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ORIGINAL ARTICLE

Temporal lobe epilepsy and changes in the M-current

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Abstract

Objective: *Acquired alterations of ion channel function occur after status epilepticus (SE). Kv7 channels mediate a sustained outward current (IM) that exerts pivotal control over neuronal excitability. Here, we investigate if pilocarpine-induced SE alters M-channel activity by quantifying the IM.* **Methods:** *Hippocampal slices were prepared from adult rats after pilocarpine-induced SE, when the animal was showing 3–5 spontaneous recurrent seizures (SRS) a day. A group of untreated, age-matched rats was used as the control group. Recordings were made using the whole-cell configuration of the patch clamp technique and current clamp mode to measure the membrane time constant.* **Results:** *The IM measured amplitude in CA1 neurons from pilocarpine-SE rats was significantly reduced compared to the control group (control, 208.72 ± 25.49 pA, n = 15; pilocarpine-SE, 49.28 ± 6.17 pA, n = 11; p < 0.05, Student's t). The time constant was 27.7 ± 17.7 msec in the control group and 48.9 ± 5.5 msec in the pilocarpine-SE group, and was significantly different (p < 0.05).* **Conclusions:** *In this study, we demonstrated that the M-current amplitude is significantly reduced in CA1 pyramidal neurons after pilocarpine-SE. Considering the acute damage that SE induces, the silent interval between injury and the onset of spontaneous seizures, and the chronic epileptic state in which the M-current was measured, we can speculate about the lack of homeostatic regulation of the intrinsic properties of neuronal excitability.*

Keywords: *Hippocampus. M-current. Pilocarpine. Status epilepticus. Epileptogenesis.*

Epilepsia del lóbulo temporal y cambios en la corriente M

Resumen

Objetivo: *Las alteraciones adquiridas en la función de canales iónicos ocurren después del estado epiléptico (SE). Los canales Kv7 determinan una corriente de salida sostenida llamada corriente M (IM), que ejerce un control fundamental sobre la excitabilidad neuronal. Investigamos si el SE inducido por pilocarpina altera la funcionalidad del canal M mediante la cuantificación de la IM.* **Métodos:** *Se prepararon rebanadas de hipocampo de ratas adultas que presentaron de 3 a 5 convulsiones espontáneas recurrentes (SRS) al día, después de haberles provocado el SE por la administración de pilocarpina. Los registros se realizaron con la técnica de fijación de voltaje en la modalidad de registro de toda la célula (whole cell).* **Resultados:** *En neuronas piramidales de la región CA1 del hipocampo de ratas que experimentaron SE, la amplitud de la IM disminuyó significativamente comparada con el grupo control (control, 208.72 ± 25.49 pA, n = 15; pilocarpina-SE, 49.28 ± 6.17 pA, n = 11; p < 0.05, Student's t). Se cuantificó la constante de tiempo (τ) de relajación. La τ se modificó significativamente (48.9 ± 5.5 mseg en el grupo pilocarpina-SE) con respecto al grupo control (27.7 ± 17.7 mseg).*

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Conclusiones: *En este estudio demostramos que la amplitud de la IM se reduce significativamente en las neuronas piramidales CA1 después del SE provocado por pilocarpina. Al considerar el daño agudo provocado por el SE, el intervalo de silencio entre la lesión, el inicio de las convulsiones espontáneas y el estado epiléptico crónico en el que se midió la IM, nos permite especular sobre la falta de regulación homeostática de algunas de las propiedades intrínsecas de la excitabilidad neuronal.*

Palabras clave: *Hipocampo. Corriente M. Pilocarpina. Estado epiléptico. Epileptogénesis.*

Introduction

Temporal lobe epilepsy (TLE) is the most common type of epilepsy in humans. Animal models of TLE are particularly useful for studying the basic neural mechanisms involved in epileptogenesis. After the induction of pilocarpine-status epilepticus (pilocarpine-SE) alterations in ion channel function occur during the acute period[1], during chronic periods following the establishment of spontaneous seizures[2] or acute and chronic periods[3]. Ion channels play essential roles in regulating neuronal excitability through the release of neurotransmitters, the generation of synaptic responses, and the propagation of action potentials (APs) along dendrites and axons. The involvement of ion channels in epilepsy is evidenced by the alteration in their function induced by channel blockers that cause seizures in experimental animals[2,4,5]. The M-current (I_M) is a slow-activating, low-threshold potassium (K^+) current that exerts inhibitory control over neuronal excitability. This inhibition can act by the action of neurotransmitters on G-protein-coupled receptors, leading to increased excitability and reduced adaptation to the frequency of neuronal firing[6,7]. The K^+ channels that generate I_M belong to the KCNQ2 and KCNQ3 family, and mutations in these channels are associated with a form of childhood epilepsy called benign familial neonatal seizures[7-9]. These channels display slowly activating and deactivating K^+ currents with distinct electrophysiological and pharmacological properties, and the activation of muscarinic acetylcholine receptors suppresses them. Because K^+ channels are critical for establishing and stabilizing resting neuronal membrane potential, a loss of K^+ channels could support neuronal hyperexcitability[2,6,7]. This study evaluated the changes in I_M after pilocarpine-SE when spontaneous and recurrent seizures occur.

Material and methods

This study is experimental, basic research. All procedures and protocols used were approved by the Research and Ethics Committees of the Faculty of Medicine of the Universidad Nacional Autónoma de México, in strict compliance with the Norma Oficial Mexicana NOM-062-ZOO-1999[10], which complies with international guidelines for animal handling. The minimum number of animals was considered to achieve statistical significance and avoid suffering. All animals (male Wistar rats weighing 99 ± 33 g [29 ± 5 days old]) were obtained from the general vivarium of the Faculty of Medicine of the UNAM.

Pilocarpine model

The model used to induce TLE was the one described by Turski et al. in 1983[11], which is briefly mentioned: Animals were injected with atropine (1 mg/kg) subcutaneously and 20 min later the dose of pilocarpine (350 ± 30 mg/kg) was applied intraperitoneally. After the appearance of SE, the animals were kept under observation for about 120 min, then they were administered diazepam (5 mg/kg), 3-4 doses, at 1-h intervals, to counteract the severity of the seizures due to SE[12]. The surviving animals were kept under close surveillance and their hydration and feeding were taken care of in the laboratory, especially during the acute recovery period, about 1 week after SE. The animals were then observed for 8 h/day, 5 days a week with a video recording system to detect the occurrence of software requirements specification (SRS) like state 5 described in the kindling, Racine, 1972[13]. Once recovered from SE, the brains of the animals were used for electrophysiological recording in slices at variable periods of time. Rats of the same age and weight, kept under the same conditions, without being treated with pilocarpine, were used as a control group.

Hippocampal slices

To obtain slices from the hippocampal region, animals were deeply anesthetized with urethane (1.25 mg/kg i.p). They were perfused intracardially with cold (4 °C) artificial cerebrospinal fluid (ACSF) with concentrations in mM of 206 sucrose, 2.8 KCl, 1 $CaCl_2$, 1 $MgCl_2$, 2 $MgSO_4$, 1.25 Na_2HPO_4, 26 $NaHCO_3$, 10 D-glucose, 0.4 ascorbic acid, saturated with 95% O_2 and 5% CO_2, pH of 7.4 and

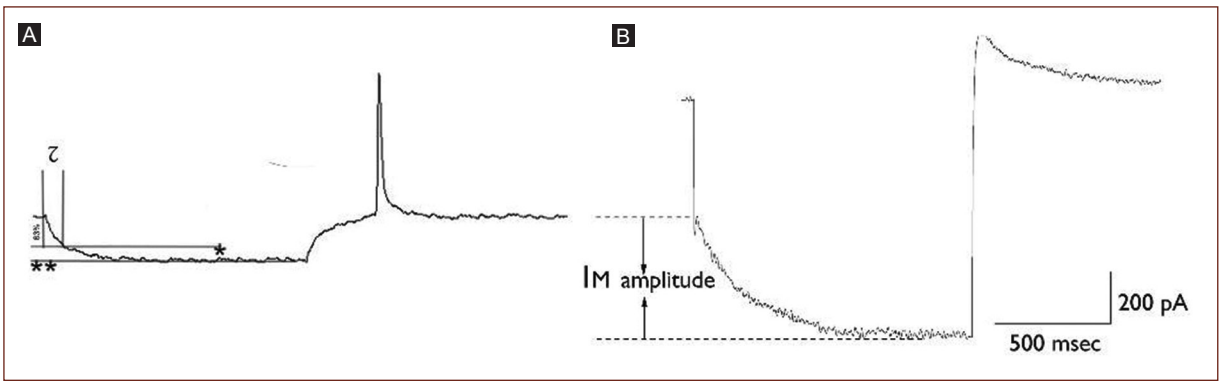

Figure 1. A: example of I_M quantification (voltage-clamp mode). The I_M relaxation amplitude is illustrated as the difference between the maximum peak and steady-state current values, **B:** changes in membrane potential (current-clamp mode) caused by applying negative current pulses of 15 nA and 50 m duration. *: indicates 63% of the maximum voltage change; **: indicates the maximum voltage deflection; τ: time constant.

osmolarity of 295 mOsm. Brains were rapidly removed and stored in cold (4 °C) ACSF containing in mM: 124 NaCl, 2.8 KCl, 2 $CaCl_2$, 2 $MgSO_4$, 1.25 Na_2HPO_4, 26 $NaHCO_3$, 10 D-glucose and 0.4 sodium ascorbate, with a pH of 7.4 and osmolarity of 295 mOsm, and saturated with 95% O_2 and 5% CO_2[14]. Hippocampal slices (350-400 μm) were obtained with a microtome-vibrator (Vibroslice 752; Campen Instruments Ltd. Lafayette, USA) and transferred to a beaker with oxygenated ACSF (95% O_2 and 5% CO_2) where they were kept at room temperature until recording. After 1 h of rest, each slice was transferred to a recording chamber in which 2 mL/min of oxygenated ACSF was continuously perfused at a constant temperature of 36 °C. The slice was held in place with a specifically designed cotton mesh. A microscope with Axioscop (Zeiss, Oberkochen, Germany) water immersion objectives (60×) equipped with a closed-circuit camera (Cohu Solid State Camera; San Diego, CA) was used. The cell bodies of the hippocampal pyramidal neurons were identified[14].

Electrophysiological recordings

Patch-clamp recordings were obtained in whole cell mode using an Axopatch 200A amplifier and pClamp 10 software (Axopatch 200A Molecular Devices, Sunnyvale, CA). Signals were filtered online at 1 kHz and digitized at 5 kHz during voltage-clamp recording. The signals were filtered at 10 kHz and digitalized at 50 kHz for the current clamp. The time constant (τ) was measured with current clamping before applying any drug to the recording chamber. The membrane time constant is the time for the potential to fall from the resting to a fraction of 63% of its final value in the charging curve when applying a small negative current pulse (0.15 nA for 30-50 m). (Fig. 1A) Digidata 1200, Axon Instruments). Filament-free borosilicate capillary glass (KIMAX-51) with an external diameter of 1.5 mm and an internal diameter of 1.0 mm (Kimble Products, USA) was used to make microelectrodes with a horizontal Flaming/Brown pipette puller model P-97 (Sutter Instrument, Novato, CA, USA). The recording electrodes were polished with a microforge and filled with a solution containing in mM: 175 KCl, 5 $MgCl_2$, 5 HEPES, 0.1 BAPTA, 5 Adenosine triphosphate, 0.3 guanosine triphosphate, and 0.1 leupeptin, with a pH of 7.4 adjusted with KOH and a resistance of 3.5-5.5 MΩ. The recordings were conducted under continuous perfusion of 1 μM tetrodotoxin (TTX) and the compound ZD7288 (4-Ethylphenylamino-1,2-dimethyl-6-methylaminopyrimidinichloride, H-channel blocker/HCN)[15], to dissect the I_M. The relaxation amplitude of the I_M was assessed in neurons from the brain tissue of control rats and pilocarpine-SE rats. For this, the difference between the maximum instantaneous peak current at the beginning of the command pulse of the voltage protocol and the steady-state current, just before the termination of the pulse, was used (Fig. 1B). The maintenance voltage to activate the I_M was set from –25 mV to –75 mV[16-18]. All chemicals were purchased from Sigma Chemical Co. (St. Louis, MO. USA).

Statistics

Commercial software (OriginPro 7.5, Microcal; Northampton, MA, USA) was used for graphing and

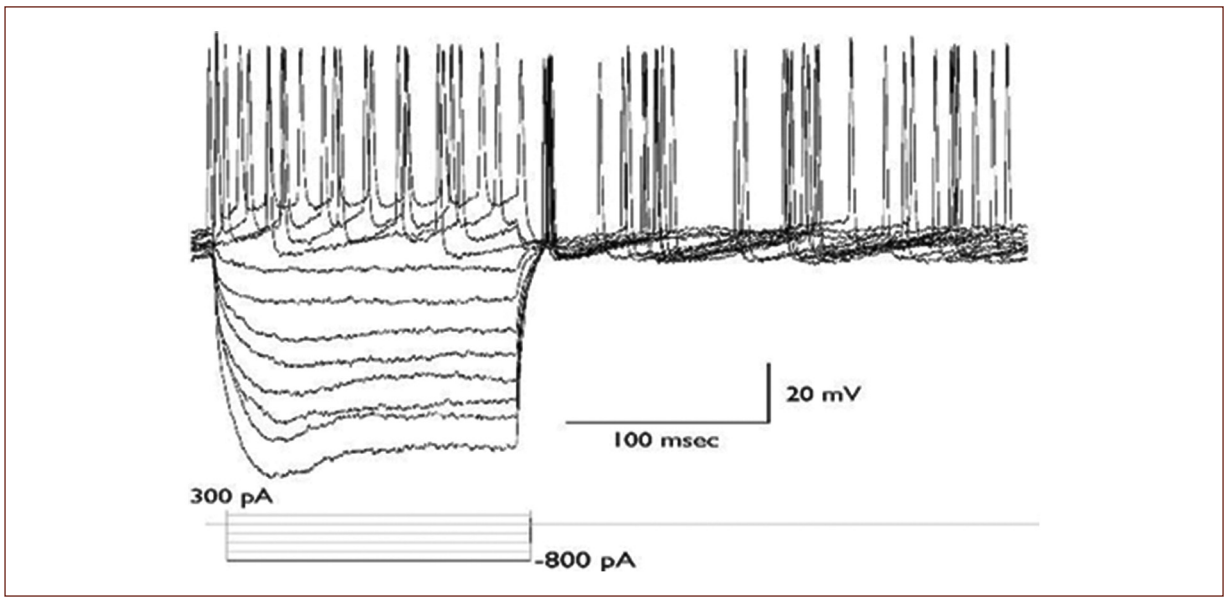

Figure 2. Example of membrane voltage response to current injection. Current pulses of 100-300 pA evoked a series of action potentials with little or no accommodation. During the injection of hyperpolarizing currents of −100 to −800 pA, neurons exhibited a voltage drop and showed a rebound upon cessation of hyperpolarization (see Methods).

statistical analysis. Student's T-test was used. Data are expressed as mean ± standard error of the mean, and a statistical significance value of $p < 0.05$ was considered.

Results

Spontaneous seizures after pilocarpine injection

In rats injected with pilocarpine, the average duration of SE was 46 ± 20 min. During the acute period of SE, there was a mortality rate of 66%. Eleven rats (34%) survived until electrophysiological recordings were obtained. During the 1st week after pilocarpine treatment, rats had, on average, one seizure per day. After 3 weeks of pospilocarpine, animals with SE exhibited 2-3 SRS daily. All animals were epileptic by the end of the 4th week.

I_M recording

I_M recordings were obtained from 60 pyramidal neurons in the CA1 region of the hippocampus. The current-clamp recording was performed at the beginning of each recording and before adding TTX to the recording chamber. Current-clamp pulses of + 300 to −800 pA were applied in 100 pA increments. Most cells showed an AP response with a gradual increase in the duration of the interval between potential and potential. This AP adaptation is characteristic of CA1 pyramidal neurons. Cells also showed the so-called "voltage sag" response, which consists of a slow hyperpolarization of the cell membrane due to the activation of the H current (Ih). Only cells that showed the characteristics of frequency adaptation and "voltage sag" were included in this study (Fig. 2). In voltage-clamp mode, responses were elicited by injecting voltage pulses of 800-1200 m duration from a holding potential of −25 mV to −75 mV in 10 mV increments (Fig. 3A). Fifty-five neurons in the control group showed on average resting membrane potential of −60 ± 0.75 mV, and sixty neurons in the pilocarpine-SE group had on average resting membrane potential of −55 ± 0.8 mV. This difference was not significant. Under these conditions, I_M appears as a slow, inward "relaxation" following an instantaneous (ohmic) drop in inward current. The current-voltage relationship revealed that increasing the amplitude of the voltage pulse increases the amplitude of I_M. The amplitude of I_M at −65 mV measured in CA1 neurons of pilocarpine-SE rats was significantly decreased compared with the control group (control: 208.72 ± 25.49 pA, n = 55; pilocarpine-SE: 49.28 ± 6.17 pA, n = 60; $p < 0.05$ Student's t-test) (Fig. 3B and

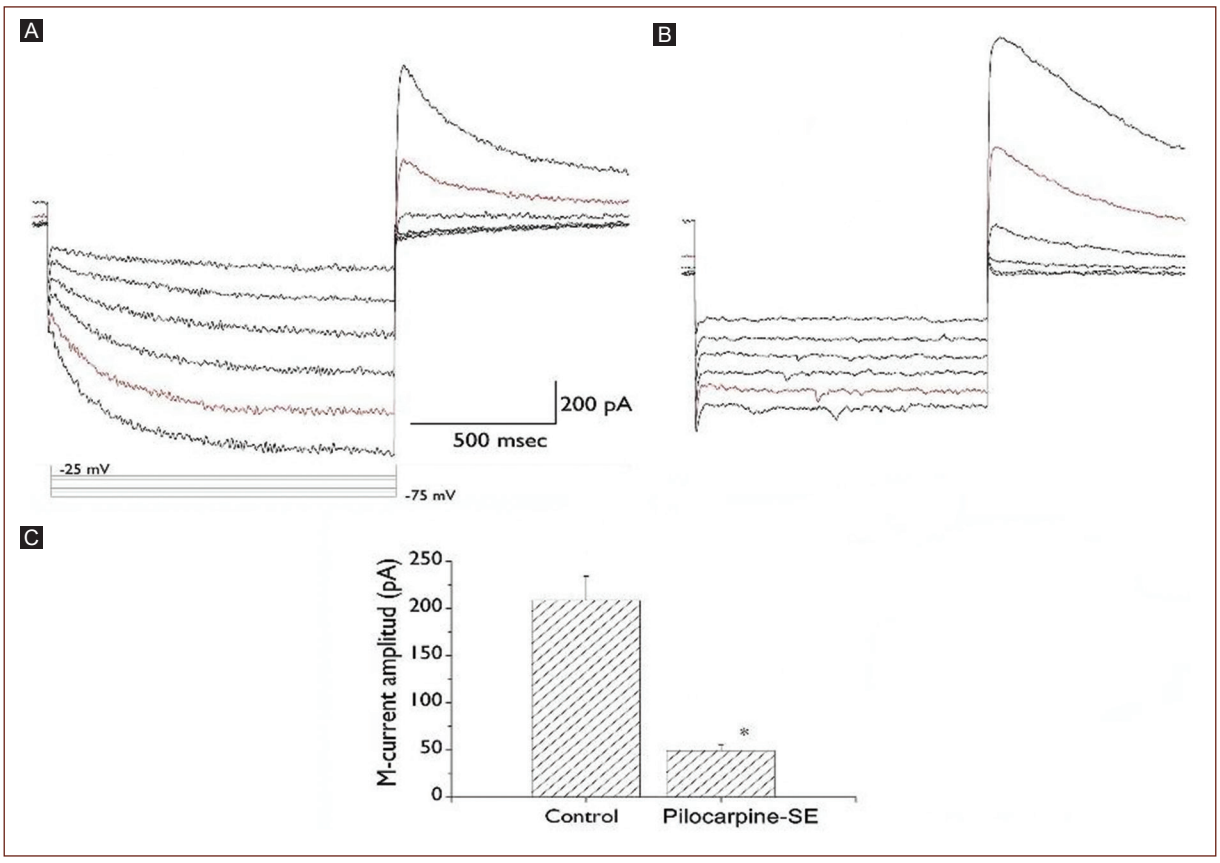

Figure 3. Representative recordings of current elicited in pyramidal neurons in hippocampal area CA1, obtained in voltage-clamp mode. **A:** control group, **B:** pilocarpine-SE group. Currents were elicited by applying hyperpolarizing voltage pulses of 1200 m duration from a holding potential of –25 mV to –75 mV in 10 mV increments (bottom of A). The I_M relaxation amplitude was determined by subtracting the instantaneous current at the beginning of the voltage pulse from the steady state at the end of the pulse, using the voltage change from –25 to –75 mV of the protocol (in red), **C:** summary of I_M amplitude. The amplitude of the I_M at –65 mV measured in hippocampal CA1 neurons of Pilocarpine-SE rats was significantly decreased compared with the control group (control, 208.72 ± 25.49 pA, n = 15; Pilocarpine-SE 49.28 ± 6.17 pA, n = 10; *p < 0.05, Student's T).

Table 1. The time constant of CA1 hippocampus neurons

CA1 neurones	Average time constant (τ)
Control (55 pyramidal neurons)	27.7 ± 17.7 msec
Pilocarpine-SE (60 pyramidal neurons)	48.9 ± 5.5 msec

The time constant of CA1 neurons was measured using whole-cell current-clamp recordings. An unpaired Student´s T-test revealed a significant increase in time constants in the pilocarpine-SE neurons compared to the control group ($p < 0.05$).

C). This study also assessed the cell surface by measuring the membrane capacitance. A significant increase in time constant was observed in pilocarpine-SE neurons (Table 1).

Discussion

In this study, we demonstrate that the amplitude of the I_M is significantly reduced in pyramidal cells of the CA1 area of the hippocampus after pilocarpine-induced SE. The channels responsible for this current are composed of KCNQ (Kv7) subunits[7], and mutations in most of them produce human and animal pathologies[19]. The importance of this current in neuronal excitability is established by the fact that a functional impairment of approximately 25% of KCNQ2/KCNQ3 heteromers seems to be sufficient to cause epileptogenesis[7].

The 23.6% reduction we observed in the I_M amplitude highlights the physiological importance of maintaining M-channel activity above a certain functional threshold. M-channels are activated by negative membrane

voltages. These non-inactivating Kv7 channels mediate a sustained outward current at negative potentials and may exert fundamental control over neuronal excitation and response patterns. M-channel activity potentially attenuates repetitive AP discharges[20]. This implies that a slight impairment of I_M converts the firing properties of neurons from a phasic pattern to a tonic pattern because M-channels may no longer function as efficient "brakes" in regulating neuronal excitability. Pharmacologically induced attenuation of M-channel activity dramatically increases neuronal firing and excitability *in vitro* such that a neuron with a phasic activity pattern can display a tonic activity pattern. Furthermore, the inhibition of synaptic M-channels can lead to increased propagation of evoked field potentials and facilitate the response to glutamate and/or GABA[21-24].

A transgenic mouse model, in which M-channel activity in the brain was reduced by mutation of KCNQ2 subunits and which suppresses M-channel activity, supported the observation that epileptic seizures, abnormal hyperactivity, attenuated afterhyperpolarization and some cognitive deficits presented by these transgenic animals may be associated with the alteration and consequent suppression of I_M[2,25]. Another known aspect to modify the state of the I_M channel is the administration of specific KCNQ blockers such as linopirdine or the compound known as XE991[2,26-28]. Administration of linopirdine causes epileptic activity in hippocampal slices and provides direct evidence of the involvement of KCNQ channels in the seizure process[26,29]. For this reason, it has been thought that these KCNQ channelopathies play an important role in human epilepsy, and it has been hypothesized that they occur after acquired disorders, such as the induction of SE. Therefore, the reduction in I_M amplitude observed could be part of the mechanism to explain the appearance of seizures after pilocarpine-induced SE, and changes in the time constant could reflect morphological alterations in the cell membrane that could be contributing to the generation of abnormal cell firing patterns. Considering the acute damage caused by SE, the silent interval between the lesion, the onset of spontaneous seizures, and the chronic status epilepticus in which I_M was measured, we can speculate about possible plastic changes, both structural and functional, that occur even in the axon hillock or initial segment. Structure in which sodium and potassium channels (Kv7), among others, are strategically distributed to regulate the neuron's firing. Apparently, the loss of the distance at which these channels are located from the neuronal soma could be contributing to the lack of homeostatic regulation of the intrinsic properties of neuronal excitability[30,31].

These findings are important for the scientific community since obtaining information on the mechanisms involved in epilepsy in humans is difficult for many reasons. The acquisition of epileptic tissue from patients undergoing epilepsy surgery is complicated since few hospital centers have the facilities to preserve it in good condition and then offer it for experimental studies. Therefore, scientifically, the use of animal models for experimentation is well accepted worldwide, which, from a morphological and functional point of view, shows alterations related to the pathologies that we observe in humans, such as epilepsy. These models allow us to postulate explanatory hypotheses about the neuronal mechanisms involved in epileptogenesis and the alterations it causes.

Conclusion

Neuronal excitability depends on several anatomo-functional factors, including membrane potential, ion channels, ion concentration, properties of the axon and dendrites, synapses, and neurotransmitters. The intrinsic electrical properties are controlled by several ion channels, including Kv7 channels, which are important regulators of brain function. KCNQ channels are also present in glial cells and regulate neuronal excitability by mediating the release of GABA through voltage-gated L-type Ca^{2+} channels.

Mutations in ion channels can be caused by various factors, including genetic and environmental factors, viral infections, and oxidative stress.

The SE caused by pilocarpine triggers a series of events that could increase the risk of mutations due to oxidative stress, inflammation, neuronal and glial damage[32], and various metabolic alterations. These factors could alter these channels' function, expression, or regulation, causing channelopathies, which manifest in neuronal diseases with significant morbidity. Therefore, a better understanding of the mechanism of epileptogenesis and channel opathies will lead to better design of drugs with anticonvulsant properties.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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