European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.875

Original Research

Biophysical Properties of ERG Channels in Octopus Neurons of Ventral Cochlear Nucleus

Caner Yıldırım, Ramazan Bal

Department of Physiology, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Objective: ERG (Ether a go go related gene) channels (Kv 11) are the members of the voltage-dependent potassium channel family, which have three subtypes as ERG1 (Kv 11.1), ERG2 (Kv 11.2), ERG3 (Kv 11.3). Electrophysiological, biophysical properties of ERG channels and their functions are not known in the cochlear nucleus (CN) neurons, which is the first relay station of auditory pathway. For that reason, we aimed to study pharmacological and biophysical properties and their functions in the octopus neurons of the ventral cochlear nucleus (VCN).

Methods: A total of 70 mice at 14-17 day-old were used for this study. Electrophysiological characterization of ERG channels was performed using patch clamp technique in CN slices.

Results: In current clamp, application of ERG channel blockers, terfenadine (10 μM) and E-4031 (10 μM), significantly increased input resistance in all the cells ($p<0.05$). Also, in octopus cells, it was found that terfenadine (10 μM) and E-4031 (10 μM) significantly reduced threshold for induction of action potentials (AP) with square current pulses ($p<0.05$). Tail ERG currents were measured under voltage-clamp. Steady state activation curve for ERG tail current was determined, yielding a half-activation voltage (V0.5) and slope factor (k factor). Steady state activation curve for ERG tail current was determined with a half-activation voltage in Octopus cell V0.5 -50.72±0.32 with a slope factor of 6.04±0.23 mV (n=3). The quasy steady-state inactivation curve for chord conductances gave for Octopus cell V0.5 value of -74.34±0.46 and the slope of 7.89±0.32 (n=3).

Conclusion: In conclusion, the findings obtained in the present study suggest that Octopus neurons express ERG channels and appear to threshold for AP induction and, possibly, resting membrane potentials in this cells.

Keywords: Auditory pathway, cochlear nucleus, electrophysiology, ERG channels, patch clamp

INTRODUCTION

ERG "ether-a-go-go-related gene" channels were named "ether-a-go-go" in 1969 because of the similarity to the leg movements of flies that were anesthetized with ether and resembled "the go-go" dance that was popular at that time (1). ERG channels, a subgroup of the voltage-gated potassium channel family, have been widely expressed both in the central nervous system (CNS) and the heart. There is not much information concerning the functional roles and electrophysiological properties of these channel currents, which were first isolated from the hippocampus area in the brain in the neuronal system (2). It was seen that studies on ERG channels were generally focused on the heart rather than the brain. Although ERG channels are expressed in many tissues, their physiological roles were best revealed in cardiac ventricular cells (3).

There are many studies that aim to understand the biophysical, pharmacological and electrophysiological properties and determine the functions of ion channels in the cochlear nucleus. These studies have described three different neuron groups that have completely different biophysical and functional properties from the morphological and electrophysiological aspect. Many ion channels in these neuron groups have been physiologically, pharmacologically and biophysically characterized, wherein their function in the relevant nucleus and the extent of their contribution to signal formation and transmission were defined (4, 5).

In all mammals, octopus nerve cells are located in the caudal and dorsal part of the Posterior Ventral Cochlear Nucleus (PVCN) in an area with clearly visible margins. It was found that other cell types are not found in this area, especially in humans (4). Each octopus nerve cell receives inputs from many auditory nerve fibers via synapses located both on their soma and dendrites. Mice have nearly 200 octopus nerve cells in each cochlear nucleus located in this area (6).

It is reported that octopus nerve cells found in mammalian PVCN detect the firing of auditory nerve fibers with excellent temporal precision and transmit this information to the upper auditory nuclei in the brain. It is known that octopus nerve cells respond with exceptionally well-timed action potential to "click" stimuli,

How to cite: Yıldırım C, Bal R. Biophysical Properties of ERG Channels in Octopus Neurons of Ventral Cochlear Nucleus. Eur J Ther 2019; 25(2): 135–41.

ORCID IDs of the authors: C.Y. 0000–0003–0091–9925; R.B. 0000–0003–3829–8669

Corresponding Author: Caner Yıldırım **E–mail:** caneryildirim27@gmail.com

Received: 04.07.2018 • **Accepted:** 03.09.2018

the beginning of sounds with a pure tone (stimulus by a sound that consists of one frequency) and periodic sounds (4) .

A study on whether ERG channels contribute to the action potential of voices has not been found in the literature. In this study, we aimed to investigate whether ERG channels had a physiological contribution in the process of transformation of auditory signals into action potential. With this purpose, we first investigated how ERG channels affected cell excitability in octopus cells characterized in the ventral cochlear nucleus using the Current Clamp technique. ERG channel currents were then isolated as tail current with the help of specific ion channel antagonist chemical agents (terfenadine and E-4031) using the Voltage Clamping technique. The activation, inactivation and deactivation kinetics and biophysical properties of these channels in the relevant cochlear nucleus neurons were determined for the first time by analyzing these currents.

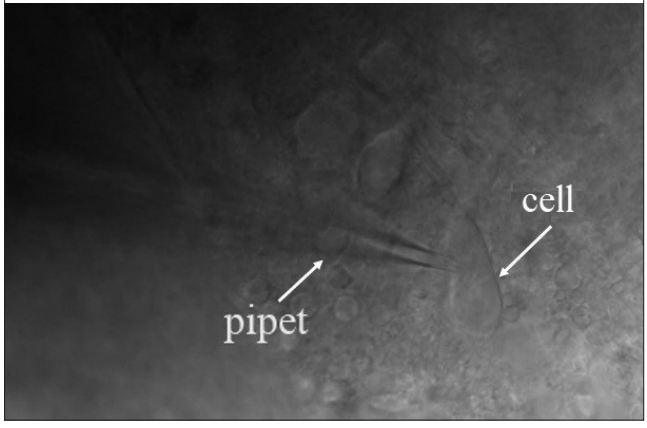
METHODS

The Electrophysiological Patch Clamp technique was used to characterize ERG channels in cochlear nucleus tissue. ERG channels were characterized by using Current Clamp and Voltage Clamp configurations. All data from the cells were obtained by whole cell configuration. An example of the whole cell configuration is shown in Figure 1.

Preparation of Brain Sections

The study began after obtaining the approval of the ethics committee of Gaziantep University Experimental Animals Studies Unit (protocol no: 06.01.2016 / 03). Animals were decapitated under anesthesia (halothane) followed by dissection without creating any physical damage and especially without stretching the cranial nerves emerging from the brain stem after placing the animal's head in continuously oxygenated normal artificial cerebrospinal fluid (aCSF). After the brain was completely taken out of the skull, it was incised coronally at an angle of approximately 60º at the inferior colliculus-superior colliculus level. The part that contains the brainstem was glued onto a Teflon block with the inferior colliculus facing down using a cyanoacrylate adhesive and then placed in a vibratome that contains the continuously oxygenated normal aCSF. Coronal sections of 175-200 µm thickness were taken with a vibrating vibratome. The obtained sections were incubated in continuously an oxygenated normal aCSF solution for approximately 15-30 minutes and then moved to a 0.3 mL volume recording chamber and through which fresh oxygenated normal aCSF solution was perfused at a speed of 4-5 mL/min for intracellular recording purposes. The temperature of the perfused aCSF solution was consistently maintained at 33ºC with a thermoregulator with a negative feedback circuit component probe at the part where the perfusion system opens to the recording chamber.

Figure 1. View of the cell with a pipette under a microscope in whole cell configuration



Solutions

Pipette solution

The constituents of the pipette solution were as follows (in mM): 108 potassium gluconate, 9 HEPES, 9 EGTA, 4.5 $MgCl_2$, 14 phosphocreatinine (tris salt), 4 ATP (Na-salt) and 0.3 GTP (tris salt). The pH of the solution was set to 7.40 with potassium hydroxide (KOH). The pipette solution was prepared as a stock solution to be used before each experiment and stored at -40ºC.

Perfusion solution

"Normal aCSF" was used as a perfusion solution in the Current Clamping. The constituents of aCSF solution were as follows: 138 mM sodium chloride (NaCl) (Merck), 4.2 mM potassium chloride (KCl) (Merck), 2.4 mM calcium chloride ($CaCl_2$) (Fluka), 1.3 mM magnesium sulfate ($MgSO_4$) (Merck), 10 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Merck), 10 mM glucose (Sigma Aldrich). This solution was continuously oxygenated with carbogen gas (95% O_2 + 5% CO_2) throughout the experiment starting at least 30 minutes prior to obtaining the brain slices. The pH of the solution was set between 7.35-7.40 using 1 M sodium hydroxide (NaOH) (7, 8).

Two types of perfusion solutions were used in the Voltage Clamping. One of these was a solution with high K^+ concentration (40 mM) in order to increase the amplitude of ERG channel currents. This solution did not contain Ca^{+2} in order to prevent Ca^{+2} -activated K^+ currents. Osmolarity of the solution was kept constant at 295-305 mOsm/L by increasing the potassium concentration from 4.2 mM to 40 mM while decreasing NaCl at the same ratio. The constituents of this solution were as follows (in mM): 102 NaCl, 40 KCl, 3.7 $MgSO_4$, 10 HEPES and 10 glucose. To this solution, 1 µM tetradotoxin (TTX) (Alexis Biochemicals (USA)) was added to block sodium currents, 1mM 4-aminopyridine (4-AP) (Sigma Aldrich), 1mM tetraethyl ammonium (TEA) (Fluka) to block I_{KDR} and I_A currents, respectively, as well as 2 mM cesium (Cs) (Sigma Aldrich) to block nonspecific cation channel currents (I_h) activated by hyperpolarization. In addition, 5 µM 6.7-Dinitroquinoxaline-2.3-dione (DNQX), 10 µM 2-amino-5-phosphonopentanoic acid (APV-5) and 1 µM strychnine were added to the solution in order to block the synaptic activities due to glutamate, GABA and glycinergic receptors, respectively. This solution was called "control aCSF".

In addition to; 10 µM 1-[2-(6-methyl-2-piridyl)ethyl]-4-(4-methylsulfonyl-aminobenzoyl) piperidine (E-4031) (Alemon lab-Israel)

was added to the "control aCSF" solution as the specific blocker in order to isolate ERG currents and a third solution called "control aCSF containing E-4031" was prepared.

Among the employed chemical agents, E-4031, terfenadine, APV-5 and Cs were dissolved in dimethyl sulfoxide (DMSO) such that the final concentration would not exceed 1/1000. It was not desired to use a higher concentration of DMSO as it could have a toxic effect on the cells. All the other chemical agents were dissolved in aCSF solution. The pH and osmolarity values were taken into account while preparing the solutions. The pH values of the perfusion solution and pipette solution were set to 7.4 and 7.35, respectively. The osmolarity of both solutions were maintained between 295-310 mOsm. Test solutions that contained a pharmacological agent were applied to the recording chamber with the perfusion system that consists of pipes and valves.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package for Social Science version 23.0 (SPSS, IBM Corp.; Armonk, NY, USA). Records obtained before applying ERG channel antagonists were used as the "control", and records obtained after applying these antagonists were used as the "test group". Normal distribution of the groups were analyzed in order to statistically evaluate the difference between the two groups before and after applying ERG channel antagonists. Regression analysis was performed to analyze the current-voltage curve of the cells. Descriptive statistics for numerical variables were expressed as group mean ± standard error (SE) (n indicates the number of animals used in the experiment). Statistical evaluation was performed using the parametric Student's t test for groups that had a normal distribution and $p<0.05$ was considered statistically significant.

RESULTS

Current Clamping Studies

Specific ERG channel antagonists, E- 4031 and terfenadine, were applied on octopus cells in the slices obtained from cochlear nuclei of 14-17 days old mice during Current Clamp recording. Resting membrane potential, input resistance and firing threshold values of cells were compared for both antagonists before and after the application. Recording periods ranged between 15 and 120 minutes. Cells were identified by considering their anatomical localizations, electrophysiological and intrinsic properties. The typical voltage response of octopus cells to the depolarizing current (Figure 2) and hyperpolarizing current (Figure 3) are provided in Figure 2 and Figure 3, respectively.

Effect of ERG Currents on Octopus Type Neurons

Effects on resting membrane potential

Effects of E-4031 and terfenadine were investigated on 6 and 10 cells respectively, in which stable intracellular recording was performed. The resting membrane potential under control conditions and after terfenadine application was measured as -61.84 mV±2.05 and -61.54 mV±1.90 (n=10), respectively in the cells on which terfenadine was applied ($p>0.05$). The resting membrane potential under control conditions and after E-4031 application was measured as -62.1 mV±1.34 and -61.7 mV±1.69 (n=6), respectively in the cells on which E-4031 was applied ($p>0.05$). There was no effect of E-4031 and terfenadine on resting membrane potential.

Effects on input resistance

Input resistance of the cells before and after terfenadine application were measured as 3.64 MΩ±0.25 and 6.38 MΩ±0.47 (n=8), respectively ($p<0.01$). Input resistance of the cells before and after E-4031 application were measured as 3.61 MΩ±0.56 and 5.24 MΩ±0.56 (n=8), respectively. The increase in input resistance as a result of blocking ERG currents with the two blockers was found to be statistically significant ($p<0.05$).

Effects on threshold value and excitability

The effect of E-4031 on threshold value and excitability was investigated in octopus type neurons. Experiments have shown that cells were stimulated by a current that was 180 pA lower in comparison to the control conditions in order to create action potential in 9 out of 14 cells ($p<0.05$) (Figure 4).

Voltage Clamping Studies

Figure 5 shows the recording samples obtained from cells perfused with the control solution in octopus type neurons in the Aa graph and in the presence of a solution that contains a pharmacological agent in the Ab graph. Ac graph, which shows ERG channel currents and currents blocked by E-4031, was obtained by subtracting Ab graph from Aa graph. Traces on the right side of the graph are large-scale presentations of tail currents in order to see and understand the currents better.

Current/voltage curves from the records obtained from octopus cells are provided in Figure 6. The steady state curve was used to generate the current/voltage curves. In the obtained tail current records, the activation curve of each cell was normalized in order to calculate the mean value and obtain a single curve. Then, it was fitted with the Boltzmann function in order to obtain the half-activation voltage value ($V_{0.5}$) of ERG channels and the slope factor (k) of the curve. After being fitted with the Boltzmann function, $V_{0.5}$ value was found to be -50.72±0.32 and the slope of the curve (k factor) was found to be 6.04±0.23 (n=3). Analysis of this curve revealed that ERG channel current activation took place at more depolarized values in comparison to -60 mV in octopus type neurons.

Voltage-dependent inactivation kinetics

Figure 7 shows the recording samples obtained from cells perfused with the control solution in octopus type neurons in the Aa graph and in the presence of a solution that contains a pharmacological agent in the Ab graph. Ac graph, which shows ERG channel currents and currents blocked by E-4031, was obtained by subtracting Ab graph from Aa graph. Traces on the right side of the graph are large-scale presentations of tail currents in order to see and understand the currents better.

Current/voltage curves created from the records obtained from octopus cells using the steady state curve are provided in Figure 8. In

Figure 2. Electrophysiological responses of the octopus cell to depolarizing current injections

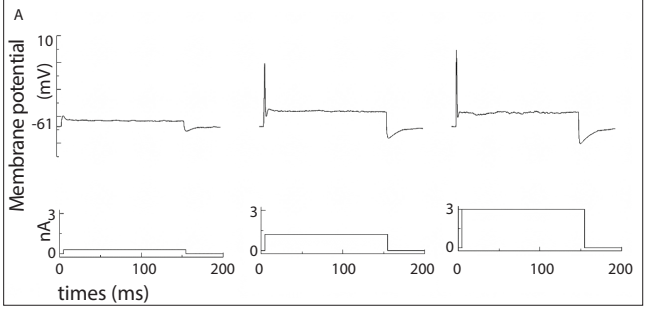


Figure 3. a, b. Electrophysiological responses of the octopus cell to hyperpolarizing current injections, (a) hyperpolarizing responses in the octopus cell, and (b) current/voltage curve of the octopus cell

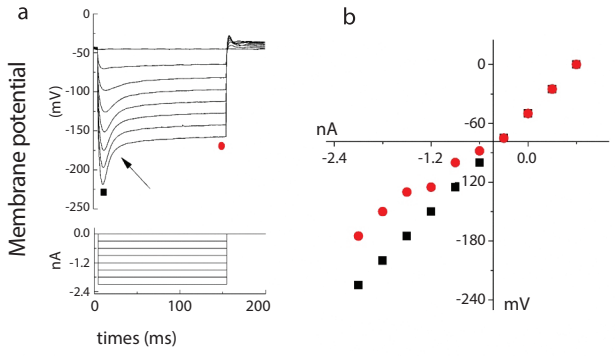
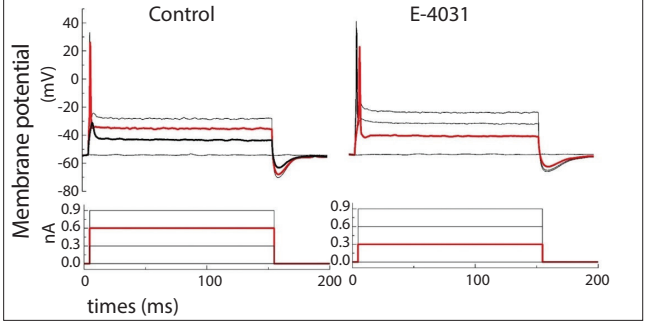


Figure 4. Effect of E-4031 on excitability in octopus cells. The cell created the first action potential with 0.6 nA under control conditions and with 0.3 nA in the presence of E-4031. Therefore, ERG channel antagonists decrease the threshold value



the obtained tail current records, the activation curve of each cell was normalized in order to calculate the mean value and obtain a single curve. Then, it was fitted with the Boltzmann function in order to obtain the half-inactivation voltage value ($V_{0.5}$) of ERG channels and the slope factor (k) of the curve. After being fitted with the Boltzmann function, $V_{0.5}$ value was found to be -74.34±0.46 and the slope of the curve (k factor) as 7.89± 0.32 (n=3).

Figure 5. Voltage-dependent activation records of octopus-type cells

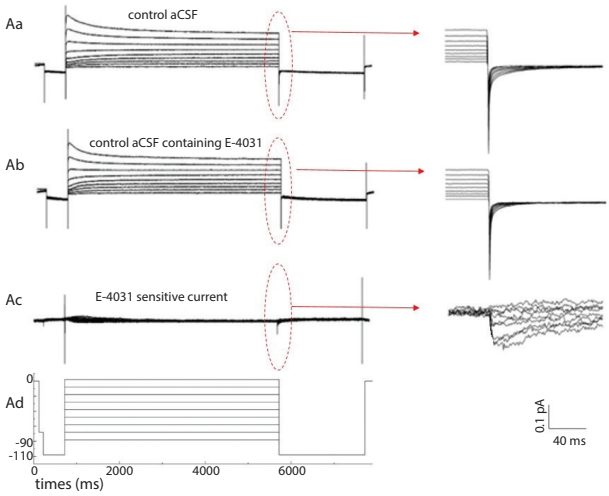
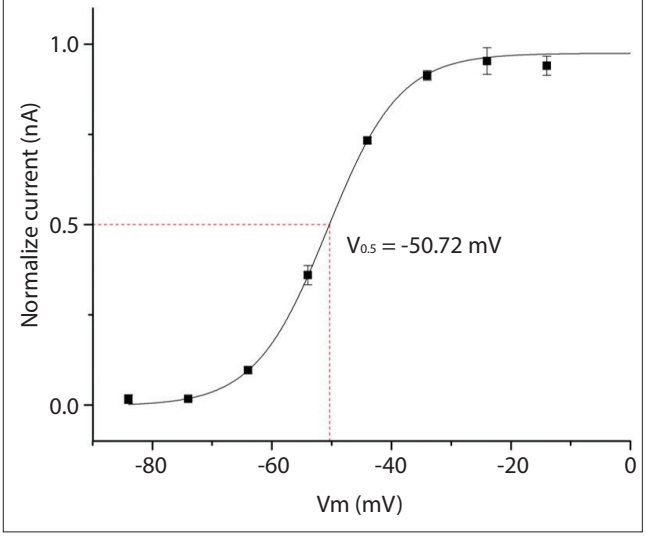


Figure 6. Steady state activation curve of octopus cells



Deactivation kinetics of octopus type cells were determined using the same protocol. The time constant was measured to be 17 ms at a membrane potential of -120 mV and 196 ms at a membrane potential of -80 mV. Accordingly, it was found that the deactivation speed was increased as the resting potential moved towards negative values in octopus cells (Figure 9).

DISCUSSION

It was found that both terfenadine and E-4031 as ERG channel blockers increased input resistance as compared to the control conditions in octopus cells. This means that some ion channels are blocked by these specific blockers. The input resistance of a neuron is associated with the amount of open ion channels on the membrane. Neurons with low input resistance have high conductance and this indicates that there are many open ion

Figure 7. Voltage-dependent inactivation records of octopus-type cells

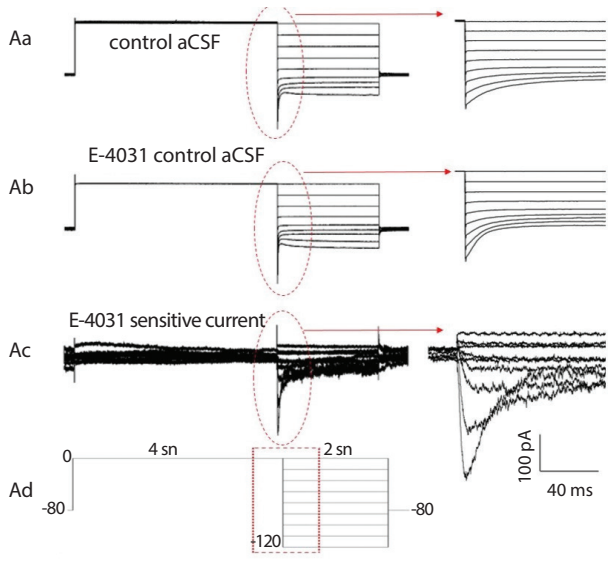
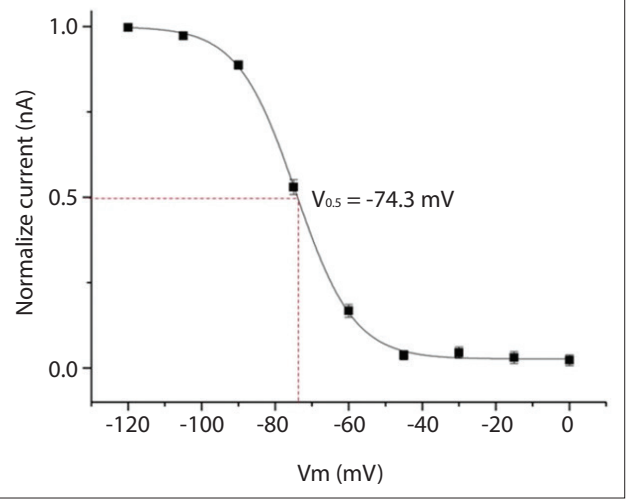


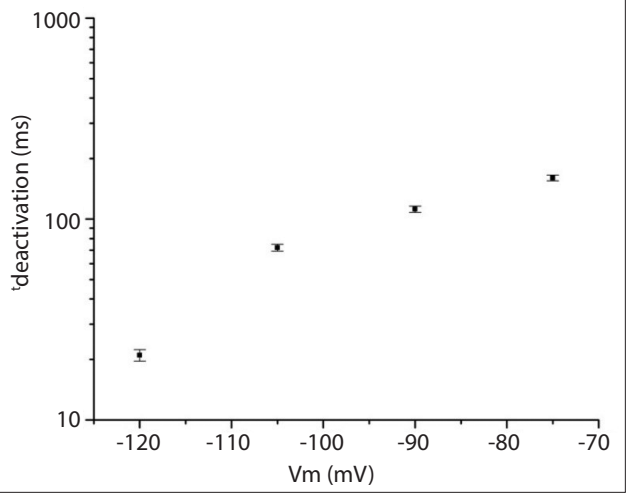
Figure 8. Steady state inactivation curve of octopus cells



channels in the membrane. On the other hand, neurons with high input resistance have low conductance and this indicates that many ion channels in the membrane are blocked. It was also shown in previous studies that both terfenadine and E-4031 specifically blocked ERG channels strongly and selectively (9).

It was found that the resting membrane potential exhibited a slight depolarization as a result of the specific blocking of ERG channels by both terfenadine and E-4031. The amount of this depolarization is approximately 0.20 mV in octopus type neurons. However, this depolarizing effect was not at a statistically significant level. In studies by Pessia et al. (10) on medial vestibular nucleus neurons, by Hardman and Forsythe (9) on medial nucleus neurons of the trapezoid body, and by Sacco et al. (11) and Niculescu et al. (12) on cerebellar purkinje neurons, it was reported that cells were depolarized in a mean value interval of approximately 0.30-2.50 mV with the inhibition of ERG channels by specific blockers but this effect was not statistically significant. In this respect, our study is similar to the aforementioned studies.

Figure 9. Deactivation kinetics of octopus cells



The current passing through ERG channels, known as inward rectifiers, in Voltage Clamping studies is directly related to the extracellular K^+ ion concentration. Therefore, the K^+ ion concentration in aCSF was raised to 40 mM in order to increase ERG channel currents and to better analyze voltage-dependent activation and inactivation kinetics. It was reported that the amplitude of ERG tail currents were increased by doing so(13). This is because the equilibrium potential, according to the Nernst equation, was calculated to be -83.4 mV for the potassium ion when K^+ concentration in aCSF ($[K^+]_o$) was 4.2 mM, whereas the same was calculated to be -25.4 mV when K^+ ion concentration was increased to 40 mM. Accordingly, the amplitude of the ERG tail current will be increased as the concentration gradient for the ERG current that enters the cell from ERG channels will increase at voltages close to the resting membrane potential (9, 11, 12).

Activation kinetics of ERG channels

As a result of the Voltage Clamping studies, it was observed that the activation threshold value of ERG channels was close to the resting membrane potential. Analyzing the steady state activation curves, it was found that the activation ratio of ERG channels was nearly 32% at the resting membrane potential (-61.1 mV) of octopus-type neurons. In other words, it was found that ERG channels were activated at higher rates at more positive values in comparison to the resting membrane potential. However, it was understood that this activation took place following a depolarization wave. This depolarization can take place physiologically under *in vivo* conditions in EPSP states as well as during action potentials that can develop spontaneously.

According to the steady state activation curve, $V_{0.5}$ was -50.7 and k factor was 6.0 in octopus type neurons. This indicates that the channels have completed their activation at 50% around -50 mV. Niculescu et al. (12) conducted studies on cerebellar purkinje

cells and reported that they measured the activation value of ERG channels at levels around $V_{0.5=}$ -44,1 mV. Hardman and Forsythe (9) conducted studies on the neurons in medial nucleus of the trapezoid body (MNTB) and reported $V_{0.5}$ values of -58 and -56 mV in postnatal 12 and 25 day old mice, respectively in analyses of voltage-dependent activation kinetics. Although age-dependent $V_{0.5}$ values were similar, the most striking difference was reported in the slope values of the curve. The k factor of the curve was 3.28 in 12 day-old mice, whereas the same increased to 8.61 in 25 day-old mice. In a study by Sacco et al. (11) it was reported that $V_{0.5}$ value was around -50,7 mV in purkinje cells. It was found that ERG channel activation values in cochlear nucleus neurons were similar to the activation values in cerebellar purkinje cells and MNTB neurons.

It should be emphasized that the data from cochlear nucleus was obtained using aCSF that does not contain Ca as in the studies conducted by Sacco et al. (11) and Niculescu et al. (12) On the other hand, Hardman and Forsythe (9) used 0.5 mM calcium chloride in their study. The k factor, i.e. the slope of the activation curve, found in the study conducted by Hardman and Forsythe (9) was much lower than the k factor values obtained in this study and other studies mentioned above. This might stem from the calcium contained in aCSF.

Inactivation kinetics of ERG channels

Analyzing the steady state inactivation curves, it was found that 34% of the tail current of ERG channels was free from inactivation (recovery state) at the resting membrane potential of octopus-type neurons (-61.1 mV). According to the voltage-dependent steady state inactivation curve of the cells, $V_{0.5}$ was -78.34 and k factor was 7.89.

Sacco et al. (11) found a $V_{0.5}$ value of -70 mV in their study on purkinje cells, whereas Shoeb et al. (14) found more depolarized values (-36 mV), and Smith et al. (15) found higher negative values (-102 mV and -90 mV, respectively) in heterologous expression studies. Hardman and Forsythe (9) conducted studies on MNTB neurons and reported $V_{0.5}$ values of -76.17 and -70.77 mV in postnatal 12 and 25 day old mice, respectively in analyses of voltage-dependent inactivation kinetics. In all studies, the slope of the inactivation curves, k ranged between 10-20 mV. For instance, Hardman and Forsythe (9) found k=17 mV in MNTB neurons. This value was lower in our study (9-10 mV). This could possibly stem from the fact that aCSF did not contain calcium in our study.

Deactivation kinetics of ERG channels

Deactivation kinetics were obtained from tail currents and measured to be 17 ms at -120 mV and 217 ms at -60 mV for octopus-type neurons. Accordingly, it was found that deactivation kinetics was faster as the membrane potential of the cells moved towards negative values. In this case, the tail current will be rapidly reset to zero, as opposed to the negativity of the cell membrane potential. Thus, the contribution to the action potential repolarization phase will be more limited. The time constants of the cell tail currents were most suitably fitted with the single exponential function at potentials between -60 and 100 mV, whereas they were fitted with a double exponential at potentials between -100 and 120 mV. In comparison to the study by Ohya et al. (16) it is apparent that deactivation time constants obtained in our study were faster (lower). This indicates that ERG channels are mostly constituted by the ERG-3 subtype, because it has been reported that the deactivation kinetics of the ERG-3 subtype was the fastest (lowest) among ERG channel subtypes (16).

CONCLUSION

Consequently, although the physiological roles of ERG channels have been defined in studies conducted on the heart and other excitable cells, it is thought that the density of these currents are considerably lower in comparison to cochlear nucleus neurons and these currents have a minimal effect on the levels of the resting membrane potential. In the light of all this information, even though it is possible to say that ERG channels were electrophysiologically detected in cochlear nucleus neurons, immunohistochemical studies and PCR studies should also be conducted to show the existence of these channels both at the protein and gene levels. In addition, advanced imaging techniques (confocal imaging) should be used as a support to reveal the spatial localizations of the channel in each cell type (somatic?, axonic? or dendritic?), the expression levels of ERG subtype channels (ERG1, ERG2, ERG3) and how much these channels contribute to total ERG currents.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (protocol no: 06.01.2016 / 03).

Peer-review: Externally peer-reviewed.

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

Acknowledgements: We thank Professor D. Ian Forsythe for his e-mail support to solve the problems.

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

Financial Disclosure: This work was supported by grants from Gaziantep University Scientific Research Projects Governing Unit (Project No.: TF.16.10) (Turkey).

REFERENCES

1. Vandenberg JI, Perry MD, Perrin MJ, Mann SA, Ke Y, Hill AP. hERG K(+) channels: structure, function, and clinical significance. Physiol Rev 2012; 92: 1393-478. [CrossRef]
2. Rampe D, Brown AM. A history of the role of the hERG channel in cardiac risk assessment. J Pharmacol Toxicol Methods 2013; 68: 13-22. [CrossRef]
3. Heo DH, Kang TC. The changes of ERG channel expression after administration of antiepileptic drugs in the hippocampus of epilepsy gerbil model. Neurosci Lett 2012; 507: 27-32. [CrossRef]
4. Bal R, Baydas G. Electrophysiological properties of octopus neurons of the cat cochlear nucleus: an in vitro study. J Assoc Res Otolaryngol 2009; 10: 281-93. [CrossRef]
5. Oertel D, Wright S, Cao XJ, Ferragamo M, Bal R. The multiple functions of T stellate/multipolar/chopper cells in the ventral cochlear nucleus. Hear Res 2011; 276: 61-9. [CrossRef]

6. Willott JF, Bross LS. Morphology of the Octopus Cell Area of the Cochlear Nucleus in Young and Aging C57bl/6j and Cba/J Mice. J Comp Neurol 1990; 300: 61-81. [CrossRef]
7. Bal R, Ozturk G, Etem EO, Him A, Cengiz N, Kuloglu T, et al. Modulation of Excitability of Stellate Neurons in the Ventral Cochlear Nucleus of Mice by ATP-Sensitive Potassium Channels. J Membr Biol 2018; 251: 163-78. [CrossRef]
8. Yildirim C, Bal R. ERG Channels Regulate Excitability in Stellate and Bushy Cells of Mice Ventral Cochlear Nucleus. J Membr Biol 2018; 251: 711-22. [CrossRef]
9. Hardman RM, Forsythe ID. Ether-a-go-go-related gene K+ channels contribute to threshold excitability of mouse auditory brainstem neurons. J Physiol 2009; 587: 2487-97. [CrossRef]
10. Pessia M, Servettini I, Panichi R, Guasti L, Grassi S, Arcangeli A, et al. ERG voltage-gated K+ channels regulate excitability and discharge dynamics of the medial vestibular nucleus neurones. J Physiol 2008; 586: 4877-90. [CrossRef]
11. Sacco T, Bruno A, Wanke E, Tempia F. Functional roles of an ERG current isolated in cerebellar Purkinje neurons. J Neurophysiol 2003; 90: 1817-28. [CrossRef]
12. Niculescu D, Hirdes W, Hornig S, Pongs O, Schwarz JR. Erg potassium currents of neonatal mouse Purkinje cells exhibit fast gating kinetics and are inhibited by mGluR1 activation. J Neurosci 2013; 33: 16729-40. [CrossRef]
13. Shibasaki T. Conductance and kinetics of delayed rectifier potassium channels in nodal cells of the rabbit heart. J Physiol 1987; 387: 227-50. [CrossRef]
14. Shoeb F, Malykhina AP, Akbarali HI. Cloning and functional characterization of the smooth muscle ether-a-go-go-related gene K+ channel - Potential role of a conserved amino acid substitution in the S4 region. J Biol Chem 2003; 278: 2503-14. [CrossRef]
15. Smith PL, Baukrowitz T, Yellen G. The inward rectification mechanism of the HERG cardiac potassium channel. Nature 1996; 379: 833-6. [CrossRef]
16. Ohya S, Horowitz B, Greenwood IA. Functional and molecular identification of ERG channels in murine portal vein myocytes. Am J Physiol Cell Physiol 2002; 283: C866-77. [CrossRef]