Physiological Properties of Hippocampal Neurons

Marco Martina and Cheng-Chang Lien

Abstract Neurons are the basic computational units of the nervous system. Information processing in the brain is critically dependent on the electrophysiological properties of individual neurons, which are determined by the presence and distribution of many functionally and pharmacologically different ion channels. The parameters that define the functional roles of individual neurons can be grouped into two major groups: on one side are cellular morphology and topology, which dictate the connectivity of each neuron; on the other side are the different electrophysiological properties of each cell type, which are defined by the combined effects of neuronal active and passive properties and shape the integrative function of each individual cell. The type and timing of neuronal responses to synaptic inputs depend on the firing pattern of each neuron, which in turn is set by the interplay of intrinsic and synaptic electrophysiological properties. In recent years it has also become clear that within each individual neuron the electrophysiological properties are not homogeneous but vary in the various cellular compartments. In particular, it has been shown that dendrites, far from being simple cellular antennas that passively conduct synaptic inputs toward the soma and the axon, are very active structures capable of actively boost synaptic inputs and, at least in some neurons, of generating action potentials that effectively propagate to the soma (Llinás and Sugimori, J Physiol 305:197–213, 1980; Stuart and Sakmann, Nature 367:69–72, 1994; Häusser et al., Neuron 15:637–647, 1995; Spruston et al., Science 268:297–300, 1995; Martina et al., Science 287:295–300, 2000). Thus, the different voltage-gated ion channels expressed by each neuron and in each cellular compartment within individual neurons play a fundamental role in shaping the electrical response of individual neurons to synaptic stimulation and ultimately in

M. Martina (✉)
Department of Physiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA
e-mail: m-martina@northwestern.edu

C.-C. Lien
Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan
e-mail: cclien@ym.edu.tw

V. Cutsuridis et al. (eds.), *Hippocampal Microcircuits*, Springer Series in Computational Neuroscience, https://doi.org/10.1007/978-3-319-99103-0_3

dictating the role of each neuron within the hippocampal network. This chapter will focus on the properties and distribution of voltage-gated ion channels in some of the major neuronal types in the hippocampus and dentate gyrus.

The Data

Comprehensive models describing the function of any brain area must take account of the large differences in the electrophysiology of individual neuronal types. Such differences are mainly the result of the properties of the ion channels expressed by each individual cell type. This chapter provides a brief review of the properties and distribution of voltage-gated ion channels in some of the main hippocampal cell types. The hippocampal formation contains three classes of glutamatergic projection neurons (pyramidal neurons of the hippocampus and granule cells and mossy cells of the dentate gyrus) and many different types of GABAergic interneurons (Freund and Buzsáki 1996, Parra et al. 1998; see also chapter "Connectivity of the Hippocampus" of this book). Hippocampal pyramidal neurons are among the most extensively studied neurons in the entire brain. Electrophysiologically, they can be grouped into three major groups, CA1, CA2, and CA3, although a recent study reports a striking heterogeneity in both intrinsic properties and synaptic connectivity along the transverse axis of CA3 (Sun et al. 2017). Furthermore, pyramidal neurons in the subiculum likely constitute a fourth neuronal class with different electrical properties (Jung et al. 2001).

CA1 Pyramidal Neurons

The recorded resting membrane potential of CA1 pyramidal neurons varies in different preparations from −64 mV (recorded in perforated patch configuration at 32 °C, Spruston and Johnston 1992) to −84 mV, inferred from the reversal potential of voltage-gated potassium currents recorded in cell-attached configuration at 34 °C (Fricker et al. 1999). These cell have typically low input resistance (27 KΩ*cm^2, measured in acute rat slices using whole-cell configuration at room temperature, Taverna et al. 2005). The background conductance of CA1 pyramidal neurons is mainly mediated by inward rectifier potassium currents (Takigawa and Alzheimer 2002), voltage-insensitive KCNK potassium currents (largely TASK3 Taverna et al. 2005), and Ih (Maccaferri et al. 1993). The voltage response of CA1 pyramidal neurons is characterized by the presence of voltage sag upon injection of hyperpolarizing current and by action potential frequency accommodation on injection of depolarizing current. About 15% of the neurons show intrinsic bursting (defined as a ratio of <0.1 between the shortest interspike interval and the mean interspike interval; Metz et al. 2005). Spike accommodation mostly depends on the properties of the voltage-gated sodium and potassium currents expressed in these

Table 1 Sodium channels of CA1 pyramidal neurons

	Soma	Dendrites	Axon
Current type	Fast/persistent (Yue et al. 2005)	Fast (Magee and Johnston 1995a, b)	Fast (Colbert and Pan 2002)
Current density	+ (Magee and Johnston 1995a, b)	+ (Magee and Johnston 1995a, b)	++
Channel subunit	Nav1.1, Nav1.2 (Gong et al. 1999) Nav1.3 RNA before p30 (Felts et al. 1997)	Nav1.1, Nav1.2 (Gong et al. 1999)	Nav1.1, Nav1.2 (Gong et al. 1999)

cells. Action potentials are normally initiated close to the soma and backpropagate into dendrites in an activity-dependent manner so that while action potentials early in a train propagate reliably, those occurring later may fail to actively invade the distal dendrites (Spruston et al. 1995). Sodium currents of CA1 pyramidal neurons recover from inactivation with a bi-exponential time course (Martina and Jonas 1997); interestingly, longer lasting depolarizations increase both the relative contribution of the slow component and its time constant (see below). Thus, during a long depolarization, sodium channels undergo cumulative inactivation, which prevents sustained fast firing. Additionally, sustained high-frequency firing is also hindered because most of the voltage-gated potassium currents of these neurons inactivate rapidly (see below), and therefore prolonged depolarizations inactivate the potassium current and interfere with action potential repolarization.

Sodium Currents Voltage-gated sodium currents are expressed in all three functional compartments (soma, axon, dendrites; see Table 1) of pyramidal neurons. The current density appears relatively uniform in the different compartments (Colbert and Pan 2002; Magee and Johnston 1995a, b, Fig. 1), although enrichment in the axon initial segment is also compatible with the experimental data (Colbert and Pan 2002) and would mirror observations in CA3 pyramidal neurons, where sodium channel density peaks in the axon at ~50 μm from the soma (see below). The density of sodium current in CA1 pyramidal cell nucleated patches is ~5 mS/cm^2 (M. Martina, unpublished observations).

The properties of the sodium current slightly differ between soma and dendrites. In particular, dendritic channels appear to undergo stronger cumulative inactivation during repetitive firing (Jung et al. 1997) and to have slower recovery from inactivation compared to somatic channels (Colbert et al. 1997). Recovery from inactivation in pyramidal neurons is described by a double exponential process, with the fast and slow components having time constant of ~2 and ~150 ms and contributing 85% and 15%, respectively, for a 30 ms-long test pulse; for 300 ms-long pulses, the values of the time constants are similar (2.6 and 351 ms, respectively), but the contribution of the slow component increases to 24% (all data were obtained at −120 mV holding potential and 22–24 °C, Martina and Jonas 1997). Abundant expression of two sodium channel subunits (Nav 1.1 and 1.2) has been detected in

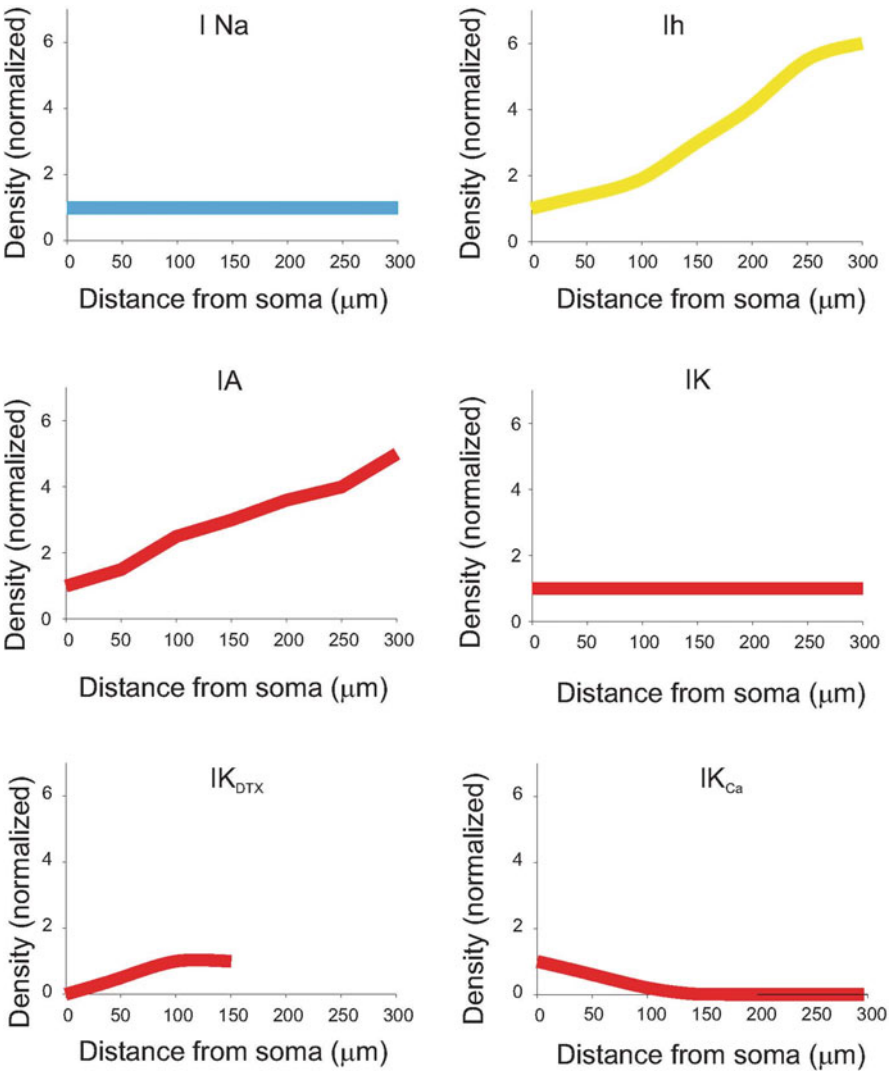

Fig. 1 Ion current density along the somatodendritic axis of CA1 pyramidal neurons. The density of each current type was normalized to its own density at the soma (except for IK_{DTX} in which it was normalized to the value in proximal dendrites). Therefore the figure only depicts the trend for each individual current, and no comparison is possible between the absolute values of the different currents

the hippocampus; type 1 channels appear to account for most of the somatodendritic staining, while type 2 staining is concentrated in the axons (Gong et al. 1999). In hippocampal pyramidal neurons, action potentials are normally initiated in the axon initial segment (Colbert and Johnston 1996). Colbert and Pan (2002) showed that initiation at this site is probably favored by a more negative activation range of

voltage-gated sodium current (sodium channel activation is shifted by ~7 mV in the hyperpolarizing direction). Modulation of Na^+ channel activation is also detected in dendritic channels. Sodium channels in distal dendritic segments have more negative activation range than in proximal dendrites. The midpoint of the activation curve is ~−12 mV for distal dendritic channels and ~−20 mV for proximal channels (Gasparini and Magee 2002), and this difference appears as the result of phosphorylation-dependent modulation since it is reproduced by staurosporine, a nonselective kinase inhibitor (Gasparini and Magee 2002). Yet, in spite of the more negative activation range of sodium channels, dendritic action potential initiation is not common and requires highly synchronized (within 3 ms) activation of ~50 synaptic inputs spread over 100 μm of the apical trunk/tuft (Gasparini et al. 2004). Moreover, the voltage threshold for dendritic action potential initiation is more positive than the somatic one (−48 ± 1 mV in the dendrites vs. -56 ± 1 mV at the soma, Gasparini et al. 2004). This apparent contradiction may be explained by the higher density of A-type potassium current in distal dendrites (Hoffman et al. 1997, Gasparini et al. 2004).

Voltage-Gated Potassium Channels CA1 pyramidal neurons express multiple types of voltage-gated K^+ channels (Storm 1990, Hoffman et al. 1997; Martina et al. 1998, Table 2). Three main components can be identified on the basis of functional and molecular analysis: an A-type current (see Table 3 for the A-type current properties), most likely mediated by Kv4 channels, which contributes ~60% of the total somatic current; a slow delayed rectifier (ID), likely attributable to Kv1 and Kv2 subunits, which contributes ~27% of the total somatic current; and a fast delayed rectifier (IK) mediated by Kv3 channels that contributes ~12% of the somatic current (Martina and Jonas 1997). The relative contribution of these components is different between the somatic and dendritic compartments (See Fig. 1). While the non-inactivating voltage-dependent currents (most likely mediated by Kv2 and Kv3 channels) show relatively constant density in the somatodendritic compartment, A-type current (mediated by Kv4 subunits Martina et al. 1998; Hoffman and Johnston 1998; Kim et al. 2005) progressively increases with distance from the soma (up to fivefold, Hoffman et al. 1997). The A-type potassium current typically activates at relatively hyperpolarized membrane potentials (starting ~−45 mV, Martina et al. 1998). Interestingly, A-type current of pyramidal neurons is highly sensitive to metabolic modulation (Hoffman and Johnston 1998). Such modulation could play an important role in regulating synaptic plasticity, as shown by the change in the threshold for induction of long-term potentiation measured in response to pharmacological blockade of this current (Ramakers and Storm 2002). Expression of dendrotoxin-sensitive (Kv1-mediated) potassium currents is spatially segregated in pyramidal neurons. This current is not expressed in the soma, but it is expressed in proximal dendrites (Fig. 2) where it contributes to the active regulation of the action potential afterdepolarization and therefore of burst firing (Metz et al. 2007).

Calcium-Dependent Potassium Channels Depolarizations produced in CA1 pyramidal neurons by iontophoretically applied glutamate are followed by hyperpolarizations which are mediated by calcium-dependent potassium channels

Table 2 Voltage-gated potassium channels of CA1 pyramidal neurons

	Soma	Dendrites	Axon
Current type	Potassium A-type (Storm 1990, Martina et al. 1998)	Potassium A-type (Hoffman et al. 1997)	Potassium A-type (Kim 2014)
Current density	+	+++	++
Channel subunit	Kv4.2 (++), Kv4.3(++)	Kv4.2, Kv4.3	Kv1.4 (?), Dendrotoxin-sensitive K^+ current (likely Kv1.1, Kv1.2, Kv1.6)
Current type	Potassium fast delayed rectifier (IK)	Potassium fast delayed rectifier (IK)	Potassium fast delayed rectifier (IK)
Current density	+ (Hoffman et al. 1997)	+ (Hoffman et al. 1997)	
Channel subunit	Kv3.1, 3.2	Kv3.1, 3.2	
Current type	Potassium slow rectifier (ID)	Potassium slow rectifier (ID)	Potassium slow rectifier (ID)
Current density	+ − (Martina et al. 1998)	+ (Chen and Johnston 2004; Metz et al. 2007)	
Channel subunit	Kv1.1 (+, Wang et al. 1994, Martina et al. 1998),1.2; Kv2.1,2.2 (Maletic-Savatic et al. 1995; Martina et al. 1998)	Kv1.3(Metz et al. 2007); Kv 1.5 (Maletic-Savatic et al. 1995); Kv2.1 (Maletic-Savatic et al. 1995; Du et al. 2000; Misonou et al. 2006)	Kv1.1; 1.2 (Wang et al. 1994)
Current type	Potassium slow rectifier (ID)	Potassium slow rectifier (ID)	Potassium slow rectifier (ID)
IK_{Ca}	+++	+ (Johnston et al. 2000); but not Slo1 (Misonou et al. 2006)	
M-current (KCNQ)	++ (Hu et al. 2007)	- (Chen and Johnston 2004)	+ Vervaeke et al. 2006
Subunits	KCNQ2; KCNQ5 Shah et al. 2002	KCNQ2; KCNQ5 Shah et al. 2002	KCNQ2 Devaux et al. 2004

Table 3 Properties of inactivating voltage-gated K^+ current in different hippocampal neurons and the MFB

	DG FS (1)	CA1 PC (1)	DGGC (2, 3)	MFB (4)
Act. $V_{1/2}$	−6.2	−3	−7.6 (3)	−26
Act. Slope (mV/e-fold)	5.75*	6.75*	10 (3)	5.2*
Inact. $V_{1/2}$	−75.5	−77.3	−65.1 (3); −67 (2)	−72
Inact. Slope	8.5	7.4	6 (3); 6.3 (2)	9.6
TEA block	No	No	Yes	Yes

In the original papers (1) and (4) activation curves were fitted with a Boltzmann function raised to the fourth power. In order to allow direct comparison with data obtained fitting a simple Boltzmann component (References 2 and 3), the slope factors reported in the papers have been divided by 4 in this table (marked by *)

References 1: Martina et al. (1998), 2: Beck et al. (1992); 3: Riazanski et al. (2001); 4: Geiger and Jonas (2000)

(Nicoll and Alger 1981). Additionally, action potential frequency is also regulated by a Ca^{2+}-dependent potassium current, although the molecular identity of the channels mediating this current remains still unclear (King et al. 2015). Calcium-dependent, charybdotoxin-sensitive potassium channels appear to be unevenly distributed along the somatodendritic axis of CA1 neurons, with channel density decreasing with distance from the soma (Poolos and Johnston 1999) so that the current mediated by these channels is almost completely absent at ∼150 μm from the soma (Johnston et al. 2000, see Fig. 1). This is in stark contrast to the A-type current density, which strongly increases along the dendrites, but also to the non-inactivating currents mediated by voltage-gated channels (most likely by Kv3 and Kv2 subunits), which are expressed at constant density throughout the somatodendritic compartment (Hoffman et al. 1997).

The data presented so far suggest that several different potassium channel subunits are expressed by CA1 pyramidal neurons. Indeed, in situ hybridization, immunostaining, and single-cell RT-PCR show that CA1 pyramidal neurons express many different potassium channel subunits, including Kv1.1, 1.2, 1.4, and 1.5 (Maletic-Savatic et al. 1995, Martina et al. 1998); Kv2.1 and 2.2 and Kv3.1, 3.2, and 3.3 (Martina et al. 1998; Du et al. 2000); and Kv4.2 and 4.3 (Serôdio and Rudy 1998; Martina et al. 1998; Rhodes et al. 2004). It is interesting that although expression of dendrotoxin-sensitive Kv1 subunits is detected in these cells, no effect of dendrotoxin, a Kv1-selective toxin (Grissmer et al. 1994), is detected on potassium currents either in nucleated patches from CA1 pyramidal neurons (Martina et al. 1998) or in focal somatic application of the toxin (Metz et al. 2007). This is consistent with reports showing that Kv1 channels are mainly expressed in presynaptic structures (Monaghan et al. 2001; Sheng et al. 1992). Whole-cell recordings, however, showed an effect of dendrotoxin on action potential initiation (Golding et al. 1999), further suggesting axonal localization of these channels. Finally, dendritic recordings and focal drug application showed that dendrotoxin-sensitive channels are also expressed in apical dendrites, where they modulate the

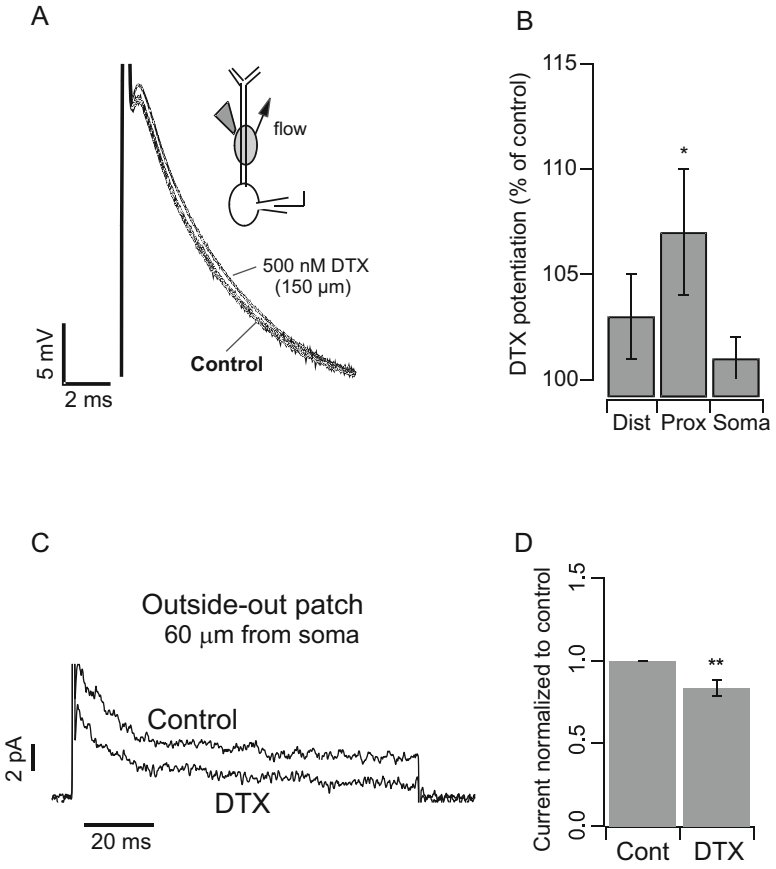

Fig. 2 Dendrotoxin sensitive currents in dendrites of CA1 pyramidal neurons (**a**) Current clamp recording of a somatic afterdepolarization (ADP) recorded in control conditions (thick line) and in the presence of focal dendritic application of dendrotoxin (DTX, thin line). The ADP is increased by DTX. (**b**) Bar chart summarizing the effects of DTX locally applied to the soma, proximal, and distal apical dendrites on the somatic ADP. (**c**) Voltage clamp outside-out dendritic recordings confirm the presence of DTX-sensitive currents in proximal apical dendrites. (**d**) Bar chart summarizing the blocking effect of DTX on dendritic potassium currents. (Figure modified from Metz et al. 2007)

size of the afterdepolarization that underlies burst firing (Metz et al. 2007). These data nicely match those obtained by histological analysis that shows expression of Kv1 subunits in the dendritic arbor of CA1 pyramidal neurons (Park et al. 2001). Thus, Kv1 subunit expression appears to be selectively absent from the soma, while present in both the axon and dendrites of CA1 pyramidal neurons.

M-Current This potassium current is mediated by members of the KCNQ family (Wang et al. 1998; Schroeder et al. 2000). M-current is expressed at very low density in the dendritic compartment of CA1 pyramidal neurons (Chen and Johnston 2004).

However, expression of KCNQ2 and KCNQ3 subunits is high in CA1 pyramidal neurons (Saganich et al. 2001), and M-type current in these neurons effectively controls burst generation (Yue and Yaari 2004). In keeping with these observations, Hu et al. (2007) have shown that M-current in CA1 pyramidal neurons is mainly localized in the perisomatic area. It has been proposed that the interaction between M-current and persistent sodium current mediates a form of theta resonance (M-resonance) in hippocampal CA1 pyramidal neurons (Hu et al. 2002).

Voltage-Gated Calcium Channels Both low- and high-voltage-activated calcium currents have been described in CA1 pyramidal neurons (Table 4). Calcium channels are primarily located at the soma, and their density decreases along the dendrites (Christie et al. 1995), although they are present in dendrites and in dendritic spines (Mills et al. 1994).

The high-voltage-activated current is itself mediated by multiple components. An omega-agatoxin IVA-sensitive (P-type) current contributes about 26% of the somatic high-threshold current (Mintz et al. 1992). N-type channels have also been described in the soma as well as dendrites and spines (Mills et al. 1994) although somatic expression appears more prominent. Nevertheless postsynaptic N-type current has been shown to play an important role in modulation of synaptic strength (Normann et al. 2000). CA1 pyramidal neurons also express large blocker-resistant high-voltage calcium current (R-type). In acutely dissociated cells, this component (defined as the fraction of calcium current available from a holding potential of −50 mV in the presence of the combined application of ω-CgTx GVIA, ω-CgTx MVIIC, ω-AgaTx IVa, and nifedipine) contributes ∼40% of the high-voltage-activated current (Sochivko et al. 2003). Interestingly, a large fraction of the tail current activated by an action potential in nucleated patches is attributable to the R-type (Metz et al. 2005). This current appears to play an important role in the regulation of the afterdepolarization that drives burst firing in CA1 pyramidal neurons. In particular, the calcium influx mediated by this tail current downregulates Kv7 potassium channels, which, when fully available, strongly attenuate the afterdepolarization (Chen and Yaari 2008). R-type currents are present also in dendrites and dendritic spines, where, together with T-type, they provide about 50% of the calcium currents evoked by backpropagated action potentials (Hoogland and Saggau 2004). The R-component in CA1 pyramidal neurons is partly mediated by α1E subunits (Sochivko et al. 2002), although other subunits also contribute as demonstrated by the fact that a current with the functional properties of the R current is still present in α1E knockout mice (Wilson et al. 2000).

The classical dihydropyridine-sensitive L-type current is also present in the soma as well as in the dendrites of pyramidal neurons (Takahashi et al. 1989; Magee and Johnston 1995a, b; Hoogland and Saggau 2004). Dihydropyridine-sensitive channels appear to be open at membrane potential around resting and therefore contribute to the neuronal calcium homeostasis (Magee et al. 1996). This current is expressed in every neuronal compartment although its density appears particularly elevated in the proximal apical dendrites. Activation at negative membrane potential and sensitivity to dihydropyridine suggest that this current is mediated by the α1D

Table 4 Voltage-gated calcium channels of CA1 pyramidal neurons

	Soma	Dendrites	Axon
T-type			
Density	++ (Magee and Johnston 1995a, b)	+ (Magee and Johnston 1995a, b)	
Subunits	Cav3.1; 3.2; 3.3 (McKay et al. 2006)	Cav 3.2; 3.3 (McKay et al. 2006)	Cav3.3 (McKay et al. 2006)
L-type			
Density	++ (Magee and Johnston 1995a, b)	++(Magee and Johnston 1995a, b)	
Subunits	Cav1.2 (Tippens et al. 2008) +++	Cav1.2 (Tippens et al. 2008) ++	Cav1.2 (Tippens et al. 2008) ++
	+ Bowden et al. 2001	++ Bowden et al. 2001	
Subunits	Cav1.3 (Veng and Browning 2002) ++	Cav1.3 (Veng and Browning 2002) ++	Cav1.3(Veng and Browning 2002) + −
	+ Bowden et al. 2001	++ Bowden et al. 2001	
N-type	++ (Christie et al. 1995)	+ − (Christie et al. 1995)	
	But NOT Cav2.2 (Chung et al. 2000)		
Density	++ Magee and Johnston (1995a, b)	+ Mills et al. 1994 (omega-CgTx-sensitive);	
		- Magee and Johnston (1995a, b)	
P/Q-type			
Density	+ (Christie et al. 1995)	+ − (Christie et al. 1995)	
	+ Hillman et al. 1991	+ Hillman et al. 1991	
	++ Stea et al. 1994		
Subunits	Cav2.1 (Day et al. 1996)	+ dendritic shaft	
	But NOT Cav2.2 (Chung et al. 2000)	Bloodgood and Sabatini 2007	
T-type (Cav2.3)	+ Metz et al. 2005	+ Dendritic spines	
	+ Wilson et al. 2000	Bloodgood and Sabatini 2007	
	+ Sochivko et al. 2002		

subunit (Cav1.3, Xu and Lipscombe 2001), which has been shown to be expressed throughout the somatodendritic compartment of CA1 pyramidal neurons (Veng and Browning 2002). However, Radzicki et al. (2013) showed that a large low-threshold nimodipine-sensitive current is still present in CA1 pyramidal neurons of Cav1.3 KO mice. The same authors also showed that Cav1.2 and 1.3 are the only L-type subunits expressed in the CA1 subfield, thus suggesting that Cav1.2 subunits mediate a large fraction of the resting calcium current in these neurons. Low-threshold T-type currents (in CA1 pyramidal cells, these currents start activating ~ -60 mV and reach full amplitude ~ -20 mV; Takahashi et al. 1991) are also present in both the somatic and dendritic compartments (Takahashi et al. 1989; Magee and Johnston 1995a, b). Dendritic T-type currents are activated by subthreshold synaptic events and produce local increases in intracellular calcium, which may be important for the regulation of synaptic strength (Magee et al. 1995). It has been shown that selective potentiation of T-type current occurs in status epilepticus and can transform CA1 pyramidal neurons from regular firing to intrinsically low-threshold bursting cells (Su et al. 2002); it has also been proposed that the increase in T-type current density associated with status epilepticus is limited to, or more prominent, in the apical dendrites where these channels facilitate dendritic depolarization by backpropagating somatic spikes (Yaari et al. 2007).

Hyperpolarization-Activated Current (Ih) The hyperpolarization-activated current is a depolarizing current (the reversal potential is ~ -20 mV) activated by hyperpolarizations more negative than ~ -60 mV and was first described in CA1 pyramidal neurons by Maccaferri et al. (1993). This current is important for regulating firing activity as well as input resistance, and its density sharply increases along the somatodendritic axis (Magee 1998; Fig. 1). It is worth stressing that such gradient in Ih density, although very prominent in CA1 pyramidal neurons as well as in layer 5 cortical pyramidal neurons (Stuart and Spruston 1998), does not appear to constitute a general property of all pyramidal neurons. Bullis et al. (2007) recently described pyramidal-like principal (PLP) neurons, a novel class of hippocampal neurons with pyramidal morphology found in the stratum radiatum. Interestingly, in these neurons the Ih gradient is inverted, showing high somatic density that declines along the dendrites. This finding further supports the notion that, although general rules may regulate ion channel distribution among different neuronal classes, extrapolations should be avoided, and a detailed study is required for each cell type.

CA3 Pyramidal Neurons

The input resistance of CA3 pyramidal neurons is in the range 120–200 KΩ cm^2 (Major et al. 1994). The **sodium currents** are functionally similar to those in CA1 pyramidal cells, although some differences were observed in the voltage-dependent inactivation (Steinhäuser et al. 1990). It was recently shown that in CA3 pyramidal

neurons, sodium channel density is maximal in the axon at 30–50 μm from the soma, which constitutes the location of first action potential generation (Meeks and Mennerick 2007).

Similar to CA1 pyramidal neurons, the voltage-gated **potassium current** of CA3 pyramidal neurons can be classified into three main components: IA, ID, and IK. Of these, the fast-activating ID and IA contribute to the repolarization of the action potential (Mitterdorfer and Bean 2002).

A direct comparison of the potassium currents in CA1 and CA3 pyramidal neurons was performed by Klee et al. (1995). The main difference found was a larger contribution of Ca-dependent current in CA3 cells (20% of total delayed rectifier vs. 10% in CA1). This finding fits well with the observed impact of SK channels on the frequency of intra-burst action potentials in CA3 pyramidal neurons.

One potentially interesting difference is that in CA3 pyramidal neurons, part of the inactivating A-type current is highly 4-AP-sensitive (Bossu et al. 1996), which suggests that channels constituted either by Kv1 subunits associated to beta subunits (which confer rapid A-type inactivation to non-inactivating Kv1 channels; Rettig et al. 1994) or by Kv3.3/3.4 subunits contribute to this current. Relatively abundant expression of Kv3.3 transcript was actually reported in CA3 pyramidal layer (Weiser et al. 1994). A larger contribution of Kv3.3 subunits to the fast transient potassium current of CA3 neurons compared to the current of CA1 neurons (which is almost entirely mediated by Kv4 subunits, see above) may favor the generation of low-threshold bursts because of the more depolarized action potential values required to activate Kv3.3 channels compared to Kv4 (Baldwin et al. 1991; Fernandez et al. 2003). Another potential difference between the potassium current of CA3 and CA1 pyramidal neurons concerns the expression by CA3 cells, at least in organotypic cultures, of a current that is down-modulated by intracellular calcium and is involved in action potential repolarization as well as in the control of synaptic transmission (Saviane et al. 2003). In keeping with this observation, two of the potassium currents of CA3 pyramidal neurons, a voltage-gated current and a Ca-dependent current, are inhibited by activation of an ACPD-sensitive quisqualate receptor (Charpak et al. 1990), suggesting that the local metabolic state influences the size of these currents and therefore the input-output function of CA3 pyramidal neurons. Along this line, Hyun et al. (2013) have shown that a current likely mediated by Kv1.2 channels is downregulated by increased intracellular calcium and causes intrinsic hyperexcitability in response to action potential trains (10 Hz). Interestingly, such potentiation was not detected in CA1 pyramidal neurons.

Similar to CA1, the **calcium current** in CA3 pyramidal neurons is the sum of multiple components (Mogul and Fox 1991). Overall the currents are similar to those of CA1 pyramidal neurons (Thompson and Wong 1991). P-type contribution to the high-threshold currents, however, is smaller in CA3 neurons than in their CA1 counterparts (14% vs. 26% Mintz et al. 1992); a detailed analysis (Avery and Johnston 1996) showed that the main difference between the currents of the two cell types is that in CA3 pyramidal neurons, the low-voltage-activated current actually comprises two different components, one inactivating and nickel sensitive (typical T-type) and one sustained and partly dihydropyridine sensitive (L-type; see

Table 5 Distribution and gating properties of dendritic Na^+ channels in the main glutamatergic cell types of the hippocampus

	DG FS (Hu et al. 2010)	CA1 PC (Magee and Johnston 1995a, b; Kim et al. 2012)	CA3 PC (Kim et al. 2012)
Conductance density vs. distance to soma	Low (+/−)	Constant (++)	Increasing (from ++ to ++++)
Act. $V_{1/2}$	N/A	−30	−37.6
Act. slope (mV/e-fold)	7.2	7.9	
Inact. $V_{1/2}$	−62	−72.9	
Inact. slope	6.9	8.0	

Xu and Lipscombe (2001)). The presence of multiple types of low-voltage-activated calcium channels may contribute to the intrinsic firing of CA3 neurons.

Recent technical advancements, such as confocally guided subcellular patch clamp techniques, have helped advancing our knowledge of the ion conductances in dendrites of CA3 pyramidal neurons (Kim et al. 2012). Interestingly, in these cells dendritic spikes are mediated by voltage-gated Na^+ channels, rather than by Ca^{2+} channels. Conversion of dendritic current density into conductance density revealed that the average ratio of Na^+ to total K^+ conductance density is 0.72. Thus, CA3 pyramidal neuron dendrites show a high Na^+-to-K^+ current ratio in comparison with other types of neurons (Table 5). The density of the different components showed differential distance dependence. For the Na^+ current, the apparent density decreased from the soma to the proximal dendrites and then increased from the proximal to the distal dendrites. In contrast, the dendritic A-type K^+ current density increased continuously from the soma to the distal dendritic region. Finally, the delayed rectifier K^+ current density was not significantly dependent on distance (Kim et al. 2012).

CA2 Pyramidal Neurons

CA2 is a unique region situated between CA3 and CA1. Several recent studies revealed that pyramidal cells in this subfield have distinctive synaptic connectivity, intrinsic membrane properties, and functional roles (Chevaleyre and Siegelbaum 2010; Kohara et al. 2014; Palacio et al. 2017; Srinivas et al. 2017; see review by Robert et al. 2018). The development over the past decade of new tools such as molecular profiling and transgenic mouse lines has enabled the reliable identification of CA2 pyramidal neurons, facilitating the investigation of the functional properties of this cell population. CA2 pyramidal neurons display unique intrinsic electrophysiological properties that are distinct from those of CA1 or CA3 pyramidal neurons. In comparison to CA1 pyramidal neurons, the resting

potential of CA2 pyramidal neurons is more hyperpolarized, with values ranging from −76 mV to −74 mV at 30–36 °C for adult mice (Zhao et al. 2007; Chevaleyre and Siegelbaum 2010; Sun et al. 2014, 2017; Piskorowski et al. 2016; Srinivas et al. 2017). Additionally, the resting potential of CA2 pyramidal neurons appears to become gradually more hyperpolarized along the transverse axis from area CA2 and throughout CA3 (Sun et al. 2017). Similarly, the input resistance exhibits a proximo-distal (from CA3c to CA2) gradient, with the lowest values measured in CA2 pyramidal neurons, ranging from 49 to 86 MΩ (∼15.5–26 KΩ cm^2) at 33–36 °C (Palacio et al. 2017; Chevaleyre and Siegelbaum 2010; Srinivas et al. 2017). The gradients in both resting potential value and input resistance may be mediated, at least in part, by a similar proximo-distal gradient in Ih (see below).

Voltage-Gated Potassium Channels Although molecular profiling studies have identified distinct mRNA expression patterns between CA1 and CA2 (Talley et al. 2001; Lein et al. 2005), the expression of different types of channels in CA2 pyramidal neurons remains largely unexplored. The expression levels of the Kv2 subunit are strikingly different in CA1 and CA2 pyramidal neurons (Palacio et al. 2017). Fluorescence immunohistochemistry in mouse brain has revealed that Kv2.1, Kv2.2, and their auxiliary subunit AMIGO-1 have the highest expression levels in CA1, with a sharp decrease at the CA1-CA2 boundary, and significantly reduced levels in CA2 pyramidal neurons (Palacio et al. 2017). Consistent with this observation, CA2 pyramidal neurons lack the prominent slow afterhyperpolarization seen in CA1 pyramidal neurons (Chevaleyre and Siegelbaum 2010; Palacio et al. 2017), and that has been attributed to Kv2-mediated currents (Liu and Bean 2014).

Hyperpolarization-Activated Current (Ih) The depolarizing membrane "sag" in response to hyperpolarizing current injection, which is caused by Ih activation, is much larger in CA1 than in CA2 pyramidal neurons (Chevaleyre and Siegelbaum 2010). This difference is consistent with the higher expression of the HCN1 subunit in CA1 pyramidal neurons compared to CA2 and CA3 (Notomi and Shigemoto 2004; Santoro et al. 2004; Srinivas et al. 2017). In agreement with the linear gradient in resting potential and input resistance across the transverse axis, CA2 pyramidal neurons exhibit the greatest sag amplitude, followed by CA3a, with CA3c having the smallest sag (Sun et al. 2017).

Dentate Gyrus Granule Neurons

Granule cells are glutamatergic projection neurons conveying information from the dentate gyrus to the CA3 area of the hippocampus. From an electrophysiological perspective, these neurons are particularly interesting among central glutamatergic neurons because the large size of their axonal terminals allows patch clamp characterization of the ion channels in the boutons (Geiger and Jonas 2000; Bischofberger et al. 2002; Engel and Jonas 2005), thus providing a rare opportunity to compare the properties and density of ion channels in the soma and the axon terminal of

Table 6 Gating properties of Na^+ channels in hippocampal neurons

	DG FS Soma (1)	CA1 PC Soma (1)	DGGC Soma (2, 4)	DGGC Bouton (3)
Act. $V_{1/2}$	−25.1	−23.9	−22.6 (2)	−38.4
			−25.8 (4)	
Act. slope (mV/e-fold)	11.5	11.8	5.8 (2); 5.2 (4)	8
Deact. τ (−40 mV)	0.13 ms	0.2 ms		0.17 ms
Inact. $V_{1/2}$	−58.3	−62.9	−56.8	−89.6
Inact. slope	6.7	10.7	6.7	6.4

References 1: Martina and Jonas 1997; 2: Ellerkmann et al. 2001; 3: Engel and Jonas 2005 4: Ellerkmann et al. 2003

an individual neuron. Granule cells have particularly negative membrane potentials (−75 mV at physiologic temperature, Lübke et al. 1998) and relatively low input resistance (38 KΩ* cm^2, Schmidt-Hieber et al. 2007), which suggests abundant expression of background potassium channels.

Sodium Current The density of sodium current in granule cells was determined in acutely dissociated rat neurons (Ellerkmann et al. 2003); thus, these measurements offer an estimate of the density in the somatic compartment. These authors found a density of ∼33 mS cm^{-2} (extrapolated from the reported 1400 pA/pF, assuming a reversal potential of 30 mV, see Fig. 1 in their paper, and a specific capacitance of 0.9 μF cm^{-2} (Gentet et al. 2000)), similar to that in the soma and dendrites of OLM interneurons. These authors also studied the expression profile of the different voltage-gated sodium channel subunits and found co-expression of several subunits in these neurons: in particular, they demonstrated expression of Nav 1.2; 1.3; 1.5; 1.6. The current activation is strongly voltage-dependent (the slope is 5.2 mV/e-fold, Table 6); similar strong voltage dependence characterizes the fast inactivation process of the current, which is half inactivated at −48 mV and has a slope of −5.8 mV/e-fold. The recovery from fast inactivation is best fit by the sum of two exponential functions: a fast component with time constant (at −80 mV) of 6.8 ms (and relative amplitude ∼90%) and a smaller slow component with time constant of 546 ms. The recovery from inactivation in somatic granule cells channels was also analyzed by Engel and Jonas (2005) using outside-out patches. Similar to Ellerkmann et al., they found that the recovery from inactivation is best fit by a double exponential function with the fast component accounting for most of the current (relative amplitude 0.8). The time constants were however faster than in dissociated neurons ($\tau_1 = 4$ ms and $\tau_2 = 65$ ms), possibly suggesting that the recovery from inactivation is actively modulated through intracellular pathways which may be differently affected in whole cell and excised patch recordings.

When long depolarizations are applied (10–300 s at −10 mV, at room temperature), the sodium current of dentate gyrus granule cells undergoes slow inactivation.

The recovery from this inactivated state is described by a bi-exponential process, with fast and slow time constants ranging in the 1–10 and 20–50 seconds, respectively (Ellerkmann et al. 2001). The importance of slow inactivation in physiologic processes remains to be explored; it is interesting, for instance, that status epilepticus deeply affects the properties of fast activation and fast inactivation of granule cells' sodium currents (half maximal activation shifts from −25.8 in control to −28.6 mV and the fast inactivation half point from −48.2 to −43.2 mV; these changes lead to a significant increase of the window current, resulting in higher neuronal excitability), while the slow inactivation appears to be unaffected (Ellerkmann et al. 2003).

The axon terminals of these neurons have been carefully studied. The gating properties of the sodium current in the mossy fiber boutons were compared to those of the somatic component; the main difference was in the inactivation kinetics that in the bouton is almost twofold faster than in somatic patches (Engel and Jonas 2005). The current density in mossy fiber bouton is 49.0 mS cm^{-2} (range: 9–138 mS cm^{-2}), which corresponds to an estimated channel density of 41 channels μm^{-2} in hippocampal MFBs. These density values are comparable to previous estimates in invertebrate axons (120 mS cm^{-2} in squid axons and 40 mS cm^{-2} in Myxicola axons; Hodgkin and Huxley 1952 and Goldman and Schauf 1973). Thus, presynaptic mossy fiber terminals have axon-like properties, expressing voltage-gated Na^+ channels at very high density. Very recently, Schmidt-Hieber et al. (2008) have used dual axo-somatic recordings and computer modeling to obtain an estimate of the sodium current density in mossy fiber axons and found that axonal sodium current density of 100 mS cm^{-2} best fit the experimental data.

Potassium Current Similar to other neurons, the potassium current of granule cells is the sum of at least two components: IA (see Table 3 for the A-type current properties) and IK (Beck et al. 1992).

Contrary to pyramidal neurons, however, the fast inactivating component in granule cells is TEA sensitive and largely mediated by Kv3.4 channels (Riazanski et al. 2001). Interestingly, these authors showed that Kv3.4 expression in granule cells is spatially segregated, showing higher expression around the axon initial segment and lower expression in the somatic compartment more distal from the axon; these data suggest a role for these channels in controlling the generation of action potentials.

The heterogeneous nature of the potassium current in granule neurons is supported by the expression of multiple ion channel subunits, including Kv1.1, 1.2, and 4.2 (Sheng et al. 1994; Tsaur et al. 1992), Kv4.3 (Serôdio et al. 1996), and GIRK1 and GIRK2 (Liao et al. 1996). Kv3.1 RNA expression was also detected in granule neurons, although at low level (Weiser et al. 1995).

The current in the mossy fiber terminal is largely dendrotoxin-sensitive (Geiger and Jonas 2000), in agreement with the prominent expression of Kv1.2 subunits (Sheng et al. 1994). Additionally, specialized voltage-activated K^+ channels of the Kv3 family and calcium-dependent, large conductance, potassium (BK) channels are present at a low density (Alle et al. 2011; but see Misonou et al. 2006). Interestingly, direct bouton recordings show that Kv3 channels efficiently contribute

to the presynaptic AP repolarization, whereas BKCa channels, which are designed and arranged not to interfere with basal AP repolarization, are activated during sustained AP trains and limit AP duration in case of KV3 hypofunction (Alle et al. 2011).

Calcium Current Voltage-gated calcium currents of granule cells include both high- and low-voltage activated currents (Blaxter et al. 1989; Fisher et al. 1990). About 40% of the current is blocked by dihydropyridines (and is therefore L-type), while P/Q-type and N-type current each accounts for about 20% of the total current (Eliot and Johnston 1994). These data suggest that T- and R-type currents account for ~23% of the total current. T-type current was described by Zhang et al. (1993) and contributes to the spike afterdepolarization (ADP). R-type current was estimated to contribute about half of the blocker-resistant current (Sochivko et al. 2002).

Calcium currents have been carefully studied in the mossy fiber bouton (Li et al. 2007). These authors found that a single bouton contains ~2000 voltage-gated calcium channels. The largest current fraction (66%) is mediated by P/Q channels, while N- and R-type contribute 26% and 8% of the total current, respectively.

Dentate Gyrus Mossy Cells

Mossy cells represent the third population of glutamatergic neurons in the hippocampal formation. These large multipolar neurons of the fascia dentata (Frotscher et al. 1991; Lübke et al. 1998) are characterized by relatively slow maximum firing rate (50 Hz at 35–37 °C, Lübke et al. 1998) and by the presence of a prominent membrane sag upon injection of hyperpolarizing currents. The resting membrane potential is between −60 and − 62 mV at 30–37 °C (Jinno et al. 2003; Lübke et al. 1998). The voltage-gated **sodium current** of mossy cells activates at potentials ≥ − 50 mV; fitting the conductance/voltage plot reveals half activation at −31 mV and (Howard et al. 2007).

The **potassium current** of these cells consists of at least three components: an A-type current, a delayed rectifier, and a third component, resistant to both 4-AP (2.5 mM) and TEA (25 mM), characterized by activation kinetics slower than the two other components (Howard et al. 2007). The kinetics and pharmacological properties strongly suggest that the A-type current is mediated by Kv4 subunits. More data are required in order to attribute the two other current components to expression of any individual channel subunit. An interesting difference in intrinsic electrophysiological properties has been reported between dorsal and ventral mossy cells. The majority of the ventral cells show intrinsic bursting, a phenotype that is never observed in dorsal mossy cells (Jinno et al. 2003). Interestingly, Ih expression is similar in bursting and non-bursting neurons; in keeping with these data, it was found that Ih in mossy cells starts activating around −65 mV, so that activation of this current is absent or minimal at resting membrane potential. Thus, in mossy cells Ih does not appear to play a role in intrinsic firing, similarly to what observed

in other neurons in different parts of the CNS (Atherton and Bevan 2005; Russo et al. 2007). Bursting in these neurons appears to depend on a phenytoin-sensitive persistent sodium current that starts activating around −50 mV (Jinno et al. 2003).

Hippocampal Interneurons

DG Basket Cells

Dentate gyrus basket cells are parvalbumin-positive fast-spiking interneurons and can be considered prototypical perisomatic inhibitory interneurons (see chapter "Connectivity of the Hippocampus"). These cells can fire at extremely high frequency (>200 Hz) and have very low input resistance (10 KΩ*cm^2, Bartos et al. 2001).

Sodium Currents Sodium currents of fast-spiking interneurons (see Table 6) are characterized by their very rapid recovery from fast inactivation, which is described (at −120 mV and room temperature) by a single exponential process with a time constant of ∼2 ms. Another typical property of the sodium current of these neurons is the extremely fast deactivation (the time constant at −40 mV and ∼23 °C is 0.13 ms; Martina and Jonas 1997). These two kinetic properties constitute the main difference between the current of basket cells and that of CA1 pyramidal neurons. Whether these differences are attributable to ion channel modulation or to expression of different subunits remains to be investigated. The sodium channel density at the soma is ∼36 mS cm^{-2} and quickly declines along the dendrites with an estimated length constant of 25 μm in basal dendrites (Hu et al. 2010).

Potassium Currents Voltage-gated potassium currents of fast-spiking DG interneurons (putative basket cells) were studied in detail using the nucleated patch technique and single-cell RT-PCR (Martina et al. 1998). Two aspects set the potassium current of these cells apart from that of pyramidal neurons or dentate gyrus granules: (1) the total current density is almost double than in CA1 pyramidal neurons (175 vs. 95 pS/μm^2), and (2) the current is characterized by the almost complete absence of time-dependent inactivation. Functional and pharmacological dissection of the total voltage-gated current shows that, similar to the current of CA1 pyramidal cells, it is composed by three main components: a highly TEA- and 4AP-sensitive fast delayed rectifier (mediated by Kv3 subunits); a slow activating, slowly inactivating component (ID, probably mediated at least in part by Kv2 channels); and an A-type (fast activating and inactivating), TEA-resistant current (mediated by Kv4 subunits, Table 3). Contrary to pyramidal neurons, though, the A-type current only contributes ∼17% of the total current, while the Kv3-like sustained current accounts for 58%. This sustained current appears ideally suited to allow effective repolarization of the fast action potential of these neurons due to extremely fast activation and deactivation kinetics (Fig. 3) and relatively positive activation potential (the activation midpoint is ∼ − 7 mV).

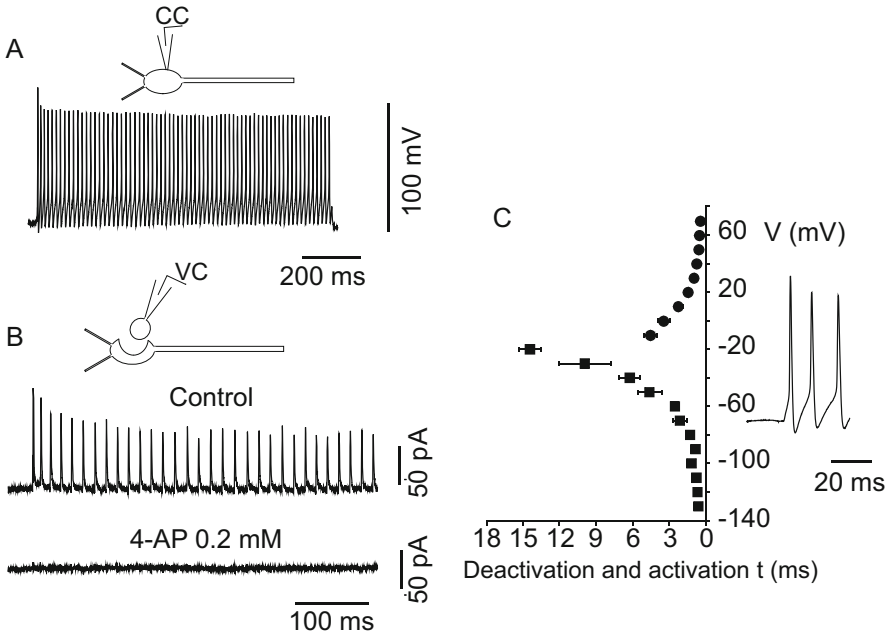

Fig. 3 Kv3 channels mediate action potential repolarization in fast-spiking interneurons of the dentate gyrus. (**a**) Current clamp recording of the firing response of a fast-spiking interneuron to the injection of depolarizing current. (**b**) The membrane potential waveform was then used as voltage stimulus to nucleated patches to study the potassium currents activated by each spike (recordings were performed after blockade of voltage-gated sodium and calcium currents). The potassium current elicited by the high-frequency action potentials was abolished by low concentration of 4-AP. (**c**) Plotting the activation and deactivation time constants of the 4-AP-sensitive current versus the voltage trajectory of the action potentials shows that asymptotic values of activation and deactivation time constants are reached at membrane potentials within the action potential range, allowing fast spike repolarization and minimum refractory period. (Figure modified from Martina et al. 1998)

Recent work has shed further light on the subcellular signaling properties of parvalbumin-positive fast-spiking interneurons (Hu et al. 2010; Table 7). Simultaneous somatodendritic recordings from basket cell dendrites show a high K^+ to Na^+ conductance ratio in BC dendrites. The Na^+ current density is a function of the distance from the soma, with 13.3 ± 2.1 pA/μm^2 (−120 mV to 0 mV) at the soma and steeply declines as a function of distance, with estimated length constants of 87 μm in apical dendrites and 25 μm in basal dendrites. In contrast, in somatic outside-out patches isolated with K^+ internal solution, voltage pulses from −120 mV to 70 mV evoked large voltage-dependent outward currents. Quantitative analysis revealed a K^+ current density of 91.5 ± 21.1 pA/μm^2 at the soma. In apical dendrites, the K^+ current density decays moderately as a function of distance, with an estimated length constant of 763 μm. In contrast, in basal dendrites, the decay is steeper, with a length constant of 57 μm. Consistent with immunocytochemical

Table 7 Gating properties of dendritic K^+ channels of hippocampal neurons

	DG FS (Hu et al. 2010)	CA1 PC (Hoffman et al. 1997)		CA3 PC (Kim et al. 2012)	
Component	Sustained (Kv3-like)	Transient	Sustained	Transient	Sustained
Act. $V_{1/2}$	−10.9 (apical) −12.6 (basal)	−1	13	−9.6	−3.8
Act. slope (mV/e-fold)	10.9 (apical) 8.9 (basal)	15	11	16	10.2
Inact. $V_{1/2}$	N/A	−56	N/A	−65.6	N/A
Inact. slope	N/A	8	N/A	7.1	N/A
TEA block	Yes	Yes	Yes	N/A	Yes
4-AP block	N/A	Yes	Little	Yes	N/A

data, analysis of dendritic K^+ current kinetics suggests that it is mainly mediated by Kv3-type channels. Such a high density of K^+ channels in basket cell dendrites contributes to unique integrative properties, leading to the rapid and temporally precise activation by excitatory inputs (Hu et al. 2010).

Calcium Currents Less is known about the calcium currents in basket cells; it has been recently shown that P/Q calcium channels mediate release at synapses of basket cells (Hefft and Jonas 2005), but a comprehensive study of the calcium currents present in these cells is still missing.

It is also worth mentioning that basket cells also express connexin36, although the strength of the electrical coupling is low and appears to decline with development. In 14-day-old mice, 92% of the cells tested are electrically coupled, although the coupling coefficient is low (0.029). In slices from 42-day-old mice, in contrast, only 30% of the cells are electrically coupled, and the coupling coefficient is further reduced (0.012, Meyer et al. 2002).

Hyperpolarization-Activated Current (Ih) Ih current contributes to the resting membrane potential and background conductance and thus mediates the fast membrane time constant of fast-spiking basket cells (Aponte et al. 2006). Ih channels of basket cells are nonselective cation channels with a slight preference for K^+ over Na^+ ions (P_{Na}/P_K is 0.36), and their activation curve has a midpoint potential (−83.9 mV) similar to other cell types (−90 to −83 mV; Franz et al. 2000). It is important to notice that Ih in basket cells displays several distinct functional properties compared with other types of central neurons. First, Ih channels in basket cells have slower activation as its activation time constant is 190 ms (at −120 mV and 21–24 °C), significantly slower than in hippocampal CA1 pyramidal neurons (64 ms) and neocortical layer 5 pyramidal neurons (84 ms), but faster than in substantia nigra dopaminergic neurons (482 ms) and thalamocortical neurons (602 ms; 22–24 °C; Franz et al. 2000). Second, both ZD7288- and Cs^+-sensitive currents evoked by hyperpolarizing test pulses from a holding potential of −50 mV show a time-dependent current component and an instantaneous component.

Ih channels are expressed in both somatodendritic and axonal domains of basket cells (Aponte et al. 2006). Somatodendritic Ih shapes the input-output relation of basket cells, whereas axonal Ih current contributes to axonal excitability and synaptic output. Ih channels in presynaptic terminals maintain facilitate spontaneous release by maintain the terminals closer to action potential threshold. A recent study (Elgueta et al. 2015) demonstrates that Ih channels enable basket cells to integrate their intrinsic activity over time and can sustain persistent firing mode characterized by the ability to generate long-lasting trains of action potentials at 50 Hz in the absence of additional inputs. Interestingly, computational models suggest that the instantaneous component in the axon may contribute to the sustained firing (Elgueta et al. 2015).

Stratum Oriens Horizontal Interneurons
Horizontal interneurons in the hippocampal CA1 area represent a relatively homogeneous population and are prototypical feedback interneurons (see chapter "Connectivity of the Hippocampus"). Many of these cells are somatostatin-expressing OLM cells (Martina et al. 2000) which are capable of repetitive firing upon injection of depolarizing current, although their maximum frequency does not reach frequencies as high as those of basket cells (Lien and Jonas 2003). These neurons are also functionally easily distinguishable from basket cells because they are often intrinsically firing due to presence of large Ih (Maccaferri and McBain 1996). Ih expression also differentiates the response to hyperpolarizing current injection of these neurons from that of basket cells because the voltage response of OLM cells is characterized by a large voltage sag, which is absent in basket cells. Another interesting difference between OLM neurons and basket cells resides in the value of the input resistance, which in OLM cells is quite high (48 $K\Omega*cm^2$, Taverna et al. 2005), due to relatively low expression of background potassium channels (Taverna et al. 2005; Torborg et al. 2006).

Sodium currents of OLM neurons have properties similar to those of dentate gyrus basket cells; in particular the recovery from fast inactivation can be fit by a single exponential function (time constant 5 ms at −120 mV and 22–23 °C, Martina et al. 2000). An interesting feature of these neurons is the capability of action potentials to undergo reliable and full amplitude backpropagation into the dendrites. In addition, strong focal excitation may also lead to dendritic action potential initiation (Martina et al. 2000). Full amplitude backpropagation is the consequence of high dendritic sodium current density (∼25 mS/cm^2, calculated from data in Martina et al. 2000). Dendritic initiation may also be favored by a ∼8 mV left shift in voltage dependence of the activation curve (midpoint was −37.8 mV for somatic patches and − 45.6 for dendritic patches). Dendritic sodium currents also contribute to boosting of excitatory synaptic inputs. As to the molecular identity of the sodium channels in these cells, recent data from the Catterall laboratory (Tai et al. 2014) suggest that Nav1.1 subunits contribute importantly to this current.

Potassium Currents Voltage-gated potassium currents are expressed at high and constant density throughout the somatodendritic compartment of OLM neurons

(Martina et al. 2000). The current composition is very similar, both in functional and molecular terms, to that of dentate basket cells (Lien et al. 2002). The total current is the sum of three components: a fast delayed rectifier (57% of the total current, mediated by Kv3 channels), an A-type current (19% of the total current, mediated by Kv4 subunits), and a slow delayed rectifier (25% of the total). In these neurons the deactivation of the Kv3 component is slower than in basket cells, most likely because of the more important contribution of the Kv3.2 subunit (Lien et al. 2002). Interestingly, this deactivation velocity appears to be finely tuned to allow the maximum firing frequency in this particular cell type (Lien and Jonas 2003). The potassium currents in OLM dendrites are very similar to the somatic ones with regard to both kinetics and sensitivity to block by broad-spectrum blockers such as TEA (Martina et al. 2000). It has also been suggested that a fraction of the TEA-sensitive current in the somatodendritic compartment of OLM cells appears to be mediated by KCNQ (M-current) channels. Although the size of this conductance is relatively small ($\sim$0.2 mS/cm^2, Lawrence et al. 2006), computer models suggest that this current may regulate the firing frequency of these neurons with minimal impact on the shape of the action potential (Lawrence et al. 2006).

Finally, little is known about voltage-gated **calcium channels** in these neurons. Poncer et al. (1997), however, showed that inhibitory potentials generated by interneurons in the CA3 stratum oriens are mediated by P/Q-type calcium channels.

Interneurons of the Stratum Radiatum-Lacunosum-Moleculare

Interneurons in this area can be classified into several classes. Vida et al. (1998) distinguished four classes: basket (BC), Schaffer associated (SA), perforant-path associated (PA), and neurogliaform (NC); most of these cells however can be classified as feedforward dendritic targeting interneurons. As it is the case in other brain areas, BCs are characterized by lower input resistance (70 MΩ) and more negative resting membrane potential (−60 mV) than the other interneurons (−56 mV, 96 MΩ; -55 mV, 84 MΩ; and − 58 mV, 75 MΩ for SA, PA, and NG, respectively). Although no comprehensive studies of the voltage-gated sodium currents in these cells are available, sensitivity to beta pompilidotoxin, a wasp toxin, shows that the sodium currents differ between radiatum and LM interneurons (Miyawaki et al. 2002), suggesting differential expression of individual subunits.

Contrary to basket cells of the stratum pyramidale and to OLM interneurons, which express Kv3.1b subunits at high level, interneurons in the stratum radiatum-lacunosum-moleculare only seldom express this subunit (21% vs. $\sim$90% of PV-positive basket cells; Sekirnjak et al. 1997). In agreement with this result, voltage-gated potassium currents of cultured interneurons of the stratum lacunosum-moleculare exhibit slow activation kinetics. Similar to other interneurons, the delayed rectifier current represents the sum of two components (a 4-AP sensitive and a 4-AP insensitive); the time to peak of the 4-AP-sensitive component is 4.2 ms at +45 mV (Chikwendu and McBain 1996; by comparison, the 20–80% rise time of Kv3-like currents at 40 mV in basket cells is $\sim$1 ms, Martina et al. 1998). The 4-AP insensitive component has much slower (and voltage-independent) activation

(the time to peak at 30 mV is 46 ms, Chikwendu and McBain 1996). It is likely that at least part of the 4-AP- and TEA-sensitive slow delayed rectifier is mediated by Kv1.1 channels, which are expressed in these cells (Rhodes et al. 1997).

Voltage-clamp recordings were performed to study calcium currents in visually identified interneurons in stratum radiatum, near the border with LM. When held at −80 mV, these cells exhibited a relatively small calcium current (0.4–1 nA in whole-cell configuration) that appeared to include at least three (L, N, and P/Q) calcium current components: the L-type component contributed ∼28% of the current, while the N-type current accounted for ∼23% of the total. The contribution of the P/Q component was more heterogeneous ranging from 0% to 30% (average ∼10%, Lambert and Wilson 1996). It is possible that the different contribution of N-type current in different cells reflected different histological classes of interneurons; this hypothesis however still needs experimental confirmation.

Low-voltage-activated calcium currents were also described in interneurons acutely dissociated from CA1 lacunosum-moleculare (Fraser and MacVicar 1991). The current size was quite small (the peak current, recorded at −30 mV, was 100 ± 7 pA, compared with ∼2 nA of TTX-sensitive sodium currents in the same neurons). This calcium current showed marked voltage-dependent inactivation, being half inactivated at −84 mV and totally inactivated at −60 mV. Less is known about dendritic calcium channels in these cells. Optical measurements however showed that action potential-associated calcium signals backpropagate into the dendrites of these neurons; indeed, backpropagated calcium signals progressively increase in size with distance from the soma (Rozsa et al. 2004). Whether this feature is the result of differential distribution of calcium channels or of other mechanisms (for instance, a different basal calcium level) remains to be investigated. These data however suggest that, similar to OLM interneurons, action potentials actively backpropagate into the dendrites of CA1 SR interneurons.

Experimental Techniques

Although conventional intracellular (sharp electrode) recordings can still provide valuable information about the electrophysiologic properties of neurons, most of the more recent literature (and of the data presented in this chapter) is based on patch clamp recordings. Some basic cellular properties appear quite different when compared using these two techniques. For example, resting membrane potential and input resistance measured with sharp electrodes and patch clamp techniques were directly compared in dentate gyrus basket cells (Staley et al. 1992), and the results obtained with the two techniques were quite different: with sharp pipette recordings, the resting potential was −74 mV and the input resistance was 54 MΩ, while the values obtained with patch clamp recordings were − 85 mV and 228 MΩ, respectively. A potential explanation for these differences is that they are the consequence of a sub-optimal seal around the sharp electrodes that leads to some current leakage and that is not present in patch clamp recordings. Therefore,

patch clamp data were preferentially used for this chapter, except when sharp electrode data were the only available. The patch clamp technique was pioneered in the late 1970s by Erwin Neher and Bert Sakmann (Neher et al. 1978) and was originally developed to allow the measurement of the currents flowing through single ion channels in cellular membranes. Briefly, small tip (~1 μm) pipettes are obtained by pulling glass capillaries, filled with saline and connected to a feedback amplifier. A tight electrical seal (in the GΩ range) is obtained between the pipette tip and the cellular membrane by applying gentle suction to the pipette. This leads to a firm attachment between the tip and the membrane, which allows several manipulations (Hamill et al. 1981) that offer invaluable tools for the study of many electrophysiological properties, varying from the cellular input resistance to the current flowing through single individual channels. The most commonly used configuration is the whole-cell configuration, in which, after obtaining the seal, continuity is obtained between the pipette and the cell interior by rupturing the cell membrane by applying brief negative pressure pulses. As a result, the pipette-cell assembly is well insulated from the bath solution. The intrapipette solution for these recordings is designed to reproduce the physiological intracellular solution (high potassium, low sodium). Whole-cell patch clamp recordings allow the accurate measurement of many basic functional properties such as resting membrane potential, input resistance, action potential threshold, amplitude, and frequency. Moreover, the voltage-clamp configuration allows recording the total ionic current flowing through the entire cell at each moment. Thus, complex voltage protocols and pharmacological tools can be used to isolate the currents mediated by individual channel types.

Although extremely successful on small isolated cells, such as acutely dissociated and cultured neurons, whole-cell voltage-clamp recordings are problematic when obtained from intact neurons having complex morphologies and large axonal and dendritic trees, as is the case for most neurons in brain slices. In this case the quality of voltage clamp is dramatically limited (see Major 1993 for a detailed discussion). Thus, data on current kinetics and voltage dependence are best obtained from excised patches and outside-out patches in particular. This configuration is obtained by pulling the pipettes away from the cell after having achieved the whole-cell mode (Hamill et al. 1981). By doing so, the lipid membrane seals the pipette tip leaving the outer side of the cell membrane exposed to the bath, while the inner side is exposed to the intrapipette solution. This configuration allows ideal voltage control and quick solution exchange, but is not always suitable for the study of channels expressed at low density in the cell membrane because the currents are often very small. An interesting variation of this technique is the nucleated patch (Sather et al. 1992). Similarly to the outside patch, the first step consists in achieving a whole-cell configuration. At this point a light suction is applied to the pipette, and the nucleus is attracted to the pipette tip. The pipette is then slowly withdrawn from the cell to obtain an outside-out patch. Because of the presence of the nucleus, the membrane has to reseal around the nucleus itself, and the result is an almost perfectly spherical outside patch comprising a large membrane area. Thus, the nucleated patch combines the possibility of precise identification of cells

in a slice with the possibility to record macroscopic currents and to obtain in almost ideal voltage-clamp conditions (Martina and Jonas 1997).

A potential pitfall common to intracellular and whole-cell patch clamp recordings is that these types of experiments lead to dialysis of the intracellular content. This fact has two main consequences: (1) it may lead to disappearance of some currents or cell functions ("rundown") due to the loss of diffusible factors into the recording pipette and (2) the intracellular ion concentrations are not the native ones but those imposed by the experimenter: this fact may become critical when examining the functional role of a conductance. A typical example is the $GABA_A$ channel, which is selective for anions and Cl^- ions in particular. Depending on the intracellular $[Cl^-]$, the $GABA_A$ conductance can be either hyperpolarizing or depolarizing. For this type of experiments, it is therefore critical to know the undisturbed cellular $[Cl^-]$. This can be obtained by establishing the electrical connection between the pipette and the cell interior not by rupturing the membrane but by inclusion in the pipette solution of a channel forming substance in the cell-attached mode (Horn and Marty 1988). By using substances that form channels selectively permeant to cations, as gramicidin, it is possible to obtain whole-cell recordings that maintain intact the neuronal chloride gradient. The technique also prevents intracellular dialysis because of the small diameter of the pores (they are only permeant to monovalent cations).

The Future

Although the hippocampus is one of the most thoroughly studied brain areas, much work is still needed to obtain a comprehensive description of the physiological properties of hippocampal neurons. In particular, future work will have to address two important aspects: one concerns the large heterogeneity of hippocampal neurons and interneurons in particular. Clearly, only a thorough study of each cell type will allow understanding of the fine tuning of hippocampal function; thus, detailed studies of the functional properties of anatomically identified neurons will be required for the many types of hippocampal neurons. With the technology of mouse genetic engineering, researchers have been able to create Cre-dependent driver lines that target specific classes of excitatory neurons (Kohara et al. 2014; Hitti and Siegelbaum 2014) as well as major classes and lineages of GABAergic neurons (Taniguchi et al. 2011). For example, using highly cell type-specific transgenic mouse lines for CA2, researchers can identify the CA2 pyramidal cells and characterize their intrinsic properties and ion channels (Kohara et al. 2014; Hitti and Siegelbaum 2014). Similarly, this approach allows reliable identification of GABAergic interneuron subtypes, thereby enabling detailed correlation between cell types and functional properties. At the same time, some technical aspects for functional studies may also require further development. Patch clamp recordings have greatly improved our knowledge of the electrophysiological properties of neurons. This technique, however, is not devoid of weaknesses. Two limitations of the

patch clamp technique are (1) the difficulty of obtaining data from small structures such as small dendrites, axons, and terminals, which results from the physical limitation in the size of the pipette tip as well as in the optical resolution necessary to distinguish such structures, and (2) the fact that the sealing process and, even more, the formation of the whole-cell configuration may cause important changes to the cellular cytoskeleton as well as to the composition of the intracellular milieu. Nowadays, increasing expectation is directed toward the development of low-toxic voltage-sensitive dyes, which may allow studying neuronal electrophysiology in intact cells. The signal to noise ratio of such dyes still represents a problem, but it is quickly improving (Baker et al. 2005). Particularly interesting is a recently developed method that allows filling neurons without the need to patch them to wash in the dye. This technique is the electrical electroporation, which has been extensively used for the delivery of DNA, RNA, and other molecules to the interior of cells. It has been shown that this technique can be effectively used to load neurons with fluorescent calcium indicators in vitro and in vivo (Nevian and Helmchen 2007). The combined use of electroporation and voltage-sensitive dyes may allow recording from cells with intact cytoskeleton and, even more importantly, obtaining detailed functional maps of small local circuitries. Another interesting technique that allows the identification of functional connections in a brain slice is the laser-scanning photostimulation (LSPS) based on glutamate uncaging. This technique allows for rapid imaging of local synaptic circuits by recording synaptic responses from a postsynaptic neuron while stimulating small clusters of presynaptic cells with high spatial resolution (Callaway and Katz 1993). A neuron is recorded in the whole-cell configuration and the slice bathing solution contains a molecularly caged form of glutamate. This molecule is then converted to the active form by submillisecond pulses of ultraviolet irradiation, which can be delivered selectively to small areas (of <100 μm diameter). It has been shown that, in most cases, this technique is selective enough to prevent activation of axons of passage, while the stimulus is sufficient to induce firing in the investigated neurons. Thus, the technique can be effectively used for mapping local circuits.

Optogenetic-assisted circuit mapping is another unprecedented development, which is based on the combination of optogenetics and patch clamp recordings. Optogenetics is a recent technology emerging from basic genetic research on microorganisms that rely on light-responsive opsin proteins to survive (see review by Deisseroth 2010, 2011). Using viral vectors, scientists can insert opsin genes, which encode light-sensitive proteins, in a specific population of neurons and control their activity with the light. Channelrhodopsin-2 (ChR2) is a light-sensitive cationic channel. By expressing ChR2 in the neuronal membrane of a select cell population, scientists can effectively drive the neurons to generate action potentials by shining blue light (470 nm). In contrast, halorhodopsin (HR) is a light-sensitive chloride pump, which transports the chloride into the cells. With a flash of amber light (589 nm), scientists can silence HR-expressing neurons. This technology permits temporally precise, cell type-targeted experiments in ex vivo brain slices as well as in vivo in anesthetized or freely moving animals. Additionally, viral-genetic

tracing allows the investigation of the intrinsic properties neuronal populations with common synaptic input or output.

Further Reading

Alle H, Kubota H, Geiger JR (2011) Sparse but highly efficient Kv3 outpace BKCa channels in action potential repolarization at hippocampal mossy fiber boutons. J Neurosci 31(22):8001–8012

Aponte Y, Lien CC, Reisinger E, Jonas P (2006) Hyperpolarization-activated cation channels in fast-spiking interneurons of rat hippocampus. J Physiol 574(Pt 1):229–243

Atherton JF, Bevan MD (2005) Ionic mechanisms underlying autonomous action potential generation in the somata and dendrites of GABAergic substantia nigra pars reticulata neurons in vitro. J Neurosci 25(36):8272–8281

Avery RB, Johnston D (1996) Multiple channel types contribute to the low-voltage-activated calcium current in hippocampal CA3 pyramidal neurons. J Neurosci 16(18):5567–5582

Baker BJ, Kosmidis EK, Vucinic D, Falk CX, Cohen LB, Djurisic M, Zecevic D (2005) Imaging brain activity with voltage- and calcium-sensitive dyes. Cell Mol Neurobiol 25(2):245–282

Baldwin TJ, Tsaur ML, Lopez GA, Jan YN, Jan LY (1991) Characterization of a mammalian cDNA for an inactivating voltage-sensitive K+ channel. Neuron 7(3):471–483

Bartos M, Vida I, Frotscher M, Geiger JR, Jonas P (2001) Rapid signaling at inhibitory synapses in a dentate gyrus interneuron network. J Neurosci 21(8):2687–2698

Beck H, Ficker E, Heinemann U (1992) Properties of two voltage-activated potassium currents in acutely isolated juvenile rat dentate gyrus granule cells. J Neurophysiol 68(6):2086–2099

Bischofberger J, Geiger JR, Jonas P (2002) Timing and efficacy of Ca2+ channel activation in hippocampal mossy fiber boutons. J Neurosci 22:10593–10602

Blaxter TJ, Carlen PL, Niesen C (1989) Pharmacological and anatomical separation of calcium currents in rat dentate granule neurones in vitro. J Physiol 412:93–112

Bloodgood BL, Sabatini BL (2007) Nonlinear regulation of unitary synaptic signals by CaV(2.3) voltage-sensitive calcium channels located in dendritic spines. Neuron 53(2):249–260

Bossu JL, Capogna M, Debanne D, RA MK, Gähwiler BH (1996) Somatic voltage-gated potassium currents of rat hippocampal pyramidal cells in organotypic slice cultures. J Physiol 495:367–381

Bowden SE, Fletcher S, Loane DJ, Marrion NV (2001) Somatic colocalization of rat SK1 and D class (CA(v)1.2) L-type calcium channels in rat CA1 hippocampal pyramidal neurons. J Neurosci 21(20):RC175

Bullis JB, Jones TD, Poolos NP (2007) Reversed somatodendritic I(h) gradient in a class of rat hippocampal neurons with pyramidal morphology. J Physiol 579(Pt 2):431–443

Callaway EM, Katz LC (1993) Photostimulation using caged glutamate reveals functional circuitry in living brain slices. Proc Natl Acad Sci U S A 90:7661–7665

Charpak S, Gähwiler BH, Do KQ, Knöpfel T (1990) Potassium conductances in hippocampal neurons blocked by excitatory amino-acid transmitters. Nature 347(6295):765–767

Chen X, Johnston D (2004) Properties of single voltage-dependent K+ channels in dendrites of CA1 pyramidal neurones of rat hippocampus. J Physiol 559:187–203

Chen S, Yaari Y (2008) Spike Ca2+ influx upmodulates the spike afterdepolarization and bursting via intracellular inhibition of KV7/M channels. J Physiol 586:1351–1363

Chevaleyre V, Siegelbaum SA (2010) Strong CA2 pyramidal neuron synapses define a powerful disynaptic cortico-hippocampal loop. Neuron 66:560–572

Chikwendu A, McBain CJ (1996) Two temporally overlapping "delayed-rectifiers" determine the voltage-dependent potassium current phenotype in cultured hippocampal interneurons. J Neurophysiol 76:1477–1490

Christie BR, Eliot LS, Ito K, Miyakawa H, Johnston D (1995) Different Ca2+ channels in soma and dendrites of hippocampal pyramidal neurons mediate spike-induced Ca2+ influx. J Neurophysiol 73(6):2553–2557

Chung YH, Shin C, Park KH, Cha CI (2000) Immunohistochemical study on the distribution of the voltage-gated calcium channel alpha(1B) subunit in the mature rat brain. Brain Res 866(1–2):274–280

Colbert CM, Johnston D (1996) Axonal action-potential initiation and Na+ channel densities in the soma and axon initial segment of subicular pyramidal neurons. J Neurosci 16(21):6676–6686

Colbert CM, Pan E (2002) Ion channel properties underlying axonal action potential initiation in pyramidal neurons. Nat Neurosci 5:533–538

Colbert CM, Magee JC, Hoffman DA, Johnston D (1997) Slow recovery from inactivation of Na+ channels underlies the activity-dependent attenuation of dendritic action potentials in hippocampal CA1 pyramidal neurons. J Neurosci 17(17):6512–6521

Day NC, Shaw PJ, AL MC, Craig PJ, Smith W, Beattie R, Williams TL, Ellis SB, Ince PG, Harpold MM, Lodge D, Volsen SG (1996) Distribution of alpha 1A, alpha 1B and alpha 1E voltage-dependent calcium channel subunits in the human hippocampus and parahippocampal gyrus. Neuroscience 71(4):1013–1024

Deisseroth K (2010) Controlling the brain with light. Sci Am 303:48–55

Deisseroth K (2011) Optogenetics. Nat Methods 8:26–29

Devaux JJ, Kleopa KA, Cooper EC, Scherer SS (2004) KCNQ2 is a nodal K^+ channel. J Neurosci 24:1236–1244

Dietrich D, Kirschstein T, Kukley M, Pereverzev A, von der Brelie C, Schneider T, Beck H (2003) Functional specialization of presynaptic Cav2.3 Ca2+ channels. Neuron 39(3):483–496

Du J, Haak LL, Phillips-Tansey E, Russell JT, CJ MB (2000) Frequency-dependent regulation of rat hippocampal somato-dendritic excitability by the K+ channel subunit Kv2.1. J Physiol 522(Pt 1):19–31

Elgueta C, Köhler J, Bartos M (2015) Persistent discharges in dentate gyrus perisoma-inhibiting interneurons require hyperpolarization-activated cyclic nucleotide-gated channel activation. J Neurosci 35(10):4131–4139

Eliot LS, Johnston D (1994) Multiple components of calcium current in acutely dissociated dentate gyrus granule neurons. J Neurophysiol 72(2):762–777

Ellerkmann RK, Riazanski V, Elger CE, Urban BW, Beck H (2001) Slow recovery from inactivation regulates the availability of voltage-dependent Na(+) channels in hippocampal granule cells, hilar neurons and basket cells. J Physiol 532(Pt 2):385–397

Ellerkmann RK, Remy S, Chen J, Sochivko D, Elger CE, Urban BW, Becker A, Beck H (2003) Molecular and functional changes in voltage-dependent Na(+) channels following pilocarpine-induced status epilepticus in rat dentate granule cells. Neuroscience 119(2):323–333

Engel D, Jonas P (2005) Presynaptic action potential amplification by voltage-gated Na+ channels in hippocampal mossy fiber boutons. Neuron 45(3):405–417

Felts PA, Yokoyama S, Dib-Hajj S, Black JA, Waxman SG (1997) Sodium channel alpha-subunit mRNAs I, II, III, NaG, Na6 and hNE (PN1): different expression patterns in developing rat nervous system. Brain Res Mol Brain Res 45:71–82

Fernandez FR, Morales E, Rashid AJ, Dunn RJ, Turner RW (2003) Inactivation of Kv3.3 potassium channels in heterologous expression systems. J Biol Chem 278(42):40890–40898

Fisher RE, Gray R, Johnston D (1990) Properties and distribution of single voltage-gated calcium channels in adult hippocampal neurons. J Neurophysiol 64(1):91–104

Franz O, Liss B, Neu A, Roeper J (2000) Single-cell mRNA expression of HCN1 correlates with a fast gating phenotype of hyperpolarization-activated cyclic nucleotide-gated ion channels (Ih) in central neurons. Eur J Neurosci 12:2685–2693

Fraser DD, MacVicar BA (1991) Low-threshold transient calcium current in rat hippocampal lacunosum-moleculare interneurons: kinetics and modulation by neurotransmitters. J Neurosci 11(9):2812–2820

Freund TF, Buzsáki G (1996) Interneurons of the hippocampus. Hippocampus 6(4):347–470

Fricker D, Verheugen JA, Miles R (1999) Cell-attached measurements of the firing threshold of rat hippocampal neurones. J Physiol 517(Pt 3):791–804

Frotscher M, Seress L, Schwerdtfeger WK, Buhl E (1991) The mossy cells of the fascia dentata: a comparative study of their fine structure and synaptic connections in rodents and primates. J Comp Neurol 312(1):145–163

Gasparini S, Magee JC (2002) Phosphorylation-dependent differences in the activation properties of distal and proximal dendritic Na+ channels in rat CA1 hippocampal neurons. J Physiol 541(Pt 3):665–672

Gasparini S, Migliore M, Magee JC (2004) On the initiation and propagation of dendritic spikes in CA1 pyramidal neurons. J Neurosci 24(49):11046–11056

Geiger JR, Jonas P (2000) Dynamic control of presynaptic Ca(2+) inflow by fast-inactivating K(+) channels in hippocampal mossy fiber boutons. Neuron 28:927–939

Gentet LJ, Stuart GJ, Clements JD (2000) (2000) direct measurement of specific membrane capacitance in neurons. Biophys J 79(1):314–320

Golding NL, Jung HY, Mickus T, Spruston N (1999) Dendritic calcium spike initiation and repolarization are controlled by distinct potassium channel subtypes in CA1 pyramidal neurons. J Neurosci 19(20):8789–8798

Goldman L, Schauf CL (1973) Quantitative description of sodium and potassium currents and computed action potentials in Myxicola giant axons. J Gen Physiol 61:361–384

Gong B, Rhodes KJ, Bekele-Arcuri Z, Trimmer JS (1999) Type I and type II Na(+) channel alpha-subunit polypeptides exhibit distinct spatial and temporal patterning, and association with auxiliary subunits in rat brain. J Comp Neurol 412(2):342–352

Grissmer S, Nguyen AN, Aiyar J, Hanson DC, Mather RJ, Gutman GA, Karmilowicz MJ, Auperin DD, Chandy KG (1994) Pharmacological characterization of five cloned voltage-gated K+ channels, types Kv1.1, 1.2, 1.3, 1.5, and 3.1, stably expressed in mammalian cell lines. Mol Pharmacol 45(6):1227–1234

Gu N, Vervaeke K, Hu H, Storm JF (2005) M-channels (Kv7/KCNQ channels) that regulate synaptic integration, excitability, and spike pattern of CA1 pyramidal cells are located in the perisomatic region. J Physiol 566(Pt 3):689–715

Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ (1981) Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. Pflugers Arch 391(2):85–100

Häusser M, Stuart G, Racca C, Sakmann B (1995) Axonal initiation and active dendritic propagation of action potentials in substantia nigra neurons. Neuron 15:637–647

Hefft S, Jonas P (2005) Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron-principal neuron synapse. Nat Neurosci 8(10):1319–1328

Hillman D, Chen S, Aung TT, Cherksey B, Sugimori M, Llinás RR (1991) Localization of P-type calcium channels in the central nervous system. Proc Natl Acad Sci U S A 88(16):7076–7080

Hitti FL, Siegelbaum SA (2014) The hippocampal CA2 region is essential for social memory. Nature 508(7494):88–92

Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 117:500–544

Hoffman DA, Johnston D (1998) Downregulation of transient K+ channels in dendrites of hippocampal CA1 pyramidal neurons by activation of PKA and PKC. J Neurosci 18(10):3521–3528

Hoffman DA, Magee JC, Colbert CM, Johnston D (1997) K+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. Nature 387(6636):869–875

Hoogland TM, Saggau P (2004) Facilitation of L-type Ca2+ channels in dendritic spines by activation of beta2 adrenergic receptors. J Neurosci 24(39):8416–8427

Horn R, Marty A (1988) Muscarinic activation of ionic currents measured by a new whole-cell recording method. J Gen Physiol 92:145–159

Howard AL, Neu A, Morgan RJ, Echegoyen JC, Soltesz I (2007) Opposing modifications in intrinsic currents and synaptic inputs in post-traumatic mossy cells: evidence for single-cell homeostasis in a hyperexcitable network. J Neurophysiol 97(3):2394–2409

Hu H, Vervaeke K, Storm JF (2002) Two forms of electrical resonance at theta frequencies, generated by M-current, h-current and persistent Na+ current in rat hippocampal pyramidal cells. J Physiol 545(Pt 3):783–805

Hu H, Vervaeke K, Storm JF (2007) M-channels (Kv7/KCNQ channels) that regulate synaptic integration, excitability, and spike pattern of CA1 pyramidal cells are located in the perisomatic region. J Neurosci 27:1853–1867

Hu H, Martina M, Jonas P (2010) Dendritic mechanisms underlying rapid synaptic activation of fast-spiking hippocampal interneurons. Science 327(5961):52–58

Hyun JH, Eom K, Lee KH, Ho WK, Lee SH (2013) Activity-dependent downregulation of D-type K+ channel subunit Kv1.2 in rat hippocampal CA3pyramidal neurons. J Physiol 591(22):5525–5540

Jinno S, Ishizuka S, Kosaka T (2003) Ionic currents underlying rhythmic bursting of ventral mossy cells in the developing mouse dentate gyrus. Eur J Neurosci 17(7):1338–1354

Johnston D, Hoffman DA, Magee JC, Poolos NP, Watanabe S, Colbert CM, Migliore M (2000) Dendritic potassium channels in hippocampal pyramidal neurons. J Physiol 525(Pt 1):75–81

Jung HY, Mickus T, Spruston N (1997) Prolonged sodium channel inactivation contributes to dendritic action potential attenuation in hippocampal pyramidal neurons. J Neurosci 17(17):6639–6646

Jung HY, Staff NP, Spruston N (2001) Action potential bursting in subicular pyramidal neurons is driven by a calcium tail current. J Neurosci 21(10):3312–3321

Kim J, Wei DS, Hoffman DA (2005) Kv4 potassium channel subunits control action potential repolarization and frequency-dependent broadening in rat hippocampal CA1 pyramidal neurones. J Physiol 569:41–57

Kim S (2014) Action potential modulation in CA1 pyramidal neuron axons facilitates OLM interneuron activation in recurrent inhibitory microcircuits of rat hippocampus. PLoS One 19(11):e113124

Kim S, Guzman SJ, Hu H, Jonas P (2012) Active dendrites support efficient initiation of dendritic spikes in hippocampal CA3 pyramidal neurons. Nat Neurosci 15:600–606

King B, Rizwan AP, Asmara H, Heath NC, Engbers JD, Dykstra S, Bartoletti TM, Hameed S, Zamponi GW, Turner RW (2015) IKCa channels are a critical determinant of the slow AHP in CA1 pyramidal neurons. Cell Rep 11(2):175–182

Klee R, Ficker E, Heinemann U (1995) Comparison of voltage-dependent potassium currents in rat pyramidal neurons acutely isolated from hippocampal regions CA1 and CA3. J Neurophysiol 74(5):1982–1995

Kohara K, Pignatelli M, Rivest AJ, Jung HY, Kitamura T, Suh J, Frank D, Kajikawa K, Mise N, Obata Y, Wickersham IR, Tonegawa S (2014) Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits. Nat Neurosci 17(2):269–279

Lambert NA, Wilson WA (1996) High-threshold Ca2+ currents in rat hippocampal interneurones and their selective inhibition by activation of GABA(B) receptors. J Physiol 492(Pt 1):115–127

Lawrence JJ, Saraga F, Churchill JF, Statland JM, Travis KE, Skinner FK, McBain CJ (2006) Somatodendritic Kv7/KCNQ/M channels control interspike interval in hippocampal interneurons. J Neurosci 26(47):12325–12338

Li L, Bischofberger J, Jonas P (2007) Differential gating and recruitment of P/Q-, N-, and R-type Ca2+ channels in hippocampal mossy fiber boutons. J Neurosci 27(49):13420–13429

Liao YJ, Jan YN, Jan LY (1996) Heteromultimerization of G-protein-gated inwardly rectifying K+ channel proteins GIRK1 and GIRK2 and their altered expression in weaver brain. J Neurosci 16(22):7137–7150

Lien CC, Jonas P (2003) Kv3 potassium conductance is necessary and kinetically optimized for high-frequency action potential generation in hippocampal interneurons. J Neurosci 23(6):2058–2068

Lien CC, Martina M, Schultz JH, Ehmke H, Jonas P (2002) Gating, modulation and subunit composition of voltage-gated K(+) channels in dendritic inhibitory interneurones of rat hippocampus. J Physiol 538(Pt 2):405–419

Lein ES, Callaway EM, Albright TD, Gage FH (2005) Redefining the boundaries of the hippocampal CA2 subfield in the mouse using gene expression and 3-dimensional reconstruction. J Comp Neurol 485:1–10

Liu PW, Bean BP (2014) Kv2 channel regulation of action potential repolarization and firing patterns in superior cervical ganglion neurons and hippocampal CA1 pyramidal neurons. J Neurosci 34:4991–5002

Llinás R, Sugimori M (1980) Electrophysiological properties of in vitro Purkinje cell dendrites in mammalian cerebellar slices. J Physiol 305:197–213

Lübke J, Frotscher M, Spruston N (1998) Specialized electrophysiological properties of anatomically identified neurons in the hilar region of the rat fascia dentata. J Neurophysiol 79(3):1518–1534

Maccaferri G, McBain CJ (1996) The hyperpolarization-activated current (Ih) and its contribution to pacemaker activity in rat CA1 hippocampal stratum oriens-alveus interneurones. J Physiol 497(Pt 1):119–130

Maccaferri G, Mangoni M, Lazzari A, DiFrancesco D (1993) Properties of the hyperpolarization-activated current in rat hippocampal CA1 pyramidal cells. J Neurophysiol 69(6):2129–2136

Magee JC (1998) Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. J Neurosci 18(19):7613–7624

Magee JC, Carruth M (1999) Dendritic voltage-gated ion channels regulate the action potential firing mode of hippocampal CA1 pyramidal neurons. J Neurophysiol 82(4):1895–1901

Magee JC, Johnston D (1995a) Characterization of single voltage-gated Na+ and Ca2+ channels in apical dendrites of rat CA1 pyramidal neurons. J Physiol 487:67–90

Magee JC, Johnston D (1995b) Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. Science 268:301–304

Magee JC, Christofi G, Miyakawa H, Christie B, Lasser-Ross N, Johnston D (1995) Subthreshold synaptic activation of voltage-gated Ca2+ channels mediates a localized Ca2+ influx into the dendrites of hippocampal pyramidal neurons. J Neurophysiol 74(3):1335–1342

Magee JC, Avery RB, Christie BR, Johnston D (1996) Dihydropyridine-sensitive, voltage-gated Ca2+ channels contribute to the resting intracellular Ca2+ concentration of hippocampal CA1 pyramidal neurons. J Neurophysiol 76:3460–3470

Major G (1993) Solutions for transients in arbitrarily branching cables: III. Voltage clamp problems. Biophys J 65:469–491

Major G, Larkman AU, Jonas P, Sakmann B, Jack JJ (1994) Detailed passive cable models of whole-cell recorded CA3 pyramidal neurons in rat hippocampal slices. J Neurosci 14:4613–4638

Maletic-Savatic M, Lenn NJ, Trimmer JS (1995) Differential spatiotemporal expression of K+ channel polypeptides in rat hippocampal neurons developing in situ and in vitro. J Neurosci 15:3840–3851

Martina M, Jonas P (1997) Functional differences in Na+ channel gating between fast-spiking interneurones and principal neurones of rat hippocampus. J Physiol 505:593–603

Martina M, Schultz JH, Ehmke H, Monyer H, Jonas P (1998) Functional and molecular differences between voltage-gated K+ channels of fast-spiking interneurons and pyramidal neurons of rat hippocampus. J Neurosci 18:8111–8125

Martina M, Vida I, Jonas P (2000) Distal initiation and active propagation of action potentials in interneuron dendrites. Science 287:295–300

McKay BE, McRory JE, Molineux ML, Hamid J, Snutch TP, Zamponi GW, Turner RW (2006) Ca(V)3 T-type calcium channel isoforms differentially distribute to somatic and dendritic compartments in rat central neurons. Eur J Neurosci 24:2581–2594

Meeks JP, Mennerick S (2007) Action potential initiation and propagation in CA3 pyramidal axons. J Neurophysiol 97:3460–3472

Metz AE, Jarsky T, Martina M, Spruston N (2005) R-type calcium channels contribute to afterdepolarization and bursting in hippocampal CA1 pyramidal neurons. J Neurosci 25:5763–5773

Metz AE, Spruston N, Martina M (2007) Dendritic D-type potassium currents inhibit the spike afterdepolarization in rat hippocampal CA1 pyramidal neurons. J Physiol 581:175–187

Meyer AH, Katona I, Blatow M, Rozov A, Monyer H (2002) In vivo labeling of parvalbumin-positive interneurons and analysis of electrical coupling in identified neurons. J Neurosci 22:7055–7064

Mills LR, Niesen CE, So AP, Carlen PL, Spigelman I, Jones OT (1994) N-type Ca2+ channels are located on somata, dendrites, and a subpopulation of dendritic spines on live hippocampal pyramidal neurons. J Neurosci 14:6815–6824

Mintz IM, Adams ME, Bean BP (1992) P-type calcium channels in rat central and peripheral neurons. Neuron 9:85–95

Misonou H, Menegola M, Buchwalder L, Park EW, Meredith A, Rhodes KJ, Aldrich RW, Trimmer JS (2006) Immunolocalization of the Ca2+−activated K+ channel Slo1 in axons and nerve terminals of mammalian brain and cultured neurons. J Comp Neurol 496:289–302

Mitterdorfer J, Bean BP (2002) Potassium currents during the action potential of hippocampal CA3 neurons. J Neurosci 22:10106–10115

Miyawaki T, Tsubokawa H, Yokota H, Oguro K, Konno K, Masuzawa T, Kawai N (2002) Differential effects of novel wasp toxin on rat hippocampal interneurons. Neurosci Lett 328:25–28

Mogul DJ, Fox AP (1991) Evidence for multiple types of Ca2+ channels in acutely isolated hippocampal CA3 neurones of the Guinea-pig. J Physiol 433:259–281

Monaghan MM, Trimmer JS, Rhodes KJ (2001) Experimental localization of Kv1 family voltage-gated K+ channel alpha and beta subunits in rat hippocampal formation. J Neurosci 21:5973–5983

Neher E, Sakmann B, Steinbach JH (1978) The extracellular patch clamp: a method for resolving currents through individual open channels in biological membranes. Pflugers Arch 375:219–228

Nevian T, Helmchen F (2007) Calcium indicator loading of neurons using single-cell electroporation. Pflugers Arch 454:675–688

Nicoll RA, Alger BE (1981) Synaptic excitation may activate a calcium-dependent potassium conductance in hippocampal pyramidal cells. Science 212:957–959

Normann C, Peckys D, Schulze CH, Walden J, Jonas P, Bischofberger J (2000) Associative long-term depression in the hippocampus is dependent on postsynaptic N-type Ca2+ channels. J Neurosci 20:8290–8297

Notomi T, Shigemoto R (2004) Immunohistochemical localization of Ih channel subunits, HCN1-4, in the rat brain. J Comp Neurol 471:241–276

Palacio S, Chevaleyre V, Brann DH, Murray KD, Piskorowski RA, Trimmer JS (2017) Heterogeneity in Kv2 channel expression shapes action potential characteristics and firing patterns in CA1 versus CA2 hippocampal pyramidal neurons. eNeuro. 4. pii: ENEURO.0267-17.2017

Park KH, Chung YH, Shin C, Kim MJ, Lee BK, Cho SS, Cha CI (2001) Immunohistochemical study on the distribution of the voltage-gated potassium channels in the gerbil hippocampus. Neurosci Lett 298:29–32

Parra P, Gulyás AI, Miles R (1998) How many subtypes of inhibitory cells in the hippocampus? Neuron 20:983–993

Piskorowski RA, Nasrallah K, Diamantopoulou A, Mukai J, Hassan SI, Siegelbaum SA, Gogos JA, Chevaleyre V (2016) Age-dependent specific changes in area CA2 of the hippocampus and social memory deficit in a mouse model of the 22q11.2 deletion syndrome. Neuron 89:163–176

Poncer JC, McKinney RA, Gähwiler BH, Thompson SM (1997) Either N- or P-type calcium channels mediate GABA release at distinct hippocampal inhibitory synapses. Neuron 18:463–472

Poolos NP, Johnston D (1999) Calcium-activated potassium conductances contribute to action potential repolarization at the soma but not the dendrites of hippocampal CA1 pyramidal neurons. J Neurosci 19:5205–5212

Price CJ, Cauli B, Kovacs ER, Kulik A, Lambolez B, Shigemoto R, Capogna M (2005) Neurogliaform neurons form a novel inhibitory network in the hippocampal CA1 area. J Neurosci 25:6775–6786

Radzicki D, Yau HJ, Pollema-Mays SL, Mlsna L, Cho K, Koh S, Martina M (2013) Temperature-sensitive Cav1.2 calcium channels support intrinsic firing of pyramidal neurons and provide a target for the treatment of febrile seizures. J Neurosci 33:9920–9931

Ramakers GM, Storm JF (2002) A postsynaptic transient K(+) current modulated by arachidonic acid regulates synaptic integration and threshold for LTP induction in hippocampal pyramidal cells. Proc Natl Acad Sci U S A 99:10144–10149

Reckziegel G, Beck H, Schramm J, Elger CE, Urban BW (1998) Electrophysiological characterization of Na+ currents in acutely isolated human hippocampal dentate granule cells. J Physiol 509:139–150

Rettig J, Heinemann SH, Wunder F, Lorra C, Parcej DN, Dolly JO, Pongs O (1994) Inactivation properties of voltage-gated K+ channels altered by presence of beta-subunit. Nature 1994(369):289–294

Rhodes KJ, Strassle BW, Monaghan MM, Bekele-Arcuri Z, Matos MF, Trimmer JS (1997) Association and colocalization of the Kvbeta1 and Kvbeta2 beta-subunits with Kv1 alpha-subunits in mammalian brain K+ channel complexes. J Neurosci 17:8246–8258

Rhodes KJ, Carroll KI, Sung MA, Doliveira LC, Monaghan MM, Burke SL, Strassle BW, Buchwalder L, Menegola M, Cao J, An WF, Trimmer JS (2004) KChIPs and Kv4 alpha subunits as integral components of A-type potassium channels in mammalian brain. J Neurosci 24:7903–7915

Riazanski V, Becker A, Chen J, Sochivko D, Lie A, Wiestler OD, Elger CE, Beck H (2001) Functional and molecular analysis of transient voltage-dependent K+ currents in rat hippocampal granule cells. J Physiol 537:391–406

Robert V, Cassim S, Chevaleyre V, Piskorowski RA (2018) Hippocampal area CA2: properties and contribution to hippocampal function. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2769-7

Rozsa B, Zelles T, Vizi ES, Lendvai B (2004) Distance-dependent scaling of calcium transients evoked by backpropagating spikes and synaptic activity in dendrites of hippocampal interneurons. J Neurosci 24:661–670

Russo MJ, Mugnaini E, Martina M (2007) Intrinsic properties and mechanisms of spontaneous firing in mouse cerebellar unipolar brush cells. J Physiol 581(Pt 2):709–724

Saganich MJ, Machado E, Rudy B (2001) Differential expression of genes encoding subthreshold-operating voltage-gated K+ channels in brain. J Neurosci 21:4609–4624

Santoro B, Wainger BJ, Siegelbaum SA (2004) Regulation of HCN channel surface expression by a novel C-terminal protein-protein interaction. J Neurosci 24:10750–10762

Sather W, Dieudonné S, MacDonald JF, Ascher P (1992) Activation and desensitization of N-methyl-D-aspartate receptors in nucleated outside-out patches from mouse neurones. J Physiol 450:643–672

Saviane C, Mohajerani MH, Cherubini E (2003) An ID-like current that is downregulated by Ca2+ modulates information coding at CA3-CA3 synapses in the rat hippocampus. J Physiol 552:513–524

Schmidt-Hieber C, Jonas P, Bischofberger J (2007) Subthreshold dendritic signal processing and coincidence detection in dentate gyrus granule cells. J Neurosci 27:8430–8441

Schmidt-Hieber C, Jonas P, Bischofberger J (2008) Action potential initiation and propagation in hippocampal mossy fibre axons. J Physiol 586:1849–1857

Schroeder BC, Hechenberger M, Weinreich F, Kubisch C, Jentsch TJ (2000) KCNQ5, a novel potassium channel broadly expressed in brain, mediates M-type currents. J Biol Chem 275:24089–24095

Sekirnjak C, Martone ME, Weiser M, Deerinck T, Bueno E, Rudy B, Ellisman M (1997) Subcellular localization of the K+ channel subunit Kv3.1b in selected rat CNS neurons. Brain Res 766:173–187

Serôdio P, Vega-Saenz de Miera E, Rudy B (1996) Cloning of a novel component of A-type K+ channels operating at subthreshold potentials with unique expression in heart and brain. Neurophysiol 75:2174–2179

Serôdio P, Rudy B (1998) Differential expression of Kv4 K+ channel subunits mediating subthreshold transient K+ (A-type) currents in rat brain. J Neurophysiol 79:1081–1091

Shah M, Mistry M, Marsh SJ, Brown DA, Delmas P (2002) Molecular correlates of the M-current in cultured rat hippocampal neurons. J Physiol 544:29–37

Sheng M, Tsaur ML, Jan YN, LY J (1992) Subcellular segregation of two A-type K+ channel proteins in rat central neurons. Neuron 9:271–284

Sheng M, Tsaur ML, Jan YN, Jan LY (1994) Contrasting subcellular localization of the Kv1.2 K+ channel subunit in different neurons of rat brain. J Neurosci 14:2408–2417

Sochivko D, Pereverzev A, Smyth N, Gissel C, Schneider T, Beck H (2002) The Ca(V)2.3 Ca(2+) channel subunit contributes to R-type Ca(2+) currents in murine hippocampal and neocortical neurones. J Physiol 542:699–710

Sochivko D, Chen J, Becker A, Beck H (2003) Blocker-resistant Ca2+ currents in rat CA1 hippocampal pyramidal neurons. Neuroscience 116:629–638

Spruston N, Johnston D (1992) Perforated patch-clamp analysis of the passive membrane properties of three classes of hippocampal neurons. J Neurophysiol 67:508–529

Spruston N, Schiller Y, Stuart G, Sakmann B (1995) Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. Science 268:297–300

Srinivas KV, Buss EW, Sun Q, Santoro B, Takahashi H, Nicholson DA, Siegelbaum SA (2017) The dendrites of CA2 and CA1 pyramidal neurons differentially regulate information flow in the cortico-hippocampal circuit. J Neurosci 37:3276–3293

Staley KJ, Otis TS, Mody I (1992) Membrane properties of dentate gyrus granule cells: comparison of sharp microelectrode and whole-cell recordings. J Neurophysiol 67:1346–1358

Stea A, Tomlinson WJ, Soong TW, Bourinet E, Dubel SJ, Vincent SR, Snutch TP (1994) Localization and functional properties of a rat brain alpha 1A calcium channel reflect similarities to neuronal Q- and P-type channels. Proc Natl Acad Sci U S A 91:10576–10580

Steinhäuser C, Tennigkeit M, Matthies H, Gündel J (1990) Properties of the fast sodium channels in pyramidal neurones isolated from the CA1 and CA3 areas of the hippocampus of postnatal rats. Pflugers Arch 415:756–761

Storm JF (1990) Potassium currents in hippocampal pyramidal cells. Prog Brain Res 83:161–187

Stuart GJ, Sakmann B (1994) Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature 367:69–72

Stuart G, Spruston N (1998) Determinants of voltage attenuation in neocortical pyramidal neuron dendrites. J Neurosci 18:3501–3510

Su H, Sochivko D, Becker A, Chen J, Jiang Y, Yaari Y, Beck H (2002) Upregulation of a T-type Ca2+ channel causes a long-lasting modification of neuronal firing mode after status epilepticus. J Neurosci 22:3645–3655

Sun Q, Srinivas KV, Sotayo A, Siegelbaum SA (2014) Dendritic Na^+ spikes enable cortical input to drive action potential output from hippocampal CA2 pyramidal neurons. elife 3. https://doi.org/10.7554/eLife.04551

Sun Q, Sotayo A, Cazzulino AS, Snyder AM, Denny CA, Siegelbaum SA (2017) Proximodistal Heterogeneity of Hippocampal CA3 Pyramidal Neuron Intrinsic Properties, Connectivity, and Reactivation during Memory Recall. Neuron 95:656–672

Tai C, Abe Y, Westenbroek RE, Scheuer T, Catterall WA (2014) Impaired excitability of somatostatin- and parvalbumin-expressing cortical interneurons in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A 111(30):E3139–E3148

Takahashi K, Wakamori M, Akaike N (1989) Hippocampal CA1 pyramidal cells of rats have four voltage-dependent calcium conductances. Neurosci Lett 104:229–234

Takahashi K, Ueno S, Akaike N (1991) Kinetic properties of T-type Ca2+ currents in isolated rat hippocampal CA1 pyramidal neurons. J Neurophysiol 65:148–155

Takigawa T, Alzheimer C (2002) Phasic and tonic attenuation of EPSPs by inward rectifier K+ channels in rat hippocampal pyramidal cells. J Physiol 539:67–75

Talley EM, Solorzano G, Lei Q, Kim D, Bayliss DA (2001) CNS distribution of members of the two-pore-domain (KCNK) potassium channel family. J Neurosci 21:7491–7505

Taniguchi H, He M, Wu P, Kim S, Paik R, Sugino K, Kvitsiani D, Fu Y, Lu J, Lin Y, Miyoshi G, Shima Y, Fishell G, Nelson SB, Huang ZJ (2011) A resource of Cre driver lines for genetic targeting of GABAergic neurons in cerebral cortex. Neuron 71:995–1013

Taverna S, Tkatch T, Metz AE, Martina M (2005) Differential expression of TASK channels between horizontal interneurons and pyramidal cells of rat hippocampus. J Neurosci 25:9162–9170

Thompson SM, Wong RK (1991) Development of calcium current subtypes in isolated rat hippocampal pyramidal cells. J Physiol 439:671–689

Tippens AL, Pare JF, Langwieser N, Moosmang S, Milner TA, Smith Y, Lee A (2008) Ultrastructural evidence for pre- and postsynaptic localization of Cav1.2 L-type Ca2+ channels in the rat hippocampus. J Comp Neurol 506:569–583

Torborg CL, Berg AP, Jeffries BW, Bayliss DA, McBain CJ (2006) TASK-like conductances are present within hippocampal CA1 stratum oriens interneuron subpopulations. J Neurosci 26:7362–7367

Tsaur ML, Sheng M, Lowenstein DH, Jan YN, Jan LY (1992) Differential expression of K+ channel mRNAs in the rat brain and down-regulation in the hippocampus following seizures. Neuron 8:1055–1067

Tsay D, Dudman JT, Siegelbaum SA (2007) HCN1 channels constrain synaptically evoked Ca2+ spikes in distal dendrites of CA1 pyramidal neurons. Neuron 56:1076–1089

Veng LM, Browning MD (2002) Regionally selective alterations in expression of the alpha(1D) subunit (Ca(v)1.3) of L-type calcium channels in the hippocampus of aged rats. Brain Res Mol Brain Res 107:120–127

Vervaeke K, Gu N, Agdestein C, Hu H, Storm JF (2006) Kv7/KCNQ/M-channels in rat glutamatergic hippocampal axons and their role in regulation of excitability and transmitter release. J Physiol 576:235–256

Vida I, Halasy K, Szinyei C, Somogyi P, Buhl EH (1998) Unitary IPSPs evoked by interneurons at the stratum radiatum-stratum lacunosum-moleculare border in the CA1 area of the rat hippocampus in vitro. J Physiol 506:755–773

Wang H, Kunkel DD, Schwartzkroin PA, Tempel BL (1994) Localization of Kv1.1 and Kv1.2, two K channel proteins, to synaptic terminals, somata, and dendrites in the mouse brain. J Neurosci 14:4588–4599

Wang HS, Pan Z, Shi W, Brown BS, Wymore RS, Cohen IS, Dixon JE, McKinnon D (1998) CNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. Science 282:1890–1893

Weiler N, Wood L, Yu J, Solla SA, Shepherd GM (2008) Top-down laminar organization of the excitatory network in motor cortex. Nat Neurosci 11:360–366

Weiser M, Vega-Saenz de Miera E, Kentros C, Moreno H, Franzen L, Hillman D, Baker H, Rudy B (1994) Differential expression of Shaw-related K+ channels in the rat central nervous system. J Neurosci 14:949–972

Weiser M, Bueno E, Sekirnjak C, Martone ME, Baker H, Hillman D, Chen S, Thornhill W, Ellisman M, Rudy B (1995) The potassium channel subunit KV3.1b is localized to somatic and axonal membranes of specific populations of CNS neurons. J Neurosci 15:4298–4314

Wilson SM, Toth PT, Oh SB, Gillard SE, Volsen S, Ren D, Philipson LH, Lee EC, Fletcher CF, Tessarollo L, Copeland NG, Jenkins NA, Miller RJ (2000) The status of voltage-dependent calcium channels in alpha 1E knock-out mice. J Neurosci 20:8566–8571

Xu W, Lipscombe D (2001) Neuronal Ca(V)1.3alpha(1) L-type channels activate at relatively hyperpolarized membrane potentials and are incompletely inhibited by dihydropyridines. J Neurosci 21:5944–5951

Yaari Y, Yue C, Su H (2007) Recruitment of apical dendritic T-type Ca2+ channels by backpropagating spikes underlies de novo intrinsic bursting in hippocampal epileptogenesis. J Physiol 580:435–450

Yue C, Yaari Y (2004) KCNQ/M channels control spike afterdepolarization and burst generation in hippocampal neurons. J Neurosci 24:4614–4624

Yue C, Remy S, Su H, Beck H, Yaari Y (2005) Proximal persistent Na+ channels drive spike afterdepolarizations and associated bursting in adult CA1 pyramidal cells. J Neurosci 25:9704–9720

Zhang L, Valiante TA, Carlen PL (1993) Contribution of the low-threshold T-type calcium current in generating the post-spike depolarizing afterpotential in dentate granule neurons of immature rats. J Neurophysiol 70:223–231

Zhao M, Choi YS, Obrietan K, Dudek SM (2007) Synaptic plasticity (and the lack thereof) in hippocampal CA2 neurons. J Neurosci 27:12025–12032