Annual Meeting Mini-Symposium

The Beat Goes On: Spontaneous Firing in Mammalian Neuronal Microcircuits

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Many neurons in the brain remain active even when an animal is at rest. Over the past few decades, it has become clear that, in some neurons, this activity can persist even when synaptic transmission is blocked and is thus endogenously generated. This "spontaneous" firing, originally described in invertebrate preparations (Alving, 1968; Getting, 1989), arises from specific combinations of intrinsic membrane currents expressed by spontaneously active neurons (Llinas, 1988). Recent work has confirmed that, far from being a biophysical curiosity, spontaneous firing plays a central role in transforming synaptic input into spike output and encoding plasticity in a wide variety of neural circuits. This mini-symposium highlights several key recent advances in our understanding of the origin and significance of spontaneous firing in the mammalian brain.

Biophysical mechanisms underlying spontaneous activity

To maintain spontaneous activity, intrinsic currents must interact to depolarize the cell membrane to threshold, elicit an action potential, and repolarize the membrane to negative potentials from which the next spike can be initiated. Several studies have identified currents responsible for the subthreshold depolarizations leading to each spike. In some neurons, this depolarization results from dynamic recruitment and activation of hyperpolarization-activated channels and T-type Ca channels (McCormick and Huguenard, 1992). In other neurons, voltage-gated Na currents and/or nonselective cation currents bring the membrane potential to threshold (Raman et al., 2000; Taddese and Bean, 2002; Do and Bean, 2003; Jackson et al., 2004).

In spontaneously active neurons exhibiting high firing rates, an additional issue arises regarding the availability of Na channels, which usually inactivate substantially during each action potential. In many neurons, recovery from inactivation is incomplete during brief interspike intervals at moderately hyperpolarized potentials. After a burst of high-frequency action potentials, such cells therefore become refractory and stop firing until Na channels are allowed to recover. In contrast, in neurons that maintain regular spontaneous firing for hundreds of consecutive action potentials, recovery between spikes must be fast enough to compensate for inactivation during spikes. In cerebellar Purkinje neurons, whose spontaneous firing rates are unusually high (~40–50 Hz) (Häusser and Clark, 1997; Womack and Khodakhah, 2002; Smith and Otis, 2003), this issue is partly resolved by Na channels with "resurgent" kinetics (Raman and Bean, 1997) (Fig. 1). With depolarization, these voltage-gated, tetrodotoxin (TTX)-sensitive Na channels open briefly and then become blocked by a voltage-dependent, open-channel blocker. This endogenous blocking protein not only limits inactivation by competing with the fast inactivation gate but also unbinds rapidly at negative potentials. Consequently, a resurgent Na current flows briefly as channels unblock (open) with repolarization. Significantly, the channels then deactivate into closed states that are readily available for reactivation, thereby shortening refractory periods and facilitating high-frequency spontaneous firing (Raman and Bean, 2001; Grieco et al., 2002; Khaliq et al., 2003). Which Na channel α subunits are targeted by the blocker? In Purkinje neurons, fast inactivation proceeds somewhat more slowly in $Na_V1.6$ channels than in other α subunits, such that $Na_V1.6$ channels have a much higher chance of binding the blocker than the fast inactivation gate. As a consequence, $Na_V1.6$ channels are more susceptible to block and unblock than other α subunits, thereby carrying most of the resurgent Na current of Purkinje cells (Raman et al., 1997). In other neurons, however, substantial resurgent Na currents can flow through non-$Na_V1.6$ α subunits, indicating that, under the right conditions, the blocker (or blockers) can interact with a variety of Na channels (Do and Bean, 2004; Grieco and Raman, 2004). Thus, the expression of a blocking protein, whose molecular identity is under active investigation, endows otherwise classical Na channel α

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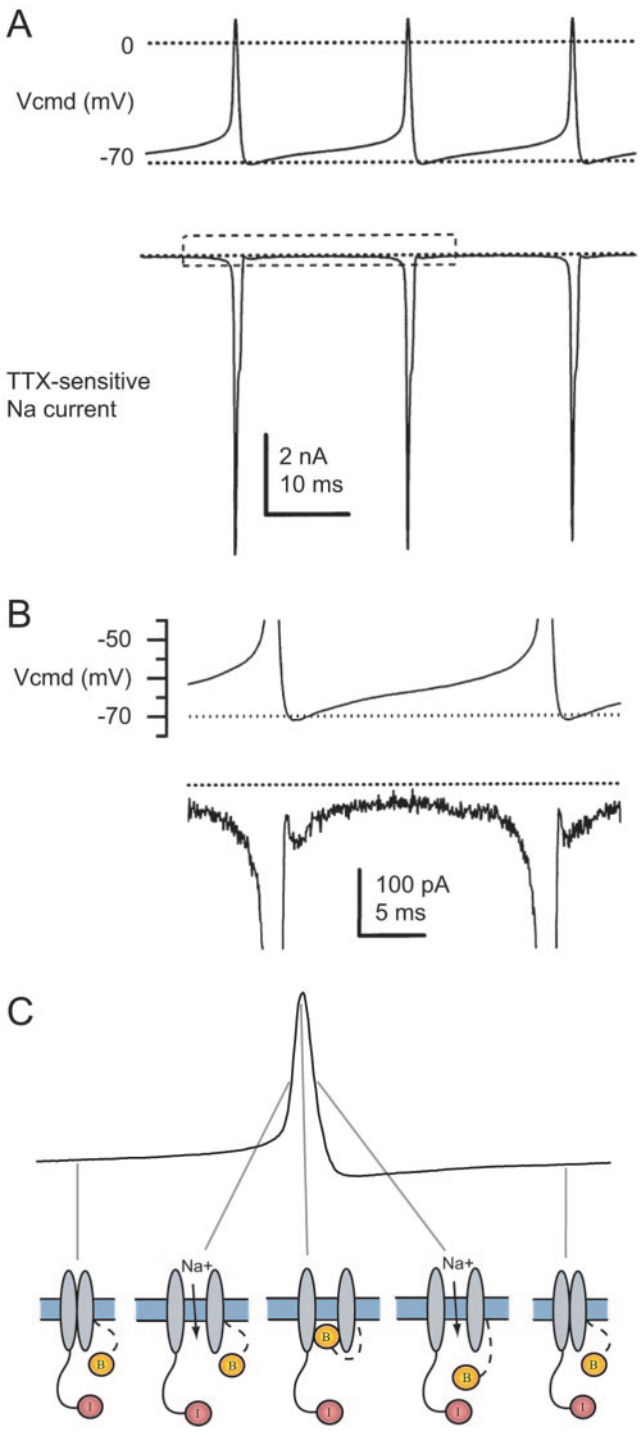

Figure 1. Ionic currents underlying spontaneous firing. *A*, Spontaneous firing in an isolated Purkinje cell (top trace). Bottom traces show underlying TTX-sensitive voltage-gated Na current activated during spiking by applying the top trace as a voltage-clamp command (Vcmd). Modified from Raman and Bean (1999). *B*, Close-up of Na current activated at subthreshold potentials, with resurgent Na current apparent on the falling phase of the action potential (dashed box in *A*). Modified from Raman and Bean (1999). *C*, Schematic illustration of Na channel gating during a single action potential. Gray lines indicate the approximate times and voltages during the spike that favor each conformation. Channels begin in the closed state, with the inactivation gate (*I*) and the blocking particle (*B*) unbound. As the spike proceeds, channels open, block, unblock (producing resurgent current), and close. Note that the binding of the inactivation gate can be prevented by binding of the blocking particle. Modified from Grieco et al. (2002).

subunits with distinctive, apparently physiologically relevant, properties.

Plasticity of spontaneous firing in cerebellar Purkinje neurons

The rapid regular firing of Purkinje neurons can thus be primarily accounted for by the macroscopic kinetics of their intrinsic voltage-gated channels, operating on a timescale of milliseconds. On a longer timescale, however, this spontaneous firing can be accelerated and slowed, or even turned on and off. Recent work by Smith and Otis (2003) has shown that long-term changes in intrinsic Purkinje neuron firing rates can occur in an activity-dependent manner. This mechanism is notable in that it constitutes a form of circuit plasticity that does not rely on changing synaptic strength. The changes in Purkinje neuron firing have been traced to modulation by the nitric oxide-cGMP signaling cascade (Fig. 2*A*). Although the role of this pathway in the vascular system is well established, its importance for signaling in the brain has been the subject of much debate. Components of the cascade are expressed throughout the brain, but they seem to be particularly important in the cerebellar cortex, in which they are especially abundant. Nitric oxide synthase is present in the granule neurons and in their axon terminals, the parallel fibers as well as in basket cells, a class of inhibitory interneurons (Bredt et al., 1990). Soluble guanylate cyclase, the canonical target for nitric oxide, is highly expressed in Purkinje neurons (Ariano et al., 1982). In addition, several potential targets of cGMP are present in Purkinje neurons, including cGMP-dependent protein kinase (PKG), cGMP-gated ion channels, and cGMP phosphodiesterase (Lohmann et al., 1981; el-Husseini et al., 1995; Bellamy and Garthwaite, 2001). Not surprisingly, cerebellar cortex has proven to be a model preparation for examining nitric oxide-cGMP physiology in the brain. Depolarizations cause biochemically detectable elevations of nitric oxide-cGMP, and stimulation of parallel fibers causes production of nitric oxide (Shibuki and Kimura, 1997). Despite this wealth of knowledge about the expression and biochemistry of this signaling cascade, there is controversy regarding its physiological roles in the cerebellum. Recent results (Smith and Otis, 2003) indicate that nitric oxide released by stimulation of parallel fibers in cerebellar slices diffuses to Purkinje neurons, in which it activates soluble guanylate cyclase. The resulting rise in cGMP activates the cGMP-dependent protein kinase (PKG) and increases firing rates in the Purkinje neurons, presumably by phosphorylation of target proteins such as ion channels. Current efforts are being focused on identifying the contribution of several candidate conductances to the modulation of firing rate, particularly Ca-activated K currents (Womack and Khodakhah, 2002) and resurgent Na currents (Raman and Bean, 2001; Grieco et al., 2002; Khaliq et al., 2003).

Bistability of Purkinje cell output

In addition to being finely modulated over long timescales, can spontaneous spiking in Purkinje cells also be turned on and off? *In vitro* studies have revealed that the membrane potential of Purkinje cells can display intrinsic bistability, in which the hyperpolarized state is quiescent and the depolarized state is characterized by persistent high-frequency spiking (Llinas and Sugimori, 1980; Williams et al., 2002). How does this relate to the firing pattern of Purkinje cells *in vivo*? Recent work has demonstrated that the membrane potential and spike output of Purkinje cells can also exhibit bistability *in vivo*. This bistability of the membrane potential implies that the instantaneous firing rate is not

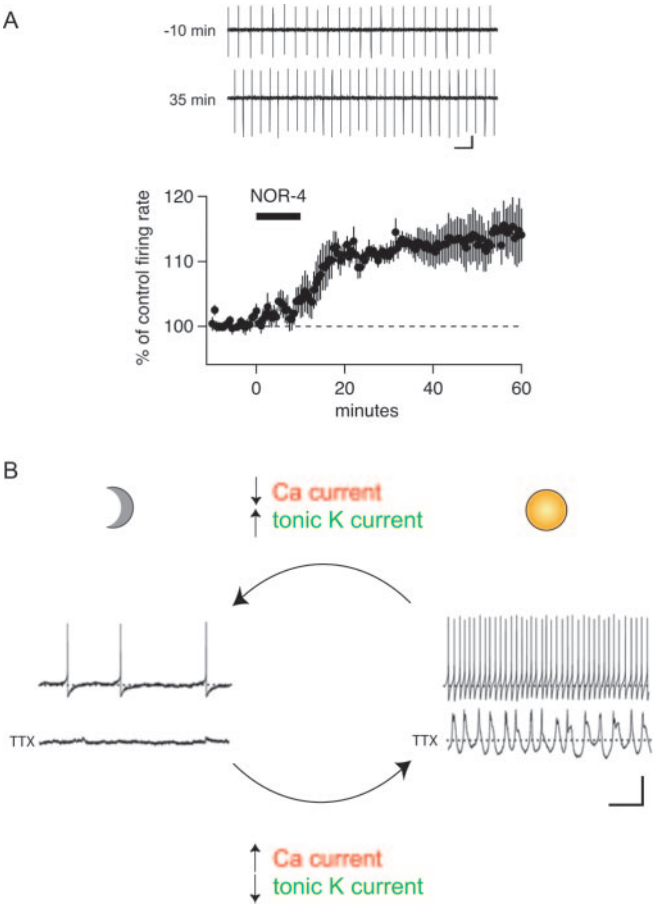

Figure 2. Plasticity of spontaneous firing. *A*, Persistent increase in spontaneous firing rate in cerebellar Purkinje cells triggered by application of the nitric oxide donor NOR-4. Top shows traces of spontaneous firing in a cell-attached recording from a Purkinje cell in a cerebellar slice 10 min before and 35 min after NOR-4 application. Calibration: 75 pA, 100 msec. Bottom shows time course of changes in average firing rate caused by NOR-4 for six Purkinje neurons. Modified from Smith and Otis (2003). *B*, Schematic illustration showing circadian regulation of spontaneous firing in SCN neurons. Left, At night, spontaneous firing rate is low (dashed line, −59 mV), and TTX fails to uncover membrane potential oscillations (−59 mV membrane potential). Right, During the day, spontaneous firing rate is high (dashed line, −54 mV), and TTX reveals a depolarized membrane potential (dashed line, −41 mV), exhibiting oscillations. These changes are attributable to modulation of L-type Ca current and tonic K current. Calibration: spiking traces, 500 msec, 40 mV; TTX traces, 500 msec, 20 mV. For details, see Pennartz et al. (2002).

only a function of the instantaneous synaptic inputs but also of the past inputs that control the state of the cell. Surprisingly, the state of Purkinje cells is often determined by input from the climbing fiber pathway, which generates a stereotypic discharge pattern known as a complex spike at a mean rate of ~1 Hz (Ito, 1984). Activation of climbing fibers by sensory input while the cell is in a hyperpolarized quiescent state often generates a sustained depolarization accompanied by high-frequency simple spike activity. Conversely, the same climbing fiber input delivered while the cell is in the active depolarized state can induce a transition to the hyperpolarized state (Y. Loewenstein and S. Mahon, unpublished data). This behavior can be captured by a simple dynamical model and is similar to a toggle switch in electronics. The emerging picture is far from complete, but clearly indicates that the common assumption that simple spike activity reflects the instantaneous activation of the parallel fibers is an oversimplification (Ghez and Thach, 2000) and that climbing fiber input, in addition to parallel fiber input, plays an important role in determining the firing pattern of simple spikes in cerebellar Purkinje cells.

Long-term modulation of spiking by inhibition in the vestibular nuclei

Like Purkinje neurons, their target neurons in the vestibular nucleus are also spontaneously active. Vestibular nucleus neurons, which participate in the circuit regulating the vestibulo-ocular reflex (VOR), change their spontaneous and stimulus-evoked firing rates in conjunction with behavioral plasticity in the VOR (du Lac, 1995; Darlington et al., 2002). Although these changes in vestibular neuron firing are commonly assumed to reflect synaptic plasticity, recent evidence suggests a role for use-dependent changes in intrinsic excitability. Persistent increases in both spontaneous and evoked firing in vestibular nucleus neurons can be induced by brief periods of synaptic inhibition or direct membrane hyperpolarization (Nelson et al., 2003). This new form of cellular plasticity, termed firing rate potentiation (FRP), provides a candidate mechanism for transforming synaptic inhibition from Purkinje neurons into behavioral changes in the VOR.

How does synaptic inhibition induce persistent increases in intrinsic excitability? Although elevations in intracellular calcium are associated with most other forms of cellular plasticity, imaging experiments indicate that intracellular Ca levels are reduced in vestibular nucleus neurons during membrane hyperpolarization. Correspondingly, firing rate potentiation can be induced by blocking voltage-gated Ca channels or by transiently replacing extracellular Ca with Mg, consistent with the idea that synaptic inhibition triggers FRP by reducing intracellular Ca levels. The signaling pathways that couple reductions in Ca to increases in excitability are under active investigation and are likely to involve calcium/calmodulin-dependent protein kinase II (CaMKII) and BK-type Ca-activated K currents. Blockade of CaMKII, which is constitutively active in vestibular nucleus neurons, produces rapid increases in intrinsic excitability via reductions in BK-type Ca-activated K currents (Smith et al., 2002). After the induction of firing rate potentiation, BK currents are reduced in vestibular nucleus neurons, and previous blockade of BK currents occludes firing rate potentiation (Nelson et al., 2003). Thus, in contrast with quiescent CNS neurons, which change their properties in response to excitatory drive and concomitant increases in calcium influx, the excitability of spontaneously firing vestibular nucleus neurons can be regulated by synaptic inhibition and decreases in calcium influx. Identification of the underlying mechanisms will enable investigations into the role of firing rate potentiation in behavioral plasticity of the VOR in genetically modified mice.

The rise and fall of spontaneous firing in the mammalian biological clock

High-frequency spontaneous firing is thus typical of many cerebellar neurons and their targets, as well as neurons in other motor centers, and may well play an important role in regulating motor control. Low-frequency spontaneous firing (at rates of <10 Hz) has been identified in neurons in brain regions that participate in homeostatic control. This is exemplified by the suprachiasmatic nucleus (SCN), because the firing rate of SCN neurons is clearly linked to behavioral and physiological output. The SCN has been recognized as the central circadian pacemaker of the mammalian brain and imposes its output onto target structures in the hypothalamus, thalamus, and other areas by way of a diurnal modulation of spontaneous discharge frequency (Schwartz et al., 1987). This diurnal rhythm originates from a cell-autonomous

process, being driven by molecular loops within clock cells that involve transcription, translation, and protein-mediated negative feedback acting on gene expression (Reppert and Weaver, 2001). One of the key issues in this field is to elucidate how membrane mechanisms transduce intracellular clock signals into a synchronized firing rate output that is broadcast to the rest of the brain and body.

To achieve progress in this area, two questions have to be addressed. First, which ionic channels regulate spontaneous firing rate of SCN neurons per se, regardless of circadian aspects? Second, which of these ionic mechanisms is subject to diurnal modulation, and how does this modulation contribute to an enhanced firing rate during the day and a decline in spontaneous firing during the night? Knowledge about spontaneous firing mechanisms has steadily accumulated over the past two decades and has highlighted the role of slowly inactivating Na currents and fast-activating K currents in shaping the membrane potential trajectories preceding and succeeding action potentials on a fast timescale (Bouskila and Dudek, 1995; Pennartz et al., 1997). However, with respect to the second question, it has proved to be a challenge to identify the ionic mechanisms responsible for regulating action potential generation on a slow timescale, stretching an average spike interval of ~120 msec during the peak of daytime firing to ~400–1000 msec during the night (Fig. 2*B*). The importance of slow firing rate regulation in the SCN prompted us to investigate the tonic spike-independent electrophysiological behavior of SCN neurons, using perforated-patch recordings in SCN slices in the presence of TTX. These experiments revealed two remarkable day–night differences: day cells were tonically depolarized with respect to night cells and exhibited spontaneous oscillations in membrane potential at a frequency of 2–7 Hz. These oscillations appeared to phase-lock to action potentials and were mediated by L-type Ca channels (Pennartz et al., 2002). The tonic membrane depolarization in day cells persisted when L-type Ca channels were blocked, despite the disappearance of oscillations, indicating the presence of at least two ionic mechanisms regulating diurnal rhythmicity. In accordance with the strong day–night difference in membrane potential oscillations, the amplitude of L-type Ca currents differed between the day and night phase. As predicted, blockade of L-type current exerted a differential day–night effect on spontaneous firing patterns (Pennartz et al., 2002; Ikeda et al., 2003). The molecular identity of the ionic current mediating the functionally dissociable tonic membrane depolarization during the daytime remains unknown. The Ca currents involved in expressing rhythmicity may also in turn regulate intracellular signaling, because day–night differences in intracellular calcium levels have been observed (Colwell, 2000; Ikeda et al., 2003). However, this issue requires additional investigation because at least one component of cytosolic Ca rhythmicity is not blocked by an L-type Ca channel antagonist (Ikeda et al., 2003).

Linking single-cell spontaneous firing to population activity

What is the relationship between the activity of single spontaneously active neurons and their neighbors in a network with recurrent excitation and inhibition? The hippocampal CA3 pyramidal cell network is a good model system to study this question and is particularly relevant because this region can initiate seizure activity. In a recent study (Cohen and Miles, 2000), the spontaneous activity of a population of several hundred CA3 neurons was studied non-invasively using extracellular multiunit recordings. This technique showed that the CA3 region of the hippocampus is spontaneously active, at a mean frequency for each cell of ~0.1–0.2 Hz (Cohen and Miles, 2000). What is the relative contribution of intrinsic cellular mechanisms and excitatory and inhibitory synapses to this activity? When both inhibitory and excitatory synaptic transmission are blocked, spontaneous firing almost doubles, indicating that single CA3 neurons can generate action potentials endogenously at a low rate of ~0.2–0.4 Hz. The activity of inhibitory neurons, either intrinsic or driven by recurrent collaterals of the pyramidal cells, thus strongly brakes CA3 population activity and prevents synchronized firing. Surprisingly, excitatory transmission only accounts for a moderate increase in population firing. This small effect seems paradoxical but results from a functional antagonism between excitatory transmission at synapses between pyramidal cells and onto inhibitory interneurons.

Although this spontaneous CA3 population activity often seems relatively unpatterned, blocking inhibition in slices from healthy animals increases activity levels and leads to bursts of activity separated by long silences, which has been compared with interictal activity (Hill et al., 1973). A similar pattern of spontaneous interictal bursting is generated by the subiculum of slices obtained after therapeutic hippocampal resection from human patients with mesial temporal lobe epilepsy (Kohling et al., 1998). However, in this tissue, GABAergic transmission enhances rather than suppresses spontaneous activity. Comparison of single-cell and population activities shows that three populations of cells exist in the epileptic focus (Cohen et al., 2002). Interneurons and a minority of pyramidal cells fire during interictal population bursts, although most pyramidal cells are strongly inhibited. GABA has depolarizing actions in a minority of pyramidal cells attributable to a pathologically elevated intracellular Cl concentration. This seemingly paradoxical role of inhibitory transmission in epileptic tissue is reminiscent of its action in the developing brain, in which spontaneous patterned population activity is ubiquitous and contributes critically to circuit formation (Penn and Shatz, 1999). Understanding the genesis and regulation of spontaneous firing in hippocampal pyramidal cells may provide important clues to understanding the transition between normal patterns of activity and pathophysiological synchronization in epilepsy.

Summary

Although spontaneous firing was originally described decades ago, investigation of its underlying molecular and biophysical mechanisms and awareness of its potential functional consequences has seen a dramatic resurgence in the past few years. This is attributable to development of new techniques for investigating channel function in isolated neurons (cloning, identification, and localization of ion channels that underlie spontaneous activity) and systems approaches for understanding the contribution of single neurons to network function. Results emerging from these techniques have led to a growing consensus that spontaneous firing is not only a prominent feature of many neuronal networks but may also serve useful functional roles, contributing to regulating information flow in different microcircuits in the brain.

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