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HCN channels in developing neuronal networks

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Abstract

Developing neuronal networks evolve continuously, requiring that neurons modulate both their intrinsic properties and their responses to incoming synaptic signals. Emerging evidence supports roles for the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in this neuronal plasticity. HCN channels seem particularly suited for fine-tuning neuronal properties and responses because of their remarkably large and variable repertoire of functions, enabling integration of a wide range of cellular signals. Here, we discuss the involvement of HCN channels in cortical and hippocampal network maturation, and consider potential roles of developmental HCN channel dysregulation in brain disorders such as epilepsy.

1. Molecular and functional characteristics of HCN channels

1.1. I_h and its functions in neurons and neuronal networks

The hyperpolarization-activated current, I_h, originally observed in motoneurons (Araki et al., 1961) and later characterized in heart (Noma and Irisawa, 1976) and retinal photoreceptors (Fain et al., 1978), has long puzzled scientists, because of its unorthodox physiological behavior which led to its nicknaming as f- (funny) or q- (queer) current (Brown and DiFrancesco, 1980; Halliwell and Adams, 1982; Pape, 1996).

I_h is a slow, non-inactivating conductance that is activated by hyperpolarization to potentials negative to- or close to typical neuronal resting membrane potential (Figure 1). This permits Na^+ and K^+ entry, providing the basis of the fundamental biophysical function of this conductance. First, tonic activation of I_h helps set the resting membrane potential at a somewhat depolarized level (Maccaferri et al., 1993;Lupica et al., 2001;Nolan et al., 2003;Meuth et al., 2006). Second, I_h reduces input resistance, so that the influence of any current on membrane potential is reduced (as per $V = I \times R$; Magee, 1998,1999;Nolan et al., 2004;Surges et al., 2004). Together with the selective subcellular localization of I_h-conducting HCN channels, these basic properties lead to opposing effects of I_h on neuronal excitability, that are governed also by type of HCN channel isoform, and the type of input reaching the cell (Santoro and Baram, 2003;Dyhrfjeld-Johnsen et al., 2008). Thus, elegant studies (Magee, 1998, 1999;Williams and Stuart, 2000,2003;Berger et al., 2001,2003;Poolos et al., 2002,2006;Wang et al., 2003;Fan et al., 2005;van Welie et al., 2006;Brager and Johnston, 2007) have

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demonstrated that dendritic I_h reduces neuronal excitability by reducing membrane resistance and dendritic summation in response to dendritic depolarizing input. In contrast, increased neuronal excitability with increase of I_h has been reported, because this current depolarizes resting membrane potential (Chen K. et al., 2001), driving the neuron closer to firing threshold of action potentials (Chen K. et al., 2001;Dyhrfjeld- Johnsen et al., 2008). Therefore, an emerging consensus view suggests that I_h is crucial for intrinsic neuronal excitability (Zhang and Linden, 2003,Beck and Yaari, 2008). In addition, the final influence of I_h on neuronal excitability is governed by a balance of opposing actions on resting membrane potential and resistance properties. In a non-firing cell, these actions of the h-current exert a stabilizing effect on the membrane potential (Maccaferri et al., 1993;Lupica et al., 2001;Nolan et al., 2003;Meuth et al., 2006;Figure 1C). They also influence rhythmicity of firing (Pape, 1996;Lüthi and McCormick, 1998;Fisahn et al., 2002;Cobb et al., 2003;Figure 1B) and resonance behavior (Magee, 1999;Ulrich, 2002;Nolan et al., 2004;Bernard et al. 2007;Narayanan and Johnston, 2007).

1.2. The molecular basis of I_h: a key to the diverse functions of this conductance

The characterization of four genes that encode I_h -generating channel molecules has shed light on the unique properties of this current (Santoro et al., 1997, Gauss et al., 1998; Ludwig et al., 1998, Santoro et al., 1998; Ishii et al., 1999). These molecular studies revealed that I_h is generated by a nonselective cation channel named HCN (*H*yperpolarization-activated *C*yclic *N*ucleotide-gated channel; Clapham, 1999). The four known isoforms (HCN1-4) can assemble into homo- or heteromeric channels with different activation kinetics, voltage dependence and cAMP-sensitivity (Kaupp and Seifert, 2001; Much et al., 2003; Robinson and Siegelbaum, 2003, Santoro and Baram, 2003; Brewster et al., 2005; Figure 1A), thus generating a broad repertoire of sensitivity to the neuronal environment, as well as a large spectrum of biophysical channel properties.

In mammalian brain, the expression patterns of HCN channel isoforms are distinct but partially overlapping (Moosmang et al., 1999; Monteggia et al., 2000; Santoro et al., 2000; Bender et al., 2001; Notomi and Shigemoto, 2004). Thus, individual neurons can express more than one HCN channel isoform (Franz et al., 2000; Santoro et al., 2000; Brewster et al., 2002; Brewster et al., 2007a), and the I_h current of such neurons reflects the properties of the contributing isoforms (Franz et al., 2000; Santoro et al., 2000; Vasilyev and Barish, 2002; Santoro and Baram, 2003; Surges et al., 2006). These properties may reflect the mathematical sum of primarily homomeric channels, may result from the formation of heteromeric channels deriving from interaction among the different isoforms expressed in an individual neuron, or result from the combination of both homomeric and heteromeric channels in the neuron (Santoro et al., 2000; Ulens and Tytgat, 2001; Chen S. et al., 2001; Simeone et al., 2005a; Simeone et al., 2005b; Dekker and Yellen, 2006; Kole et al., 2006; Budde et al., 2008). In heterologous systems, promiscuous heteromerization of almost all HCN channel isoforms has been described (Chen S. et al., 2001; Proenza et al., 2002; Altomare et al., 2003; Much et al., 2003, Whitaker et al., 2007), and evidence is increasing that heteromeric channels, with properties differing from the properties of pure homomeric channels (Chen. S et al., 2001; Ulens and Tytgat, 2001), also play a role in brain *in vivo* (Brewster et al., 2005; Kuisle et al., 2006; Budde et al., 2008). However, in rodent hippocampus, heteromerization seems to be restricted, and is governed by network activity (Much et al., 2003; Brewster et al., 2005; Brewster et al., 2007b; Zha et al., 2008).

Interestingly, for channels that function primarily at subthreshold membrane potential levels, HCN channels are endowed with remarkable plasticity of function. This plasticity involves short-term regulation of channel activity through cellular metabolites (DiFrancesco and Tortora, 1991; Wang et al., 2002; van Welie et al., 2004; Simeone et al., 2005b; Pian et al.,

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2006; Zolles et al., 2006; Fogle et al., 2007; Pian et al., 2007) or phosphorylation (Zong et al., 2005; Poolos et al., 2006) as well as longer-lasting modulation via regulation of expression (Bräuer et al., 2001; Brewster et al., 2002, 2005), heteromerization (Proenza et al., 2002; Altomare et al., 2003; Much et al., 2003; Brewster et al., 2005; Whitaker et al., 2007; Zha et al., 2008) or subcellular transport of channel isoforms (Bender et al., 2007; Brewster et al., 2007a; Shin and Chetkovich, 2007). A potential association of HCN channel isoforms with β-subunits or scaffolding proteins may add further variety to the channels' functions (Gravante et al., 2004; Kimura et al., 2004; Qu et al., 2004; Santoro et al, 2004). Thus, rather than functioning solely as 'membrane stabilizers', HCN channels are in an excellent position to fine-tune a neuron's responses to external stimuli by integrating a wide range of cellular signals. In fact, essential brain functions such as theta resonance underlying learning and memory (Nolan et al., 2004, Wang et al., 2007), thalamic rhythm generation (Ludwig et al., 2003; Budde et al., 2005, Kuisle et al., 2006) or the subcortical control of motor behavior (Nolan et al., 2003; Chan et al., 2004) may depend on this property of the HCN channels.

Recent work suggests that the properties of the HCN channels highlighted above are particularly important during neuron and network development. Maturation requires developing neurons to modulate both their intrinsic properties as well as their firing behaviors to a constantly changing neuronal milieu. Ion channels such as the HCN channels, that are endowed with high plasticity of function may be particularly suited for this process (Zhang and Linden, 2003; Beck and Yaari, 2008). Consistent with this notion, an age-dependence of the properties of I_h, suggesting age-specific roles of this current, has been described in several brain regions (Bayliss et al., 1994; Vasilyev and Barish, 2002, 2004; Tanaka et al., 2003; Bajorat et al., 2005; Surges et al., 2006).

Thus, a significant body of work has focused on this current and its building blocks, the HCN channels, over the past few years, contributing to an increasing understanding of the role of HCN channels in normal and pathological neuronal and network activities (Robinson and Siegelbaum, 2003; Santoro and Baram, 2003; Frere et al., 2004; Herrmann et al., 2007; Dyhrfjeld-Johnsen et al., 2008; Richichi et al., 2008). This information, and specifically the new perspectives on the role of I_h in developing hippocampal and cortical networks, is the focus of the following paragraphs.

2. Developmental aspects of HCN channels

2.1. The transition from immature to mature network activity involves changes in HCN isoform expression levels

In hippocampus, patterns of network activity depend, at least in part, on the expression levels and specific combinations of HCN isoforms that are present in certain neuronal populations at a given developmental period. For instance, in hippocampal area CA3, I_h may contribute critically to age-specific hippocampal network activity. The principal network activity in neonatal CA3 is low-frequency (0.1–0.3 Hz), synchronized population discharges (intracellularly seen as "giant depolarizing potentials", GDPs) that are believed to contribute to network differentiation (Ben-Ari, 2002). Importantly, CA3 pyramidal cells govern the generation of GDPs, which are driven by spontaneous burst activity originating from these cells (Sipilä et al., 2005). The capacity of these neurons to generate these spontaneous bursts is reduced when HCN channels are blocked, resulting in disruption of GDP generation (Bender et al., 2005). This indicates that HCN channel activity may be crucial for network synchronization in neonatal CA3 (Bender et al., 2005; but see Sipilä et al., 2006). At the molecular level, HCN isoforms 1, 2 and 4 (and low levels of HCN3) are expressed in area CA3, in both principal cells and interneurons (Moosmang et al, 1999; Santoro et al., 2000; Bender et al., 2001; Notomi & Shigemoto, 2004). Expression commences as early as postnatal day 2 (Bender et al., 2001; Vasilyev and Barish, 2002; Bender et al., 2005; Brewster et al., 2007a),

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and the number of cells expressing HCN channels is highest during the neonatal period (Bender et al., 2005). Remarkably, h-current density also peaks during the first postnatal week in CA3 pyramidal cells and declines thereafter (Vasilyev and Barish, 2002), suggesting that HCN expression may underlie the age-specific function of the current and is regulated to enable the synchronizing function of I_h. Related findings, demonstrating a modulating effect of I_h on the regularity of burst firing in neonatal CA3 (Agmon and Wells, 2003), further support this notion.

Developmental changes of HCN channel expression also occur in CA1. In CA1 pyramidal cells, quantitative changes in HCN1, HCN2 and HCN4 isoform expression constitute a "molecular switch" from an early-postnatal preponderance of slow-activating, cAMP-sensitive isoforms (HCN2 and 4) to a mature stage in which the major contribution to I_h-properties comes from the fast-activating, cAMP-insensitive HCN1 isoform (Surges et al., 2006; Brewster et al., 2007a). Interestingly, the time course of these changes correlates with the developmental transition from the slow network oscillations that prevail in immature CA1 towards mature network activity, including theta frequency (LeBlanc and Bland, 1979; Garaschuk et al., 1998). The HCN expression changes may contribute to this transition via modulation of neuronal resonance behavior (Magee, 1998; Hutcheon and Yarom, 2000; Ulrich, 2002; Narayanan and Johnston, 2007). Thus, with I_h-activation accelerating during development (Surges et al., 2006), pyramidal cells may get closer to their preferred (mature) firing frequency (Pike et al., 2000; Ulrich, 2002; Bernard et al., 2007).

2.2. Subcellular distribution of HCN channels: Developmental patterns and implications

The functions of the HCN channels depend not only on their expression levels, but also on their sub-cellular localization (Magee, 1998; Poolos et al., 2002; Santoro and Baram 2003; Williams and Stuart, 2003; Berger et al., 2003; Aponte et al., 2006; Bender et al., 2007; Ying et al., 2007). This localization can vary significantly among neuronal types and may include somatic and dendritic, as well as axonal compartments (Figure 2). For instance, in cortical and hippocampal pyramidal cells, HCN channels localize preferentially to dendrites, where they control the integration and summation of synaptic input (Magee, 1998, 1999; Stuart and Spruston, 1998; Williams and Stuart, 2000, 2003; Berger et al., 2001, 2003; Poolos et al., 2002; Lörincz et al., 2002; Wang et al., 2003; Notomi and Shigemoto, 2004; Brewster et al., 2007a). In cortical and hippocampal interneurons, these channels are often found in the somatic compartment, where they regulate cell properties such as the resting membrane potential (Maccaferri and McBain, 1996; Lupica et al., 2001). Axonal HCN channels have been identified in a subgroup of interneuron populations (Notomi and Shigemoto, 2004; Lujan et al., 2005; Aponte et al., 2006; Brewster et al., 2007a), as well as in certain excitatory neurons (Cuttle et al., 2001; Soleng et al., 2003; Bender et al., 2007). In these neurons, the channels localize predominantly to axon terminals, where they seem to modulate neurotransmitter release (Southan et al., 2000; Klar et al., 2003; Aponte et al., 2006; Bender et al., 2007).

2.2.1. Developmental regulation and age-specific functions of axonal HCN channels—

Recent data suggest that the sub-cellular localization of HCN channels is also subject to developmental regulation. For example, in rodent perforant path, the major afferent pathway to the hippocampus, HCN1 channel isoforms are expressed in axon terminals that abut on dendrites of the dentate gyrus granule cells (Figure 3). Interestingly, this expression is specific to both an age window and the type of axons involved: in the perforant path, which can be subdivided into a medial and a lateral portion, only axons of the medial portion (medial perforant path, mPP) express HCN1 channels, whereas the axons of the lateral perforant path, that originate in a separate neuronal population in the entorhinal cortex (Amaral and Witter, 1995), are devoid of this channel. In addition, HCN1 channel expression is robust in immature mPP, and gradually decreases with maturation (Figure 3A–D). As described above for area CA3, the age-specific subcellular localization of the HCN1 channels to mPP axons is associated

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with a specific developmental *function* of I_h: the current prevents a variant of short-term depression (STD), promoting synaptic strengthening. Thus, in a stimulation paradigm that determines STD of mPP firing, a form of synaptic plasticity that is attributable to presynaptic mechanisms (Harris and Cotman, 1985;Dietrich et al., 1997), blocking I_h caused an increase of STD in immature but not in mature mPP, suggesting that synaptic properties in mPP are modulated by HCN channel activity in an age-dependent manner (Figure 3E). These findings raise the possibility that pre-synaptic I_h might enhance the probability and reliability of neurotransmitter release at immature mPP synapses, an effect that might involve a tonic depolarization of the presynaptic membrane potential (Beaumont and Zucker, 2000;Southan et al., 2000;Mellor et al., 2002;Agmon and Wells, 2003;Aponte et al., 2006). Because reliability of neuronal firing is a prerequisite for stabilization of synaptic contacts at perforant path/granule cell synapses (Frotscher et al., 2000), the expression of HCN1 specifically in axon terminals of immature mPP can be seen as a contribution of the channels to the maturation of network connectivity.

2.2.2. Developmental regulation and age-selective function of dendritic HCN channels—Developmental regulation of the sub-cellular distribution of the HCN channels has been described also for the dendritic compartment. In mature rat hippocampus, dendrites of CA1 pyramidal cells express channels of both the HCN1- and HCN2-type (Lörincz et al., 2002; Notomi and Shigemoto, 2004; Brewster et al., 2007a), whereas HCN4 type channels are barely detectable in these dendritic domains. In contrast, during the first two postnatal weeks, only HCN1 channels localize to these dendrites, whereas HCN2 channels, although expressed in the soma neonatally, are only detectable in the dendrites starting in the third postnatal week (Brewster et al., 2007a). These findings predict that dendritic I_h in the immature hippocampus would be comprised of homomeric HCN1 channels, and would possess biophysical properties that differ from those of adult-type dendritic I_h. The developmental trigger for this delayed dendritic transport of HCN2 channels is not yet known. Developmental transitions in hippocampal network activity that occur during this developmental period might be involved (see above). Alternatively, isoform-specific interaction between HCN channel isoforms and chaperone/transport-related proteins may be responsible (e.g., Gravante et al., 2004; Kimura et al., 2004; Santoro et al., 2004; Shin et al., 2008). Developmental expression profiles of individual interacting proteins would then govern the trafficking of individual HCN channels to dendrites and an onset of this trafficking. Finally, in heterologous systems, heteromerization might contribute to transport of HCN channels to the membrane (Proenza et al., 2002; Altomare et al., 2003; Much et al., 2003; Whitaker et al., 2007). Stable heteromerization of HCN1/HCN2 involves mature glycosylation of the HCN1 isoform, and may be age-dependent (Brewster et al., 2007b; Zha et al., 2008), potentially influencing the transport of HCN2 to the dendritic compartment early in life. Because the function of dendritic HCN channels in dendritic summation and neuronal excitability is crucial for network stability (Magee, 1998, 1999; Berger et al., 2001; Williams and Stuart, 2003; Wang et al., 2003; van Welie et al., 2004; Fan et al., 2005; Brager & Johnston, 2007; Tsay et al., 2007), further examination of the unique developmental mechanisms determining HCN1 and HCN2 channel trafficking to the dendrites, and their contribution to dendritic I_h, is important. It is tempting to speculate that dendritic I_h conducted by homomeric HCN1 channels would have properties (e.g., rapid kinetics, minimal response to fluctuating cAMP levels) that promote selective stabilization of neuronal connectivity by influencing dendritic summation to the developing neuronal somata (Magee, 1999).

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3. The role of neuronal activity in developmental HCN regulation

3.1. Neuronal activity is a driving force for developmental HCN expression changes

The findings summarized above demonstrate a remarkable evolution of the expression and subcellular localization of the HCN channels during the early-postnatal period in hippocampus. This raises the question of the regulation of these changes. Generally, the developmental organization of neuronal networks is governed by genetic as well as environmental elements. Among the latter, neuronal activity has long been recognized to be a key determinant (Goodman and Shatz, 1993; Constantine-Paton and Cline, 1998), suggesting that evolving network activity may influence the developmental expression of the HCN channels as well.

The effects of neuronal activity on the expression of the HCN channels in developing hippocampus were discovered in studies employing network activity bursts (experimental seizures) induced by the glutamate agonist kainic acid and by hyperthermia (Brewster et al., 2002). These bursts provoked alteration of the expression patterns of the HCN channels that co-varied with seizure duration, as well as persistent changes in the biophysical properties of I_h. Thus, the abnormal activity bursts shifted the voltage dependence of I_h in the depolarizing direction and caused a slowing of its activation and deactivation kinetics – changes that resulted in a generally larger h-current in hippocampal CA1 pyramidal cells (Chen K. et al., 2001; Kamal et al., 2006). These changes persisted for months and, together with the observed increase of perisomatic IPSCs (Chen et al., 1999), led to increased rebound firing and hyperexcitability in the hippocampal network (Dube et al., 2000, 2006; Chen K. et al., 2001). The molecular basis for these physiological changes consisted of reduced expression of the fast-activating and -deactivating HCN1 isoform, decreasing its proportional contribution to the HCN channel pool and accounting for the slowing of I_h kinetics. Decreased HCN1 protein levels also increased the stochastic probability of formation of HCN1/HCN2 heteromers (Figure 4A), and a doubling of heteromeric HCN1/HCN2 channels (Brewster et al., 2005; Zha et al., 2008). The biophysical properties of these heteromers are not fully known, and available data suggest that they may not intermediate to those of HCN1 or HCN2 homomers (Chen S. et al., 2001). It is tempting to speculate that the unusual properties of the I_h recorded after seizures (slowed kinetics, depolarized activation curve and modest cAMP response) are a result of increased contribution of heteromeric channels to the total cellular I_h. Importantly, both the molecular and physiological changes in the channels endured for months, suggesting that the pathological (seizure) activity bursts interfered with (‘corrupted’) the normal developmental program of HCN channel expression in hippocampus (Figure 4B).

3.2. How does network activity regulate HCN channel expression and function?

The intracellular signaling mechanisms that mediate activity-dependent changes of HCN channel expression have been partially elucidated. Using organotypic hippocampal cultures as an *in vitro* seizure model, Richichi and colleagues (2008) found that the seizure-induced reduction of HCN1 mRNA and protein expression required Ca^{2+}-influx into the bursting neurons via Ca^{2+}-permeable AMPA-receptors, followed by activation of CaM Kinase II. Analysis of the HCN1 gene promoter further revealed a highly conserved binding site for the transcription factor *N*euronal *R*estrictive *S*ilencing *F*actor (NRSF/REST), and the expression of this factor was enhanced by the network activity bursts (Richichi et al., 2007) suggesting that, further downstream of CaM Kinase II, NRSF might be involved in the pathway by which activity-bursts regulate HCN1 channel expression (Richichi et al., 2007). Interestingly, no part of this pathway was involved in the upregulation of HCN2 mRNA by seizure-like network bursts (Richichi et al., 2008), suggesting that multiple, isoform-specific signaling mechanisms contribute to activity-dependent regulation of hippocampal HCN transcription.

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Network activity may also regulate the function of HCN channels via post-translational mechanisms. In the *in vitro* model described above, seizure-like network activity increased the stable heteromerization of HCN1/HCN2 (as found also *in vivo*, Brewster et al., 2005). Interestingly, the increased association of HCN1/HCN2 was not attributable solely to a stochastic phenomenon resulting from reduced HCN1 channel expression and increased probability of each HCN1 molecule's interaction with an HCN2 subunit (Figure 4A). Rather, an additional mechanism for this activity-induced heteromerization of HCN1 and HCN2 isoforms involved enhanced HCN1 channel glycosylation by network activity bursts (Zha et al., 2008), and preferential stable co-assembly of glycosylated HCN1 with the HCN2 isoforms. Thus, *in vivo* and *in vitro*, both transcriptional and post-translational regulatory mechanisms are triggered by hippocampal network activity to influence HCN expression, co-assembly and trafficking. These, in turn, govern persistent changes in the properties of I_h.

3.3. Activity governs trafficking of HCN channels to subcellular compartments

The age-specific localization of HCN channels to subcellular compartments, discussed above, has recently been found to be largely governed by age-dependent neuronal activity. For dendritic transport, Shin and Chetkovich (2007) used organotypic hippocampal slice cultures to study the developmental evolution of dendritic HCN1 expression and the mechanisms that govern it. They found that enrichment of HCN1 channels in the distal segment of CA1 pyramidal cell dendrites did not occur when neuronal activity was blocked, or when they transected the temporoammonic pathway, suggesting that neuronal activity deriving from afferent innervation is a major driving force for the transport of HCN1 channels to their proper distal dendritic location. Similar mechanisms may function in the mature hippocampus: In hippocampal slices from young adult rats that were theta-burst-stimulated to induce LTP, Fan et al. (2005) observed an activity-dependent, dynamic modulation of dendritic I_h in CA1 neurons that correlated with altered expression levels of the HCN1 subunit. However, because acute slices were used in this study, a dynamic regulation of the dendritic transport of HCN1 channels could not be demonstrated. Interestingly, both studies reported a role for CaM Kinase II-activity in regulating dendritic HCN1, concordant with the findings of Richichi et al. (2008) on the activity-dependent regulation of HCN1 transcription (see above).

Axonal distribution of HCN1 during development was also activity-dependent (Bender et al., 2007): When organotypic entorhino-hippocampal cultures were incubated for a week with tetrodotoxin (TTX), suppressing >90% of action potentials (Denac et al., 2000), this led to increased presynaptic presence of HCN1 channels. This finding is consistent with a suppressive effect of network activity on the expression of these channels in perforant path axon terminals. TTX did not affect the transcription and translation levels of HCN1 channels in the cells of axonal origin, i.e., the entorhinal cortex layer II stellate cells, indicating that the activity-dependent regulation was at the post-translational, trafficking level (Bender et al., 2007).

4. Interactions of HCN channels with other conductances

The findings described above indicate that the balance of HCN isoform expression is critical for network maturation in hippocampus, and presumably other regions of the brain. However, HCN channels are unlikely to be the only determinants of this process. In fact, the intricate interplay of I_h and other conductances in processes such as dendritic information processing in cortical neurons (Williams and Stuart, 2003; Day et al., 2005) or rhythm generation in entorhinal cortex (Dickson et al., 2000; Fransen et al., 2004) and thalamus (Lüthi and McCormick, 1998; Budde et al., 2005) suggests that establishment of network functions requires a coordinated expression program of several conductances, which may homeostatically influence one another (MacLean et al., 2003; Santoro and Baram, 2003; Misonou and Trimmer, 2004; Moody and Bosma, 2005; Meuth et al., 2006; Schulz et al., 2007; Budde et al., 2008).

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Likely candidates for this process include potassium channels, for which a developmental regulation of hippocampal expression has been shown (Maletic-Savatic et al., 1995; Tinel et al., 1998; Grosse et al., 2000; Antonucci et al., 2001; Smith et al., 2001; Tansey et al. 2002; Falk et al., 2003; Kanaumi et al., 2008). Some of these channels show interesting parallels to the HCN channels. Thus, in CA1 pyramidal cells, Kv 4.2 (A-type) channels localize preferentially to the distal dendrites (Maletic-Savatic et al., 1995; Hoffman et al., 1997; Cai et al., 2004), where they control both backprogation of action potentials into the dendritic tree (Hoffman et al., 1997; Bernard et al., 2004) and forward propagation of depolarization out of dendritic branches in which activated synapses are located (Cai et al., 2004; Chen et al., 2006). Like the HCN channels, the dendritic expression of Kv 4.2 channels commences early postnatally and then gradually increases with maturation (Maletic-Savatic et al., 1995; compare to Brewster et al., 2007a). Expression and subcellular trafficking of Kv 4.2 channels are regulated by neuronal activity (Tsaur et al., 1992; Bernard et al., 2004; Kim et al., 2007), and this regulation involves CaM kinase II (Varga et al., 2004), although it is not yet clear whether CaM kinase II also contributes to the transcriptional regulation of Kv 4.2, as it does for HCN1 (Richichi et al., 2008). In view of these parallels and the important integrative functions of both channel types in dendrites, one may suspect that they are homeostatically regulated: Indeed, data from invertebrate systems suggest that HCN- and A-type-channels are co-regulated on the transcriptional level (MacLean et al., 2003; Schulz et al., 2007). However, whether such co-regulation also occurs in mammalian neurons, and whether it includes developmental regulation, remains to be determined.

Homeostatic interaction may exist also between the HCN channels and others that contribute to the regulation of the resting membrane potential (e.g. Kir-, K_{leak}-, Na_{leak}- channels; Day et al., 2005; Meuth et al., 2006; Budde et al., 2008). However, information on the developmental regulation of these channels is sparse. In addition, mice deficient in the HCN1-isoform show no compensatory changes of the corresponding conductances, arguing against an extensive homeostatic linkage of these and HCN channels (Nolan et al., 2004, 2007). Further co-regulation of HCN- and other channels is apparent from the phenotype of mouse mutants such as *stargazer*, which is deficient in Ca^{2+} channel function (Letts et al., 1998), yet endowed with increased I_h in cortical neurons (DiPasquale et al., 1997 and see below).

5. Developmental dysregulation of HCN channels and brain pathology

Taken together, these findings support the framework of a coordinated expression of HCN channels in the developing hippocampus as an integral part of a developmental program that is regulated by neuronal activity. In this scenario, age-specific complements of HCN channel isoforms contribute to patterns of network activity. Network activity, in turn, promotes changes of HCN channel expression and distribution that support the integration of previously incoherent neuronal assemblies into a progressively maturing hippocampal network. This process requires a fine-tuned interplay between activity (i.e., the neuronal environment) and the HCN channels (i.e., determinants of intrinsic neuronal excitability) that is naturally sensitive to disturbances. Factors that interfere with this process, e.g., abnormal neuronal activity such as seizures, may have a long-lasting impact, because resulting errors (e.g. abnormal wiring) may be integrated into the developing network. In the worst case, these errors could promote pathological network function. Indeed, evidence for a critical role of a developmental dysregulation of HCN channels in the genesis of brain pathologies is emerging:

1) After experimental prolonged febrile seizures, hippocampal HCN channel expression and co-assembly were altered persistently. The coordinated expression changes were associated with a depolarization shift of h-channel activation and a slowing of the activation and deactivation kinetics of somatic and dendritic channels (Chen K. et al., 2001; Dyhrfjeld-Johnsen et al., 2008), thus modifying I_h and causing enduring hippocampal hyperexcitability

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(Chen K. et al., 2001; Brewster et al., 2002, 2005; Santoro and Baram, 2003; Kamal et al., 2006; Dyhrfjeld-Johnsen et al., 2008), that, in a subset of animals, may lead to frank epilepsy (Dube et al., 2006). In this context, it is worthwhile noting that abnormal expression levels of HCN1 channels have also been detected in the hippocampus of patients with temporal lobe epilepsy (associated with a history of early-life seizures; Bender et al., 2003). The full mechanistic relationship of the persistently altered HCN channel levels and the transformation of a 'normal' neuronal network to one generating spontaneous synchronized activity bursts (epileptic seizures) remains to be determined (Dube et al., 2007).

Recently, HCN expression and localization changes were also observed in adult models of temporal lobe epilepsy. Thus, down-regulation of HCN1 expression was reported after status epilepticus induced by kainic acid (Shah et al., 2004; Powell et al., 2008), pilocarpine (Jung et al., 2007) and after kindling (Powell et al., 2008). This down-regulation became specifically evident during the chronic period when epilepsy was established (Jung et al., 2007). These changes, although in some respects differing from the changes in the developing brain, generally support the notion of a potentially epileptogenic effect of seizure-induced HCN alterations. Importantly, several of these studies suggest that expression changes within the dendritic compartment could be particularly critical for epileptogenesis (Jung et al. 2007). In addition, reduced dendritic transport of HCN1 channels or reduced association of HCN1 with the adaptor protein TRIP8b in the chronic period (resulting in diminished transport of HCN1 channels to CA1 pyramidal cell dendrites) may also contribute to epileptogenesis (Shin et al., 2008). This new evidence supports a role for post-translational regulation of HCN subunit association in defining the distribution and function of these channels (Zha et al., 2008). In summary, HCN channels are altered by abnormal neuronal activity such as seizures in both mature and developing hippocampus, and these alterations accompany, and perhaps promote, the epileptogenic process. The precise role of these channels in governing neuronal excitability is still not fully understood, as discussed above, and may be age- and even model-specific (e.g., see Zhang et al., 2006).

2) Developmental dysregulation of cortical and/or thalamic HCN channel expression may contribute to epileptogenesis in genetic models of absence epilepsy: In two models, the Wistar Albino Glaxo/Rijswijk (WAG/Rij) and the Genetic Absence Epileptic Rats of Strasbourg (GAERS), the relative contribution of HCN1 channels to the channel pool and thalamic I_h was increased in thalamocortical relay (TC) neurons, resulting in reduced cAMP responsiveness of I_h (Budde et al., 2005; Kuisle et al., 2006). These changes were observed before the onset of absence seizures, suggesting that they might be a cause rather than a consequence of the seizure activity (Budde et al., 2005; Kuisle et al., 2006; Pape et al., 2007). Weakened cAMP actions could contribute to the generation of absences by facilitating burst discharges in TC neurons, promoting synchronization in the thalamocortical network (Budde et al., 2005; Kuisle et al., 2006). Similar mechanisms may underlie the spontaneous absence seizures in mice deficient in the HCN2 subunit (Ludwig et al., 2003). The basis of thalamic HCN1 upregulation in GAERS and WAG/Rij rats is unclear: Genomic analyses have not revealed mutations of the HCN1 gene (Gauguier et al., 2004; Rudolf et al., 2004) so that a developmental dysregulation due to abnormalities in the thalamic network (Dutuit et al., 2000, 2002) is plausible.

Dysfunction of cortical I_h might also contribute to corticothalamic network abnormalities, and the nature of the changes may be model-specific. Thus, in the *stargazer* mutant (see Section 4), enhanced I_h was observed in layer V pyramidal neurons of temporoparietal cortex, resulting in a lower threshold for aberrant thalamocortical spike-wave oscillations *in vivo* (DiPasquale et al., 1997). In contrast, in WAG/Rij rats with absence seizures, reduced I_h and lower expression levels of the HCN1 isoform compared to non-epileptic Wistar rats were found in pyramidal cells of somatosensory cortex (Strauss et al., 2004), and these changes were also associated with an increase in seizure activity (Schridde et al., 2006; Kole et al., 2007).

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Interestingly, early suppression of seizure activity in WAG/Rij rats by chronic treatment with ethosuximide prevented the neocortical downregulation of HCN1 expression as well as the establishment of absence seizures, suggesting that in neocortex altered expression of HCN isoforms may be a consequence and not the cause of seizure activity (Blumenfeld et al., 2008). These findings further imply that seizures regulate HCN1 channel expression in cortex, as described above for hippocampus and thalamus.

It should be noted that the HCN channels are only one family of ion channels where developmental dysregulation may contribute to human disease and specifically to epilepsy: For example, the KCNQ2/3 channels generate a slowly-activating outward (potassium) current (I_M,) upon membrane depolarization (Cooper and Yan, 2003). These channels are partially active at rest, and function to stabilize resting membrane potential and control repetitive neuronal firing. Mutations of these channels result in neonatal seizures (benign neonatal familial seizures, BNFC), and these seizures usually remit within the first months of life (Jentsch, 2000). Similarly, in rodents, controlled mutation of the channels during the 2–3 neonatal weeks, but not later in life, results in an epileptic phenotype (Peters et al., 2005). The basis of this age-sepcific pathology may derive from the fact that during the first weeks of life GABAergic inhibition is not yet fully established (Ben-Ari, 2002) so that KCNQ channels provide essential repolarizing, inhibitory function to the neuron (Okada et al., 2003). These functions may be supported by an age-specific expression of KCNQ isoforms or splice variants (Tinel et al., 1998; Smith et al., 2001; Weber et al., 2006; Geiger et al., 2006; Kanaumi et al., 2008). Later, when GABA assumes the role of the major inhibitor of neuronal firing, dysfunction of KCNQ2/3 channels no longer suffices to elicit abnormal hyperexcitability and seizures.

6. Conclusions and future perspectives

The roles of ion channels in neuronal networks are generally considered in the 3-dimensional mature network. This review introduces a fourth, developmental dimension, that consists of a dynamic and continuously changing vector. Using the HCN channels as examples, we find that the expression and the functions of the channels evolve with network development, and this evolution contributes to--and is in turn affected by--the developmental process. Disturbances of normal HCN channel function at a given developmental age will therefore lead to network derangements that differ from those caused by HCN channel dysfunction at a later age. Understanding the developmental aspects of ion channel expression, transport, assembly and function may thus provide us with valuable insights into the maturation of neuronal networks, as well as into the pathogenesis of certain developmental disorders.

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List of Abbreviations

AMPA
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

BNFC
benign neonatal familial seizures

fEPSP
field excitatory postsynaptic potential

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GAERS
Genetic Absence Epileptic Rats of Strasbourg

GDP
giant depolarizing potential

HCN
hyperpolarization-activated cyclic nucleotide-gated channel

IPSC
inhibitory postsynaptic current

LTP
long-term potentiation

mPP
medial perforant path

NRSF/REST
neuronal restrictive silencing factor/RE1 silencing factor

STD
short-term depression

TC
thalamocortical

TTX
tetrodotoxin

WAG/Rij
Wistar Albino Glaxo/Rijswijk

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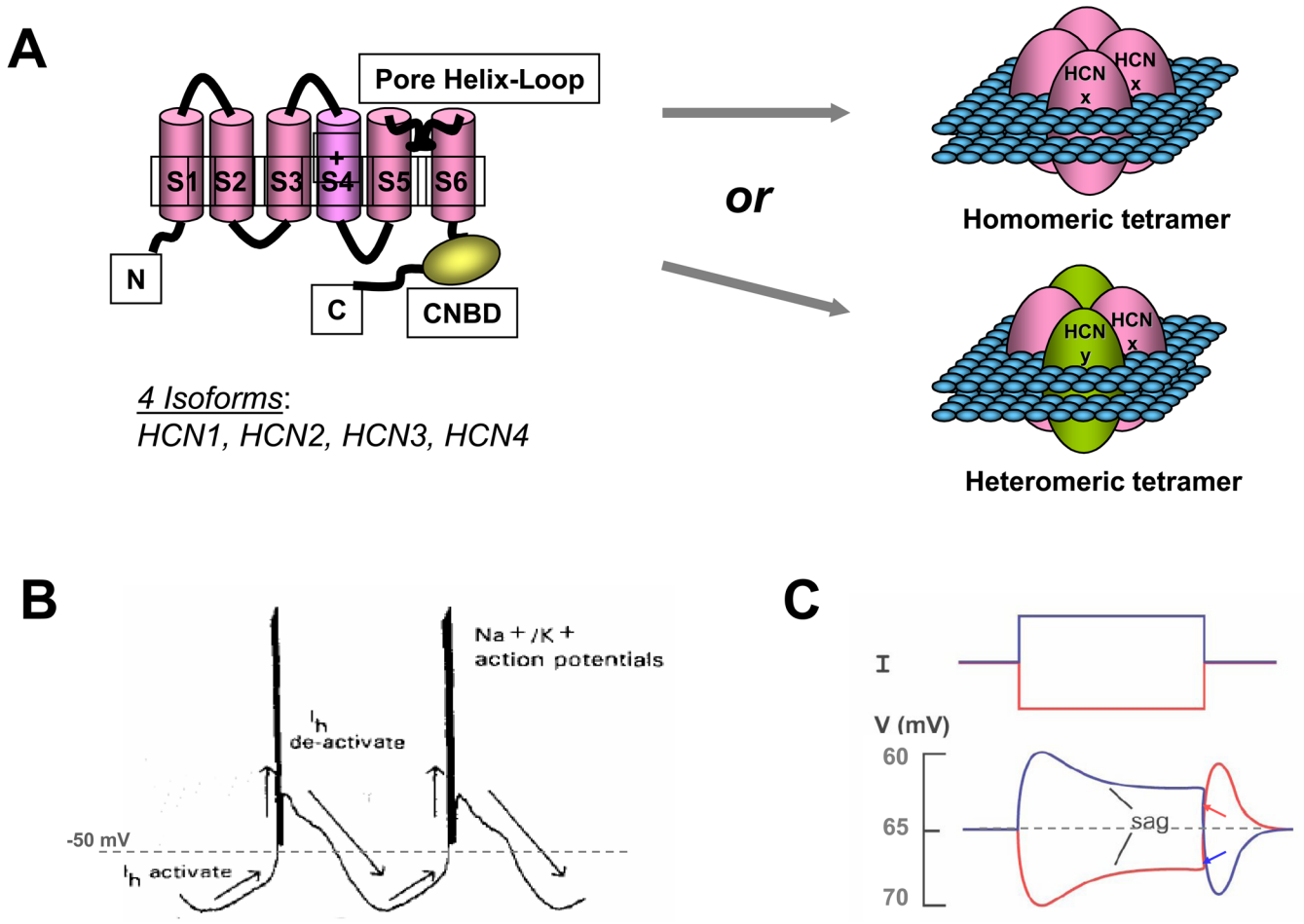

Figure 1. Molecular and functional characteristics of HCN channels and I_h

A) HCN channels are composed of four isoforms that can assemble as homomeric or heteromeric tetramers. Each of these isoforms, coded by the HCN1, 2, 3 and 4 genes, contains six transmembrane segments, with a positively charged S4 voltage sensor, similar to the voltage sensors of depolarization-activated potassium channels. HCN channels are non-selective cation channels that conduct primarily Na^+ ions at the negative membrane potentials at which they activate (Robinson and Siegelbaum, 2003). A characteristic feature of the HCN channels is the presence of a 120-amino-acid cyclic nucleotide binding domain in the cytoplasmic carboxy terminus (CNBD) which mediates their responses to cyclic AMP. B) Note: I_h activation following an action potential produces a slow depolarization that may activate other cation channels (Ca^{2+}, Na^+) and thus trigger a new action potential. I_h then deactivates (modified from Pape, 1996). C) Current clamp recordings illustrate the stabilizing actions of I_h on the resting membrane potential (dashed line): A hyperpolarizing input elicits a slow, depolarizing "sag" in membrane potential, reflecting I_h activation (red trace). Similarly, a depolarizing input yields a hyperpolarizing "sag" in membrane potential, reflecting I_h deactivation (blue trace). Note the rebound de- and hyperpolarization at the end of the hyperpolarizing resp. depolarizing input (arrows; modified from Poolos et al., 2002).

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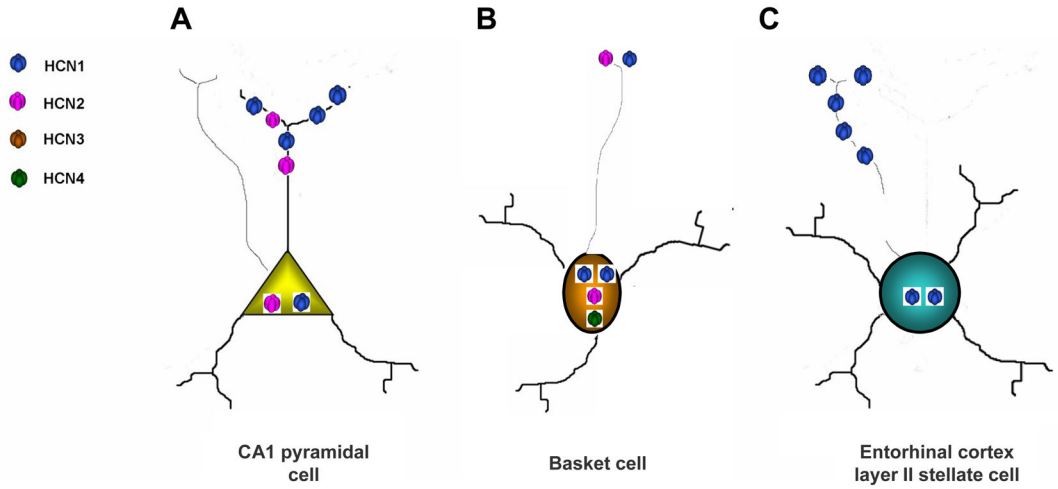

Figure 2. The subcellular localization of HCN channels in cortical and hippocampal neurons is neuron-type- and isoform-specific

HCN channels can localize to somatic, dendritic and axonal compartments of neurons, and these locations differ among neuronal populations. In CA1 pyramidal cells (A), HCN channels preferentially occupy dendritic locations (Lörincz et al., 2002; Notomi & Shigemoto, 2004; Brewster et al., 2007a), whereas in GABAergic interneurons, somatic HCN expression is more pronounced (B; Notomi & Shigemoto, 2004; Brewster et al., 2007a). Axonal localization is found in certain interneurons (e.g. basket cells, B; Notomi & Shigemoto, 2004; Aponte et al., 2006; Brewster et al., 2007a) and in layer II stellate cells of entorhinal cortex (C; Bender et al., 2007). The subcellular distribution is isoform-specific. Thus, HCN1- and HCN2-, but not HCN4-containing channels were detected in axon terminals of interneurons that express all three isoforms (B; Aponte et al., 2006; Brewster et al., 2007a).

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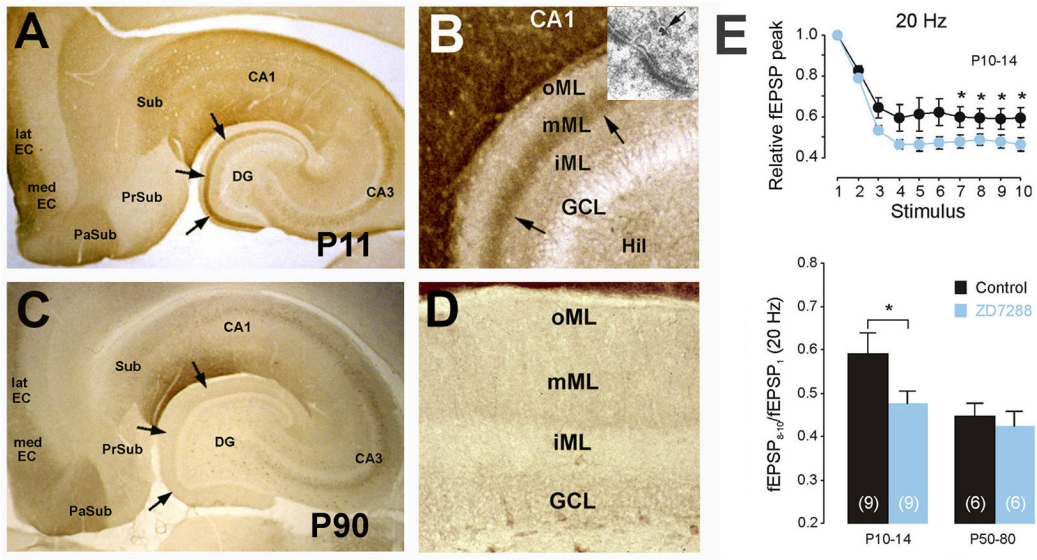

Figure 3. Presynaptic localization of functional HCN1 channels in perforant path axon terminals is age-specific

A) Robust expression in the termination zone of the medial perforant path in dentate gyrus molecular layer of immature (A, C), but not adult rats (B, D), suggests an age-specific presynaptic location of HCN1 channels in this pathway (inset in C: electron microscopy/ immunogold-detection of HCN1 in an axon terminal; Bender et al., 2007). Blockade of these channels with the selective I_h-inhibitor ZD7288 resulted in increased short-term-depression (STD) of neurotransmission in medial perforant path of P10-14 rats after stimulation with 20 Hz (E, top panel), suggesting that the channels are active and influence transmitter release at the immature age. In slices from adult rats with little HCN1 in perforant path (B, D), no effect of ZD7288 on STD (expressed as ratio of $fEPSP_{8-10}/fEPSP_1$) was detected (E, bottom panel; with permission of Journal of Neuroscience).

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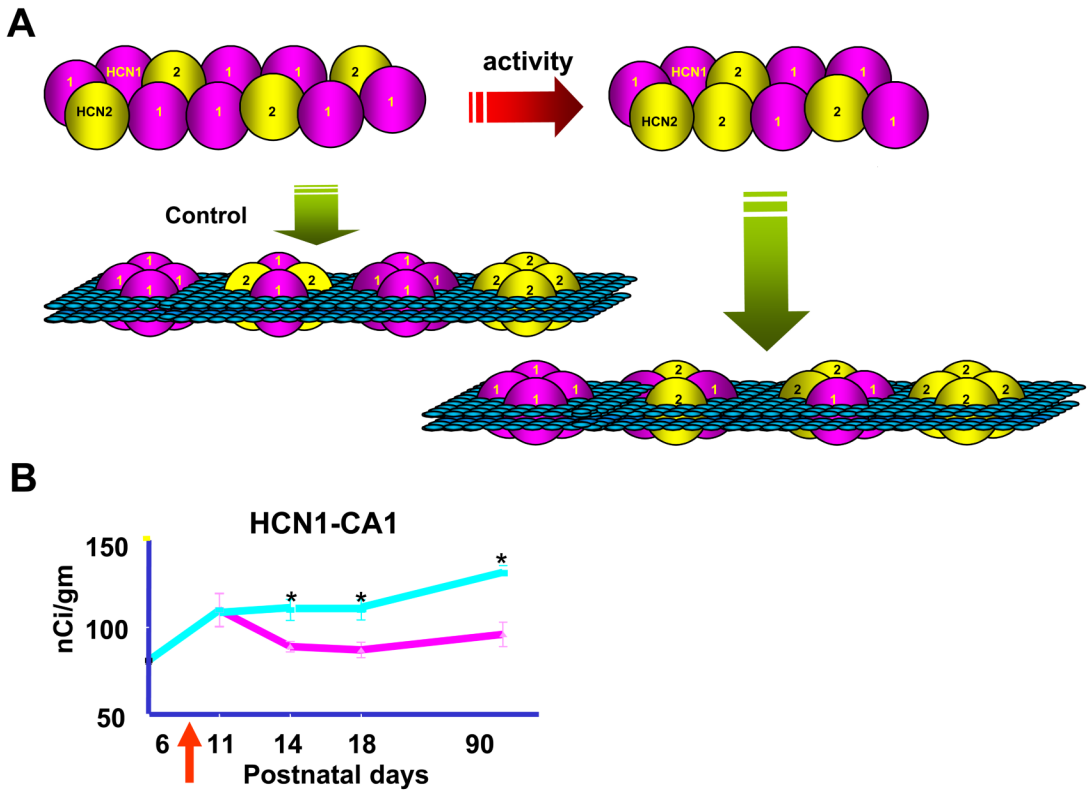

Figure 4. Activity-dependent changes in HCN channel expression and molecular rearrangements

Expression levels of HCN isoforms in developing hippocampus are differentially influenced by neuronal activity. Activity burst or seizures (red arrow in A) provoked reduction of the HCN1 isoform (fuchsia-colored spheres in A) and increased mRNA but not protein expression of the HCN2 isoform (yellow spheres in A). Decreased HCN1 protein levels further increased the stochastic probability of formation of HCN1/HCN2 heteromeric channels (A, green arrows), which may generate an h-current with distinctive biophysical properties (Chen S. et al., 2001). B) Seizure-induced expression changes of the HCN1 isoform (fuchsia-colored line) endured for months, suggesting that the normal developmental expression program of these channels (blue line) has been corrupted by the early-life seizures (red arrow).