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Opinion

Hippocampal Area CA2: An Overlooked but Promising Therapeutic Target

Vivien Chevaleyre[1,*] and Rebecca A. Piskorowski[1]

While the hippocampus has long been recognized as a brain structure specialized in mapping 'space' in rodents, human studies and now recent data from rodents have shown that its function extends well beyond spatial coding. Recently, an overlooked area of the hippocampus, CA2, has emerged as a critical region for social memory. This area is also uniquely altered during several pathologies such as schizophrenia and age-related dementia. Because of its singular connectivity, we propose that area CA2 resides at the interface between emotional brain activity and higher cognitive function. Furthermore, because of the unique expression of multiple neuromodulator receptors in area CA2, we posit that this region may represent a fruitful therapeutic target for diseases where social dysfunction occurs.

Trends

The hippocampal CA2 area of the brain displays unique properties and connectivity that may be linked to disease.

CA2 pyramidal neurons play a crucial role in the formation of social memory.

Inhibitory neurons are highly concentrated in area CA2 and are uniquely altered in the hippocampus during several neurological disorders.

The CA2 area is preferentially altered during schizophrenia and neurodegenerative diseases, and may be responsible, at least in part, for the social memory dysfunction phenotype in these diseases.

The **hippocampus** (see Glossary) is a brain structure long recognized as being crucial for the formation of long-term episodic memories. Recent pioneering work has revealed that area CA2 of the hippocampus, while long overlooked, might be playing an important role in hippocampal activity and function. In this article we first describe the singular properties and connectivity of CA2, and then highlight how this area is uniquely altered in schizophrenia and epilepsy, as well as in neurodegenerative diseases commonly associated with aging. In addition, given the distinct molecular expression profile and proposed function of CA2, we present the idea that this area constitutes a promising target for the development of potential therapeutics to treat a variety of psychiatric disorders and/or neurodegeneration.

CA2: Unique Connectivity for a Unique Function

Most of the knowledge about cellular properties, connectivity, and function of area CA2 is derived from studies performed in rodents. In mice, CA2 neurons present unique physiology and molecular make-up, setting them apart from CA1 and CA3 neurons. CA2 pyramidal neurons (PNs) bear distinct intrinsic properties such as a more hyperpolarized resting membrane potential and specific action potential firing patterns [1]. In addition, the receptors for numerous neuromodulators are either specifically expressed in area CA2 or their expression is higher in this region (recently reviewed in [2]). Thus, CA2 activity is poised to be influenced by a myriad of neuromodulators including opioids, vasopressin, oxytocin, estrogens, corticoids, and substance P. The cellular composition of CA2 is also distinct; in rats, it contains the highest concentration of different classes of interneurons present in all three CA regions, including parvalbumin (PV)-, reelin-, calbindin- and calretinin-expressing cells [3]. The PV^+ interneurons in rat CA2 also display divergent dendritic morphologies and axonal projections [4]. Furthermore, in experiments performed with dorsal hippocampal slices from male mice, the PV^+ interneurons in CA2 express a unique activity-dependent form of **long-term depression** (iLTD) that depends

[1]Centre National de la Recherche Scientifique (CNRS) Unité Mixte de Recherche 8118, Team Synaptic Plasticity and Neural Networks, Université Paris Descartes, 75006 Paris, France

*Correspondence: vivien.chevaleyre@parisdescartes.fr (V. Chevaleyre).

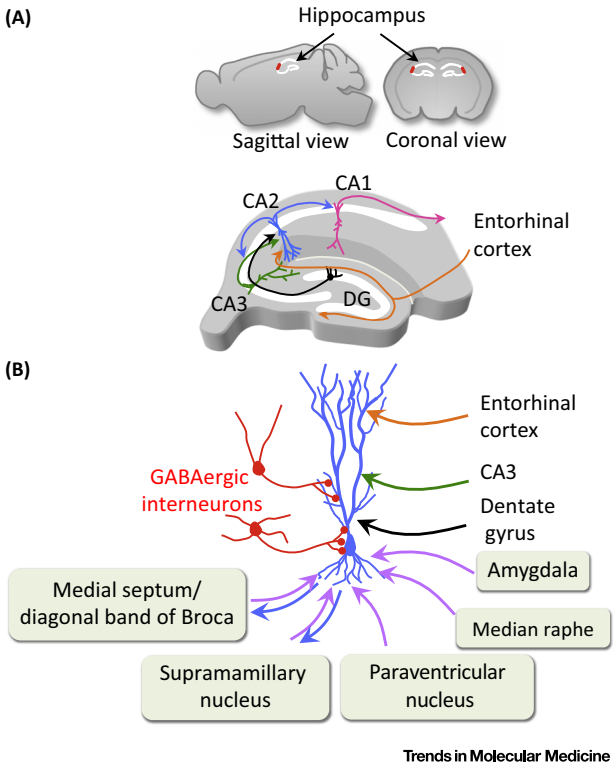

Figure 1. Neuronal Connectivity of Area CA2. (A) Top: schematic representation of the hippocampus and area CA2 (in red) in sagittal and coronal sections of mouse brain. Bottom: representation of the intra-hippocampal connectivity of areas CA1, CA2, and CA3. CA stands for *cornu ammonis* because these regions together resemble the horns of the Egyptian god Amun. CA1 (pink), CA2 (blue), and CA3 (green). CA2 pyramidal neurons receive glutamatergic inputs from the dentate gyrus, CA3 pyramidal neurons and the entorhinal cortex. CA2 pyramidal neurons project to both areas CA1 and CA3. (B) In addition to corticohippocampal inputs, CA2 pyramidal neurons also receive inputs from the septum/diagonal band of Broca, the median raphe, the amygdala, as well as from the hypothalamic supramammillary and paraventricular nuclei. Bidirectional connections with the septum and the supramammillary nucleus have also been described. Area CA2 contains a very high density of GABAergic interneurons, and inhibitory transmission has been shown to powerfully control excitatory inputs from CA3.

on δ-opioid receptor (DOR) activation [5]. This iLTD results in a large increase in the excitatory drive from CA3 inputs that is sufficient to allow recruitment of CA2 by CA3 PNs [6]. While plasticity of inhibitory transmission is known to control the strength and plasticity at excitatory synapses [7], such control by inhibition is more crucial in CA2, where excitatory synapses between CA3 and CA2 do not express activity-dependent synaptic plasticity in mouse and rat dorsal hippocampal slices [2].

Area CA2 also exhibits unique connectivity (Figure 1) with intra- and extra-hippocampal structures. Indeed, studies performed in acute slices from mouse hippocampus have shown that CA2 PNs receive powerful input from the dentate gyrus [8] and **entorhinal cortex** [1], which contains input rich in processed sensory information. Furthermore, the dendritic architecture and active properties highly favor the integration of distal excitatory inputs in these cells [9,10]. In mice, the CA2 receives input from the **septum** and the **raphe nucleus** [11], and a projection from the basal nucleus of the **amygdala** to ventral CA2 has been reported in rats [12]. Several hypothalamic regions, including the **paraventricular nucleus** (PVN) and the **supramammillary nucleus** (SuM), uniquely target CA2 [11,13,14]. These nuclei are active during social, novel, and rewarding events, and their activation likely results in the release of neuropeptides in response to social interactions or stress [15,16]. The projection from the SuM to CA2 has also been described in monkeys and humans, and is established during early embryonic

Glossary

Alzheimer's disease (AD): a neurodegenerative disease resulting in memory impairments, impaired cognition, and dementia.
Amygdala: a region of the limbic system and temporal lobe crucial for emotional behavior.
Amyloid cores: extracellular aggregates of improperly folded proteins.
β-Amyloid precursor: proteolysis of this protein generates β-amyloid polypeptides, the main component of plaques found in Alzheimer's disease.
Argyrophilic grain disease: a neurodegenerative disease in limbic structures characterized by dendritic projections detected by Golgi staining.
Childhood-onset neuronal ceroid lipofuscinosis (NCL): a group of inherited neurodegenerative diseases characterized by accumulation of lipopigments in neurons, leading to blindness, epilepsy and cognitive impairments.
Corticobasal degeneration: a neurodegenerative disease characterized by cell loss in the cerebral cortex and basal ganglia, and resulting in motor deficits.
Dystrophic neurites: abnormally shaped or swollen axons and dendrites, observed in neurodegenerative diseases.
Elevated plus maze: an elevated platform composed of open and enclosed arms. Based the inherent aversion of rodents to open spaces, the time spent in each region is indicative of anxiety.
Entorhinal cortex: located in the medial temporal lobe, acts as a hub between the hippocampus and neocortex.
Hippocampus: temporal lobe brain structure of the limbic system, plays a central role in memory formation.
Leak potassium current: potassium conductance that contributes to the resting membrane potential.
Lewy body dementia: neurodegenerative dementia affecting older adults that is characterized by the accumulation of α-synuclein protein within the cytoplasm of neurons.
Long-term depression (LTD): a lasting decrease in the strength of synaptic transmission as a result of synaptic plasticity.