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REVIEW

Persistent sodium currents in neurons: potential mechanisms and pharmacological blockers

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Abstract

Persistent sodium current (I_{NaP}) is an important activity-dependent regulator of neuronal excitability. It is involved in a variety of physiological and pathological processes, including pacemaking, prolongation of sensory potentials, neuronal injury, chronic pain and diseases such as epilepsy and amyotrophic lateral sclerosis. Despite its importance, neither the molecular basis nor the regulation of I_{NaP} are sufficiently understood. Of particular significance is a solid knowledge and widely accepted consensus about pharmacological tools for analysing the function of I_{NaP} and for developing new therapeutic strategies. However, the literature on I_{NaP} is heterogeneous, with varying definitions and methodologies used across studies. To address these issues, we provide a systematic review of the current state of knowledge on I_{NaP}, with focus on mechanisms and effects of this current in the central nervous system. We provide an overview of the specificity and efficacy of the most widely used I_{NaP} blockers: amiodarone, cannabidiol, carbamazepine, cenobamate, eslicarbazepine, ethosuximide, gabapentin, GS967, lacosamide, lamotrigine, lidocaine, NBI-921352, oxcarbazepine, phenytoine, PRAX-562, propofol, ranolazine, riluzole, rufinamide, topiramate, valproaic acid and zonisamide. We conclude that there is strong variance in the pharmacological effects of these drugs, and in the available information. At present, GS967 and riluzole can be regarded *bona fide* I_{NaP} blockers, while phenytoin and lacosamide are blockers that only act on the slowly inactivating component of sodium currents.

Keywords Persistent sodium current · Slow inactivation · Epilepsy · Sodium channel blocker · Neuron

Abbreviations

CBD	cannabidiol
CNS	central nervous system
CRMP-2	collapsin response mediator protein 2
DRG	dorsal root ganglion
EC_{50}	half-maximal effect concentration
EC_{max}	maximal effect size
EPSP	excitatory postsynaptic potential
hERG	human Ether-a-go-go-Related Gene
HP	holding potential
IC_{50}	half-maximal inhibitory concentration
I_{NaP}	persistent sodium current
I_{NaT}	transient sodium current
IPSP	inhibitory postsynaptic potential
n.s.	not significant
TTX	tetrodotoxin
$V_{0.5}$	midpoint voltage
VGSC	voltage-gated sodium channels

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Introduction

Voltage-gated sodium current is a fundamental component of excitable cells in all animals with active movement. It is mediated by sodium-selective cation channels, which appeared in evolution before the origin of nervous systems [137]. In mammals, the main (α) subunit of voltage-gated sodium channels (VGSC) consists of 4 identical motives, each of which containing 6 transmembrane segments, a pore-forming loop and a voltage sensor in the fourth membrane-spanning helix. A core feature of voltage-gated sodium currents is their fast inactivation following activation by membrane depolarization [91]. In most recordings, however, a small portion of the sodium current does not vanish within a few milliseconds

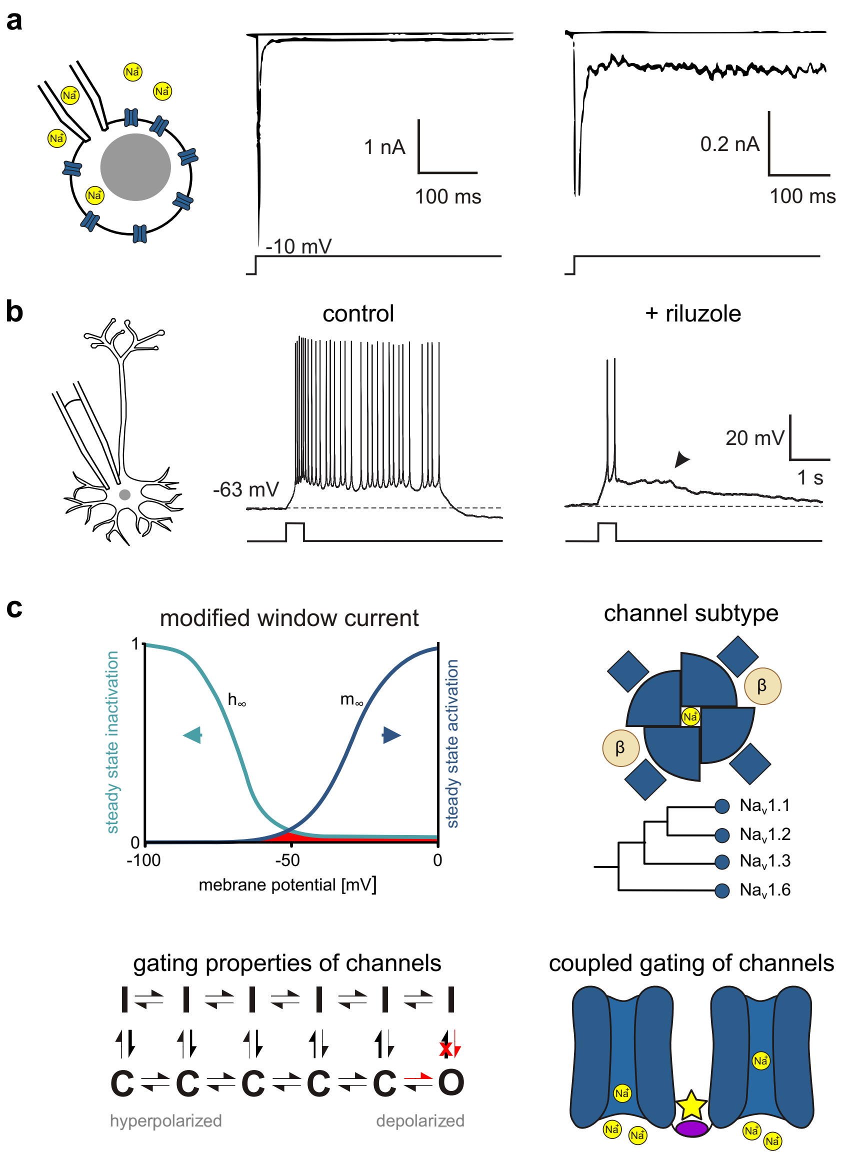

Fig. 1 Physiological characterization of persistent sodium current. **a** Persistent sodium current (I_{NaP}) is a small fraction of isolated voltage-dependent sodium current, typically measured with voltage clamp in transfected cells or dissociated neurons (left). I_{NaP} (right) is the persisting inward current component following a transient fast Na^+-mediated inward current (middle). Adapted from French et al. [70] with permission. **b** An example for I_{NaP}-dependent bursting behaviour recorded in current clamp mode. I_{NaP} contributes to neuronal bursting during a depolarizing current step as well as to the followed plateau potential (indicated by arrowhead). Right panel shows response of neuron to depolarizing current step after bath application of I_{NaP} blocker riluzole (10 µM). Adapted from Sheroziya et al. [197] with permission. **c** Schematic diagrams of potential mechanisms underlying I_{NaP}: the modified window currents hypothesis (top left) claims that I_{NaP} (red) emerges in the 'window' between activation (m_∞) and inactivation (h_∞) of sodium currents in the Hodgkin-Huxley-model, where h∞ approaches a small positive value as $V \to \infty$ [162, 210]. Arrows indicate potential mechanisms of I_{NaP} block by shift of activation to the right or left shift inactivation. A second hypothesis focuses on gating properties of sodium channels (bottom left). Taddese and Bean [216] assume a preference for inactivated states depending on membrane potential (thick arrows). The 'modal gating' hypothesis assumes a (temporary) failure of inactivation that allows inactivated channels to open (red). Another hypothesis claims that I_{NaP} depends on different channel subunit isoforms (top right; scheme of an α subunit with complementary β subunits and a phylogenetic tree of neuronally expressed α subunits). Finally, the supramolecular gating hypothesis (bottom right) argues that interactions between single sodium channels alters their gating kinetics (indicated by star)

(Fig. 1A). This persistent sodium current component (I_{NaP}) has been defined as a 'non-inactivating or slowly inactivating sodium current' [49, 119]. Note that, although the name of the current contains the word 'persistent', slowly inactivating components are explicitly included. Thus, an unambiguous identification of I_{NaP} requires the demonstration of a non- or slowly inactivating component in VGSC-mediated currents.

I_{NaP} is thought to contribute to multiple cellular functions. It regulates the excitability of neurons [15, 69, 121, 130] and, specifically, of axons [160, 213], it amplifies excitatory and inhibitory postsynaptic potentials (EPSP/IPSP) [38, 72, 174, 211, 212, 234], and it contributes to pacemaking [27, 116, 120, 229], resonance [99, 233, 249], bursting behaviour in adult [17, 214] and immature neurons [196, 197, 201, 220], place cell tuning [95] and network oscillations [114]. An example for I_{NaP}-dependent bursting behaviour in immature entorhinal cortex neuron is shown in Fig. 1B. I_{NaP} is up-regulated in several disorders, underlining its clinical importance and therapeutic potential. These pathophysiological situations include hypoxia [86, 94], demyelination [85, 225], neurogenic pain [126], paroxysmal extreme pain disorder [63], temporal lobe epilepsy [235], monogenetic epileptic syndromes [139, 206, 239], neurodegeneration [103, 168, 173, 178, 199], hemiplegic migraine [20, 40], and spasticity following traumatic brain or spinal cord injury [32, 136]. I_{NaP} has been described to increase with aging [140], and it is acutely modulated by protein kinase C [4, 14, 67], G-protein subunits [141, 143], acetylcholine [156, 248], dopamine [79, 80, 152] and endogenous polyamines [65, 183]. These modulations may be of importance for the effects of drugs used in neurological or psychiatric disorders, e.g. substances affecting cholinergic or dopaminergic transmission.

Pharmacological blockers of persistent sodium current allow assessing its function in physiological experiments on living animals, brain slices, or single cells (in the latter, the current component can also be eliminated by the biophysical approach of dynamic clamp [210]). More importantly, blockers of I_{NaP} with favourable safety profile may be efficient drugs in the different clinical conditions listed above. However, there is no established standard for the use and validation of I_{NaP} blockers in different laboratory preparations, experiments on living animals or clinical treatment of humans. Previous reviews have already established that there is a large range of putative I_{NaP} blockers [206, 239], in addition to the even wider range of global sodium channel blocking substances [133, 200]. We will provide an overview of present knowledge on their selectivity for I_{NaP}, their potency, and their specific effects on different kinetic properties of sodium channels. The review shall provide an up-to-date basis for experimental and translational work on this important regulator of cellular excitability. It will also highlight some conceptual and semantic problems with the concept of 'persistent sodium currents', which are reflected in the heterogeneity of protocols used to study I_{NaP}.

I_{NaP} – Characteristics and Underlying Mechanisms

The mechanisms underlying persistent sodium currents are not completely understood and are, most likely, heterogeneous. Here, we will briefly review the dominant hypotheses about the structural or functional basis for I_{NaP} (Fig. 1C). One potential explanation for the occurrence of I_{NaP} results from the canonical kinetic model of voltage-activated sodium currents, as described in the original Hodgkin-Huxley model. The overlap of steady-state activation and inactivation curves creates a range of potentials where some Na^+ channels are activated while inactivation is not complete. This forms a 'window' of potentials where some sodium current should be present at any time. Modulation of the voltage-dependence of activation or inactivation can alter the size of the window current and, hence, I_{NaP} (see, e.g. the discussion of carbamazepine below). However, French et al. [70] showed that the properties of I_{NaP} are not fully explained by the 'window current'—for example, I_{NaP} conductance increases with more depolarized membrane potentials, while the window current should decrease. In addition, this 'window current' overestimates I_{NaP} in simulations [210]. The contradiction arises partly, because the original Hodgkin-Huxley model does consider activation and inactivation to be independent of each other and assumes complete inactivation with increasing depolarization. Taddese and Bean [216] proposed a modified version of the 'window current' in mammalian neurons. In this model, steady-state inactivation is dependent on steady-state activation [3, 10, 11, 29], resulting in a small remaining current component even at highly positive voltages. This modified window current (Fig. 1C top left) can account for the presence of I_{NaP} at depolarized potentials and has been implemented in computational models [162].

A second approach derives I_{NaP} from complicated gating schemes of sodium channels using more flexible Markov models (Fig. 1C bottom left). Early models, derived from measurements in squid axons, suggested two different open states [41, 46]. Later modifications of these models for mammalian cells assume only one single open state. Persistent opening does then result from one of two alternative mechanisms: i) a preference of more depolarized channels to enter inactivation even when closed [10, 38, 216]; ii) modal gating of sodium channels, which can enter a non-inactivating state with sustained, burst-like openings [5, 171]. It has to be noted that from a kinetic standpoint the Markov model of Taddese and Bean [216] and the modified window current are identical.

The third hypothesis for the mechanism underlying I_{NaP} is the existence of a separate channel subtype with the respective kinetic properties [57]. Indeed, there are nine different known α subunits of VGSC, opening the possibility that I_{NaP} is a property of one or several specific subunits. However, evidence from the last decades supports the idea that many different α subunits can produce I_{NaP}, at least those with strong expression in the brain (for $Na_v1.1$ see [6, 112]; for $Na_v1.2$ see [43, 186]; for $Na_v1.3$ see [60, 215]; and for $Na_v1.6$ see [186, 232]); Fig. 1C top right). Amongst these subunits,

$Na_v1.6$ seems to be responsible for a major portion of I_{NaP} in the central nervous system (CNS) [186]. However, about half of the persistent sodium current remains after selective knockout of $Na_v1.6$ in rat neocortical layer 5 pyramidal neurons, pointing towards the importance of further subunits [115]. Nevertheless, the strong contribution of $Na_v1.6$ may be responsible for the well-known left shift of the activation curve when comparing I_{NaP} to the transient component of sodium current (I_{NaT}) [49, 119]. This shift would result from the biophysical properties of $Na_v1.6$, which activates at more hyperpolarized membrane potentials than Na^+ currents mediated by the other subunits [96] (note that this left shift would increase the window current, see Fig. 1C, top left). This is supported by the right-shift of the activation curve for persistent sodium currents in hippocampal CA1 neurons of mice lacking functional $Na_v1.6$ [182]. Conversely, though, selective knockout of $Na_v1.6$ in cortical pyramidal neurons left the voltage-dependence of activation unchanged [115].

In dorsal root ganglion (DRG) neurons, $Na_v1.8$ and $Na_v1.9$ have been suggested to be responsible for I_{NaP} [119]. These subunits mediate a long-lasting, non-inactivating current component in transduction of sensory signals, which are particularly important for nociceptive stimuli [2]. A special feature of these subunits is their low sensitivity to the sodium channel blocker tetrodotoxin (TTX). Whereas $Na_v1.1$-$Na_v1.4$, $Na_v1.6$ and $Na_v1.7$ can be blocked by nanomolar concentrations of TTX, $Na_v1.8$ and $Na_v1.9$ require millimolar concentrations [1]. However, in measurements of I_{NaP}, TTX-resistant components are frequently regarded as leak current and, hence, subtracted before analysis. This may lead to an underestimation of the role of $Na_v1.8$ and $Na_v1.9$. In any case, it is unlikely that $Na_v1.8$ and $Na_v1.9$ are responsible for I_{NaP} in cortical neurons, as single cell transcriptomics of human and mouse cortex show no expression of both *SCN10A* ($Na_v1.8$) and *SCN11A* ($Na_v1.9$) [90].

The major pore forming α-subunits of sodium channels are complemented by two auxiliary β subunits. There is evidence that the presence of the β4 subunit increases persistent sodium currents, while adding the β1 subunit neutralizes this effect [6]. Knock out of β1 can lead to a paradoxical effect of sodium channel blockers, which then enhance, rather than suppress, persistent sodium current [226].

Finally, recent evidence suggests the existence of coupled gating between different individual voltage-gated sodium channels [44, 101]. This supra-molecular cooperativity may also be involved in the generation of persistent sodium current (Fig. 1C bottom right) [185].

In summary, there is evidence for several different mechanisms underlying I_{NaP}, including contributions by specific molecular subtypes of α or auxiliary subunits and effects of gating kinetics. None of the explanations seems to account for all observations, and they are not mutually exclusive, suggesting convergence of several mechanisms to the generation of persistent sodium currents in many excitable cells.

Electrophysiological Isolation of I_{NaP}

Different voltage clamp protocols are used to isolate the persistent sodium current components in cells or isolated membranes. One frequently used protocol focusses on the early sodium current component, using depolarizing voltage steps of 50—500 ms duration (Fig. 2A). The inward current that persists at the end of this step is then defined as persistent component (Fig. 1A and 2A). Historically, this protocol did underly the first description of 'late sodium current' in frog axons [57]. This brief 'step pulse' method does, however, not exclude that the apparently persistent component inactivates with a slower time course, which is not visible within the time window of the test pulse.

In addition to the well-known fast inactivation of I_{NaT} with a time constant of < 10 ms, there are intermediate inactivation with a time constant of ~ 100 ms [71] and slow inactivation with a time constant ≥ 1 s [184]. It has to be noted that intermediate inactivation is not generally embraced by the literature and many inactivation protocols with pulse lengths greater than 100 ms likely study both fast and intermediate inactivation [71]. In the following, we will use the terms fast, intermediate and slow inactivation for the three kinetic components described here. In order to test for these additional types of inactivation, especially slow inactivation, long current pulses and repetitive activation steps have been used.

A simple option for testing slow inactivation employs very long stimuli to test whether activation of sodium current is impaired after them in comparison to before. A typical protocol for this purpose consists of three steps (Fig. 2B): First, a long (1 – 30 s) depolarizing pulse (e.g. -30 mV) from hyperpolarized potentials, then a brief (0.5–1 s) recovery pulse to hyperpolarized potentials and finally a short (15 ms) test pulse to a depolarized potential (e.g.—30 mV; see [92, 166, 195]). In theory, the recovery pulse allows fast, but not slow, inactivated channels to recover from inactivation. The test pulse then determines this fraction of channels, such that the slowly inactivated fraction can be calculated (Fig. 2B). We will call this protocol entry into slow inactivation.

Alternatively, the voltage dependence of slow inactivation was examined using a protocol in which long voltage pulses varying between -120 and + 50 mV (1–10 s duration) were followed by a recovery pulse to a hyperpolarized potential (duration 0.5–1 s) and a test pulse (10 ms duration) to depolarized potential (e.g. -10 mV). This protocol allows to analyse the voltage-dependent amount of inactivated channels and offers a fuller picture of the effects of a drug (Fig. 2C). We will call this protocol slow steady state inactivation.

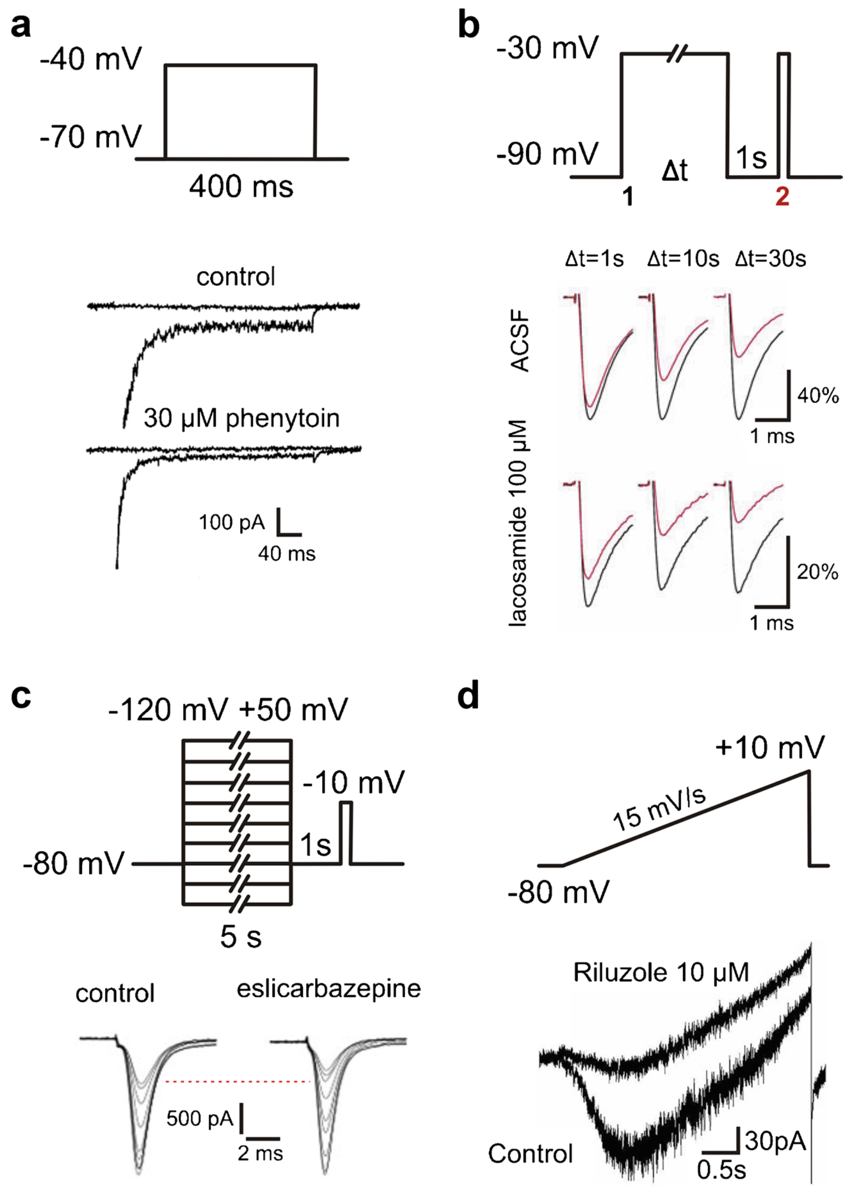

Fig. 2 Different voltage clamp protocols for persistent sodium currents and exemplary drug effects. **a** Voltage step protocol (top) with exemplary current traces showing the effect of 30 µM phenytoin (bottom; adapted with permission from Chao and Alzheimer [42]). **b** Voltage step protocol for entry into slow inactivation with pulses of variable durations (top) with exemplary current traces showing the effect of 100 µM lacosamide (bottom; adapted with permission from Holtkamp et al. [92]). **c** Voltage step protocol for slow steady state inactivation (top) with exemplary current traces showing the effect of 250 µM eslicarbazepine (bottom; adapted with permission from Hebeisen et al. [87]). **d** Voltage ramp protocol (top) with current traces showing the effect of 10 µM riluzole (bottom; adapted with permission from Nakamura et al. [163])

A problem with both approaches lies in the theoretical assumption that there are only fast and slow inactivation: The length of the recovery pulse is inconsistent in the literature and after longer recovery pulses, channels might have already recovered from intermediate inactivation.

If sodium channels were to undergo fast, intermediate and slow inactivation, at some point there would eventually be no current and the term 'persistent' sodium current would obviously be misleading [45]. However, for both of the aforementioned examples, inactivation never fully completes during the depolarizing pulses. Whether or whether not there is then truly persistent, non-inactivating sodium current, remains an open question.

Another more broadly applied approach employs slow voltage ramps, typically with velocities of 10–70 mV/s ranging from -80—+10 mV (Fig. 2D). At these slow depolarization velocities, the transient component I_{NaT} is thought to inactivate, such that the remaining component should isolate I_{NaP}. However, depolarizing a cell at such slow speed may induce some slow inactivation, leading to a potential underestimation of the remaining I_{NaP}. This pitfall explains the hysteresis of slow current components (I_{NaP}) between ascending and descending voltage ramps, a well-known hallmark of persistent sodium current [25]. Different ramp speeds may lead to different resulting currents, including potential distortions of the 'true' I_{NaP}. For example, Fleidervish and Gutnick [64] found that a high depolarization speed of 233 mV/s induced action currents (a Na_V-generated escape phenomenon in voltage clamp recordings) in cortical pyramidal neurons, while slower ramps of 70 mV/s did not. The velocity of voltage ramps may also affect the apparent effectiveness of I_{NaP} blockers, if these have differential effects on different inactivation components. For instance, slower ramp speeds result in larger TTX-susceptible current components and fast ramp speeds underestimate the effect of phenytoin (see Table 1, [45]). Frequently, ramps can be employed in neurons with complex morphology to reduce the space-clamp error [12, 162]. In such experiments, the difference between ramp-induced currents in the absence and presence of TTX is measured and taken as a proxy for I_{NaP}, as long as TTX resistant sodium channels are absent [163]. The validation with TTX is important, as leak, potassium and calcium currents are also being evoked with this protocol. Interpretation of the resulting traces is complex, as exemplified by a study characterizing fluoxetine as an apparent I_{NaP} blocker, based on a ramp protocol that actually displays a clear potassium current block [100]. Altogether, voltage ramp measurements are less precise than step-protocols, but they are easier to implement in complex, extended cells like naturally differentiated neurons in ex vivo brain slices. Slow command voltage changes reduce the space-clamp error and help to avoid voltage-clamp escape phenomena like 'action currents'. Arguably, they are a somewhat more physiological command than a sudden voltage step.

Few papers have studied the effect of slow inactivation protocols on subsequent ramps. While these protocols might be one of the best ways of assessing persistent sodium current, they are very difficult to record and therefore only seldomly employed [45, 123, 242].

Pharmacology of I_{NaP}

Our systematic literature search identified 2586 PubMed results for persistent, slowly or late inactivating sodium currents in combination with blocking, reducing or inhibiting drug actions. Our search term was '(((persistent) OR (slow inactivation) OR (late)) AND (sodium current)) AND ((block) OR (inhibit) OR (reduce))'. Papers were first screened for pharmacological agents with potential clinical applications, i.e. excluding endogenous substances (e.g. acetylcholine), toxins (e.g. saxitoxin), chemicals without present or planned clinical use (e.g. insecticides or dyes) and intracellular agents (e.g. QX-314). After identification of potential blockers, a second literature search was conducted with '(((persistent) OR (slow inactivation) OR (late)) AND (sodium current)) AND *substance name*') for each substance. Papers were considered eligible when appropriate voltage clamp protocols for either non-inactivating or slowly inactivating sodium currents were applied to CNS neurons or to cells expressing $Na_v1.1$, $Na_v1.2$, $Na_v1.3$ or $Na_v1.6$. We will now discuss the actions of the identified substances used in I_{NaP}-related research as listed in Table 1 (see also Fig. 3 for an overview). We will consider their specificity, affinity and different mechanisms of action. Where applicable, clinically relevant information such as blood concentrations and blood–brain-barrier interactions (a major problem for clinical translation) will be included. Concentrations are given as IC_{50} or EC_{50} values, respectively.

Amiodarone

Amiodarone is a type III antiarrhythmic agent typically used for treatment of ventricular and supraventricular arrhythmia. It predominantly inhibits the human Ether-a-go-go-Related Gene (hERG) potassium channel that mediates a delayed rectified outward potassium current and contributes to the repolarization of cardiac myocytes. The IC_{50} for this effect is 9.8 µM [117]. There is only one study that assessed the effects of amiodarone on I_{NaP} in cortical neurons [205]. Here, the authors saw a > 50% inhibition of I_{NaP} with a ramp protocol at a concentration of 10 µM (Table 1). For $Na_V1.5$, the isoform most prevalent in the heart, IC_{50} values were in a similar range [75, 142, 243]. Although amiodarone is a highly lipophilic molecule, its concentration in the brain only reaches 10% of the heart tissue concentration after intravenous administration in the rat [180]. Therefore, it is not suitable for use as an I_{NaP} blocker in neurons in in vivo approaches both in experiments or clinical settings.

Cannabidiol

Besides the well-known hallucinogenic compound tetrahydrocannabinol, *cannabis sativa* contains more than 100 cannabinods including cannabidiol (CBD). CBD has been used as an anti-seizure drug for patients with Dravet syndrome, a severe epileptic encephalopathy resulting from loss-of-function mutants of $Na_v1.1$ [54]. The substance is also known for its anxiolytic and sedative effects [50]. Cannabinoids typically act via the G_i-protein-coupled cannabinoid receptors CB_1 in the brain or CB_2 in peripherereal tissues [58]. CBD, at concentrations of 100 nM, acts as a non-competitive antagonist at CB_1 receptors [222]. It also binds to the serotonin receptor 5-HT1a at the same concentration [188] and activates K_v7 channels with an EC_{50} of 200 nM [255]. Concerning sodium currents, CBD blocks I_{NaP} in step protocols, but seems to be even more efficient in blocking transient, rather than persistent sodium currents (Table 1). For $Na_v1.7$ Huang et al. [98] report preferential block of fast inactivation with slow binding kinetics (see discussion of phenytoin), while for $Na_v1.8$ CBD preferentially blocks slow inactivation [254]. Effects of CBD seem to require rather high concentrations: Ghovanloo et al. [76] report CBD to block the transient component (I_{NaT}) of all sodium channel isoforms with an IC_{50} of around 3 µM, while Hill et al. [89] estimate the IC_{50} of CBD for brain-expressed sodium channels even tenfold higher. However, this might be an artefact of using plastic instead of glass reservoirs and tubing [255]. Based in

Table 1 List of drug effects sorted by studies. Studies included had to be performed on neuronal sodium channels or neurons. Furthermore, they needed to employ either a step protocol or ramp protocol for measuring I_{NaP} or a protocol for slow inactivation. Only voltage clamp protocols were eligible to be included in this list. Whenever possible EC_{50} or IC_{50} values are given. HP: holding potential, n.s.: not significant, $V_{0.5}$:midpoint voltage, IC_{50}: half-maximal inhibitory concentration, EC_{50}: half-maximal effect concentration, EC_{max}: maximal effect size

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
Amiodarone					
10 µM	rat neocortical neurons	60 mV/s ramp	-77% peak amplitude	not assessed	Spadoni et al. [205]
Cannabidiol					
1 µM	HEK293 cells expressing human $Na_v1.1$	step pulse 180 ms	n.s. effect on amplitude	n.s. shift of midpoint voltage ($V_{0.5}$) of steady state inactivation 500 ms	Patel et al. [170]
	HEK293 cells expressing human $Na_v1.6$	step pulse 180 ms	n.s. effect on amplitude	n.s. shift of $V_{0.5}$ of steady state inactivation 500 ms	
	rat striatal neurons	step pulse 180 ms	-36% peak amplitude	4 mV left shift of steady state inactivation 500 ms	
3 µM	HEK cells expressing a human $Na_v1.6$ mutation	step pulse 100 ms	IC_{50} 6 µM	-50% amplitude at holding potential (HP) -60 mV (IC_{50} 3 µM)	Ghovanloo et al. [76]
1 µM	HEK cells expressing human $Na_v1.2$	step pulse 50 ms	n.s. effect on peak amplitude	-22% average current density; n.s. effect on peak current density n.s. shift of $V_{0.5}$ of steady state inactivation 500 ms	Mason and Cummins [150]
Carbamazepine					
10 µM	HEK293 cells expressing human $Na_v1.3$	step pulse 100 ms	-20% amplitude (EC_{50} 16 µM E_{max} -46%)	3 mV left $V_{0.5}$ of steady state inactivation 500 ms (EC_{50} 14 µM E_{max} 8 mV)	Sun et al. [215]
100 µM	HEK293 cells expressing $Na_v1.3$	entry into slow inactivation 10 s	IC_{50} 406 µM	n.s. effect on amplitude at holding potential (HP) -120 mV (IC_{50} 2464 µM)	Sheets et al. [195]
1 mM		slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	19 mV $V_{0.5}$ left shift of steady state inactivation 500 ms	
100 µM	Scn1b wildtype mouse dissociated dentate gyrus neurons	50 mV/s ramp	-48% peak amplitude 8 mV $V_{0.5}$ left shift	-32% peak amplitude (HP -100) 8 mV $V_{0.5}$ left shift of activation	Uebachs et al. [226]
100 µM	N1E-115 neuroblastoma cells	slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	not assessed	Niespodziany et al. [166]
250 µM	N1E-115 neuroblastoma cells	entry into slow inactivation 30 s slow steady state inactivation 5 s	n.s. effect on amplitude n.s. effect on $V_{0.5}$	n.s. $V_{0.5}$ left shift of activation -24% amplitude (HP -80 mV; HP -100 mV IC_{50} 822 µM; HP -80 mV IC_{50} 399 µM; HP -60 mV IC_{50} 109 µM) 7 mV $V_{0.5}$ left shift of steady state inactivation 500 ms	Hebeisen et al. [87]
100 µM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms	-56% peak amplitude (IC_{50} 77 µM)	-13.8% peak amplitude (IC_{50} 2307 µM, HP -120 mV)	Kahlig et al. [111]
		entry into slow inactivation 8 s	-63% peak amplitude (IC_{50} 44 µM)		

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
30 µM	Neuro-2a cells	500 mV/s ramp	-22% peak amplitude	-13% peak amplitude (HP -100 mV, IC_{50} 56 µM)	Wu et al. [245]
Cenobamate					
100 µM	rat CA3 pyramidal neurons	step pulse 150 ms	-74% amplitude (IC_{50} 53 µM)	-5% peak amplitude (HP -80 mV; IC_{50} > 500 µM)	Nakamura et al. [163]
		15 mV/s ramp	-68% peak amplitude (IC_{50} 53 µM)	6 mV $V_{0.5}$ left shift of steady state inactivation 500 ms (EC_{50} 48 µM EC_{max} 10 mV)	
		entry into slow inactivation 8 s	-68% peak amplitude		
100 µM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms entry into slow inactivation 8 s	-56% peak amplitude (IC_{50} 72 µM) IC_{50} 67 µM	amplitude: IC_{50} 1719 µM, HP -120 mV	Kahlig et al. [111]
Eslicarbazepine					
300 µM	Scn1b wildtype mouse dissociated dentate gyrus neurons	50 mV/s ramp	-22% peak amplitude 2 mV left shift of activation	not assessed	Doeser et al. [55]
250 µM	N1E-115 neuroblastoma cells	entry into slow inactivation 30 s slow steady state inactivation 5 s	-41% amplitude 31 mV $V_{0.5}$ left shift	n.s. $V_{0.5}$ shift of activation -6% amplitude (HP -80 mV; HP -100 mV IC_{50} 15,744 µM; HP -80 mV IC_{50} 3106 µM; HP -60 mV IC_{50} 562 µM) n.s. $V_{0.5}$ shift of steady state inactivation 500 ms	Hebeisen et al. [87]
300 µM	rat dissociated dentate granule neurons	entry into slow inactivation 1 s	-4% peak amplitude	-23% peak amplitude (HP -90 mV)	Holtkamp et al. [93]
		entry into slow inactivation 10 s	-8% peak amplitude		
		entry into slow inactivation 30 s	-6% peak amplitude		
100 µM	CHO/HEK with $Na_v1.1$	slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	not assessed	
		entry into slow inactivation 10 s	n.s. effect on peak amplitude		
	CHO/HEK with $Na_v1.2$	slow steady state inactivation 10 s	10 mV $V_{0.5}$ left shift	not assessed	
		entry into slow inactivation 10 s	-48% peak amplitude		
	CHO/HEK with $Na_v1.3$	slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	not assessed	
		entry into slow inactivation 10 s	n.s. effect on peak amplitude		
	CHO/HEK with $Na_v1.6$	slow steady state inactivation 10 s	6 mV $V_{0.5}$ left shift	not assessed	
		entry into slow inactivation 10 s	-54% peak amplitude		
300 µM	ND7/23 cells with $Na_v1.6$	slow steady state inactivation 30 s	17 mV $V_{0.5}$ left shift	3 mV $V_{0.5}$ left shift of fast	Bayraktar et al. [21]
		step pulse 100 ms	n.s. effect on amplitude	steady state inactivation 100 ms	
		175 mV/S ramp	n.s. effect on amplitude	n.s. $V_{0.5}$ shift of activation	
Ethosuximide					
750 µM	rat thalamocortical neurons	200 mV/s ramp	-40% peak amplitude	n.s. effect on amplitude (HP -70 mV)	Leresche et al. [135]

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
1 mM	rat CA1 pyramidal neurons	step pulse 250 ms	small n.s. decrease in amplitude	not assessed	Niespodziany et al. [165]
10 mM	rat TC neuron	75 mV/s ramp	-37% peak amplitude	not assessed	Broicher et al. [33]
Gabapentin					
5 µM	rat DRG neurons	20 mV/s ramp	-70% peak amplitude	n.s. effect on amplitude (HP -120 mV)	Yang et al. [250]
GS967					
1 µM	mouse hippocampal pyramidal neurons with a $Na_v1.2$ mutation	step pulse 200 ms	-92% amplitude	not assessed	Anderson et al. [8]
	tsA201 cells transfected with a $Na_v1.2$ mutation	step pulse 200 ms	IC_{50} 0.4 µM	IC_{50} 19 µM for amplitude (HP -90 mV)	
200 nM	mouse hippocampal pyramidal neurons with a $Na_v1.6$ mutation	step pulse 200 ms	-93% amplitude	n.s. effect on amplitude (HP -120 mV)	Baker et al. [18]
5 µM	Xenopus oozytes transfected with $Na_v1.1$ mutations	step pulse 70 ms	-70% amplitude	-10% peak amplitude (HP -90 mV)	Barbieri et al. [20]
1 µM	ND7/23 cells transfected with a $Na_v1.6$ mutation	step pulse 100 ms slow steady state inactivation 1 s with 5 ms recovery pulse	-83% amplitude 15 mV left shift	n.s. effect on amplitude (HP -120 mV)	Bunton-Stasyshyn et al. [35]
1 µM	ND7/23 cells transfected with $Na_v1.6$ wildtype	step pulse 80 ms	no I_{NaP} found	n.s. effect on amplitude (HP -120 mV) 17 mV left shift of steady state inactivation 500 ms	Wengert et al. [240]
	mouse subiculum pyramidal neurons with $Na_v1.6$ wildtype	65 mV/s ramp	-49% peak amplitude	not assessed	
1 µM	HEK cells expressing wild type human $Na_v1.2$ channels	step pulse 50 ms	-45% current density	-35% peak current density (HP -100 mV)	Mason and Cummins [150]
3 µM	mouse hippocampal fast-spiking neuron	25 mV/s ramp	-78% area under the curve	not assessed	Auffenberg et al. [16]
Lacosamide					
100 µM	mouse N1E-115 neuroblastoma cells	entry into slow inactivation 30 s	-43% peak amplitude	-28% amplitude at HP -100 mV -29% amplitude at HP -60 mV n.s. $V_{0.5}$ shift of steady state inactivation 500 ms	Errington et al. [59]
100 µM	HEK293 cells expressing $Na_v1.3$	entry into slow inactivation 10 s	IC_{50} 415 µM	n.s. effect on amplitude at HP -120 mV (IC_{50} 51 mM) -25% peak amplitude at HP -80 mV	Sheets et al. [195]
1 mM		slow steady state inactivation 10 s	42 mV $V_{0.5}$ left shift	n.s. $V_{0.5}$ shift of steady state inactivation 500 ms	
300 µM	mouse dissociated hippocampal neurons	50 mV/s ramp	-50% peak amplitude	not assessed	Uebachs et al. [227]

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
100 µM	N1E-115 neuroblastoma cells	slow steady state inactivation 10 s	33 mV $V_{0.5}$ left shift	not assessed	Niespodziany et al. [166]
250 µM	N1E-115 neuroblastoma cells	entry into slow inactivation 10 s steady state inactivation 5 s	-14% peak amplitude 43 mV $V_{0.5}$ left shift	n.s. $V_{0.5}$ left shift of activation -20% peak amplitude (HP -80 mV) n.s. $V_{0.5}$ shift of steady state inactivation 500 ms	Hebeisen et al. [87]
100 µM	rat dissociated hippocampal granule cells	entry into slow inactivation 1 s entry into slow inactivation 10 s entry into slow inactivation 30 s	-8% peak amplitude -14% peak amplitude n.s. effect on peak amplitude	4 mV $V_{0.5}$ left shift of fast steady state inactivation	Holtkamp et al. [92]
100 µM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms entry into slow inactivation 8 s	-9.6% amplitude (IC_{50} 832 µM) IC_{50} 269 µM	not assessed	Kahlig et al. [111]
Lamotrigene					
100 µM	rat dissociated hippocampal neurone	slow steady state inactivation 9 s entry into slow inactivation 6 s	11 mV $V_{0.5}$ left shift -69% peak amplitude	-7% amplitude at HP -90 mV (IC_{50} 1490 µM) -98% amplitude at HP -60 mV (IC_{50} 7 µM)	Kuo and Lu [124]
1 µM	rat neocortical pyramidal neurons	60 mV/s ramp	n.s. effect on amplitude	n.s. effect on amplitude (HP -65 mV)	Spadoni et al. [205]
100 µM	rat neocortical layer 5 pyramidal neurons	10 mV/s ramp	not quantified but similar to 100 µM phenytoin	responses 'still inducible'	Berger and Lüscher [26]
30 µM	HEK cells expressing $hNa_v1.2$	slow steady state inactivation 30 s	11 mV $V_{0.5}$ left shift	n.s. effect on amplitude at HP -100 mV (IC_{50} 2.6 mM) -33% peak amplitude at HP -60 mV (IC_{50} 172 µM) n.s. shift of activation n.s. shift of fast steady state inactivation 10 ms	Jones et al. [107]
100 µM	N1E-115 neuroblastoma cells	slow steady state inactivation 10 s	7 mV $V_{0.5}$ right shift	not assessed	Niespodziany et al. [166]
100 µM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms entry into slow inactivation 8 s	-55.4% amplitude (IC_{50} 78 µM) -72.8% amplitude (IC_{50} 39 µM)	-13.8% peak amplitude (IC_{50} 1249 µM, HP -120 mV)	Kahlig et al. [111]
Lidocaine					
30 nM	rat dissociated CA1 pyramidal neurons	step pulse 500 ms	-53% amplitude	n.s. effect on amplitude (HP -100 mV)	Hammarstrom and Gage [86]
10 µM	rat DRG neurons	15 mV/s ramp	'obvious' effect, not quantified	'little' effect, not quantified	Dong et al. [56]
100 µM	HEK293 cells expressing $Na_v1.3$	entry into slow inactivation 10 s	IC_{50} 284 µM	-6% amplitude at HP -120 mV (IC_{50} 1462 µM)	Sheets et al. [195]
1 mM		slow steady state inactivation 10 s	48 mV $V_{0.5}$ left shift	20 mV $V_{0.5}$ left shift of steady state inactivation 500 ms	

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
NBI-921352					
41 nM	HEK293 cells expressing a $hNa_v1.6$ mutation	step pulse 20 ms	-50% amplitude	IC_{50} 33 µM, HP -120 mV IC50 53 nM, HP -62 mV	Johnson et al. [106]
Oxcarbazepine					
10 µM	NG108-15 cells	100 mV/s ramp	-40% peak amplitude		Huang et al. [97]
3 µM				-9 mV shift of fast steady state inactivation 30 ms -61% amplitude (HP -80 mV)	
250 µM	N1E-115 neuroblastoma cells	entry into slow inactivation 30 s slow steady state inactivation 5 s	n.s. effect on amplitude 28 mV $V_{0.5}$ left shift	-24% amplitude (HP -80 mV HP -100 mV IC_{50} 2000 µM; HP -80 mV IC_{50} 805 µM; HP -60 mV IC_{50} 173 µM) 17 mV left $V_{0.5}$ shift of steady state inactivation 500 ms	Hebeisen et al. [87]
100 µM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms	-57.8% amplitude (IC_{50} 123 µM)	IC_{50} 1035 µM, HP -120 mV	Kahlig et al. [111]
		entry into slow inactivation 8 s	IC_{50} 42 µM		
Phenytoin					
75 µM	N1E-115	entry into slow	20 mV $V_{0.5}$ left shift		Matsuki et al. [151]
100 µM	neuroblastoma cells	inactivation 60 s		-6% amplitude at HP -100 mV -42% amplitude at HP -80 mV	
100 µM	rat CA1 neurons	slow steady state inactivation 16 s	15 mV $V_{0.5}$ left shift	-10% amplitude at HP -90 mV (IC_{50} 600 µM) -95% amplitude at HP -50 mV (IC_{50} 7 µM) n.s. $V_{0.5}$ shift of fast steady state inactivation 100 ms	Kuo and Bean [123]
		entry into slow inactivation 12 s	-85% peak amplitude		
34 µM	rat neocortical and neostriatal neurons	step pulse 400 ms	-50% amplitude (EC_{50} 34 µM)	not assessed	Chao and Alzheimer [42]
		50 mV/s ramp	no $V_{0.5}$ shift		
60 µM	hippocampal neurons in culture	single channel recordings in outside-out patches	-77% amplitude of late (50 – 100 ms) currents	-60% amplitude (HP -100 mV)	Segal and Douglas [192]
75 µM	rat neocortical layer 5 pyramidal neurons	7.3 mV/s ramp	-40% peak amplitude (EC_{50} 78 µM, EC_{max} -90%)	not assessed	Lampl et al. [130]
1 µM	rat neocortical pyramidal neurons	60 mV/s ramp	n.s. effect on amplitude	n.s. effect on amplitude (HP -65 mV)	Spadoni et al. [205]
100 µM	rat CA1 pyramidal neurons	step pulse 250 ms	-54% amplitude	not assessed	Niespodziany et al. [165]
100 µM	rat CA1 pyramidal neurons	50 mV/s ramp	-58% peak amplitude	-27% amplitude (HP -70 mV)	Yue et al. [251]

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
100 µM	rat neocortical pyramidal neurons	50 & 100 mV/s ramp	n.s. effect on amplitude	9 mV $V_{0.5}$ left shift of fast steady state inactivation	Colombo et al. [45]
		10 mV/s ramp step pulse 10 s 50 mV/s ramp after 10 s slow steady state inactivation	-34% peak amplitude -26% amplitude 7 mV $V_{0.5}$ left shift		
		50 mV/s ramp after 200 ms depolarizing prepulse	-20% peak amplitude (EC_{50} 28 µM)		
		50 mV/s ramp after 500 ms depolarizing prepulse	-25% peak amplitude (EC_{50} 18 µM)		
100 µM	N1E-115 neuroblastoma cells	slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	not assessed	Niespodziany et al. [166]
100 µM	tsA201 cells transfected with a $Na_v1.2$ mutation	step pulse 200 ms	-88% amplitude (IC_{50} 16 µM)	-40% amplitude (IC_{50} 143 µM, HP -120 mV)	Anderson et al. [8]
50 µM	rat CA1 pyramidal neurons	step pulse 50 ms	n.s. effect on amplitude	-14% amplitude at HP -120 mV	Zeng et al. [253]
		slow steady state inactivation 10 s	8 mV $V_{0.5}$ left shift	-24% amplitude at HP -100 mV	
		entry into slow inactivation 10 s	-40% amplitude	-39% amplitude at HP -80 mV (IC_{50} 73 µM) n.s. $V_{0.5}$ shift of fast steady state inactivation 50 ms 7 mV $V_{0.5}$ left shift of steady state inactivation 500 ms	
4 µM	mouse hippocampal pyramidal neurons with a $Na_v1.6$ mutation	step pulse 200 ms	-45% peak amplitude	n.s. effect on amplitude (HP -120 mV)	Baker et al. [18]
100 µM	mouse CA1 pyramidal cells	50 mV/s ramp	-62.5% peak amplitude	not assessed	Kang et al. [114]
	mouse CA1 PV + basket cells	50 mV/s ramp	-78.9% peak amplitude		
100 µM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms	-57.8% amplitude (IC_{50} 60 µM)	not assessed	Kahlig et al. [111]
		entry into slow inactivation 8 s	IC_{50} 48 µM		
PRAX-562					
100 nM	HEK-293 cells expressing $hNa_v1.6$ perfused with ATX-II	step pulse 200 ms	-45% amplitude (IC_{50} 141 nM)		Kahlig et al. [111]
1 µM		entry into slow inactivation 8 s	-72.3% peak amplitude (IC_{50} 317 nM)	-13.8% peak amplitude (IC_{50} 8.4 µM, HP -120 mV) 12 mV $V_{0.5}$ left shift of steady state inactivation 500 ms 3 mV left shift of activation	

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
Propofol					
10 µM	rat neocortical pyramidal neurons	53 mV/s ramp	-75% peak amplitude (IC_{50} 4 µM)	n.s. effect on amplitude (HP -70 mV)	Martella et al. [149]
56 µM	rat medial geniculate body neurons	step pulse 1 s	-45% amplitude	not assessed	Shi et al. [198]
Ranolazine					
10 µM 3 µM	NG108-15 cells	70 mV/s ramp 70 mV/s ramp	-58% peak amplitude -41% peak amplitude	15 mV $V_{0.5}$ left shift of fast steady state inactivation 100 ms	Wu et al. [244]
30 µM	tsA201 cells transfected with $Na_v1.1$	step pulse 200 ms	-9% peak amplitude (IC_{50} 54 µM)	n.s. effect on $V_{0.5}$ of fast steady state inactivation 100 ms n.s. effect on amplitude (HP -120 mV, IC_{50} 871 µM)	Kahlig et al. [109]
30 µM	nucleated somatic patches of rat CA1 pyramidal neurons	400 mV/s ramp	n.s. effect on amplitude	n.s. effect on amplitude (HP -65 mV)	Park et al. [167]
10 µM	rat cultured hippocampal neurons	slow steady state inactivation 10 s entry into slow inactivation 10 s	10 mV $V_{0.5}$ left shift -31% amplitude	5 mV $V_{0.5}$ left shift of fast steady state inactivation 100 ms	Kahlig et al. [110]
Riluzole					
10 µM	rat neocortical pyramidal neurons	step pulse 250 ms	-100% amplitude IC_{50} 2 µM	9 mV $V_{0.5}$ left shift of fast steady state inactivation	Urbani and Belluzzi [228]
		14 mV/s ramp	-100% peak amplitude (identical to 0.3 µM TTX)	(EC_{50} 50 µM; EC_{max} 21 mV)	
10 µM	rat preBötC respiratory pacemaker neurons	20 mV/s ramp	-85% peak amplitude	-8% spike amplitude	Del Negro et al. [53]
1 µM	rat neocortical neurons	60 mV/s ramp	-80% peak amplitude (IC_{50} 550 nM)	-50% amplitude (HP -65 mV)	Spadoni et al. [205]
25 µM	rat isolated suprachiasmatic nucleus neurons	100 mV/s ramp	-100% peak amplitude	not assessed	Kononenko et al. [122]
10 µM	rat CA1 pyramidal neurons	step pulse 250 ms	-56% amplitude	not assessed	Niespodziany et al. [165]
0.5 µM	rat G93A SOD1 mutant cultured motoneurones	10 mV/s ramp	-56% area under the curve	not assessed	Kuo et al. [125]
3 µM	rat preBötC respiratory pacemaker neurons	step pulse 50 ms	-64% amplitude at HP -100 mV -73% amplitude at HP -80 mV -80% amplitude at HP -60 mV	-23% amplitude at HP -100 mV -61% amplitude at HP -80 mV (EC_{50} 2.4 µM) -90% amplitude at HP -60 mV 10 mV $V_{0.5}$ left shift of fast steady state inactivation	Ptak et al. [175]
5 µM	rat mesencephalic layer V neurons	33.3 mV/s ramp	-81% peak amplitude	-11% amplitude (HP -80 mV, EC_{50} 51.6 µM)	Wu et al. [242]
10 µM	rat CA1 pyramidal neurons	50 mV/s ramp	-90% peak amplitude	-30% amplitude (HP -70 mV)	Yue et al. [251]

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
5 µM 10 µM	rat ventral horn neurones	16 mV/s ramp 16 mV/s ramp	-70% peak amplitude -74% peak amplitude	not assessed	Theiss et al. [221]
10 µM	rat hypoglossal motor neurons	42 mV/s ramp	not quantified in presence of Ca^{2+} blockers	not assessed	Lamanauskas and Nistri [128]
10 µM	mouse superior cervical ganglion neurons	10 mV/s ramp	-70% peak amplitude	-28% amplitude (HP -80 mV)	Lamas et al. [129]
1 µM	cultured embryonic G93A SOD1 mouse cortical neurons	step pulse 80 ms	-48% amplitude	n.s. effect on amplitude (HP -60 mV)	Pieri et al. [173]
10 µM 3 µM	neuroblastoma & glioma NG108-15 cells	70 mV/s ramp 70 mV/s ramp	-55% peak amplitude -34% peak amplitude	13 mV $V_{0.5}$ left shift of fast steady state inactivation	Wu et al. [244]
10 µM	compressed rat DRG neurons	26.7 mV/s ramp	-60% peak amplitude (IC_{50} 4 µM)	n.s. effect on amplitude (HP -80 mV)	Xie et al. [246]
200 µM 500 µM				-59% amplitude (HP -80 mV) -82% amplitude (HP -80 mV)	
10 µM	nucleated somatic patches of rat CA1 pyramidal neurons	400 mV/s ramp 10 mV/s ramp	-73% peak amplitude no I_{NaP} found	-33% amplitude 13 mV $V_{0.5}$ left shift of fast steady state inactivation	Park et al. [167]
20 µM	rat hypoglossal motor neurons	35 mV/s ramp	not quantified	not assessed	Bellingham [25]
10 µM	rat CA3 pyramidal neurons	15 mV/s ramp	-80% peak amplitude	n.s. effect on amplitude (HP -80 mV)	Nakamura et al. [163]
Rufinamide					
100 µM	N1E-115 neuroblastoma cells	slow steady state inactivation 10 s	9 mV $V_{0.5}$ right shift	not assessed	Niespodziany et al. [166]
100 µM	Xenopus oocytes with	step pulse 50 ms	n.s. effect on amplitude	n.s. $V_{0.5}$ shift of fast steady state inactivation	Gilchrist et al. [78]
	hNa$_v$1.1	entry into slow inactivation 10 s	n.s. effect on amplitude or $V_{0.5}$		
		slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	8 mV $V_{0.5}$ right shift of activation	
	Xenopus oocytes with hNa$_v$1.2 Xenopus oocytes with hNa$_v$1.3 Xenopus oocytes with hNa$_v$1.6			n.s. $V_{0.5}$ shift of fast steady state inactivation n.s. $V_{0.5}$ shift of fast steady state inactivation 5 mV $V_{0.5}$ right shift of fast steady state inactivation	
Topiramate					
100 µM	rat neocortical layer V pyramidal neurons	80 mV/s ramp entry into slow inactivation 800 ms	-40% peak amplitude -65% peak amplitude	7 mV $V_{0.5}$ left shift of fast steady state inactivation 300 ms	Taverna et al. [218]
2 µM	HEK293 cells expressing human Na$_v$1.3	step pulse 100 ms	-22% amplitude (EC_{50} 61 nM E_{max} -30%)	1.5 mV $V_{0.5}$ left shift of steady state inactivation 500 ms (EC_{50} 3 µM E_{max} 3 mV)	Sun et al. [215]

Table 1 (continued)

Drug	Preparation	Protocol for I_{NaP}	Effect on I_{NaP}	Effect on I_{NaT}	Study
Valproic acid					
200 µM	dissociated rat neocortical pyramidal neurons	40 mV/s ramp	-80% peak amplitude (EC_{50} 14 µM, EC_{max} -80%)	n.s. effect on amplitude (HP-70 mV)	Taverna et al. [217]
100 µM	rat neocortical pyramidal neurons	53 mV/s ramp	-80% peak amplitude	n.s. effect on amplitude (HP -70 mV)	Martella et al. [149]
10 µM	mouse superior cervical ganglion neurons	10 mV/s ramp	-55% peak amplitude	n.s. effect on amplitude (HP -80 mV)	Lamas et al. [129]
1 mM	HEK-293 cells expressing $hNa_V1.6$ perfused with ATX-II	step pulse 200 ms slow entry into slow inactivation 8 s	-2% amplitude -18% peak amplitude	-11% peak amplitude at HP -120 mV	Kahlig et al. [111]
Zonisamide					
100 µM	N1E-115 neuroblastoma cells	slow steady state inactivation 10 s	n.s. effect on $V_{0.5}$	not assessed	Niespodziany et al. [166]

these data, CBD should not be used as an CNS I_{NaP} blocker and likely exerts its neurotherapeutic effects via non-sodium channel mediated pathways.

Carbamazepine

For a long period of time, carbamazepine has been one of the most popular anti-seizure drugs worldwide. This is due to its good efficacy in focal epilepsy and its low costs [172]. It is also a first line drug in other paroxysmal neurological diseases such as episodic ataxia type 1 [131], trigeminal neuralgia [219], paroxysmal extreme pain disorder [63] or secondary dyskinesia [68]. Carbamazepine affects voltage activated calcium channels, especially $Ca_v2.1$, at low potency with an IC_{50} of 452 µM [203]. In addition, at 3 µM it suppresses 70% of D-type potassium currents in NG108-15 cells [97].

The main effect of carbamazepine however, is a left shift of the fast inactivation curve of sodium currents at 10–100 µM [87, 195, 215, 226] (Table 1). This effect leads to an earlier inactivation of sodium channels, which then already begins at more negative potentials. Therefore, a reduction of the persistent sodium current should also be expected under the window current hypothesis, which is reflected in step and ramp protocols [111, 215, 226]. However, multiple studies show a lack of action of carbamazepine on slowly inactivating sodium current at concentrations up to 1 mM [87, 166, 195] with the exception of Kahlig et al. [111]. Weighing the evidence, carbamazepine seems to preferentially target I_{NaT}, rather than I_{NaP} (Table 1).

Cenobamate

The latest anti-seizure drug being approved by the European Medicines Agency is cenobamate [61]. It is used as a third-line therapy for multi-drug-resistant focal epilepsy. Cenobamate is known for its potentiation of $GABA_A$-mediated currents with EC_{50} values in the range of 42 to 194 µM [194]. At high concentrations it inhibits L-type calcium currents with an IC_{50} of 350 µM and has little effects on $K_V7.1$ (IC_{50} 1.3 mM) and $K_V11.1$ (IC_{50} 1.8 mM) [7].

Concerning persistent sodium current, cenobamate has been found to block both the non-inactivating and the slowly inactivating current component with an IC_{50} of 50–70 µM [110, 163] (Table 1), which is well below the reported plasma concentration of 170 µM [34]. It also shifts the fast inactivation to the left, but this effect is much less pronounced than its suppressing effect on I_{NaP}. The substance could thus be used as a persistent sodium current blocker, but one has to keep in mind that the positive modulation of $GABA_A$ receptors occurs at similar concentrations. Thus, systemic effects may be dominated by either of these

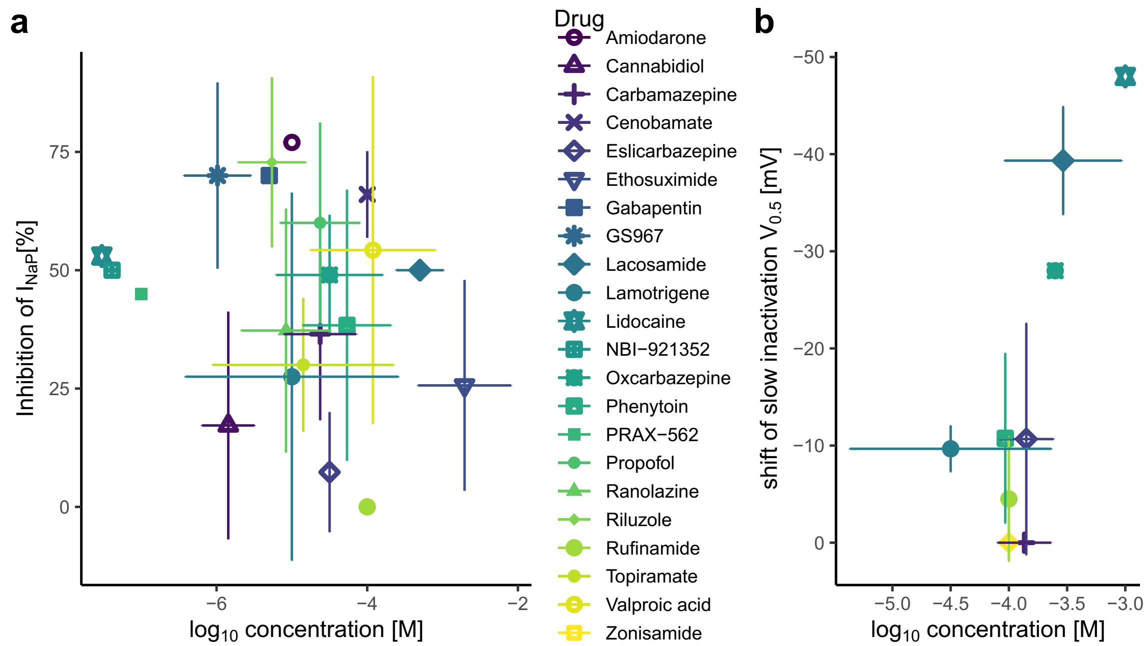

Fig. 3 Summary of drug effects with respect to protocol. Each study value listed in the table was considered as a separate datum, values plotted are mean ± SD. **a** Inhibition of persistent sodium current (I_{NaP}) assessed by step pulse or ramp protocols plotted vs drug concentration (values taken from [8, 16, 18, 20, 35, 42, 45, 53, 55, 76, 86, 114, 122, 125, 129, 130, 135, 149, 150, 163, 165, 170, 173, 175, 205, 215, 217, 221, 226–228, 240, 244, 246, 251, 253]). **b** Shift of the half point of voltage-dependent slow steady state inactivation curve plotted vs drug concentrations (values taken from [21, 78, 93, 107, 110, 124, 151, 166, 195, 226, 253])

mechanisms. It is presently difficult to imagine how the substance can isolate specific effects of I_{NaP} in native brain tissue.

Eslicarbazepine

Eslicarbazepine is an anti-seizure drug that was developed in order to bypass the side effects of carbamazepine and its potentially harmful metabolite carbamazepine-10,11-epoxide [187]. Like carbamazepine, it also affects calcium channels, with a preference for $Ca_v3.2$ (a subunit mediating T-type calcium currents) at an IC_{50} of 62 µM [203]. The effects of eslicarbazepine on sodium currents are different from those of carbamazepine. It does not affect the amplitude or fast inactivation of transient sodium currents. Contrary to carbamazepine it shifts the slow inactivation to more hyperpolarized potentials at 300 µM [21, 87, 93] (Table 1). Because of its slow binding kinetics and/or its lack of action on fast inactivation, 300 µM eslicarbazepine does not affect the persistent sodium current when measured with brief voltage steps or fast ramps [21], while afflicting mild effects in slow ramps [55]. Therefore, the substance should be evaluated as a blocker of I_{NaP}, in virtue of being an enhancer of slowy inactivating sodium currents. In complex tissues or living organisms, its efficacy on $Ca_v3.2$ at similar concentrations should warrant caution.

Ethosuximide

Ethosuximide is an odd anti-seizure drug used solely to treat absence seizures, while it is not effective against other types of seizures and therefore not commonly employed. Its main mechanism of action is thought to be a partial block of T-type calcium current in thalamic neurons with an EC_{50} of 200 µM [48]. In addition, at 250 µM there is a partial block of the Na^+/K^+ ATPase [77]. At concentrations of 20–50 mM I_{NaT} is reduced by ethosuximide in the squid giant axon in a voltage-independent manner [66]. Reliable block of persistent sodium current in neurons can only be obtained at rather high concentrations of 1–10 mM [33, 135] which exceed typical plasma levels of 0.3–0.7 mM [81]. Thus, while it might preferentially effect I_{NaP}, ethosuximide cannot be used as an I_{NaP} blocker, at least in complex preparations containing multiple ion channels.

Gabapentin

Gabapentin is one of the top 10 most prescribed drugs in the world, as it is commonly used for neuropathic pain in polyneuropathies and other chronic pain conditions. Its main mechanism of action is a block of N-type voltage gated calcium channels via an interaction with the α2δ-1 subunit which gabapentin binds with a K_d of 59 nM [169]. One study has shown that 5 µM gabapentin blocks I_{NaP} in dorsal root ganglion cells, using a ramp protocol [250] (Table 1). However, DRG neurons express Na_v1.7, 1.8 and 1.9, i.e. isoforms with peculiar kinetics, which are not dominant in most central nervous neurons. Taken together with the well described effects on calcium channels, gabapentin is probably not a good candidate for being a general blocker of I_{NaP}.

GS967

GS967, now known as Prax330, is a novel compound initially synthesized for treating cardiac arrhythmias [23]. Until now, no clinical trials have been published for this compound, although a phase I trial has been completed (ACTRN12617001512314). Nonetheless, GS967 has been found to be effective in animal models of monogenetic epilepsy and hemiplegic migraine [9, 16, 18]. With regard to possible mechanisms of action, no studies have been published so far examining effects on calcium channels or other molecular targets. However, GS967 reduces I_{NaP} measured with both ramp and short step pulse protocols (Table 1) at concentrations of 0.2–1 µM [9, 240]. It also shifts the fast inactivation curve to more hyperpolarized potentials (Table 1). At this point of time, there is no study evaluating the effect of the drug on slow sodium current inactivation in neurons. Evidence from cardiac slow (2 s) steady state inactivation, however, suggests that GS967 may also be effective in blocking slowly inactivating sodium current. [88]. Taken together, GS967 is a potent blocker of persistent sodium current, and might therefore be a good candidate for further translational studies.

Lacosamide

Lacosamide has been used to treat focal epilepsy and is also one of the few drugs approved for managing status epilepticus. Recently, however, there has been increased awareness concerning cardiac arrhythmia after administration of lacosamide [247]. Although lacosamide halfs calcium influx via N-type calcium channels (Ca_V2.2) in cortical neurons at 200 µM [157], its main mechanisms of action appears to involve slowly inactivating sodium currents and/while binding collapsin response mediator protein 2 (CRMP-2) [28], which influences trafficking of Na_v1.7 [113]. Similar to eslicarbazepine, lacosamide does not affect fast and intermediate inactivation and has only very small effects on I_{NaP} voltage step protocols [111]. However, at 100–250 µM it shifts of the midpoint voltage ($V_{0.5}$) of slow inactivation by 40 mV to the left [62, 87]. This mechanism may underlie the 50% reduction in the ramp protocol observed at 300 µM [227]. Suggested underlying mechanisms are that lacosamide prefers fast inactivation, but has very slow binding kinetics [104] (see discussion of phenytoin), that it preferentially affects channels with slow inactivation [92] or that its interaction with CRMP-2 confers an enhancement of slow inactivation [158]. Keeping in mind the clinically used serum concentration of 20–40 µM [144] lacosamide should be considered as a potent enhancer of slow inactivation. It has, however, lacking effectiveness for I_{NaP} understood as the non-inactivating component in the brief step protocol.

Lamotrigine

Lamotrigine is currently the best drug for treating focal epilepsy [145, 147], as it is well tolerated and, in some patients, even stabilizes mood. This is why lamotrigine has also entered the realm of psychiatric disease and is currently used for treating bipolar disorder or depression [47]. Another beneficial property of lamotrigine is its efficacy in generalized epilepsy, while other sodium channel blockers tend to aggravate seizures in these patients. This unique profile is linked to a broad range of mechanisms of action: Lamotrigine inhibits high-voltage-activated Ca^{2+} currents with an EC_{50} of 12 µM [209], which in turn reduces the release of glutamate [236]. It also reduces the uptake of serotonin, noradrenaline and dopamine at concentrations of 200–400 µM [204] and, at 100 µM, lamotrigine induces the expression of GABA-A β3 subunits [237]. Lamotrigine seems to bind slowly to sodium channels, which explains the modest effects on the non-inactivating current component at concentrations of 80–100 µM [111, 205] (Table 1). Accordingly, lamotrigine shifts the slow inactivation to more hyperpolarized potentials and exerts inhibition on I_{NaT} amplitude at depolarized membrane potentials [107, 111, 124] (Table 1). These effects occur in a range of 7–40 µM which is comparable to clinical plasma concentrations of 20 µM [118]. In general, the size of these effects is comparatively low (Fig. 3 A and B) and given the effects on calcium- and $GABA_A$-channels, it should not be regarded as a specific I_{NaP} blocker.

Lidocaine

Lidocaine is one of the most popular local anaesthetics and therefore often used to block nerve conduction during surgery. Due to its low bioavailability it is generally not administered orally [52]. In intensive care medicine, intravenous lidocaine has been used for treating ventricular arrhythmia or status epilepticus in rare cases [252]and it is recommended as an anti-arrhythmic drug during resuscitation [202].

Its mechanism of action is mainly based on the block of sodium channels, though it also blocks HCN channels at 20–50 µM [154]. Lidocaine is one of the few drugs whose binding site in VGSC has been well established: its inhibitory effect is primarily caused by disrupting the coupling between the voltage sensors of the sodium channel via long-range stabilization of the third transmembrane domain in the activated state[161].

Most of the studies concerning lidocaine and persistent sodium current have been performed in myocytes [19, 22, 37, 102, 108, 238]. For neuronal channels, lidocaine at high concentration (300 µM—1 mM) does have major effects on both slow and fast sodium current inactivation [195]. However, one study in neurons shows a remarkable effect of lidocaine at 30 nM on the non-inactivating current component in a short pulse protocol [86]. Clinical use cases typically involve lidocaine levels in the range of 1–10 µM [36]. Thus, while the drug appears to be a blocker of I_{NaP}, its cardiac side effects restricts its use to preparations in the laboratory.

NBI-921352

This is a novel compound which was developed as a specific $Na_v1.6$ inhibitor by Xenon Pharmaceuticals [106]. Potent effects on I_{NaP} appear quite possible (Table 1), but data on persistent or slowly inactivating components in neurons is yet missing.

Oxcarbazepine

Like eslicarbazepine, oxcarbazepine is a derivate of carabamazepine. It is used for focal epilepsy, neuropathic pain and sometimes also during alcohol withdrawal [191]. It is one of the few anti-seizure drugs which are not teratogenic [224]. Unlike carabamazepine and eslicarbazepine, it has been shown to also affect voltage-gated calcium channels, particularly N-type, at concentrations of 2–50 µM [208]. In addition, at 10 µM it suppresses 50% of D-type potassium currents [97]. With regard to sodium currents, oxcarbazepine seems to affect both slow and fast inactivation, with a stronger effect on slow inactivation at 10–100 µM (Table 1). It therefore bridges the gap between carbamazepine (predominantly acting on fast inactivation) and eslicarbazepine (predominantly acting on slow inactivation). The observed effects in ramp and step protocols in neuroblastoma/-glioma cells make it quite possible that the drug inhibits I_{NaP} (Table 1). However, there is no data on effects of oxcarbazepine on I_{NaP} in naturally differentiated neurons. This may be a matter of concern, as oxcarbazepine is the only antiepileptic drug which has been shown to reliably destroy glioma cells. In one study on cells derived from patients with brain tumours, the IC_{50} for induction of apoptosis was 45 µM [51]. Out of three studies on oxcarbazepine which are relevant for this review, two were carried out on neuroblastoma/-glioma cells [87, 97], where the drug might induce apoptosis cascades [51]. Hence, more evidence is needed to classify oxcarbazepine with respect to effects on I_{NaP}.

Phenytoin

Phenytoin is one of the oldest anti-seizure and antiarrhythmic drugs [134]. Nowadays, due to its non-linear pharmacokinetics and severe side effects its use is typically restricted to inpatients [74, 179]. Serum levels of phenytoin are typically at 3–10 µM, where it has a 50% inhibitory effect on calcium channels [155]. Being one of the best characterized sodium channel blockers (Table 1), phenytoin does appear to be a prime example of a drug that affects intermediate inactivation [71, 253]. This explains why the drug does not have an effect on I_{NaP} measured with short voltage steps or fast ramps. However, it strikingly inhibits later phases of currents evoked by voltage steps as well as currents evoked by slow ramps (Table 1). It has been suggested that phenytoin exhibits its effects by slowly binding sodium channels in the fast inactivated state [123]. This argument seems to be at odds, however, with the remaining sensitivity of intermediate inactivation to phenytoin after intracellular proteolysis by papain or pronase [253], which completely abolishes fast inactivation [181]. Therefore, if the effect of phenytoin would target fast inactivation after slowly binding to sodium channels, it should not be active after proteolysis. The substance remains active, however, after intracellular application of papain, suggesting that phenytoin does not inhibit sodium currents by affecting fast inactivation [253]. Thus, phenytoin does not directly interact with the fast inactivation gate. Nevertheless, the observed block can be explained by an interaction with the channel which depends on the graded movement of the activating gating charge. In this way, the drug would mimic and compete with natural fast inactivation [123]. Consequently, papain should enhance the speed of phenytoin block, as confirmed by Quandt [176] in neuroblastoma cells, but contested by Zeng et al. [253] in CA1 pyramidal cells. Is I_{NaP} then generally only a byproduct of a failure of intermediate inactivation? Probably not, as other blockers like riluzole or GS967 manage to suppress I_{NaP} measured with early steps or fast ramps. Once again, the term 'persistent' sodium current is misleading, because it is also applied to slow inactivation patterns at different time scales. Thus, employing phenytoin as an I_{NaP} blocker appears possible, but one has to keep these limitations in mind.

Propofol

Propofol is a sedative drug commonly used to induce loss of consciousness during narcosis, especially in patients that develop postoperative nausea from volatile anaesthetics. It is typically used at concentrations of 10–50 µM [189]. Propofol is also the last escalation step in order to suppress status epilepticus. At lower concentrations, the drug has addictive properties, like benzodiazepines. It has to be administered intravenously and can induce vasodilation and transient apnoea [189]. Thus, propofol is only used in intensive care settings. The drug predominantly acts on $GABA_A$ receptors by binding their β subunits and potentiates GABA induced currents fivefold at 2 μM or even opens the channels directly at 30 μM [84].

Regarding suppression of I_{NaP} propofol is surprisingly potent in neurons at 10–60 μM (Table 1). However, the reported effects on GABA receptors occur in a similar concentration range, again impeding causal analysis in complex preparations. The combination of all known actions of propofol may explain its efficacy in status epilepticus. In no way can it be regarded a specific I_{NaP} blocker. In addition, its low bioavailability and addictiveness limit any prolonged use in outpatients.

PRAX-562

PRAX-562 is a novel compound specifically synthesised as a persistent sodium current blocker by Praxis Precision Medicines. It was shown to be effective as an antiseizure drug in the maximal electroshock seizure model in mice [111]. Interestingly, amongst all drugs discussed in this review, it is the only substance inducing a small left shift of I_{NaT} activation. Available data from HEK-cells suggest that it acts as an I_{NaP} blocker by modulating both, fast and slow inactivation, but data from neurons are missing, as are data on potential further molecular targets.

Ranolazine

Ranolazine is a second-line drug in chronic stable angina pectoris and has shown some efficacy in microvascular coronary dysfunction as well as anti-arrhythmic activity [177]. In myocytes, it blocks persistent sodium currents (IC_{50} 6 μM) and delayed rectifier potassium currents (IC_{50} 12 μM) [83]. While ranolazine can cross the blood brain barrier, the CNS concentration only reaches one third of the plasma levels [109]. Ranolazine at 3–30 μM is effective in blocking I_{NaP} measured with ramps and steps [110, 244], while also significantly affecting slow inactivation (Table 1). It does have a higher affinity for I_{NaP} over I_{NaT}, therefore making it an attractive persistent sodium current blocker. In systemic applications, however, the aforementioned effects on the heart and the low blood brain barrier passage must be taken into considerations.

Riluzole

For 28 years, riluzole has been the only approved drug in amyotrophic lateral sclerosis, where it prolongs life expectancy by around 2–3 months [24]. Interestingly, unlike many other drugs on this list, it is not effective in neuropathic pain [73]. This might be due to its low affinity for calcium channels, with IC_{50} values well above 10 μM [24]. However, at clinically used levels of 1–2 μM riluzole does enhance calcium dependent K^+ currents and reduces presynaptic transmitter release [24].

Traditionally, riluzole has been the most popular blocker of I_{NaP}. The drug affects both ramp and step protocols with IC_{50} values well below 10 μM (Table 1). It also has effects on fast inactivation, though these are rather moderate compared to, e.g., carbamazepine (Table 1). Surprisingly, there is no data directly showing effects on slow inactivation, while indirect evidence from slow ramps and other readouts suggests an effect on intermediate inactivation [160]. Riluzole is one of the most useful I_{NaP} blockers, because it does not affect calcium currents at relevant concentrations and its effects on I_{NaP} have been shown in many different types of neurons [53, 163, 228].

Rufinamide

Rufinamide is a sparsely used anti-seizure drug for patients with Lennox-Gastaut syndrome. It inhibits metabotropic glutamate receptors 5 (mGluR5) at 100 μM, which can be measured by reduced quisqualate-induced phosphoinositol turnover [13]. At the same time, it inhibits slow and fast inactivation of sodium channels, especially $Na_v1.6$, at 100 μM. However, ramp or step protocols for the assessment of effects on I_{NaP} are missing in the literature. It has been suggested that rufinamide exerts a preferential effect on intermediate inactivation, similar to phenytoin [138]. In any case, more data is required to assess its effects on I_{NaP} more completely.

Tetrodotoxin

Tetrodotoxin (TTX) is a poisonous agent found in puffer fish, where it is synthesised by bacteria [164]. It is considered the most effective sodium channel blocker, as it directly occludes sodium ion permeation through the open channel [132]. While transient sodium channels are typically blocked at concentrations of 1 μM, persistent sodium currents are efficiently blocked at lower concentrations of 20–50 nM in rodent brain slices [207, 231, 251]. However, Taddese and Bean [216] found the TTX at very low concentrations of 5 nM has equal effects on transient and persistent currents in tuberomammillary neurons, casting doubt on its specificity for I_{NAP}. Therefore, TTX may be a useful tool for experimental work on I_{NaP}, but careful controls for effects on I_{NaT} are required in each specific preparation. Notwithstanding, most studies use low micromolar concentrations of TTX to achieve complete absence of sodium currents [70, 163, 212]. Anyway, TTX has no potential for clinical use, due to its well-known capability to paralyse the diaphragm [164].

Topiramate

Topiramate is typically used in genetic generalized epilepsy, idiopathic intracranial hypertension and in the prevention of migraine episodes. However, its use is often limited by remarkable word-fluency difficulties [159]. At 10 μM, topiramate increases GABA mediated Cl^- influx into neurons by 75% [241], it inhibits $Ca_v2.3$ with an IC_{50} of 51 μM [127] and exerts weak inhibition of carbonic anhydrases [193]. Concerning I_{NaP}, topiramate is a mildly efficient blocker in both step and ramp protocols. In one study [215] topiramate has a very potent effect on non-inactivating sodium current measured with step pulses with an EC_{50} of 61 nM, but the effect size is limited to a maximum of -30%. To our knowledge there is no data showing its effects on slow inactivation. The observed effects are present at clinically relevant concentrations of 2–20 μM [153], but importantly do only exert a partial block of I_{NaP}. Thus, topiramate is not a convincing candidate for use as a selective and efficient persistent sodium current blocker.

Valproic acid

Valproic acid is the first-choice drug for genetic generalized epilepsy [146, 148], but is also used for stabilizing mood in bipolar disorder and preventing episodes of migraine. Due to its high teratogenicity its use in fertile women is strictly controlled in most countries [223]. This severe side-effect might be mediated by epigenomic effects through inhibition of histone deacetylases with IC_{50} values of 0.5–3 mM [82], well within the range of clinically used serum concentrations which range between 0.3–0.7 mM [31]. In addition, valproic acid at 0.5 mM potentiates GABAergic inhibition via a complex modulation of enzymes in GABA metabolism, and also infers with second messenger pathways [105]. Valproate is a potent blocker of persistent sodium current as assessed by ramps and step protocols in neurons (Table 1). These effects occur in the range of 10–100 μM which is well below the clinically used concentrations. Whether it does or does not affect I_{NaT} remains a controversial issue, with more evidence against (see Table 1) than for such an effect [230]. The marked effect on persistent sodium current might explain the efficacy of valproate in treating status epilepticus. However, as valproic acid has particularly many off-target effects, we do not recommend it as a pharmacological tool to isolate $I_{NaP.}$

Zonisamide

Zonisamide is an anti-seizure drug used in focal epilepsy, with particularly widespread application in Asia. It inhibits T-type Ca^{2+} currents and alters the metabolism of dopamine, 5-HT, and acetylcholine [30]. Although it has been described as a sodium channel blocker, this notion is mostly based on data from sea worm axons [190]. In the only study on mammalian channels in mouse derived neuroblastoma cells, zonisamide had no effect on slow inactivation (Table 1). Therefore, it should not be used as an I_{NaP} blocker.

Summary and recommendations

The very existence of a persistent sodium current as a separate, clearly definable entity is a controversial topic. The lack of clarity may be, at least in part, explained by the misleading word 'persistent', which should be understood as: 'non-inactivating or slowly inactivating voltage-activated sodium current.' Additional confounding issues are the poorly understood inactivation mechanisms of sodium channels, both from an electrophysiological and structural point of view. The typically employed voltage clamp protocols do not pick up all components of persistent or slowly inactivating sodium current, such that data is often incomplete. Brief voltage steps, in particular, are unable to assess slowly inactivating components. If one wants to characterise the entire effects of a drug on persistent sodium currents, one should also check for alterations of slow inactivation kinetics (notice the lack of respective of data in Fig. 3B). When using ramp protocols, only slow rates of voltage change (≤ 10 mV/s) do span over time periods of tens of seconds and are therefore able to address slow or intermediate inactivation.

Until now, the literature splits clinically employed sodium channel blockers into several types depending on the mechanism of inactivation which they enhance. Carbamazepine is considered as an archetypic fast inactivation enhancer, while lacosamide is considered to be the prototypic slow inactivation enhancer. However, most of the above-described drugs affect all three types of inactivation.

Based on our systematic literature search, we conclude that there is no pharmacological blocker of I_{NaP} that does not somehow affect transient current components. This is not surprising, since I_{NaP} is most likely a result of specific gating properties of the same sodium channels which mediate I_{NaT}, rather than a separate molecular subtype. Typically, blockers of I_{NaP} affect I_{NaT} at higher concentrations, such that they can be considered relatively specific as long as low concentrations are applied.

Another point of concern are the off-target effects of the most effective I_{NaP} blockers. Consistently, these drugs target both voltage gated sodium and calcium channels. This is not unexpected, because both channel families have a common evolutionary ancestor [137] and share a major properties of their 3D structure [39]. Taking all these caveats into account, claims that a specific physiological phenomenon is mediated by I_{NaP} should be based on similar effects of more than one drug, or on the additional use of alternative approaches, like genetic manipulation or dynamic voltage clamp [210].

In this review, we show that for CNS neurons GS967 and riluzole are the ‘best’ persistent sodium current blockers in vitro, as they significantly affect non-inactivating sodium current components measured with both ramp protocols and short voltage steps (Fig. 3A). The ‘best’ substance for enhancing intermediate inactivation is phenytoin and for slow inactivation there is lacosamide (Fig. 3B). Substances like NBI-921352 and PRAX-562 show promise for being specific blockers of I_{NaP}, but the present evidence is very limited. TTX and lidocaine are very useful tools for pharmacological isolation of I_{NaP}, but cannot be used for CNS purposes in vivo. Based on the available evidence, cannabidiol, ethosuximide, gabapentin, rufinamide and zonisamide should not be employed as *bona fide* persistent sodium current blockers either due to missing data or due to lacking potency (Fig. 3). Clinical translation of ranolazine and amiodarone is hindered by low penetrance of the blood–brain-barrier and simultaneous action on cardiac myocytes. High potential for confounding off target effects limits the use of cenobamate, eslicarbazepine, lamotrigine, oxcarbazepine, propofol, topiramate and valproic acid in complex preparations. And last, while still being sodium channel specific, carbamazepine exerts its main effect on fast inactivation.

Wherever possible, future studies should use a combination of brief voltage steps, voltage ramps and steady state inactivation protocols for fast, intermediate and slow inactivation. Step length for brief pulses should be around 50 ms, and they should be repeated at different voltages in order to consider voltage dependent shifts of persistent sodium currents. Ramps should be employed at around 50 mV/s (or even slower when slow inactivation component shall be directly assessed by voltage ramps; see above). TTX subtraction protocols are recommended. Slow steady state inactivation should be assessed by applying steps of 5–10 s duration, intermediate inactivation with 500 ms to 1000 ms steps and fast inactivation with 50 ms to 100 ms steps. Even if we don’t fully understand I_{NaP}, we should try to measure it with comparable parameters to facilitate comparisons and to support the further development of therapeutic strategies for conditions involving pathophysiological effects of persistent sodium currents.

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