

A TIME TO CONVULSE, A TIME TO STOP

Age-dependent Modulation of Hippocampal Excitability by KCNQ Channels

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Recently, mutations of KCNQ2 or KCNQ3, members of the KCNQ-related K⁺-channel (KCNQ-channel) family, were identified as cause of benign familial neonatal convulsions (BFNCs). However, the exact pathogenic mechanisms of age-dependent development and spontaneous remission of BFNCs remain to be elucidated. To clarify the age-dependent etiology of BFNCs, we determined age-dependent functional switching of KCNQ channels, γ -aminobutyric acid (GABA)ergic, and glutamatergic transmission in rat hippocampus. The effects of inhibitors of KCNQ channel, GABA, and glutamate receptors on propagation of neuronal excitability and neurotransmitter release were determined by 64-channel multielectrode-dish (MED64), whole-cell recording, in vitro release technique, and in vivo microdialysis biosensor, with rat hippocampus from the day of birth (P0) to postnatal day 56 (P56). Inhibition of KCNQ channels enhanced depolarization-induced glutamate and GABA releases during P0-P7, but not during P14-P28. Inhibition of KCNQ channels magnified neuronal excitability propagation from P0 to P14 (maximal at P3), but this effect disappeared by P28. GABA_A-receptor inhibition surprisingly reduced neuronal excitability propagation during P0-P3, but not at P7. α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/glutamate-receptors inhibition reduced propagation of neuronal excitability throughout the study period. KCNQ-channel inhibition shortened spike-frequency adaptation, but this stimulation was more predominant during P < 7 than P > 14. During the first week of life, KCNQ channels performed as a predominantly inhibitory system, whereas after this period, GABAergic transmission switched from an excitatory to an inhibitory function. Conversely, glutamatergic transmission has acquired as excitatory

function from P0. These findings suggest that the pathogenic mechanisms of age-dependent development and spontaneous remission of BFNCs are, at least partially, associated with the interaction between age-dependent reduction of inhibitory KCNQ-channel activity and age-dependent functional switching of the GABAergic system from excitatory to inhibitory action in neonatal CNS.

COMMENTARY

In recent years, our understanding of the etiology of many idiopathic epilepsy syndromes has made a quantum leap since the initial discovery of the mutation in the gene coding for the α -4 subunit of the nicotinic acetyl choline receptor in a kindred with autosomal dominant nocturnal frontal lobe epilepsy (1). Subsequent discoveries of ion-channel mutations associated with idiopathic epilepsies involved several syndromes such as benign familial neonatal convulsions and febrile convulsion syndromes that have an age-dependent phenotypic expression. We intuitively understood that the age-specific appearance and remission of such syndromes had to have their basis in age-specific expression of the ion channels involved, and possible development-specific appearance of channels that may compensate for the mutations that result in a loss of function of the involved channel.

Okada et al. approached this problem by studying the effect of specific inhibitors of the potassium channels, KCNQ channels that have been implicated in benign familial neonatal convulsions, and inhibitors of γ -aminobutyric acid (GABA)ergic and glutamatergic receptors on rat hippocampal slices obtained from the day of birth (P0) to postnatal day 56 (P56). By using a 64-channel multielectrode system, they were able to study fiber volley (FV), field excitatory postsynaptic potentials (fEPSPs), and population spikes (PSs) evoked by stimulation of the Schaffer collateral path (the CA3 axon collateral that synapses with the CA1 neurons) after application of specific antagonists. Dup996, a specific antagonist of the KCNQ channels, magnified the propagation of FVs and fEPSPs during P0-P14, and it disappeared completely by P28. Bicuculline, an inhibitor of GABA_A receptors, reduced the amplitude of FV, fEPSPs, and PSs, as well as reduced the propagation of FVs and fEPSPs

during P0–P3, but not at P7. From P14 to P28, it demonstrated the expected enhancement of amplitude of FVs, fEPSPs, and PSs, and enhanced the propagation of FVs and fEPSPs. These data recall the work of Cherubini et al. (2), who demonstrated that most of the “excitatory” drive in immature neurons is mediated by GABA acting on GABA_A receptors. This function is taken over by the AMPA system with maturation. But how is inhibition achieved in the immature hippocampus? The data from Okada et al. suggest that it is during this period when GABA is excitatory that the potassium currents mediated by the KCNQ channels play a crucial role. They confirm the role of KCNQ channels by showing spike-frequency adaptation (SFA) in CA1 neurons in the presence of Dup996. Within the first week of life, this inhibitor of KCNQ channels shortened SFA and increased the number of spikes much more prominently than in slices from animals that were P > 14.

The work of Okada et al. is an elegant demonstration of how the ontogeny of GABAergic inhibition related to the age-related functional switching of the GABAergic system interacts with the KCNQ channels in a manner consistent with the age-dependent appearance of neonatal convulsions and their remission in the syndrome of BFNCs.

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References

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