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Review

Functional features of the rat subicular microcircuits studied in vitro

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Abstract

The subiculum has a strategic position in controlling hippocampal activity and is now receiving much experimental attention. However, information regarding this structure remains fragmented and there are important gaps in our knowledge between what we know about the subicular architecture and its biological function. In recent years a substantial amount of in vitro experimentation has explored many aspects of the functional organization of the subicular microcircuits. Here we review these recent findings. We aim to identify the rules that govern the operation of subicular microcircuits in vitro and to relate these to the role of the subiculum in the intact brain.

Keywords: Subiculum; Slices; Patch-clamp; Pair recordings; Bursting; Microcircuits

Contents

1. Introduction

The subiculum is a pivotal structure that controls the output and input activity to the hippocampus. An accumulating body of evidence now suggests that this structure has a decisive role in both normal and pathological brain function. Specifically, it is crucially involved in spatial encoding [3,70,79,80], mnemonic functions [25,31,32,59,87] and in devastating human conditions such as Alzheimer's disease [16,20,46], schizophrenia [1,26,27,61,62] and temporal lobe epilepsy [2,10]. In most cases, the role of the subiculum is different but complementary to that of the hippocampus [17,68]. During spatial navigation for instance, subicular cells exhibit place fields that are modulated by the animal's head-direction and are insensitive to environmental landmarks, in contrast to hippocampal place cells [65,66,80,81]. It has been suggested that subicular cells encode a universal location-specific map that assists the hippocampus to form context-specific representations [67].

Most of the remarkable functions of the subiculum derive from its unique properties. Not only is it strategically placed to relate hippocampal, cortical and subcortical activity, but it also exhibits particular cellular and network features. However, until relatively recently the subiculum has been demoted to a secondary place compared with the hippocampus. Here, we review recent findings on the intrinsic organization of subicular microcircuits studied in vitro. We aim to delineate functional subicular

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networks and to put these in relation with their role in the normal brain.

2. Principal cell types

The subiculum is a three-layered allocortex composed of a range of electrophysiological neuronal types. Early studies in the 1990s showed that principal glutamatergic neurons can be classified as bursting and regular-spiking cells [47,48,76,78]. Bursting cells respond with a burst of 2–5 action potentials during the initial 50–60 ms of a supra-threshold current injection. Following this initial firing, some bursting cells can burst again while others fire single action potentials or remain silent (Fig. 1). These two firing patterns are sub-classified as strong and weak bursting, respectively [55,73].

Regular-spiking subicular neurons respond to supra-threshold current pulses by firing of single action potentials (Fig. 1). Some regular-spiking cells exhibit prominent adaptation while others fire in a tonic fashion [55]. Interestingly, some bursting cells switch to a regular-spiking pattern upon membrane depolarization [47,55,76]. However, a regular-spiking cell cannot be transformed into a bursting cell by changing resting membrane potential.

Electrophysiologically, bursting cells have lower input resistance compared to adapting regular-spiking cells but not to tonic cells [30,55]. Bursting cells exhibit prominent sags and rebounds in response to long hyperpolarizing current pulses [76]. Sags seem to be produced by I_H whereas low- (LVA) and high-voltage activated (HVA) Ca^{2+} currents together with I_H shape rebounds induced by depolarization of the membrane potential from hyperpolarized levels [49,55]. Another prominent feature of bursting cells is the presence of an after-depolarization (ADP) following single spikes [37,55]. It seems that regular-spiking, but not bursting subicular cells show NADPH-diaphorase activity and a lower effect of the neuropeptide somatostatin [28,29].

Some data suggests that the bursting and regular-spiking cells may project to different brain regions. By combining antidromic and orthodromic stimulation with sharp recordings in vitro, Stewart [75] explored this issue in the ventral subiculum. He found that bursting cells are likely to project to the presubiculum and that regular-spiking cells project to the entorhinal cortex. Different subcortical targets of bursting and regular-spiking cells have been also suggested based on their spatial distribution [30,55] and the topography of subicular projections to the anteroventral thalamic nucleus, the mammilary bodies and the nucleus accumbens [36].

The proportion of bursting and regular-spiking cells of the subiculum has been a matter of debate. It was initially reported that between 70 and 100% cells were of the bursting type [47,48,76,78]. This led to the general assumption that the subiculum is a bursting structure (in contrast to its CA1 input area). However, subsequent data suggested that only about 50% of cells were bursters [5]. Greene and Totterdell [30] helped to clarify this apparent discrepancy by showing that there are different deep-to-superficial and proximo-to-distal distributions of bursting and regular-spiking cells in the subiculum (see also Refs. [34,55]). It was also reported that there is a difference in somatic size and shape between these two groups [30,55], and this may significantly affect cell sampling during visual-assisted patch recordings [54].

But, do subicular bursting cells actually burst? Using cell-attached recordings, which do not alter the cell firing capability, we recently showed that the majority of the strong (∼75%) but not weak (∼22%) bursting cells fire bursts in response to local synaptic activation [51]. Near 55% of the weak bursting subicular cells were not synaptically activated and the remaining 20% responded with single action potentials. This was similar to the regular-spiking group which remained silent in most cases (∼87%) or fired single spikes. Therefore, at least under the in vitro conditions, it is the strong bursting phenotype that has a functional bursting capacity.

It is likely that the different synaptic responsiveness of strong versus weak bursting cells is related to the ionic mechanisms underlying subicular bursting, as synaptic inputs were found to be similar for all cell types [44,51]. There is data suggesting that Na^+ currents boost EPSPs elicited by hippocampal afferent stimulation, and that this mechanism could differentially affect regular-spiking and bursting cells [15]. Both Ca^{2+} [76,78] and Na^+ persistent currents [47,55] were suggested to underlie burst firing. Recent work has suggested that a Ca^{2+} tail current but not a Ca^{2+} spike could shape the ADP that drives subicular bursting [37]. According to this data, the strong and the weak bursting phenotypes would result from different amount of Ca^{2+} tail currents, which are differently contributed by multiple Ca^{2+} channel subtypes. A relatively small fraction of the HVA Ca^{2+} tail current appears to be mediated by the L-type current whereas the

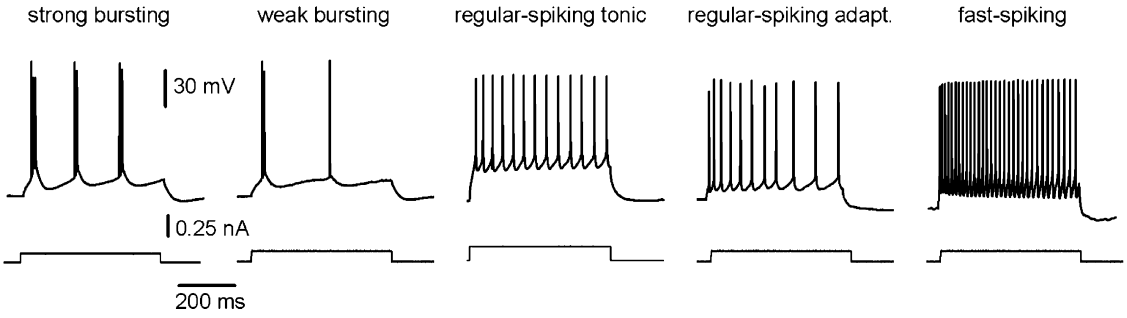

Fig. 1. Electrophysiological heterogeneity of subicular cell types. Glutamatergic cells of the subiculum are either intrinsic bursters of regular-spiking neurons. Bursting cells can be divided in strong and weak bursting cells according to the number of bursts elicited by depolarizing current pulses. Regular-spiking cells can fire with different degree of adaptation. Putative GABAergic interneurons of the subiculum exhibit a fast-spiking firing pattern.