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Review

Cajal-Retzius cells and GABAergic interneurons of the developing hippocampus: Close electrophysiological encounters of the third kind

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ABSTRACT

In contrast to the large number of studies investigating the electrophysiological properties and synaptic connectivity of hippocampal pyramidal neurons, granule cells, and GABAergic interneurons, much less is known about Cajal-Retzius cells. In this review article, we discuss the possible reasons underlying this difference, and review experimental work performed on this cell type in the hippocampus, comparing it with results obtained in the neocortex. Our main emphasis is on data obtained with in vitro electrophysiology. In particular, we address the bidirectional connectivity between Cajal-Retzius cells and GABAergic interneurons, examine their synaptic properties and propose specific functions of Cajal-Retzius cell/GABAergic interneuron microcircuits. Lastly, we discuss the potential involvement of these microcircuits in critical physiological hippocampal functions such as postnatal neurogenesis or pathological scenarios such as temporal lobe epilepsy.

1. Introduction

Modern textbooks and review articles describing the synaptic connectivity of the hippocampal network consider usually only three main neuronal populations: pyramidal and granule cells (both glutamatergic and excitatory in nature), and a large heterogeneous group of "inhibitory" GABAergic interneurons (Freund and Buzsáki, 1996; Spruston and McBain, 2007; Pelkey et al., 2017). Our most recent knowledge on the morphofunctional connectivity between these three cell ensembles is based on experiments performed on rodent hippocampal slices in vitro. In fact, in addition to seminal work performed with classic intracellular recordings (reviewed by Miles and Traub, 1991), the development of visually-guided patch-clamp measurements on pre-selected neurons (coupled to post-hoc anatomical recovery) has unleashed the power of high-resolution whole-cell recordings for the study of cell type-specific synaptic transmission and membrane excitability (Booker et al., 2014). However, an interesting point to consider is that most patch-clamp data have yielded snapshots of a still immature network, slowly transitioning to a more adult-like stage. In fact, although technical improvements in the slicing procedure now allow patch-clamp recordings even in tissue obtained from aging rodents (Moyer and Brown, 1998; Geiger et al., 2002), the last two weeks of the first postnatal month have long been (and still are) considered the golden period to obtain the best preparations for visually-guided electrophysiological measurements. Surprisingly, despite the wealth of studies focusing on the three aforementioned cellular populations (i.e., pyramidal, granule cells, and GABAergic interneurons), a fourth group of cortical neurons (Cajal-Retzius cells) has received much less attention from hippocampal electrophysiologists. Thus, for a long time, models of hippocampal synaptic integration and fast information processing have ignored the impact of this latter population. Prominent reviews article have described Cajal-Retzius cells as a "mystery" or even "mystic" neurons (Soriano and Del Río, 2005; Kirischuk et al., 2014).

Here, our purpose is to provide readers with an updated view on hippocampal layer-specific connectivity that incorporates recent physiological studies in vitro addressing the potential role of Cajal-Retzius cell/GABAergic interneuron microcircuits in the regulation of the developing postnatal hippocampus.

2. Hippocampal Cajal-Retzius cell and electrophysiology: a brief history of an initially difficult encounter

We will not address here a general historical perspective on the discovery of Cajal-Retzius cells and will redirect the readers to excellent reviews already available (Gil et al., 2014; Martínez-Cerdeño and Noctor, 2014). We will just mention that the realization that Cajal-Retzius cells are an individual and specific cell type was a long and difficult process, hampered both by technical and conceptual hurdles,

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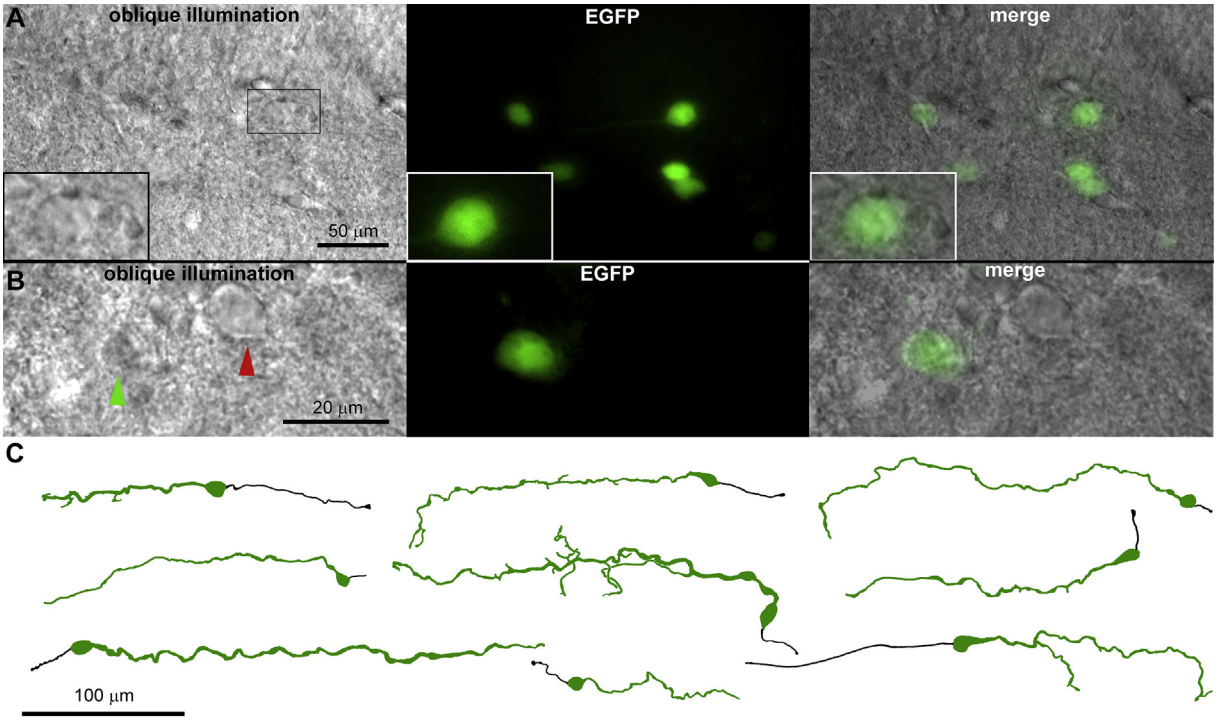

Fig. 1. Cajal-Retzius cells in a living hippocampal slice from CXCR4-EGFP transgenic mice. (A) Left panel: notice the apparent unhealthy aspect of a group of Cajal-Retzius cells visualized in the hippocampal fissure region between stratum lacunosum-molecul are and the outer molecular layer of the dentate gyrus. An individual neuron is shown at increased magnification, the boxes indicate the corresponding regions. Notice the flat, glial-like, appearance and the non-smooth/non-homogeneous membrane, which make it difficult to distinguish the soma from the background (oblique illumination). Middle panel: fluorescent image of the same slice for EGFP. Right panel: overlapping the two images allows the easy localization of Cajal-Retzius cells. P20 mouse. Unpublished observation. (B) Similar to (A) in a P7 animal. Notice the different appearance of a Cajal-Retzius cell (green arrowhead) compared to a nearby interneuron (red arrowhead). Unpublished observation. (C) Camera lucida tracing of several biocytin-filled EGFP-expressing neurons. Notice the tadpole-like appearance with the main dendrite (green) and the axon (black) emerging from opposite sides of the soma. Modified with with permission from Marchionni et al. (2010), ©John Wiley & Sons, Inc.

as these cells show increasing levels of morphological complexity when studied and compared, as it happened, in different mammalian species (Meyer et al., 1999). However, despite these potential experimental confounds and variability, the combination of modern anatomical (Radnikow et al., 2002; Sava et al., 2010; Anstötz et al., 2016), immunohistochemical (Ogawa et al., 1995; del Río et al., 1995; Martínez-Galán et al., 2001; Stumm et al., 2002; Borrell and Marín, 2006; Anstötz et al., 2016, 2018a) and genetic techniques (Soda et al., 2003; Bielle et al., 2005; Tissir et al., 2009; Chowdhury et al., 2010; Gil-Sanz et al., 2013; Anstötz et al., 2018a) allows clear criteria for their unequivocal identification.

Electrophysiologists can easily recognize Cajal-Retzius cells in living neocortical slices prepared from young rodent pups, roughly up to the second postnatal week (Zhou and Hablitz, 1996; Kilb and Luhmann, 2000; Luhmann et al., 2000; Chan and Yeh, 2003; Kirmse et al., 2005; Cheng et al., 2006; Kirmse and Kirischuk, 2006; Cosgrove and Maccaferri, 2012). In particular, these neurons occupy the marginal zone/layer I, and are oriented parallel to the pial surface. Structurally, they display a typical tadpole-like morphology, with a variable degree of dendritic complexity, and with the axon emerging from the opposite side of the main dendritic trunk. Several studies have used these simple, but very effective, criteria to record visually-identified neocortical Cajal-Retzius cells, thus allowing the study of their membrane properties/conductances (Zhou and Hablitz, 1996; Hestrin and Armstrong, 1996; Mienville and Barker, 1997; Kilb and Luhmann, 2000; Luhmann et al., 2000; Radnikow et al., 2002; Kirmse et al., 2005) and firing patterns (Zhou and Hablitz, 1996; Hestrin and Armstrong, 1996; Luhmann et al., 2000; Radnikow et al., 2002; Kirmse et al., 2005). In addition, the discovery of an apparent absence of spontaneous glutamatergic synaptic events (Kilb and Luhmann, 2001; Soda et al., 2003; Kirmse and Kirischuk, 2006; Cosgrove and Maccaferri, 2012), suggested a critical role of GABAergic input for their integrative functions (Mienville, 1998; Kirmse et al., 2007; Dvorzhak et al., 2010).

Although Cajal-Retzius cells are abundant and easy to find in neocortical slices prepared at early developmental stages, they become extremely rare in tissue obtained after the second postnatal week, making electrophysiological studies of their roles and properties at more developed neocortical stages unpractical. Several hypotheses regarding their progressive disappearance have been proposed (Marin-Padilla, 1990; Parnavelas and Edmunds, 1983; Sarnat and Flores-Sarnat 2002; Derer and Derer, 1990). However, it seems now reasonably established that this phenomenon reflects a developmentally-driven apoptotic process (Derer and Derer 1990; del Río et al., 1995; Naqui et al., 1999; Tissir et al., 2009; Chowdhury et al., 2010; Anstötz et al., 2014, 2016; Ledonne et al., 2016).

As previously mentioned, most patch-clamp studies in the hippocampus are commonly performed on slices obtained from animals older than the second postnatal week. It is likely that electrophysiologists ignored Cajal-Retzius cells in this region because they assumed that these neurons would disappear, similarly to what was described in neocortical networks. Despite this being a “psychologically-plausible” explanation, we think that additional factors might have played a role. In fact, anatomical/immunohistochemical evidence for a prolonged persistence of Cajal-Retzius cells in the hippocampus (compared to the neocortex, see Del Río et al., 1996; Supèr et al., 1998) was available, but not routinely taken into account by electrophysiological studies.

We suppose that the most important factor explaining this surprising lack of attention may be related to the conventional wisdom that guides electrophysiologists in the choice of their target neurons. Since the development of visually-guided patch-clamp in slices, efforts