Lecture 08. Diseases of Ion Channels

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Pre-class assignment: Complete the Lecture 8 diagnostic quiz (in the Extra Pre-lecture Activities folder) by Friday, Feb. 1 at 12:20 PM.

Lecture Objectives:

1. To learn how the disruption of the function of ion channels leads to some neurological diseases.

    a. To know what changes in ion channels can disrupt their function and lead to disease or death.

    b. To know some of the many diseases of ion channels and the types of mutations that cause them.

2. To learn to appreciate the importance of having a good set of ion channels!

Lecture Outline

The importance of ion channels is revealed by the severe consequences of altering their normal function. In this lecture, we will explore some links between ion channel dysfunction and disease, with the emphasis on so-called channelopathies.

1. **Remember from the beginning of my lectures that channels and ion flows are targeted by many animals to kill other animals. Classic examples of this include:**

    A. Puffer fish and newts use tetrodotoxin, a sodium channel blocker, for defense, There are many such toxins – e.g. those used by cone snails to hunt prey.
    B. Humans kill other humans by altering the potassium gradient in lethal injection procedures.

2. **How can channel function go awry in disease?**

    A. Changes in the promoter of the channel gene can lead to too few or too many channels.
    B. Changes in the channel coding region of the gene that can lead to loss of function or a change (gain) of function, both of which can be bad.
    C. Defective regulation of channel function - by second messengers for example.
    D. Auto-antibodies to channels that disrupt their function.

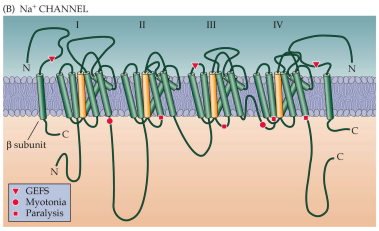
3. **Examples of channel disruption in disease.**

A. First K channel cloned was shaker, which was identified as a mutation in fruit flies that led to an abnormal shaking when they were exposed to ether.

B. Equine hyperkalaemic periodic paralysis.
a. Symptoms of hyperexcitability and paralysis in quarter horses.
b. An autosomal dominant mutation found in1 in 50 quarter horses – traced to single ancestor and a mutation in the muscle sodium channel.

C. Human hyperkalaemic periodic paralysis (HyperPP), paramyotonia congenital (PC) and potassium aggravated myotonias (PAM)
a. Lead to muscle hyperexcitability or weakness exacerbated by potassium or cold. Usually onset in second decade of life and dominant with linkage to the sodium channel expressed in muscle (called SCN4A).
b. Triggered by a rise in potassium levels.
c. Sodium channels fail to inactivate properly.
d. Cloned mutations reveal single amino acid changes in parts of the channel important for inactivation.

D. Febrile seizures and GEFS.



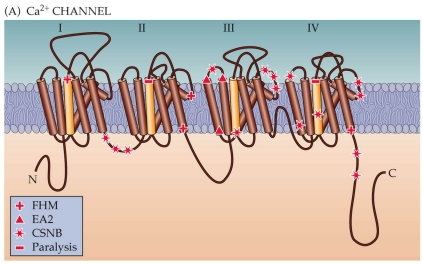
a. Convulsions during fever affecting about 3% of children under 6 – some develop general epilepsy later in life so called Generalized epilepsy with febrile seizures (GEFS).

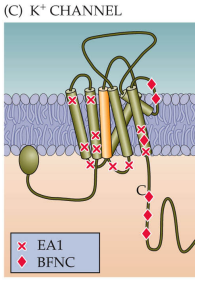
b. Mapped to beta subunit of the neuronal sodium channel (SCN1B). The mutation slows the rate of inactivation leading to hyperexcitability.

E. Episodic Ataxia Type-1 (EA1).
a. Attacks of imbalance and uncoordinated movements triggered by things like stress or alcohol that can last minutes or hours.
b. Autosomal dominant mutation affecting the peripheral and central nervous system.
c. Gene maps to Kv1.1, a potassium channel expressed in synaptic terminals and dendrites of neurons.
d. Expression of the different mutations leads to a non-functional channel or a channel with reduced potassium conductance and a prolonged action potential. Because affected individuals are heterozygote for the mutation, the mutated subunit must alter the conductance in channels formed by both normal and mutant subunits.

F. Familial hemiplegic migraine (FHM)
a. migraines lasting 1-3 days

b. calcium channel mutations – some in pore and others elsewhere, with slightly different symptoms depending on location.





Study Questions:

1. What are some of the ways that channel function can be disrupted to lead to disease states?

2. What are some of the diseases of ion channels? What channels are affected and how do the changes lead to the disease?