Hippocampal Formation and Unique Properties of CA2 Region

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Parkinson's disease (PD) is a neurodegenerative disease that affects both motor and non-motor functions. Although motor impairment is a prominent clinical sign of PD, additional neurological symptoms may also occur, particularly in the preclinical and prodromal stages. Among these symptoms, social cognitive impairment is common and detrimental. Interestingly, the hippocampal CA2 region, with its unique properties, has attracted the attention of scientists due to its potential association with social cognitive functions.

memory hippocampus CA2

1. Introduction

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by the loss of dopaminergic neurons in the pars compacta of the substantia nigra, a loss that is unfortunately irreversible [1]. Studies have described many non-motor symptoms that appear in the early stages of PD [2][3], in particular, social cognitive decline such as perception, language, and decision-making [4], as well as temporal-order memory deficits [5]. Interestingly, the hippocampal CA2 region, with its unique properties, has attracted the attention of scientists due to its potential association with social cognitive functions.

2. The Hippocampal Formation and the Unique Properties of the CA2 Region

The hippocampal formation (HF) is located within the medial temporal lobe in all mammalian species, close to the adjacent cerebral cortex, enabling its many crucial connections to various cortical regions. HF is a critical functional unit that contributes significantly to many vital cognitive processes in both humans and animals, including learning and memory [6], fear processing [7], spatial orientation [8], and social behavior [9]. HF includes the cornu ammonis (CA) and the dentate gyrus areas. Ramón and Cajal divided the CA into two parts: the superior region, composed predominantly of small-body neurons, and the inferior region, composed of larger vertebral-body neurons. This division was later refined by Rafael Lorente de Nó, who identified four subregions within the CA area: CA1, CA2, CA3, and CA4. He observed that the neurons in CA2 and CA3 were larger than those in CA1 and that the CA2 subregion did not receive mossy fiber projections from the DG but instead received inputs via the Schaffer collateral fibers originating in CA3 [10]. However, Dudek et al. determined that the extent to which mossy fibers project into CA2 and synapse onto CA2 pyramidal neurons is species dependent [11]. The nomenclature and

function have long been subjects of controversy, with debate over whether it is a distinct or transitional region between CA1 and CA3. However, current research suggests that CA2 possesses a unique biological structure [12], which requires further investigation in humans [13]. Interestingly, researchers have also indicated that CA2 may be proportionally larger in primates than in rodents [11].

CA2 exhibits unique morphological features, including a more loosely packed stratum pyramidal in comparison to CA1. In addition, pyramidal neurons in CA2 have an oval and dense soma, which is the largest among excitatory neurons within CA regions. Neurons in CA2 are also characterized by a hyperpolarized resting membrane potential and display specific action potential firing patterns [14]. Furthermore, the afferent and efferent connections of the CA2 field have distinct origins and terminations compared to other regions of the hippocampal formation. For instance, an optogenetic study demonstrated functional monosynaptic inputs from the DG via longitudinal projections to the CA2 area [15]. Other data suggest that CA2 neurons have more extensive functional synaptic connections with the deep area of CA1 than with the superficial layer [15] and that they also exhibit stronger innervation to CA1 than to CA3 [14]. However, the degree of synaptic connectivity between layer III EC afferents and distant branches of CA2 neurons may vary between species. In particular, fibers originating from layer III EC neurons and traversing the stratum lacunosum-moleculare in the CA1 region play a role in this variation [14].

Recently, CA2 has been shown to play a central role in social behavior. Molecular markers such as Purkinje cell protein 4 (PCP4), a regulator of G protein signaling 14 protein (RGS14), and striatum-enriched protein–tyrosine phosphatase (STEP), help to identify the specific population of neurons in the CA2 region [11][12][15][16][17][18]. Lee et al. demonstrated that RGS14 deletion imparts a substantial capacity for SC-CA2 synapse, whereas wild-type CA2 neurons exhibited little LTP [16]. Researchers discovered a loss of inhibitory neurons in CA2 in a neuropsychiatric disorder-like mouse model. These mice exhibited impaired social cognition and reduced synaptic plasticity in CA2, which may be related to the loss of PV+ interneurons [19]. In addition, CA2 activates a disinhibitory circuit from the lateral septum to the ventromedial hypothalamus (LS-VMHv1), which is modulated by the signaling pathway of arginine vasopressin (AVP), a hormone and neurotransmitter, to promote social aggression [20]. Dysfunctions in this signaling pathway have also been associated with neuropsychiatric disorders such as depression, anxiety, and autism spectrum disorders. Furthermore, researchers have speculated that the CA2 region is crucial for the formation and retrieval of memories related to social encounters [21]. Although arginine vasopressin receptor 1B (AVPR1B) mRNA is highly expressed in CA2 pyramidal neurons in both humans and rodents [12][21], one study demonstrated that AVPR1B -deficient mice were unable to recognize other mice in the “social novelty test” and also showed impaired chronological-order memory [22].

Another test showed that AVPR1B knockout mice could not discriminate the object they explored and recognize its location like the control group [23]. AVPR1B deficiency in CA2 impaired social memory enhancement [24]. In addition to AVPR1B, oxytocin receptors, another social neuropeptide receptor, are also highly expressed in CA2 [25][26]. In addition, genetic evidence suggests that CA2 injury impairs social recognition in mice [22]. Interestingly, the CA2 area of the hippocampus is the only region that receives vasopressinergic input from both the paraventricular nuclei of the hypothalamus and the supramammillary nuclei (SuM)—a critical factor in the regulation of social cognitive behaviors [27][28][29][30]. Interestingly, terminals belonging to the SuM have been found to express

substance P [11], which plays a central role in PD. Furthermore, research suggests that these particular SuM afferents expressing substance P specifically target CA2 in rats and have the ability to influence plasticity in pyramidal neurons located in CA2 [31]. The SuM-to-CA2 projection has also been reported in monkeys and humans and occurs during early embryonic development [32]. The reason for enhanced social performance may involve the circuit from dorsal CA2 to ventral CA1 [33], spike timing-dependent plasticity in CA2 [34], the negative regulatory role of CA2 in hippocampal sharp-wave ripples [35][36], and the distinct dendritic properties of CA2 compared to CA1 [37]. In addition, mineralocorticoid receptors (MRs) have been shown to facilitate CA2-dependent behaviors [38].

In summary, CA2 pyramidal neurons possess numerous distinctive morphological, physiological, and synaptic characteristics, as well as intrinsic and extrinsic connections that distinguish them from other CA regions (see **Table 1**), and more DEGs that are unique for CA2 regions have been described [11]. Despite the identification of several molecular markers in this area by current studies, our understanding of its functional properties, including its unique physiology, signaling and resilience, and behavioral role, particularly in synaptic plasticity and PD, remains limited.

Table 1. Proteins that are highly expressed in CA2 neurons and their functions.

Name	Function	References
PCP4	Identification of the DG and CA2 regions	[12][15]
RGS14	Restriction of CA2 synaptic plasticity	[15][16][18]
STEP	LTP inhibition at EC-CA2 synapses	[15]
A1R	LTD enhancement at SC-CA2 synapses	[39][40]
AVPR1B	Enhancement of synaptic potentiation at SC-CA2 synapses Facilitation of social behavior	[21][24][26]
OXTR	Enhancement of synaptic potentiation at SC-CA2 synapses Facilitation of social behavior	[26][41]
MRs;	Facilitation of CA2-dependent behaviors	[38]
group III mGluRs;	Restriction of CA2 synaptic plasticity	[42]
cholinergic receptors	Induction of LTD at SC and EC CA2 synapses	[43][44]
Related to PD		
Substance P	Induction of SC and EC-CA2 synaptic plasticity	[31]
α-synuclein	Controversial	[45][46][47][48][49][50][51][52][53]

Name	Function	References
		[54]

PCP4: Purkinje cell protein 4; RGS14: regulator of G protein signaling 14 protein; STEP: striatum-enriched protein–tyrosine phosphatase; A1R: A1 adenosine receptor; AVPR1B: vasopressin 1b receptor; OXTR: oxytocin receptor; MRs: mineralocorticoid receptors; Group III mGluRs: Group III metabotropic glutamate receptors.

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