

Functions of voltage- and calcium-activated potassium channels in the hippocampus and medial entorhinal cortex

**Doctoral thesis by
Christoph Hönigsperger**

Institute of Basic Medical Sciences, Faculty of Medicine,
University of Oslo, PB 1103 Blindern, 0317 Oslo, Norway



Oslo, 2015

© **Christoph Hönigsperger, 2016**

*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo*

ISBN 978-82-8333-190-5

All rights reserved. No part of this publication may be reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard
Printed in Norway: 07 Media AS – www.07.no

ACKNOWLEDGEMENTS

The work presented in the thesis was done at the Institute of Basic Medical Sciences, University of Oslo, between December 2010 and August 2015 and supported by a grant from the Norwegian Research Council.

First, I would like to thank my supervisor Professor Johan Frederik Storm for his support, help and careful guidance and giving me the opportunity to work in his lab. Without him the work in this thesis couldn't have been done.

I would also like to thank my colleagues at the Storm lab Pedro Mateos-Aparicio Moreno, Mate Marosi, Maximiliano Jose Nigro, Anna Maria Giglio, Ricardo Murphy, Nicholas Hagger-Vaughan, Bjørn Erik Juel, Cecilie Petterson Oksvold, Sturla Molden and Hua Hu for their help in the lab and many interesting discussions about science, and life outside of the university. I appreciate very much the international atmosphere I have been working in, during the last years.

Special thanks to my co-supervisor Professor Paul Heggelund for his valuable scientific input and comments on the manuscripts and thesis. Thanks also to Johannes Helm for the help with microscope installation and settings.

Last, I would like to express my deepest gratitude to my great family for their love, patience and understanding during these years. Thank you so much!

Contents

ACKNOWLEDGEMENTS	3
LIST OF PAPERS.....	5
ABBREVIATIONS.....	6
INTRODUCTION.....	7
Overview	7
Spike repolarization.....	7
Spike afterpotentials	8
Fast after-hyperpolarization (fAHP).....	8
Medium after-hyperpolarization (mAHP)	9
Slow after-hyperpolarization (sAHP)	9
After-depolarization (ADP)	10
Resonance.....	10
Kv7/M channels.....	11
Kv2 channels	12
Ca ²⁺ -activated K ⁺ channels	14
Dorso-ventral differences in the hippocampus.....	16
AIMS.....	18
METHODS.....	19
RESULTS AND DISCUSSION	21
Paper I.....	21
Paper II	22
Paper III.....	23
Paper IV	23
REFERENCE LIST.....	25
PAPERS	42

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to by the Roman numerals in the text.

- PAPER I** **HÖNIGSPERGER C**, MAROSI M, MURPHY R, STORM JF. Dorsoventral differences in Kv7/M-current and its impact on resonance, temporal summation and excitability in rat hippocampal pyramidal cells. *J. Physiol. (Lond.)* 593.7, 1551-1579, 2015
- PAPER II** **HÖNIGSPERGER C**, NIGRO MJ, STORM JF. Physiological roles of Kv2 channels in entorhinal cortex layer II stellate cells revealed by Guanylyl cyclase inhibitor. *Submitted to Journal of Physiology*.
- PAPER III** MATEOS-APARICIO P, **HÖNIGSPERGER C**, STORM JF. Dorsoventral differences in the sAHP and excitability of dentate gyrus granule cells of rats and mice. *Manuscript*.
- PAPER IV** WANG K, MATEOS-APARICIO P, **HÖNIGSPERGER C**, RAGHURAM V, WU W, RIDDER MC, SAH P, MAYLIE J, STORM JF, ADELMAN JP. IK1 channels do not contribute to the slow afterhyperpolarization in pyramidal neurons. Accepted for publication in *eLife*.

ABBREVIATIONS

ACSF	Artificial cerebrospinal fluid
ADP	After-depolarization
AHP	After-hyperpolarization
BLA	Basolateral amygdala
BK	Large conductance Ca^{2+} -activated K^{+} channel
CA1	Cornus ammonis 1
cAMP	Cyclic adenosine monophosphate
ChTx	Charybdotoxin
DGC	Dentate granule cell
D-V	Dorsoventral
fAHP	Fast after-hyperpolarization
f/I	Firing rate versus current input
GTx	Guangxitoxin-1E
I_M	$\text{Kv}7/\text{M}$ potassium current
I_K	Delayed rectifier potassium current
IK1	Intermediate conductance calcium-activated potassium current1
IR-DIC	Infrared-differential interference contrast
$I_{s\text{AHP}}$	Slow after-hyperpolarization current
Kv	Voltage-gated potassium channel
L II	Layer II
mAHP	Medium after-hyperpolarization
mEC	Medial entorhinal cortex
sAHP	Slow after-hyperpolarization
SC	Stellate cell
SK	Small conductance calcium-activated potassium channel

INTRODUCTION

Overview

The neuron (nerve cell) is a specialized cell type within the nervous system, which receives information in the form of electrical and chemical signals from other neurons. These signals can change the neuronal membrane potential and initiate an action potential (spike) after passing a certain voltage threshold. The action potential is then rapidly propagated along the axon and passes signals to other neurons. More than 60 years ago Hodgkin and Huxley discovered the ionic mechanisms underlying the generation and propagation of action potentials in the giant squid axon (Hodgkin & Huxley, 1952). The rapid depolarization and repolarization during an action potential is mediated by flow of Na^+ - and K^+ - currents through the neuronal membrane. Later it has been shown that neuronal membranes contain ion channels that are selectively permeable for different ionic species and have highly diverse structures and functions (Hille, 2001). Hippocampal pyramidal cells, for example, exhibit multiple K^+ currents which contribute differently to the 1) resting membrane potential, 2) subthreshold behavior, 3) spike repolarization, and 4) after-potentials following spikes (Storm, 1990). As a consequence, these pyramidal cells can fire over a wide range of frequencies in response to varying current inputs, and exhibit complex voltage responses and firing patterns.

In the present thesis, I investigated the functions of different voltage- and calcium-activated K^+ currents in the hippocampus and medial entorhinal cortex including Kv7/M current (I_M) (paper I), Kv2 current (I_K) (paper II) and the current mediating the slow after-hyperpolarization following a spike train (sAHP, I_{sAHP}) (paper III, IV).

These currents have important roles in modulating neuronal excitability and other intrinsic electrophysiological properties (Storm, 1990), and are involved in epilepsy and other neurodegenerative diseases (Jentsch, 2000; Shah & Aizenman, 2014).

The following section summarizes several functional roles of K^+ currents in neurons.

Spike repolarization

The rapid depolarization during a spike is caused by activation of Na^+ channels, followed by a repolarizing phase due to fast inactivation of Na^+ channels and activation of K^+ channels, as described by the original work of Hodgkin & Huxley in the giant squid axon (Hodgkin & Huxley, 1952). Later, it was shown that a variety of K^+ channels contribute to the somatic spike repolarization in central mammalian neurons including large conductance Ca^{2+} -activated K^+ channels (BK channels), Kv4 channels and Kv3 channels (Storm, 1990; Bean, 2007).

Interestingly, in many mammalian central neurons, Kv1 channels have little or no effect on somatic spike repolarization but contribute to spike repolarization in axons of layer 5 pyramidal cells (Kole *et al.*, 2007) and axonal terminals of dentate granule cells (Geiger & Jonas, 2000; Alle *et al.*, 2011).

Kv2 channels can also contribute to somatic spike repolarization. Thus, knock-down of Kv2 mRNA in cultured CA1 pyramidal cells increased spike widths during high frequency synaptic stimulation (Du *et al.*, 2000). Furthermore, block of Kv2 channels by Guangxitoxin-1E in acutely isolated CA1 pyramidal cells and sympathetic neurons can increase the width of the single spikes and reduce maintained firing (Liu & Bean, 2014).

In contrast, expression of a dominant negative Kv2 pore mutant in cultured cortical pyramidal cells had no effects on spike repolarization (Guan *et al.*, 2013).

In **Paper II**, we studied the role of Kv2 channels in medial entorhinal cortex (mEC) layer II stellate cells using the novel Kv2 blocker Guangxitoxin-1E (Herrington *et al.*, 2006; Liu & Bean, 2014). We found that Kv2 channels regulate spike repolarization during repetitive firing but had little or no impact on the first spike of the train.

Spike afterpotentials

A characteristic feature of many neurons is to adapt and decrease spike firing in response to prolonged stimulation. This adaptation is partly caused by outward currents underlying after-hyperpolarizations (AHPs) that follow repetitive spike firing and counteract the excitatory drive of a depolarizing stimulation (Calvin & Schwindt, 1972; Madison & Nicoll, 1984; Storm, 1990).

In CA1 pyramidal cells, a spike or a spike train is usually followed by a sequence of AHPs: a fast AHP (fAHP) lasting 2-5 ms, a medium AHP (mAHP) lasting 50-100 ms, and a slow AHP (sAHP) lasting more than 1 s (Storm, 1987; Storm, 1989; Storm, 1990). Increasing the stimulation intensity and the number of spikes per train causes an increase in the corresponding mAHP and sAHP which limits spike firing and serves as a “brake” during strong repetitive discharge. Between fAHP and mAHP, spikes can also be followed by an after-depolarization (ADP) lasting 20-40 ms (Storm, 1987; Jensen *et al.*, 1996). If the ADP crosses the spike threshold, it can initiate another spike followed by another ADP, and so on, thus generating a burst (spike cluster). Bursts are a characteristic mode of spike firing *in vivo* (Kandel & Spencer, 1961), and are thought to be more important for reliable neural coding than single spikes (Lisman, 1997).

Until now a variety of membrane currents that contribute to AHPs and the ADP in central neurons have been discovered.

Fast after-hyperpolarization (fAHP)

Ca²⁺-activated K⁺ current of the BK type (I_C) contributes to the somatic fAHP and spike repolarization in a variety of neurons (Adams *et al.*, 1982; Storm, 1987; Shao *et al.*, 1999; Hu *et al.*, 2001; Faber & Sah, 2003). In contrast, dendritic recordings in CA1 pyramidal cells suggested that I_C does not affect the waveform of back-propagating spikes, due to a lack of I_C in dendritic compartments (Poolos & Johnston, 1999). Poolos & Johnston (1999) suggested that the lack of dendritic I_C in the dendrites may contribute to slow spike repolarization and increased Ca²⁺ influx during back-propagating spikes and synaptic stimulation.

Recordings from axon terminals in hippocampal mossy fibers revealed fast spike repolarization and a prominent fAHP (Geiger & Jonas, 2000), which are mediated by Kv1 and Kv3 channels under basal conditions (Alle *et al.*, 2011). However, when these and other Kv channels are blocked, BK channels can repolarize pre-synaptic spikes and thereby limit transmitter release (Hu *et al.*, 2001; Alle *et al.*, 2011).

In **Paper II** we demonstrated in mEC layer II stellate cells that also Kv2 channels contribute to the somatic fAHP during repetitive firing, but not following a single spike.

Medium after-hyperpolarization (mAHP)

In CA1 pyramidal cells Kv7/M-channels and HCN/h channels underlie the mAHP at subthreshold and hyperpolarized potentials, and control excitability and spike frequency adaptation (Storm, 1989; Gu *et al.*, 2005).

In other cell types calcium-activated K⁺ channels of the SK type mainly contribute to the mAHP and thereby play a similar role in controlling repetitive firing patterns (Faber & Sah, 2007; Faber, 2009; Vogalis *et al.*, 2003; Mateos-Aparicio *et al.*, 2014; Gu *et al.*, 2008).

In **Paper I** we investigated the properties of Kv7/M-channels in CA1 pyramidal cells along the dorso-ventral hippocampal axis. We found that dorsal pyramidal cells show a bigger, more readily activated Kv7 current, a larger Kv7-dependent mAHP, and a stronger impact of other Kv7-related properties than ventral pyramidal cells.

In **Paper II** we demonstrated that Kv2 channels can contribute to the somatic mAHP during repetitive firing in mEC layer II stellate cells.

Slow after-hyperpolarization (sAHP)

The sAHP in hippocampal CA1 pyramidal neurons is attributed to a slow Ca²⁺-activated K⁺ current (Hotson & Prince, 1980; Gustafsson & Wigström, 1981; Lancaster & Adams, 1986) that controls late spike rate adaptation and excitability during repetitive firing (Madison & Nicoll, 1984; Storm, 1990; Faber & Sah, 2002; Vogalis *et al.*, 2003). The sAHP is strongly reduced by a variety of neuromodulators such as monoamines and peptides that act through common intracellular signaling cascades including cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), protein kinase C (PKC) and phospholipase C (Madison & Nicoll, 1982; Madison & Nicoll, 1986; Pedarzani & Storm, 1993; Pedarzani & Storm, 1995; Vogalis *et al.*, 2003).

Despite long-standing research, the molecular mechanisms underlying the sAHP remain controversial (Andrade *et al.*, 2012). Recent findings suggest that multiple types of potassium channels may contribute to the sAHP, which are indirectly gated via diffusible Ca²⁺-sensors and an increase in phosphatidylinositol 4,5-bisphosphate (Andrade *et al.*, 2012).

Recently it was reported that the sAHP and the IsAHP were partially reduced in CA1 pyramidal neurons by TRAM-34, which blocks intermediate-conductance Ca²⁺-activated K⁺ channels (SK4, IKCa, KCa3.1), and the sAHP was reported to be absent in CA1 pyramidal

neurons from IK1 null mice, strongly suggesting that IK1 channels underlie the sAHP (King *et al.*, 2015).

In **Paper IV** we have investigated the sensitivity of the sAHP and the IsAHP to TRAM-34 in pyramidal neurons of CA1 and the basolateral amygdala. We found no evidence that TRAM-34 affects the sAHP and IsAHP measured in current and voltage clamp. In addition, IK1 knock-out mice also exhibited a characteristic IsAHP.

In **Paper III** we investigated the electrophysiological properties of dentate granule cells along the hippocampal dorsoventral axis and found that dorsal granule cells show a bigger sAHP and reduced excitability compared to ventral granule cells.

After-depolarization (ADP)

In CA1 pyramidal cells block of the persistent sodium current (I_{NaP}) (Azouz *et al.*, 1996) and the R-type calcium current (Metz *et al.*, 2005) reduce the ADP. Conversely, block of different voltage-activated K^+ currents including A-type K^+ current (I_A) (Magee & Carruth, 1999), D-type K^+ current (I_D) (Metz *et al.*, 2005), and Kv7/M-type K^+ current (I_M) (Yue & Yaari, 2004), increases the ADP and facilitates bursting.

Little is known how Kv2 channels regulate firing patterns in central neurons.

In **Paper II** we found that block of Kv2 channels by Guanyxitoxin-1E increased the ADP and facilitated bursting in mEC layer II stellate cells.

Resonance

Electrical oscillations in brain networks are generated by coherent activation of a large number of neurons and are associated with specific behavioral states (Steriade *et al.*, 1993). Theta oscillations are a prominent type of network oscillation found e.g. in the hippocampus in the form of rhythmic activity in the theta frequency band. They are present during locomotion and REM sleep (Buzsáki, 2002).

Network oscillations depend in principle on the synaptic connections of the neuronal network and on intrinsic properties of the single neurons. It has been shown that neurons in different brain areas generate intrinsic oscillatory voltage responses, and respond best to oscillatory inputs at certain frequencies called resonance (Hutcheon & Yarom, 2000). The resonance properties are generated by an inter-play of passive and active membrane properties. The passive properties include the capacitance and leak conductance that act as a low-pass filter, thereby attenuating the effects of high-frequency inputs. In contrast, active properties are determined by specific voltage-gated currents which attenuate inputs at low frequencies. The combination of both mechanisms generates a band-pass filter that enables the strongest voltage response at a certain frequency (resonance frequency).

Voltage-gated currents that mediate resonance include Ca^{2+} current (I_T) in olivary neurons (Lampl & Yarom, 1997) and thalamic neurons (Puil *et al.*, 1994), HCN/h current (I_H), TEA-sensitive K^+ current and persistent sodium current (I_{NaP}) in neocortical pyramidal neurons (Gutfreund *et al.*, 1995; Hutcheon *et al.*, 1996).

CA1 pyramidal show I_H - and I_M -dependent resonance (H-resonance and M-resonance) at hyperpolarized and depolarized membrane potentials, respectively, and in particular M-resonance can be amplified by I_{NaP} (Hu *et al.*, 2002; Hu *et al.*, 2009).

Recent studies suggested that I_H -dependent resonance varies in CA1 pyramidal cells along the dorsoventral axis (Marcelin *et al.*, 2012a; Dougherty *et al.*, 2013).

In **Paper I** we also investigated whether I_M contributes to differences in resonance properties, and found stronger I_M -dependent resonance in dorsal than in ventral CA1 pyramidal cells.

Kv7/M channels

The M current (I_M), mediated by M-type voltage-gated K^+ channels, was first described in frog sympathetic ganglion neurons, and is inhibited by muscarinic acetylcholine receptor (mAChR) agonists (hence the name “M current”; Brown & Adams, 1980). Later, I_M was also found in mammalian hippocampal pyramidal cells and in other neurons (Halliwell & Adams, 1982; Schroeder *et al.*, 2000a; Brown & Passmore, 2009). I_M activates at subthreshold potentials, from about -60mV, it has slow activation and deactivation kinetics (tens of milliseconds), and does not inactivate. As a consequence, the sustained activity of I_M below spike threshold plays an important role in reducing cellular excitability in many neuronal cell types (Storm, 1990; Marrion, 1997).

Later studies found that I_M is carried by heteromeric combinations of Kv7.2 and Kv7.3 channels (encoded by KCNQ2/3 genes) in sympathetic ganglion neurons (Wang *et al.*, 1998), with a possible contribution of Kv7.5 (KCNQ5) in other neurons (Schroeder *et al.*, 2000a; Shah *et al.*, 2002; Tzingounis *et al.*, 2010).

A subsequent important discovery was that muscarinic inhibition of I_M depends on activation of phospholipase C (PLC) and a decrease in membrane phosphatidylinositol 4,5-bisphosphate (PIP₂) levels (Suh & Hille, 2002; Zhang *et al.*, 2003).

In CA1 pyramidal cells, inhibition of I_M can regulate multiple cellular properties including spike frequency adaptation (Madison & Nicoll, 1984), the medium after-hyperpolarization (Storm, 1989; Storm, 1990; Gu *et al.*, 2005; Gu *et al.*, 2008), the after-depolarizations and burst-firing (Yue & Yaari, 2004), the spike threshold (Shah *et al.*, 2008), and the theta resonance at depolarized potentials (M-resonance) (Hu *et al.*, 2002; Hu *et al.*, 2009). In hippocampal and neocortical axons, I_M can regulate pre-synaptic excitability and transmitter release (Vervaeke *et al.*, 2006; Sun & Kapur, 2012), M-resonance (Alle *et al.*, 2009), and the resting membrane potential (Battfeld *et al.*, 2014).

Kv7 channels are encoded by the KCNQ gene family, which contains 5 members (KCNQ1-5; Kv7.1-7.5). Mutations in 4 out of 5 genes are associated with diseases including cardiac diseases and arrhythmia/congenital deafness (KCNQ1; long-QT syndrome), neonatal epilepsy (KCNQ2/3; benign familial neonatal convulsions), and progressive hearing loss (KCNQ4) (Jentsch, 2000).

The KCNQ subunits are structurally related to other Kv subunits and have 6 transmembrane segments that contain a pore-forming P-loop and a positively charged voltage sensor (Jentsch,

2000). Together, four KCNQ subunits form a functional channel that can assemble as hetero- or homomers depending on the individual subunits (Jentsch, 2000).

The KCNQ/Kv7 subunits have different expression patterns and functions: KCNQ1, associated with β -subunit KCNE1, mediates a delayed rectifier K^+ current which repolarizes cardiac action potentials (Sanguinetti *et al.*, 1996) and mediates trans-epithelial K^+ -flux in the inner ear (Vetter *et al.*, 1996). In the intestine, KCNQ1 can also assemble with KCNE3, mediating a fast-activating, constitutively open K^+ current involved in chloride secretion (Schroeder *et al.*, 2000b).

KCNQ2/3 are the main subunits underlying I_M and show overlapping expression patterns in various brain areas including sympathetic ganglia (Wang *et al.*, 1998), neocortex and hippocampus (Cooper *et al.*, 2000; Battefeld *et al.*, 2014). At the subcellular level, Kv7.2 and Kv7.3 bind to Ankyrin G, which mediates co-localization of Kv7 channels with voltage-gated Na^+ channels at the axon initial segment (Pan *et al.*, 2006). Kv7.2 and Kv7.3 channels are also highly expressed in axonal nodes of Ranvier (Devaux *et al.*, 2004; Pan *et al.*, 2006). Conditional suppression of KCNQ2 in mice causes cortical hyper-excitability and seizures (Peters *et al.*, 2005; Soh *et al.*, 2014), but no or only modest effects are observed in mice with suppression of KCNQ3 (Soh *et al.*, 2014). It has been reported that β -secretase BACE1, involved in Alzheimer's disease, can associate with Kv7/M channels as a β -subunit, thereby amplifying I_M and changing its kinetics (Hessler *et al.*, 2015).

KCNQ4 is expressed in sensory outer hair cells, and in brain stem nuclei in the central auditory pathway. Thus, they are involved in a dominant form of progressive hearing loss (Kubisch *et al.*, 1999; Kharkovets *et al.*, 2000). Alternative splice variants of KCNQ4 channels have been reported, and they differ in their voltage-dependence and modulation by the Ca^{2+} -binding protein calmodulin (Xu *et al.*, 2007).

KCNQ5 is expressed throughout the mammalian brain and can contribute to I_M (Lerche *et al.*, 2000; Schroeder *et al.*, 2000a; Shah *et al.*, 2002; Tzingounis *et al.*, 2010). Association with β -subunit KCNE1 can slow activation and increase Kv7.5 currents, while KCNE3 inhibits Kv7.5 currents (Roura-Ferrer *et al.*, 2009). At the subcellular level, KCNQ5 is localized to postsynaptic sites of inhibitory synapses, and controls excitability and network functions through synaptic inhibition (Fidzinski *et al.*, 2015).

Investigations of the Kv7 channels are presented in **Paper I**.

Kv2 channels

The cDNA of rat Kv2.1 (rat: drk1, human: KCNB1) was initially isolated by expression cloning in oocytes. These channels mediate a delayed rectifier K^+ current (I_K) with a high activation threshold (-15 mV) and slow activation kinetics (Frech *et al.*, 1989). [The term "delayed rectifier" usually refers to a broader class of K^+ currents which are similar to the kinetics and voltage-dependence of the K^+ -current in squid axon described by Hodgkin & Huxley (1952), and it is distinct from the typical "A-type" K^+ current that has faster activation and inactivation kinetics (Rudy, 1988; Storm, 1990).]

The second member of the Kv2 family, Kv2.2 (rat: *cdrk*, human: *KCNB2*) shows similar kinetics as Kv2.1. It can form functional heteromers with Kv2.1 in oocytes (Blaine & Ribera, 1998).

Both Kv2.1 and Kv2.2 K⁺ channels are widely expressed in the nervous system, but show different cellular or subcellular distributions (Trimmer, 1991; Hwang *et al.*, 1993; Maletic-Savatic *et al.*, 1995). Noteworthy, Kv2.1 channels form clusters on the soma and the proximal dendrites of pyramidal cells and interneurons adjacently to astrocytic processes (Scannevin *et al.*, 1996; Du *et al.*, 1998). Kv2.1 channel clusters are also found in the axon initial segment of cultured hippocampal pyramidal cells (Sarmiere *et al.*, 2008).

Kv2.1 channels mediate a delayed rectifier current, I_K , in cultured rat hippocampal pyramidal neurons (Murakoshi & Trimmer, 1999) and globus pallidus neurons (Baranauskas *et al.*, 1999). Knock-down of Kv2.1 mRNA in cultured CA1 pyramidal neurons revealed a frequency-dependent increase in spike broadening and Ca²⁺ entry during synaptic stimulation (Du *et al.*, 2000). Transient expression of Kv2 pore mutants also reduced spike repolarization in cultured sympathetic neurons (Malin & Nerbonne, 2002), and reduced maintained repetitive firing in these neurons and in pyramidal neurons from the motor cortex (Malin & Nerbonne, 2002; Guan *et al.*, 2013). A selective Kv2 blocker, Guangxitoxin-1E (GTx), has been isolated from tarantula venom. GTx broadens spikes in pancreatic β -cells, thereby enhancing glucose-dependent insulin secretion (Herrington *et al.*, 2006). In isolated CA1 pyramidal neurons and sympathetic neurons, application of GTx reduced spike repolarization, depolarized inter-spike trajectories, and disrupted repetitive firing (Liu & Bean, 2014).

Several lines of evidence suggest that Kv2 channels are involved in homeostatic regulation of neuronal excitability in normal and diseased brains (Misonou *et al.*, 2005; Misonou, 2010; Shah & Aizenman, 2014). Under basal conditions the cytoplasmatic C-termini of Kv2.1 channels are highly phosphorylated, but can be de-phosphorylated by Ca²⁺ influx and activation of the Ca²⁺/calmodulin-dependent phosphatase calcineurin (Misonou *et al.*, 2004; Misonou *et al.*, 2005; Park *et al.*, 2006). As a consequence, the de-phosphorylation disrupts the clustered localization of Kv2.1 and shifts its activation threshold to more negative potentials (Misonou *et al.*, 2004). This reduces neuronal excitability in cultured neurons in an activity-dependent manner (Mohapatra *et al.*, 2009). Kv2 channels may therefore have a neuroprotective role by dampening neuronal excitability (Misonou *et al.*, 2005). In contrast, Kv2.1 can also trigger apoptotic cell death through K⁺ efflux induced by oxidants and staurosporine in cortical neurons (Pal *et al.*, 2003).

It has been shown that the activity of Kv2.1 are modulated by a variety of signals including: 1) activation of ionotropic glutamate receptors during kainate-induced seizures (Misonou *et al.*, 2004; Misonou *et al.*, 2005); 2) activation of muscarinic receptors (Mohapatra & Trimmer, 2006); 3) during ischemia and activation of cyclin e1 (Misonou *et al.*, 2008; Shah *et al.*, 2014); 4) small ubiquitin like-proteins (Plant *et al.*, 2011); and 5) nitric-oxide associated pathways (Steinert *et al.*, 2011).

Kv2.1 channels may also have non-electrical properties. In cultured hippocampal pyramidal neurons, about 70 % of Kv2.1 channels are non-conducting, and their conductance depends on surface channel density (Fox *et al.*, 2013). Especially Kv2.1 clusters may serve as platforms for delivery of other Kv-channels and proteins (Deutsch *et al.*, 2012).

It has also been reported that Kv2.1 channels promote exocytosis by interactions with the SNARE protein syntaxin in neuroendocrine cells (Singer-Lahat *et al.*, 2007) and dorsal-root-ganglion neurons (Feinshreiber *et al.*, 2010).

Investigations of the Kv2 channels are presented in **Paper II**.

Ca²⁺-activated K⁺ channels

Ca²⁺-activated K⁺ channels are opened by increases in intracellular Ca²⁺ levels, in contrast to voltage-dependent K⁺ channels such as Kv7/M channels and Kv2 channels, as described above. However Ca²⁺-activated K⁺ channels of the BK-type are also voltage-dependent and open during membrane depolarizations, even when intracellular Ca²⁺ levels are constant (Hille, 2001). Ca²⁺-activated K⁺ channels were initially discovered in molluscan neurons (Meech, 1974) and were later also found in many vertebrate cell types (Adams *et al.*, 1982; Rudy, 1988; Latorre *et al.*, 1989; Storm, 1990).

Later, different subtypes of Ca²⁺-activated K⁺ channels were described, with different single channel conductance: small-conductance (SK, 4-14 pS), intermediate-conductance (IK, 20-80 pS) and big-conductance (BK, 100-250 pS) (Vergara *et al.*, 1998; Hille, 2001). SK, IK, and BK channels can also be distinguished by their voltage-dependence, Ca²⁺ sensitivity and pharmacology (Hille, 2001).

SK channels are blocked by a number of pharmacological agents including the bee venom apamin (Hugues *et al.*, 1982; Blatz & Magleby, 1986), some bicuculline salts (Johnson & Seutin, 1997) and the scorpion toxin scyllatoxin (Castle & Strong, 1986).

SK channels constitute of three subtypes SK1-3 (K_{Ca}2.1-3) encoded by KCNN1-3 (Köhler *et al.*, 1996), and have 6 transmembrane domains with a pore forming P loop region. The different SK channel subtypes are widely expressed in the brain, where SK1-2 are prominently expressed in the neocortex and hippocampus, and SK3 are predominantly found in phylogenetically older brain areas including basal ganglia, thalamus and the brain stem (Stocker & Pedarzani, 2000; Sailer *et al.*, 2002; Sailer *et al.*, 2004). At the subcellular level, SK1-3 are localized to somato-dendritic compartments and varicose fibers (Sailer *et al.*, 2002; Sailer *et al.*, 2004; Ballesteros-Merino *et al.*, 2014).

SK channels can contribute to the mAHP and reduce repetitive firing patterns in different neuronal cell types (Vogalis *et al.*, 2003; Faber & Sah, 2007; Faber, 2009; Mateos-Aparicio *et al.*, 2014). [Previously it was suggested that SK channels mainly contribute to the sAHP. However this possibility was discarded by later studies (Faber & Sah, 2007; Andrade *et al.*, 2012).]

In addition SK channels were found to regulate dendritic integration and synaptic plasticity in CA3-CA1 Schaffer collateral synapses (Gu *et al.*, 2008; Lin *et al.*, 2008), and enhance memory formation after block of SK channels with apamin (Stackman *et al.*, 2002).

The intracellular C-terminus of SK channels contains protein kinase A dependent phosphorylation sites, which mediate reduction of SK2 surface expression in COS7 cells (Ren *et al.*, 2006), in pyramidal neurons in the lateral amygdala through activation of β -adrenergic

receptors (Faber *et al.*, 2008), and in hippocampal pyramidal neurons after induction of long-term-potentialiation (LTP) (Lin *et al.*, 2008).

SK channels have been suggested as targets for treatment of neurological disorders like schizophrenia, depression, and Parkinson's disease (Faber, 2009).

IK channels (SK4, IK_{Ca} or K_{Ca}3.1) were first cloned from the human pancreas, and are blocked by charybdotoxin and TRAM-34 (Ishii *et al.*, 1997; Wulff *et al.*, 2000), but are weakly affected by SK channel blocker apamin and BK channel blocker iberiotoxin (Ishii *et al.*, 1997). IK channels mediate currents similar to the originally described "Gardos channels" in erythrocytes (Gardos, 1958). They are additionally found in myenteric neurons in the intestine (Nguyen *et al.*, 2007) lymphocytes, and in different endo- and epithelial tissues (Wulff *et al.*, 2007). Recent findings suggest that IK channels are also expressed in central neurons (Turner *et al.*, 2015), where these channels reduce summation of excitatory post-synaptic potentials (EPSPs) in cerebellar Purkinje neurons (Engbers *et al.*, 2012). Moreover, they contribute to the sAHP and they reduce excitability in CA1 pyramidal cells (King *et al.*, 2015). In myenteric neurons an IK-sensitive sAHP that was blocked by TRAM-34 has also been reported (Nguyen *et al.*, 2007).

BK channels, originally cloned and expressed from *Drosophila* (*dSlo*) (Atkinson *et al.*, 1991; Adelman *et al.*, 1992), consist of 6 transmembrane domains (S1-S6). They comprise a pore-forming P-loop, a voltage-sensing domain similar to other Kv channels, and an additional transmembrane segment (S0) for coupling with auxiliary β -subunits (Jan & Jan, 1997; Meera *et al.*, 1997). So far, 4 different β -subunits (β 1-4) have been identified in mammals which show different expression and modulate kinetics, Ca²⁺ sensitivity, and pharmacology of BK α -subunits (Orio *et al.*, 2002). For example, β 4 is expressed mainly in the brain, slows the activation kinetics, increases the Ca²⁺-sensitivity, shifts the activation threshold of BK current to more negative potentials, and makes the BK α -subunit resistant to the BK channel blockers charybdotoxin and iberiotoxin (Meera *et al.*, 2000; Behrens *et al.*, 2000). At the frog neuromuscular junction, BK channels regulate transmitter release through modulation of pre-synaptic Ca²⁺ influx (Robitaille & Charlton, 1992). Later, BK channels were also found at pre-synaptic sites and somata in the rat brain (Knaus *et al.*, 1996). In rat CA1 pyramidal cells, BK channels contribute to the somatic spike repolarization, and mediate the fAHP (Storm, 1987; Shao *et al.*, 1999). At hippocampal pre-synaptic terminals, BK channels do not affect waveforms and transmitter release under basal conditions, but they can repolarize pre-synaptic spikes and thereby reduce transmitter release when other Kv channels are blocked (Hu *et al.*, 2001; Alle *et al.*, 2011).

Investigations of Ca²⁺-activated K⁺ channels are presented in **Paper III and Paper IV**.

Dorso-ventral differences in the hippocampus

The hippocampus is a medial temporal lobe structure which is found in different mammalian species, including rat, monkey and human. In rat and other rodents the hippocampus is orientated along the dorso-ventral (septo-temporal) axis, which corresponds to a posterior-anterior orientation in primates. The hippocampus is critically involved in memory formation, initially described in patient H.M. (Henry Molaison), who suffered from severe memory loss after bilateral hippocampal resection (Scoville & Milner, 1957).

Subsequent studies in rats found a role of the hippocampus in spatial memory, based on the discoveries of place cells (O'Keefe & Dostrovsky, 1971) and the impairment of spatial memory after hippocampal lesions (Morris *et al.*, 1982). In addition, the hippocampus is also involved in contextual fear memory (Kim & Fanselow, 1992).

Later work suggested that the hippocampus differs in its functions, connections, and gene expression along the dorso-ventral axis (Moser & Moser, 1998; Fanselow & Dong, 2010; Strange *et al.*, 2014). For example, lesions in dorsal but not ventral hippocampus of rats impair spatial memory in a Morris water maze test (Moser *et al.*, 1993). Conversely, ventral hippocampal lesions reduce defensive fear response (Kjelstrup *et al.*, 2002) and affect feeding behavior (Bannerman *et al.*, 2002). Moreover, stimulation of the ventral but not the dorsal hippocampus increases locomotion through activation of the nucleus accumbens and the dopaminergic pathways of the mesolimbic system (Wu & Brudzynski, 1995; Zhang *et al.*, 2002; Peleg-Raibstein & Feldon, 2006). The activation of the dopaminergic reward-pathways by the ventral hippocampus may be of particular importance for early goal-oriented learning during spatial navigation (Ruediger *et al.*, 2012).

Anatomical data suggest that cortical areas involved in spatial navigation (retrosplenial cortex) are connected to the dorsal hippocampus via dorsal parts of the entorhinal cortex, whereas areas involved in emotional processing (infralimbic and prelimbic cortices) are connected to the more ventral parts of entorhinal cortex and hippocampus (Jones & Witter, 2007; Strange *et al.*, 2014). The projections from hippocampus to subcortical areas are also different along the hippocampal dorso-ventral axis. The dorsal hippocampus preferentially targets small parts of the dorsal (rostral) lateral septum, the mammillary body and the anterior hypothalamic nucleus, whereas the ventral hippocampus targets the more ventral parts of lateral septum, the medial preoptic nucleus, the hypothalamic periventricular zone, the ventromedial hypothalamic nucleus and the medial parts of nucleus accumbens and amygdala (Groenewegen *et al.*, 1987; Risold & Swanson, 1996; Risold & Swanson, 1997; Kishi *et al.*, 2006; Strange *et al.*, 2014).

Gene expression data indicate multiple molecular domains along the hippocampal dorso-ventral axis with sharply defined borders (Dong *et al.*, 2009; Fanselow & Dong, 2010). The individual domains are defined by an overlap of many genes with common expression boundaries. Moreover, the number of domains may vary between different hippocampal subfields. In CA1, for example, a dorsal, an intermediate and a ventral domain have been described (Dong *et al.*, 2009), whereas in CA3, nine expression domains have been found along its dorso-ventral axis (Thompson *et al.*, 2008). In these studies a large number of genes encode for proteins involved in cell adhesion, axon guidance, neuropeptides, neurotransmitter receptors, ion channels and transcription factors.

Electrophysiological recordings show that hippocampal pyramidal neurons have spatially selective firing fields (O'Keefe & Dostrovsky, 1971), and the field size increases almost linearly along the dorso-ventral axis (Jung *et al.*, 1994; Maurer *et al.*, 2005; Kjelstrup *et al.*, 2008; Royer *et al.*, 2010). In parallel, CA1 pyramidal neurons also differ in synaptic plasticity (Papatheodoropoulos & Kostopoulos, 2000; Maggio & Segal, 2007) and in their intrinsic properties (Dougherty *et al.*, 2012; Marcelin *et al.*, 2012a; Marcelin *et al.*, 2012b; Dougherty *et al.*, 2013). These findings include dorso-ventral differences in the ability to induce long-term potentiation (LTP) (Papatheodoropoulos & Kostopoulos, 2000) and to modulate LTP by corticosteroids (Maggio & Segal, 2007). Furthermore, dorsal and ventral CA1 pyramidal cells differ in their intrinsic excitability (Dougherty *et al.*, 2012), expression of HCN genes (encoding for hyperpolarization-activated cyclic nucleotide gated (HCN) channels), HCN-dependent h -current (I_h) and I_h -dependent functions (Marcelin *et al.*, 2012a; Dougherty *et al.*, 2013). In addition, Marcelin *et al.*, 2012b found dorso-ventral differences in Kv4.2 protein levels and Kv4.2 mediated current. The properties and impact of other K^+ -dependent membrane currents along the hippocampal dorso-ventral axis remain unknown. Given the importance of I_M in regulating excitability, spike rate adaptation and other important functions in central neurons, we investigated its role in CA1 pyramidal neurons along the dorso-ventral axis (see **Paper I**). It's not known whether other hippocampal cell types also differ in their intrinsic properties. In **Paper III**, we investigated the basic electrical properties of dentate granule cells along the dorso-ventral axis.

AIMS

The aims of this Ph.D.-project were:

- 1) Test whether dorsal and ventral CA1 pyramidal cells differ with respect to Kv7/M-current (I_M) and I_M -related functions, including resonance, temporal summation, and excitability (**Paper I**).
- 2) Investigate the electrical properties and functions of Kv2 channels in layer II stellate cells in medial entorhinal cortex (**Paper II**).
- 3) Test whether dentate granule cells differ in their intrinsic properties along the hippocampal dorso-ventral axis (**Paper III**).
- 4) Test whether IK1 channels (SK4; KCNN; intermediate conductance Ca^{2+} -activated K^+ channels) underlie the sAHP and control repetitive firing in CA1 pyramidal cells (**Paper IV**).

METHODS

The majority of our experiments were performed with patch-clamp recordings from neurons in acute slices from rat or mouse brains.

The patch-clamp method allows measurements of whole-cell or single-channel currents flowing across cellular membranes through ion channels. Measurements of small currents in the picoampere range (10^{-12} A) requires a low-noise recording technique, achieved by a high-resistance seal (“gigaseal”, $> 10^9 \Omega$) between the cellular membrane and the pipette tip. The method can be used to measure either the current flow, by controlling the voltage of a cell membrane (voltage clamp), or to measure the voltage response, by manipulating the current through the pipette (current clamp). The voltage-clamp method is particularly useful for determining the voltage dependence and kinetics of membrane currents, whereas current clamp is commonly used for studying physiological voltage responses such as action potentials and after-hyperpolarizations (AHPs).

The patch-clamp technique allows different recording configurations, including cell-attached, inside-out, outside-out and whole-cell recordings, each with its own advantages and disadvantages. Cell-attached recordings are noninvasive and leave the intracellular environment intact, which is especially important if the channel gating is under metabolic control and effected by intracellular second messengers. A disadvantage is that the membrane potential can't be measured directly, and the ionic composition inside the cell cannot be changed.

The inside-out patch is achieved by establishing a cell-attached configuration followed by retraction of the pipette and excision of the patch. In this way, the cytosolic side of the membrane is exposed to the extracellular medium, which allows systematic investigation of intracellular messengers involved in ion channel gating. The main disadvantage is that cytosolic factors are lost which may affect ion channel gating. Further, some ion channels are also anchored to the cytoskeleton and may not be retained after patch excision.

The outside-out patch is achieved by first establishing a cell-attached configuration followed by brief suction, i.e. applying negative pressure to the patch pipette, leading to the rupture of the patch membrane and “break-in” to the intracellular environment. After achieving the “whole-cell” configuration the pipette is slowly retracted leading to excision of an “outside-out” patch. This configuration is useful for studying extracellular factors involved in ion channel gating. The disadvantages are similar to those described in inside-out patches, i.e. loss of intracellular messengers and possible retention of ion channels anchored to the cytoskeleton.

A special form of outside-out patch - the nucleated patch- was used in paper II in order to study macroscopic Kv2 current under improved voltage and space clamp conditions. This configuration is achieved in a manner similar to that of the outside-out patch, but additional negative pressure during pipette retraction extracts also the nucleus and larger parts of the cellular membrane. The main advantage of the nucleated patch compared to the conventional outside-out patch is an improved signal-to-noise ratio since the larger membrane surface results in larger current and increased stability during longer recording periods.

The whole-cell recording configuration was used in the majority of the experiments. The advantage of this configuration is to measure the summed response of all ion channels that determine the intrinsic properties of the cell. In contrast, the whole-cell configuration also causes loss of cytosolic molecules through the dialysis with the intracellular pipette solution, and this may affect the cellular responses.

To enable stable whole-cell patch clamp recordings of visually identified neurons under controlled, standardized conditions, we chose an acute brain slice preparation.

Before slice preparation, rats and mice were deeply anaesthetized with Suprane (desflurane) followed by rapid decapitation. The brain was quickly removed (<1min) and transferred to a petri-dish, containing an ice-cold (0°C) sucrose-based cutting medium with low Na⁺ concentration, and saturated with 95% O₂/5% CO₂ for better tissue preservation (see Methods in the papers). Acute slices were cut from hippocampus or entorhinal cortex in sucrose-based artificial cerebrospinal fluid (aCSF) with a vibratome. The slices were immediately transferred to a submerged holding chamber and incubated at 30-32°C for ~30 min. The slices were then stored at room temperature (20-24°C) before being transferred to the recording chamber, containing aCSF (see Methods in the papers). Recordings were done at 34-35°C, which is close to the normal brain temperature of rats and mice *in vivo* (36-37°C).

Prior to recording, a patch pipette was pulled from borosillate glass and filled with an intracellular solution containing either potassium methylsulfate, potassium gluconate, or potassium methanesulfonate. The pipette was then positioned close to the surface of the brain slice, viewed with an upright microscope with infrared-differential interference contrast (IR-DIC) optics. While entering the recording chamber, positive pressure was applied to the inside of the pipette, which avoids clogging of the pipette tip with dirt and tissue debris. The seal formation between pipette and cell membrane was monitored by observing current responses evoked by small negative voltage pulses. Approaching the cell membrane usually decreased the current response, due to an increase in seal resistance. The release of positive pressure was followed by gentle suction led to a further increase in seal resistance until a “gigaseal” was reached. After cancelling the remaining capacitive currents of the pipette, the current trace appeared flat. Whole-cell recordings were finally achieved by applying brief negative pressure to the inside of the pipette, causing rupture of the cell membrane below the patch and the appearance of a cellular capacitive transient.

RESULTS AND DISCUSSION

Paper I

It has been suggested that the hippocampus differs in its functions, connections and gene expression along the dorso-ventral (D-V) axis (Moser & Moser, 1998; Bannerman *et al.*, 2004; Fanselow & Dong, 2010; Strange *et al.*, 2014).

In this study we aimed to determine the role of Kv7/M-channels in regulating the intrinsic properties of dorsal and ventral CA1 pyramidal cells in young, 3-4 week old rats.

Our voltage-clamp recordings indicated that dorsal CA1 pyramidal cells exhibit a larger Kv7/M-current, I_M , and a hyperpolarizing shift in its activation range compared to ventral pyramidal cells. Using current-clamp recordings, we found that I_M had a stronger impact on voltage responses in dorsal than ventral pyramidal cells.

We found that temporal summation was similar in dorsal and ventral CA1 pyramidal cells under normal conditions but stronger in dorsal than in ventral cells when Kv7/M-channels were blocked with XE991. Thus, Kv7/M-channels seem to “normalize” temporal summation under normal conditions. However, this finding also suggest that suppression of Kv7/M-current by acetylcholine or other cholinergic agonists (Brown & Adams, 1980; Halliwell & Adams, 1982; Storm, 1989) may enhance temporal summation and facilitate synaptic integration, preferably in the dorsal compared to the ventral pyramidal cells.

We hypothesized that a stronger Kv7/M-current in dorsal vs. ventral cells could also affect I_M -dependent resonance (M-resonance) in the theta frequency range (Hu *et al.*, 2002; Hu *et al.*, 2009). Indeed, we found that dorsal cells showed prominent M-resonance at subthreshold potentials, while M-resonance was weaker and rarely found in ventral cells. However, application of the selective Kv7/M-channel opener retigabine strongly increased M-resonance in ventral cells. This suggested that functional Kv7/M-channels are present in the ventral cell population, but normally weakly activated within the subthreshold voltage range.

Interestingly, it has been suggested that differences in resonance properties along the hippocampal D-V axis may contribute to the D-V difference in theta rhythmicity (Royer *et al.*, 2010). In addition, previous studies reported D-V differences in HCN-dependent resonance and temporal summation in CA1 pyramidal cells (Marcelin *et al.*, 2012a; Marcelin *et al.*, 2012b; Dougherty *et al.*, 2013). This raised the question whether D-V differences in I_M , I_h , or other intrinsic membrane currents can account for differences in place field size along the hippocampal D-V axis (Jung *et al.*, 1994; Maurer *et al.*, 2005; Kjelstrup *et al.*, 2008; Royer *et al.*, 2010). Although several factors may contribute to this D-V gradient, experiments in HCN1 knock-out mice showed larger place fields in hippocampal pyramidal cells (Hussaini *et al.*, 2011) presumably reflecting the relevance of intrinsic currents *in vivo*.

We also found that Kv7/M-channels have a stronger impact on spike threshold, the Kv7-dependent mAHP, excitability and spike adaptation in dorsal than in ventral pyramidal cells. Moreover, the f/I curves, as probed with somatic injection of depolarizing current pulses, were steeper (i.e. the excitability was more sensitive to the input) in ventral compared to dorsal cells as previously found by Dougherty *et al.*, (2012). In parallel, ventral cells exhibited also weaker spike frequency adaptation than dorsal cells. However, when Kv7/M-channels were

blocked, the D-V difference in f/I curves and spike adaptation were abolished, suggesting that they were directly caused by D-V differences of I_M . Notably, it has been reported that the ventral hippocampus is more susceptible to epileptiform activity than the dorsal hippocampus (Bragdon *et al.*, 1986; Derchansky *et al.*, 2004). This may be partially due to reduced Kv7/M-channel activity in ventral compared to dorsal pyramidal cells.

Paper II

The roles of different potassium channels in regulating excitability and spike properties in the medial entorhinal cortex (mEC) have so far been characterized only to a very limited extent. In paper II we investigated the electrical properties of Kv2 channels in layer II stellate cells using the recently identified Kv2 channel blocker Guanyxitoxin-1E (GTx-1E).

First, we performed voltage-clamp recordings from nucleated patches and found that 100 nM GTx-1E inhibited a delayed-rectifier current (I_K), but had no effects on the transient A-type current (I_A), as previously found (Liu & Bean, 2014).

In current clamp, wash-in of 100 nM GTx increased burst firing and excitability when starting from moderate spike rates (10 spikes/s). In contrast, at higher spike rates (70 spikes/s), wash-in of GTx decreased maintained firing and spike amplitudes and depolarized inter-spike-intervals following the first spike. With lower doses of GTx (10 and 30 nM), we found that block of Kv2 channels increased burst-firing and excitability by increasing the after-depolarization (ADP), and by reducing the fast and medium after-hyperpolarizations (fAHPs, mAHPs) during repetitive firing in LII SCs.

Previously, it has been shown that block of Kv7/M-type K^+ current with linopirdine has only weak effects on ADP and firing patterns in LII SCs (Yoshida & Alonso, 2007). A recent study reported that block of Kv7/M-channels with XE991 increased the excitability of LII SCs (Nigro *et al.*, 2014), but did not increase the ADP and burst-firing as found in pyramidal cells of the hippocampus and mEC (Yue & Yaari, 2004; Gu *et al.*, 2005; Yoshida & Alonso, 2007). Thus, our present results combined with those of previous studies suggest that Kv2 channels in LII SCs have a strong impact on ADPs and burst-firing in contrast to the impact of Kv7/M-channels. It has been shown that, postsynaptic burst-firing paired with presynaptic activity can lead to induction of long-term potentiation (LTP) (Magee & Johnston, 1997; Thomas *et al.*, 1998). It remains to be determined whether Kv2 channels can regulate LTP induction by modulating the ADP and burst-firing in LII SCs.

We also found that block of Kv2 channels with GTx caused an increase in spike broadening during repetitive firing, but had no effect on the first spike. This indicates that Kv2 channels contribute directly to late spike repolarization. However, this effect may also be indirectly due to more depolarized inter-spike trajectories after Kv2 blockade, followed by incomplete recovery of inactivation of voltage-gated Na^+ channels, thereby reducing spike amplitudes and activation of other repolarizing K^+ channels.

The block of Kv2 channels and its effects on inter-spike trajectories, spike repolarization and Na^+ channel availability are also probably the main reason for an observed reduction in maintained firing during higher spike rates, as previously suggested in other cell types (Du *et al.*, 2000; Tong *et al.*, 2013; Guan *et al.*, 2013; Liu & Bean, 2014).

Paper III

In this study, we compared the sAHP amplitude, the excitability and the firing pattern of dentate granule cells (DGCs) at different locations along the hippocampal dorso-ventral axis in juvenile and adult rats, and adult mice. In all age groups tested, the sAHP amplitude, and spike frequency adaptation were more prominent, i.e. the excitability was lower, in the dorsal than in the ventro-intermediate DGCs. Our results from current clamp experiments were confirmed when we used different intracellular solutions and slicing procedures. In addition, morphological reconstructions of previously recorded DGCs indicated that the dorso-ventral differences in sAHP amplitude, spike frequency adaptation and excitability were not correlated with variations in dendritic and axonal lengths. In addition, using whole-cell voltage clamp recordings, we found that the current underlying the sAHP (I_{sAHP}) showed a bigger peak amplitude and slower kinetics in dorsal than ventral DGCs.

It has been suggested that different channel types may underlie the I_{sAHP} of DGCs. One study found that knock-out of Kv7.2 or Kv7.3 in mice decreased the I_{sAHP} peak amplitudes in DGCs (Tzingounis & Nicoll, 2008). Additionally, we have previously shown in CA1 pyramidal cells that the I_M mediated by Kv7/M-channels causes dorso-ventral differences in several I_M -dependent properties including excitability and spike frequency adaptation (paper I). Therefore, it is relevant to ask whether I_M may also contribute to dorso-ventral differences in I_{sAHP} in the DGCs. A recent study showed that DGCs with short axons (less than 10 μM) show reduced or absent I_M (Martinello *et al.*, 2015). Conversely, we have shown that dorso-ventral differences in sAHP amplitude, spike rate adaptation and excitability were not correlated to variations in axonal (and dendritic) length, even in DGCs with very short axons, i.e. less than 10 μM . Further, we observed D-V differences in I_{sAHP} amplitude and kinetics in presence of 5 mM TEA, which partially blocks Kv7/M-channels (Storm, 1990; Battefeld *et al.*, 2014). Hence, a major contribution of I_M to dorso-ventral differences in I_{sAHP} in DGCs seems unlikely. Tanner *et al.*, 2011 found that K_{ATP} channels may contribute to sAHP following a spike train in DGCs. They concluded that the K_{ATP} channel opening was due to ATP depletion in response to spike firing. In our present study, we observed D-V differences in I_{sAHP} amplitude and kinetics while Na^+ channels and spike firing were blocked with TTX. Thus, although some ATP depletion might conceivably also be caused by the calcium influx that triggered the sAHP, our findings indirectly suggest that K_{ATP} channels are not the main cause for the observed dorso-ventral differences in I_{sAHP} in DGCs.

Future experiments will be needed to identify the mechanism underlying the dorso-ventral differences in sAHP, spike accommodation and excitability in DGCs. The reduced sAHP amplitude and higher excitability in ventral DGCs may contribute to an early onset of epileptiform activity in the ventral hippocampus in models of temporal lobe epilepsy (Derchansky *et al.*, 2004; Toyoda *et al.*, 2013).

Paper IV

Our aim was to test whether intermediate conductance Ca^{2+} activated K^+ channels (IK1) underlie the slow after-hyperpolarization, sAHP, in CA1 pyramidal cells, as recently suggested (King *et al.*, 2015).

Using somatic whole-cell voltage clamp, we first recorded a prominent I_{sAHP} tail current in response to depolarizing voltage pulses in CA1 pyramidal cells in rat hippocampal slices. To test whether IK1 channels underlie the I_{sAHP} , we bath-applied the potent IK1 blocker TRAM-34 (Wulff *et al.*, 2000) or delivered the drug intracellularly via the patch pipette, but found no effects of TRAM-34 during a time course of 25 minutes. In some experiments, we also applied the cholinergic agonist carbachol after the 25 minutes. Carbachol potently blocked the I_{sAHP} , as previously shown (Benardo & Prince, 1982; Cole & Nicoll, 1984; Storm, 1990). In a separate experiment, the I_{sAHP} amplitude was monitored during wash-in of the IK1 blocker charybdotoxin (ChTx) (Ishii *et al.*, 1997). Again, block of IK1 channels had no significant effect on I_{sAHP} . To test whether TRAM-34 and ChTx were able to block IK1 channels, both compounds were bath-applied to HEK293 cells transiently expressing IK1 channels which rapidly blocked IK1 currents. Next we investigated the effects of TRAM-34 on AHPs and excitability in CA1 pyramidal cells in current clamp configuration. Similar to our findings in voltage clamp, TRAM-34 had no effects on mAHP/sAHP amplitudes, and did not change excitability in response to depolarizing current pulses. In a different set of experiments we bath-applied a combination of K^+ channel blockers, including TRAM-34, XE991 to block Kv7 channels, and apamin to block SK channels, as previously used by King *et al.* (2015). This mixture of K^+ channel blockers suppressed the mAHP but again had no effects on the sAHP. In our study, the effects of TRAM-34 in pyramidal neurons of the basolateral amygdala (BLA) were also measured, but again no effect on the I_{sAHP} , excitability, or spike properties were found, in agreement with our findings in CA1 pyramidal neurons. Finally, our experiments in IK1 knock-out mice revealed a prominent I_{sAHP} that seemed indistinguishable from that of wild type mice.

In conclusion, our experimental data indicate that IK1 channels do not contribute to the current underlying the sAHP and have no effects on excitability in pyramidal cells in BLA or CA1. Our present data are inconsistent with the recent study that reported a reduction in I_{sAHP} and sAHP in CA1 pyramidal cells after block of IK1 channels with TRAM-34 (King *et al.*, 2015). This discrepancy may be due to a combination of several factors: 1) run-down of I_{sAHP} during whole-cell recordings has previously been observed and cannot be excluded in the absence of time plots. 2) The Ca^{2+} influx and, hence, I_{sAHP} , may differ between synaptic stimulation (King *et al.*, 2015) and injection of somatic current pulses, due to recruitment of e.g. different Ca^{2+} sources. This could affect activation of IK1 channels depending on its subcellular localization.

Further, it has been proposed that the sAHP is mediated by multiple classes of K^+ channels which are gated by diffusible cytosolic Ca^{2+} sensors such as hippocalcin or neurocalcin combined with changes in membrane phosphatidylinositol 4,5-bisphosphate levels (Andrade *et al.*, 2012). More experiments will be needed to unequivocally identify the molecular components underlying the I_{sAHP} , using gene manipulations of different pore-forming and accessory Kv subunits, together with cloned components and specific pharmacological tools.

REFERENCE LIST

Adams PR, Constanti A, Brown DA, & Clark RB (1982). Intracellular Ca²⁺ activates a fast voltage-sensitive K⁺ current in vertebrate sympathetic neurones. *Nature* **296**, 746-749.

Adelman JP, Shen KZ, Kavanaugh MP, Warren RA, Wu YN, Lagrutta A, Bond CT, & Alan North R (1992). Calcium-activated potassium channels expressed from cloned complementary DNAs. *Neuron* **9**, 209-216.

Alle H, Ostroumov K, Geiger J, & Storm JF (2009). M-current, persistent Na⁺ current, and subthreshold resonance recorded in mossy fiber boutons (MFBs) in rat hippocampus. Program No.42.2/D10.2009 Neuroscience Meeting Planner. Society for Neuroscience, Chicago, IL, USA. Online. 2009.

Ref Type: Abstract

Alle H, Kubota H, & Geiger JRP (2011). Sparse But Highly Efficient Kv3 Outpace BKCa Channels in Action Potential Repolarization at Hippocampal Mossy Fiber Boutons. *The Journal of Neuroscience* **31**, 8001-8012.

Andrade R, Foehring RC, & Tzingounis AV (2012). The calcium-activated slow AHP: cutting through the gordian knot. *Frontiers in Cellular Neuroscience* **6:47**.

Atkinson NS, Robertson GA, & Ganetzky B (1991). A component of calcium-activated potassium channels encoded by the *Drosophila* slo locus. *Science* **253**, 551-555.

Azouz R, Jensen MS, & Yaari Y (1996). Ionic basis of spike after-depolarization and burst generation in adult rat hippocampal CA1 pyramidal cells. *The Journal of Physiology* **492**, 211-223.

Ballesteros-Merino C, Watanabe M, Shigemoto R, Fukazawa Y, Adelman JP, & Luján R (2014). Differential subcellular localization of SK3-containing channels in the hippocampus. *The European Journal of Neuroscience* **39**, 883-892.

Bannerman DM, Deacon RMJ, Offen S, Friswell J, Grubb M, & Rawlins JNP (2002). Double dissociation of function within the hippocampus: Spatial memory and hyponeophagia. *Behavioral Neuroscience* **116**, 884-901.

Bannerman DM, Rawlins JNP, McHugh SB, Deacon RMJ, Yee BK, Bast T, Zhang WN, Pothuizen HHJ, & Feldon J (2004). Regional dissociations within the hippocampus--memory and anxiety. *Neuroscience & Biobehavioral Reviews* **28**, 273-283.

Baranauskas G, Tkatch T, & Surmeier DJ (1999). Delayed rectifier currents in rat globus pallidus neurons are attributable to Kv2.1 and Kv3.1/3.2 K⁺ channels. *The Journal of Neuroscience* **19**, 6394-6404.

Battefeld A, Tran BT, Gavrilis J, Cooper EC, & Kole MHP (2014). Heteromeric Kv7.2/7.3 channels differentially regulate action potential initiation and conduction in neocortical myelinated axons. *The Journal of Neuroscience* **34**, 3719-3732.

Bean BP (2007). The action potential in mammalian central neurons. *Nature Reviews Neuroscience* **8**, 451-465.

Behrens R, Nolting A, Reimann F, Schwarz M, Waldschütz R, & Pongs O (2000). hKCNMB3 and hKCNMB4, cloning and characterization of two members of the large-conductance calcium-activated potassium channel beta subunit family. *FEBS Letters* **474**, 99-106.

Benardo LS & Prince DA (1982). Cholinergic excitation of mammalian hippocampal pyramidal cells. *Brain Research* **249**, 315-331.

Blaine JT & Ribera AB (1998). Heteromultimeric Potassium Channels Formed by Members of the Kv2 Subfamily. *The Journal of Neuroscience* **18**, 9585-9593.

Blatz AL & Magleby KL (1986). Single apamin-blocked Ca-activated K⁺ channels of small conductance in cultured rat skeletal muscle. *Nature* **323**, 718-720.

Bragdon AC, Taylor DM, & Wilson WA (1986). Potassium-induced epileptiform activity in area CA3 varies markedly along the septotemporal axis of the rat hippocampus. *Brain Research* **378**, 169-173.

Brown DA & Adams PR (1980). Muscarinic suppression of a novel voltage-sensitive K⁺ current in a vertebrate neurone. *Nature* **283**, 673-676.

Brown DA & Passmore GM (2009). Neural KCNQ (Kv7) channels. *British Journal of Pharmacology* **156**, 1185-1195.

Buzsáki G (2002). Theta Oscillations in the Hippocampus. *Neuron* **33**, 325-340.

Calvin WH & Schwindt PC (1972). Steps in production of motoneuron spikes during rhythmic firing. *Journal of Neurophysiology* **35**, 297-310.

Castle NA & Strong PN (1986). Identification of two toxins from scorpion (*Leiurus quinquestriatus*) venom which block distinct classes of calcium-activated potassium channel. *FEBS Letters* **209**, 117-121.

Cole AE & Nicoll RA (1984). Characterization of a slow cholinergic post-synaptic potential recorded in vitro from rat hippocampal pyramidal cells. *The Journal of Physiology* **352**, 173-188.

Cooper EC, Aldape KD, Abosch A, Barbaro NM, Berger MS, Peacock WS, Jan YN, & Jan LY (2000). Colocalization and coassembly of two human brain M-type potassium channel subunits that are mutated in epilepsy. *Proceedings of the National Academy of Sciences* **97**, 4914-4919.

Derchansky M, Shahar E, Wennberg RA, Samoilova M, Jahromi SS, Abdelmalik PA, Zhang L, & Carlen PL (2004). Model of frequent, recurrent, and spontaneous seizures in the intact mouse hippocampus. *Hippocampus* **14**, 935-947.

Deutsch E, Weigel AV, Akin EJ, Fox P, Hansen G, Haberkorn CJ, Loftus R, Krapf D, & Tamkun MM (2012). Kv2.1 cell surface clusters are insertion platforms for ion channel delivery to the plasma membrane. *Molecular Biology of the Cell* **23**, 2917-2929.

Devaux JmJ, Kleopa KA, Cooper EC, & Scherer SS (2004). KCNQ2 is a nodal K⁺ channel. *The Journal of Neuroscience* **24**, 1236-1244.

Dong HW, Swanson LW, Chen L, Fanselow MS, & Toga AW (2009). Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1. *Proceedings of the National Academy of Sciences* **106**, 11794-11799.

Dougherty KA, Islam T, & Johnston D (2012). Intrinsic excitability of CA1 pyramidal neurones from the rat dorsal and ventral hippocampus. *The Journal of Physiology* **590**, 5707-5722.

Dougherty KA, Nicholson DA, Diaz L, Buss EW, Neuman KM, Chetkovich DM, & Johnston D (2013). Differential expression of HCN subunits alters voltage-dependent gating of h-channels in CA1 pyramidal neurons from dorsal and ventral hippocampus. *Journal of Neurophysiology* **109**, 1940-1953.

Du J, Tao-Cheng JH, Zerfas P, & McBain CJ (1998). The K⁺ channel, Kv2.1, is apposed to astrocytic processes and is associated with inhibitory postsynaptic membranes in hippocampal and cortical principal neurons and inhibitory interneurons. *Neuroscience* **84**, 37-48.

Du J, Haak LL, Phillips-Tansey E, Russell JT, & McBain CJ (2000). Frequency-dependent regulation of rat hippocampal somato-dendritic excitability by the K⁺ channel subunit Kv2.1. *The Journal of Physiology* **522**, 19-31.

Engbers JDT, Anderson D, Asmara H, Rehak R, Mehaffey WH, Hameed S, McKay BE, Kruskic M, Zamponi GW, & Turner RW (2012). Intermediate conductance calcium-activated potassium channels modulate summation of parallel fiber input in cerebellar Purkinje cells. *Proceedings of the National Academy of Sciences* **109**, 2601-2606.

Faber ESL (2009). Functions and modulation of neuronal SK channels. *Cell Biochemistry and Biophysics* **55**, 127-139.

Faber ESL, Delaney AJ, Power JM, Sedlak PL, Crane JW, & Sah P (2008). Modulation of SK channel trafficking by beta adrenoceptors enhances excitatory synaptic transmission and plasticity in the amygdala. *The Journal of Neuroscience* **28**, 10803-10813.

Faber ESL & Sah P (2002). Physiological role of calcium-activated potassium currents in the rat lateral amygdala. *The Journal of Neuroscience* **22**, 1618-1628.

Faber ESL & Sah P (2003). Ca²⁺-activated K⁺ (BK) channel inactivation contributes to spike broadening during repetitive firing in the rat lateral amygdala. *The Journal of Physiology* **552**, 483-497.

Faber EL & Sah P (2007). Functions of SK channels in central neurons. *Clinical and Experimental Pharmacology and Physiology* **34**, 1077-1083.

Fanselow MS & Dong HW (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* **65**, 7-19.

Feinshreiber L, Singer-Lahat D, Friedrich R, Matti U, Sheinin A, Yizhar O, Nachman R, Chikvashvili D, Rettig J, Ashery U, & Lotan I (2010). Non-conducting function of the Kv2.1 channel enables it to recruit vesicles for release in neuroendocrine and nerve cells. *Journal of Cell Science* **123**, 1940-1947.

Fidzinski P, Korotkova T, Heidenreich M, Maier N, Schuetze S, Kobler O, Zuschratter W, Schmitz D, Ponomarenko A, & Jentsch TJ (2015). KCNQ5 K⁺ channels control hippocampal synaptic inhibition and fast network oscillations. *Nature Communications* **6:6254**.

Fox PD, Loftus RJ, & Tamkun MM (2013). Regulation of Kv2.1 K⁺ conductance by cell surface channel density. *The Journal of Neuroscience* **33**, 1259-1270.

Frech GC, VanDongen AMJ, Schuster G, Brown AM, & Joho RH (1989). A novel potassium channel with delayed rectifier properties isolated from rat brain by expression cloning. *Nature* **340**, 642-645.

Gardos G (1958). The function of calcium in the potassium permeability of human erythrocytes. *Biochimica et Biophysica Acta* **30**, 653-654.

Geiger JRP & Jonas P (2000). Dynamic Control of Presynaptic Ca²⁺ Inflow by Fast-Inactivating K⁺ Channels in Hippocampal Mossy Fiber Boutons. *Neuron* **28**, 927-939.

Groenewegen HJ, der Zee EV-V, te Kortschot A, & Witter MP (1987). Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. *Neuroscience* **23**, 103-120.

Gu N, Hu H, Vervaeke K, & Storm JF (2008). SK (KCa₂) channels do not control somatic excitability in CA1 pyramidal neurons but can be activated by dendritic excitatory synapses and regulate their impact. *Journal of Neurophysiology* **100**, 2589-2604.

Gu N, Vervaeke K, Hu H, & Storm JF (2005). Kv7/KCNQ/M and HCN/h, but not KCa₂/SK channels, contribute to the somatic medium after-hyperpolarization and excitability control in CA1 hippocampal pyramidal cells. *The Journal of Physiology* **566**, 689-715.

Guan D, Armstrong WE, & Foehring RC (2013). Kv2 channels regulate firing rate in pyramidal neurons from rat sensorimotor cortex. *The Journal of Physiology* **591**, 4807-4825.

Gustafsson B & Wigström H (1981). Evidence for two types of afterhyperpolarization in CA1 pyramidal cells in the hippocampus. *Brain Research* **206**, 462-468.

Gutfreund Y, Yarom Y, & Segev I (1995). Subthreshold oscillations and resonant frequency in guinea-pig cortical neurons: physiology and modelling. *The Journal of Physiology* **483**, 621-640.

Halliwell JV & Adams PR (1982). Voltage-clamp analysis of muscarinic excitation in hippocampal neurons. *Brain Research* **250**, 71-92.

Herrington J, Zhou YP, Bugianesi RM, Dulski PM, Feng Y, Warren VA, Smith MM, Kohler MG, Garsky VM, Sanchez M, Wagner M, Raphaelli K, Banerjee P, Ahaghotu C, Wunderler D, Priest BT, Mehl JT, Garcia ML, McManus OB, Kaczorowski GJ, & Slaughter RS (2006). Blockers of the delayed-rectifier potassium current in pancreatic β -cells enhance glucose-dependent insulin secretion. *Diabetes* **55**, 1034-1042.

Hessler S, Zheng F, Hartmann S, Rittger A, Lehnert S, V+Âlkel M, Nissen M, Edelmann E, Saftig P, Schwake M, Huth T, & Alzheimer C (2015). β -Secretase BACE1 regulates hippocampal and reconstituted M-currents in a β -subunit-like fashion. *The Journal of Neuroscience* **35**, 3298-3311.

Hille B (2001). *Ion channels of excitable membranes*, 3 ed. Sunderland, MA: Sinauer.

Hodgkin AL & Huxley AF (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology* **117**, 500-544.

Hotson JR & Prince DA (1980). A calcium-activated hyperpolarization follows repetitive firing in hippocampal neurons. *Journal of Neurophysiology* **43**, 409-419.

Hu H, Shao LR, Chavoshy S, Gu N, Trieb M, Behrens R, Laake P, Pongs O, Knaus HG, Ottersen OP, & Storm JF (2001). Presynaptic Ca²⁺-activated K⁺ channels in glutamatergic hippocampal terminals and their role in spike repolarization and regulation of transmitter release. *The Journal of Neuroscience* **21**, 9585-9597.

Hu H, Vervaeke K, Graham LJ, & Storm JF (2009). Complementary theta resonance filtering by two spatially segregated mechanisms in CA1 hippocampal pyramidal neurons. *The Journal of Neuroscience* **29**, 14472-14483.

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. *The Journal of Physiology* **545**, 783-805.

Hugues M, Romey G, Duval D, Vincent JP, & Lazdunski M (1982). Apamin as a selective blocker of the calcium-dependent potassium channel in neuroblastoma cells: voltage-clamp and biochemical characterization of the toxin receptor. *Proceedings of the National Academy of Sciences U S A* **79**, 1308-1312.

Hussaini SA, Kempadoo KA, Thuault SJ, Siegelbaum SA, & Kandel ER (2011). Increased size and stability of CA1 and CA3 place fields in HCN1 knockout mice. *Neuron* **72**, 643-653.

Hutcheon B, Miura RM, & Puil E (1996). Subthreshold membrane resonance in neocortical neurons. *Journal of Neurophysiology* **76**, 683-697.

Hutcheon B & Yarom Y (2000). Resonance, oscillation and the intrinsic frequency preferences of neurons. *Trends in Neurosciences* **23**, 216-222.

Hwang PM, Fotuhi M, Brecht DS, Cunningham AM, & Snyder SH (1993). Contrasting immunohistochemical localizations in rat brain of two novel K⁺ channels of the Shab subfamily. *The Journal of Neuroscience* **13**, 1569-1576.

Ishii TM, Silvia C, Hirschberg B, Bond CT, Adelman JP, & Maylie J (1997). A human intermediate conductance calcium-activated potassium channel. *Proceedings of the National Academy of Sciences U S A* **94**, 11651-11656.

Jensen MS, Azouz R, & Yaari Y (1996). Spike after-depolarization and burst generation in adult rat hippocampal CA1 pyramidal cells. *The Journal of Physiology* **492**, 199-210.

Jentsch TJ (2000). Neuronal KCNQ potassium channels: physiology and role in disease. *Nature Reviews Neuroscience* **1**, 21-30.

Johnson SW & Seutin V (1997). Bicuculline methiodide potentiates NMDA-dependent burst firing in rat dopamine neurons by blocking apamin-sensitive Ca²⁺-activated K⁺ currents. *Neuroscience Letters* **231**, 13-16.

Jones BF & Witter MP (2007). Cingulate cortex projections to the parahippocampal region and hippocampal formation in the rat. *Hippocampus* **17**, 957-976.

Jung MW, Wiener SI, & McNaughton BL (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *The Journal of Neuroscience* **14**, 7347-7356.

Kandel ER & Spencer WA (1961). Electrophysiology of hippocampal neurons: II. after-potentials and repetitive firing. *Journal of Neurophysiology* **24**, 243-259.

Kharkovets T, Hardelin JP, Safieddine S, Schweizer M, El-Amraoui A, Petit C, & Jentsch TJ (2000). KCNQ4, a K⁺ channel mutated in a form of dominant deafness, is expressed in the inner ear and the central auditory pathway. *Proceedings of the National Academy of Sciences U S A* **97**, 4333-4338.

Kim JJ & Fanselow MS (1992). Modality-specific retrograde amnesia of fear. *Science* **256**, 675-677.

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 Reports* **11**, 175-182.

Kishi T, Tsumori T, Yokota S, & Yasui Y (2006). Topographical projection from the hippocampal formation to the amygdala: A combined anterograde and retrograde tracing study in the rat. *The Journal of Comparative Neurology* **496**, 349-368.

Kjelstrup KB, Solstad T, Brun VH, Hafting T, Leutgeb S, Witter MP, Moser EI, & Moser MB (2008). Finite scale of spatial representation in the hippocampus. *Science* **321**, 140-143.

Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, & Moser MB (2002). Reduced fear expression after lesions of the ventral hippocampus. *Proceedings of the National Academy of Sciences U S A* **99**, 10825-10830.

Knaus HG, Schwarzer C, Koch RO, Eberhart A, Kaczorowski GJ, Glossmann H, Wunder F, Pongs O, Garcia ML, & Sperk G (1996). Distribution of high-conductance Ca(2+)-activated K⁺ channels in rat brain: targeting to axons and nerve terminals. *The Journal of Neuroscience* **16**, 955-963.

Köhler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J, & Adelman JP (1996). Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* **273**, 1709-1714.

Kole MHP, Letzkus JJ, & Stuart GJ (2007). Axon initial segment Kv1 channels control axonal action potential waveform and synaptic efficacy. *Neuron* **55**, 633-647.

Kubisch C, Schroeder BC, Friedrich T, Lütjohann B, El-Amraoui A, Marlin S, Petit C, & Jentsch TJ (1999). KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness. *Cell* **96**, 437-446.

Lampl I & Yarom Y (1997). Subthreshold oscillations and resonant behavior: two manifestations of the same mechanism. *Neuroscience* **78**, 325-341.

Lancaster B & Adams PR (1986). Calcium-dependent current generating the afterhyperpolarization of hippocampal neurons. *Journal of Neurophysiology* **55**, 1268-1282.

Latorre R, Oberhauser A, Labarca P, & Alvarez O (1989). Varieties of calcium-activated potassium channels. *Annual Review of Physiology* **51**, 385-399.

Lerche C, Scherer CR, Seeböhm G, Derst C, Wei AD, Busch AE, & Steinmeyer K (2000). Molecular cloning and functional expression of KCNQ5, a potassium channel subunit that may contribute to neuronal M-current diversity. *Journal of Biological Chemistry* **275**, 22395-22400.

Lin MT, Luján R, Watanabe M, Adelman JP, & Maylie J (2008). SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. *Nature Neuroscience* **11**, 170-177.

Lisman JE (1997). Bursts as a unit of neural information: making unreliable synapses reliable. *Trends in Neurosciences* **20**, 38-43.

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. *The Journal of Neuroscience* **34**, 4991-5002.

Madison DV & Nicoll RA (1982). Noradrenaline blocks accommodation of pyramidal cell discharge in the hippocampus. *Nature* **299**, 636-638.

Madison DV & Nicoll RA (1984). Control of the repetitive discharge of rat CA1 pyramidal neurones in vitro. *The Journal of Physiology* **354**, 319-331.

Madison DV & Nicoll RA (1986). Cyclic adenosine 3',5'-monophosphate mediates beta-receptor actions of noradrenaline in rat hippocampal pyramidal cells. *The Journal of Physiology* **372**, 245-259.

Magee JC & Carruth M (1999). Dendritic voltage-gated ion channels regulate the action potential firing mode of hippocampal CA1 pyramidal neurons. *Journal of Neurophysiology* **82**, 1895-1901.

Magee JC & Johnston D (1997). A synaptically controlled, associative signal for hebbian plasticity in hippocampal neurons. *Science* **275**, 209-213.

Maggio N & Segal M (2007). Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. *The Journal of Neuroscience* **27**, 5757-5765.

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. *The Journal of Neuroscience* **15**, 3840-3851.

Malin SA & Nerbonne JM (2002). Delayed rectifier K⁺ currents, I_K, are encoded by Kv2 α -subunits and regulate tonic firing in mammalian sympathetic neurons. *The Journal of Neuroscience* **22**, 10094-10105.

Marcelin B, Liu Z, Chen Y, Lewis AS, Becker A, McClelland S, Chetkovich DM, Migliore M, Baram TZ, Esclapez M, & Bernard C (2012a). Dorsoventral differences in intrinsic properties in developing CA1 pyramidal cells. *The Journal of Neuroscience* **32**, 3736-3747.

Marcelin B, Lugo jN, Brewster AL, Liu Z, Lewis AS, McClelland S, Chetkovich DM, Baram TZ, Anderson AE, Becker A, Esclapez M, & Bernard C (2012b). Differential dorso-ventral distributions of Kv4.2 and HCN proteins confer distinct integrative properties to hippocampal CA1 pyramidal cell distal dendrites. *Journal of Biological Chemistry* **287**, 17656-17661.

Marrion NV (1997). Control of M-current. *Annual Review of Physiology* **59**, 483-504.

Martinello K, Huang Z, Lujan R, Tran B, Watanabe M, Cooper EC, Brown DA, & Shah MM (2015). Cholinergic afferent stimulation induces axonal function plasticity in adult hippocampal granule cells. *Neuron* **85**, 346-363.

Mateos-Aparicio P, Murphy R, & Storm JF (2014). Complementary functions of SK and Kv7/M potassium channels in excitability control and synaptic integration in rat hippocampal dentate granule cells. *The Journal of Physiology* **592**, 669-693.

Maurer AP, VanRhoads SR, Sutherland GR, Lipa P, & McNaughton BL (2005). Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* **15**, 841-852.

Meech RW (1974). The sensitivity of *Helix aspersa* neurones to injected calcium ions. *The Journal of Physiology* **237**, 259-277.

Meera P, Wallner M, Song M, & Toro L (1997). Large conductance voltage- and calcium-dependent K(+) channel, a distinct member of voltage-dependent ion channels with seven N-terminal transmembrane segments (S0-S6), an extracellular N terminus, and an intracellular (S9-S10) C terminus. *Proceedings of the National Academy of Sciences U S A* **94**, 14066-14071.

Meera P, Wallner M, & Toro L (2000). A neuronal β subunit (KCNMB4) makes the large conductance, voltage- and Ca²⁺-activated K⁺ channel resistant to charybdotoxin and iberiotoxin. *Proceedings of the National Academy of Sciences U S A* **97**, 5562-5567.

Metz AE, Jarsky T, Martina M, & Spruston N (2005). R-type calcium channels contribute to afterdepolarization and bursting in hippocampal CA1 pyramidal neurons. *The Journal of Neuroscience* **25**, 5763-5773.

Misonou H (2010). Homeostatic regulation of neuronal excitability by K⁺ channels in normal and diseased brains. *The Neuroscientist* **16**, 51-64.

Misonou H, Mohapatra DP, Park EW, Leung V, Zhen D, Misonou K, Anderson AE, & Trimmer JS (2004). Regulation of ion channel localization and phosphorylation by neuronal activity. *Nature Neuroscience* **7**, 711-718.

Misonou H, Mohapatra DP, & Trimmer JS (2005). Kv2.1: A voltage-gated K⁺ channel critical to dynamic control of neuronal excitability. *NeuroToxicology* **26**, 743-752.

Misonou H, Thompson SM, & Cai X (2008). Dynamic regulation of the Kv2.1 voltage-gated potassium channel during brain ischemia through neuroglial interaction. *The Journal of Neuroscience* **28**, 8529-8538.

Mohapatra DP, Misonou H, Pan SJ, Held JE, Surmeier DJ, & Trimmer JS (2009). Regulation of intrinsic excitability in hippocampal neurons by activity-dependent modulation of the Kv2.1 potassium channel. *Channels (Austin)* **3**, 46-56.

Mohapatra DP & Trimmer JS (2006). The Kv2.1 C terminus can autonomously transfer Kv2.1-like phosphorylation-dependent localization, voltage-dependent gating, and muscarinic modulation to diverse Kv channels. *The Journal of Neuroscience* **26**, 685-695.

Morris RGM, Garrud P, Rawlins JNP, & O'Keefe J (1982). Place navigation impaired in rats with hippocampal lesions. *Nature* **297**, 681-683.

Moser E, Moser MB, & Andersen P (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *The Journal of Neuroscience* **13**, 3916-3925.

Moser MB & Moser EI (1998). Functional differentiation in the hippocampus. *Hippocampus* **8**, 608-619.

Murakoshi H & Trimmer JS (1999). Identification of the Kv2.1 K⁺ channel as a major component of the delayed rectifier K⁺ current in rat hippocampal neurons. *The Journal of Neuroscience* **19**, 1728-1735.

Nguyen TV, Matsuyama H, Baell J, Hunne B, Fowler CJ, Smith JE, Nurgali K, & Furness JB (2007). Effects of compounds that influence IK (KCNN4) channels on afterhyperpolarizing potentials, and determination of IK channel sequence, in guinea pig enteric neurons. *Journal of Neurophysiology* **97**, 2024-2031.

Nigro MJ, Mateos-Aparicio P, & Storm JF (2014). Expression and functional roles of Kv7/KCNQ/M-channels in rat medial entorhinal cortex layer II stellate cells. *The Journal of Neuroscience* **34**, 6807-6812.

O'Keefe J & Dostrovsky J (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research* **34**, 171-175.

Orio P, Rojas P, Ferreira G, & Latorre R (2002). New disguises for an old channel: MaxiK channel β -subunits. *News In Physiological Sciences* **17**, 156-161.

Pal S, Hartnett KA, Nerbonne JM, Levitan ES, & Aizenman E (2003). Mediation of neuronal apoptosis by Kv2.1-encoded potassium channels. *The Journal of Neuroscience* **23**, 4798-4802.

Pan Z, Kao T, Horvath Z, Lemos J, Sul JY, Cranstoun SD, Bennett V, Scherer SS, & Cooper EC (2006). A common ankyrin-G-based mechanism retains KCNQ and NaV channels at electrically active domains of the axon. *The Journal of Neuroscience* **26**, 2599-2613.

Papathodoropoulos C & Kostopoulos G (2000). Decreased ability of rat temporal hippocampal CA1 region to produce long-term potentiation. *Neuroscience Letters* **279**, 177-180.

Park KS, Mohapatra DP, Misonou H, & Trimmer JS (2006). Graded regulation of the Kv2.1 potassium channel by variable phosphorylation. *Science* **313**, 976-979.

Pedarzani P & Storm JF (1993). Pka mediates the effects of monoamine transmitters on the K⁺ current underlying the slow spike frequency adaptation in hippocampal neurons. *Neuron* **11**, 1023-1035.

Pedarzani P & Storm JF (1995). Dopamine modulates the slow Ca(2+)-activated K⁺ current IAHP via cyclic AMP-dependent protein kinase in hippocampal neurons. *Journal of Neurophysiology* **74**, 2749-2753.

Peleg-Raibstein D & Feldon J (2006). Effects of dorsal and ventral hippocampal NMDA stimulation on nucleus accumbens core and shell dopamine release. *Neuropharmacology* **51**, 947-957.

Peters HC, Hu H, Pongs O, Storm JF, & Isbrandt D (2005). Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior. *Nature Neuroscience* **8**, 51-60.

Plant LD, Dowdell EJ, Dementieva IS, Marks JD, & Goldstein SAN (2011). SUMO modification of cell surface Kv2.1 potassium channels regulates the activity of rat hippocampal neurons. *The Journal of General Physiology* **137**, 441-454.

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. *The Journal of Neuroscience* **19**, 5205-5212.

Puil E, Meiri H, & Yarom Y (1994). Resonant behavior and frequency preferences of thalamic neurons. *Journal of Neurophysiology* **71**, 575-582.

Ren Y, Barnwell LF, Alexander JC, Lubin FD, Adelman JP, Pfaffinger PJ, Schrader LA, & Anderson AE (2006). Regulation of surface localization of the small conductance Ca²⁺-activated potassium channel, Sk2, through direct phosphorylation by cAMP-dependent protein kinase. *Journal of Biological Chemistry* **281**, 11769-11779.

Risold PY & Swanson LW (1996). Structural evidence for functional domains in the rat hippocampus. *Science* **272**, 1484-1486.

Risold PY & Swanson LW (1997). Connections of the rat lateral septal complex1. *Brain Research Reviews* **24**, 115-195.

Robitaille R & Charlton MP (1992). Presynaptic calcium signals and transmitter release are modulated by calcium-activated potassium channels. *The Journal of Neuroscience* **12**, 297-305.

Roura-Ferrer M, Etxebarria A, Sole L, Oliveras A, Comes N, Villarroel A, & Felipe A (2009). Functional implications of KCNE subunit expression for the Kv7.5 (KCNQ5) channel. *Cellular Physiology and Biochemistry* **24**, 325-334.

Royer S, Sirota A, Patel J, & Buzsaki G (2010). Distinct representations and theta dynamics in dorsal and ventral hippocampus. *The Journal of Neuroscience* **30**, 1777-1787.

Rudy B (1988). Diversity and ubiquity of K channels. *Neuroscience* **25**, 729-749.

Ruediger S, Spirig D, Donato F, & Caroni P (2012). Goal-oriented searching mediated by ventral hippocampus early in trial-and-error learning. *Nature Neuroscience* **15**, 1563-1571.

Sailer CA, Hu H, Kaufmann WA, Trieb M, Schwarzer C, Storm JF, & Knaus HG (2002). Regional differences in distribution and functional expression of small-conductance Ca²⁺-activated K⁺ channels in rat brain. *The Journal of Neuroscience* **22**, 9698-9707.

Sailer CA, Kaufmann WA, Marksteiner J, & Knaus HG (2004). Comparative immunohistochemical distribution of three small-conductance Ca²⁺-activated potassium channel subunits, SK1, SK2, and SK3 in mouse brain. *Molecular and Cellular Neuroscience* **26**, 458-469.

Sanguinetti MC, Curran ME, Zou A, Shen J, Specter PS, Atkinson DL, & Keating MT (1996). Coassembly of KVLQT1 and minK (IsK) proteins to form cardiac IKS potassium channel. *Nature* **384**, 80-83.

- Sarmiere PD, Weigle CM, & Tamkun MM (2008). The Kv2.1 K(+) channel targets to the axon initial segment of hippocampal and cortical neurons in culture and in situ. *BioMedCentral Neuroscience* **9**, 112.
- Scannevin RH, Murakoshi H, Rhodes KJ, & Trimmer JS (1996). Identification of a cytoplasmic domain important in the polarized expression and clustering of the Kv2.1 K+ channel. *The Journal of Cell Biology* **135**, 1619-1632.
- Schroeder BC, Hechenberger M, Weinreich F, Kubisch C, & Jentsch TJ (2000a). KCNQ5, a novel potassium channel broadly expressed in brain, mediates M-type currents. *Journal of Biological Chemistry* **275**, 24089-24095.
- Schroeder BC, Waldegger S, Fehr S, Bleich M, Warth R, Greger R, & Jentsch TJ (2000b). A constitutively open potassium channel formed by KCNQ1 and KCNE3. *Nature* **403**, 196-199.
- Scoville WB & Milner B (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry* **20**, 11-21.
- Shah MM, Mistry M, Marsh SJ, Brown DA, & Delmas P (2002). Molecular correlates of the M-current in cultured rat hippocampal neurons. *The Journal of Physiology* **544**, 29-37.
- Shah MM, Migliore M, Valencia I, Cooper EC, & Brown DA (2008). Functional significance of axonal Kv7 channels in hippocampal pyramidal neurons. *Proceedings of the National Academy of Sciences U S A* **105**, 7869-7874.
- Shah NH, Schulien AJ, Clemens K, Aizenman TD, Hageman TM, Wills ZP, & Aizenman E (2014). Cyclin E1 regulates Kv2.1 channel phosphorylation and localization in neuronal ischemia. *The Journal of Neuroscience* **34**, 4326-4331.
- Shah NH & Aizenman E (2014). Voltage-gated potassium channels at the crossroads of neuronal function, ischemic tolerance, and neurodegeneration. *Translational Stroke Research* **5**, 38-58.
- Shao LR, Halvorsrud R, Borg-Graham L, & Storm JF (1999). The role of BK-type Ca²⁺-dependent K⁺ channels in spike broadening during repetitive firing in rat hippocampal pyramidal cells. *The Journal of Physiology* **521**, 135-146.
- Singer-Lahat D, Sheinin A, Chikvashvili D, Tsuk S, Greitzer D, Friedrich R, Feinshreiber L, Ashery U, Benveniste M, Levitan ES, & Lotan I (2007). K⁺ channel facilitation of exocytosis by dynamic interaction with syntaxin. *The Journal of Neuroscience* **27**, 1651-1658.

- Soh H, Pant R, LoTurco JJ, & Tzingounis AV (2014). Conditional deletions of epilepsy-associated KCNQ2 and KCNQ3 channels from cerebral cortex cause differential effects on neuronal excitability. *The Journal of Neuroscience* **34**, 5311-5321.
- Stackman RW, Hammond RS, Linardatos E, Gerlach A, Maylie J, Adelman JP, & Tzounopoulos T (2002). Small conductance Ca²⁺-activated K⁺ channels modulate synaptic plasticity and memory encoding. *The Journal of Neuroscience* **22**, 10163-10171.
- Steinert J, Robinson S, Tong H, Hausteiner M, Kopp-Scheinflug C, & Forsythe I (2011). Nitric oxide is an activity-dependent regulator of target neuron intrinsic excitability. *Neuron* **71**, 291-305.
- Steriade M, McCormick DA, & Sejnowski TJ (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science* **262**, 679-685.
- Stocker M & Pedarzani P (2000). Differential distribution of three Ca²⁺-activated K⁺ channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Molecular and Cellular Neuroscience* **15**, 476-493.
- Storm JF (1987). Action potential repolarization and a fast after-hyperpolarization in rat hippocampal pyramidal cells. *The Journal of Physiology* **385**, 733-759.
- Storm JF (1989). An after-hyperpolarization of medium duration in rat hippocampal pyramidal cells. *The Journal of Physiology* **409**, 171-190.
- Storm JF (1990). Chapter 12 Potassium currents in hippocampal pyramidal cells. *Progress in Brain Research* **83**, 161-187. Elsevier.
- Strange BA, Witter MP, Lein ES, & Moser EI (2014). Functional organization of the hippocampal longitudinal axis. *Nature Reviews Neuroscience* **15**, 655-669.
- Suh BC & Hille B (2002). Recovery from muscarinic modulation of M current channels requires phosphatidylinositol 4,5-bisphosphate synthesis. *Neuron* **35**, 507-520.
- Sun J & Kapur J (2012). M-type potassium channels modulate Schaffer-collateral CA1 glutamatergic synaptic transmission. *The Journal of Physiology*.
- Tanner GR, Lutas A, Martínez-François JR, & Yellen G (2011). Single K(ATP) channel opening in response to action potential firing in mouse dentate granule neurons. *The Journal of Neuroscience* **31**, 8689-8696.

Thomas MJ, Watabe AM, Moody TD, Makhinson M, & O'Dell TJ (1998). Postsynaptic complex spike bursting enables the induction of LTP by theta frequency synaptic stimulation. *The Journal of Neuroscience* **18**, 7118-7126.

Thompson CL, Pathak SD, Jeromin A, Ng LL, MacPherson CR, Mortrud MT, Cusick A, Riley ZL, Sunkin SM, Bernard A, Puchalski RB, Gage FH, Jones AR, Bajic VB, Hawrylycz MJ, & Lein ES (2008). Genomic anatomy of the hippocampus. *Neuron* **60**, 1010-1021.

Tong H, Kopp-Scheinflug C, Pilati N, Robinson SW, Sinclair JL, Steinert JR, Barnes-Davies M, Allfree R, Grubb BD, Young SM, & Forsythe ID (2013). Protection from noise-induced hearing loss by Kv2.2 potassium currents in the central medial olivocochlear system. *The Journal of Neuroscience* **33**, 9113-9121.

Toyoda I, Bower MR, Leyva F, & Buckmaster PS (2013). Early activation of ventral hippocampus and subiculum during spontaneous seizures in a rat model of temporal lobe epilepsy. *The Journal of Neuroscience* **33**, 11100-11115.

Trimmer JS (1991). Immunological identification and characterization of a delayed rectifier K⁺ channel polypeptide in rat brain. *Proceedings of the National Academy of Sciences U S A* **88**, 10764-10768.

Turner R, Kruskic M, Teves M, Scheidl-Yee T, Hameed S, & Zamponi G (2015). Neuronal expression of the intermediate conductance calcium-activated potassium channel KCa3.1 in the mammalian central nervous system. *Pflügers Archiv: European Journal of Physiology* **467**, 311-328.

Tzingounis AV, Heidenreich M, Kharkovets T, Spitzmaul G, Jensen HS, Nicoll RA, & Jentsch TJ (2010). The KCNQ5 potassium channel mediates a component of the afterhyperpolarization current in mouse hippocampus. *Proceedings of the National Academy of Sciences U S A* **107**, 10232-10237.

Tzingounis AV & Nicoll RA (2008). Contribution of KCNQ2 and KCNQ3 to the medium and slow afterhyperpolarization currents. *Proceedings of the National Academy of Sciences U S A* **105**, 19974-19979.

Vergara C, Latorre R, Marrion NV, & Adelman JP (1998). Calcium-activated potassium channels. *Current Opinion in Neurobiology* **8**, 321-329.

Vervaeke K, Hu H, Graham LJ, & Storm JF (2006). Contrasting effects of the persistent Na⁺ current on neuronal excitability and spike timing. *Neuron* **49**, 257-270.

Vetter DE, Mann JR, Wangemann P, Liu J, McLaughlin KJ, Lesage F, Marcus DC, Lazdunski M, Heinemann SF, & Barhanin J (1996). Inner ear defects induced by null mutation of the *isk* gene. *Neuron* **17**, 1251-1264.

Vogalis F, Storm JF, & Lancaster B (2003). SK channels and the varieties of slow after-hyperpolarizations in neurons. *The European Journal of Neuroscience* **18**, 3155-3166.

Wang HS, Pan Z, Shi W, Brown BS, Wymore RS, Cohen IS, Dixon JE, & McKinnon D (1998). KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. *Science* **282**, 1890-1893.

Wu M & Brudzynski SM (1995). Mesolimbic dopamine terminals and locomotor activity induced from the subiculum. *NeuroReport* **6**.

Wulff H, Kolski-Andreaco A, Sankaranarayanan A, Sabatier J-M, & Shakkottai V (2007). Modulators of small- and intermediate-conductance calcium-activated potassium channels and their therapeutic indications. *Current Medicinal Chemistry* **14**, 1437-1457.

Wulff H, Miller MJ, Hansel W, Grissmer S, Cahalan MD, & Chandy KG (2000). Design of a potent and selective inhibitor of the intermediate-conductance Ca(2+)-activated K(+) channel, IKCa1: A potential immunosuppressant. *Proceedings of the National Academy of Sciences U S A* **97**, 8151-8156.

Xu T, Nie L, Zhang Y, Mo J, Feng W, Wei D, Petrov E, Calisto LE, Kachar B, Beisel KW, Vazquez AE, & Yamoah EN (2007). Roles of alternative splicing in the functional properties of inner ear-specific KCNQ4 channels. *Journal of Biological Chemistry* **282**, 23899-23909.

Yoshida M & Alonso A (2007). Cell-type-specific modulation of intrinsic firing properties and subthreshold membrane oscillations by the M(Kv7)-current in neurons of the entorhinal cortex. *Journal of Neurophysiology* **98**, 2779-2794.

Yue C & Yaari Y (2004). KCNQ/M channels control spike afterdepolarization and burst generation in hippocampal neurons. *The Journal of Neuroscience* **24**, 4614-4624.

Zhang H, Craciun LC, Mirshahi T, Rohács T, Lopes CMB, Jin T, & Logothetis DE (2003). PIP2 activates KCNQ channels, and its hydrolysis underlies receptor-mediated inhibition of M currents. *Neuron* **37**, 963-975.

Zhang WN, Bast T, & Feldon J (2002). Effects of hippocampal *N*-methyl-D-aspartate infusion on locomotor activity and prepulse inhibition: Differences between the dorsal and ventral hippocampus. *Behavioral Neuroscience* **116**, 72-84.