Chapter

Neural Circuits and Some New Factors Involved in Hippocampal Memory

Ruiying Jing, Qiujie Cai, Wen Li and Xinhua Zhang

Abstract

Humans and other primates have memory, and the hippocampus plays a critical role in this process. The neural circuitry is one of the structural foundations for the hippocampus in exerting memory function. To understand the relationship between the hippocampus and memory, we need to understand neural circuits. Past research has identified several classical neural circuits involved in memory. Although there are challenges with the study of hippocampal neural circuits, research on this topic has continued, and some progress has been made. Here, we discuss recent advances in our understanding of hippocampal neural circuit mechanisms and some of the newly discovered factors that affect memory. Substantial progress has been made regarding hippocampal memory circuits and Alzheimer's disease. However, it is unclear whether these novel findings regarding hippocampal memory circuits hold promise for human memory studies. Additional research on this topic is needed.

Keywords: hippocampal, memory, neural circuits, Alzheimer's disease

1. Introduction

Since the description by Scoville and Milner of profound anterograde amnesia in a patient known as H.M. following bilateral temporal lobe resection [1], the hippocampus and surrounding temporal lobe structures have been extensively studied for their role in memory. Subsequently, our understanding of the neurophysiological bases of hippocampal function was greatly enhanced by two breakthroughs: Bliss and Lomo's finding [2] of activity-dependent long-term potentiation (LTP) of synaptic transmission in the hippocampus, and the discovery of hippocampal place cells and neurons that encoded the spatial position of an animal reported by O'Keefe and Dostrovsky [3]. These discoveries stimulated researchers to study the types of memories related to the neural circuits of the hippocampus. Here, we discuss neural circuits and efferent or afferent fibers related to the hippocampus, including the entorhinal cortex to the hippocampus [4], hippocampus to the prefrontal cortex [5], and vDBChATs-dNGIs [6]. We also discuss LIS1, Fos, SynCAM1, BDNF, Smad3, Oxytocin, and DISC1, factors that influence memory insofar as they relate to the development of memory and memory consolidation. With recent technological advances, causal investigations of specific neural circuits relating to the hippocampus and Alzheimer's disease (AD) have helped us to understand the pathogenesis of AD and improve the clinical treatment of AD patients.

2. Cytoarchitecture and functional characteristics in the hippocampus

The hippocampus is an elongated structure with a longitudinal axis extending in a C-shaped fashion, which can be functionally divided into dorsal, intermediate, and ventral parts [7, 8]. Along the transverse axis, it can be further divided into the CA1, CA3, and dentate gyrus (DG). There is a canonical trisynaptic pathway within the hippocampus, involving information proceeding from the entorhinal cortex (EC) to the DG, then to the CA3, and finally to the output node CA1 [9].

The DG has three layers, including the molecular layer, granule cell layer, and polymorphic cell layer [10]. The molecular layer mainly comprises dendrites of the dentate granule cells and the fibers of the perforant path that originate in the entorhinal cortex. The granule cell layer is the principal cell layer, which is largely composed of densely packed granule cells. The granule cell layer encloses a cellular region and forms the third layer of the DG, which is called the polymorphic cell layer. The DG plays a key role in learning, memory, and adult neurogenesis [11]. This region generates new neurons that are integrated into brain circuits [12].

The CA3 area is the largest in the hippocampus and forms the major route of information flow [13]. One of the most prominent features of the CA3 is that there are extensive interconnections among the principal cells via the circulating collateral fiber system [14]. The axon collateral branches of CA3 pyramidal cells form synapses with the apical dendrites of CA3 pyramidal cells in other regions and spread throughout most of the region to form an associative network [15].

The CA1 area, with its widespread projections, is a key output node of the hippocampal memory circuit, which transfers excitatory information out of the hippocampus proper via direct projections to deep layers of the EC or subiculum [16]. The CA1 is composed of densely packed large pyramidal neurons that play an important role in long-term memory and related spatial tasks and behavior [17]. Human CA1 pyramidal neurons exhibit distinctive morphological complexities, which have important computational implications [18]. Many additional functions have been proposed for the CA1, including novelty detection, input comparison, and enrichment of hippocampal output, possibly by redistributing information from the CA3 to a larger number of output neurons [19].

3. The hippocampus and memory

Memory is the ability to use the past to serve the present or future. Without it, we are destined to enter the eternal present. In the twentieth century, Richard Simon introduced the term "engram" to describe the neural matrix used to store and recall memories [20]. Memory is actually a continuous process between nerve cells [21]. Essentially, a population of neurons is activated that undergoes persistent chemical and/or physical changes to become an engram; the neurons reactivate the engram by cues available at the time of the experience [22]. The criteria and experimental strategies in the study discussed by Morris and colleagues to evaluate synaptic plastic memory have become landmarks in evaluating the importance of the existence of engrams [23, 24].

The hippocampus is important for the storage and retrieval of declarative memories, including memories for perception, imagination, and recall of scenes and events [25, 26]. Studies have shown that spatial memory is closely related to the hippocampus. This is because the "place cells" in the hippocampus make the hippocampus necessary for spatial memory activities [27]. If the hippocampus is damaged, humans may not be able to remember where they have been and how to get to where they want to go. For example, AD is a progressive and neurodegenerative disorder of the cortex and hippocampus, characterized by progressive cognitive decline and

a prominent loss of hippocampal-dependent memory [28]. Degeneration of basal forebrain cholinergic neurons is a hallmark of AD. Its function depends on the nerve growth factor (NGF), which is transported retrogradely from the synthetic sites in the cortex and hippocampus [29]. Studies have found that patients with Parkinson's disease (PD) also experience a variety of nonmotor symptoms, the most important being cognitive impairment that in many cases can lead to dementia [30]. There is also evidence that the CA1, CA2–3, CA4-DG, and the subiculum are involved in the poor neurocognitive scores of PD memory caused by impairment. Furthermore, because the CA3 is essential for recall, it is expected that atrophy of the CA3 subregion will also affect the episodic memory recollection process in PD patients.

4. Neural circuits and neurite connections involved in hippocampal learning and memory

4.1 The Papez circuit

In the 1930s, Papez et al. discovered that there was a major circuit in the limbic system, called the Papez circuit, involving hippocampus→fornix→papillary body→papillary thalamic tract→prethalamic nucleus→cingulate gyrus→ hippocampus [31, 32] (**Figure 1**). The hippocampus is the central part of this circuit. This circuit acts as the neural basis for emotional expression. It has been shown that axons transmitting emotional impulses originate from the hippocampus and are projected to the thalamus through the papillary body, where physiological emotional effects such as changes in heartbeat, respiration, and body temperature are produced, and nerve fibers are projected to the cingulate gyrus and the frontal lobe of the cerebral cortex after cell replacement to produce a clear emotional experience. Finally, the signal returns to the hippocampus through the projection of the cortex, and then emotional memory will be generated. Later studies have shown that the Papez circuit is also an important brain structure closely related to learning and memory [33, 34]. Therefore, if this circuit is damaged, it will lead to the amnestic syndrome, and different lesions will produce different forms of memory impairment.

4.2 The trisynaptic circuit

The trisynaptic circuit transmits signals between the entorhinal area and the hippocampus structure (**Figure 2**). This circuit first starts in the cortex of the

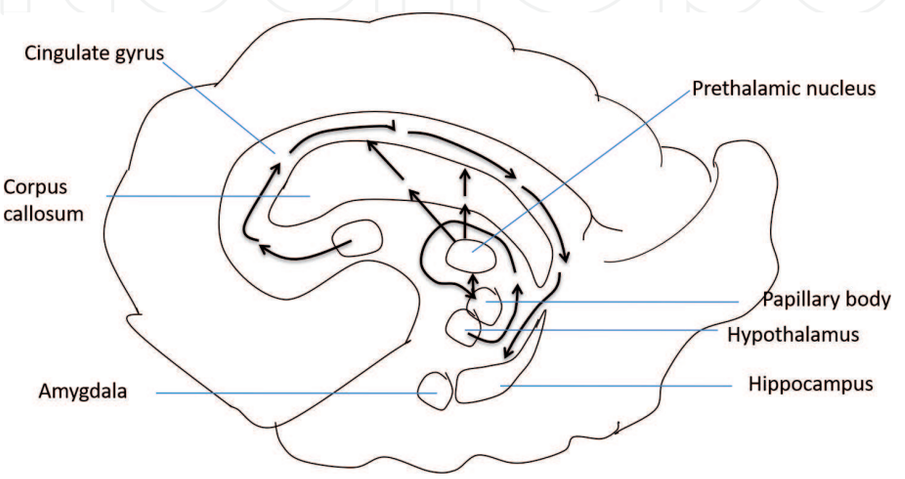

Figure 1.
The Papez circuit.

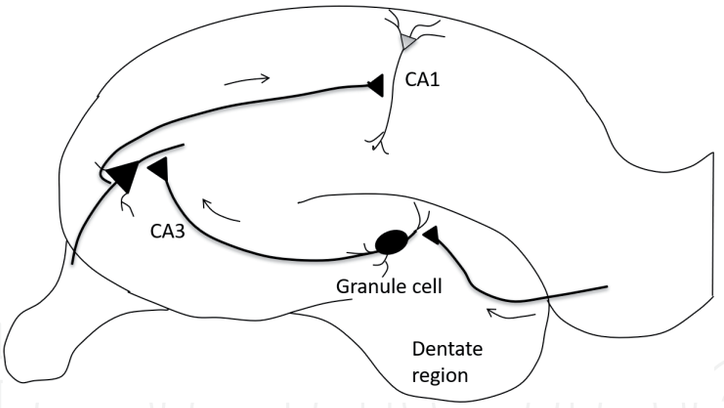

Figure 2.
The trisynaptic circuit.

entorhinal area, where neuronal axons form a perforating circuit and end in the DG granular cell dendrites [35]. The axons of the DG granular cells then form mossy fibers projecting to the hippocampal CA3 area, where they form a second synaptic connection with the dendrites of pyramidal cells. The third synaptic connection occurs between the axons of pyramidal cells in the CA3 area and dendrites of pyramidal cells in the CA1 area, and then the CA1 pyramidal cells transmit the axons to the entorhinal area. The trisynaptic circuit is, therefore, closely related to and forms an important foundation for learning and memory.

4.3 The entorhinal cortex (EC)

The EC is generally perceived as a major input and output structure of hippocampal formation and contributes to cognitive processes and memory formation [36]. The EC is subdivided into two components, the lateral EC (LEC) and medial EC (MEC), according to the differential distribution of EC projections to the DG [37]. In 1893, Santiago Ramon y Cajal [38] described two classical pathways from the EC to the hippocampus (**Figure 3**). One is the long-range pathway: EC layer 2 → DG → CA3 → CA1 area; the other is the short-range or direct pathway: EC layer 3 → CA1 area. However, it is unclear how the hippocampal neurons form specific connection pathways to transmit different information, and how they participate in hippocampal learning functions. Recently, a study [4] found a direct lateral EC-dorsal CA1 (dCA1) circuit that was critically involved in olfactory associative learning. Studies have shown that excitatory pyramidal cells in the hippocampal CA1 region have highly variable molecular, morphological, and electrophysiological

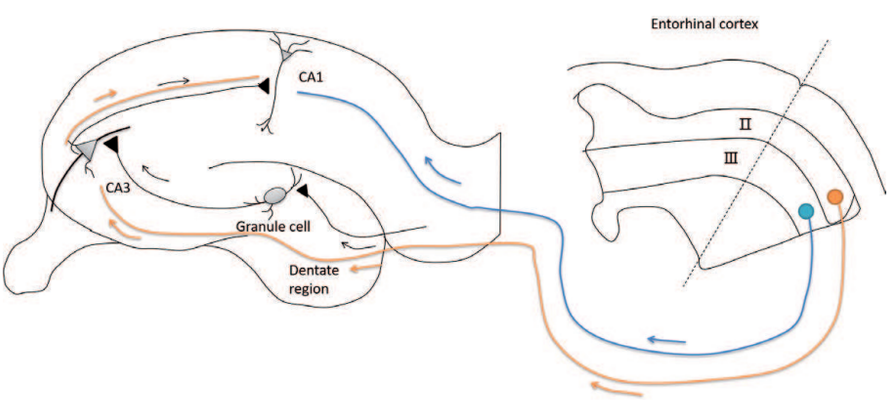

Figure 3.
Pathways from the entorhinal cortex to the hippocampus.

characteristics along the dorso-ventral [39, 40], proximal-distal [40–42], and radial (superficial-deep) axes [39, 40, 43–47]. Subdivisions of deep and superficial pyramidal cells in the CA1 have been recognized for many years, especially along the radial axis. Deep and superficial pyramidal cells are generated at different times and express different genes [39, 40, 43, 48]. *In vivo* recording studies have reported different spiking patterns between these two sublayers; deep cells are more likely to burst and exhibit more spatially tuned firing than superficial cells, and they spike differentially in the hippocampal theta rhythm and during sharp-wave ripple activities [46]. Further study revealed that inhibition of the excitatory synaptic transmission from the LEC to CA1 complex pyramidal cells, or the discharge activity of the CA1 complex pyramidal cells using optogenetic methods, significantly delayed the olfactory association during mice learning [49]. The optogenetic method mentioned above is injecting NpHR or Arch into some mice's hemispheres and then using yellow illumination to identify the mice that include NpHR or Arch. Then researchers can make a comparison between special mice and normal mice. The study also implanted optetrodes into mices' dCA1 to record the olfactory-related firing activities of neurons in the CA1 region of the hippocampus, it was found that the firing of complex pyramidal cells established different preferences for odor cues during learning [49]. These experimental findings revealed that there was a specific neural pathway involved in brain-related learning in the classic circuit from the EC to hippocampus involving cells, synaptic connections, learning behaviors, and neural discharges.

4.4 The prefrontal cortex

The hippocampus and the prefrontal cortex are closely related to advanced cognitive functions of the brain such as learning and memory [50]. Previous studies showed that neural projections from the hippocampus to the prefrontal cortex had the characteristics of a single synapse, were unidirectional, and displayed ipsilateral projections [51]. In brief, the hippocampus-prefrontal lobe projection mainly originates from the subiculum of the ventral hippocampus and the CA1 and ends in the medial, orbitofrontal, and lateral parts of the prefrontal lobe (**Figure 4**). The projection from the prefrontal lobe to the hippocampus is indirectly from the prefrontal lobe to the cingulate gyrus, parahippocampal gyrus, entorhinal cortex, then to the hippocampus [52], which transmits information from prefrontal lobes to important nuclei of the hippocampus [53, 54]. There are also reports that some nerve fibers in the prefrontal lobe project directly to the hippocampus, but the number was low [55, 56].

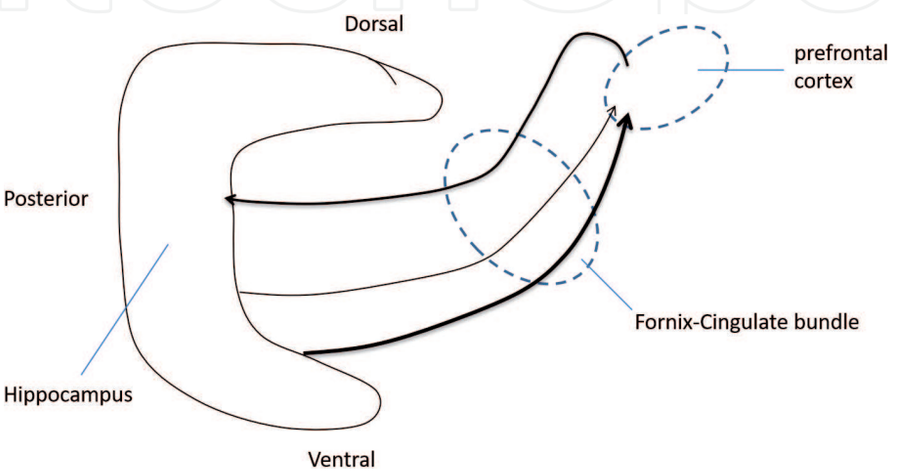

Figure 4.
The pathway from the hippocampus to the prefrontal cortex.

Humans are faced with different environments every day and need to make the right choices through learning and memory in order to find their goals. A recent study [5] found that when an animal runs a specific route and then stops to rest or sleep, place cells [3] are repeatedly released in the same (forward) or opposite (reverse) order as when it ran, and at a faster rate than animals' running. This phenomenon is called memory replay, and this replay has a very important role in the prefrontal cortex circuit which helps the animal remember the path it has taken in the past and makes the right choice among multiple alternative paths.

To understand hippocampus-prefrontal cooperative activities during memory replay and whether memory replay affects animal learning and decision-making, researchers trained rats to learn to find their way in a W-maze [57]. In this task, the rat needs to learn two different rules to get the reward, a simple task and a complex task—in the simple task, the animal only needs to remember the beginning and end positions, then they can successfully find and get the reward; in the complex task, the animal needs to remember the path it has just run and then select the path it has not passed yet among the two available paths to get a reward, this process requires working memory. In this task, most of the memory replay occurred when the animals stayed at the reward site, had just completed a path, or were about to choose the next path [58–61]. The study found that the hippocampus was involved in the processes of both reverse and forward replay. Further studies analyzed whether the content of the hippocampus forward and reverse memory replays changed with learning. They found that the content of forward and reverse replay is different in the different learning stages. In the early stage of learning, reverse replay preferred to the paths that the animal had actually passed before, and thus researchers could accurately predict the animal's past choices from the content of the hippocampal reverse replay. In contrast, forward replay referred to the pathway that the animal will choose next, but this correspondence does not become apparent until later in learning. The dynamic processes of hippocampal reverse and forward replays in the learning process showed that reverse memory replay was very important for animals to remember the past path for learning, and the forward replay was very important for action planning after zoological learning [62, 63]. Besides the W-maze, we can also use the Barnes maze [64] to get the same conclusion. In summary, this study first distinguished the different functions of hippocampal reverse and forward memory replays in spatial learning memory tasks. Reverse memory replay helps to weigh and remember the path to the goal in the past, while forward memory replay is important for planning actions in the future. Moreover, this study for the first time quantitatively described the replay of cooperative memory between the prefrontal cortex and the hippocampus and confirmed its association with animal behavioral choices, to suggest a possible mechanism for the prefrontal cortex to participate in spatial learning.

4.5 vDBChATs-dNGIs

Acetylcholine modifies neuronal excitability, alters presynaptic neurotransmitter release, and coordinates the firing of groups of neurons [65–67]. Recently, researchers used optogenetics, single synaptic tracing, and electrophysiological recording techniques to show that cholinergic neurons in the vertical diagonal band of Broca (vDBChATs) and newly generated immature neurons (NGIs) in the dorsal hippocampus (dNGIs) of adult mice formed a single synaptic connection (vDBChATs-dNGIs synaptic connection) (**Figure 5**); this synaptic transmission was essential for the survival of dNGIs, andthe vDBChATs directly innervate dNGIs. This circuit is mediated by muscarinic cholinergic receptor 1 (M1) on neonatal neurons [68]. In this study, researchers injected a kind of virus that includes mCherry

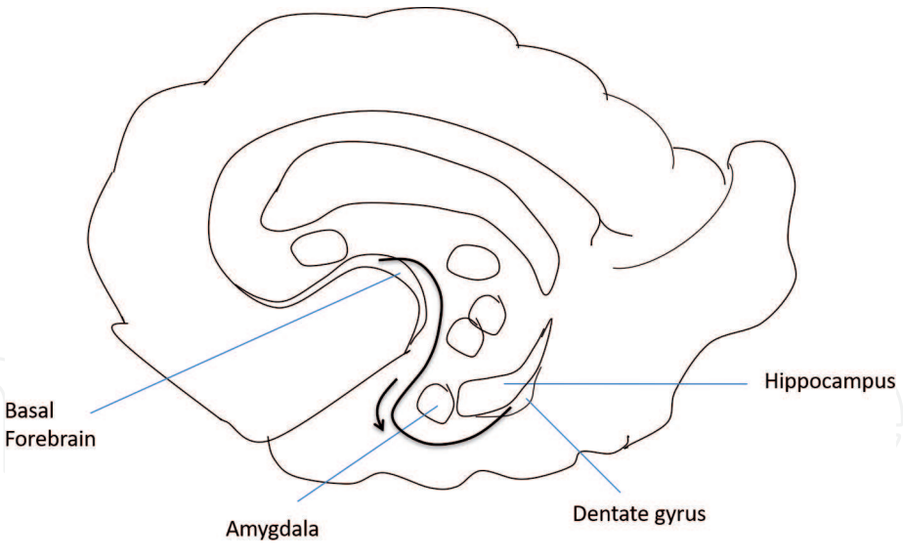

Figure 5.
The vDBChATs-dNGIs circuit.

into the vDB region of some mice. Three days later, in the dDG, mCherry was exclusively expressed in a group of granular cells that were predominately located in the inner one-third of the granule cell layer. Most of these mCherry+ cells expressed doublecortin (DCX, mCherry+DCX+). DCX has been widely established as a marker of immature neurons [69], so mCherry+DCX+ cells are one kind of newly generated NGIs in the dNGIs mentioned above. The study found that using optogenetic technology to enhance vDBChATs-dNGIs synaptic transmission improved spatial learning memory. Furthermore, in the AD transgenic mouse model, the use of optogenetic technology to enhance the synaptic transmission of the neural circuit saved the spatial memory loss of the model mice [70].

5. Factors affecting hippocampal learning and memory

5.1 LIS1

An interesting candidate molecule supporting synaptic integrity is LIS1, which is related to lissencephaly [71, 72]. LIS1 deficits in specific hippocampal neuron populations significantly changed the excitatory synaptic transmission in adult-born Lis1+/− DG projection neurons and dendritic spine density and excitatory synaptic aggregation on hippocampal CA1 projection neurons that lost Lis1 expression from postnatal 20 days [73, 74]. Moreover, the loss of LIS1 after childhood destroys the structure and cell composition of the hippocampus, the connection with other brain regions, and the dependence on the cognition of hippocampal circuits [75, 76].

5.2 Fos

Increasing evidence has shown that sparse neuron groups distributed in many areas of the brain constitute the neural matrix of various behaviors [22, 77]. One sign of these active neuron sets is the instantaneous expression of a group of genes called immediate early genes, one of which encodes the Fos transcription factor, composed of eight members with at least partial functional redundancy (Fos, Fosb, c-Fos, Fosl1, Fosl2, Jun, Junb, and Jund) [78–81]. A long-standing hypothesis is that once activated by a significant stimulation, the neurons expressing Fos will undergo modification, which is helpful to encode specific experience characteristics, so

that even if a subset of these neurons are subsequently reactivated, it is enough to trigger memories of the initial experience [82]. Compared with non-Fos-activated neurons, Fos-activated neurons in the hippocampal CA1 region have been shown to stably encode context information [77].

5.3 SynCAM 1

The expression of the synaptic cell adhesion molecule, SynCAM 1, in forebrain neurons, which is also known as a cell adhesion molecule 1 (Cadm1) and Necl-2, is a candidate protein used to evaluate the role of different regions of synaptic tissue proteins [83]. SynCAM 1 belongs to four homophilic and heterophilic membrane protein families of the immunoglobulin superfamily, which are expressed at the peak of synaptic formation and exist until adulthood. This marks the edge of excitatory postsynaptic sites, which is sufficient to induce functional excitatory presynaptic specialization [84]. Studies on knockout and overexpression of the hippocampal CA1 region in mice have shown that SynCAM 1 is necessary to promote excitatory synaptic input of excitatory neurons in vivo [85]. SynCAM 1 also accelerated synapse maturation, which improved the stability of newly formed synapses and in turn increased the likelihood of survival of adult-born neurons [86]. SynCAM 1, therefore, regulates the input of excitatory mossy fibers into the interneurons and major neurons in the hippocampal CA3 region to balance network excitability [87].

5.4 Brain-derived neurotrophic factor (BDNF)

BDNF is one of the most widely distributed and studied neurotrophic factors in mammalian brains. It has a direct impact on memory through various mechanisms. BDNF regulates many different cellular processes involved in the maintenance and development of normal brain function, by binding and activating the TrkB, which is a member of the larger family of Trk receptors [88]. For example, during embryogenesis, BDNF–TrkB signaling promotes the differentiation of cortical progenitor cells and then promotes differentiation of cortical progenitor cells into neurons (i.e., neurogenesis) [89]. The single nucleotide polymorphism of BDNF most likely affects memory through long-term potentiation (LTP), which is important for memory persistence [90]. In the human BDNF gene, a single nucleotide polymorphism leads to an amino acid substitution of valine (Val66Val) to methionine at amino acid residue 66 (Val66Met), which changes the secretion of the mature peptide. This alteration has been related to cognitive deficits among carriers [91]. The effects of BDNF on LTP are also mediated by the TrkB receptor. Especially in the hippocampus, this neurotrophin is thought to act on both pre and postsynaptic compartments, modulating synaptic efficacy, not only by changing the presynaptic transmitter release but also by increasing postsynaptic transmitter sensitivity to induce a long-lasting increase in synaptic plasticity [92, 93].

In the elderly with normal cognition, the presence of BDNF Val66Met is associated with greater hippocampal atrophy and faster cognitive decline [94]. BDNF polymorphism is associated with larger DG volumes within the anterior hippocampus (head) in Met-carriers compared to Val/Val homozygotes. The total hippocampal volume predicted the performance on visuospatial memory tasks in Met-carriers [95]. Although little is known about the process of memory consolidation, it is known that a hippocampal BDNF-positive autoregulatory feedback loop is necessary to mediate memory consolidation via the CCAAT-enhancer-binding protein β (C/EBPβ) [96].

BDNF also mediates the influence of many factors on memory. First, TLQP62, which is a neuropeptide derived from the neurotrophin-inducible VGF (nonacronymic) protein, is capable of inducing increased memory in the mouse

hippocampus by promoting neurogenesis and synaptic plasticity through BDNF and its receptor tyrosine receptor kinase B (TrkB) [97, 98]. When TLQP62 promotes BDNF expression, which in turn activates the BDNF/TrkB/CREB (cAMP response element-binding protein) pathway that upregulates VGF expression, there is a VGF-BDNF regulatory loop that appears to regulate neurogenesis [99]. In addition, as is well known, exercise can promote the formation of memory, which is also inseparable from BDNF levels. Lactate, a metabolite released during exercise by muscles, crosses the blood–brain barrier and accumulates in the hippocampus, where it promotes the formation of learning and memory by inducing BDNF expression through silent information regulator 1-dependent induction of the PGC1a/FNDC5 pathway [100]. In addition, the increase of the microglia-dependent proBDNF/BDNF ratio following persistent inflammatory pain leads to cell death of the CA1 and DG neurons. Then, this subsequently causes a cognitive deficit in learning and spatial memory functions [29]. Furthermore, in postmenopausal women, the lower plasma BDNF levels are associated with significantly worse memory performance and changes in the function of the working memory circuit [101].

5.5 Smad3

Smad3 is an intracellular molecule involved in the transforming growth factor-β signaling cascade, which is strongly expressed by granulosa cells of the DG of adult mice [102]. Smad3 deficiency promotes dopaminergic neurodegeneration and α-synuclein aggregation in substantia nigra striatum [103]. Endogenous Smad3 signaling plays important role in neurogenesis and LTP induction of adult DG, which are two forms of hippocampal plasticity related to learning and memory, and which decrease with age and neurological diseases [102].

5.6 Oxytocin

Oxytocin is a brain plasticity regulator of neuronal growth factors, cytoskeleton proteins, and behavioral changes, and is important for short-term hippocampal-dependent memory [104] and regulates neuronal excitability, network oscillatory activity, synaptic plasticity, and society memory [105]. In the SH3 domain and ankyrin repeat-containing, the protein 3 (SHANK3) deficient model related to autism, abnormal neuronal morphology and altered synaptic protein levels are recovered by oxytocin [106]. Early changes of the oxytocin signal may interfere with the maturation of neurons and could have both short-term and long-term pathological consequences [107]. At the molecular level, neurodevelopmental disorders include numerous changes in cytoskeleton rearrangement and neurogenesis, leading to various synaptic diseases [108].

5.7 Disrupted-in-schizophrenia 1 (DISC1)

DISC1 is a strong candidate susceptibility gene for a series of neuropsychiatric diseases [109, 110]. Reports of both DISC1 point mutations (L100P and Q31L) heterozygotes and DISC1 transgenic mice [111, 112] found that the combination of adolescent isolation (from 5 to 8 weeks) and DISC1 L100P mutation damaged the social memory of adults. In addition, adolescent isolation aggravates adult neurogenesis defects in the hippocampus of L100P mice, but has no similar effect on WT mice, and leads to long-term continuous changes in synaptic transmission and plasticity of the hippocampal network of DISC1 L100P mice [113, 114]. There is also a possible sex-dependent effect of DICS1. In the test of significant gene–environment interactions in the amphetamine-induced anxiety in male animals and the

amphetamine-induced locomotion in female animals, we surprisingly found that gene–environment interactions improved social memory in not only male but also female animals, but JIA alone disrupted spatial memory and recognition memory only in male animals [115].

6. Expectations

The hippocampus, as an important part of the limbic system involved in learning and memory, has been extensively studied for many years. With increased aging in China, the incidence of AD, a progressive degenerative brain disease, is increasing every year. The main clinical symptoms are memory loss and cognitive impairment. Entropic cortex to the hippocampus, hippocampus to the prefrontal cortex, and vDBChATs-dNGIs with the hippocampus as the central link may play important role in spatial memory and declarative memory. Moreover, the damage of any link in the cycle leads to the loss of recent memory. By studying the hippocampal memory circuit and various influencing factors, we hope to improve spatial memory and declarative memory by intervening in every link of the hippocampal memory circuit. At the same time, we can provide new ideas and methods for the treatment of memory impairment-related diseases such as AD, which are helpful to the recovery and improvement of memory function in the damaged hippocampus. Considering the influence of BDNF and other factors on the memory circuit and the effects of various diseases related to memory impairment, we should also extensively study some influencing factors as intervention targets for Huntington's disease, depression, schizophrenia, bipolar disorder, and other diseases. These studies can provide prevention strategies and treatment methods for memory decline caused by force majeure factors such as sex and age. Furthermore, studies on its influencing factors will open other research avenues.

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