Loss of HCN channel mediated $I_h$ current following seizures accounts for movement dysfunction

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Hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channel mutations are linked to disorders characterized by the occurrence of recurrent seizures (epilepsies) and HCN channel dysfunction has also been observed following evoked seizures in otherwise typical brains.\textsuperscript{1,2} Whether HCN channels contribute to the behavioral co-morbidities associated with epilepsy has received limited attention, despite extensive work to show that they serve as key regulators of neuronal excitability. A recent article,\textsuperscript{3} co-authored by us, provides evidence that experimental seizures disrupt HCN channel function and that this type of disruption leads to long-term impairments in skilled motor behavior. Given that interictal motor impairments are observed following experimental seizures\textsuperscript{4} and clinical epilepsy,\textsuperscript{5} this new study suggests an intriguing possibility that HCN channels represent a novel therapeutic target to treat co-morbidities of this disorder.

HCN channels provide a diverse set of contributions to brain excitability. At the level of individual neurons, the current mediated by HCN channels, referred to by many names including $I_h$, affects integration of synaptic input as well as patterns of action potential firing.\textsuperscript{6-7} It has previously been shown that HCN channels serve as a mechanism to restrict spatial firing fields within entorhinal cortex.\textsuperscript{6} HCN channels also restrict hippocampal-dependent spatial memory.\textsuperscript{7} In our recent work,\textsuperscript{3} we sought to examine the role of HCN channels for networks located in motor cortex. The study manipulated HCN channels using 3 separate approaches. Repeated experimental seizures were used as they reduce $I_h$ in layer 5 pyramidal cells that make up the cortical spinal tract. The pharmacological blocker ZD7288 was locally applied within motor cortex and global HCN1 knockout (HCN1\textsuperscript{KO}) mice were used as a genetic strategy. In order to examine network function of motor cortex, in vivo studies were performed using standard intracortical microstimulation (ICMS) to systematically measure evoked forelimb movement responses across sites within neocortex.

With short-train ICMS parameters, stimulation at individual sites within motor cortex predominantly results in responses on the contralateral side of the body that are characterized by simple flexion or extension across a single joint. With repeated seizures there was a substantial increase in the number of stimulation sites that exhibited complex forelimb movement responses rather than the simple flexion or extension movements.\textsuperscript{3} These new complex forelimb responses occurred as combinations of simple movement responses and were present contralateral to stimulation and often bilaterally. This result was also seen after direct application of ZD7228 and in HCN1\textsuperscript{KO} mice. Additionally, no further change in ICMS responses occurred when the effects of ZD7228 were tested in HCN1\textsuperscript{KO} mice. Since experimental seizures had previously been shown to impair skilled motor behavior,\textsuperscript{4} additional experiments tested whether genetic or pharmacological manipulation of HCN channels also affected skilled motor behavior in awake behaving rodents.\textsuperscript{3} HCN1\textsuperscript{KO} mice exhibited decreased performance and atypical movements on a skilled forelimb-reaching task. Na\textsuperscript{i}ve rats given local...
infusion of ZD7288 within motor cortex also displayed decreased performance and abnormal movements on the same behavioral task. Collectively, these data were interpreted as evidence that HCN channels typically segregate overlapping patterns of neocortical motor output and contribute to skilled motor behavior.

Future studies on HCN channels need to address several questions if they are to be a target for treating behavioral comorbidities in epilepsy. We need to fully understand the mechanisms of HCN channel dysfunction following seizures. For instance, like many ion channels, the diversity of protein subunits, heteromeric nature of their protein complexes, auxiliary regulatory proteins, splice variants as well as cell-type and sub-cellular localization of HCN channels all need to be addressed following repeated seizures relative to normal function. Studies also need to continue to identify candidate intracellular regulatory signaling pathways that may reverse seizure-induced disruptions in HCN channels. The effects of altering these signaling pathways on the aforementioned properties of HCN channels will have to be tested. An additional consideration is how experience-dependent rehabilitation interacts with neocortical HCN channels in normal states and following seizures. Viral gene transduction could also be useful for proof of principle studies to see how exogenous replacement of these channels affects altered neural systems and behavior.

There is sparse clinical data for how seizures affect neocortical HCN channels and motor cortex. In one study, a subset of individuals undergoing surgery to treat perirolandic epilepsy exhibited increased overlap of movement representations. This increase in overlap of representations may be similar to the complex multiple movement responses observed by the present authors. This work raises the possibility that HCN channel dysfunction is present in individuals that live with epilepsy and that evoked motor responses may be a diagnostic tool to test for this phenomenon. Broadly, this new work highlights HCN channels as potential therapeutic targets to treat motor disturbances that arise from epilepsy.

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