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Review

Electrically coupled excitatory neurones in cortical regions

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ABSTRACT

Gap junctions between inhibitory neurones in cortical regions have been well documented over the years. However, although the presence of electrical coupling between pyramidal cells has been supported by dye-coupling and recordings of fast prepotentials called 'spikelets', direct evidence for such coupling remains sparse. Electrical coupling between pyramids has however been shown to play a significant role in oscillatory network activity, spatial exploration and learning and memory and full characterization of these synapses are overdue. In this review, an overview of the known properties of these electrical synapses is given, focusing on a study in the CA1 region of the hippocampus.

This article is part of a Special Issue entitled Electrical Synapses.

Contents

1. Introduction

Electrical synapses between neurones are thought to play a crucial role in the generation and the maintenance of hippocampal oscillations (Ylinen et al., 1995; Deans et al., 2001; Hormuzdi et al., 2001; Traub et al., 2001; Buhl et al., 2003; Bennett and Zukin, 2004 for review). To date, gap junctions have been most convincingly demonstrated in inhibitory neurones, particularly between cells of the same class (Fukuda and Kosaka, 2000; Zhang et al., 2004; Galarreta et al., 2004). In the rat hippocampus, gap junctions have been studied between the dendrites of PV-immunopositive interneurones (Katsumaru et al., 1988; Fukuda and Kosaka, 2000; Fukuda et al., 2006), between the dendrites of interneurones located in SO and SLM (Zhang et al., 2004; Zsiros and Maccaferri, 2005), between interneurones that express cannabinoid type 1 (CB1) receptors (Galarreta et al., 2004, 2008) and between cholecystokinin (CCK) immunopositive interneurones (Iball and Ali, 2011). Anatomical studies revealed the ultrastructure of gap junctions between

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interneurones (Fukuda and Kosaka, 2000; Tamás et al., 2000; Szabadics et al., 2001; Simon et al., 2005) and demonstrated that Connexin 36 (Cx36) is the major protein expressed at these synapses in adult rodents (Condorelli et al., 1998; Venance et al., 2000; Baude et al., 2007; Ma et al., 2011). Although in vitro and in vivo recordings revealed that gamma oscillations are disrupted in Cx36 knock-out mice, these oscillations are not abolished (Hormuzdi et al., 2001; Buhl et al., 2003). In these studies, fast ripple oscillations were also not affected suggesting that gap junctions between interneurones might not be the only electrical synapses involved in oscillatory activity. Despite evidence for dye-coupling between pyramidal cells (MacVicar and Dudek, 1980; MacVicar et al., 1982; Church and Baimbridge, 1991; Baimbridge et al., 1991; Schmitz et al., 2001), recordings of carbenoxolone-sensitive spikelets elicited by antidromic stimulation of neighboring pyramidal cells (Schmitz et al., 2001) and evidence for electrical spikelets in CA3 pyramidal cells following mossy fibers activation (Vivar et al., 2012), electrical coupling between pyramidal cells has proved more difficult to demonstrate and quantify directly with only a few studies in the entorhinal cortex (Dhillon and Jones, 2000), in the hippocampus and neocortex (MacVicar and Dudek, 1981; Mercer et al., 2006; Wang et al., 2010). This review aims to give an overview of what is known about these electrical synapses; focussing on a study that presented the first direct evidence of electrical coupling between CA1 pyramidal cells (Mercer et al., 2006; see also comments in Bennett and Pereda, 2006).

2. Direct evidence of electrical coupling between pyramidal cells in the CA1 region of the hippocampus

The lack of evidence for electrical coupling between pyramidal cells has made their existence controversial for many years. This may be explained by a low probability of finding such a coupling. Only 19 of 1370 pairs of simultaneously recorded pyramidal cells, whose somata were in the CA1 region, were electrically coupled (Mercer et al., 2006). Given that the tested area (within 50 μm) contained 50–70 pyramidal cells, it was estimated that >70% of pyramidal cell located close to the border of *stratum radiatum* is coupled to a neighbor. Interestingly, the hit rate in CA1 (approximately 1:72) was higher than the probability of finding electrically coupled pairs of pyramidal cells in the neocortex (1:200) (Wang et al., 2010). This might be explained however by differences in slice preparation and techniques used. In agreement with computer modeling studies (Traub and Bibbig, 2000), intracellular recordings in CA1 suggested that one pyramidal cell was typically electrically coupled to more than one other pyramidal cell (Mercer et al., 2006).

Electrical coupling between pyramidal cells in CA1 was demonstrated firstly by the depolarization of one of the two cells that leads to the depolarization of the coupled cell with a coupling ratio at a steady state of 0.25±0.080 (Mercer et al., 2006). Action potentials (APs) elicited in one of the cells activated 'spikelets' in the coupled cell with onset latencies of 0.35±0.13 ms (Fig. 1a, b, c). 'Spikelet' 10–90% rise times were 1.5±0.31 times and their widths at half amplitude

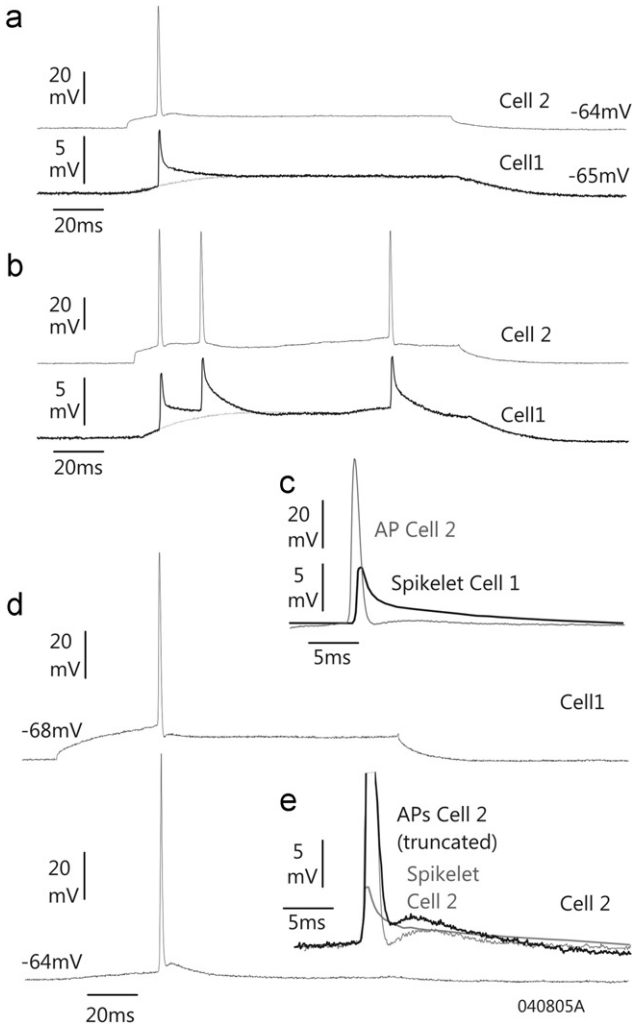

Fig. 1 – Action potentials in one CA1 pyramidal cell activate 'spikelets' in a coupled, follower cell which can elicit action potentials in that cell (a) and (b) Supra-threshold current pulses injected into Cell 2 generate APs that activate 'spikelets' in Cell 1. (c) The AP recorded in Cell 2 and the 'spikelet' recorded in Cell 1 are superimposed (with different gains) illustrating the delay to activation of the 'spikelet' and its slower time course. The shape of the 'spikelet' was obtained by subtracting from the original records the spike artifact and the underlying current-activated depolarization. (d) An AP generated in Cell 1 elicits a 'spikelet' in Cell 2 that activates an AP. (e) The Cell 2 AP activated by a 'spikelet' (illustrated in (d)) and an AP activated by direct current injection (as in (a)) and the 'spikelet' in Cell 2 are superimposed to illustrate the effect that the underlying 'spikelet' with its prolonged time course has on the shape of the spike AHP (after hyperpolarization). (From Mercer et al., 2006).

2.1±1 times longer than the APs that elicited them. These 'spikelets' could reach spike threshold resulting in full action potentials in the coupled cell that could, in turn, elicit 'spikelets' and APs in the other cell (Fig. 1d, e). This suggested that electrical coupling may affect the firing properties of the electrically coupled cells. Onset latencies that were measured