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Research Report

Fast oscillations trigger bursts of action potentials in neocortical neurons in vitro: A quasi-white-noise analysis study

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ABSTRACT

Purpose: Recent evidence supports the importance of action potential bursts in physiological neural coding, as well as in pathological epileptogenesis. To better understand the temporal dynamics of neuronal input currents that trigger burst firing, we characterized spectral patterns of stimulation current that generate bursts of action potentials from regularly spiking neocortical neurons in vitro. *Methods:* Sharp microelectrodes were used for intracellular recording and stimulation of cortical neurons in rat brain slices. Quasi-white-noise (0–2 kHz) and "chirp" sine wave currents of decreasing wavelength were applied to represent a broad spectrum of stimulation frequencies. Action potential-related averaging of the stimulation current variations preceding bursting was used to characterize stimulation current patterns more likely to result in a burst rather than a single-spike response. *Results:* Bursts of action potentials were most reliably generated by a preceding series of ≥2 positive current transients at 164±37 Hz of the quasi-white-noise, and to sine wave currents with frequencies greater than 90 Hz. The intraburst action potential rate was linearly related to the frequency of the input sine wave current. *Conclusions:* This study demonstrates that regularly spiking cortical neurons in vitro burst in response to fast oscillations of input currents. In the presence of positive cortical feedback loops, encoding input frequency in the intraburst action potential rate may be safer than producing a high-frequency regular output spike train. This leads to the experimentally testable and therapeutically important hypothesis that burst firing could be an antiepileptogenic and/or anti-ictogenic mechanism.

1. Introduction

Bursts are clusters of two or more action potentials occurring at a rate of greater than 100 Hz, separated from the remainder of the spike train by a longer interspike interval (Cattaneo et al., 1981b; Lisman, 1997; Snider et al., 1998). Bursts have been considered to be a hallmark of epileptogenic tissue both in brain slices in vitro (Sanabria et al., 2001) and in

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different species including humans in vivo (Wyler and Ward, 1986). It has been suggested that bursts may be a powerful mechanism to synchronize extended neuronal networks (Chagnac-Amitai and Connors, 1989) and therefore be causally related to the process of ictogenesis and, by way of kindling, of epileptogenesis.

Besides a pathophysiological role, bursts have also been considered as a way the neocortex might represent information under physiological conditions. The search for such a "neural code" (i.e., how for example features of a sensorial stimulus are represented in neuronal spike trains) is a major goal of neurophysiological research (Bialek et al., 1991). Although the controversy with regard to information coding by neural networks previously had been focused on whether neurons read out the average rate of an afferent spike train versus whether they utilize precise temporal structure (König et al., 1995; Sejnowski and Paulsen, 2006; Shadlen and Newsome, 1994; Softky, 1995; deCharms and Zador, 2000; Stevens and Zador, 1998), bursts have been suggested as a third non-exclusive basis of neural encoding (Crick, 1984). In some experiments, such as computing the orientation of a stimulus in primary visual cortex, bursts may contain more information about spatial frequency and orientation of the stimulus than single spikes (Cattaneo et al., 1981a). Bursts are often able to produce a post-synaptic response when isolated spikes are ineffective, and single bursts are sufficient to produce long-term potentiation (LTP) and long-term depression (LTD) in hippocampus (Huerta and Lisman, 1993, 1995). Furthermore, coincident bursts are considered to be the most efficient means to drive a post-synaptic cell (Lisman, 1997) and have been implicated as a homeostatic mechanism to maintain neuronal excitability (Buzsaki et al., 2002). Given this evidence for the importance of bursts as a physiological as well as a pathophysiological mechanism, it is crucial to understand which neuronal input currents trigger burst firing. Of interest is a subclass of pyramidal cells, mostly located in layer V, which produce trains of bursts when a DC step is injected intracellularly in vitro (Connors and Gutnick, 1990; Connors et al., 1982; McCormick et al., 1985). These neurons are referred to as "intrinsically bursting" to indicate that their firing pattern in response to DC steps reflects membrane characteristics rather than features of the stimulating current (Franceschetti et al., 1995; Guatteo et al., 1996). However, to be involved in neural representation, bursts should not be restricted to a certain class of neurons nor triggered only by DC steps. It has therefore been suggested that any nerve cell may be able to produce bursts if exposed to specifically tuned current transients (Connors and Gutnick, 1990). Understanding the properties of current transients that trigger bursts would also be important to understand how neurons may be recruited to give rise to seizures (Wyler and Ward, 1986), in order to develop monitoring and therapeutic stimulation protocols, as well as drug therapies to treat epilepsy.

The specific objective of this study was to characterize the spectral properties of input currents that generate burst firing in regular spiking neurons by intracellular recording and stimulation in rat neocortical slices. We injected quasi-white-noise current, an efficient method to test many different stimuli frequencies simultaneously (Sakai, 1992), and used action potential-related averaging to characterize the spectral properties of current underlying single spiking versus bursting.

2. Results

All neurons had a stable resting membrane potential more negative than −65 mV and action potential peaks exceeding 0 mV. Although all neurons were not morphologically reconstructed, their regular spiking patterns in response to DC injection indicated that they could be classified with a high degree of certainty as pyramidal cells (Connors and Gutnick, 1990; Connors et al., 1982; McCormick et al., 1985; van Brederode and Snyder, 1992). Here we define a burst of action potentials as a cluster of two or more action potentials occurring at a rate of greater than 100 Hz and separated from the remainder of the spike train by a longer interspike interval. During the pre-stimulus sequences, none of the neurons produced trains of bursts in response to flat DC steps, indicating that the cells were not "intrinsically bursting".

We found that the number of bursts increased either with increasing DC offsets or with greater white noise SD (Fig. 1). We restricted our subsequent analyses to the N3 sequences, because these produced the most consistent bursting.

Spike trains triggered by DC step current (mean: 0.9 nA) were very regular, occurring at a mean frequency of 19±0.8 Hz

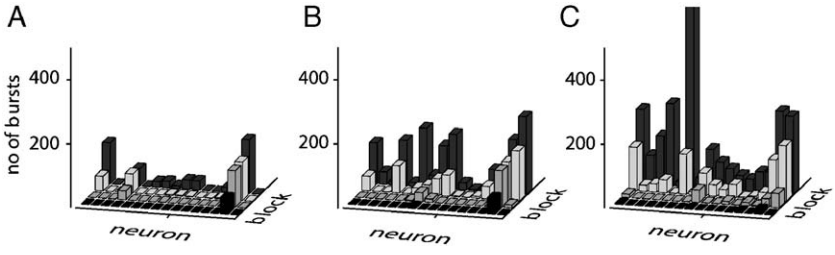

Fig. 1 – Testing the effectiveness of stimulation sequences N1 (plot A), N2 (plot B) and N3 (plot C) in triggering bursts of action potentials. For each of the 16 neurons, the absolute number of bursts occurring during a 35-s experimental block of stimulation current is plotted. Along the "block" axis, the standard deviation of the quasi-white-noise stimulation currents increases from rows 2 to 4. The first block row shows almost no bursting during steps of pure DC stimulation, indicating that none of the neurons could be classified as "intrinsically bursting". Plots A–C show that higher standard deviation of quasi-white-noise current or higher DC offsets triggered greater bursting.