Fifth lecture

Leakage Current Across Cell Membrane

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Fourth Stage

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2023- 2024

Leakage Current Across Cell Membrane

Non-gated channels are ion channels that are always open. Another common name for these channels is “leak” channels, because they simply allow ions to pass through the channel without any impedance.

There for An ion channel in a cell membrane that is always open, making the membrane permeable to ions. Synonym: nongated channel.

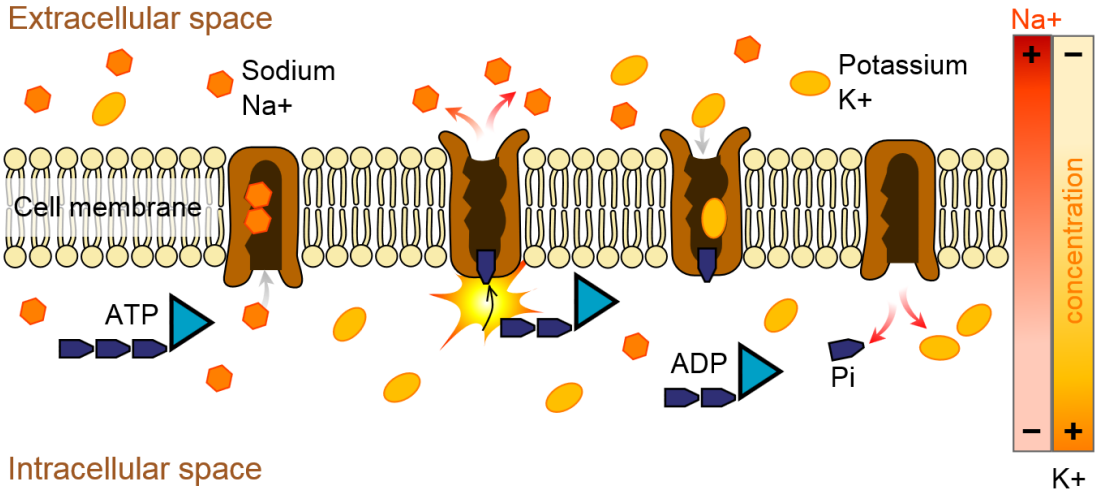
What generates the resting membrane potential is the K+ that leaks from the inside of the cell to the outside via leak K+ channels and generates a negative charge in the inside of the membrane vs the outside. At rest, the membrane is impermeable to Na+, as all of the Na+ channels are closed.

Who can the leakage?

In neurons, potassium ions are maintained at high concentrations within the cell while sodium ions are maintained at high concentrations outside of the cell. The cell possesses potassium and sodium leakage channels that allow the two cations to diffuse down their concentration gradient.

Types Of Leakage

Leakage channels are the simplest type of ion channel, in that their permeability is more or less constant. The types of leakage channels with the greatest significance in neurons are potassium and chloride channels.



What are motor neuron diseases?

Motor neuron diseases (MNDs) are a group of progressive neurological disorders that destroy motor neurons, the cells that control skeletal muscle activity such as walking, breathing, speaking, and swallowing. This group includes diseases such as amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome.

Messages or signals from nerve cells in the brain (upper motor neurons) are typically transmitted to nerve cells in the brain stem and spinal cord (lower motor neurons) and then to muscles in the body. Upper motor neurons direct the lower motor neurons to produce muscle movements.

When the muscles cannot receive signals from the lower motor neurons, they begin to weaken and shrink in size (muscle atrophy or wasting). The muscles may also start to spontaneously twitch. These twitches (fasciculations) can be seen and felt below the surface of the skin.

When the lower motor neurons cannot receive signals from the upper motor neurons, it can cause muscle stiffness (spasticity) and overactive reflexes. This can make voluntary movements slow and difficult. Over time, individuals with MNDs may lose the ability to walk or control other movements.

MNDs are classified according to whether the loss of function (degeneration) is inherited (passed down through family genetics); sporadic (no family history); and whether they affect the upper motor neurons, lower motor neurons, or both.

In cases where a motor neuron disease is inherited, it is usually caused by mutations in a single gene. These conditions are usually inherited in one of several patterns:

- Autosomal dominant means that a person needs to inherit only one copy of the defective gene from one parent with the disorder to be at risk of the disease. There is a 50 percent chance that a child of an affected person will inherit the abnormal gene and develop the disease.
- Autosomal recessive means a person must inherit a copy of the defective gene from each parent. These parents are likely to be asymptomatic (without symptoms of the disease). Autosomal recessive diseases often affect more than one person in the same generation (e.g., siblings).
- X-linked inheritance occurs when the female parent carries the gene on one X chromosome and passes the disorder along to male children. Male children inherit an X chromosome from female parent and a Y chromosome from their male parent. Male children have a 50 percent risk of inheriting the abnormal X chromosome and developing the disease. Female children inherit an X chromosome from each parent. Female children have a 50 percent chance of inheriting their female parent's X chromosome and a safe X chromosome from their male parent, which usually makes them asymptomatic carriers of the mutation.

Though there are several types of MNDs, they all cause muscle weakness

that gradually worsens over time and leads to disability. In some cases, these diseases are fatal. Respiratory insufficiency, a condition in which the lungs cannot properly take in oxygen or expel carbon dioxide, is a feature of most MNDs. Symptoms may include breathlessness, shortness of breath that occurs while lying down, recurrent chest infections, disturbed sleep, poor concentration and/or memory, confusion, morning headaches, and fatigue.

Common Motor Neuron Diseases

1.Amyotrophic lateral sclerosis (ALS), also known as classical motor neuron disease, affects both the upper and lower motor neurons. It causes rapid loss of muscle control and eventual paralysis. Many doctors use the term motor neuron disease and ALS interchangeably.

Early symptoms of ALS usually include muscle weakness or stiffness in a limb or muscles of the mouth or throat (so-called bulbar muscles). Gradually almost all the muscles under voluntary control are affected, and individuals lose their strength and the ability to speak, eat, move, and even breathe. Most people with ALS die from respiratory failure, usually within three to five years from the onset of symptoms. However, about 10 percent of people with ALS survive for 10 or more years.

2.Progressive bulbar palsy (PBP), also known as progressive bulbar atrophy, attacks the lower motor neurons connected to the brain stem. The brain stem (bulbar region) controls the muscles needed for swallowing, speaking, chewing, and other functions.

Symptoms, which worsen over time, include trouble chewing, speaking, and swallowing. Individuals may also have weakness in their tongue and facial muscles, twitches, and a reduced gag reflex. They may also experience weakness in their arms or legs, but it is less noticeable than other symptoms.

Because they have difficulty swallowing, individuals are at risk of choking and inhaling food and saliva into the lungs. People can also have emotional changes and may begin to laugh or cry at inappropriate times (called pseudobulbar affect or emotional lability). Some symptoms of stroke and myasthenia gravis are similar to those of progressive bulbar palsy and must be ruled out prior to diagnosis.

3.Primary lateral sclerosis (PLS) affects only the upper motor neurons, causing the movements in the arms, legs, and face to be slow and difficult. The disorder often affects the legs first, followed by the torso, arms and hands, and, finally, the muscles used for swallowing, speaking, and chewing.

The legs and arms become stiff, clumsy, slow, and weak, making it difficult to walk or carry out tasks requiring fine hand coordination. Speech may become slowed and slurred. Individuals may have difficultly balancing, increasing the risk of falls. Affected individuals may also experience emotional changes and become easily startled.

4.Progressive muscular atrophy (PMA) is a rare disease marked by slow but progressive damage to only the lower motor neurons. It largely affects men, and usually at a younger age than most other adult-onset MNDs. Weakness is typically seen first in the hands and then spreads into the lower body, where it can be severe. The torso muscles and breathing may become affected. Exposure to cold can worsen symptoms. Other symptoms may include:

- Muscle wasting (shrinking)
- Clumsy hand movements
- Twitches
- Muscle cramps

5.Spinal muscular atrophy (SMA) is an inherited disease that affects lower motor neurons. It is the most common genetic cause of infant mortality. Defects in the *SMN1* gene result in a loss of the SMN protein, which causes the lower motor neurons to deteriorate, producing muscle weakness and wasting. This weakness is often worse in the proximal muscles, which are closer to the center of the body (e.g., torso, thigh, and arm), than distal muscles which are further away (e.g., hands and feet).

SMA is classified into three main types—based on age of onset, severity, and progression of symptoms. Generally, the earlier symptoms start to appear, the greater the impact on motor function. All three main types are caused by defects in the *SMN1* gene.

6.Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare, genetically distinct form of SMA. The disorder is caused by mutations in the *IGHMBP2* (immunoglobulin helicase μ-binding protein 2) gene. Symptoms appear during infancy, between ages 6 weeks and 6 months. Children with SMARD1 suddenly may be unable to breathe due to diaphragm paralysis and may develop weakness in their

distal muscles.

7.Congenital SMA with arthrogryposis is a rare disorder that appears at birth. Symptoms include severe muscle contractures, making babies unable to extend or flex the affected joints. In the majority of cases, both the arms and legs are affected. Other symptoms include scoliosis, chest deformity, respiratory problems, unusually small jaws, and drooping of the eyelids.

8.Kennedy's disease (also known as spinal and bulbar muscular atrophy, bulbo-spinal muscular atrophy, X-linked spinal and bulbar muscular atrophy) is an X-linked recessive disease that affects men. It is caused by mutations in the gene for the androgen receptor. Daughters of individuals with Kennedy's disease are carriers and have a 50 percent chance of having a son affected with the disease.

The onset of symptoms varies but most commonly the disease is first recognized between 20 and 40 years of age. Generally, the disease progresses very slowly. Early symptoms may include:

- Tremor of outstretched hands
- Muscle cramps during physical activity
- Muscle twitches
- Weakness of the facial, jaw, and tongue muscles, leading to problems with chewing, swallowing, and speaking

9.Post-polio syndrome (PPS) can strike polio survivors up to four decades after they have recovered from the initial illness, which can cause major damage to motor neurons. Symptoms include fatigue, muscle and joint weakness, and pain that slowly gets worse over time, muscle atrophy and twitches, and decreased tolerance to cold. These symptoms appear most often among muscle groups affected by the initial polio illness. Other symptoms include difficulty breathing, swallowing, or sleeping.

Older people and those individuals most severely affected by the earlier disease are more likely to experience symptoms. Some individuals experience only minor symptoms, while others develop muscle atrophy that may be mistaken for ALS. PPS is usually not life-threatening. Doctors estimate that 25 to 50 percent of survivors of polio generally develop PPS.

How are motor neuron diseases diagnosed and treated?

Diagnosing MNDs

In many cases, there are no specific tests to diagnose MNDs. Symptoms may vary among individuals and, in the early stages, may be similar to those of other diseases, making diagnosis difficult. However, there are gene tests for SMA, Kennedy's disease, and some causes of familial ALS.

A physical exam should be followed by an extensive neurological exam. The exam assesses motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior.

The following two tests, which may be considered an extension of the neurological examination, are the most important. These tests, usually done together, can identify the differences between muscles diseases and MNDs.

1. Electromyography (EMG) is used to diagnose disorders of lower motor neurons, as well as disorders of muscle and peripheral nerves. It assesses the electrical activity during movement and at rest.
2. A nerve conduction study is usually done in combination with an EMG. Nerve conduction studies measure the speed and size of the impulses in the nerves from small electrodes taped to the skin.

Additional tests may include:

- Laboratory tests of blood, urine, or other substances can rule out muscle diseases and other disorders that may have symptoms similar to MNDs.
- Magnetic resonance imaging (MRI) can help diagnose brain and spinal cord tumors, eye disease, inflammation, infection, and vascular irregularities that may lead to stroke. MRI can also detect and monitor inflammatory disorders such as multiple sclerosis and can document brain injury from trauma. It is often used to rule out diseases that affect the head, neck, and spinal cord. Magnetic resonance spectroscopy is a type of MRI scan that measures chemicals in the brain and may be used to evaluate the integrity of the upper motor neurons.

- Muscle or nerve biopsy can help confirm nerve disease and nerve regeneration; however, it is an invasive procedure and many experts do not believe it is needed to diagnose MND.

Treating MNDs

There is no cure or standard treatment for MNDs. Symptomatic and supportive treatment can help individuals be more comfortable while maintaining their quality of life. Multidisciplinary clinics, with specialists from neurology, physical therapy, respiratory therapy, and social work are particularly important in the care of individuals with MNDs.

Medication

- Riluzole is the first drug approved by the U.S. Food and Drug Administration (FDA) to treat ALS, however it cannot reverse the damage already done to motor neurons.
- Edaravone, an antioxidant approved by the FDA to treat ALS, slows down the decline of physical function and prevents disease progression in people with ALS.
- Nusinersen, the first drug to treat children and adults with SMA approved by the FDA, is a type of treatment called anti-sense oligonucleotide therapy and works by increasing the SMN protein necessary for the muscles and nerves to work normally.
- Onasemnogeme abeparovec-xioi (Zolgensma™) gene therapy was approved by the FDA for children less than 2 years old who have infantile-onset SMA. A safe virus delivers a fully functional human SMN gene to the targeted motor neurons, which in turn improves muscle movement and function, and also improves survival.
- Muscle relaxers such as baclofen, tizanidine, and the benzodiazepines may reduce muscle stiffness and help muscle spasms.
- Botulinum toxin injections may be used to treat muscle stiffness by weakening overactive muscles. They may be injected into the salivary glands to stop drooling.

Excessive saliva also can be treated with medications such as amitriptyline, glycopyrrolate, and atropine.

Supportive therapies

- Physical therapy and rehabilitation may help improve posture, prevent joint immobility, and slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce stiffness, as well as increase range of motion and circulation. Some individuals require additional therapy for speech, chewing, and swallowing difficulties. Applying heat may relieve muscle pain. Assistive devices such as supports or braces, orthotics, speech synthesizers, and wheelchairs may help some people maintain independence.
- Proper nutrition and a balanced diet are essential to maintaining weight and strength. People who cannot chew or swallow may require a feeding tube.
- Non-invasive positive pressure ventilation (NIPPV) , also known as ventilators, can prevent sleep apnea at night. Some individuals may also require assisted ventilation during the day due to muscle weakness in the neck, throat, and chest.

The outlook for individuals with MNDs varies depending on the type and the age the symptoms begin. MNDs, such as PLS or Kennedy's disease, are usually not fatal and progress slowly. People with SMA type III may be stable for long periods. Some forms of MND, such as the severe form of SMA and ALS, are fatal.