Alterations in hyperpolarization-activated cyclic nucleotide-gated cation channel (HCN) expression in the hippocampus following pilocarpine-induced status epilepticus

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INTRODUCTION

Temporal lobe epilepsy (TLE), such as spontaneous seizure involving the hippocampal formation, is the most prevalent form of refractory epilepsy, and the mechanisms converting the normal hippocampus into an epileptic one are not fully understood. In laboratory rodents, status epilepticus (SE)-inducing insults such as continuous perforant path stimulation and administration of pilocarpine have been shown to produce a condition with spontaneous limbic seizures and hippocampal sclerosis (1). Numerous previous studies have focused on the neurodegeneration of the hippocampus in TLE rodent animal models, including pilocarpine-induced SE, since specific patterns of neuronal loss occur in both principal neurons and interneurons (2-5).

On the other hand, hyperpolarization-activated cyclic nucleotide-gate cation channel (HCN) is found in a variety of peripheral and central neurons (6, 7). HCNs mediate hyperpolarization-activated cation currents ($I_h$) in the heart and brain (6, 7). In the mature hippocampus, HCN is expressed in pyramidal and nonpyramidal neurons (8, 9) where it contributes to the resting membrane potential, hyperpolarizing events and rebound excitation (7, 10, 11), thus regulating rhythmic electrical activity. Therefore, HCN plays an important role in regulating rhythmic electrical activity, and the abnormality of its function or expression is linked to pathological hyperexcitability (12).

RESULTS AND DISCUSSION

HCN1 immunoreactivity in the epileptic hippocampus

As shown in Fig. 1 and 2, HCN1 immunoreactivity was selectively detected in the stratum lacunosum-moleculare, some hilar neurons and CA2-3 pyramidal cells (Fig. 1A1-A4). However, an elevation in HCN1 immunoreactivity in all the hippocampal formation compared to the control was observed at 30 min following SE (Fig. 1B2, B3, and B4, 2A). Interestingly, at 12 hrs after pilocarpine treatment, HCN1 immunoreactivities were strongly enhanced throughout the hippocampus, particularly the somata and dendritic processes of the presumed interneurons, nerve fibers of CA1-3, and dentate hilar neurons (Fig. 1C1-C4, 2A, and 2B), but its immunoreactivity was un-changed in the granule cell layer of the dentate gyrus following the time course after SE (Fig. 2B). Moreover, HCN1 immunoreactivity in stratum lacuno-
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Fig. 1. The HCN1 expressions in the hippocampus following pilocarpine-induced SE. HCN1 immunoreactivity is selectively detected in the stratum lacunosum-molecular and some hilar neurons (arrows in panel A1 and A4). However, HCN1 immunoreactivities at 30 min-12 hrs following SE are significantly enhanced in CA1-3 and the stratum lacunosum-molecule (B1-B3 and C1-C3). In addition, HCN1-positive interneurons and hilar neurons are increased (arrows and open arrows in panel B2, B4, C2, and C4). Nevertheless, at 2 weeks following SE, HCN1 immunoreactivities are down-regulated to levels similar to the control (D1-D4). Bar = 280 μm (panels A1, B1, C1, D1, and E1), 50 μm (panels A2-A4, B2-B4, C2-C4, D2-D4, and E2-E4).

Fig. 2. Quantitative analyses of HCN1 immunoreactive interneurons (A) and immunodensity (B) in normal and epileptic hippocampi following pilocarpine-induced SE (mean ± S.E.M). Significant differences from the control group, *P < 0.05, **P < 0.01.