protein			
HCN1	dCA1	The anxiolytic effect of HCN1 knockdown.	[105]
HCN4	dHPC	Anxiogenic effect of HCN4 knockdown.	[104]
Neurotransmitter systems			
NMDAR	vHPC	NMDAR agonists increased anxiety.	[158]
		NMDAR antagonists reduced anxiety.	
$GABA_AR$	vHPC	$GABA_AR$ agonists reduced anxiety.	[158]
		$GABA_AR$ antagonists increased anxiety.	
AChE	vHPC	AChE inhibitor alleviated anxiety.	[160]
	HPC	knockdown of AChE increased anxiety	[161]
D1/D2R	vHPC	The anxiolytic effect of D1/D2R antagonists.	[165]
	vCA3	Anxiogenic effect of D1/D2R antagonists.	[167]
nNOS	HPC	Chronic stress increased the level and activity of hippocampal nNOS	[168]
		Enhancement of nNOS-CAPON coupling is anxiogenic.	[168]
			[169]
	vHPC	Downregulating of nNOS is anxiolytic.	[171]
AEA /CB1R	HPC	Enhancement of the ECBs signaling is anxiolytic.	[174]
			[177]
	vHPC	Reduced CB1R in GABAergic neurons and activated CB1R in glutamatergic neurons are anxiolytic	[178]
Neuropeptide systems			
CRH/CRHR1	dHPC	Intervention with CRHR1 is anxiolytic.	[182]
	vHPC	CRHR1 antagonist is anxiolytic.	[183]
NPS	vHPC	The anxiolytic effect of NPS.	[184]
			[185]
			[186]
RXFP3	vHPC	Anxiogenic effect of RXFP3 agonists.	[187]
Cytokine			
IL-1β	DG	Increasing IL-1β is anxiogenic.	[189]
NLRP3	vHPC	Deletion of NLRP3 is anxiogenic.	[192] [193]
	vHPC	Activation of microglial NLRP3 in CMS.	[194]

HCN, hyperpolarization-activated cyclic-nucleotide-gated channels; NMDAR, N-methyl-D-aspartate receptor; $GABA_AR$, gamma amino butyric acid A receptor; AChE, acetylcholinesterase; D1/D2R, dopamine D1 and D2 receptor; $5\text{-}HT_4R$, 5-hydroxytryptamine 4 receptor; $5\text{-}HT_{1A}R$, $5\text{-}HT_{1A}$ receptor; $5\text{-}HT_{2C}R$, $5\text{-}HT_{2C}$ receptor; nNOS, neuronal nitric oxide synthase; CAPON, carboxy-terminal PDZ ligand; AEA, arachidonoyl ethanolamide or anandamide; CB1R, cannabinoid 1 receptor; ECB, endocannabinoid; CRH, corticotropin-releasing hormone; CRHR1, corticotropin-releasing hormone receptor 1; NPS, neuropeptide S; RXFP3, relaxin-family peptide 3 receptor; IL-1β, interleukin-1β; NLRP3, nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3; HPC, hippocampus; dHPC, dorsal HPC; vHPC, ventral HPC; DG, dentate gyrus; dCA1, dorsal cornu ammonis 1; vCA3, ventral cornu ammonis 3.

The $GABA_AR$ antagonist blocks anxiolytic-like behaviors induced by the infusion of NMDAR antagonists into CA3 [159].

Hyperactivity of cholinergic systems is associated with the processes of hippocampus-modulated anxiety. One study showed that the administration of an acetylcholine esterase (AChE) inhibitor into the vHPC increases cholinergic activity and significantly alleviates anxiety responses [160]. In contrast, another study found that specific knockdown of AChE in the hippocampus promotes anxiety-like behaviors [161].

Dopamine (DA) is one of the neurotransmitters most active in anxiety responses, and its effects can be mediated by both D1 and D2 receptors expressed in the hippocampus [162, 163]. Several studies have revealed that the dopaminergic system modulates anxiety *via* its interaction with the glutamatergic or cholinergic system in the hippocampus. SCH23390, a DA D1 receptor antagonist, has synergistic anxiolytic effects with the NMDAR antagonist MK801 but is ineffective when injected into dCA1 alone [164]. However, the DA D2 receptor antagonist sulpiride suppresses the anxiolytic responses induced by MK801 in dCA1 [164].

Moreover, the D1 and D2 receptor antagonists alleviate the cholinergic anxiogenic effect of nicotine in the vHPC [165, 166]. Nicotine-induced DA release likely promotes anxiety responses, with DA antagonists reversing the anxiogenic effect by blocking D1 and D2 receptors. However, another study suggested that intra-hippocampal injection of SCH23390 or sulpiride into vCA3 blocks cholestasis-induced anxiolytic-like behaviors [167].

The neuronal messenger neuronal nitric oxide synthase (nNOS) is strongly expressed in the hippocampus and is involved in stress responses and anxiety-like behaviors. Chronic stress increases the expression and activity of nNOS in the hippocampus and contributes to stress-induced emotional behaviors [168]. Our previous studies have demonstrated that chronic stress enhances the coupling of nNOS with its carboxy-terminal PDZ ligand (CAPON) and induces anxious phenotypes [168, 169]. Blocking the nNOS-CAPON interaction ameliorates chronic stress-induced anxiety by promoting synaptogenesis [170]. Moreover, short-term running exercise exerts anxiolytic effects by increasing *Nos1* DNA methylation and downregulating the expression of nNOS in the vHPC [171].

Endocannabinoids (ECBs), such as arachidonoyl ethanolamide (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG), are relevant for anxiety regulation and stress responses. AEA and 2-AG levels in the dHPC are altered by diverse chronic stressors [172, 173]; elevation of AEA levels by inhibition of dHPC fatty-acid amide hydrolase and the ECB transporter attenuate anxiety responses [174]. Intra-vHPC injection of an AEA reuptake inhibitor has anxiogenic and anxiolytic effects in the elevated plus maze and the Vogel conflict tests, respectively; this discrepancy may be due to differences in the stress experienced by the subjects prior to the behavioral tests [175]. The hippocampus contains high levels of cannabinoid 1 (CB1) receptors, which are mainly expressed on the axon terminals of CCK^+ interneurons, but at lower levels in glutamatergic, serotonergic, and cholinergic axon terminals. Evidence suggests that cannabinoid signaling in the hippocampus protects against stress-induced behavioral changes [176]. Injecting Δ^9-tetrahydrocannabinol, a CB1 receptor agonist, into the vHPC increases the cAMP response element-binding protein (CREB) activation and attenuates anxiety behaviors [177]. Stimulation of the hippocampal CB1 receptors suppresses the release of neurotransmitters and increases BDNF expression [177]. A study has suggested that electroacupuncture exerts an anxiolytic effect *via* downregulating CB1Rs in GABAergic neurons and activating CB1Rs in glutamatergic neurons in the vHPC, thus reducing the release of glutamate and inhibiting the anxiety circuit related to the vHPC [178].

In addition to the diverse neurotransmitter systems, corticotropin-releasing hormone (CRH) acts as a neuropeptide that mediates anxiety and stress-related affective disorders in the hippocampus. Several studies have found that CRH exerts anxiety-regulating functions by affecting the expression or release of other neurotransmitters or neuropeptides. For instance, injecting CRH into the HPC suppresses the expression of Spexin, which plays an anxiolytic role [179]. CRH receptor type 1 (CRHR1), widely expressed in the hippocampus, has been demonstrated to be a potential drug target for anxiolytics in animals [180, 181]. Studies indicate that predator scent exposure stress increases the level of *Crhr1* mRNA in the dorsal hippocampus, and inhibition of *Crhr1* expression in the hippocampus significantly reverses the anxiety behaviors caused by chronic stress [182]. However, there is little research on whether CRHR1 in the vHPC is involved in the regulation of anxious behavior. Only one study has suggested that intra-vHPC injection of a CRHR1 antagonist increases the time spent in the open arms of an elevated plus maze test [183].

Neuropeptide S (NPS), acting *via* the NPS receptor (NPSR), has been shown to have anxiolytic effects. NPS significantly decreases anxiety-like behaviors when injected into the vHPC, possibly through its potential effects on short-term and long-term synaptic plasticity [184]. For instance, NPS reduces the magnitude of LTP and PPF at the vCA3-vCA1 synapses and induces anxiolytic response not only in normal mice but also in mice with high anxiety-related behavior [185, 186].

Activation of the relaxin family peptide 3 receptor (RXFP3) in the vHPC elicits anxiogenic phenotypes [187]. RXFP3 is mainly expressed in GABAergic SOM^+ and PV^+ neurons of all vHPC subregions, and its stimulation might inhibit interneuronal activity [188].

The hippocampus is vulnerable to neuroinflammation and oxidative stress, which are associated with anxiety disorders. Lipopolysaccharide (LPS) induces the downregulation of BDNF and the neuropeptide VGF, and of the neuroinflammatory and oxidative responses in the DG, which are attributable to the elevation of interleukin-1β (IL-1β) [189]. Inhibition of IL-1β activity ameliorates LPS-induced disorders in the DG and results in an anxiolytic effect. Recent studies indicate that IL-1β inhibits TrkB-mediated BDNF signaling and CREB, which regulate BDNF and VGF expression [190, 191]. Thus, BDNF and VGF downregulation appears to be the anxiogenic mechanisms of IL-1β. The NLRP3 (nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3) inflammasome, is related to the onset and development of a variety of CNS diseases, including anxiety. Deletion of NLRP3 impairs synaptic transduction in vCA3-vCA1 and causes anxiety-like behaviors [192]. However, some studies have indicated that activation of NLRP3 inflammasome in the hippocampus induces anxiety-like behavior [193, 194].

Hippocampal Circuit Plasticity Underlies Anxiety

It is commonly recognized that the hippocampus and multiple brain regions coordinate to regulate anxiety. The vHPC is at the center of the complex neural circuits underlying anxiety regulation [99, 195, 196]. Recently, the application of optogenetics and chemogenetics have provided important insight into the anxiety circuits associated with the hippocampus. Hippocampal input and output nodes play anxiety-regulating roles together with connected upstream nuclei, including the EC, BLA, posterior basolateral amygdala (BLP), median raphe nucleus (MRN), and downstream nuclei, including the medial prefrontal cortex (mPFC), lateral septum (LS), anteromedial part of the bed nucleus of the stria terminalis (amBNST), lateral hypothalamic area (LHA), and amygdala (Fig. 2).

Hippocampal Afferent Circuits Underlie Anxiety *Entorhinal cortex-hippocampus circuits* The EC (including the lateral and medial regions) is one of the major input sources to the hippocampus. However, there are relatively few reports on the relationship between EC and chronic stress or emotional disorders [100, 197, 198], especially anxiety disorders. One study suggested that tactile enrichment induces the activation of neurons in the vDG and increases the presynaptic input from the LEC. Chemogenetic activation of the projection reduces anxiety [100]. Therefore, its connection with the hippocampus in anxiety is not fully understood and needs further exploration.

Amygdala-hippocampus circuits The amygdala receives sensory stimuli associated with threats and plays a role in processing anxiety-associated events [199–201]. In addition, structural BLA and BLP connections to the vHPC have been confirmed [78, 79, 202, 203]. Robust connections and common functions between the amygdala and the vHPC facilitate the elucidation of the neural mechanism underlying anxiety at the circuit level. Felix-Ortiz *et al*. and Pi *et al*. showed that the BLA and BLP provide glutamatergic inputs to pyramidal cells in vCA1, revealing the structural and physiological heterogeneity between BLA-vCA1 and BLP-vCA1 inputs [78, 204].

CRS induces an increase in spine density and glutamatergic signaling in BLA-vHPC, leading to anxiety-like phenotypes in mice [205]. Transient optogenetic activation of the BLA terminals in vCA1 elicits significantly high anxiety behavior. In contrast, optogenetic inhibition of the BLA-vCA1 circuit attenuates the expression of anxiety-like behaviors [78].

By injecting anterograde monosynaptic viral tracers into BLP or BLA in a Calb1-IRES2-Cre-D: Ai9 transgenic mouse, Pi *et al*. found that the BLP and BLA innervate non-overlapping, lamina-specific vCA1 cell populations along the radial axis [204]. Specifically, BLP projects to calbindin1-positive vCA1 cells in the superficial pyramidal layer, and BLA projects to calbindin1-negative vCA1 cells

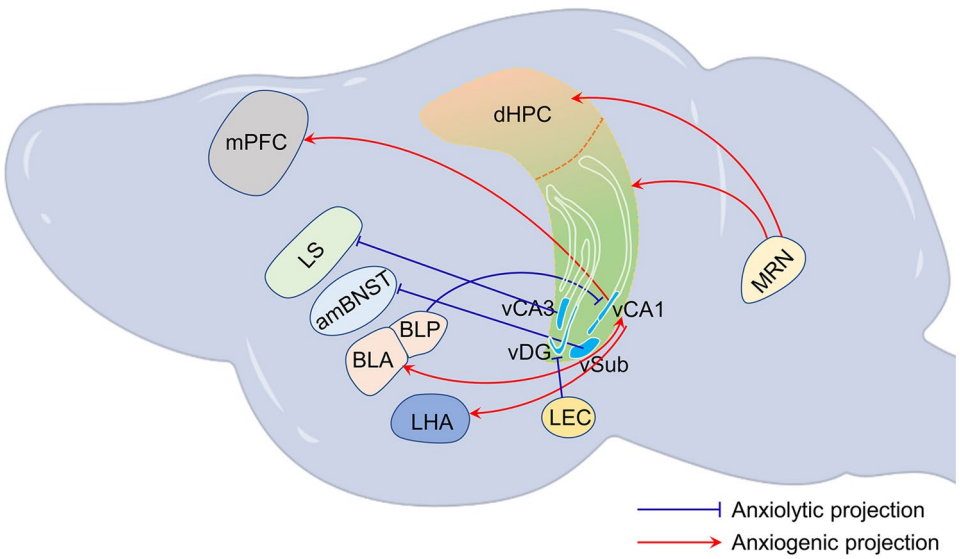

Fig. 2 Upstream and downstream connection networks of the hippocampus that are implicated in anxiety-like behaviors. The sources of inputs into the hippocampus implicated in anxiety are the BLA, BLP, LEC, and MRN. The output regions of the hippocampus implicated in anxiety are the LHA, mPFC, BLA, amBNST, and LS. dHPC, dorsal hippocampus; vCA3, ventral CA3; vCA1, ventral CA1; vSub, ventral subiculum; amBNST, anteromedial part of the bed nucleus of the stria terminalis; BLA, basolateral amygdala; BLP, posterior basolateral amygdala; LHA, lateral hypothalamic area; LEC, lateral entorhinal cortex; LS, lateral septum; mPFC, medial prefrontal cortex; MRN, median raphe nucleus.

in the deep pyramidal layer. Photoactivation of the BLP-vCA1 inputs elicits an anxiolytic effect, while photoinhibition drives an anxiogenic effect. By contrast, BLA-vCA1 inputs play an opposing role in modulating anxiety-like behaviors compared to the BLP-vCA1 circuit, which is consistent with the studies of Felix-Ortiz *et al*. [78, 204]. Calbindin1 expressed in superficial neurons may be a crucial molecule that contributes to the anxiolytic effect. To confirm the anxiolytic roles of calbindin1-positive vCA1 neurons in the BLP-vCA1 circuit, a Cre-responding ChR2 construct was expressed in the vCA1 of the Calb1-IRES2-Cre-D knock-in mouse and the photoactivation of $vCA1^{Calb1+}$ somata induced an amelioration of anxiety [204].

Raphe nucleus - hippocampus circuits Serotonergic neurons originating in the raphe nuclei mainly project to the hippocampus, where almost all serotonin receptor subtypes are expressed [206, 207]. An *in vivo* microdialysis study found that anxiety-related aversive conditions increase extracellular serotonin within the vHPC [208]. Ohmura *et al.* found that blue light delivered to ChR2 variant-containing serotonergic terminals from the dorsal raphe nucleus and MRN in the vHPC induce serotonergic activation and generate anxiety-related behaviors [209]. Photostimulation of serotonin neurons in the MRN also induces anxiety-like behaviors [210]. However, serotonergic activation in the MRN is unable to induce anxiety-related behaviors in a $5\text{-}HT_{2C}$ receptor knockout line. Thus, serotonergic MRN neurons play anxiogenic roles *via* the $5\text{-}HT_{2C}$ receptors in the vHPC [209].

A recent finding showed that optogenetic manipulation of the serotonergic MRN neurons induces an anxiogenic-like effect in both male and female mice [210]. Another study suggested that the activation of serotonergic MRN neurons facilitates the anxiety response in female mice, partly through its input to the dHPC [211]. The serotonergic receptor underlying anxiety regulation in the dHPC might be the $5\text{-}HT_{1A}$ receptor because the injection of its agonist into the dHPC drives the expression of anxiety behavior [212]. Therefore, the regulation of anxiety by serotonergic signaling in female and male mice may be mediated by different serotonergic receptor subtypes in the dHPC and vHPC.

Hippocampal Efferent Circuits Underlie Anxiety Many studies have shown that glutamatergic projections from the vHPC to several downstream structures are involved in the regulation of anxiety.

vHPC-mPFC The direct single synaptic projection from vHPC to mPFC is a key component of anxiety-related circuits. Mounting evidence shows that the synchronization of the theta-frequency of the vHPC-mPFC circuit transmits anxiety-related information which is correlated with avoidance of the open arms in the elevated plus maze test [213–215]. vHPC-mPFC terminal inhibition using optogenetic techniques wipes out the theta-frequency synchronization, which is responsible for increased exploration in the open arms [216]. Inhibition of the theta-frequency communication of the vHPC-mPFC by abolishing the disinhibition functions of the mPFC results in open-arm exploration [217]. The anxiogenic role of the vHPC-mPFC circuit was also confirmed by the hM3Dq-mediated activation of the vCA1 neurons projecting to the mPFC, whereas hM4Di-mediated inactivation had the opposite effects [218].

vHPC-LS The glutamatergic vHPC fibers also largely innervate the LS, which is also implicated in anxiety [219, 220]. Disconnecting the ipsilateral input from the vHPC to the LS by an asymmetrical disconnection increases open-arm exploration by rats, suggesting that the vHPC and the LS synergistically regulate anxiety-like behaviors [221]. Moreover, the chemogenetic activation of projections from vHPC to LS suppresses the expression of anxiety-like behaviors, whereas their inhibition has opposite behavioral outcomes [218]. The LS receives dense glutamatergic fiber inputs from the vCA3 pyramidal layer, but few from the vCA1 pyramidal cells.

vHPC-amBNST The amBNST receives strong glutamatergic innervation from the ventral SUB/CA1. High-frequency vSUB/CA1 stimulation elicits NMDAR-mediated LTP in the amBNST, which promotes an anxiolytic effect [222]. Elaboration of the synaptic plasticity in the vSUB/CA1-amBNST circuit will advance our understanding of the role of the vHPC in anxiety regulation.

vHPC-LHA The LHA is implicated as an important brain region in the regulation of anxiety; it receives direct and exclusive outputs from pyramidal neurons in CA1 and the SUB of the vHPC. A recent study has found that a group of vCA1 pyramidal neurons send glutamatergic input into the LHA, and optogenetic activation of these neurons is anxiogenic [223].

vHPC-Amygdala vCA1 neurons make synaptic connections with the basal amygdala (BA) and lateral amygdala (LA) [224, 225]. Studies have shown that the theta frequency synchronization between vCA1 and LA is significantly enhanced in innate anxiety [224], while the synchronization between vCA1-BA and vCA1-mPFC conveys contextual information efficiently, contributing to contextual fear responses [225].

Conclusion

As a key region for information processing in the CNS, the hippocampus receives inputs from subcortical regions and sends outputs to a variety of downstream regions to mediate different behavioral and physiological functions, thus completing the adaptive regulation of the brain to the environment.

Anatomical and pharmacogenetic studies have shown extensive and close connections among the many subregions in the hippocampus and complex interconnections among its various neurons. These results suggest that the accurate regulation of microcircuitry in the hippocampus is an important basis for its physiological function. Most current studies on the hippocampus and anxiety regulation are limited to the connections between the subregions in the hippocampus and extra-hippocampal regions, as well as the regulation of the local inhibitory circuits in the subregions. However, the mechanism of neural networking between the subregions of the hippocampus in anxiety regulation remains unclear. The main challenges are as follows: (1) heterogeneity of the dorsal-ventral structure and gradient connections in the longitudinal axis; (2) complex anatomical connections between the ipsilateral and contralateral hippocampus; and (3) types and projection complexity of principal neurons and interneurons in the hippocampus. These problems make it difficult to dissect the neural networks in the hippocampus that regulate anxiety-related behavior. Recently, with the extensive application of single-cell transcriptomics and other new techniques, it has been shown that the hippocampus is a highly heterogeneous tissue with many cell subpopulations with different functional and connectivity characteristics. Therefore, future studies may focus on the synchronization of activities of hippocampal neural networks between different types of neurons in each subregion, especially the precise neural circuits mediated by different subsets of neurons in the vHPC, to understand the basis of neural circuits underlying different behaviors. This will also provide more accurate and effective targets for the development of new anxiolytic drugs.

In preclinical and clinical anxiety trials, the glutamatergic and GABAergic systems, the neuropeptide systems, and the endocannabinoid systems show positive prospects for future drug development. In the hippocampus of rodents, excitatory and inhibitory neurotransmitter systems, the cholinergic, dopaminergic, and serotonergic systems, have been established as critical components of anxiety-related behaviors. Therefore, these hippocampal molecules will also provide more reference points for the development of new and more effective therapeutic targets.

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