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Original Article

ERG Channels Contribute to the Excitability of Pyramidal Neurons in Hippocampal CA1

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ABSTRACT

Objective: Ether-a-go-go-related genes (ERG; Kv11) include three different erg channels, namely, Kv11.1, Kv11.2, and Kv11.3 or ERG1, ERG2, and ERG3. The aim of this study is to investigate the effects of ERG channel blockers on the biophysical properties of pyramidal cells in the hippocampus CA1 area.

Methods: The characterization of ERG currents was obtained using the whole cell configuration of the patch clamp technique. In the current clamp, we used selective ERG channel blockers (E-4031 (10 μM), dofetilide (1 μM), ergtoxin (200 nM), and terfenadine (10 μM)), which significantly incremented the input resistance of the pyramidal neurons ($P < .05$). All other ERG channel blockers except dofetilide have significantly increased neuronal excitability of hippocampal CA1 pyramidal neurons ($P < .05$). They also increased the action potential (AP) firing rate of cells in response to a square current pulse ($P < .05$).

Results: In the voltage clamp, the biophysical characteristic of ERG channels was determined by the measurement of tail currents. The E-4031-isolated current was observed at nearly −65 mV. The voltage-depended activation and inactivation curve of ERG channels was fitted with Boltzmann function, resulting in the $V_{1/2}$ value of −48.95 mV, the slope factor of 4.54 mV and the $V_{1/2}$ value of −77.35 mV, the slope factor of 10.58 mV, respectively. The exponential function is used to determine deactivation kinetics of ERG channels. It was observed that the rate of deactivation increased when the membrane potential was more hyperpolarized.

Conclusion: In conclusion, both current and voltage clamp studies showed that ERG channels contribute to the modulation of excitability and frequency of AP in pyramidal neurons of the hippocampus in mice.

Keywords: ERG channels, excitability, hippocampus, neurophysiology, electrophysiology

INTRODUCTION

The "ether-a-go-go-related gene" (ERG) potassium channels were first discovered in drosophila.[1] Despite that it has been studied in many tissues, the physiological roles of ERG channels are best demonstrated in cardiac myocytes cells. In these cells, ERG currents contribute to repolarization phase of the AP and the plateau formation.[2] Moreover, ERG channels are studied in neuronal cells, including medial vestibular nuclei neurons,[3] medial nucleus of the trapezoid body,[4] cerebellar Purkinje neurons,[5] and cochlear nucleus neurons.[6]

ERG channels are known to have unusual biophysical properties. Due to the structural properties of these channels, the inactivation kinetics are much faster than the activation kinetics so that the greatest conductance occurs during repolarization.[4] Furthermore, one of the reasons for the inactivation kinetics to be faster than activation in the ERG channels is that the selectivity filter is formed by the carbonyl atoms of the GFG sequence. Most of the other voltage-gated potassium channels are formed by carbonyl atoms of the GYG sequence.[7,8] ERG channels have a role as strong inward rectifiers that conduct outward currents in hyperpolarized membrane potentials. However, unlike conventional inward rectifier channels, they must be initially stimulated to be activated by depolarization,[9] whereas the voltage-gated Kv channels are typically activated by depolarization of the membrane.[10,11]

The hippocampus is a highly complex structure that is responsible for consolidating memory in the human brain. The dendrites of pyramidal neurons have many voltage-gated ion channels, some of which are present at very high concentrations.[12] Also in the hippocampus, it is one of the most stained structures by anti-ERG antibodies. One of the densely stained cell types is pyramidal cells located in the CA1 and CA3 regions.[13] While ERG2 channels are reported not to be expressed in pyramidal neurons in the hippocampus, ERG1 and ERG3 channels are reported to be expressed extensively.[14,15] While ERG channel expressions are heavily labeled in the hippocampus area, there are little data on the properties of biophysical currents. In the present study, we investigated the biophysical properties of ERG channels in the pyramidal neurons and their contribution to passive and active membrane properties such as resting membrane potential, input resistance, number of AP, and excitability.

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METHODS

Preparation of Hippocampal Slices

Hippocampal slices were prepared from BALB/c strain mice. Animals were treated in compliance with the guidelines of Gaziantep University Animal Experiments Local Ethics Committee. We have started experiments after obtaining ethical approval from Gaziantep University Local Animal Use Committee (Gaziantep, Turkey; approval date and number: June 25, 2017/39). Immediately after decapitation, the head of the animal was submersed and oxygenated with artificial cerebrospinal fluid (aCSF), and then the brain was quickly removed from the head. After removal, the hippocampus was placed on the teflon block through the superglue. Slices of the hippocampus were cut at a thickness of 300-350 μm using a vibratome (Frederick Haer and Co, Newbrunswick, ME, Canada). The slices were transferred to the recording chamber for recording. In the recording chamber, the slices were perfused with aCSF at a rate of 4 mL/min, and the temperature of the aCSF was kept at constant of 33°C with a feedback-controlled heater (Warner Instruments, Hamden, CT, USA).[16–21]

Solutions and Chemicals

The pipette solution is composed of 110 mM of potassium gluconate, 14 mM of phosphocreatine (Tris salt), 4.5 mM of $MgCl_2$, 9 mM of EGTA, 9 mM of HEPES, 4 mM of ATP (Na-salt), and 0.3 mM of GTP (tris salt). pH of the pipette solution was adjusted to 7.4 with KOH.[6]

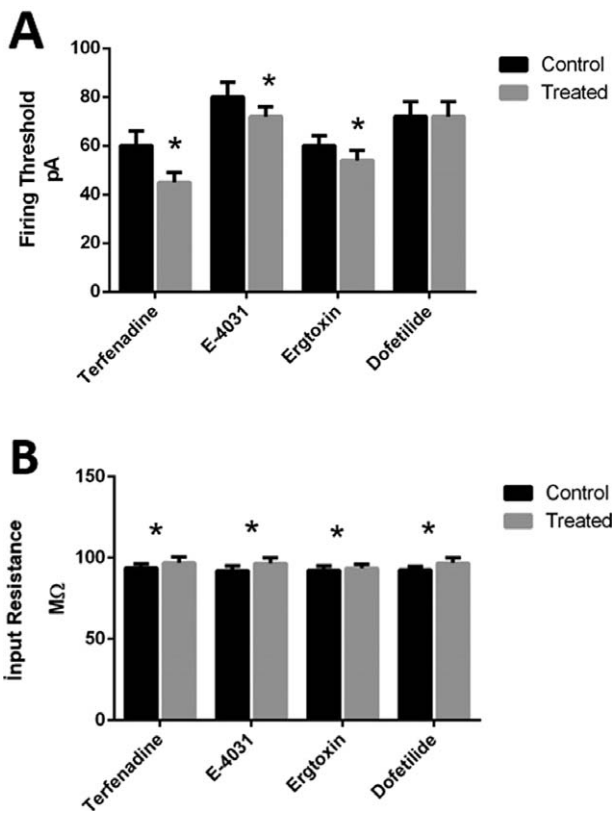
Two different extracellular perfusion solutions were used in this study. The aCSF was used as the extracellular solution, which contains 138 mM of NaCl (Merck), 10 mM of HEPES (Merck), 10 mM of glucose (Merck), 4.2 mM of KCl (Merck), 2.4 mM of $CaCl_2$ (Merck), and 1.3 mM of $MgSO_4$ (Sigma Aldrich). pH of the solution was adjusted to 7.40 using NaOH.[23]

To isolate ERG currents in voltage clamp experiments, we used "high potassium-containing aCSF." To make the amplitude of the ERG channel currents more visible, the K^+ concentration of the solution was increased to 40 mM.[5] Also, this solution was prepared as calcium free to avoid the activation of Ca^{2+}-dependent K^+ channels. To keep the osmolarity of the solution constant at 295-305 mOsm/L, the NaCl concentration in the solution was reduced. Thus, "high potassium aCSF" was prepared with the following constituents: 102 mM of NaCl, 40 mM of KCl, 10 mM of glucose, 10 mM of HEPES, and 3.7 mM of $MgSO_4$.

Main Points

- In this study, the characterization of ERG channels was performed using the parch clamp technique.
- ERG channel antagonists were found to increase excitability in pyramidal neurons in the CA1 region.
- Biophysical properties of ERG channels were determined by voltage clamp studies.
- As a result, it was determined that ERG channels contribute to cell excitability in pyramidal neurons in the CA1 region.

Figure 1. (A) When ERG channel blockers were applied to the pyramidal neurons, they easily stimulate according to their control situations (except dofetilide). The application of dofetilide did not change cell excitability. (B) All the ERG channel blockers increased the input resistances of the cells as statistically significant (*$P < .05$).



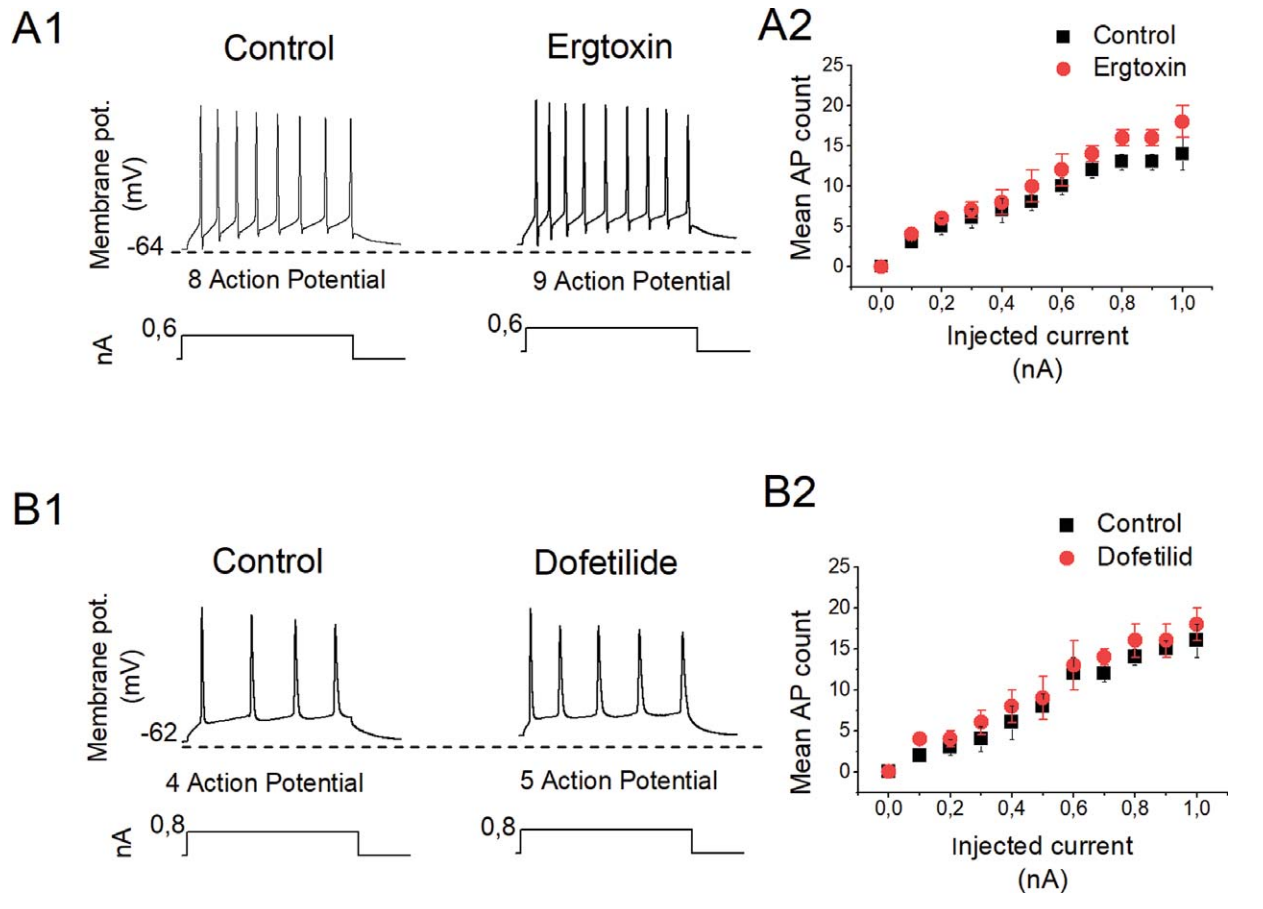
To inhibit the ERG channel in the current clamp experiments, ergtoxin (200 nM; Alemon lab, Israel), E-4031 (10 μM; Alemon Lab, Israel), terfenadine (10 μM; Sigma Aldrich), and dofetilide (1 μM; Alemon Lab, Israel) were used. DMSO was used to dissolve E-4031 and terfenadine. The final concentration of DMSO never exceeded 0.1%. In the voltage clamp studies, 10 μM of E-4031 1-[2-(6-methyl-2-pyridyl) ethyl]-4-(4-methylsulfonylaminobenzoyl) piperidine (Alemon Lab, Israel) was used to isolate the E-4031 isolated current.

To prevent synaptic activity, synaptic blockers were added to aCSF. A 10 μM APV-5, 5 μM DNQX, and 1 μM strychnine were added to block glutamatergic NMDA, AMPA, and glycinergic receptors, respectively. A 1 μM tetrodotoxin (Alexis Biochemicals, USA) was added to block voltage-dependent sodium channels; 1 mM CsCl was added to block mixed cation channels; and 1 mM tetraethylammonium (Fluka) and 1 mM 4-aminopyridine (4-AP) (Sigma Aldrich) were added to inhibit delayed rectifier K^+ current and transient outward K^+ current, respectively.[6]

Table 1. Passive and Active Membrane Properties of CA1 Pyramidal Neurons

Input resistance (MΩ) (mean ± SE)	Capacitance (pF) (mean ± SE)	Resting membrane potential (mV) (mean ± SE)	Time constant (ms) (mean ± SE)	AP amplitude (mV) (mean ± SE)
84.6 ± 4.7 (n = 80)	-63.7 ± 2.4 (n = 80)	-64.4 ± 3.4 (n = 80)	22.6 ± 3.8 (n = 80)	74 ± 6.2 (n = 80)

Figure 2. Effect of ERG channel blockers, (A1) ergtoxin, (B1) dofetilide, on the number of APs induced by square current pulses of 150 ms in pyramidal neurons. (A1) Application of ergtoxin increased the number of APs induced from 8 to 9 at the given current amplitude. (B1) Application of dofetilide increased the number of APs from 4 to 5. (C1) Application of ergtoxin increased the number of APs from 8 to 9. (D1) Application of dofetilide increased the number of APs from 4 to 5. (A2 and B2) The increase in the number of APs upon the application of ergtoxin (1 μM) and dofetilide (10 μM) was plotted as a function of varying current amplitudes, respectively.

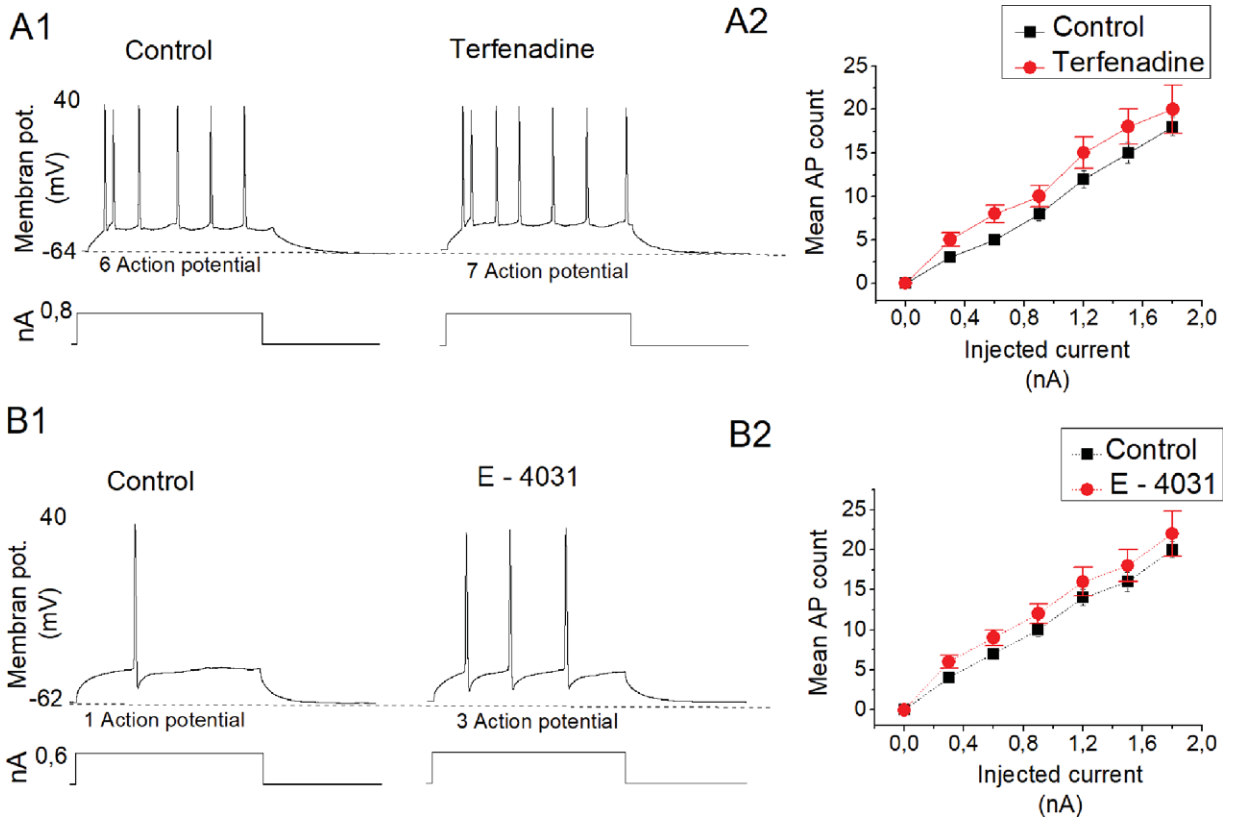


Intracellular Recordings and Data Acquisition

Intracellular recordings were obtained with the whole-cell configuration using the patch clamp technique. Patch pipettes were obtained using borosilicate glass capillaries (GC150F-10, Harvard Apparatus; Flaming/Brown micropipette puller, Model P-97, Sutter Instrument). We only used pipettes with a resistance between 5 and 7 MΩ. Series resistance ranges from 6 to 13 MΩ (compensated by 70%, 10 μs lag), which was between Rinput and Rinput/10. All the records were obtained by the whole-cell configuration using an Axopatch-200B amplifier, and then transferred to a computer equipped with an A/D converter and the Digidata 1440 series (Axon Instruments, Foster City, CA, USA), and the current and voltage recordings were sampled at 10–40 kHz. Data were analyzed offline. The junction potential was measured to be –12 mV, and therefore, all recordings were compensated for –12 mV.[23]

Analysis of the voltage-dependent activation, inactivation, and deactivation kinetics was performed using OriginPro 2018 (64-bit; SR1 b9.5.1.195), and the voltage-dependent steady-state

Figure 3. Effect of ERG channel blockers, (A1) terfenadine and (B1) E-4031, on the number of APs induced by square current pulses of 150 ms in pyramidal neurons. (A1) Application of terfenadine increased the number of APs induced from 6 to 7 at the given current amplitude. (B1) Application of E-4031 increased the number of APs from 1 to 3. (C1) (A2 and B2) The increase in the number of APs upon the application of terfenadine (10 μM) and E-4031 (10 μM) was plotted as a function of varying current amplitudes, respectively.



activation and inactivation curves were fitted with the Boltzmann function (equation 1):

$$I(v) = 1/(1 + \exp(V1/2 - Vm)/k) \quad (1)$$

where I(v) is the normalized current, Vm is the test potential, $V_{0.5}$ is the potential for half-maximal activation, and k is a slope factor measuring the apparent gating charge.

The exponential function is used to determine deactivation kinetics of ERG channels. To determine the rate of deactivation, the decay phase of tail currents was fit with either a single or double exponential of the forms.

Exponential function (equations 2 and 3):

$$I(t) = A \exp(t/\tau) + C \quad (2)$$

or

$$I(\tau) = A \text{ fast } \exp(t/\tau \text{ fast}) + A \text{ slow } \exp(t/\tau \text{slow}) + C \quad (3)$$

Equations 2 and 3 are single and double exponential functions, respectively, where τ refers to the time constant of deactivation, A is the amplitude of each component, and C is a constant.

Finally, the graphics was drawn using OriginLab (OriginPro 2018 (64-bit; SR1 b9.5.1.195) and Graph Pad Prism 8.

Statistical Evaluation of the Data

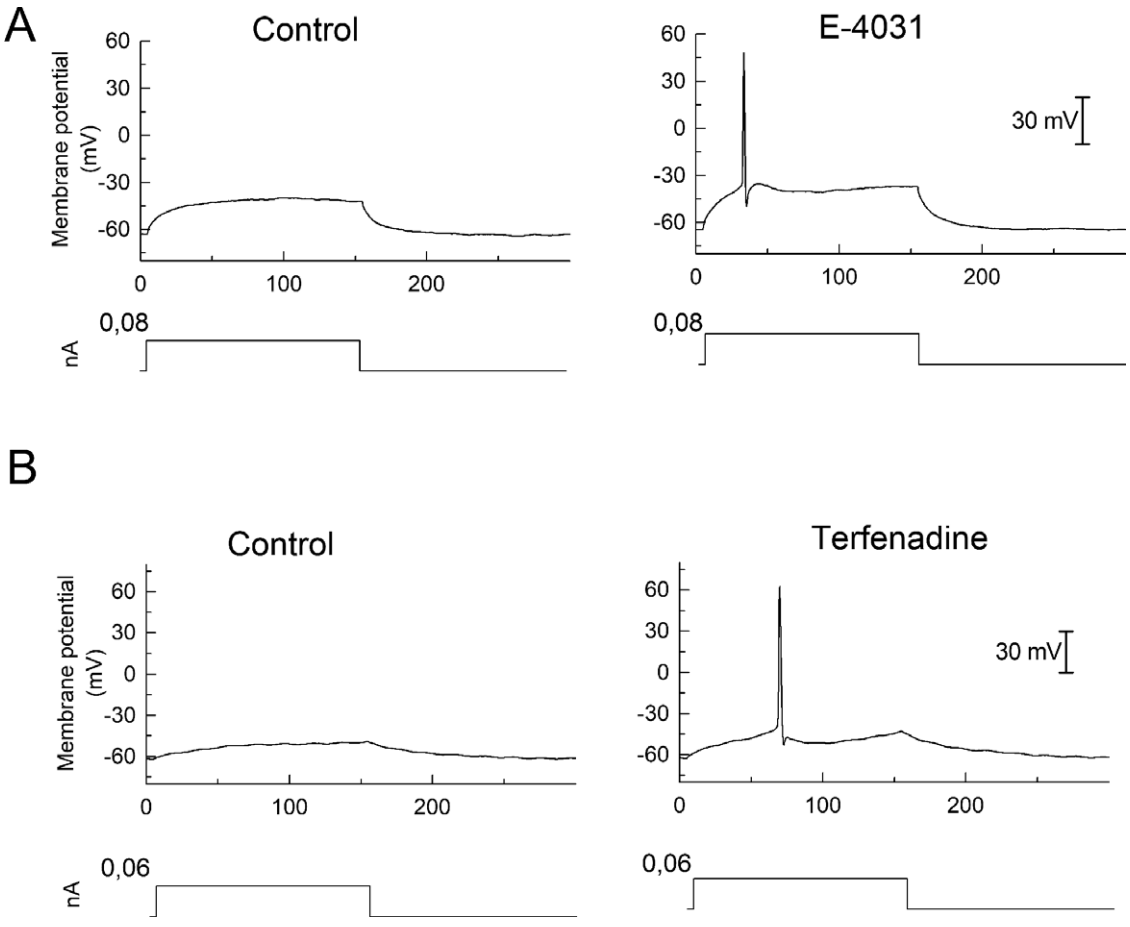
Statistical evaluation was done using the Statistical Package for Social Sciences Version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. Descriptive statistics for numerical variables are presented as mean ± S.E.M. (n = number of cells). Student t test was performed to determine the statistical difference. The threshold for the statistical significance was set at $P < .05$.

RESULTS

Current Clamp Experiments

The data presented in this study consist of electrophysiological recordings obtained from 80 pyramidal neurons in the CA1

Figure 4. Effects of terfenadine and E-4031 on excitability of pyramidal neuron. (A) While an 80-pA current did not cause the neuron to reach threshold for AP induction, the same amplitude of current (80 pA) induces APs after the application of E-4031. (B) The 60-pA current did not induce any AP, but it caused the neuron to fire APs after the application of terfenadine.



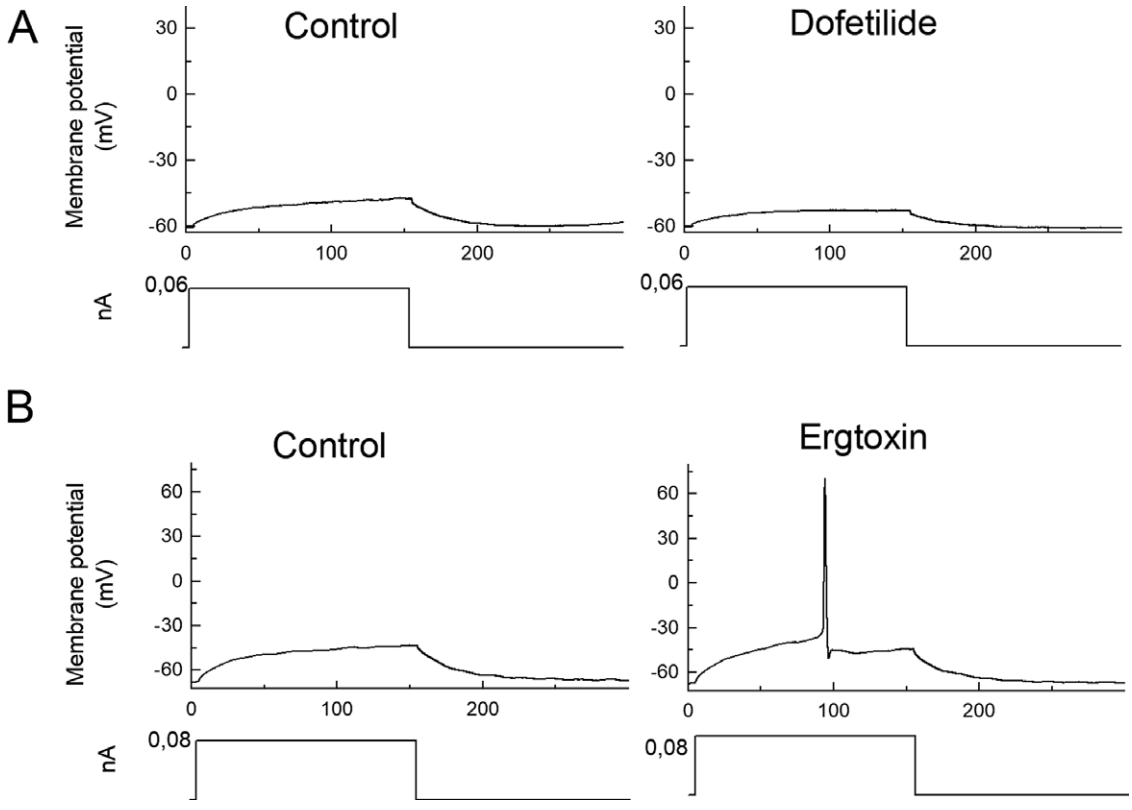
region in the hippocampus of mice. The identification of the cells was done as previously described.[25] The input resistance, capacitance, time constant, amplitude of the AP, and the resting membrane potential of the cells were measured, and these values are shown in Table 1.

ERG channels may be selectively inhibited by E-4031, dofetilide, terfenadine, and ergtoxin.[2,6] All the ERG channel blockers in pyramidal neurons caused slight depolarization of the membrane potentials. However, this effect was not significant ($P > .05$).

The application of all the ERG channel blockers increased the input resistance of pyramidal neurons (terfenadine, from 93.7 ± 2.6 MΩ to 96.9 ± 3.7 MΩ (n = 10); E-4031, from 92.1 ± 2.8 MΩ to 96.5 ± 3.4 MΩ (n = 10); dofetilide, from 92.4 ± 2.4 MΩ to 96.8 ± 3.1 MΩ (n = 10); and ergtoxin, from 92.2 ± 2.8 MΩ to 93.6 ± 1.4 MΩ (n = 10)). The increase in the input resistance was found to be significant in all the cases ($P < .05$) (Figure 1B).

The application of ERG channel blockers increased the number of APs in cells induced by the injection of square current pulses (Figures 2 and 3). The application of terfenadine increased the number of APs induced by square current pulses in every cell tested. The number of APs was plotted as a function of current amplitude injected in Figures 2 and 3. However, the amplitude of the threshold current for the induction of AP in different pyramidal cells tested varied too much. For example, a current amplitude of 0.6 nA was not large enough for one neuron to fire an AP, whereas the same current amplitude was enough to fire 10 APs for another neuron. Therefore, the error bars of the mean values increased due to large variations in the responses of neurons to currents injected, and statistical significance did not appear in the relationship as shown in Figure A2. For that reason, the statistical comparisons before and after the blockers were based on the recordings of 6-7 AP during 150 ms current pulses, for which different current amplitudes were required in different neurons. The application of ergtoxin (1 μM), dofetilide (10 μM), terfenadine (10 μM), and E-4031 (10 μM) increased the number of APs by 21.6 ± 6.48% (n = 8), 16 ± 3.48% (n = 10), 18.6 ± 6.48% (n = 10), and 12 ± 1.48% (n = 10), respectively.

Figure 5. Effects of dofetilide and ergtoxin on excitability of pyramidal neuron. (A) Dofetilide did not reduce the inhibitory effect of ERG channels on cell excitability and did not affect cell excitability. (B) While an 80-pA square current pulse did not cause the neuron to reach threshold for AP induction, the same amplitude of square current pulse (80 pA) induces APs after the application of ergtoxin.



ERG channel blockers are known to increase the excitability of cells. It was tested whether these blockers showed the same effect in pyramidal cells. For example, when a 60 pA current was injected to the cell, the cell did not fire APs, but when the ERG channel blockers were applied to the cell, it was observed that the cells fired the APs at the same current injection. It should be noted that because of the different size, dendritic branching and synaptic input numbers of the pyramidal cells, in order to fire the AP, the amplitudes of the currents to reach the threshold to the cells were different. All other ERG channel blockers except dofetilide significantly increased the excitability of the cells ($P < .05$). When the ERG currents in the cells were blocked according to the control situations, it was seen that they reached their threshold value more easily for firing (Figure 4 and Figure 5).

Voltage Clamp Experiments

Voltage dependence activation

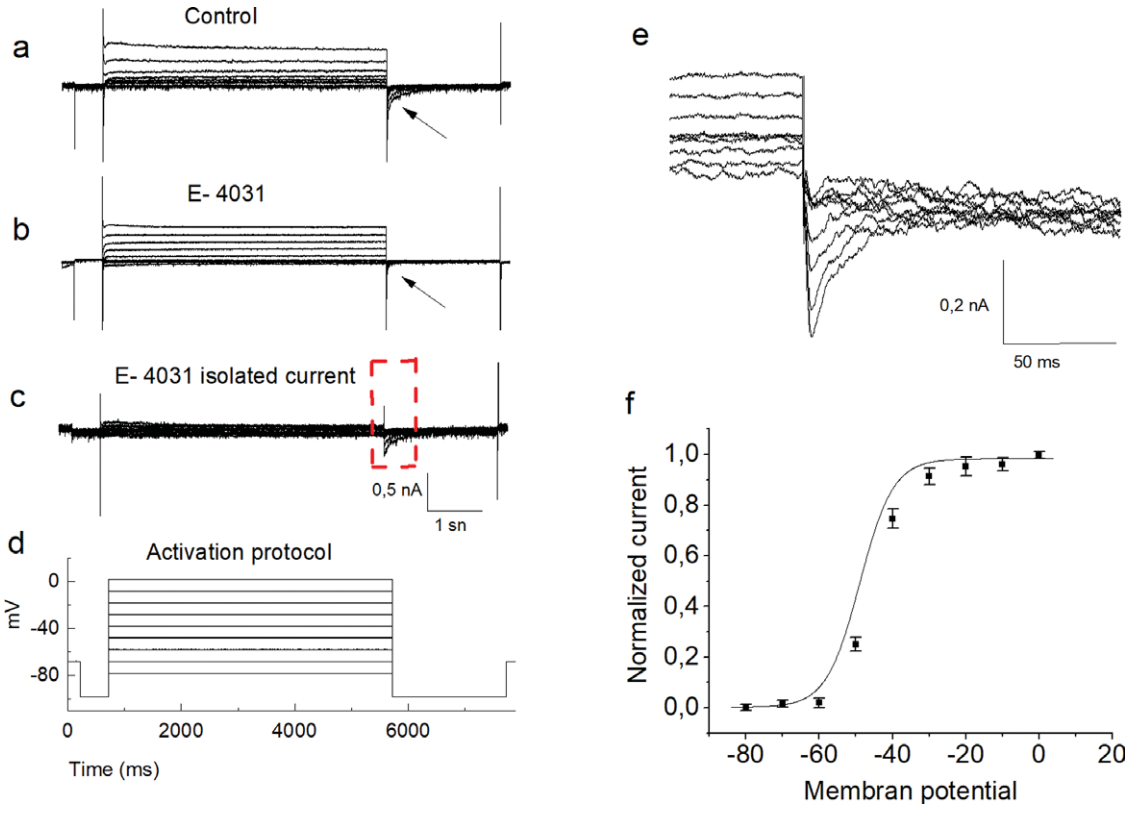
In voltage clamp studies, tail currents were obtained using a voltage protocol given in Figure 6D. According to this protocol, the holding potential of neurons was adjusted to –70 mV after that the membrane potential was stepped to a range of potential from –120 mV to 0 mV in 10 mV increments for 5 seconds and then step to –110 mV. The tail currents were observed at around –100 mV.

The activation curve of the ERG channels was obtained by plotting the amplitude of the normalized tail currents. The E-4031 isolated current was observed at nearly –65 mV, and the amplitude of the tail current increased gradually with more depolarized membrane potential. The curve was fitted with the Boltzmann function and gave a V1/2 value of –48.95 mV and a slope factor of 4.54 mV (Figure 6).

Voltage dependence of inactivation

To study the voltage-dependent steady-state inactivation of ERG channels, the voltage was stepped to 0 mV for 4 seconds to activate ERG channels completely[25] and then was stepped to a range of potential between –120 and 0 mV in 15 mV steps for 2 seconds to allow quick recovery from inactivation (Figure 7D). It should be noted that ERG channels are expected to deactivate at membrane voltages where ERG channels are recovered from inactivation.[2,4,5,8,25,26] Therefore, the decay phase of the tail currents was thought to represent deactivation of ERG channels, which were fitted by an exponential function. The amplitudes of the tail currents were extrapolated at the

Figure 6. Voltage-dependent activation of E-4031 isolated ERG current in pyramidal neurons. The ERG current studied with the voltage protocol shown in (D). ERG currents were isolated by a pharmacological approach. After eliminating all other known ionic currents, the current traces recorded were thought to include ERG current as well as the unblocked components of the other currents and the leak currents. The application of a specific ERG channel antagonist, E-4031, was supposed to block the current through ERG channels. E-4031-isolated current (shown in C) was obtained by subtracting the current traces in the presence of E-4031 (shown in B) from the current traces recorded in control conditions (shown in A). (C) The subtracted traces, E-4031 isolated currents. An enlarged scale of the tail current traces (shown in red rectangular area in panel C) is shown in (E). (F) Activation curve of the ERG channels. Each data point represents mean value from eight pyramidal neurons.



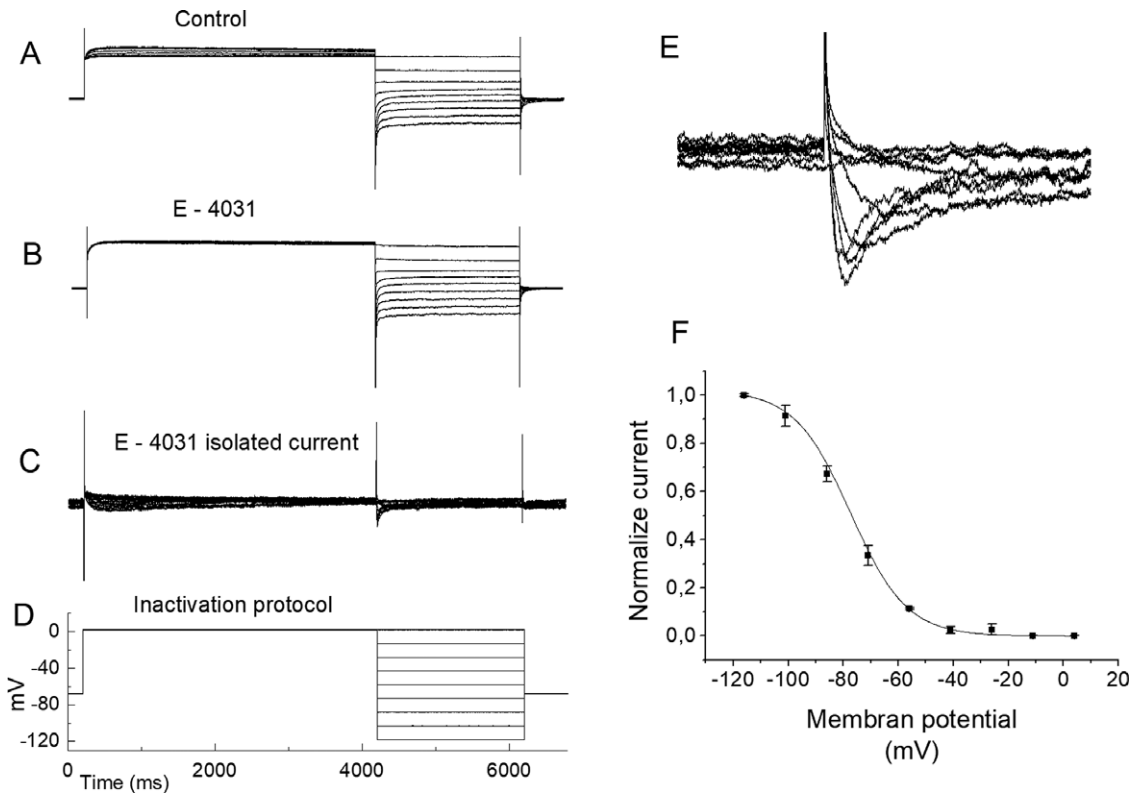
beginning of the hyperpolarizing voltage steps, namely, the end of the depolarizing voltage step during the exponential fitting procedure. The steady-state inactivation curve for ERG channels was constructed by plotting amplitude of the normalized tail currents as a function of voltage steps. The curve was fitted with the Boltzmann function, leading to a V1/2 value of –77.35 mV and a slope factor of 10.58 mV (Figure 7). The same voltage protocol was used to study deactivation kinetics. The traces induced by voltage steps between –120 and –100 mV were fitted best with double exponential, while the traces induced by voltage steps that were more depolarized than –100 mV were fitted best with a single exponential. The rate of deactivation increases as the membrane potential becomes more hyperpolarized (the time constant was 22 ms at –120 mV and 108 ms at –90 mV) (data not shown).

DISCUSSION

In the present study, we found that (1) all ERG channel antagonists caused an increase in the input resistance of the pyramidal neurons. (2) The application of ERG channel blockers increases the number of APs induced by DC current pulses. (3) An increase in the excitability of cells was observed when the ERG channels were blocked in pyramidal neurons. APs were induced by less amount of current injection after the application of ERG channel blockers (except dofetilide) compared to control. (4) The activation curve for ERG channels had a V1/2 value of –48.95 mV and a slope factor of 4.54 mV, the tail current first appeared at around –65 mV, and the amplitude of the tail current increased gradually with more depolarized membrane potential.

In the current study, according to the Boltzmann fitting of the steady-state activation curve, we obtained a V1/2 value of –48.95 mV and a slope factor of 4.54 mV. These data are comparable to those of others[4,5,25] and our previous study.[6] The value of V1/2 in the activation curve of Purkinje cells was found to be –50.7 mV[27] and V1/2 was –56 and –58 mV in neurons of medial nucleus of trapezoid body (MNTB) in 12- and 25-day-old mice, respectively.[4] In the pyramidal neurons, values of voltage dependence of ERG channels steady-state inactivation (–77.35 mV) were comparable to those in the Purkinje neurons (–70.6 mV)

Figure 7. Voltage dependence kinetics of E-4031-isolated ERG current in pyramidal neurons. The E-4031 isolated current was isolated by subtracting the currents recorded in the presence of the E-4031 (B) from the control currents shown in (A). The inactivation voltage protocol is given in (D). (E) An enlarged scale of the tail current traces (shown in red rectangular area in (C)) is shown. E-4031-isolated current clearly shows the hooks. (F) Inactivation curve of the ERG channels. Each data point represents the mean value from six pyramidal neurons.



and MNTB neurons (V1/2 of –72 mV).[4,25] According to the activation curve, the tail current first appeared at around –65 mV, and the amplitude of the tail currents became larger at more depolarized potential, namely, the threshold of activation of ERG channels in pyramidal neurons was found to be close to resting membrane potential of the neurons. According to the steady-state inactivation curve, roughly 20% of ERG channels was ready to activate from the resting potentials of –64.4 ± 3.4 mV. These suggest that 20% of ERG channels activates following depolarization at resting potentials, and more depolarized potentials and deactivation tail currents seem to insert its effect on excitability.

The blockage of ERG currents resulted in an increased number of APs. There are other reports demonstrating that the blockage of ERG currents increases neuronal excitability in cerebellar Purkinje neurons, embryonic serotonergic neurones, mouse spinal cord, medial vestibular nucleus neurones, mouse auditory brainstem neurons, neonatal mouse Purkinje cells, and ventral cochlear nucleus neurons in mice.[3–6,9,22,25,27,28]

The increase in the number of APs after the application of ERG channel blockers during current stimulation could be accounted for only partially by the increase in input resistance, since with a larger input resistance, the same amplitude of the current results in larger depolarizations, and therefore more number of APs. Namely, the increase in input resistance decreases the amount of excitatory current necessary to depolarize the cell. The increase in the number of APs is also likely to be partially due to the block of potassium ion efflux through ERG channels, which has a depressing effect on excitability because greatest conductance occurs during repolarization with a hyperpolarized membrane potentials upon activation by depolarization. Block of the conductance by ERG channel blockers eliminates the hyperpolarizing effect ERG current, flow of which normally occurs during repolarization upon depolarization otherwise. The absence of the ERG current seems to be the major factor for the changes in the number of APs during current stimulation.

According to the Fano, the role of ERG channels is probably the modulation of excitability and transmitter release in rat hippocampal slices.[14] In this respect, any pathologies in ERG channel expressions or ERG channels mutations may lead to excessive excitability of neurons by removing this inhibitor effects. In accord with this statement, Chiesa et al.[29] speculated that one

of the underlying causes of hyperexcitability and hippocampal epileptic activity might be associated with ERG channel mutations or insufficient expressions of the ERG channel genes.

CONCLUSION

In conclusion, the findings suggest that ERG channels may have an inhibitoric effect on neuronal excitability. Therefore, the elimination of the naive inhibitory effect of ERG channels with its specific blockers would increase the frequency of the AP in response to current pulses and may cause hyperexcitability.

Ethics Committee Approval: For this study, ethical approval was obtained from Gaziantep University Local Animal Use Committee (Gaziantep, Turkey; approval date and number: June 25, 2017/39).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.Y.; Design - C.Y.; Supervision - R.B.; Materials - C.Y., Z.C.; Data Collection and/or Processing - C.Y., R.B., Z.C.; Analysis and/or Interpretation - C.Y.; Literature Search - R.B.; Writing Manuscript - C.Y., R.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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