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HCN Channels: From the Role in Chronic Cerebral Hypoperfusion-Induced Cognitive Impairments to a New Therapeutic Target for Vascular Dementia

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Abstract

Hyperpolarization-activated cyclic nucleotide-gated channels are concentrated in cortical and hippocampal pyramidal cell dendrites, where they play an important role in determining synaptic integration and plasticity phenomena. These channels have been suggested to be involved in physiological processes such as cognition as well as pathophysiological states such as epilepsy, pain, Parkinson's disease (PD) and Alzheimer's disease (AD). Recent evidences from our own researches have suggested that the learning and memory impairments caused by chronic cerebral hypoperfusion (CCH) are associated with a change of HCN1/HCN2 expression; therefore these channels may also be therapeutic targets for treatment of vascular dementia.

Keywords: Vascular dementia; HCN channels; Chronic cerebral hypoperfusion

Review

Vascular dementia (VaD) is the second leading form of dementia after Alzheimer's disease (AD) among western countries [1]. It is a progressive disease caused by cerebrovascular diseases with the pathologic features of reduced blood flow in the brain that affects cognitive abilities [2-4]. Accordingly, the cognitive impairment associated with vessel disorders is an increasingly important and recognised area of the medicine of VaD patients. CCH is a common consequence of various cerebral vascular disorders and hemodynamic changes that contributes to the risk of VaD. In rodents, the bilateral common carotid artery occlusion (2VO) model is so far the most effective and frequently-used experimental model to evaluate the relation between chronic cerebral hypoperfusion and vascular disease-related dementia [2,5-7]. However, the progress on understanding the basis of the disease and developing treatments is not encouraging. There are no drugs licensed for the treatment of VaD. In this context, we reviewed the discoveries from our own research based on 2VO model that the role of HCN channels in CCH-induced cognitive impairments and hypothesise a new therapeutic target toward developing novel treatments for dementia of vascular origin.

HCN channels are cation channels that open at membrane voltages close to resting membrane potentials and are directly regulated by the binding of cAMP. It was identified in the late 1970s in sinoatrial node cells and neurons [8-11]. The HCN channel family is comprised of four subtypes (HCN1-4). The predominant forms in the hippocampus and cortex are HCN1 and HCN2 [12,13]. In pyramidal and neocortical neurons, they show a large gradient of expression that can be 60-fold increase from somatic to distal apical dendritic membranes [14]. The channels are formed by heteromeric or homomeric complexes and carry the hyperpolarization-activated current, Ih. In neuronal dendrites, Ih is proposed to be responsible for several important cellular functions and plays a fundamental role in controlling cellular excitability, rhythmic activity, dendritic integration, synaptic transmission, and plasticity phenomena [15-17] that participates in the pathogenic mechanism of certain neurological diseases in humans such as epilepsy [18-20], pain [21], PD [22,23], and AD [24]. As expected from the established role of HCN channels in neurons, they may also potentially be involved in the process of cognitive declines originated from vascular risks.

In fact, It has been [25] demonstrated that in cerebellar Purkinje cells, Ih stabilizes the integrative properties of Purkinje cells and ensures their input-output function. Using generalized and regional knockout mice, that deletion of the HCN1 channel causes a great reduction of Ih and the current in cells from HCN1-/- mice showed little dependence on voltage at potentials from 50 mV to 70 mV. These changes alter the integrative properties of Purkinje cells and thereby impair motor learning and memory function. Further study from Nolan et al. [16] has showed that forebrain restricted deletion of HCN1 dramatically slows the activation and deactivation kinetics of Ih, thus modifying dendritic integration of CA1 pyramidal cells and resulting in enhanced LTP and spatial memory. What's more, Matt et al. [26] identified that oriens-lacunosum moleculare interneuron cells in slices from HCN2-/- mice showed a alteration of Ih current, which reduced GABAergic output onto distal dendrites of CA1 pyramidal and caused an increased LTP in direct perforant pathway. While, data from Thuault et al. has showed that forebrain-restricted HCN1 channels deletion induces a substantial loss of Ih, that altered the intrinsic persistent neural firing and impaired executive memory function [27]. And another study has further clarified the reduction of hippocampal HCN1 expression and Ih associates with a spatial learning deficit [28]. It seems that learning and memory are regulated by HCN channels/Ih currents that integrate synaptic information is well identified. On the other hand, a change of HCN channels can also be seen in response to cerebral ischemia [29]. Therefore, HCN channels as interesting targets may offer excellent opportunities for the development of novel drugs to treat cognitive deficits of vascular origin.

Our research from Li et al. [30] has described for the first time that the down regulation of HCN1 mRNA in the hippocampal CA1 pyramidal neurons and neocortex under CCH condition is associated

with the spatial learning and memory impairments. These data opened new insights for further investigation of the physiological and pathological significances of HCN1 in vascular dementia and provided additional information for the characterization of HCN channels as a new prospective target for the medication of vascular dementia.

Further study from Li et al. [31] has identified that 5 weeks after induction of hypoperfusion, the reduction of HCN1 surface expression and increase in HCN2 surface expression in hippocampal CA1 may be implicated in the cognitive deterioration. In fact, properties of Ih are likely to be determined by diverse HCN subunits expression patterns across the cell membrane [32,33]. In hippocampal CA1 neurons, Ih are probably mediated by both heteromeric and homomeric HCN complexes [34] and HCN1 subunit is likely to interact with other HCN1 subunits to form homomeric channels due to the fact that amount of HCN1 protein is much higher than HCN2 [35]. When rats suffered from CCH, the ratio of HCN2/HCN1 surface expression in CA1 area was increased [31]. And this should increase the propensity of the HCN2 isoform's interaction with HCN1, which might augment HCN1/HCN2 heteromerization and result in a higher contribution of heteromeric HCN channels to the macroscopic Ih accordingly [35]. Providing the homomeric HCN1 channels conduct fast-kinetic currents with modest cAMP gating and homomeric HCN2 channels conduct slower-kinetic Ih currents with robust cAMP-evoked shifts in voltage dependence [34,36-38], the properties of heteromeric HCN complexes should be differ from those of homomeric ones. Therefore, the increased ratio of surface HCN2/HCN1 should significantly modify the properties of the macroscopic Ih in CA1 pyramidal cells and contribute to pathological alteration of the hippocampal network, which may be responsible for cognitive impairments caused by CCH (A mechanistic explanation in Figure 1). These data have further clarified that surface expression of HCN subunits may be involved in the pathogenesis of vascular dementia and finding out an effective compound acting on surface HCN1/HCN2 may be a promising therapy strategy for vascular dementia.

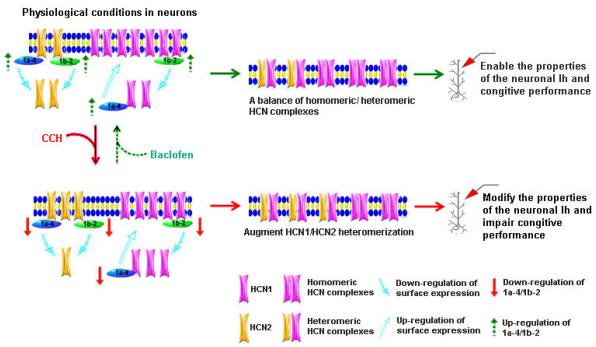

Figure 1: A mechanistic explanation for the change of HCN surface expression is implicated in the cognitive deterioration under CCH and baclofen ameliorates cognitive impairment via restoring the changed HCN surface expression. Hypoperfusion significantly reduced the protein levels of 1a-4 and 1b-2, which lead to a reduction of HCN1 surface expression and increase in HCN2 surface expression. The ratio of HCN2/HCN1 surface expression was increased. And this should increase the propensity of the interaction of HCN2 isoform's with HCN1, which might augment HCN1/HCN2 heteromerization and result in a higher contribution of heteromeric HCN channels to the macroscopic Ih accordingly. The altered Ih should contribute to pathological alteration of the hippocampal network and may be responsible for cognitive impairments caused by CCH. Baclofen can increase the expression and enhance the function of 1a-4 and 1b-2 in CCH rats that restores the decreased HCN1 surface expression and increased HCN2 surface expression, which ameliorates the cognitive impairment caused by CCH.

The findings of Li et al. [31] have several profound implications. First, they indicated that the increased ratio of HCN2/HCN1 surface expression in CA1 modify the properties of Ih. It is the changed Ih eventually contribute to the cognitive impairments in rats with CCH. Second, the changed Ih can result from the imbalance of HCN2/HCN1 surface expression, not just a reduction of HCN1 and increase in HCN2. Last, the findings of Li et al. also revealed that baclofen, a GABAB receptor agonist, has neuroprotective effects against chronic cerebral hypoperfusion. Its efficacy possibly via not only increasing the expression of TRIP8b (1a-4) and TRIP8b (1b-2) but also regulating the function of TRTP8b, then restored the balance of HCN1/HCN2 surface expression and reversed the cognitive deficits induced by CCH (Figure 1). Thus, the compounds act on accessory/regulatory protein resulting in restoring the balance of HCN1/HCN2 surface expression or directly/indirectly changing the Ih (activation or inhibition) may be promising and indispensable drugs for treatment of disease.

There are a set of proteins (such as MiRP1, Filamin A, TRIP8b, Caveolin 3, tamalin, Mint2, S-SCAM, Nedd4-2 and KCR1) that affect the correct function of HCN ion channels by interaction at different levels [8,39-47]. However, among which, only the TRIP8b's functional significances were well identified. Tetratricopeptide repeat–containing Rab8b interacting protein (TRIP8b), an accessory protein, that regulates the cell surface expression and dendritic localization of HCN channels in an isoform-dependent manner [48,49]. In the brain, more than ten isoforms of TRIP8b are expressed [50]. A quantitative real-time PCR analysis demonstrated that TRIP8b (1a-4) and TRIP8b (1a)

are the most abundant TRIP8b mRNA species in the brain, representing 30%–40% and 25%–30% of total TRIP8b mRNA, respectively. While TRIP8b (1b-2) expressed at somewhat lower levels, accounts for 10%–15% of total brain TRIP8b mRNA [51]. TRIP8b (1a-4) strongly increases HCN1 surface expression [51,52] and decreases the surface expression of HCN2 [53]. While TRIP8b (1b-2) has been reported to produce a potent downregulation in the surface expression of HCN1 and HCN2 [43]. Therefore, TRIP8b acts as a gatekeeper of neuronal HCN channel activity that provides one of the most promising therapeutic targets for treating VaD.

In addition to auxiliary subunits, many intracellular molecules, including small molecules (e.g. cAMP, PIP2, protons) and protein kinases (e.g. Src, p38-MAPK, PKC, cGKII, Ca2+/CaMKII), that influence HCN channel gating, kinetics and surface expression [37,54,55]. In fact, selective serotonin reuptake inhibitor (SSRI) antidepressants, whose primary action is based on the inhibition of 5-HT reuptake in the central nervous system, have been used with FDA approved drugs for dementia in AD. And they play a positive role in hindering the progression of the AD and improving patients' cognitive performance [56-59]. Providing the large overlap between AD and VaD in clinical symptomatology, pathophysiology and neurochemical mechanisms [60-63], an effective treatment for AD may also offer benefits as a symptomatic treatment in VaD. Although most of the effects of antidepressants have been ascribed to their functions of neurogenesis activity, neurotrophin modulation and reduction of proteotoxicity [64-67], it is possible that acting on HCN channels may also contribute to or be responsible for antidepressants' efficacy on dementia since there is an interaction between the serotonergic systems and HCN channels [68-70] and SSRI antidepressants inhibit 5-HT reuptake that can regulate the properties and trafficking of HCN channels via a way of activating PLC-PKA and p38-MAPK signaling pathways (Figure 2) [54,71-73]. It is worth mentioning that we have recently observed that fluoxetine can ameliorate cognitive impairments induced by CCH via down-regulation of HCN2 surface expression in the hippocampal CA1 area in rats (The data have not been published) and data from others also have showed that SB202190, a p38-MAPK inhibitor, can significantly reduce neuronal apoptosis in the hippocampus and rescue spatial learning and memory deficits in a rat model of vascular dementia [74]. In additional, acetylcholinesterase inhibitors such as galantamine have a long-term safety and cognitive effects in the treatment of probable VaD or AD with cerebrovascular disease [75-78]. Because acetylcholine generally exerts an inhibitory effect on Ih via a cAMP signaling way [54], galantamine may have a high propensity to modulate HCN channels, which may also participate in the mechanisms of its efficacy. What's more, CaMKII increases channels surface expression through the interacting protein TRIP8b (1a-4) or reduces the HCN gene transcription via Neuronal Restrictive Silencing Factor (NRSF) in pathological conditions [54], this target may also provide interventions for the treatment of VaD.

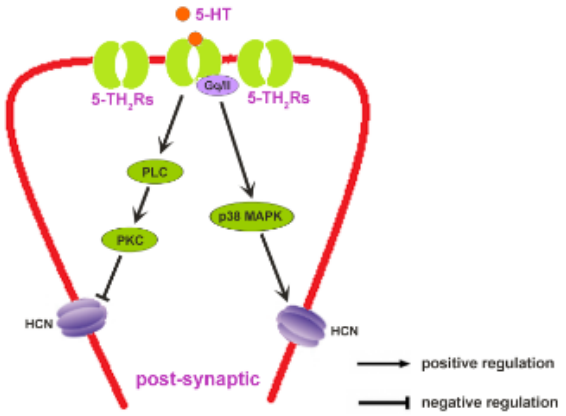

Figure 2: The modulation of HCN channels by 5-HT and related intracellular signal pathways. 5-HT binds to specific G-coupled receptors and modulates the activity of HCN channels via the PLC-PKC or p38-MAPK signaling pathways. Activation of PKC suppresses the activation of HCN channels and diminishes HCN surface expression, whereas p38-MAPK causes a positive shift of HCN channels voltage-dependent activation.

Furthermore, based on the fact that vascular dementia is a progressive disease, it seems that clarifying mechanisms of the disease process in a temporal manner is particularly important in terms of the intervention of disease. Luo et al. [79] have detected the dynamic change of HCN1/HCN2 expression in CA1 at different stages of cognitive impairment caused by CCH. Data have showed that the altered patterns of both HCN1 and HCN2 surface expression may be implicated in the early stage (4w) of spatial learning and memory impairments. Interestingly, the long-lasting cognitive impairments caused by CCH may partially attribute to the interference of HCN2 surface expression rather than HCN1. The increased surface expression of HCN2 subunits in the later stage of CCH (8w and 12w) lead to an imbalance of HCN2/HCN1 surface expression that could alters the hippocampal network as discussed above. What's more, the increased surface expression of HCN2 subunits may constrain the cognitive performance by elevating Ih, since the increased Ih can lead to the decrease of input resistance and result in reduced synaptic summation. Therefore, HCN2 channels are more likely to be a novel therapeutic target for cognitive dysfunction in the progress of VaD.

In the present, the treatment of VaD is limited to control vascular risk factors and there are no existing FDA approved treatment options for VaD. Thus, finding out effective treatments would be beneficial and imperative. The disorder of surface HCN subunits expression can cause cognitive defects under CCH condition, at least in rodents, that may be involved in the pathological process of VaD. Therefore, the potential compounds act on surface HCN subunits, especially can down-regulate HCN2 surface expression in the progress of VaD, would be a promising therapeutic strategy for the disease. What's more, compounds can regulate the accessory protein (such as TRIP8b) or protein kinases (such as PKC and p38-MAPK) may also have great potential to develop into effective drugs. However, there are also some crucial points should be considered. The subtype specificity has not yet

been achieved in a satisfactory manner that the most important goal in the development of drugs targeting HCN channels will be the design of subtype-specific compounds probably. For the same reasons, it will be necessary to search for compounds that are selective for heteromeric/homomeric channels. In additional, the compounds acting on intracellular molecules then regulate HCN channels requires a good penetration through the plasma membrane. And intracellular molecules affect the function of HCN ion channels may also have multiple biological effects to other effector proteins, which will generate adverse effects in treatment. Therefore, drug developing should avoid these inadequacies. The consideration of these points is likely to yield a better understanding of HCN channels' potential role as a promising target and perhaps result in better therapies.

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