

H-CHANNELS AS A THERAPEUTIC TARGET IN EPILEPSY

Pharmacological Upregulation of H-channels Reduces the Excitability of Pyramidal Neuron Dendrites

Poolos NP, Migliore M, Johnston D
Nat Neurosci 2002;5(8):767-774

The dendrites of pyramidal neurons have markedly different electrical properties from those of the soma, owing to the nonuniform distribution of voltage-gated ion channels in dendrites. It is thus possible that drugs acting on ion channels might preferentially alter dendritic, but not somatic, excitability. By using dendritic and somatic whole-cell and cell-attached recordings in rat hippocampal slices, we found that the anticonvulsant lamotrigine selectively reduced action-potential firing from dendritic depolarization, while minimally affecting firing at the soma. This regional and input-specific effect resulted from an increase in the hyperpolarization-activated cation current (I_h), a voltage-gated current present predominantly in dendrites. These results demonstrate that neuronal excitability can be altered by drugs acting selectively on dendrites, and suggest an important role for I_h in controlling dendritic excitability and epileptogenesis.

Gabapentin Increases the Hyperpolarization-activated Cation Current I_h in rat CA1 pyramidal cells.

Surges R, Freiman TM, Feuerstein TJ
Epilepsia 2003;44(2):150-156

PURPOSE: Gabapentin (GBP) is a commonly used drug in the treatment of partial seizures, but its mode of action is still unclear. The genesis of seizures in temporal lobe epilepsy is thought to be crucially influenced by intrinsic membrane properties. Because the I_h substantially contributes to the intrinsic membrane properties of neurons, the effects of GBP on the I_h were investigated in CA1 pyramidal cells of rat hippocampus.

METHODS: CA1 pyramidal cells in hippocampal slices were examined by using the whole-cell patch-clamp technique.

RESULTS: GBP increased the I_h amplitude in a concentration-dependent manner mainly by increasing the conductance, without significant changes in the activation properties or in the time course of I_h . The effects ranged from 20% at 50 μM , 25% at 75 μM , to 35% at 100 μM GBP (at -110 mV). In the presence of intracellular cyclic adenosine monophosphate (cAMP), the effects of GBP on I_h were similar to those obtained in the absence of cAMP.

CONCLUSIONS: These results suggest that GBP increases the I_h through a cAMP-independent mechanism. Because the applied GBP concentrations were in a clinically relevant range, the observed effect may contribute to the anticonvulsant action of GBP in partial seizures and may represent a new concept of how this anticonvulsant drug works.

COMMENTARY

H-current is a depolarizing, noninactivating cationic current that is activated by hyperpolarization. In neurons, it frequently functions as a pacemaker current, triggering a depolarizing ramp after hyperpolarizing events, such as inhibitory postsynaptic potentials. Although the H-current is a major regulator of neuronal excitability, it has not typically been viewed as a candidate therapeutic target for anticonvulsant drugs, which, undoubtedly, is because of the very recent recognition of the significant role of this ion channel in neurons. This lack of attention to a therapeutic role is certain to change after a series of recent publications that have characterized the effects of various anticonvulsants on H-current conductance and demonstrated plastic changes in the properties of H-current in animal models of epilepsy.

By using patch-clamp recordings in the dendrites and soma of hippocampal CA1 pyramidal neurons, Poolos et al. found that the anticonvulsant lamotrigine selectively reduced depolarization-induced action potential firing in dendrites. The authors also showed that, in these neurons, H-current is present predominantly in the dendrites, and further, that the impact

of lamotrigine on action-potential firing was due to selective augmentation of the conductance. This increase in H-current conductance was caused by a drug-induced shift in the voltage dependence of activation of H-current to more depolarized levels closer to the neuronal resting potential. This study is the first to demonstrate an anticonvulsant targeting H-current. Clearly, this mechanism could be important to the regulation of dendritic excitability in hippocampal neurons, thereby reducing seizures. An additional, obvious implication of these findings is that H-current may be a useful target for future antiepileptic drug (AED) development.

Further support for the concept that H-current may be a viable target for AEDs resulted from a second publication in which Surges et al. demonstrated that another AED, gabapentin, also augmented H-current in CA1 pyramidal neurons when applied at clinically relevant concentrations (i.e., concentrations achieved as free serum levels in patients). The effect was mechanistically distinct from the activation curve shift described by Poolos et al. because gabapentin augmented H-current by increasing the conductance of these channels, with no effects on the voltage dependence of activation. Although other cellular effects of gabapentin have been described, its actions on H-current are most clearly related to a possible antiepileptic action.

A final piece of the puzzle supporting the idea that H-currents may be important new targets for therapeutic intervention for epilepsy came from a series of studies that examined H-current regulation in animal models of epilepsy. H-current is augmented in a number of animal models of epilepsy and hyperexcitability, including a rat febrile seizure model and the stargazer epileptic mouse mutant. A recently published review by Chen et al. summarizes these data (1). Thus, H-current not only may serve as a drug target, but it also may play a role in the underlying disease process of epilepsy.

Clearly, a new concept is beginning to emerge concerning the potential role of H-current as a therapeutic target and

player in the development of epilepsy. However, the picture is complex. H-current alone is incapable of generating activity. It acts in concert with other regenerative conductances within neurons, and the relative ensemble of such conductances varies in a cell- and region-specific manner in the brain. Blocking H-current in some areas of the brain (such as thalamus) (2,3) may have a net anticonvulsant effect, whereas augmenting H-current in other areas (such as hippocampus) may decrease excitability. Further complexities derive from potential interactions between mechanisms determining the underlying disease process of epilepsy. For example, in the febrile seizure model of epilepsy, an augmented H-current in hippocampal CA1 neurons is evident concurrent with enhanced γ -aminobutyric acid (GABA)ergic inhibition (reviewed in Chen et al.). This interactive combination of events serves to synchronize activity powerfully in this region, contributing to hyperexcitability.

Therefore the relative efficacy of H-current modulators in blocking seizure activity may vary, depending on the area of the brain that is generating the seizures and on the underlying epileptogenic mechanisms in a given animal model or patient population. Resolving these issues will be a necessary component in drug-development efforts that target this promising, novel ion channel regulating seizures.

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References

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