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Research Report

Predicting synchronous and asynchronous network groupings of hippocampal interneurons coupled with dendritic gap junctions

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ABSTRACT

Direct electrical communication between central nervous system (CNS) neurons including those in the hippocampus is well-established. This form of communication is mediated by gap junctions and it is known that this coupling is important for brain rhythms such as gamma (20–80 Hz) which occur during active behavioural states. It is also known that gap junctions are present at several locations along the dendrites of hippocampal interneurons including parvalbumin-positive basket cell types. Weakly coupled oscillator theory, which uses phase response curves (PRCs), has been used to understand and predict the dynamics of electrically coupled networks. Here we use compartmental models of hippocampal basket cells with different levels of basal and apical spike attenuation together with the theory to show that network output can be broken down into three groupings: synchronous, asynchronous and antiphase-like patterns. Moreover, quantified PRCs can be used as a rule of thumb to determine the occurrence of a particular grouping under weak coupling conditions, which in turn implies that spike delays are critical factors in determining network output. In moving beyond weak coupling to encompass the full physiological regime of coupling strengths with network simulations, we note that it is important to be able to differentiate between these different groupings as it affects how the network responds with modulation. Specifically, an asynchronous grouping provides more dynamic richness as a larger range of phase-locked states can be expressed with strength changes. From a functional viewpoint it may be that modulation of electrically coupled networks are key to controlling cell assemblies that contribute to information coding brain substrates.

1. Introduction

Communication between central nervous system (CNS) neurons occurs chemically via inhibitory and excitatory synapses, and electrically via gap junctions. Whereas synapses mediate a slower mode of signal transmission, gap junctions provide a means of direct and fast communication believed to be important in producing synchronous network activities (Hormuzdi et al., 2004). A gap junction channel consists of 12 connexin (Cx) proteins, six on the

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presynaptic side and six on the postsynaptic side, and is formed when the membranes of two cells are close enough together to form a direct channel through which particles can flow. These connections consist of clusters of channels that are not static pores but can open and close, being modulated by age, pH, phosphorylation and other factors (Connors and Long, 2004). The physiological range of gap junction connections is 10–3000 pS based on a unitary gap junction conductance of 10–300 pS and 1–10 gap junction channels per electrical connection (Galarreta and Hestrin, 2001; Srinivas et al., 1999). Of the different types of Cx proteins, Cx36 gap junction proteins are found between interneurons or inhibitory cells in the CNS (Meier et al., 2002; Parenti et al., 2000; Söhl et al., 2005; Srinivas et al., 1999).

Interneurons have diverse characteristics and they make critical contributions to rhythmic activities in particular and distinct ways (Buzsáki, 2006 (chp.3); McBain and Fisahn, 2001). For example, parvalbumin-positive (PV+) inhibitory basket cells fire preferentially on the descending phase of hippocampal theta oscillations which occur during movement and exploration (Klausberger et al., 2003). One of the most characteristic patterns of the awake brain is gamma oscillations (30–80 Hz) which have been recorded in many brain regions including the hippocampus (Buzsáki, 2006 (chp 9)). Basket cells in the hippocampus form mutually inhibitory networks (Sik et al., 1995) and it is clearly the case that they are major players in producing gamma rhythms both *in vitro* and *in vivo* (e.g., Gloveli et al., 2005; Hajos et al., 2004; Tukker et al., 2007). These basket cells target perisomatic regions of the pyramidal cell and thus can exert significant control over their output. Furthermore, network models incorporating experimentally derived synaptic characteristics produce robust and coherent gamma oscillations (Bartos et al., 2007), thus suggesting that synchronous output from basket cell networks are important contributors to gamma rhythms.

Gap junction coupling contributes to mechanisms underlying gamma generation in the hippocampus (e.g., Csicsvari et al., 2003), and it is notable that gamma oscillations are selectively impaired in Cx36 knockout mice (Buhl et al., 2003). In addition to inhibitory synapses, PV+ basket cells are electrically coupled through gap junctions at multiple locations between their apical and basal dendrites (Fukuda and Kosaka, 2000; Bartos et al., 2001). Interestingly, axo-axonic (or chandelier) and bistratified inhibitory cell types are also endowed with Cx36 dendrodendritic gap junctions (Baude et al., 2007) and exhibit significant gamma modulation *in vivo* (Hajos et al., 2004). This suggests that dendritic gap junctions on different inhibitory cell types may play important roles in shaping network gamma output. Given this, it is essential to understand how non-proximally located gap junctions contribute to producing synchronous output in these types of inhibitory cell networks. However, due to the high degree of technical difficulty in recording from dendrites of particular interneurons, the inability to both record from and identify the gap junction location on a given interneuron, and the inability to experimentally control all system parameters, models and theory are needed to provide insight and understanding, and to guide and suggest experiments. For this, we need not only to consider compartmental models, but also to consider models that incorporate characteristics that are specific to the inhibitory cell type.

Several theoretical and modeling studies have clearly shown that cellular, intrinsic properties affect the particular network patterns that arise in electrically coupled networks (Chow and Kopell, 2000; Lewis and Rinzel, 2003; Pfeuty et al., 2003; Saraga et al., 2006; Sherman and Rinzel, 1992), and in networks with both electrical and inhibitory coupling (Gao and Holmes, 2007; Kopell and Ermentrout, 2004; Lewis and Rinzel, 2003; Pfeuty et al., 2005; Skinner et al., 1999). Proximal and distal connections on dendrites can have opposite effects on network output, and this can be modulated by intrinsic properties of the cell (Crook et al., 1998; Gansert et al., 2007; Lewis and Rinzel, 2004; Saraga and Skinner, 2004). In particular, weakly coupled oscillator theory has been used to predict whether synchronous output could be obtained in electrically coupled networks (Lewis and Rinzel, 2003), and characteristics of phase response curves (PRCs) have been shown to be good predictors of synchronous network output (Pfeuty et al., 2003).

In this paper we aim to determine whether inhibitory networks produce synchronous or asynchronous output when coupled with gap junctions on their active dendrites. We do this using compartmental models, simulations and theoretical insights. We modify our previously developed compartmental model of a hippocampal basket cell (Saraga et al., 2006) in which the dendrites are active, containing voltage-gated channels as is known from experiment (Maccaferri et al., 2004), to express spike attenuation characteristics as experimentally observed. We generate PRCs and use weakly coupled oscillator theory to predict the network output, and find that quantified PRCs can be used as rules of thumb in predicting the synchronous or asynchronous output, which in turn suggests critical cellular characteristics.

2. Results

2.1. *Basket cell models*

Although there is evidence for voltage-gated channels in the dendrites of hippocampal interneurons (Martina et al., 2000), details as to their densities and distributions are incomplete for basket cells at present. However, it is known that there is an approximately 15% spike attenuation when recordings are performed on dendrites at about 50 μm from the soma with perhaps some differences between basal and apical dendrites (M. Martina, unpublished observations, Maccaferri et al., 2004). We thus built three basket cell models (Cell 1, Cell 2 and Cell 3) with different intrinsic properties such that they exhibit different amounts of basal and apical spike attenuation. This difference is accomplished mainly by varying the sodium channel densities — the channel densities and other cell properties are shown in Table 1. Each model cell has the same morphology and passive properties as used in our previously developed basket cell compartmental model (Saraga et al., 2006; and see Section 4.1), and exhibits spike shape and frequency characteristics of basket cells (see Table 1). In particular, all cells spontaneously fire in the gamma frequency