



## A Persistent Little Current With a Big Impact on Epileptic Firing

### An increase in persistent sodium current contributes to intrinsic neuronal bursting after status epilepticus.

Chen S, Su H, Yue C, Remy S, Royeck M, Sochivco D, Opitz T, Beck H, Yaari Y. *J Neurophysiol.* 2011;105(1):117-129.

Brain damage causes multiple changes in synaptic function and intrinsic properties of surviving neurons leading to the development of chronic epilepsy. In the widely used pilocarpine-status epilepticus (SE) rat model of temporal lobe epilepsy (TLE), a major alteration is the marked increase in the fraction of intrinsically bursting CA1 pyramidal cells. Here we have differentiated between two types of bursting phenotypes, namely, bursting in response to threshold-straddling excitatory current pulses (low-threshold bursting), and bursting only in response to suprathreshold stimuli (high-threshold bursting). Low-threshold bursting prevailed in 46.5% of SE-experienced neurons sampled 1-4 weeks after pilocarpine-SE, but was rarely seen in control neurons (1.9%). As previously shown, it appeared to be driven predominantly by a T-type  $\text{Ca}^{2+}$  current ( $I_{\text{CaT}}$ ) in the apical dendrites. After blocking low-threshold bursting with  $\text{Ni}^{2+}$ , the same neurons still manifested a high-threshold bursting phenotype. Another 40.1% of SE-experienced neurons displayed only a high-threshold bursting phenotype, and the remaining 13.4% of these neurons were nonbursters. Altogether, high-threshold bursting prevailed in 86.6% of SE-experienced neurons, but only in 33.0% of control neurons. Several lines of evidence indicated that high-threshold bursting is driven by persistent  $\text{Na}^{+}$  current ( $I_{\text{NaP}}$ ) at or near the soma. Congruently,  $I_{\text{NaP}}$  was 1.5-fold larger in SE-experienced versus control neurons. We conclude that an increase in  $I_{\text{NaP}}$ , conjointly with an increase in  $I_{\text{CaT}}$ , strongly contributes to the predominance of bursting phenotypes in CA1 pyramidal cells early after pilocarpine-SE, and therefore likely plays a role in the development of a chronic epileptic condition in this TLE model.

### Commentary

Inward sodium current through specific membrane proteins (channels) constitutes the currency of neuronal firing. The transient voltage-dependent sodium current,  $I_{\text{NaT}}$ , with its all-or-none threshold behavior and rapid activation and inactivation, is responsible for the upstroke of the action potential. A smaller but longer lasting sodium current, carried through the same channels, comprises the persistent sodium current ( $I_{\text{NaP}}$ ).  $I_{\text{NaP}}$  is activated in the subthreshold voltage range and serves to augment excitability by adding to other currents that depolarize the cell (1). Though minute by comparison with the transient sodium current (comprising only a small percentage of the peak  $I_{\text{NaT}}$ ),  $I_{\text{NaP}}$  does not inactivate and persists for hundreds of milliseconds; these biophysical features allow the depolarization engendered by  $I_{\text{NaP}}$  to mediate more sustained neuronal excitation. For example, owing to its long-duration kinetics and activation at voltages traversed during interspike intervals in trains of action potentials,  $I_{\text{NaP}}$  lowers the threshold for action potential generation, sustains repetitive firing, and enhances depolarizing synaptic currents (2). These excitability enhancing effects of  $I_{\text{NaP}}$  suggest that it can facilitate epileptic burst firing.

$I_{\text{NaP}}$  is present in neurons in a wide variety of brain areas and across mammalian species; it has emerged as a critical player in the modulation of neuronal firing in both normal and pathological states (3). Mutations in genes coding for sodium channel subunits have been identified in several epilepsy syndromes, including Dravet syndrome and generalized epilepsy with febrile seizures plus (4, 5). Although many other molecular mechanisms are involved in epilepsies caused by sodium channel mutations (e.g., loss-of-function of *SCN1A* (4,5)), some epilepsy patients with gain-of-function mutations in the sodium channel gene *SCN1A* (6), and epileptic mice with *Scn2a* mutations (7), have been reported to express increased  $I_{\text{NaP}}$  as a pathophysiological consequence. Furthermore, a growing number of antiepileptic drugs appear to function, at least in part, by reducing  $I_{\text{NaP}}$  (8, 9).

Here, Chen and colleagues expand the potential roles of  $I_{\text{NaP}}$  to acquired epilepsy, in this case, temporal lobe epilepsy (TLE). Using a well-recognized animal model of TLE, induced by pilocarpine, the authors examine the role of  $I_{\text{NaP}}$  in the bursting behavior of hippocampal CA1 pyramidal neurons. Under normal conditions, CA1 neurons do not burst. However, in chronic epilepsy models, many CA1 neurons exhibit bursting behavior, that is, generate multiple action potentials in response to a stimulus that ordinarily evokes a single spike. The investigators previously demonstrated that low-threshold calcium current ( $I_{\text{CaT}}$ ), localized in the apical dendrites, contributes to inducible bursting in CA1 neurons, because

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blocking this current (with nickel ions,  $\text{Ni}^+$ ) or studying it in  $I_{\text{CaT}}$  knockout mice reduces but does not completely eliminate burst firing. Bursting in a proportion of CA1 neurons was not affected by  $I_{\text{CaT}}$  inhibition (10, 11). The present experiments establish that  $I_{\text{NaP}}$  contributes the missing piece—high-threshold bursting in epileptic CA1 neurons is abolished by blocking somatically localized  $I_{\text{NaP}}$ .

Chen and colleagues made rats epileptic by intraperitoneal injection of pilocarpine. This treatment caused acute status epilepticus in most rats; the status was stopped after 2 hours by benzodiazepine administration. Some rats received pilocarpine but did not develop status epilepticus; these animals served as controls. One to 4 weeks after status epilepticus, rats developed spontaneous recurrent seizures, the defining characteristic of chronic epilepsy. When slices of hippocampus from these rats were studied electrophysiologically, a large proportion of CA1 pyramidal neurons from rats that experienced status epilepticus demonstrated bursting properties. Bursting neurons could be divided into two types: high-threshold or low-threshold, depending upon the amount of current required to elicit bursting. Many more bursting neurons were found among CA1 cells from status epilepticus-exposed rats than from controls. About 46% of CA1 neurons in status epilepticus-exposed rats demonstrated low-threshold bursting, compared to only 2% of neurons from control rats. When this low threshold bursting was abolished by  $\text{Ni}^+$  application, these neurons retained the ability to burst in response to a larger stimulus (hence “high threshold” bursting). In addition, many other CA1 neurons that did not burst in response to low threshold stimulation did so to higher stimulation. Altogether, about 86% of status-epilepticus-exposed CA1 neurons demonstrated high threshold bursting. As described above, the authors previously showed that low-threshold bursting was due to activation of apical calcium current; here, they demonstrate that somatically generated  $I_{\text{NaP}}$  also contributed to the bursting behavior in status epilepticus-exposed CA1 cells. Furthermore,  $I_{\text{NaP}}$  was 1.5-fold larger in CA1 neurons from rats that underwent pilocarpine-induced status epilepticus.  $I_{\text{NaP}}$ -induced bursts were eliminated with application of the sodium channel blocker tetrodotoxin, whereas maneuvers to block  $I_{\text{CaT}}$  (including  $\text{Ni}^+$  application or severing the distal dendrites where  $I_{\text{CaT}}$  is concentrated) did not reduce  $I_{\text{NaP}}$  bursts at the soma. Up-regulation of  $I_{\text{NaP}}$  could not be explained by shifts in the voltage-dependence of its activation.

These findings suggest that at least two currents contribute to CA1 neuron bursting behavior following pilocarpine-induced status epilepticus in rats:  $I_{\text{NaP}}$  and  $I_{\text{CaT}}$ . These cationic inward currents augment depolarization near threshold and thereby enhance neuronal firing. Though the enhanced persistent sodium current fades about 1 month following status epilepticus, it might orchestrate hyperexcitable network firing and contribute to creation of an enduring epileptic condition. Though it might be premature to suggest that a drug could be designed to target  $I_{\text{NaP}}$ , this remains an

enticing possibility. The involvement of other ionic currents that affect neuronal excitability, for example,  $I_{\text{h}}$ ,  $I_{\text{M}}$ ,  $I_{\text{A}}$ ,  $I_{\text{K(Ca)}}$ , should also be considered in the conversion of CA1 neurons from regular-firing to burst-firing. All of these currents are differentially distributed along the neuronal surface, operate at various membrane potentials, and exhibit a specific developmental profile. A pro-epileptic action of enhanced  $I_{\text{NaP}}$  is supported by recent work using the pilocarpine model of chronic TLE reports enhancement of  $I_{\text{NaP}}$  in dentate granule cells, which provides a mechanism by which these neurons generate action potentials with aberrant timing in relationship to excitatory postsynaptic potentials (12). Together, the *interplay* of ionic conductances governs intrinsic cellular excitability, the dysfunction of which can contribute to the hyperexcitability underlying epilepsy.

by Carl E. Stafstrom, MD, PhD

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