

COMMENTARY

Fast inactivation of Nav1.3 channels by FGF14 proteins: An unconventional way to regulate the slow firing of adrenal chromaffin cells

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Action potentials (APs) in neurons and neuroendocrine cells are sustained by the transient activation of voltage-gated sodium (Nav) channels during cell depolarization (Hille, 2001). Although many different channels contribute to shape the APs, set the frequency, and determine the mode of AP firing (tonic firing versus slow bursts), Nav channels (Nav1.1–Nav1.9) play a major role in these events (Bean, 2007). To effectively contribute to AP firing, Nav channels activate and inactivate rapidly and then recover from fast inactivation to allow for subsequent APs (Hodgkin and Huxley, 1952). Recovery from fast inactivation is a key mechanism which sets the refractory period during which an excitable cell acquires an increased threshold for eliciting an AP and is unable to trigger full amplitude APs (Goldin, 2003; Ulbricht, 2005). Recovery from fast inactivation is usually sufficiently rapid for many Nav channels to maintain repetitive firing at high frequencies (>50 Hz) with little decay in AP amplitude. However, recovery from fast inactivation can occur also at lower rates, with time constants of 50–400 ms (“slow recovery”) that are significantly shorter than those of conventional “slow inactivation” developing very slowly (several seconds) when cells are held at negative resting potentials (Ulbricht, 2005). Slow recovery from fast inactivation involves a distinct molecular mechanism responsible for use-dependent Nav availability, which affects the firing frequency during repetitive cell activity (Milescu et al., 2010; Goldfarb, 2012). This new slow recovery process, first described for the Nav channels of cerebellar granule neurons (Goldfarb et al., 2007), has rapid onset and competes with the conserved IFM motif on the DIII–DIV linker for access within the pore to inactivate the open channel (red oval in Fig. 1 A). Regulatory proteins belonging to the family of intracellular fibroblast growth factor homologous factors (iFGFs; blue/white ovals) mediate the slow recovery from fast inactivation that lasts hundreds of milliseconds (black arrow). The mechanism is now denoted as “long-term inactivation” (Dover et al., 2010; Barbosa and Cummins, 2016) to distinguish it

from the slow (or ultraslow) inactivation, which exhibits such slow onset kinetics that only in unusual circumstances will it influence Nav availability during normal firing (Ulbricht, 2005; Silva, 2014).

The potential role(s) of long-term inactivation in regulating Nav availability during cell firing remains unclear. Particularly, it is not yet clear whether this phenomenon may include all or only some of the neuronal and neuroendocrine identified Nav channels, nor is it clear how the long-term inactivation pathway interferes with the fast onset and fast recovery of inactivation (up and down red arrows in Fig. 1 A). In neurons, this is of particular relevance given the coexistence and different localization of various Nav channels (Nav1.1–Nav1.3, Nav1.6–Nav1.9) at the soma, proximal dendrites, and axonal initial segments that may be regulated by iFGF-mediated long-term inactivation, as was shown for the Nav1.6 channel of hippocampal pyramidal neurons (Venkatesan et al., 2014).

This point is also important for neuroendocrine cells, such as the spontaneously slow-firing chromaffin cells (CCs) of the adrenal medulla, which predominantly express TTX-sensitive neuronal Nav1.3 and Nav1.7 channels (Lingle et al., 2018; Carbone et al., 2019). Rodent CCs undergo spontaneous or squared-pulse-evoked APs that, depending on Nav availability, will display spike trains (0.5–10 Hz) or bursts of APs (Vandael et al., 2015; Guarina et al., 2017; Milman et al., 2021). Interestingly, the Nav channels of mouse CCs recover from fast inactivation with two exponential components with short and long time constants (Vandael et al., 2015). The time course of the slow component is comparable to the recovery from long-term inactivation in neurons (50–400 ms), suggesting that the Nav channels in mouse CCs may undergo the same iFGF-dependent slow recovery from fast inactivation that regulates mouse CCs excitability and catecholamine (CA) release during cell activity.

In an earlier issue of the *Journal of General Physiology*, two articles by Chris Lingle’s laboratory report novel findings about

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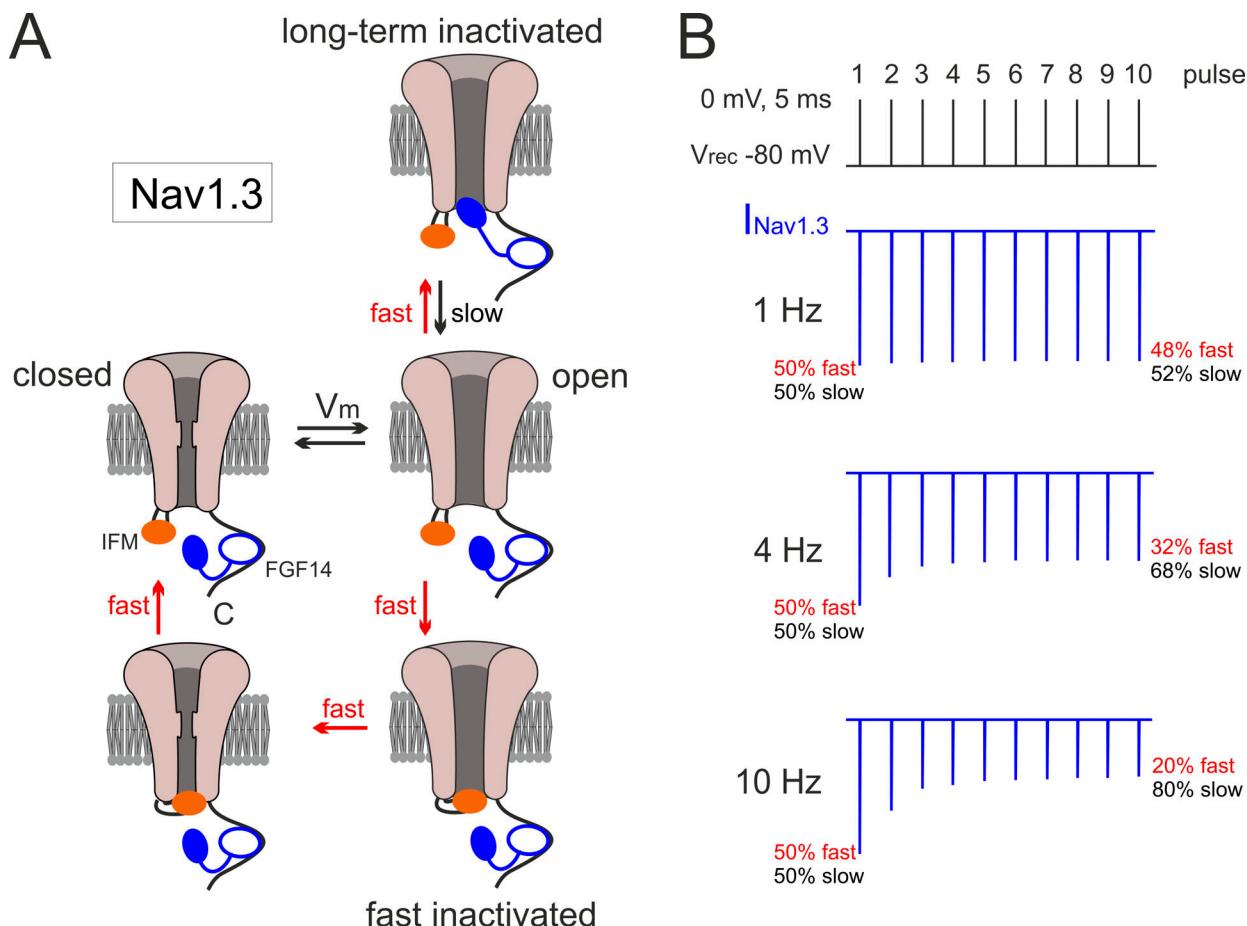


Figure 1. Schematic model for the Nav1.3/FGF14 protein interactions that regulate fast and slow recovery from inactivation and determine Nav availability during pulse trains of varying frequency in rodent chromaffin cells. (A) A simplified schematic diagram of Nav1.3 channel transitions between closed, open, fast, and long-term inactivated states derived from Dover et al. (2010), Milescu et al. (2010), Venkatesan et al. (2014), and the two articles from Martinez-Espinosa et al. (2021a, 2021b). The endogenous IFM inactivation particle in the DIII–DIV cytoplasmic loop (red oval) and the N terminus of the FGF14 protein (blue oval), with its core domain (white oval) tethered to the C terminus of the channel, compete for access within the pore to inactivate the open channel during step depolarization. The two inactivation particles compete for docking within the open pore (fast and long-term inactivated states). The onset of fast and long-term inactivation is comparably fast (a few milliseconds; up and down red arrows in right panels). Recovery from long-term inactivation is slow (50–400 ms) and may occur while the channel is open (black arrow) or closed (not shown). Recovery from fast inactivation is fast and proceeds through the closed state of the channel (horizontal and up red arrows; Kuo and Bean, 1994). The closed and fast inactivated states preceding the two indicated to the left are not shown for simplicity (see Goldfarb, 2012). **(B)** Nav1.3 currents (blue traces) recorded from mouse chromaffin cells during voltage-clamp commands with a 10-pulse train of increasing frequency. Nav current amplitudes are drawn after having interpolated the data of Figs. 8, 10, and S1 of Martinez-Espinosa et al. (2021a). Steps of 5 ms to 0 mV from -80 mV holding potentials (V_h) were applied at 1, 4, or 10 Hz. Nav1.3 current amplitudes decrease progressively during the 10-pulse trains. At 1 Hz the amplitude attenuation is nearly detectable, while at 10 Hz it is remarkable. The percentage of occupancies in the fast and slow recovery pathways calculated by Martinez-Espinosa et al. (2021a, 2021b) are indicated in red (fast recovery) and black (slow recovery). After terminating the first depolarizing step, Nav channels are equally distributed (50%) in both the fast and slow pathway. With increasing frequency, Nav availability is strongly attenuated. Nav channels accumulate in the slow recovery pathway during the pulse train: 52% at 1 Hz, 68% at 4 Hz, and 80% at 10 Hz.

the slow recovery pathway from Nav channel inactivation in rodent CCs, thereby shedding light on a FGF14-mediated regulation of long-term Nav1.3 channel inactivation that helps in defining the complex AP firing modes of CCs (Martinez-Espinosa et al., 2021a; Martinez-Espinosa et al., 2021b). The two articles together clarify an enduring unresolved issue concerning the Nav channel isoforms expressed in rat and mouse CCs and offer new evidence to the mechanisms that regulate the iFGF-mediated slow recovery from Nav1.3 channels inactivation. This allows for extending the concept of long-term inactivation to an increasing number of Nav channels and excitable cell types (Goldfarb et al., 2007; Laezza et al.,

2009; Dover et al., 2010; Goldfarb, 2012; Venkatesan et al., 2014).

Why study the mechanisms of slow recovery from fast Nav inactivation in rodent CCs?

Several groups, including Lingle's laboratory, have been pioneers in identifying the origins of spontaneous and evoked AP firings in rat and mouse CCs (Lingle et al., 2018). In their columnar arrangement in intact adrenal glands, CCs are effectively regulated by the splanchnic nerve activity ("neurogenic control"). Release of ACh from the sympathetic nerve terminals stimulates nicotinic and muscarinic receptors on CCs, which

leads to increased AP firing, opening of voltage-gated calcium channels (Cav), Ca^{2+} entry through open Cav channels, and Ca^{2+} -dependent release of CAs into the bloodstream to prepare different body organs for the fight-or-flight response (García et al., 2006). CCs express a multitude of voltage-gated Nav, Cav, and Kv channels that, together with BK, SK, and TASK channels, allow for generating spontaneous “neuron-like” tonic or burst firing patterns even when CCs are isolated from the gland and kept in primary culture (Lingle et al., 2018; see Table 1 in Carbone et al., 2019). Under these conditions, CCs can drive a sustained “nonneurogenic” release of CAs upon stimulation that mimics the body’s response to various secretagogues (histamine, low pH, hypoxia, and hyperkalemia; Wallace et al., 2002; Inoue et al., 2008; Salman et al., 2013; Guarina et al., 2017).

Neurogenic and nonneurogenic CA release is regulated by AP firing and are therefore strictly controlled by Nav availability. Yet, the Nav channels of rat and mouse CCs possess interesting unsolved peculiarities. First, rat CCs have been reported to express Nav1.7 (SCN9A) channels (Wada et al., 2008), though the Nav1.3 isoform (SCN3A) is the predominant species expressed in mouse CCs (Vandael et al., 2015), and the Nav currents in rat and mouse CCs possess steady-state inactivation properties consistent with a single Nav component (Lou et al., 2003; Vandael et al., 2015). This suggests that Nav currents in CCs are carried by either Nav type or by a mixture of Nav1.3 and Nav1.7 channels with similar voltage-dependent activation and inactivation gating (Lou et al., 2003; Vandael et al., 2015). The presence of a single type of rapidly inactivating TTX-sensitive Nav current in rodent CCs therefore greatly simplifies the analysis of fast and slow recovery from rapid inactivation undertaken by Martinez-Espinosa et al. (2021a, 2021b) in the earlier issue of JGP. Second, although multiple channels may contribute to AP adaptation in CCs (Vandael et al., 2012; Martinez-Espinosa et al., 2014), use-dependent changes in Nav availability appears as a possible mechanism to regulate frequency, amplitude, and mode of AP firing (Vandael et al., 2015). CCs respond to constant current injection with trains of APs whose frequencies hardly exceed 10–15 Hz (Solaro et al., 1995; Vandael et al., 2012; Martinez-Espinosa et al., 2014; Carbone et al., 2019). During such sustained depolarization, CCs typically exhibit a progressive decline in AP frequency and amplitude (adaptation) due mainly to a cumulative increase of SK currents between APs (Vandael et al., 2012). Block of SK channels by apamin increases AP frequency and AP decline, suggesting that Nav availability changes drastically with AP frequency and contributes to AP adaptation in CCs.

Who are the actors of Nav channels long-term inactivation in CCs?

The two articles by Martinez-Espinosa et al. (2021a, 2021b) in the earlier issue shed new light on many of the unsolved questions about CCs’ excitability and bring new evidence concerning the role of Nav channels in three key aspects of the phenomenon. First, what is the main Nav channel isoform expressed in rodent CCs? Second, does the on-off kinetics of long-term inactivation develop independently of fast recovery and play a role on AP firing adaptation? And third, which are the intracellular

molecular components that interfere with the endogenous fast inactivation to promote the slow recovery from inactivation? Using rat CCs and properly designed voltage clamp paired-pulse protocols, the authors show first that recovery from Nav channel inactivation exhibits two exponential components of similar magnitude but with short (3–30 ms) and long time constants (50–400 ms; Martinez-Espinosa et al., 2021a). Both processes are complete even after brief depolarizing pulses to 0 mV (5 ms) that fully inactivate the channels. Nav channels enter into the fast or slow recovery paths via largely independent (competing) inactivation mechanisms with similar onset time and independent of voltage (red arrows in Fig. 1 A). During trains of brief depolarization, the two recovery paths are largely independent but develop with time constants that differ by an order of magnitude. The fraction of Nav channels in the fast recovery state recovers fully, whereas the fraction in the slow recovery state recovers only partially during repetitive stimulation. Depending on the frequency of the pulse train (1–10 Hz), the slow recovery pathway will cause Nav channels to accumulate in the long-term inactivated state, reducing in a use-dependent manner the Nav current amplitude (Nav availability) during high-frequency pulse trains (10 Hz). Fig. 1 B, derived from data in Martinez-Espinosa et al. (2021a), shows how inward Nav1.3 currents decrease progressively during trains of 10 pulses at 1, 4, and 10 Hz and how the percentage of slowly recovering Nav channels increases at the end of the train with increasing frequency (52% at 1 Hz, 68% at 4 Hz, and 80% at 10 Hz). In other words, the dual independent inactivation pathways (fast and slow) dynamically regulate Nav availability by promoting use-dependent accumulation in the slow recovery pathway. It appears as if Nav channels effectively “measure” the frequency of APs and convert changes in AP frequency into Nav current availability (up to 80% at 10 Hz at -80 mV holding potential; see Fig. 1 B).

In the second article, taking advantage of the existence of Nav1.3 (Nassar et al., 2006) and FGF14 (Wang et al., 2002) KO mice, Martinez-Espinosa et al. (2021b) identify the molecular components that regulate long-term inactivation of Nav channels in mouse CCs. They first show that nearly half of Nav1.3 KO CCs do not possess TTX-sensitive fast-inactivating Nav currents; the remaining cells exhibit Nav currents of smaller size compared with WT cells. This agrees with quantitative RT-PCR data, which support the existence of a dominant fraction of the SCN9A α -subunit (Nav1.3) and a minor contribution of the SCN9A α -subunit (Nav1.7) in mouse CCs (Vandael et al., 2015), proving unambiguously that Nav1.3 is the major isoform contributing to Nav currents in mouse CCs. This challenges the enduring view that Nav1.7 is the dominant sodium channel in neuroendocrine cells. The authors also provide evidence that rat CCs express Nav1.7 and Nav1.3 channels in a ratio of ~3:1, suggesting a partial contribution of Nav1.3 channels to the total Nav currents also in rat CCs. Thus, the Nav1.3 channel, which is mainly expressed in central and sensory neurons (Cummins et al., 2001; Catterall et al., 2005), appears to also be the main Nav channel responsible of CCs electrical activity. Another central finding of the article is the identification of the molecular entities regulating the slow recovery from fast inactivation. The authors show that deletion of FGF14 proteins in FGF14 null mice causes a marked

reduction in the number of mouse CCs exhibiting the slow component of recovery from fast inactivation. Although the onset of fast inactivation is more rapid than in WT CCs, deletion of the slow recovery component preserves the fast recovery process, confirming that the two processes are largely independent. Finally, the authors show that the use-dependence of Nav current reduction during trains of brief stimuli in WT cells is completely abolished in FGF14 null cells, demonstrating the key role of FGF4-mediated inactivation in regulating Nav availability during cell firing.

Present and future perspectives

Together, the two articles show unequivocally that mouse and rat CCs express TTX-sensitive fast inactivating Nav1.3 channels, and that their slow recovery from fast inactivation sets the fractional Nav availability that regulates the frequency and size of spontaneous and evoked AP firing. To accomplish this, Nav1.3, like other Nav isoforms (Goldfarb, 2012; Navarro et al., 2020), interacts with intracellular FGF subunits to drive the channel during fast inactivation into a long-term inactivation state, and the kinetics of this process sets Nav availability and AP firing. The present findings on the recovery of Nav channels from inactivation allow for more precise interpretation of the recent reports on the different firing modes and secretory activity of rodent CCs summarized into two recent reviews (Lingle et al., 2018; Carbone et al., 2019). There are, however, still open questions on how Nav availability may contribute to the transition of CCs from spontaneously firing to slow wave bursting (Wallace et al., 2002; Martinez-Espinosa et al., 2014; Vanda et al., 2015; Guarina et al., 2017; Milman et al., 2021). As suggested by Martinez-Espinosa et al. (2021b), this might be solved using dynamic clamp experiments to evaluate the impact of conventional fast inactivation versus dual pathway fast inactivation on patterns of CC firing.

It is also worth underscoring that these two articles in *JGP* go beyond the role of the Nav1.3/FGF14 partnership in regulating neuroendocrine cells electrical activity. They provide a general view on how Nav1.3, like other Nav channels (Nav1.2, Nav1.5, and Nav1.6), could interact with various iFGF proteins in central neurons and other excitable cells to act as a molecular “leaky integrator” that detects APs, measures the frequency, and regulates neuronal firing to provide modulatory signals to numerous brain functions (Navarro et al., 2020).

Acknowledgments

Olaf S. Andersen served as editor.

This work was supported by residual funds of the Telethon Foundation (grant no. GGP15110) to Emilio Carbone.

The author declares no competing financial interests.

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