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THEORETICAL REVIEW

Anxiety and hippocampal neuronal activity: Relationship and potential mechanisms

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Abstract

The hippocampus has been implicated in modulating anxiety. It interacts with a variety of brain regions, both cortical and subcortical areas regulating emotion and stress responses, including prefrontal cortex, amygdala, hypothalamus, and the nucleus accumbens, to adjust anxiety levels in response to a variety of stressful conditions. Growing evidence indicates that anxiety is associated with increased neuronal excitability in the hippocampus, and alterations in local regulation of hippocampal excitability have been suggested to underlie behavioral disruptions characteristic of certain anxiety disorders. Furthermore, studies have shown that some anxiolytics can treat anxiety by altering the excitability and plasticity of hippocampal neurons. Hence, identifying cellular and molecular mechanisms and neural circuits that regulate hippocampal excitability in anxiety may be beneficial for developing targeted interventions for treatment of anxiety disorders particularly for the treatment-resistant cases. We first briefly review a role of the hippocampus in fear. We then review the evidence indicating a relationship between the hippocampal activity and fear/anxiety and discuss some possible mechanisms underlying stress-induced hippocampal excitability and anxiety-related behavior.

Keywords Anxiety · Dentate gyrus · CA1 · Excitability · Fear · Hippocampus · Hypothalamus · Neurogenesis · Stress

Introduction

Anxiety is an emotion characterized by enhanced vigilance and reactivity to threat that leads to a variety of defensive behaviors. These behaviors act to prevent or minimize harm to the organism in the face of aversive stimuli. This is an adaptive response that is crucial for survival (Craske & Stein, 2016). However, abnormalities in neural circuits involved in mood and anxiety due to genetic or acquired factors, such as stress, result in pathological anxiety disorders that include five main types of generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder (PTSD), and social phobia or social anxiety disorders (Craske & Stein, 2016). First-line drugs for treatment of anxiety disorders are the selective serotonin reuptake inhibitors (SSRIs) that are widely used as antidepressant, but other medications, such as tricyclic antidepressants, buspirone, and pregabalin, also may be used. Nevertheless, many patients suffering from PTSD, phobia, panic, and other anxiety disorders fail or insufficiently respond to available treatments (Bandelow et al., 2017). This suggests that other mechanisms may be involved in the pathogenesis of anxiety disorders.

The hippocampus, located in the medial temporal lobe of the brain, is not only implicated in cognitive functions but also plays an important role in the regulation of emotional behaviors, particularly anxiety states (Bannerman et al., 2004; Revest et al., 2009). These distinct functions are in part

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attributed to differential regulation of anxiety and cognitive functions along the dorso-ventral axis of the hippocampus, with growing evidence that indicates the ventral hippocampus is highly implicated in anxiety processing (Bannerman et al., 2002; Kheirbek et al., 2013; Kjelstrup et al., 2002).

Previous studies have shown a relationship between increased hippocampal activity and enhanced anxiety. For example, significant activation of the ventral hippocampus has been shown to occur in the anxiogenic versus nonanxiogenic environment in mice (Schoenfeld et al., 2016), and inactivation of the ventral but not dorsal hippocampus was found to induce anxiolytic effects in rats (Bannerman et al., 2004). Pain-related anxiety also is associated with changes in the hippocampal activity (Ploghaus et al., 2001), and patients with epilepsy, particularly temporal lobe epilepsy, which involves hyperexcitability of the hippocampus (Navidhamidi et al., 2017), exhibit anxiety (García-Morales et al., 2008). Results from other studies also suggest aberrant activity within the hippocampus of patients with different anxiety disorders, including PTSD (Carey et al., 2004; Tural et al., 2018), whereas chronic treatment with SSRI citalopram in the patients with anxiety disorders resulted in significant deactivation of several brain regions, including hippocampus (Carey et al., 2004). These data suggest the importance of neuronal activity in the processing of anxiety information in the hippocampus.

The hippocampal formation generally consists of several subdivisions, including the dentate gyrus (DG), the hippocampus proper (refer to the four cornu ammonis [CA] fields: CA4, CA3, CA2, CA1), and subiculum. The DG is a main gateway to the hippocampus that receives afferents from other brain regions. The principal neurons of the DG are the granule cells (GCs) that receive excitatory inputs from entorhinal cortex layer II cells via perforant path axons and project to the CA3 region through mossy fibers (MF; the axons of the DG GCs). Cells in the CA3 region then project to the CA1 region and then the subiculum, which in turn projects back to the entorhinal cortex. The subiculum is the final stage in the pathway, combining information from the CA1 projection and entorhinal cortex layer III to also send information along the output pathways of the hippocampus. In this review article, we discuss briefly the relevance of fear responses in the hippocampus with anxiety. We then present evidence that indicates a relationship between neuronal activity in different subregions of the hippocampus and anxiety and discuss some possible mechanisms underlying stress-induced hippocampal excitability and anxiety-related behavior.

Fear, hippocampal activity, and anxiety

Anxiety disorders are marked by excessive or persistent fear in the face of actual threats or even nonthreatening stimuli (Graham & Milad, 2011). Hence, a deeper understanding of the neural mechanisms involving fear and its decrease may lead to further progress in the development of more appropriate treatments for anxiety disorders. An excessive fear may be due to increased fear acquisition or impaired fear extinction. Impaired fear extinction particularly has been shown in PTSD and panic disorder and is thought to be a key mechanism in the etiology of these disorders (Blechert et al., 2007; Michael et al., 2007). Fear extinction has been shown to be context-dependent (Garfinkel et al., 2014; Vlachos et al., 2011). Studies of Pavlovian fear conditioning (a model for studying anxiety disorders) and extinction in humans and rodents particularly indicate a general deficit in contextual processing in both PTSD and panic disorder (Eskandarian et al., 2013; Garfinkel et al., 2014; Santos et al., 2013). This suggests that a dysfunction in contextual processing may explain fear extinction deficit observed in PTSD and panic disorder.

The hippocampus has been shown to be an essential brain area in the processing of contextual fear information, with the DG, CA3, and CA1 subregions supporting the acquisition of contextual fear, and the DG and CA1 supporting retrieval of contextual fear memory (Bernier et al., 2017; Morellini et al., 2017). Furthermore, both the DG and CA1 contribute to contextual fear extinction (Bernier et al., 2017; Morellini et al., 2017). Because aversive experiences are not completely identical, fear responses must be generalized to related stimuli that have an adequate degree of similarity to the initial event (Dymond et al., 2015). Although generalization of fear learning is an adaptive process, its overgeneralization is maladaptive and appears to be a feature of a number of anxiety disorders (Dunsmoor & Paz, 2015; Dymond et al., 2015). Thus, it is essential to discriminate among similar experiences and limit generalization to prevent inappropriate behavioral responses (Dunsmoor & Paz, 2015). The DG seems to play an important role in both fear generalization and discrimination, since it has been shown to contribute to overgeneralization of fear under stressful conditions (Lesuis et al., 2021). In addition, the DG is critically involved in pattern separation—a function that is critical for discrimination of highly similar, but not identical, experiences or events (Rolls, 1996; Treves & Rolls, 1994), and such process is likely to be essential for the discrimination between threatening and safe contexts. A relationship between deficient pattern separation and anxiety disorders has been reported in previous studies (Balderston et al., 2017; Bernstein & McNally, 2018), which may be in part due to overgeneralization of fear. In support of this view, lower behavioral pattern separation was found to be associated with increased generalization of threat expectancies in human (Lange et al., 2017). Pattern separation, however, has been suggested to be a predictor of anxiety under high levels of trait worry but not under baseline conditions (Bernstein & McNally, 2018).

Both innate/learned fear and anxiety responses in rodents are associated with hippocampal activity (Orsini et al., 2011; Peng et al., 2019), whereas suppression of fear responses reduces the hippocampal excitability (Zhang et al., 2017). For example, greater c-fos expression, as a marker for neuronal activity, was observed in the ventral CA1/subiculum during a conditioned fear cue compared with an extinguished cue (Orsini et al., 2011). Moreover, excitability of the DG GCs was increased in the anxiogenic versus nonanxiogenic environment in mice (Schoenfeld et al., 2016), whereas optogenetic inhibition of the DG was found to impair contextual fear acquisition and increase generalization of fear when very similar contexts must be distinguished (Bernier et al., 2017). An impairment in contextual fear extinction in mice deficient adiponectin receptor 2 also was associated with increased intrinsic excitability of the DG (Zhang et al., 2017). Furthermore, glucocorticoids have been shown to mediate aversive experience-induced increase in fear generalization via enhancing the size of DG cell population that is activated by the aversive stimulus, and inhibiting this neuronal population was found to decrease fear memory generalization (Lesuis et al., 2021). The hippocampal hyperexcitability also is observed in pathologic anxiety, as an excessive or persistent fear state. For example, fearful phenotype in a mouse model of panic disorder was found to be due to hippocampal hyperexcitability (Santos et al., 2013). SSRIs have been shown to prevent fear generalization and increase subsequent extinction (Pedraza et al., 2019) as well as decrease the hippocampal hyperactivity in PTSD patients (Tural et al., 2018). Some studies indicate that activity in the DG is necessary for both the acquisition and extinction of learned fear (Bernier et al., 2017; Denny et al., 2014), but distinct ensembles of DG GCs (fear engram cells) are activated during these processes (Denny et al., 2014; Lacagnina et al., 2019). Lacagnina et al. (2019) suggested that there is a competition between fear acquisition and extinction neurons in the hippocampus that determines whether fear is expressed or inhibited after extinction training. In this study, optogenetic inhibition of extinction neurons during extinction training enhanced fear after extinction, whereas inhibition of fear acquisition neurons during fear training decreased spontaneous recovery of fear after extinction. In contrast, stimulation of fear acquisition engrams enhanced fear, whereas stimulation of extinction GCs inhibited fear and prevented fear relapse. Because the relapse of fear is a major challenge for the treatment of anxiety and fear disorders (Vervliet et al., 2012), interventions that potentiate the activity of the hippocampal extinction neurons or inhibit reactivation of the fear acquisition neurons may be a treatment option for anxiety. Together, these data show that both physiological and pathological fear/anxiety responses are associated with changes in the hippocampal activity.

Changes in the excitability of CA1 neurons could influence the activity of other brain structures involved in fear/anxiety, including the prefrontal cortex (PFC), basal amygdala (BLA), hypothalamus, and nucleus accumbens (Cenquizca & Swanson, 2007; Loureiro et al., 2016; Swanson, 1981; Tannenholz et al., 2014) via direct projections to these brain areas. Activity in projections from the ventral CA1 to the PFC and basal amygdala are needed for contextual fear expression (Kim & Cho, 2017, 2020) and fear memory in pain processing (Nakamura et al., 2010). Growing evidence suggests an important role of medial PFC in encoding and consolidation of extinction memories (Laurent & Westbrook, 2009; Milad & Quirk, 2002). The ventral hippocampal projections have been indicated to induce a significant feed-forward inhibition of pyramidal neurons in the infralimbic region of the mPFC, via activating PV+ interneurons, and lead to relapse of extinguished fear, whereas pharmacogenetic inhibition of the ventral hippocampus projections to infralimbic region or GABAergic receptor blockade in the infralimbic decreased fear relapse after extinction (Marek et al., 2018). The relapse of fear may interfere with the efficacy of neurobehavioral interventions in patients with trauma and stress-related disorders, including PTSD. The ventral hippocampus projections to the PFC also were found to regulate adrenergic-mediated plasticity of glutamatergic neurotransmission in the PFC during development, such that neonatal lesioning of the ventral hippocampus-PFC projections resulted in impaired fear extinction and α1-adrenergic regulation of glutamatergic synaptic plasticity in the PFC (Bhardwaj et al., 2014).

The ventral hippocampal projections to the BLA are needed for contextual fear expression (Kim & Cho, 2020). These projections also are involved in regulation of generalized fear in nonthreatening environments (pathological fear generalization), and inhibiting glutamatergic projections from the ventral hippocampus that terminate within the BLA has been shown to reduce fear generalization (Ortiz et al., 2019). Signals related to fear extinction have also been shown to be processed within projections from the hippocampus to lateral amygdale (Lesting, Narayanan, et al., 2011a). In addition, previous studies have indicated a synchronized activity at theta rhythm between the hippocampus and BLA during retrieval of fear memory and fear extinction (Lesting, Narayanan, et al., 2011a; Seidenbecher et al., 2003). This theta coupling was found to increase during retrieval of conditioned fear and decrease during extinction learning (Lesting, Narayanan, et al., 2011a). A sustained amygdala-hippocampal theta rhythm synchronization has been demonstrated in mice with temporal lobe epilepsy accompanied by impaired extinction of fear memory in the animals (Lesting, Geiger, et al., 2011b). This nonextinguished fear memory in epileptic mice may contribute, at least in part, to anxiety symptoms in temporal lobe epilepsy (García-Morales et al., 2008).

The ventral hippocampus also sends projections to the hypothalamus and regulates stress responses as well as fear- and anxiety-related behaviors. The hypothalamic paraventricular nucleus (PVN) is a component of the hypothalamic-pituitary-adrenal (HPA) axis that produces corticotropin-releasing hormone (CRH) and consequently glucocorticoids following stress exposure and has been shown to contribute to pathophysiology anxiety (Shim et al., 2019). Ventral subiculum projects to the PVN and has been shown to play a role in the buffering of stress responses through indirect suppression of the HPA axis activity that results largely from the mediation of glucocorticoid feedback (Jacobson & Sapolsky, 1991; Ulrich-Lai & Herman, 2009), but gamma-aminobutyric acid (GABA)-ergic projections from the ventral subiculum to the PVN have also been suggested to mediate the inhibitory role of the hippocampus on the HPA axis activity (Herman & Mueller, 2006; Tafet & Nemeroff, 2020). This negative regulation of the HPA axis, however, is impaired by the hippocampal lesions (Dedovic et al., 2009; Jacobson & Sapolsky, 1991), which in turn can lead to increased levels of stress hormones and persistent activation of the HPA axis, which is known to be a hallmark of a number of neuropsychiatric conditions (Sapolsky, 2000; Terpstra et al., 2017). A population of ventral CA1 neurons was also found to project to the lateral hypothalamus (LH). The ventral CA1 projections to the LH have been shown to regulate some aspects of the fear response and anxiety, including modulation of the autonomic nervous system and regulation of the release of stress hormones via an effect on the HPA axis (i.e., increases the HPA axis activity) (Fakhoury et al., 2020). The ventral CA1-LH projections also control innate avoidance (a defensive response to perceived threats that enables a subject to avoid harmful stimuli) and anxiety-like behaviors, such that activation of the ventral CA1-LH pathway increased anxiety and avoidance behavior (Jimenez et al., 2018). Thus, although anxiety is adaptive under normal conditions, overstimulation of these pathways may lead to anxiety disorders (Jovanovic & Ressler, 2010; Kheirbek et al., 2012).

The ventral hippocampus is linked to medial shell of the nucleus accumbens, and dysregulation of neurotransmission in the ventral hippocampus-nucleus accumbens shell has been demonstrated to underlie in part hippocampal-mediated affective disruptions observed in neuropsychiatric disorders (Loureiro et al., 2016). For example, an increase in the ventral hippocampus-nucleus accumbens activity following chronic variable stress in both male and female mice was associated with anxiety-like behavior in both sexes (Muir et al., 2020). In addition, glutamatergic projections from the ventral hippocampus to the nucleus accumbens shell have been proposed to contribute to overreliance on habitual responses seen in neuropsychiatric illnesses, such as addiction and obsessive–compulsive disorder (a type of anxiety disorder) likely in part via an effect on behavioral flexibility (Barker et al., 2018). Behavioral flexibility is the ability to redirect goal-oriented behaviors to adapt to continuously changing conditions and its perturbation is particularly observed in obsessive–compulsive disorder (Gillan et al., 2015). Inactivating projections from the ventral hippocampus to the nucleus accumbens shell was found to restore expression of goal-directed behavior and reduce previously reinforced behavior (Barker et al., 2018). Stress has been shown to shift behavior from goal-directed to habitual behavior (Smeets et al., 2019) and lead to a loss of behavioral flexibility, which in turn may contribute to certain stress-related anxiety disorders (Barker et al., 2018). Additionally, pharmacological manipulation of the ventral hippocampus-nucleus accumbens pathway that enhances neuronal activity in the nucleus accumbens shell was found to control the formation of contextual fear memory in rats (Loureiro et al., 2016).

Together, these data suggest although the activity in the ventral hippocampus projections is needed for innate and learned fear/anxiety as well as stress adaptation, persistent neuronal activity in these pathways may interfere with hippocampus' ability and other brain areas associated with anxiety processing to reduce fear inhibition and increase risk for fear-related anxiety disorders. In line with this idea, inhibiting hippocampal inputs to the medial PFC was shown to reduce innate anxiety (Kjaerby et al., 2016). Hence, identifying the neural mechanisms underlying aberrant activity in the ventral hippocampus projection structures regulating fear- and anxiety-like behavior, such as the HPA axis, medial PFC, BLA, and medial shell of the nucleus accumbens, may be beneficial for developing targeted interventions for treatment of anxiety disorders, particularly for the treatment-resistant cases.

Adult neurogenesis, hippocampal activity, and anxiety

Neural plasticity is a principal feature of adult brain function, allowing adaptation to environmental changes. The DG, a critical part of the hippocampus, is a highly plastic region in the mammalian brain due to its ability for generating adult-born GCs (Zhao et al., 2008). Neurogenesis occurs in the DG subgranular zone containing a range of cell types with different stages of maturity; putative neural stem cells or quiescent neural progenitors that rapidly divide progenitors. Progenitors in turn divide and cause immature neurons, which then become mature GCs (Catavero et al., 2018).

A few lines of evidence indicate that both mature and immature GCs play a role in mediating anxiety (Anacker et al., 2018; Samuels et al., 2015). For example, mature GCs in the ventral DG are activated during attacks or

exploring anxiogenic environments, and adult-born neurons have been shown to inhibit this population of stress-responsive cells and protect against the anxiogenic effects of chronic social defeat (Anacker et al., 2018). In addition, reducing the immature adult-born GCs has been shown to increase anxiety-like behavior in a novelty suppressed feeding test (Deng & Gage, 2015). Mice lacking newborn neurons also fail to indicate adaptive behavioral responses to ambiguous threat cues and exhibit moderate levels of anxiety-like behavior (Glover et al., 2017). An impaired functional integration of newly born neurons was also observed in a genetic mouse model of higher trait anxiety (Sah et al., 2012). In addition, deletion of tropomyosin receptor kinase B (TrkB)—a receptor for brain-derived neurotrophic factor (BDNF)—in adult progenitors in mice caused a substantial loss of adult-born neurons and was associated with a remarkably increased anxiety-like behavior in the animals (Bergami et al., 2009).

There are conflicting results regarding effects of adult hippocampal neurogenesis on fear responses. Selective knockdown of newborn neurons was found to impair fear extinction (Deng et al., 2009; Stone et al., 2011). In addition, an increase in fear extinction memory 2 weeks after acute stress coincided with enhanced activation of newborn neurons (Kirby et al., 2013), suggesting new neurons via increasing fear extinction may contribute to adaptive response of the brain to acute stress and thereby may prevent excessive anxiety behavior. Although fear extinction is known to be one of the most effective treatment for anxiety disorders (Graham & Milad, 2011), it is not an erasure of the fear memory but instead involves a type of safety learning that may be recovered after extinction. Thus, interventions targeting forgetting process may represent a potentially alternative approach for treating anxiety disorders with excessive fear. In this respect, increasing neurogenesis with hippocampal neurogenesis enhancers during prolonged extinction training has been shown to promote forgetting of remote contextual fear memory (Ishikawa et al., 2016) and prevent spontaneous fear recovery after fear extinction learning (Martínez-Canabal et al., 2019). Nevertheless, there are studies showing that suppressing neurogenesis can reduce fear-related responses in rats (Winocur et al., 2006) or have no effect (Shors et al., 2002; Zhang et al., 2008). Although, it is not yet clear, neurogenesis manipulations conducted at different time points with respect to context-dependent encoding of fear and extinction memories may, at least in part, contribute to regulation of fear-related behaviors. Furthermore, some studies have reported that effects of adult neurogenesis on fear responses in mice depend on intensity of the aversive experience and whether the aversive stimulus is predictable or unpredictable (Glover et al., 2017; Seo et al., 2015). For example, neurogenesis has been shown to increase fear generalization and anxiety behavior in response to unpredictable but not predictably cued threats in mice (Glover et al., 2017).

Acute activation of the GCs in the ventral DG using optogenetic technique has been shown to reduce innate anxiety-like behavior in mice (Kheirbek et al., 2013). It has been suggested that activating the ventral DG is more likely to influence newborn GCs than older GCs (Snyder et al., 2009). Newborn GCs , which form ~10% of GCs, are more excitable and more plastic compared with mature GCs (Schmidt-Hieber et al., 2004), and their activation in the ventral DG have been shown to be involved in anxiolytic/antidepressant-related effects (Wu & Hen, 2014). Newborn GCs seem to decrease the excitability of mature GC (Marín-Burgin et al., 2012). Mature GC, which account for ~90% of the entire GCs population, are less easily elicited and are active preferentially during attacks or exploring anxiogenic environments (Anacker et al., 2018). A reduction in mature GC excitability can increase sparse coding in the GC layer (Ikrar et al., 2013). The sparse coding is critical for the function of pattern separation, which in turn has been shown to play a role in fear and anxiety responses (Rolls, 1996; Treves & Rolls, 1994). Neurogenesis-mediated decrease in the excitability of mature GCs also has been suggested to improve cognitive flexibility, i.e., the ability to flexibly switch between multiple tasks or concepts allowing to control actions and to adapt to continuously changing conditions that may help to reduce anxiety-like behavior (Anacker & Hen, 2017; Wilson et al., 2018). Some drugs used for anxiety disorders, such as SSRI fluoxetine and pregabalin, have been shown to accelerate GC maturation (Åmellem et al., 2017; Lempel et al., 2017). Whether this mechanism contributes to the therapeutic effects of these drugs on anxiety disorders remains unknown, but acceleration in the GC maturation could shorten window of sensitivity of young highly recruitable GCs and thus decrease the plasticity and overall activity of the DG, which in turn may influence anxiety behavior.

There are conflicting results about a role of neurogenesis in maintaining the overall DG network activity level and anxiety (Aoki et al., 2017). For example, a decrease in excitability of the DG and subsequently increased anxiety-like behavior (Macedo et al., 2018) induced by repeated social defeat stress in rodents is attributed to a reduction in neurogenesis (Aoki et al., 2017). In addition, the therapeutic effect of some anxiolytics has been associated with an enhanced rate of neurogenesis and normalization of the DG hypoactivity in a mouse model of trait anxiety (Sah et al., 2012). These studies suggest a role of neurogenesis in maintaining the overall DG activity and anxiety. In contrast, other studies have indicated that neurogenesis has no effect on the DG activity and anxiety-related behavior. For instance, cold water swim stress was found to enhance the DG GCs

activity and anxiety-like behaviors in mice, while preventing the stress-induced changes in activity of the DG GCs by physical exercise resulted in anxiolytic effects in the animals. In this study, despite an increase in neurogenesis following exercise, new neurons were not involved in decreased anxiety-like behavior or the DG activity reduction. Instead exercise increased local inhibitory mechanisms in the ventral DG, which in turn could decrease the GC excitability (Schoenfeld et al., 2013). This suggests that neurogenesis is not essential for maintaining the overall DG activity and anxiety-like behavior, consistent with the study that indicated long-term exercise decreased anxiety-like behavior in mice lacking new neurons (Schoenfeld et al., 2016). In another study, the therapeutic effect of chronic treatment with some anxiolytics in a genetic mouse model of trait anxiety, which had a lower rate of hippocampal neurogenesis and the DG hypoactivity compared with normal anxiety-like behavior controls, was associated with normalization of the DG hypoactivity but not neurogenesis (Sah et al., 2012). Thus, the authors suggested that normalization of the hippocampal hypoactivity may be a neurobiological marker for successful behavioral remission (Sah et al., 2012). These data propose that the level of neuronal network activity in the DG, but not neurogenesis, likely has an essential role in anxiety-based behaviors. Based on this suggestion, strategies designed to suppress the ventral DG activity may be effective for the treatment of anxiety disorders.

Stress hormone receptors are absent in neuronal progenitor cells (Saaltink & Vreugdenhil, 2014), but both mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) are present on new neurons (Wong & Herbert, 2005) and may act in concert to indirectly mediate effects of stress on the neurogenic process. MRs are activated in response to low levels of glucocorticoids and have been shown to induce an anxiolytic phenotype, in part via facilitating the formation of extinction fear memory in the ventral hippocampus (Xing et al., 2014). Furthermore, animal studies demonstrate chronic treatment with antidepressants enhances MR density in the hippocampus (Heegde et al., 2015). These data suggest that increasing activity or expression of brain MRs may improve anxiety disorders, at least in part via an effect on new neurons. In contrast to MRs, high levels of glucocorticoids activate GRs that have been shown to decrease proliferation of progenitor cells and neural differentiation (Anacker et al., 2013) and alter correct integration of newborn cells in the adult hippocampus (Fitzsimons et al., 2013). This suggests that activating GRs in the hippocampal newborn neurons could contribute to anxiety behavior. The level of GR expression has been proposed to directly regulate excitation-inhibition balance (Saaltink & Vreugdenhil, 2014). Excitation-inhibition balance has been demonstrated to control excitability in many brain circuits, including the hippocampus (Bhatia et al., 2019). An imbalance between the hippocampal glutamate and GABA has been shown in a PTSD mouse model (Gao et al., 2014) and following chronic stress (Kazi & Oommen, 2014). Disruption in excitation-inhibition balance also has been implicated in stress-induced anxiety disorders (Roshan-Milani et al., 2021). Because GRs are found on newborn GCs, thus changes in the expression of GRs on new neurons are likely to influence the DG excitability. This idea is supported by the studies that indicated a reduction in GR or GR knockdown in newborn GCs resulted in the DG hyperexcitability and altered functional integration of newborn neurons into the adult hippocampal circuits involved in fear (Fitzsimons et al., 2013; Kino, 2015).

A link between neurogenesis and the HPA axis activity has been shown in previous studies. For example, inhibiting adult neurogenesis in mice following exposure to a mild stressor resulted in increased HPA activity (Schloesser et al., 2009). The hippocampal neurogenesis also was found to normalize glucocorticoid levels after stress in mice (Snyder et al., 2011). In addition, it has been shown that stimulatory effect of SSRI fluoxetine on neurogenesis, which contributes to its anxiolytic impact, requires rhythmic changes in stress hormones (Huang & Herbert, 2006). This suggests that some SSRIs-resistant patients may have disturbances in the HPA axis activity, and thus concurrent manipulation of the HPA axis might improve effectiveness of SSRIs in these patients (Huang & Herbert, 2006). Although it is not yet clear, the effect of adult neurogenesis on the HPA axis activity may in part be via altering the electrophysiological properties at CA1/subiculum synapses containing neurons that project to the hypothalamus (Schloesser et al., 2009).

Some possible mechanisms underlying changes in the DG excitability in anxiety

Ion channels and synaptic plasticity in anxiety Neuronal activity, including intrinsic excitability and synaptic transmission in hippocampus, has been shown to modulate anxiety responses in rodents. The intrinsic excitability is affected by the conductance of voltage-gated ion channels, which are expressed on soma and/or dendrites of neurons and modulate the temporal summation of the synaptic inputs and ability to influence action potential generation (Shim et al., 2018).

Large-conductance voltage and Ca^{2+}-dependent K^+ (BK) channels, which regulate hippocampal neuronal excitability (Mehranfard et al., 2014, 2015), have been demonstrated to be involved in stress-induced anxiety (Guo et al., 2012) and pain-associated anxiety-like behaviors (Zhao et al., 2020). BK channel opening results in rapid efflux of K^+ and hyperpolarization of membrane potential (Jaffe et al., 2011). These channels are formed by a pore-forming α subunit (Torres et al., 2014) and accessory β subunits (Behrens et al., 2000), with α, β2, β4 subunits, which are primarily

expressed in the central nervous system (Piwonska et al., 2008). Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase that has been shown to be involved in anxiety (Libert et al., 2011), likely in part by modulating intrinsic and synaptic properties of the DG GCs via deacetylation of BK channel α subunits. Under chronic stress conditions, BK channel α subunit membrane expression was decreased, and SIRT1 effect on synaptic transmission or intrinsic properties was impaired and resulted in increased anxiety behavior (Yu et al., 2018). A significant downregulation of α-pore forming subunit of BK channels also has been shown in the DG and stratum lucidum of the CA3 area in epileptic rats in the pilocarpine model of temporal lobe epilepsy, which may in part be a cause of anxiety symptoms in epileptic states, which are common in temporal lobe epilepsy (García-Morales et al., 2008).

Mature DG GCs have been shown to fire action potentials, preferentially in bursts. The GC bursting has been suggested to play an important role in proper transferring information from MF synapses to CA3 (Dumenieu et al., 2018). The low voltage-activated T-type calcium channels have been shown to mediate burst firing of mature GCs in rodents, such that mice lacking Cav3.2 T-type calcium channels showed impairment in burst firing, synaptic plasticity, and effective information transfer from mature GCs to the CA3 (Dumenieu et al., 2018), as well as impaired memory retrieval for context-cued trace fear conditioning and passive avoidance (Chen et al., 2012) accompanied by increased anxiety (Gangarossa et al., 2014). Inhibition of Cav3.2 T-type calcium channels have been shown to decrease the retrieval of context-associated fear memory (Chen et al., 2012), and thus Cav3.2 channel blockers might be effective for treating PTSD and panic disorder, both of which have a deficit in contextual fear processing.

In addition to ionic conductance, synaptic plasticity principally regulates information processing in the hippocampal MF-CA3 synapses (Daoudal & Debanne, 2003). Disturbances in synaptic plasticity at MF-CA3 synapse induced by early-life stress have been associated with increased anxiety-like behavior in adolescent mice (Shin et al., 2016). In addition, acute traumatic stress has been demonstrated to increase anxiety in rats (Sood et al., 2013) and cause impairment of long-term potentiation (LTP) in the MF-CA3 synapse (Chen et al., 2010). A mechanism for acute stress-induced impairment of the hippocampal MF LTP has been suggested to be due to deleterious effect of a sustained and profound increase in cyclic AMP (cAMP)-specific phosphodiesterase-4 (an enzyme that catalyzes the hydrolysis of cAMP and decreases phosphorylation of cAMP-response element binding protein (pCREB) activity induced by enhanced circulating corticosterone levels on MF LTP (Chen et al., 2010)). This is supported by the study that indicated chronic administration of phosphodiesterase-4 inhibitor rolipram increased cAMP and pCREB in the hippocampus and produced anxiolytic-like effects in mice (Li et al., 2009).

Neuronal plasticity has been shown to be regulated by dendritic morphology. A decrease in BDNF level was found to cause a significant reduction in dendritic complexity in the DG neurons and impair extinction of fear conditioning in the transgenic mouse reproducing the Val66Met SNP (Met66 allele) of humans accompanied by anxiety-like behavior (Chen et al., 2006; Frielingsdorf et al., 2010). In addition, deletion of TrkB in adult progenitors in mice decreased the growth of dendrites and spines in adult-born GCs, impaired the synaptic plasticity in synapses on newborn neurons, and was associated with a remarkably increased anxiety-like behavior in the animals (Bergami et al., 2008). In another study, dendritic retraction in the DG of adult offspring of parental morphine exposure was associated with anxiety-like behavior in rats (Li et al., 2014). Since hippocampal-dependent memory needs both synaptic and forms of dendritic plasticity (Dan & Poo, 2006), thus, alterations in dendritic plasticity can lead to changes in synaptic strength (Sjöström et al., 2008) and network activity (Minerbi et al., 2009), which in turn may affect anxiety behavior via impairing fear extinction memory.

Together, these data indicate that changes in the intrinsic neuronal excitability could modulate the processing of information and GC output. The GC output has been shown to be important for various cognitive functions, including discrimination of similar contexts (Gilbert et al., 2001; McHugh et al., 2007; Nakashiba et al., 2012). Other studies have also indicated that although the GC output is not needed for fear retrieval (Bernier et al., 2017; Nakashiba et al., 2012), it can increase its precision (Bernier et al., 2017; Nakashiba et al., 2012; Pignatelli et al., 2019; Ruediger et al., 2011). The DG likely thereby could decrease interference between similar contextual threats and prevent overgeneralization of fear and anxiety disorders.

GABA neurotransmission Hippocampal GABAergic deficits, particularly decreases in α_1- and/or α_2 GABA type A receptor (GABAAR) subtypes are associated with anxiety behavior in rodents. For example, a decrease in the α_1-$GABA_A$ subtype in the hippocampus induced by early-life stress was associated with anxiety-like behavior in adult male rats (Mahmoodkhani et al., 2020), and inhibition of the principal neurons of the DG and CA3 by increasing $GABA_AR$ function via α_2-containing $GABA_A$ receptors suppressed anxiety in mice (Engin et al., 2016). An increase in local inhibitory mechanisms in the hippocampus of stressed rats following physical exercise was also associated with anxiolytic effect and blocking $GABA_A$ receptors in the ventral DG reversed the anxiolytic effect of physical exercise (Schoenfeld et al., 2013). In

addition, serotonergic median raphe fibers have been shown to principally target GABAeric interneurons in the DG and thereby suppress the firing of the GCs (Halasy et al., 1992). This suggests that the therapeutic effect of SSRIs in anxiety disorders may, at least in part, be by decreasing the DG activity via an effect on GABAergic neurotransmission. Inhibitory GABAergic interneurons also contribute to the GCs sparse neural activity (Gonzalez et al., 2018), which in turn has been shown to be essential for the function of pattern separation (Rolls, 1996; Treves & Rolls, 1994), and thus fear and anxiety responses (Bernier et al., 2017).

A growing body of evidence suggests that GABA has a prominent role in the control of the hippocampal neurogenesis. GABAergic interneurons make initial connections with adult-born GCs before the onset of glutamatergic synaptogenesis and play an important role in maturation and integration of newborn GCs (Alvarez et al., 2016; Chancey et al., 2013; Heigele et al., 2016). In this respect, an imbalance between GABA and glutamate neurotransmission has been proposed to cause deficits in proper integration of newborn GCs and contribute to pathogenesis of psychiatric diseases, including anxiety disorders (Saaltink & Vreugdenhil, 2014; Sah et al., 2012). Moreover, parvalbumin (PV)-expressing interneurons (basket cells) are known to control the survival of newborn GCs in the hippocampal neurogenic niche and to inhibit the activation of quiescent neural stem cells through GABA release (Song et al., 2012, 2013), suggesting that PV-expressing interneurons may control aberrant neurogenesis and excessive anxiety. This is supported by the study that indicated a significant decrease in PV-expressing interneurons in the DG of mice lacking Cend1 (a neuronal-lineage specific modulator) resulted in an aberrant neurogenesis and increased number of newborn neurons accompanied by enhanced anxiety in these animals (Segklia et al., 2019). A reduction in firing frequency of PV-expressing interneurons, via reducing activity of voltage-dependent Kv3.1 ion channels in the DG PV cells, also was associated with anxiety-like behavior (Medrihan et al., 2020), whereas selective activation of these interneurons in the DG produced an anxiolytic effect and facilitated fear extinction in mice (Zou et al., 2016). These findings are further supported by the evidence that indicated an increase in GABAergic neurotransmission of PV interneurons, via genetic ablation of cyclin-dependent kinase 5 (Cdk5) in PV interneurons in mouse brain, was associated with decreased anxiety-like behavior in the animals (Rudenko et al., 2015). These data suggest that Cdk5 and Kv3.1 may be promising therapeutic targets for a number of conditions related to inhibitory interneuronal dysregulation, including anxiety disorders.

Role of hilar DG mossy cells Hilar glutamatergic mossy cells are a major population of hilar neurons (Buckmaster & Jongen-Rêlo, 1999; Fujise et al., 1998), which target mature GCs via projecting directly to these cells (Buckmaster et al., 1996; Ribak et al., 1985) and indirectly via local GABAergic interneurons that synapses onto GCs (Scharfman, 1995). The mossy cells excite both inhibitory GABAergic neurons and GCs, but the net effect of mossy cell excitation on GCs seems to be inhibitory (Jinde et al., 2012). This supports a role of hilar glutamatergic in the DG sparse activity and pattern separation (Myers & Scharfman, 2009), which in turn may contribute to anxiolytic effects of mossy cells. In this regard, therapeutic effect of chronic SSRI treatment has been shown to be in part via increasing neuronal activity of the hippocampal mossy cells, whereas chemogenetic inhibition of mossy cells impaired behavioral responses to chronic administration of SSRI (Oh et al., 2020). Moreover, sonic hedgehog is expressed by hilar mossy cells and acts as a neurotrophic factor. Sonic hedgehog ablation in the adult DG has been shown to cause a significant degeneration of mossy cells (Gonzalez-Reyes et al., 2019), a condition that has been shown to induce increased anxiety-like behavior (Jinde et al., 2012). In addition, mice lacking mossy cells exhibited increased anxiety-like behavior (Scharfman, 2016). An increase in the excitability of hilar mossy cells has been shown via activating dopamine D2 receptor, a receptor that is involved in anxiolytic effect of dopamine system following chronic stress (Choi et al., 2017). Nevertheless, under certain conditions, such as severe seizures, mossy cell excitation of GCs is powerful and results in GC hyperexcitability (Botterill et al., 2019), which in turn may contribute to symptoms of anxiety seen in temporal lobe epilepsy.

Another mechanism through which mossy cells influence anxiety may be via an effect on neurogenesis. Mossy cells have been shown to control adult neural stem cell quiescence via a dynamic balance between direct (glutamatergic) and indirect (GABAergic) pathways. Moderate activation of mossy cell increases neural stem cell quiescence through dominant indirect pathway, whereas high mossy cell activation increases neural stem cell activation through dominant direct pathway. In contrast, mossy cell inhibition or ablation leads to a transient increase of neural stem cell activation, but neural stem cell depletion only occurs after chronic ablation of mossy cells (Yeh et al., 2018). These data suggest that compounds that target mossy cell activity may be potential candidates for the development of new anxiolytic medications.

Some possible mechanisms underlying the CA1 excitability in anxiety

L-type Ca2+ channels are formed by the Cav1 family (Cav1.1-Cav1.4) and are implicated in psychiatric disorders (Casamassima et al., 2010). The Cav1.2 and Cav1.3

isoforms are expressed in the hippocampus and are known to regulate neuronal excitability and synaptic plasticity (McKinney et al., 2009). A decrease in Cav1.2 and Cav1.3 in CA1 pyramidal neurons in mice lacking Tenascin-C was found to impair fear extinction (Morellini et al., 2017) and increase anxiety-like behavior (Kawakami & Matsumoto, 2011).

Lipocalin-2, an innate immune protein, has been shown to control the CA1 neuronal excitability via regulating dendritic spine density and morphology under stress conditions. Lipocalin-2 is upregulated in the hippocampus following stress and prevents stress-induced increase in dendritic spine density and morphology, as an adaptive response for maintaining homoeostasis. However, disruption of the lipocalin-2 gene in mice resulted in increased proportion of mushroom spines and higher spine density in both CA1 and CA3, correlated with CA1 neuronal hyperexcitability and anxiety-like behavior in the animals (Mucha et al., 2011).

Dysregulation of cannabinoid type 1 receptor signaling in the ventral hippocampus was also found to increase neuronal activity in the ventral hippocampus projections to nucleus accumbens and has been suggested to mediate cannabinoid-induced neuropsychiatric disorders (Loureiro et al., 2016).

Serotonin (5-HT) and its receptors also appear to play an important role in control of the CA1 neuronal excitability and anxiety-related behavior. For example, 5-HT has been shown to suppress the ventral hippocampal inputs to the medial PFC via activating presynaptic 5-HT1B receptors and decrease innate anxiety (Kjaerby et al., 2016). 5-HT has also been shown to hyperpolarize CA1 pyramidal neurons through activating 5-HT1A receptors in rats, but 5-HT responses of CA1 neurons are attenuated following prolonged exposure to high levels of corticosterone without any change in 5-HT1A mRNA levels. This reduction in 5-HT responsiveness of CA1 neurons seems to be due to a significant decrease in the ratio of MR/GR mRNA expression, leading to an impairment in interaction between 5-HT and stress hormones. This is because corticosteroid receptors have been shown to increase 5-HT responses, but chronically exposure to high corticosterone levels reduces both MR and GR mRNA expression, with a greater decrease in MR mRNA expression than that in GR. This is consistent with the idea that states increasing MR expression is effective in treatment of anxiety disorders.

An imbalance in excitation-inhibition also could alter the CA1 excitability and cause anxiety. For example, withdrawal from 1-day flurazepam use in rats was associated with anxiety-like behavior and CA1 hyperexcitability due to an increase in CA1 neuron α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamatergic receptor -mediated excitation (Van Sickle et al., 2004). In addition, long-term treatment with benzodiazepine anxiolytics has been shown to decrease sensitivity to the benzodiazepine via reducing level of synaptic $GABA_A$ receptors (Nicholson et al., 2018). A reduction in $GABA_A$ receptor-mediated inhibition (Zeng & Tietz, 1999) also has been demonstrated in CA1 pyramidal neurons following benzodiazepine treatment, which may in part contribute to a reduction in anxiolytic effect of benzodiazepines (Kanematsu et al., 2002).

Effect of age and sex differences on the hippocampal function and anxiety

Epidemiological reports show higher incidence rates of anxiety- and fear-based disorders in women than men (Breslau et al., 1997; Foa & Street, 2001; McLean et al., 2011; Tolin & Foa, 2006). Despite this striking sex difference in anxiety prevalence, the neurobiological mechanisms that can lead to higher levels of anxiety in females remain largely unclear.

Sex differences in anxiety disorders in part may be due to differences in fear generalization and extinction between male and female (Lynch 3rd et al., 2013; Matsuda et al., 2015; Ribeiro et al., 2010; Voulo & Parsons, 2017), although the direction of these differences is not consistent. Several studies have reported a higher extinction rate in male rodents than females (Matsuda et al., 2015; Ribeiro et al., 2010; Voulo & Parsons, 2017). In another study, female rats showed enhanced fear response to neutral context, whereas male rats indicated the ability to discriminate between the two contexts (Lynch 3rd et al., 2013). This increase in generalization of fear in females compared with males may contribute to more vulnerability of females to fear generalization disorders, such as PTSD (Dunsmoor & Paz, 2015). Differential activation of the extracellular signal-regulated kinase activation in the ventral hippocampus has been associated with sex differences in contextual fear and may be a factor contributing to the differences seen in anxiety disorders between male and females (Gresack et al., 2009).

Sex differences have been observed in stress response circuitry. For example, compared with males, female rodents have greater HPA axis activation and subsequent higher levels of glucocorticoids (Bangasser, 2013; Kitay, 1961; Viau et al., 2005; Weinstock et al., 1998), a state that is thought to cause anxiety. Chronic elevation of glucocorticoids has been associated with sexual morphological differences in the hippocampal CA3 neurons correlated with differences in composition and spectrum of glutamate receptors (Liu et al., 2006). These differential responses of male and female CA3 neurons to chronically increased glucocorticoid have been proposed to contribute, at least in part, to differential susceptibility to chronic stress and stress-related disorders in males and females (Liu et al., 2006).

Gender differences in dendritic characteristics of locus coeruleus (LC), a principal component of the stress response, also may underlie greater susceptibility of females to the effects of stressful events than males, in part, via an effect on the hippocampus. In one study, the LC neurons in female rats were found to have a greater dendritic extension and complexity compared with males, suggesting the LC neurons in females may be subjected to greater connections with various afferents that terminate onto LC processes (Bangasser et al., 2011). This in turn may cause sex differences in the LC effects on the hippocampus. The LC has been reported to be critical to context fear extinction in part via an effect on the hippocampal function (Abraham et al., 2012; Chai et al., 2014). The LC is also thought to be a potent modulator of the hippocampal ventral subiculum activity (Lipski & Grace, 2013)—a hippocampal region that has been implicated in fear (Maren, 1999), stress, and anxiety (Herman & Mueller, 2006; Mueller et al., 2004).

Unlike adult-onset stressors, some studies show that males are much more susceptible to stress during development and are more likely to develop anxiety (Liu et al., 2001; Sun et al., 2021), at least in part, via inducing functional alterations in the hippocampus. For example, exposure to glucocorticoids during the juvenile period caused an increase in MR expression and a decrease in the ratio of GR/MR in the hippocampus of adult animals accompanied by increased anxiety-like behavior. In this study, females had a greater expression of GR and GR/MR ratio than males, accompanied by lower levels of anxiety-like behavior (Liu et al., 2001).

In addition to sex, prevalence of anxiety symptoms is affected by age. Although there are variations in prevalence estimates of anxiety disorders among the elderly, as a whole, prevalence of anxiety symptoms is reported to increase with age (Himmelfarb & Murrell, 1984; Scrable et al., 2009; Zung, 1986). In particular, generalized anxiety disorder has been shown to be more common in older than younger adults (Lenze & Wetherell, 2011). This may in part be due to the effects of aging on the hippocampal structure and function. For example, neurogenesis has been shown to decrease with age. The reduced neurogenesis in aging appears to involve predominantly inhibitory interneurons in the hippocampus and cause a hyperexcitable state over time. This has been suggested to enhance the excitatory drive of projection neurons that carry information from the hippocampus to other brain regions related to anxiety processing, including the hypothalamus, principally the PVN, which in turn could increase the level of HPA axis activity and the appearance of anxiety-like behavior (Scrable et al., 2009). Compared with younger counterparts, older adults have an higher level of corticosteroids, which in turn could desensitize brain glucocorticoid receptors (Sapolsky et al., 2000), alter the activity of glutamatergic N-methyl-D-aspartate receptor (Weiland et al., 1997), and cause synaptic and morphological alterations in the hippocampus (Conrad, 2008; McLaughlin et al., 2009; Tata & Anderson, 2010), which in turn may contribute to greater susceptibility of older adults to anxiety.

Aberrant activation of the hippocampal microglia also may underlie anxiety in older adults. Aberrant microglia activity is associated with many neurological and psychiatric disorders, including anxiety (Tränkner et al., 2019). It has been reported that long-lasting stress causes microglia activation in several brain regions involved in stress response, including the CA3 and DG (Ramirez et al., 2017; Wohleb et al., 2011), and is associated with depressive- and anxiety-like behavior (Wang et al., 2018). An increase in microglia numbers in the DG has been associated with enhanced anxiety-like behavior in both aged mice and a mouse model of high trait anxiety (Rooney et al., 2020). Microglia have been shown to regulate CA1 neuronal excitability and innate fear response, and manipulations that increase microglia activation were found to increase ventral CA1 neuronal excitability accompanied by increased innate fear (Peng et al., 2019). This may increase risk for anxiety, supported by the studies that indicate a strong fear emotion may cause anxiety and lead to PTSD (Blechert et al., 2007; Michael et al., 2007).

Together, these data suggest that although neural basis of age and sex differences in anxiety disorders remains largely unclear, it may in part involve sex differences in fear extinction, neurogenesis, and response of hippocampus to stress. In this regard, sex- and age-specific approaches may be required to enhance the treatment efficacy for anxiety disorders. Further research is needed to identify the underlying mechanisms of age- and sex-related anxiety disorders.

Conclusions

Anxiety disorders are marked by excessive fear responses likely due to potentiation of fear acquisition and/or a deficit in fear extinction. Presently, extinction-based therapies are recommended for treatment of certain anxiety disorders, such as PTSD and panic disorders in both which fear extinction are compromised. Fear extinction is induced during retrieval, when fear retrieval is repeated without reinforcement (Rossato et al., 2010). Previous studies have suggested a role for the DG in acquisition of fear memory. However, recent data show that the DG also plays a role in retrieval of fear memory (Bernier et al., 2017). The dentate network activity has been shown to determine the efficacy of memory retrieval (Pignatelli et al., 2019) and to increase its precision (Bernier et al., 2017; Pignatelli et al., 2019). The DG GC firing is normally sparse (Diamantaki et al., 2016; Neunuebel & Knierim, 2012)—a feature that is essential for cognition and behavior (Diamantaki et al., 2016; Jung & McNaughton, 1993; Neunuebel & Knierim, 2012) and

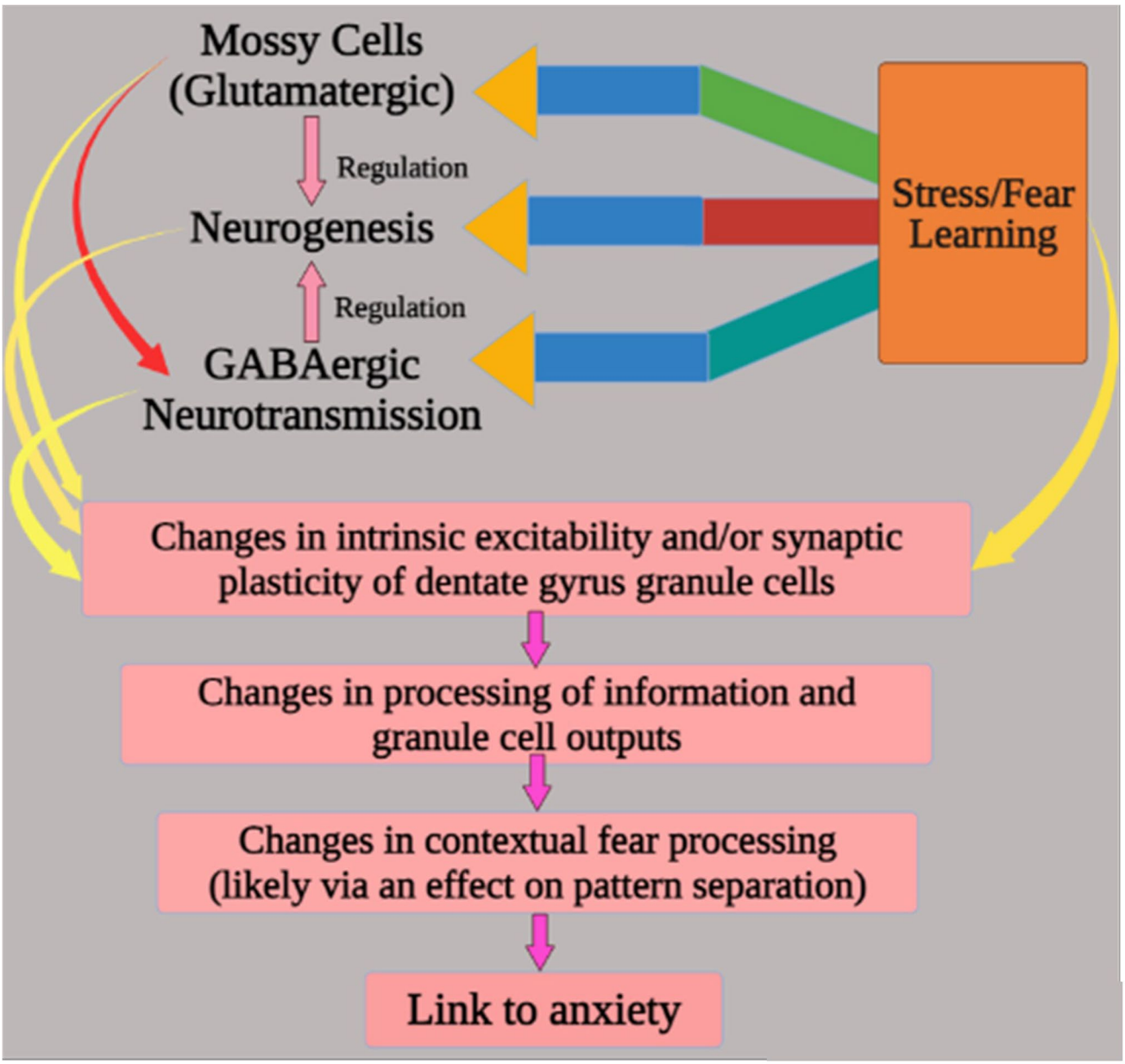

Fig. 1 Association between the dentate gyrus activity, fear and anxiety

is thought to facilitate discrimination of similar contextual memories to minimize interference, likely via contributing to pattern separation (Kim et al., 2020). The DG thereby may play a role in discrimination between threatening and safe contexts and disruptions in the DG sparse activity may increase susceptibility to anxiety. This is supported by studies that indicate aberrant GC excitability and GC-output are associated with increased anxiety behaviors. These data suggest that excitability and functional plasticity of GC-CA3 may be involved in behavioral responses to environmental threats and to enable stressful conditions. These findings encourage further study of the DG circuit function and plasticity as a way to identify mechanisms through which context generalization, fear acquisition, and fear extinction can be modulated. Because fear generalization (Kheirbek et al., 2012; Lissek et al., 2010) and extinction (Bouton et al., 2001; Mineka & Zinbarg, 2006) are believed to play important roles in the etiology and treatment of anxiety disorders, a more thorough understanding of the DG contributions to these processes will likely help to identify more effective therapeutic strategies. Newborn GCs, mossy cells, and local GABAergic interneurons in the DG—particularly PV-expressing interneurons—act as modulators of GC activity to provide inhibitory control on the GC activity and to

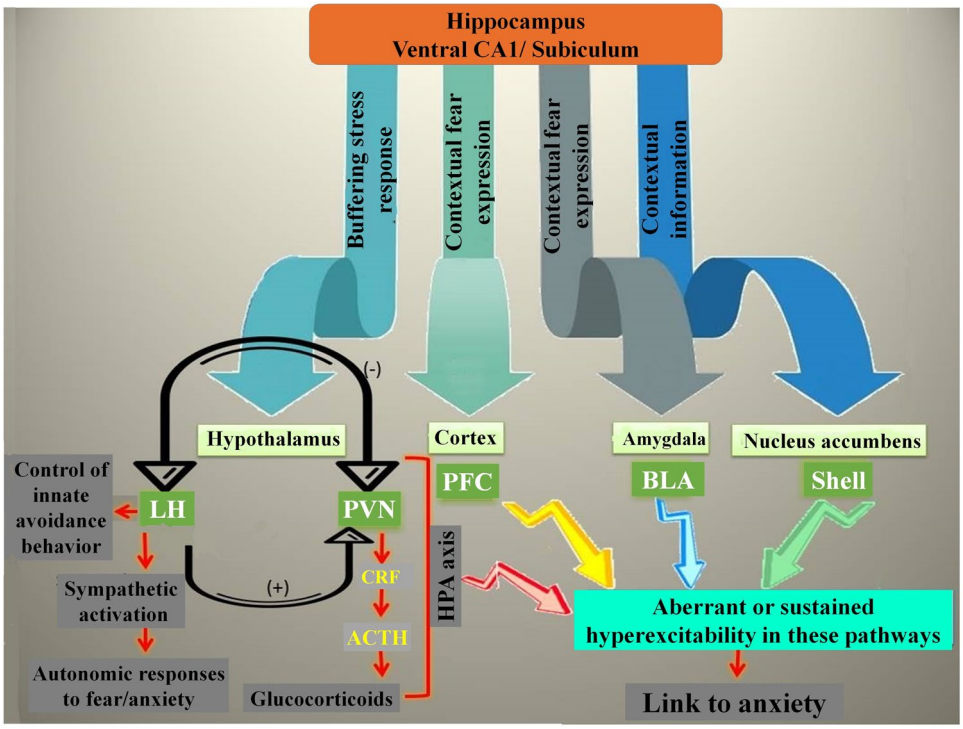

Fig. 2 Association between the hippocampal activity and brain regions involved in anxiety

influence pattern separation and thereby likely constitute an adaptive mechanism to optimally encode contextual information. In particular, newborn GCs and PV-expressing interneurons have been shown to influence fear extinction. Future studies should aim at elucidating how newborn GCs and PV-expressing interneurons orchestrate extinction of fear memory in the DG.

In addition to GC activity, growing evidence indicate that anxiety also is associated with increased neuronal excitability in the CA1 area. Activity in the ventral hippocampal CA1/subiculum and its projections to the BLA, PFC, and hypothalamus are needed for innate and learned fear/anxiety as well as stress adaptation, behavioral flexibility, and reward-related decision making, but overstimulation of these pathways may lead to strong fear emotion, potentiation of stress responses, and less behavioral flexibility—all of which may cause anxiety and lead to anxiety disorders. Disruption in behavioral flexibility in particular may contribute to anxiety-related to habitual behaviors, such as addiction and obsessive–compulsive disorder.

Changes in hippocampal neuronal excitability may be due to fear learning, exposure to stressful experiences, or be independent of fear/stress due to biological causes. Thus, identifying underlying causes of the ventral hippocampal hyperactivity in neural circuits involved in fear/anxiety and stress response may help to determine appropriate treatment for each anxiety disorder. A theoretical explanation for a relation between hippocampal activity and anxiety is presented in Figs. 1 and 2.

Declarations

Conflict of interest The authors have declared no conflict of interest.

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