How Epilepsy Affects Action Potentials

Written by Aaliyah Beatrice Nakato Nsubuga

Abstract

Epilepsy is a neurological disorder characterized by recurrent seizures resulting from abnormal neuronal activity. Central to this pathology is the disruption of action potentials which are the fundamental electrical signals enabling neuronal communication. Under normal conditions, action potentials are generated through a regulated sequence of ion channel activations, maintaining neural stability. In epilepsy, genetic mutations, brain injuries, or infections can alter ion channel function, leading to neuronal hyperexcitability and the emergence of seizures. This paper explores the mechanisms by which epilepsy affects action potential generation and firing and neurotransmitter imbalances. By understanding these mechanisms, we can identify gaps in existing research and apply these to develop more targeted epilepsy treatments.

Introduction

Epilepsy is one of the most common neurological brain disorders worldwide, affecting more than 50 million people worldwide of all ages. It causes seizures, which occur when neurons fire electrical signals too quickly and erratically in the brain. At the core of epilepsy, lies an electrical malfunction in the brain which is the disruption of action potentials. This electrical impulse enables neurons to communicate. Understanding how action potentials are generated, regulated, and disrupted provides critical insight into neurological disorders like epilepsy, where abnormal action potentials lead to excessive and uncontrolled brain activity.

An action potential is a rapid, temporary change in membrane potentials that allows neurons to send signals. It is a nerve impulse that carries information from one neuron to the next. For this process to occur properly, neurons need a balance of positive and negative ions inside and outside the membrane, and functioning ion channels that open and close at the right times.

Epilepsy makes people more vulnerable to frequent, unprovoked seizures. These seizures happen when neurons fire too quickly and erratically. Causes of epilepsy can be structural, genetic, infectious, metabolic, immune, and unknown but what they have in common is the brain's normal electrical signals.

The purpose of this paper focuses on how epilepsy affects action potentials due to faulty ion channels, imbalanced excitatory and inhibitory signals, and how neurons become hyperexcitable, firing action potentials too often or at the wrong time.

Epilepsy

There are different causes of epilepsy, including genetic mutations, brain damage, infections, strokes, and tumors. Genetic conditions passed down in families result in altered neuronal function from birth, affecting channels such as sodium, potassium, and calcium channels (Banerjee & Jirsa, 2024; Brennan, Baram, & Poolos, 2016). Brain damage from injuries, infections, or other events can disrupt neuronal function, resulting in seizures. Head injuries, such as those from car accidents, cause neuronal damage (Bromfield, Cavazos, & Sirven, 2006). Infections like meningitis or encephalitis, caused by viral inflammation of the brain, may also lead to epilepsy (National Institute of Neurological Disorders and Stroke, 2025). Additionally, strokes that cause loss of blood flow lead to tissue death, as can brain tumors (World Health

Organization, 2024).

Seizures vary in type and origin, classifying epilepsy into four main categories: generalized epilepsy, focal epilepsy, combined generalized and focal epilepsy, and unknown epilepsy (Sherrell, 2021). Generalized epilepsy affects both sides of the brain. These seizures can be motor—such as jerking movements, muscle twitching, and full-body spasms—or non-motor, including absence seizures causing staring, sudden stops in movement, brief twitches, and fluttering eyelids (Sherrell, 2021). Focal epilepsy involves seizures localized to one part of the brain; these may remain localized or spread, often beginning with an aura, which feels like uneasiness in the stomach (Sherrell, 2021). Focal seizures can include motor symptoms such as muscle twitching and spasms or non-motor symptoms like changes in emotions and thoughts (Sherrell, 2021). Some individuals have combined generalized and focal epilepsy, such as in Dravet syndrome, a rare severe epilepsy beginning in infancy, characterized by prolonged seizures and developmental challenges (Sherrell, 2021). Unknown epilepsy is diagnosed when seizure origin cannot be determined, with symptoms including motor tonic-clonic seizures (stiffening, loss of consciousness, rhythmic jerking, convulsing, loss of bowel control) and non-motor symptoms like vacant staring and stillness (Sherrell, 2021).

Although treatments such as anti-epileptic drugs, surgery, and dietary therapies exist, one-third of patients have drug-resistant epilepsy, not responding well to medication (Wirrell, 2020). Understanding the contribution of action potentials to seizure activity remains important for advancing treatment (Stafstrom, 2007).

Membrane Potential and Action Potential Phases

Membrane potential refers to the difference in electrical charge between the inside and

outside of a neuron. At rest, the inside of the neuron is more negatively charged than the outside, causing the resting membrane potential to be around –70 mV (Resting potential Definition and Examples, 2019). A high concentration of positively charged sodium ions and negatively charged chloride ions are found outside the cell, while positively charged potassium ions and organic anions are concentrated inside the cell (Resting potential Definition and Examples, 2019). The resting membrane potential is maintained by the sodium-potassium pump, a transport protein that uses energy to actively pump 3 Na^+ ions out and 2 K^+ ions in, maintaining a negative charge inside the cell (Resting potential Definition and Examples, 2019). The neuron is surrounded by extracellular fluid and contains intracellular fluid, with the membrane acting as a barrier to keep these two fluids separate (Themes, 2016).

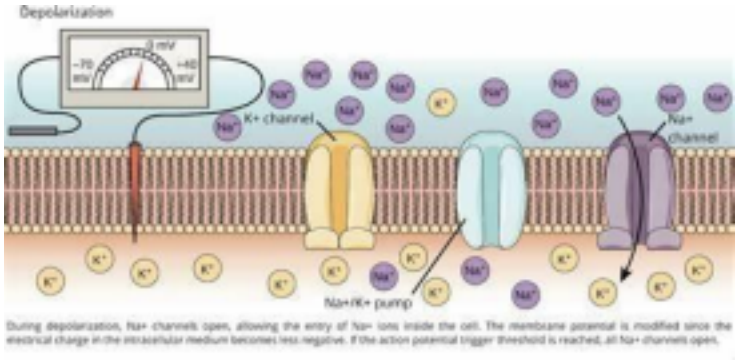

Figure 1. Resting potential is the difference in electrical potential across the plasma membrane when the cell is not stimulated or when the cell is in a state of relaxation

An action potential is a rapid, temporary change in membrane potentials that allows neurons to send electrical signals. The phases of an action potential are as follows: The resting membrane potential is approximately –70 mV. When the neuron reaches the threshold of around –55 mV, an action potential is initiated. During depolarization, Na^+ channels open, allowing sodium ions to rush into the cell and causing the membrane potential to spike to +40 mV (rising phase). In the repolarization phase, Na^+ channels close while K^+ channels open, permitting

potassium ions to exit the cell and restoring the negative charge inside. During hyperpolarization, open potassium channels increase K^+ permeability, making the membrane potential more negative and preventing the neuron from firing another action potential immediately (refractory period). Finally, the membrane potential returns to its resting state (Themes, 2016; Threshold Potential, 2019).

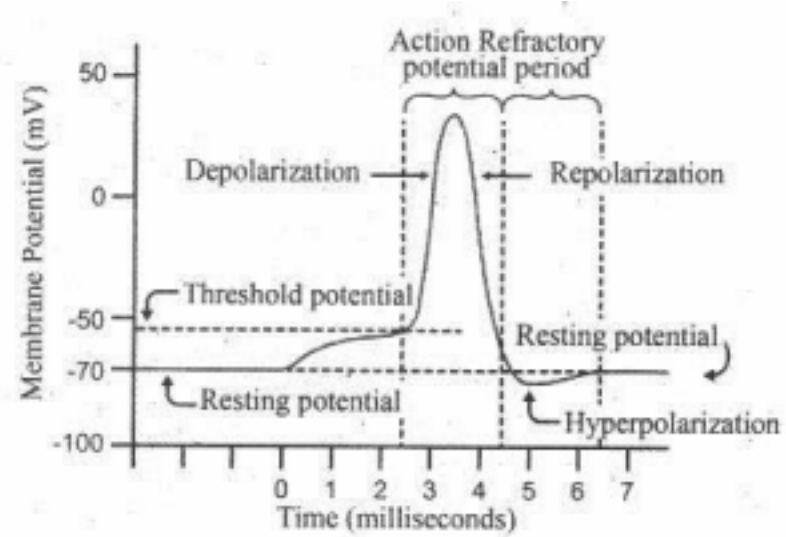

Figure 2. A visual diagram of a full action potential

Pathophysiology of Epilepsy

The relationship between epilepsy and action potentials centers on two key characteristics of seizures: neuronal hyperexcitability and hypersynchrony. Hyperexcitability means neurons are more likely to fire action potentials unusually, while hypersynchrony means they fire together simultaneously (Banerjee & Jirsa, 2024; Themes, 2016). Normally, an action potential is generated when sodium (Na^+) channels open, allowing sodium ions into the cell and causing depolarization. Na^+ channels then close while potassium (K^+) channels open, allowing K^+ to exit and restore the resting potential (Themes, 2016). In epilepsy, Na^+ channels stay open longer than normal, depolarizing neurons excessively, and K^+ channels may not open properly, which prevents the neuron from returning easily to its resting state, leading to repetitive, uncontrolled

neuronal firing (Brennan, Baram, & Poolos, 2016; Banerjee & Jirsa, 2024).

Another key factor is neurotransmitter imbalance, as the brain requires a balance between excitation and inhibition for normal function. Glutamate is the main excitatory neurotransmitter, while gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter. In epilepsy, increased excitatory transmission and decreased inhibitory transmission further elevate neuron firing and seizure risk (Chen et al., 2023; Perucca, White, & Bialer, 2023).

Structural brain abnormalities also contribute to seizures. One hallmark of seizure-prone neurons in epileptic brain tissue is the paroxysmal depolarizing shift (PDS), a prolonged depolarization of the neuron membrane potential by 20–70 mV. During seizures, many neurons may undergo synchronized PDS, causing waves of excessive electrical activity to spread across the brain (Laryushkin et al., 2023; Bromfield, Cavazos, & Sirven, 2006). Generally, this synchronized activity involves both hemispheres; in focal seizures, it may remain localized but still cause significant dysfunction in the affected area (Sherrell, 2021). Disruptions in K^+ channels prolong action potentials, making it harder to restore neurons to resting potential and reducing inhibitory control (Ni et al., 2025). Once initiated, hyperexcitability amplifies and spreads to neighboring neurons, sustaining a continuous cycle (Banerjee & Jirsa, 2024).

Gaps in Research

While it is understood that epilepsy disrupts neuronal excitability, more research is needed to clarify how specific ion channels and neurotransmitters contribute to abnormal action potentials. Current treatments focus on seizure control rather than correcting underlying action potential dysfunctions. Researchers are pursuing precision medicine approaches, but progress is gradual (Wirrell, 2020). Treatment accessibility is also a concern; the Intersectoral

Global Action Plan on Epilepsy (IGAP) reports that 75% of people in lower-income countries lack access to treatment, limiting research on epilepsy's impact across diverse populations (How the ILAE works, 2021). Emerging studies suggest neuroinflammation may alter neuronal firing patterns, but exact mechanisms remain unclear (Banerjee & Jirsa, 2024).

Treatments

Epilepsy is a condition that usually requires long-term treatment. Most current treatments aim to stabilize action potential generation and reduce neuronal hyperexcitability. Antiepileptic drugs (AEDs) work by targeting specific ion channels. For example, sodium channel blockers like carbamazepine reduce sodium influx, thereby decreasing neuronal excitability (Wirrell, 2020; Brennan, Baram, & Poolos, 2016).

New therapies also focus on restoring the excitatory-inhibitory balance by enhancing GABA activity or reducing glutamate release to help prevent seizures from spreading (Perucca, White, & Bialer, 2023; Chen et al., 2023). In cases of drug-resistant epilepsy, treatments such as vagus nerve stimulation, ketogenic diets, or surgical removal may be used (Wirrell, 2020; World Health Organization, 2024).

Conclusion

Epilepsy results from disrupted electrical signaling in the brain, primarily through changes in action potential generation. With continued understanding of how ion channels, neurotransmitters, and action potentials in epilepsy, more precise and equitable treatment strategies can be developed.

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