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Hyperpolarization-activated cation current I_h of dentate gyrus granule cells is upregulated in human and rat temporal lobe epilepsy

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Abstract

The hyperpolarization-activated cation current I_h is an important regulator of neuronal excitability and may contribute to the properties of the dentate gyrus granule (DGG) cells, which constitute the input site of the canonical hippocampal circuit. Here, we investigated changes in I_h in DGG cells in human temporal lobe epilepsy (TLE) and the rat pilocarpine model of TLE using the patch-clamp technique. Messenger-RNA (mRNA) expression of I_h-conducting HCN1, 2 and 4 isoforms was determined using semi-quantitative *in-situ* hybridization. I_h density was ~1.8-fold greater in DGG cells of TLE patients with Ammon's horn sclerosis (AHS) as compared to patients without AHS. The magnitude of somatodendritic I_h was enhanced also in DGG cells in epileptic rats, most robustly during the latent phase after status epilepticus and prior to the occurrence of spontaneous epileptic seizures. During the chronic phase, I_h was increased ~1.7-fold. This increase of I_h was paralleled by an increase in HCN1 and HCN4 mRNA expression, whereas HCN2 expression was unchanged. Our data demonstrate an epilepsy-associated upregulation of I_h likely due to increased HCN1 and HCN4 expression, which indicate plasticity of I_h during epileptogenesis and which may contribute to a compensatory decrease in neuronal excitability of DGG cells.

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Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2012.02.133.

Keywords

Hippocampus; Rat pilocarpine model; Patch-clamp; h-Current; Human; Temporal lobe epilepsy

1. Introduction

The hyperpolarization-activated current I_h is a slowly activating, non-inactivating depolarizing cationic current which is activated by hyperpolarization beyond −50 to −70 mV. These unique biophysical properties provide the basis for the diverse roles ascribed to this current, i.e. control of resting membrane potential, passive membrane properties, pacemaker activity, rebound burst firing in heart and brain, reduction of dendritic summation and the presence of certain types of resonance behavior in neurons [1-8].

The specific function of h-channels in each neuronal population depends strongly on the voltage- and time-dependent properties of I_h. An important molecular mechanism for generating functionally diverse I_h is the differential expression of the four underlying HCN1-4 subunits. Homomeric channels formed by these HCN subunits display very different kinetics, steady-state voltage dependence and sensitivity to modulation by cAMP in heterologous expression systems [2]. Thus, regulation of the relative abundance of HCN subunit protein is likely to represent a key mechanism for plasticity of I_h. Importantly, the functional properties of I_h and the expression of the corresponding subunits are differentially modulated during postnatal development as well as in both acquired and genetic forms of epilepsy in a region- and time-dependent manner in different *in vitro* and *in vivo* models [6,9-18]. An emerging "leitmotiv", at least in CA1 hippocampal or neocortical neurons, seems to be the downregulation of the HCN1-subunit along with a decrease in somatodendritic I_h, followed, via an enhanced input resistance, by neuronal hyperexcitability in the chronic state.

Thus, a significant body of work has implicated alteration of HCN channels expression and altered magnitude and properties of I_h in epilepsy [reviewed in 8,19]. In temporal lobe epilepsy (TLE), the large majority of existing studies has focused on animal models and on the hippocampal pyramidal cell layer [20]. Remarkably, an early study suggested that changes in HCN expression might arise also in the dentate gyrus [21]. Therefore, here, we focus on the DGG cells, and examine somatodendritic I_h currents and the HCN expression levels in DGG cells of people with TLE and underlying Ammon's horn sclerosis (AHS) and in the rat pilocarpine-model of TLE.

2. Material and methods

2.1. Pre- and postsurgical assessment of epilepsy patients

All patients had conventional scalp EEG recordings or intracranial recordings and brain MRI prior to neurosurgery. The histological grading of human hippocampus was performed according to Wyler and colleagues [22]. Investigation of human cerebral tissue was approved by the local ethics committee and written informed consent was obtained from each patient.

2.2. Pilocarpine-induced status epilepticus (SE)

Procedures on animals were performed in accordance with local guidelines and experiments were approved by the local animal care and use committee. Pilocarpine treatment of rats was carried out and animals were monitored as described in Supplementary material.

2.3. Semi-quantitative in situ hybridization (ISH) in rat hippocampus

ISH was carried out as described previously [10,21,23,24] on specimens obtained 30-60 days after SE. For details see Supplementary material.

2.4. Electrophysiology

Electrophysiological recordings of DGG cells were performed in both human and rat hippocampal slices using conventional patch clamp technique and established experimental procedures. See Supplementary material for details.

2.5. Data analysis

I_h amplitudes in response to voltage steps were determined as the difference of the end of the instantaneous current component and the current amplitude in the steady-state. The reversal potential V_{rev}, was determined by analysis of tail currents and subsequent linear regression analysis (see Fig. 1C and Supplementary material). The conductance-voltage curves were fitted with a Boltzmann function of the form.

$$f(V) = 1 / \left(1 + e^{-(V-V_{50})/\text{slope}} \right) \tag{1}$$

with V_{50} being the voltage of half-maximal activation.

The activation time course of I_h was fit with exponential functions of the form.

$$f(t) = \sum A_i^* e^{-t/\tau i} + c. i = 1 \quad \text{or} \quad 2. \tag{2}$$

Unpaired student's t-test was used for statistical analyses. P values <0.05 were considered as significant. All data are given as means $\pm$ SEM.

3. Results

3.1. I_h recordings in human TLE

Properties of I_h recorded in DGG cells from seven TLE patients with AHS (AHS-group) were compared to those from three patients without AHS (non-AHS). The clinical data of the patients are summarized in Supplementary Table 1. The intrinsic membrane properties of DGG cells were not significantly different between both groups (Supplementary Table 2). Gross morphology was not different between groups, as described previously [25]. However, upon a hyperpolarizing voltage step from −50 to −90 mV for 5 s, we observed slowly developing inward current which was more pronounced in the AHS-group (Fig. 1A1 and B1). These currents were blocked by the I_h-channel blocker ZD7288 (40 μM, $n = 8$) in neurons from both tissues (Fig. 1A2 and B2) and had similar reversal potentials (AHS: −38.1 mV, $n = 7$; non-AHS group: −39.4 mV, $n = 6$; Fig. 1C), consistent with reported reversal potentials of I_h [5,13]. Application of 2 mM Cs$^+$ in two recordings also blocked this current component (data not shown). Taken together, these findings indicate that the recorded time-dependent inward currents were a result of activation of I_h channels.

The mean I_h amplitudes measured with hyperpolarizing voltage steps from −50 to −90 mV ($p = 0.0056$, $n = 8$ non-AHS; $n = 7$ AHS; Fig. 1D) and I_h current densities normalized to the cell capacitance were significantly higher in the AHS-group ($p = 0.0077$, $n = 8$ nonAHS; $n = 7$ AHS; Fig. 1D). The voltage-dependence of activation was significantly shifted to more depolarized potentials in the AHS-group (non-AHS group: $V_{50} = -85.9 \pm 2.3$ mV; AHS-group: $V_{50} = -78.2 \pm 2.7$ mV; $p = 0.0001$, Fig. 2A and D). The kinetics of I_h activation

contained a fast and a slow component, and was examined by fitting with a bi-exponential function. The time constants of activation did not differ between groups (Fig. 2B). Likewise, the relative contribution of the fast current component to the total current amplitude varied between 66% and 73% in a voltage range between −90 and −120 mV in both groups and was not significantly different (Fig. 2C).

3.2. I_h recordings in rat pilocarpine model of TLE

Similar to the human, a slowly activating, non-inactivating inward conductance was seen upon voltage steps to −103 mV which was completely blocked by ZD7288 (60 μM) both in control ($n = 22$) and epileptic rats ($n = 22$, Fig. 3A, upper traces). Subtraction of the two traces allowed isolating I_h (Fig. 3A, lower trace).

We examined the magnitude of I_h in control and pilocarpine treated rats at two different time points: 7–9 days following SE (latent phase, no spontaneous generalized seizures) and in the chronic epileptic phase 35–63 days following SE (all spontaneous generalized seizures). I_h density was enhanced in both groups, but most pronouncedly in the latent period (Fig. 3B, $p < 0.0001$ and $p = 0.0041$ for the latent and chronic group, respectively). This increase could not be explained by a change in driving force, as the reversal potential of I_h did not differ between groups (controls: −35.9 ± 2.3 mV, $n = 8$; pilocarpine-treated rats: −36.8 ± 2.3 mV, $n = 8$). The time course of activation was best fit with a mono-exponential equation with no significant differences between controls and pilocarpine-treated animals neither at early nor at late stages following SE (Fig. 3C).

To understand the neurobiological basis of the persistent increase in I_h in DGG cells of epileptic rats, we investigated the expression of the genes coding for the h-channels. We compared mRNA expression of HCN1, 2 and 4 channel isoforms in chronically epileptic, pilocarpine-treated rats versus the control group. Whereas HCN2 expression was not different in both groups (not shown), expression of HCN1 mRNA was significantly increased by 22% in the pilocarpine-treated (67.9 ± 4.0 nCi/gm) compared to control rats (55.4 ± 3.2 nCi/gm; $p < 0.05$, Fig. 4A). This effect was more pronounced for the HCN4 channel isoform. HCN4 mRNA level was enhanced by 52% in the granule cell layer of epileptic (70.75 ± 6.4 nCi/gm) relative to controls rats (46.75 ± 1.0 nCi/gm; $p < 0.05$; Fig. 4B).

4. Discussion

The principal findings of the current studies are that (1) I_h density is greater in granule cell of the dentate gyrus in TLE patients with AHS as compared to those without AHS. (2) Similar findings are observed in the rat pilocarpine-model of TLE, where I_h changes precede the onset of chronic epilepsy. (3) Voltage-dependence but not kinetics of I_h is altered in the epileptic state, which might result from augmented contribution of HCN1 and HCN4 to the total HCN channels pool that conducts I_h.

4.1. Molecular mechanism of I_h upregulation

The observed upregulation of I_h in both human and rat DGG cells is most likely due to an enhanced expression of HCN1 and, at least in rat hippocampus, HCN4 subunit, as shown in Fig. 4 and as found previously [21]. This is in line with the observed shift of voltage-dependence of I_h to more depolarized potentials in tissue from people with TLE due to AHS. In general, h-channels composed of HCN1 subunits display faster I_h activation than those composed of HCN2 and HCN4 subunits [13,26]. Strikingly, current kinetics was not faster in the AHS-group or in epileptic rats as compared to controls. This might be a result of the concomitant increase of HCN4 subunits. Furthermore, the properties of I_h in native

hippocampus only partially overlap those of currents recorded in heterologous systems: in human and rat hippocampus, in addition to the intrinsic biophysical properties of each HCN isoform, a number of interacting molecules influence channel properties [18,27, reviewed in 28].

What are the molecular mechanisms and pathways involved in the upregulation of I_h and HCN channels in DGG cells? Although this question has not been directly addressed in the present work, a number of recent studies provide insights into regulation of HCN expression in association with seizures and epilepsy. In the kainic acid-induced SE model of TLE, *downregulation* of HCN1 expression in CA1 pyramidal region was caused by an upregulation of a repressing transcription factor, neuron-restrictive silencer factor (NRSF) which suppresses transcription of a number of genes, amongst them the *HCN1* gene [20]. In addition, a reduction of HCN1 expression has been shown to involve transient Ca^{2+}-permeable AMPA receptor activation with subsequent activation of Ca^{2+}/calmodulin-dependent protein kinase II during *in-vitro* experiments in hippocampal slices [29]. Little is known, however, about mechanisms of *upregulation* of HCN expression. Reduction of NRSF levels might take place, or the enhanced expression might result from a myriad of cellular mechanisms that influence ion channel expression [30].

4.2. Significance for the pathophysiology of TLE and potential clinical implications

In previous studies, I_h expression appears to be differentially modulated in acquired and genetically caused epilepsies in a region- and time-dependent manner. For instance, in rat models of genetically caused absence epilepsies, impaired I_h with a concomitant decrease of HCN1 expression was found in cortical neurons [12], whereas thalamocortical neurons showed an decrease in cAMP responsiveness, explained by an increase of HCN1 expression [31,32]. Both phenomena favor onset of absence seizures. In models of acquired TLE, I_h currents and expression of underlying HCN1 and HCN2 subunits were temporarily reduced in dendrites of the entorhinal cortex following kainate-induced SE [11]. A further study found sustained reduction in HCN1 and 2 expression following kainate-induced SE in the CA1 region [16]. Likewise, in the rat pilocarpine model of TLE, dendritic I_h of CA1 pyramidal cells was progressively reduced during epileptogenesis, because of permanent reduction of HCN1-subunit expression and a persistent alteration of I_h-modulating phosphorylation pathways [6,15,18]. The significance of HCN1 downregulation is further strengthened by the observation that a primary loss of the HCN1 subunit facilitates onset of seizures and of epilepsy [33,34]. In a model of seizure-inducing hypoxia, somatic I_h in rat CA1 pyramidal was decreased [14], and a complex region-specific regulation of HCN1 and 2 in an *in vitro* model of epilepsy has been described, with commensurate alteration of burst activity [17].

Taken together, downregulation of I_h seems to be a leitmotiv in the early phases of epileptogenesis and epilepsy. However, relatively few studies in animal models have explored potentially compensatory alterations in HCN isoform expression and I_h in the chronic and even 'end stage' of TLE. Even fewer yet are studies in human tissue. In human neocortical neurons of patients with TLE, Wierschke and co-workers reported on reduced I_h density in patients with higher seizure frequencies; these observations support the notion that I_h contributes importantly to the regulation of neuronal excitability [35].

Focusing on the dentate gyrus, a major gateway into the hippocampal formation, we report here a robust, epilepsy-associated upregulation of I_h in DGG of human and rat hippocampus. Our findings are in line with a recent study reporting enhanced I_h in DGG of people with TLE with severe AHS as compared to those with mild or moderate AHS [36]. Whereas the mechanisms leading to this increase of HCN1 expression and I_h density are not fully understood, the teleological purpose is intriguing: augmented I_h in the epileptic dentate

gyrus might serve as an attempt to compensate for abnormal hyperexcitability in the circuit for example, by dampening dendritic summation [1]. Alternatively, in response to augmented inhibition (hyperpolarizing), the increase in I_h might promote rebound depolarization and contribute to hyperexcitability of epileptic tissue [5,9]. Whereas other ion channels are also altered in epileptic DGG cells [37,38], the changes in I_h reported here should contribute to neuronal firing behavior, and might provide a drug target to both existing and future medications (see below).

4.3. Temporal profile of I_h upregulation

In human tissue, it is not possible to time the onset of HCN expression and I_h changes, because tissue is only available from chronic epileptic tissue. Therefore, the current studies employed also tissue from animal models. In the rat pilocarpine model employed here, an I_h upregulation was already present in the latent stage preceding the onset of spontaneous seizures, and may thus contribute to their onset. This increased I_h was associated with, and hence is likely a result of, an upregulation of both HCN1 and HCN4 mRNA in neurons of the dentate gyrus. Given the importance of I_h in attenuating postsynaptic potentials at dendrites and limiting their spread in pyramidal neurons of CA1 region and layer five of the somatosensory cortex [39,40], our data suggest that upregulation of I_h might be a protective mechanism resulting in maintained dentate gyrus gating. Dendrites of DGG neurons in rats without epilepsy have no or little I_h [41]. In view of the considerable increase of I_h, it is tempting to speculate that somatodendritic I_h in DGG neurons plays a role in signal integration only under pathophysiological circumstances such as epileptogenesis and chronic epilepsy, but not under physiological conditions.

4.4. Implications for epilepsy therapy

I_h is a target for the anticonvulsants acetazolamide, gabapentin and lamotrigine, all of which increase I_h [42–44]. It is therefore also possible that the observed upregulation of I_h renders its modulation by these antiepileptic drugs more effective, thereby dampening excitability. Such a mechanism operating in DGG cells may be particularly relevant in chronic epilepsy, when granule cells are one of the major preserved cell populations after the profound loss of neurons in the CA1, CA3 and CA4 subfields. Therefore, defining and understanding the changes in I_h and in its 'building blocks', the HCN channels, both in humans and animal models is important. The knowledge is a prerequisite for using this important channel as target for epilepsy therapy and prevention in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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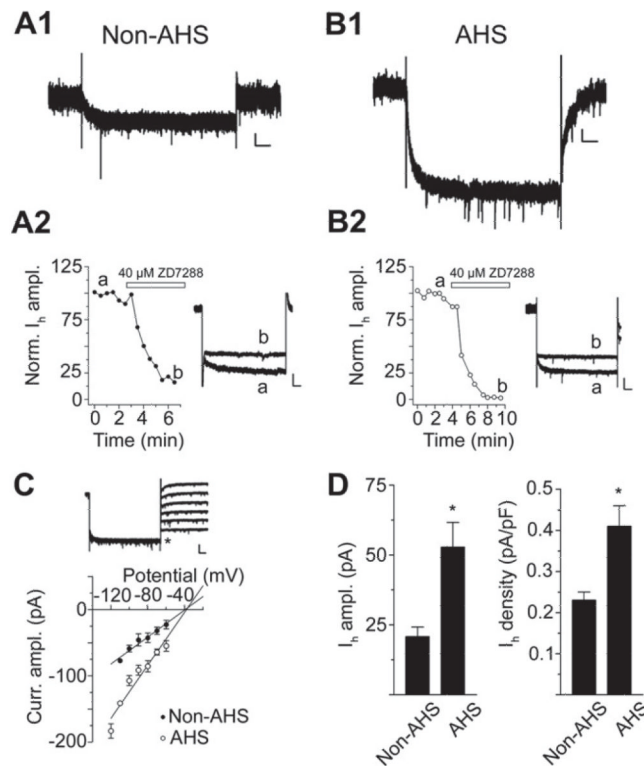
Fig. 1.
I_h density is greater in DGG neurons of people with TLE due to AHS. I_h is elicited by voltage steps from −50 to −90 mV in both DGG neurons from the non-AHS (A1) and AHS-group (B1). Scaling 10 pA/0.5 s. The inward current is blocked by ZD7288 in both groups (A2, B2). Scaling 50 pA/0.1 s. (C) Reversal potential was around −39 mV in both conditions (upper panel, tail currents indicated with an asterisk, Scaling 100 pA/0.5 s; bottom panel; filled symbols: non-AHS group; open symbols: AHS-group). (D) I_h amplitudes (left panel) and current densities at −90 mV (right panel) were significantly greater in people with AHS.
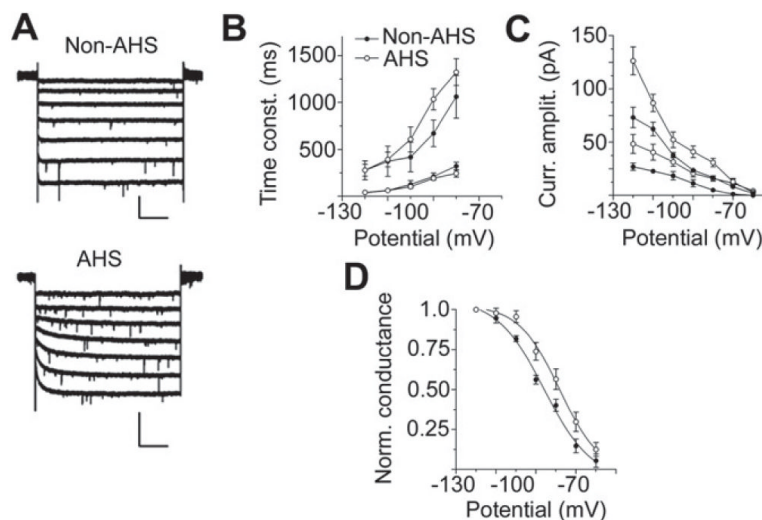
Fig. 2.
Activation properties of I_h in human DGG neurons. (A) A family of current traces was elicited by stepping the voltage from −50 mV to more hyperpolarized potentials in 10 mV-steps (from −60 to −120 mV) in the non-AHS (upper panel) and AHS-group (lower panel). Scaling 100 pA/1 s. (B) Fast and slow time constants were not different in both conditions at different command potentials (filled symbols: non-AHS group; open symbols: AHS-group). (C) The amplitudes from the fast (the upper data points under each condition) and the slow time component (the lower data points under each condition) were derived from the bi-exponential fitting paradigms. There was no significant difference in the relative contributions of the fast and slow current component between both conditions. Symbols as in (B). (D) The voltage-dependence of activation was significantly shifted to more depolarized potentials in the AHS-group. Symbols as in (B).
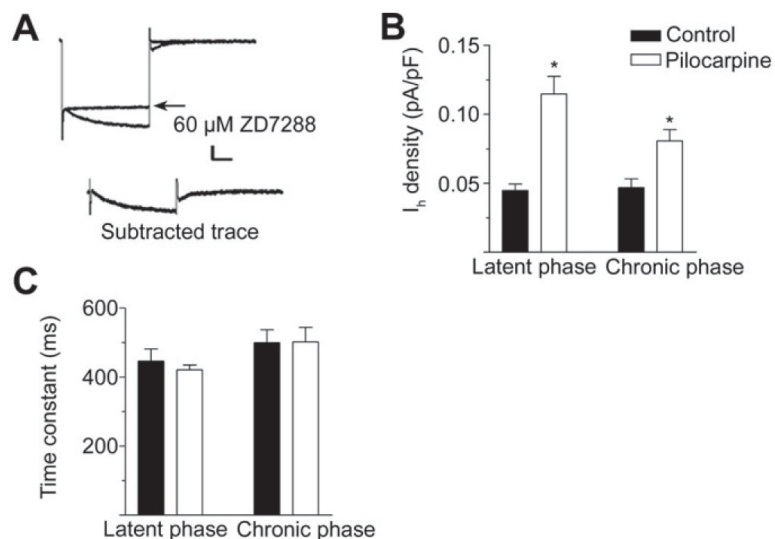
Fig. 3.
I_h density is upregulated in DGG cells of rat hippocampal slices in the latent and chronic phase following pilocarpine-injection. (A) Inward currents elicited upon a voltage step from −63 to −103 mV in the absence and presence of ZD7288 (upper panel, indicated by an arrow). Lower trace obtained after subtraction of traces in the absence and presence of ZD7288. Recordings from a control animal. Scaling 10 pA/0.5 s. (B) I_h current densities during the latent and chronic phase (sham-control animals: black bars, SE-experienced animals: white bars). (C) Time constants at a potential of −103 mV were not different in controls and pilocarpine rats during latent ($p = 0.49$, $n = 9$ and 10 cells) and chronic phase ($p = 0.96$, $n = 13$ and 12 cells). Symbols as in (B).
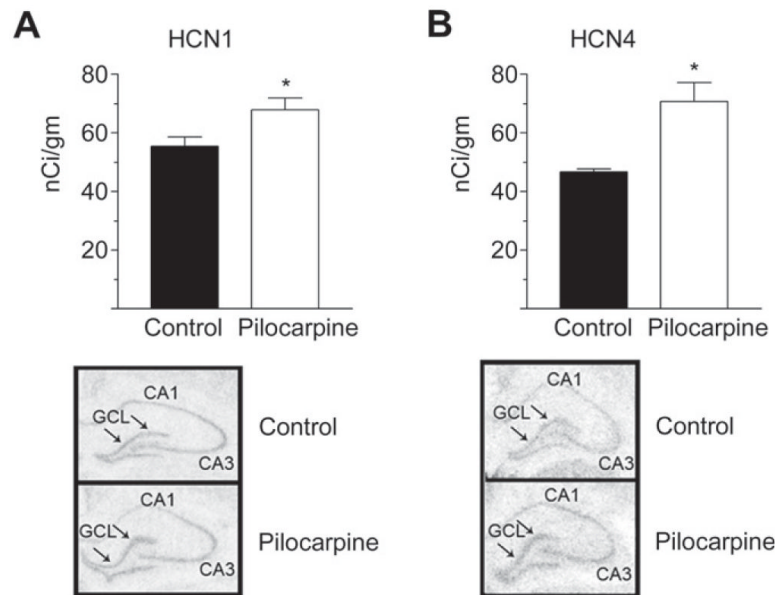
Fig. 4.
Expression of both HCN1 and HCN 4 subunits is increased in epileptic animals following pilocarpine-induced SE. As depicted in the photomicrographs (A and B lower panels), HCN1 and HCN4 subunit mRNA signals were significantly increased in the granule cell layer (GCL) of the pilocarpine-group (A and B upper panels), with relatively little change in expression over the pyramidal cell layer of CA3. Brains from 4-9 animals were used per group. Asterisk indicates $p < 0.05$.