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The role of the CA3 hippocampal subregion in spatial memory: A process oriented behavioral assessment

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ABSTRACT

Computational models, behavioral data, and electrophysiological data suggest that the CA3 subregion of the hippocampus may support multiple mnemonic processes critical to the formation and subsequent retrieval of spatial memories. Multiple researchers have proposed that the CA3 subregion contains an autoassociative network in which synaptic connections between CA3 neurons that represent different components of a memory are strengthened via recurrent collateral connections. As a result, it has been suggested that the CA3 autoassociative network may support multiple processes including the formation of spatial arbitrary associations, temporary maintenance of spatial working memory, and spatial pattern completion. In addition, the CA3 subregion has been suggested to be involved in spatial pattern separation. The separation of patterns is hypothesized to be accomplished based on the low probability that any two CA3 neurons will receive mossy-fiber input synapses from a similar subset of dentate gyrus cells. The separation of patterns also may be enhanced by competitive inhibition within CA3 and dentate gyrus. This review will focus on the mnemonic processes supported by CA3 neurons and how these processes may facilitate the encoding and retrieval of spatial information. Although there is growing evidence indicating that the hippocampus plays a role in the processing of nonspatial information as well, the scope of the present review will focus on the role of the CA3 subregion in spatial memory.

1. Introduction

Since the early 1960s, the hippocampus has been one of the most studied structures in the mammalian brain. Based on many years of research, the hippocampus has been determined to be highly involved in learning and memory. Although a great deal of progress has been made in understanding how the hippocampus processes information and what types of information the hippocampus may process, there is still debate as to the precise function of this structure. As discussed in a publication by Manns and Eichenbaum (2005), early descriptions of the hippocampal formation suggested that information was serially processed through the hippocampal subregions via a trisynaptic loop (Lorente De Nó, 1933; Ramon y Cajal, 1995). Information was suggested to enter via entorhinal cortex projections to dentate gyrus with serial projections from the dentate gyrus to the CA3 subregion, which projects serially to the CA1 subregion. The CA1 subregion has projections to the subiculum that in turn has projections back to entorhinal cortex to complete the trisynaptic loop. Based on this idea, a lesion or damage to any anatomical component of the trisynaptic loop would cause the serial processing loop to fail resulting in hippocampal dysfunction. Early studies tested rats with lesions in dentate gyrus, CA3, or CA1 on a working memory version of the radial eight-arm maze. The results demonstrated that a lesion to the dentate gyrus (Emerich and Walsh, 1989; McLamb et al., 1988; Tilson et al., 1987, Walsh et al., 1986), CA1 (Davis et al., 1987; Davis et al., 1986; Davis and Volpe, 1989), or CA3 (Handelmann and Olton, 1981; Jarrard, 1983) all resulted in deficits similar to complete hippocampal lesions. Rats with lesions of dentate gyrus (Nanry et al., 1989; Sutherland et al., 1983), CA1 (Auer et al., 1989; Block, 1999; Nunn et al., 1994; Olsen et al., 1994; Whishaw et al., 1994), or CA3 (Sutherland et al., 1983) also showed deficits comparable to complete hippocampal lesions on the Morris water maze. Therefore, early behavioral studies involving selective lesions to hippocampal subregions suggested that a lesion to any subregion results in a deficit similar to a complete hippocampal lesion. These data could be considered support for the existence of a trisynaptic loop. However, more recent anatomical studies discussed below have demonstrated that the hippocampal anatomical connections are not serial but rather there are projections from entorhinal cortex to each hippocampal subregion (Amaral and Witter, 1995; Witter, 1993). Based on the hippocampal architecture and connectivity, recent models and behavioral studies have demonstrated that the various subregions of the hippocampus may support specific processing functions (Bennett et al., 1994; Gilbert and Kesner, 2003, 2006; Gilbert et al., 2001; Gold and Kesner, 2005; Granger

Abbreviations: CA1, Cornu ammonis 1; CA3, Cornu ammonis 3; DG, Dente gyrus; NMDA, N-methyl-D-asparate.

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et al., 1996; Guzowski et al., 2004; Hasselmo and McClelland, 1999; Hasselmo et al., 2002; Jensen and Lisman, 1996; Kesner and Hopkins, 2006; Kesner and Rolls, 2001; Kesner et al., 2000; Kesner et al., 2004; Kesner et al., 2005; Lee and Kesner, 2002, 2003, 2004a,b; Lee et al., 2004; Lee et al., 2005b; Leutgeb et al., 2004; Lisman, 1999; Marr, 1971; McClelland and Goddard, 1996; McNaughton and Morris, 1987; McNaughton and Nadel, 1989; Mizumori et al., 1999; O'Reilly and McClelland, 1994; Rogers et al., 2006; Rolls, 1989, 1996; Rolls and Kesner, 2006; Samsonovich and McNaughton, 1997; Samura and Hattori, 2005; Shapiro and Olton, 1994; Tanila, 1999; Treves, 2004; Treves and Rolls, 1992, 1994; Vazdarjanova and Guzowski, 2004; Wallenstein and Hasselmo, 1997; Wiebe et al., 1997). In addition, recent research has shown that the mnemonic processes supported by each hippocampal subregion can be functionally dissociated using behavioral and electrophysiological measures (Gilbert and Kesner, 2003, 2006; Gilbert et al., 2001; Hunsaker et al., 2006; Jerman et al., 2006; Kesner and Hopkins, 2006; Kesner et al., 2000; Kesner et al., 2004; Lee and Kesner, 2004a,b; Lee et al., 2005a,b; Leutgeb et al., 2004; Rolls and Kesner, 2006; Vazdarjanova and Guzowski, 2004). This review will focus on the mnemonic processes supported by CA3 neurons and how these processes may facilitate the encoding of spatial information. Although there is growing evidence indicating that the hippocampus plays a role in the processing of nonspatial information as well, the scope of the present review will focus on the role of the CA3 subregion in spatial memory.

2. Basic hippocampal anatomy

For a complete review of hippocampal anatomy, please see Amaral and Witter (1995). The main input into the hippocampal system is from entorhinal cortex, which receives inputs from multiple cortical regions and all sensory modalities. The cortical inputs that terminate on the superficial layers (I, II, and III) of the entorhinal cortex comprise the primary inputs to the hippocampus (Witter, 1993). In the rat, the cortical inputs to the superficial layers of entorhinal cortex originate in the olfactory domain of the telencephalon, perirhinal cortex, and pre- and parasubiculum. The entorhinal cortex then projects directly to the dentate gyrus, CA3, and CA1 subregions (Amaral and Witter, 1995; Witter, 1993). Cells in layer II of entorhinal cortex project primarily to the dentate gyrus and also to CA3/2. The projections that terminate in the CA1 region originate in layer III of the entorhinal cortex. The primary projection of the entorhinal cortex is to the DG. The connections between entorhinal cortex, DG, and CA3 are generally reported to be feed-forward (Ishizuka et al., 1990; Witter, 1993). The DG granular neurons project to CA3 pyramidal neurons via mossy fiber projections. The neurons that comprise CA3, in turn, project to CA1 neurons via the Schaffer collaterals. Recurrent collateral connections exist within both the DG and CA3 that serve to interconnect neurons within these respective regions. The DG recurrent pathway includes a layer of excitatory interneurons, the hilus, which interconnects granule cells and a layer of inhibitory interneurons that provide recurrent inhibition. The CA3 subregion has extensive interconnections among the principal cells via a recurrent collateral fiber system (Amaral and Witter, 1995). The primary output from the hippocampus to neocortex originates in CA1 and projects to subiculum, entorhinal cortex, and parahippocampal structures (Witter, 1993). In addition to the projections originating in CA1, projections out of Ammon's horn originate in CA3. Swanson and Cowan (1977) report that the septal region of CA3 projects to the dorsal subiculum, parasubiculum, and the cingulate. Many researchers have reported that CA3 projects to the lateral and medial septal nuclei (Amaral and Witter, 1995; Gaykema et al., 1991; Risold and Swanson, 1997). The lateral septum then has projections to the medial septum (Jakab and Leranth, 1995), which in turn projects to subiculum and eventually entorhinal cortex (Amaral and Witter, 1995; Jakab and Leranth, 1995).

One of the most prominent features of the CA3 subregion cytoarchitecture is that there are extensive interconnections among the principal cells via a recurrent collateral fiber system forming an autoassociative network (Amaral and Witter, 1995). Multiple researchers have suggested that the hippocampus, and specifically the CA3 subregion of the hippocampus, contains an autoassociative network that may support a number of mnemonic processes including the formation of arbitrary associations, pattern completion, and working memory (Alvarez and Squire, 1994; Bennett et al., 1994; Bunsey and Eichenbaum, 1993; Granger et al., 1996; Gluck and Myers, 1997; Hasselmo et al., 1996; Jensen and Lisman, 1996; Kesner et al., 2000; Marr, 1971; McClelland and Goddard, 1996; McNaughton and Nadel, 1989; Redish et al., 2001; Rolls, 1996; Rolls and Kesner, 2006; Treves and Rolls, 1992, 1994; Wallenstein and Hasselmo, 1997; Wiebe et al., 1997). The term autoassociative means that synaptic connections between neurons that represent different components of a memory are strengthened. The CA3 subregion of the hippocampus is considered an autoassociative network because of the aforementioned recurrent excitatory connections and synaptic modification among CA3 neurons (Rolls and Kesner, 2006). For detailed descriptions of autoassociative networks see Hertz et al. (1991), Rolls and Treves (1998), and Rolls and Deco (2002). CA3 also receives converging inputs from multiple input pathways; for example, perforant path inputs from the entorhinal cortex, mossy fiber inputs from the dentate gyrus, and its own outputs fed back as inputs via the recurrent collaterals (Amaral and Witter, 1995). Most of the synaptic connections embedded in those different pathways in CA3 are modifiable in their strength (Marr, 1971; Treves and Rolls, 1994). The aforementioned anatomical and physiological characteristics inspired many theoretical and computational models to assign specific processes to CA3 (Hasselmo and McClelland, 1999; Hasselmo et al., 2002; Jensen and Lisman, 1996; Kesner et al., 2000; Kesner et al., 2005; Lisman, 1999; Marr, 1971; McNaughton and Nadel, 1989; O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000; Rolls, 1996; Rolls and Kesner, 2006; Samsonovich and McNaughton, 1997; Shapiro and Olton, 1994; Treves and Rolls, 1992; Treves and Rolls, 1994; Wiebe et al., 1997).

3. Spatial arbitrary associations

The CA3 autoassociative network has been suggested to be responsible for the formation of arbitrary associations or paired associate learning (Bennett et al., 1994; Gilbert and Kesner, 2003; Hasselmo and McClelland, 1999; Kesner et al., 2000; Kesner et al., 2005; McNaughton and Nadel, 1989; Rolls, 1996; Rolls and Kesner, 2006; Wallenstein and Hasselmo, 1997; Wiebe et al., 1997). For example, Rolls and Kesner (2006) suggest that information from parietal cortex regarding the location of an object may be associated with information from temporal cortex regarding the identity of the object (see also Rolls, 1996). Therefore, CA3 could enable the organism to remember a particular object and its location. To test this hypothesis, Gilbert and Kesner (2003) trained rats with CA3, CA1, or dentate gyrus lesions on a successive discrimination go/no-go task to examine object-place paired associate learning. This task has been shown to be sensitive to complete hippocampal lesions (Gilbert and Kesner, 2002). In this task, two paired-associates were reinforced that consisted of one particular object (A) in one particular location (1) and a different object (B) in a different location (2). Mispairs that were not reinforced included object (A) in location (2) and object (B) in location (1). Rats should learn that if an object was presented in its paired location then the rat should displace the object to receive a reward (Go). However, the rat should withhold displacing the object if it was not in its paired location (No-Go). In a second task, rats were trained on a successive discrimination go/no-go task to examine odor–place paired-associate learning. In this task, the same procedure was used, except that rats needed to learn that when an odor was