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Hippocampal CA2 Region: A New Player in Social Dysfunctions

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Abstract

For social species, normal social cognitive functions are essential for individuals to survive in a social group. Various neuropsychiatric disorders, including schizophrenia, autism and bipolar disorder are characterized by the impairments in social cognition. The hippocampus has been at the forefront of research in learning and memory for several decades. Hippocampal dysfunction contributes to learning and memory impairments as well as a range of social dysfunctions. However, precise contributions of different hippocampal sub-regions to differential aspects of cognitive functions remain unclear. This review first describes several key features of social abnormalities related to neuropsychiatric disorders, and then introduces the behavioral tasks used in animal models to assess each feature. Second, it gives a basic description of CA2 anatomy followed by an overview of its known functions. Third, it highlights a number of recent findings that associate the abnormalities of the hippocampal CA2 area and social dysfunctions in both animal models and human patients.

Keywords: Hippocampus; CA2; Memory; Schizophrenia; Autism; Social dysfunction

Introduction

Many animals, including humans, are social species. Social cognitive functions, such as social interaction and social memory, enable individuals to survive in a social group. Impairments in these functions are prominent traits in major neuropsychiatric disorders, such as schizophrenia, autism and bipolar disorder. Despite recent advances in the etiology of these disorders, the genetic and physiological underpinnings are still poorly understood.

The hippocampus is one of the most thoroughly studied structures in the brain, and has long been considered the hub of learning and memory. Hippocampal dysfunction contributes to learning and memory impairments observed in a range of neuropsychiatric disorders [1-6]. However, precise contributions of different hippocampal subregions to the maintenance of normal cognitive function remain unclear. Increasing evidence indicates that CA2, a small area interposed between CA3 and CA1 in hippocampus, plays an important role in pathology of some neuropsychiatric disorders.

In the present review, I first describe several major social abnormalities related to neuropsychiatric disorders, and how to assess those using rodent models. Second, I will provide the description of CA2 anatomy and its known functions. Finally, I will review some evidence that link CA2 to neuropsychiatric disorders.

Manifestation and assessment of social dysfunctions in animal models

Social dysfunction is a hallmark of various psychiatric diseases. Although considerable efforts are focused on understanding the genetic causes, and tremendous progress has been made, diagnosis of social dysfunction is still based on several categories of behavioral criteria. For example, the World Health Organization requires the presence of three key elements on diagnosing autism spectrum disorder (ASD): reduced social interactions, impaired communication and stereotyped behaviors [7]. Social dysfunctions can be characterized by, although not limited to, these three key features. Developing animal models to assess the social dysfunctions mentioned above has been challenging, since symptoms may be unique to humans and are often variable between human patients. Nonetheless, behavioral neuroscientists have made great efforts to develop standardized assays for social dysfunctions in animal models. Author will review assays that address aforementioned three aspects of social dysfunctions individually.

In humans, abnormal social interactions manifest in lack of interest in peers, failure to maintain eye contact and meaningful social interaction. In rodents, the assays of social interaction parameters include nose-to-nose sniffing, chasing, pushing, mounting in group social settings [8-12]. Such parameters can be scored manually or automated off-line by using video tracking system. More targeted measures of social interaction can be achieved in a three-chamber assay where an animal is given free choice to interact with a novel object or a novel conspecific, that are constrained in two separated chambers (social approach) [13-16]. The apparatus in this task is designed to allow transmission of social cues, such as visual, olfactory, auditory and tactile contact between two animals but no aggressive and sexual interactions. Wild type subjects spend more time in the chamber containing the novel conspecific than in the chamber containing the novel object, whereas subjects with social dysfunctions display otherwise. The three-chamber assay can also be used to test an animal's social recognition: the ability to recognize familiar versus novel conspecifics. Rodents have natural inheritance to explore and interact with novel conspecifics versus familiar conspecifics, presumably due to their intact social memory. The social recognition or social memory is measured by the amount of time the subject spend with a novel conspecific versus a familiar conspecific [17-20]. Thus, in both assays wild type subjects tend to spend more time in the chamber with a novel conspecific.

Unlike humans, rodents do not rely heavily on language to communicate. Among the sensory cues rodents use to communicate, olfactory cues are of critical importance. Interestingly, interaction with cagemates who have just consumed novel flavored food resulted in the subject choosing food of the same flavor in preference to a completely novel flavored food [19,21-23], suggesting that rodents exchange meaningful information through olfactory signals. Pheromones are another important type of sensory cue that rodents relay upon. Mice and rats mark their territories with urinary scent as well as explore urinary scent marks in a cage and sniff urine soaked cotton swabs [24,25]. Olfactory communication can be quantified by scoring subjects' interaction with pheromones compared to a non-biological scent. Pheromones elicit higher levels of sniffing than non-social odors [19,26].

Human repetitive behaviors include motor stereotypies, repetitive use of objects, resistance to change, and a narrow range of interests. Wide-type rodents exhibit spontaneous motor activities, including climbing, jumping and self-grooming. Repetitive behavior in rodents is usually measured by repetitive self-grooming. Mouse models with social dysfunction may self-groom for up to 2 minutes at a time, whereas wild type control mice generally groom for just several seconds [27]. Marble burying is another type of repetitive behavior [28]. Experimenters score the repetitive digging behavior by counting the remaining unburied marbles. Both behaviors can be scored manually or automated by software off-line. Other tests of repetitive behavior may include utilizing a standard T-maze. In this case, the animals are tested on their flexibility of learning. Animals are required to find food reward placed in the opposite arm of the T-maze from where they first learned to find the reward, which is referred to as reversal learning task [13,29,30]. An autism mouse model performed well on the initial acquisition stage but failed on reversal learning [31].

CA2 as a functional hippocampal sub region

Since the famous 1957 case study of patient H.M., who lost the ability to form anterograde memories after surgical removal of the hippocampus to treat epilepsy, the hippocampus has been at the core of research in bases of memory and memory-related neurological disorders. Extensive research led to the discoveries of neurophysiological mechanisms of memory at both cellular and circuit level, and detailed depiction of anatomical connectivity within hippocampus. The classic view of hippocampal anatomy divides hippocampus into three major subdivisions: dentate gyrus (DG), CA3 and CA1, each plays key roles in different aspects of learning and memory. Recently, the role of a long-neglected subdivision of the hippocampus, CA2, has come to light. An increasing body of evidences suggests that CA2 itself is far more than a passive transition region between CA1 and CA3 but a functional unit [32-40].

Anatomical and neurophysiological evidences have pointed to CA2 as the only subregion in the hippocampus where spatial learning components within hippocampus-surrounding areas (including entorhinal cortex, subiculum, parahipocampal areas) converge [33]. So how does CA2 integrate the differential incoming cues routed by distinct learning components? Several interventional studies have shed some light on this question. Knockout of vasopressin 1b receptor (V1bR) in mouse CA2 resulted in impairment in tasks that require remembering the temporal order of presented objects [41]. Recently, in vivo recording in behaving rats demonstrates that individual CA2 cells display standard firing patterns as in CA1 and CA3. However, CA2 differs from the other two subregions in that ensemble of CA2 cells do not maintain their spatial coding over time [36]. Taken together, these studies suggest that CA2 may participate in associating spatial and temporal information during learning, yet absent for memory consolidation.

Link between CA2 and social dysfunctions

Hippocampal dysfunction contributes to learning, memory and social impairments in a range of neuropsychiatric disorders, but the precise contributions of different hippocampal subregions remain largely unclear. As mentioned above, CA2 cells have weak coding for space, but what is their role in encoding emotional and social aspects of cognition? Recent discoveries extend our understanding of the association between CA2 and social functions, particularly social memory.

Gene expression profiling revealed that a number of social abnormality-related genes are preferentially expressed in CA2. Vasopressin 1b receptor (V1bR), one principal receptor mediating social aggression in rodents, was found prominent expression within the CA2 pyramidal cells but much lower expression in the hypothalamic paraventricular nucleus and amygdala [41]. Knockout of vasopressin 1b receptor in mouse CA2 reduces aggression and impairs social recognition, but spares spatial learning [42]. The adenosine A1 receptor has strongest immunoreactivity in adult rat CA2 [43]. mRNA expression of a neurotrophic factors, fibroblast growth factor (FGF-2), increases only in CA2 after controlled stress [44]. In addition, a G-protein signaling component, RGS14, is highly enriched in CA2 pyramidal neurons and plays a role in regulating synaptic plasticity [35].

Hitti and Siegelbaum showed that genetic inactivation of CA2 pyramidal cells in adult mice led to pronounced impairment of social memory [32]. Animals with CA2 inactivation lost the ability to recognize a familiar conspecific, thus spending same amount of time interacting with the familiar conspecific in a three-chamber social novelty test. This was not due to the loss of general memory function in these mice since they performed normally in several other hippocampus-dependent behaviors. Reversely, in a separate study, excitation of vasopressin 1b receptors (Avpr1b) in CA2 markedly enhanced social memory in mice during acquisition, but not during retrieval [38]. This enhancement can be blocked by Avpr1b antagonist. In Avpr1b knockout mice, lentiviral delivery of Avpr1b into the dorsal CA2 restored the social attack behavior [45]. Furthermore, a lesion study confirmed that specific excitotoxic NMDA inactivation of CA2 impaired social recognition in mice [39].

Several indications exist that CA2 pathology is a potential substrate for a number of neuropsychiatric disorders. Piskorowski et al. [37] reported that in the 22q11.2 mouse model (a mouse model for neuropsychiatric disorders, including autism and schizophrenia), the density of parvalbumin-expressing interneurons was decreased specifically in CA2 of adult mice. CA2 pyramidal neurons displayed a more hyperpolarized resting membrane potential, which made them less responsive to input stimulation. Social memory was also impaired in this mouse line assessed by direct interaction test. Similarly, reduction in parvalbumin immunoreactivity in CA2 [46,47], as well as AMPA [48] and histamine H3 receptors [49], was also observed in schizophrenia patients. Also in the 22q11.2 mouse line, Takahashi et al. demonstrated that in contrast to wild-type mice, heterozygous pups used invariable vocal sequences with less complicated call types, which resulted in inefficient maternal approach [50]. This suggests that neonatal maternal care and social communication play a critical role in

the development of normal social functions in later adult life. Further studies may help pinpoint the neural substrate of the neonatal social communication inefficiency, which is absent in this study. In Parkinson's disease patients, the elevated expression of amyloid beta peptide in CA2 was associated with dementia [51].

Conclusion

Social cognition is a complex behavior. Intact social memory and communication ability are essential for this process. Functional deficits in social memory underscore various neuropsychiatric disorders. Different hippocampal subregions collectively serve as fundamental substrates of cognitive functions, particularly learning and memory. Among them, the CA2 area displays distinct neurochemical and structural features than the others. Recently, it has been revealed that the CA2 mediates social recognition and plays an important role in social memory formation. Compromising CA2 by genetic and pharmacological manipulations results in disruptions of social cognitive functions. Recently, brain-derived neurotrophic factor (BDNF) has been suggested to play an important role in neuropsychiatric diseases, including Schizophrenia. BDNF mRNA and proteins are expressed in CA2 [52-54]. BDNF is essential for neuronal plasticity, a functional necessity for learning and memory. Therefore, deficits in BDNF signaling as well as BDNF mRNA polymorphisms may have indications in social dysfunctions observed in neuropsychiatric disorders [55,56].

While rodents and humans do not share the full spectrum of social dysfunction features, investigating social dysfunctions in animal models and identifying common neural mechanisms are essential from both scientific and clinical perspective. In that regard, elucidating the functions CA2 play in social cognition deficits will help pave the road for future treatment evaluation and drug development.

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