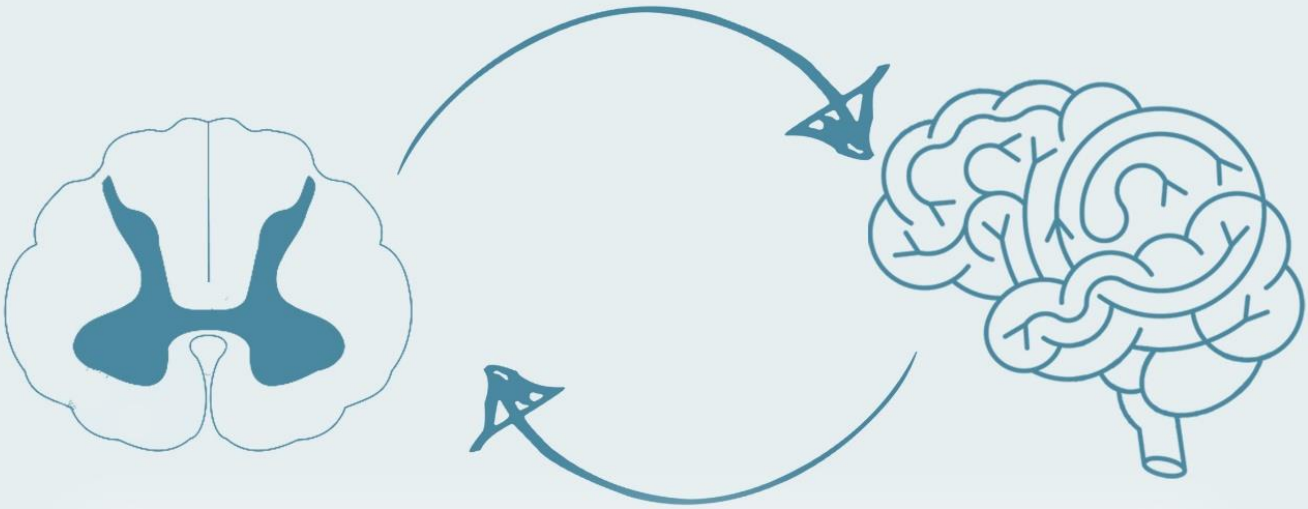

CNS

physiology

slides | sheets

number: 2

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At the end of this sheet you should be able to understand the general characteristics of action potential and some of its clinical applications in the CNS spectrum.

Action potential is produced by several types of stimuli. It starts with a depolarization phase (caused by the opening of the sodium voltage-gated channels), and ends with a repolarization phase (caused by the opening of potassium voltage-gated channels).

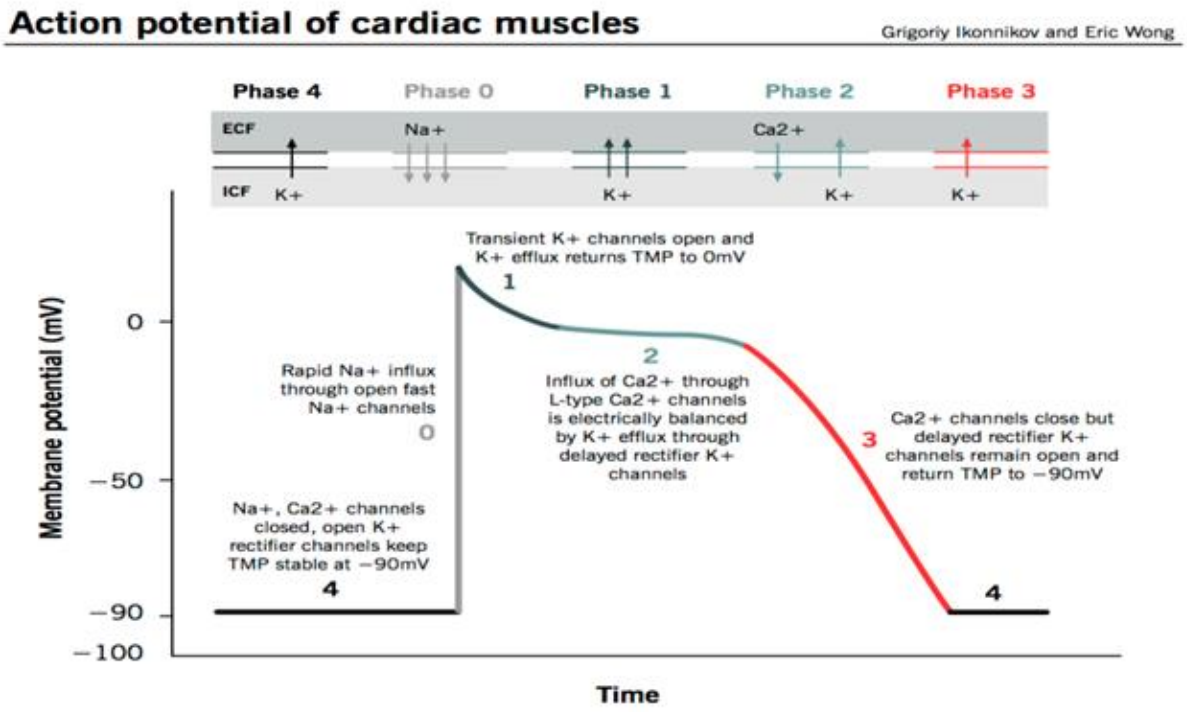
Remember:

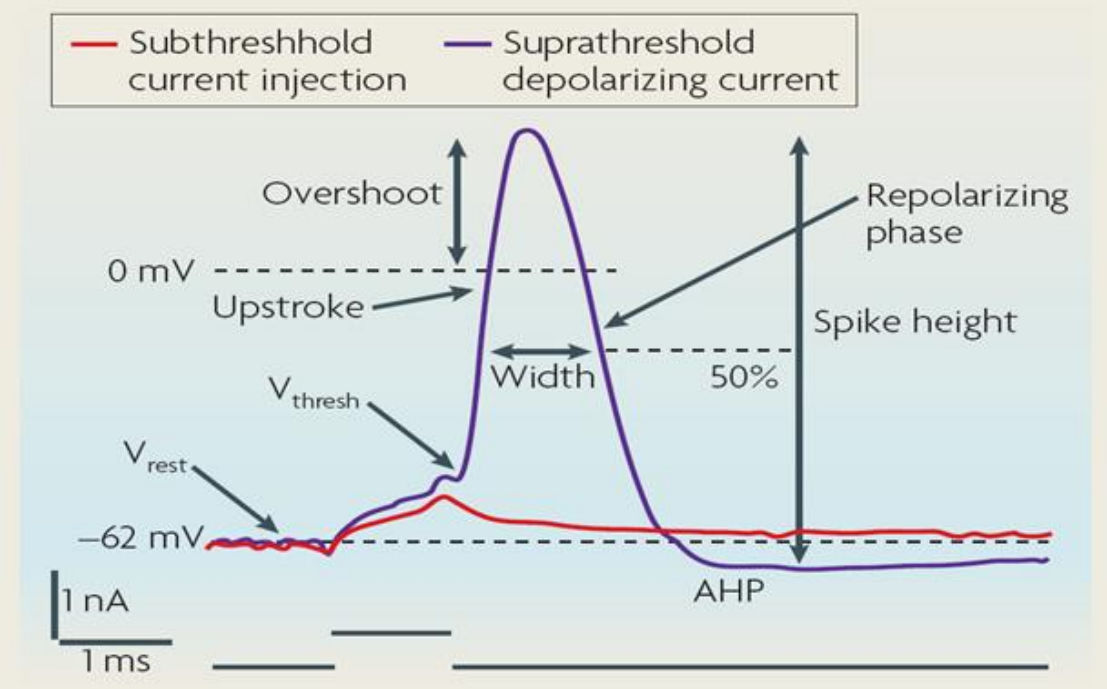
The action potential follows the **ALL or NONE** principle, which means it has the same shape, peak, threshold every time the cell is excited, causing the action potential to move from axon hillock to axon terminal.

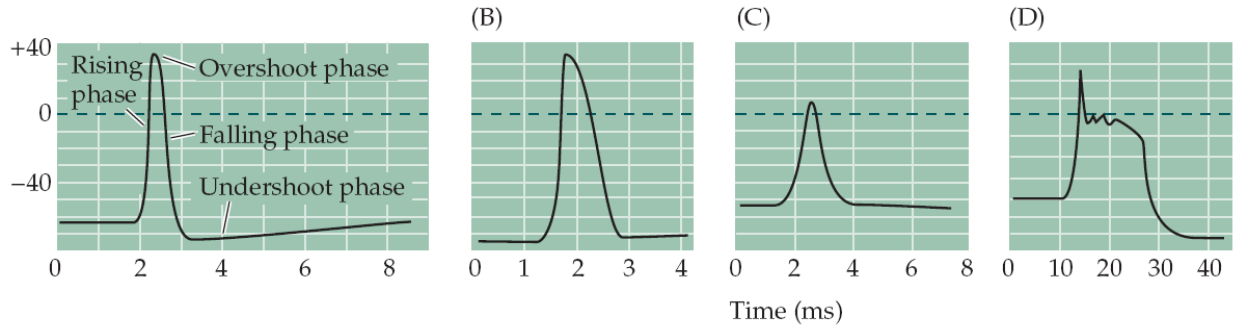
- **The threshold** is determined by the potential which causes the opening of the sodium voltage gated channels (since the action potential starts when they open).
- **The peak of the action potential** is determined by the time by which the sodium channels close (inactivation) and the potassium channels open (activation).
- **The relative refractory period** is determined by the after-hyperpolarization period, which affects differentiation and frequency of stimuli.
- **The frequency of the action potential** is determined by the number of stimuli (when increasing the number of stimuli, the frequency of the action potential increases without affecting the peak and width).
- **The width of the action potential** is determined by the number of sodium channels (more sodium channels means faster ion flow so less width), that's why inhibiting sodium channels with drugs affects the width of the action potential.

Therefore, different neurons can have action potentials with different threshold, peak, refractory period, firing frequency and width based on the parameters mentioned above.

The following diaphragm resembles the role of Ca^{+2} channels to prevent tetanization in cardiac muscle (longer refractory period means more time for the muscle to relax)







Now, have a look at the previous diagram and notice the different types of AP shapes in different cell types. Remember that the shape of AP is constant in the same cell type but could be different in different types of cells

In figure (D) in the previous diagram you can see an AP of the inferior olive cells in the brain stem of the brain. (it resembles an action potential like that of cardiac muscle cells)

Channellopathies:

genetic mutation in one or more ions' channels, resulting in a different action potential than the normal one. It's one of the causes of epilepsy. For example, when we have a neuron with a specific number of ion channels which determines maximal frequency, if it gets mutated, the shape and frequency of action potential will change, therefore resulting in diseases/abnormalities.

If we have a mutation in an ion voltage gated channel in the PNS, it will result in pain and arrhythmia. If this mutation occurred in a muscle, it will result in myotonic and periodic paralysis. If this mutation occurred in cerebellum or brain stem, it will result in ataxia (dysregulation or lack of coordination of movements) or ***hyperekplexia*** (inappropriate starting response بيجفل فجأة).

Any Channellopathy in the brain's cortex will result in migraine or epilepsy.

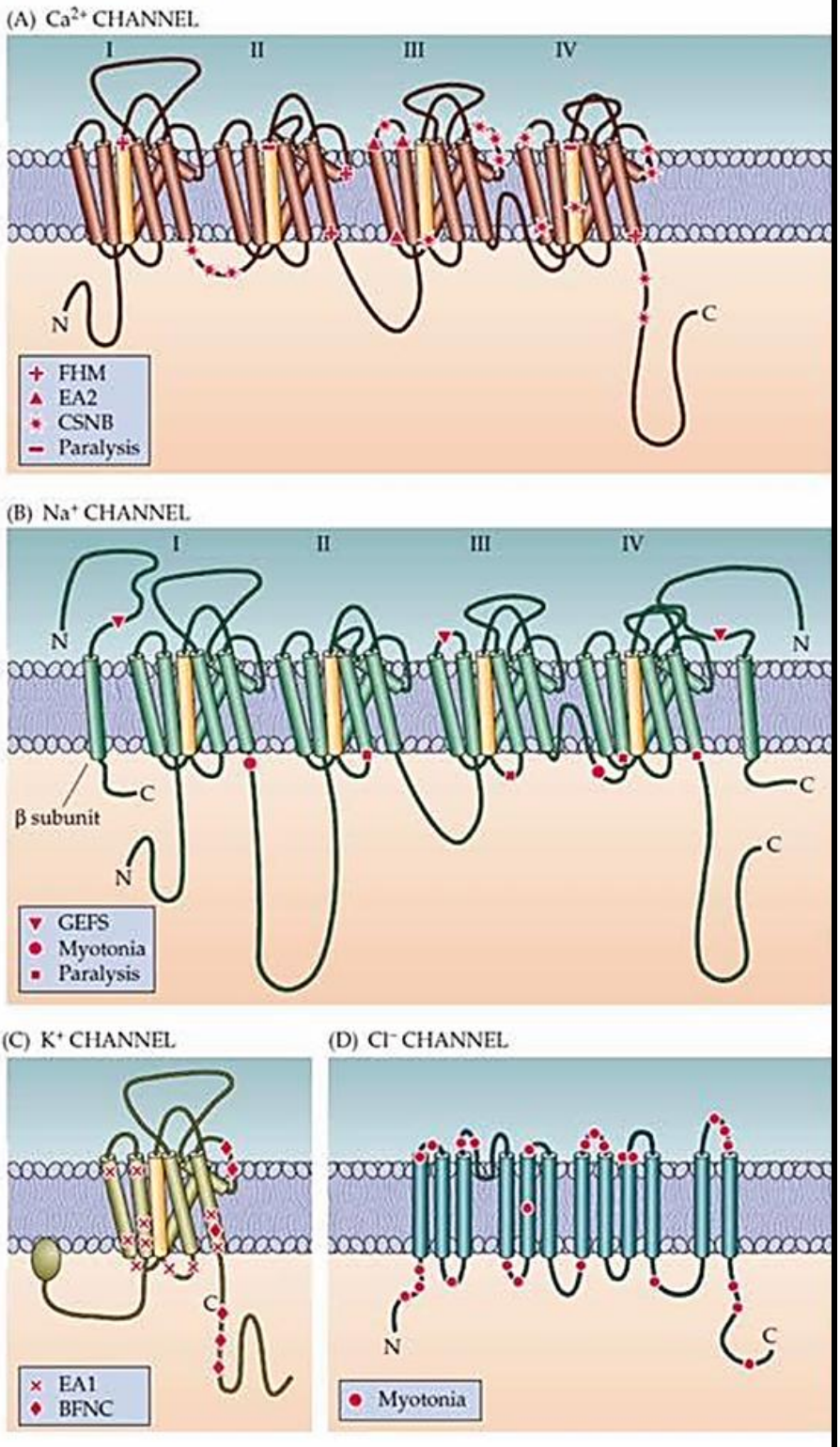
Box D

Diseases Caused by Altered Ion Channels

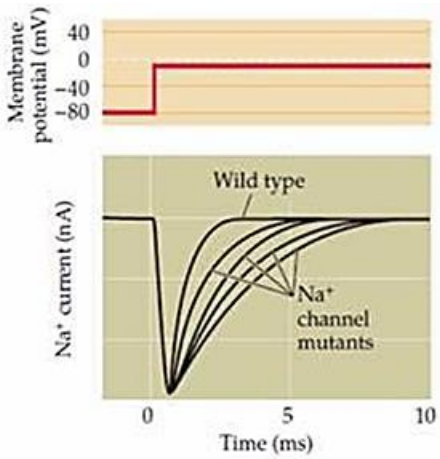
Several genetic diseases, collectively called *channelopathies*, result from small but critical alterations in ion channel genes. The best-characterized of these diseases are those that affect skeletal muscle cells. In these disorders, alterations in ion channel proteins produce either myotonia (muscle stiffness due to excessive electrical excitability) or paralysis (due to insufficient muscle excitability). Other disorders arise from ion channel defects in heart, kidney, and the inner ear.

Channelopathies associated with ion channels localized in brain are much more difficult to study. Nonetheless, voltage-gated Ca^{2+} channels have recently been implicated in a range of neurological diseases. These include episodic ataxia, spinocerebellar degeneration, night blindness, and migraine headaches. *Familial hemiplegic migraine* (FHM) is characterized by migraine attacks that typically last one to three days. During such episodes, patients experience severe headaches and vomiting. Several mutations in a human Ca^{2+} channel have been identified in families with FHM, each having different clinical symptoms. For example, a mutation in the pore-forming region of the channel produces hemiplegic migraine with progressive cerebellar ataxia, whereas other mutations cause only the usual FHM symptoms. How these altered Ca^{2+} channel properties lead to migraine attacks is not known.

Episodic ataxia type 2 (EA2) is a neurological disorder in which affected individuals suffer recurrent attacks of abnormal limb movements and severe ataxia. These problems are sometimes accompa-



Genetic mutations in (A) Ca^{2+} channels, (B) Na^{+} channels, (C) K^{+} channels, and (D) Cl^{-} channels that result in diseases. Red regions indicate the sites of these mutations; the red circles indicate mutations. (After Lehmann-Horn and Jurkat-Kott, 1999.)



Mutations in Na^+ channels slow the rate of inactivation of Na^+ currents. (After Barchi, 1995.)

nied by vertigo, nausea, and headache. Usually, attacks are precipitated by emotional stress, exercise, or alcohol and last for a few hours. The mutations in EA2 cause Ca^{2+} channels to be truncated at various sites, which may cause the clinical manifestations of the disease by preventing the normal assembly of Ca^{2+} channels in the membrane.

X-linked *congenital stationary night blindness* (CSNB) is a recessive retinal disorder that causes night blindness, decreased visual acuity, myopia, nystagmus, and strabismus. Complete CSNB causes retinal rod photoreceptors to be nonfunctional. Incomplete CSNB causes subnormal (but measurable) functioning of both rod and cone photoreceptors. Like EA2, the incomplete type of CSNB is caused by mutations producing truncated Ca^{2+} channels. Abnormal retinal function may arise from decreased Ca^{2+} currents and neurotransmitter release from photoreceptors (see Chapter 11).

A defect in brain Na^+ channels causes *generalized epilepsy with febrile seizures* (GEFS) that begins in infancy and usually continues through early puberty. This defect has been mapped to two mutations: one on chromosome 2 that encodes an α subunit for a voltage-gated Na^+ channel, and the other on chromosome 19 that encodes a Na^+ channel β subunit. These mutations cause a slowing of Na^+ channel inactivation (see figure above), which may explain the neuronal hyperexcitability underlying GEFS.

Another type of seizure, *benign familial neonatal convulsion* (BFNC), is due to K^+ channel mutations. This disease is characterized by frequent brief seizures commencing within the first week of life and disappearing spontaneously within a few months. The mutation has been mapped to at least two voltage-gated K^+ channel genes. A reduction in K^+ current flow through the mutated channels probably accounts for the hyperexcitability associated with this defect. A related disease, episodic ataxia type 1 (EA1), has been linked to a defect in another type of voltage-gated K^+ channel. EA1 is characterized by brief episodes of ataxia. Mutant channels inhibit the function of other, non-mutant K^+ channels and may produce clinical symptoms by impairing action potential repolarization. Mutations in the K^+ channels of cardiac muscle are responsible for the irregular heartbeat of patients with long Q-T syndrome. Numerous genetic disorders affect the voltage-gated channels of skeletal muscle and are responsible for a host of muscle diseases that either cause muscle weakness (*paralysis*) or muscle contraction (*myotonia*).

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In short, ion channels are integral membrane proteins with characteristic features that allow them to assemble into multimolecular aggregates. Collectively, these structures allow channels to conduct ions, sense the transmembrane potential, to inactivate, and to bind to various neurotoxins. A combination of physiological, molecular biological and crystallographic studies has begun to provide a detailed physical picture of K^+ channels. This work has now provided considerable insight into how ions are conducted from one side of the plasma membrane to the other, how a channel can be selectively permeable to a single type of ion, how they are able to sense changes in membrane voltage, and how they gate the opening of their pores. It is likely that other types of ion channels will be similar in their functional architecture. Finally, this sort of work has illuminated how mutations in ion channel genes can lead to a variety of neurological disorders (Box D).

Neurotoxins have similar effects to Channellopathies, which affects neuron's function. However, sometimes they have therapeutic uses (e.g. Botox).

Resting membrane potential (RMP) is determined by conductance and concentration of ions (mainly sodium, potassium, and calcium) across the cellular membrane. if it became more negative or less negative, it will affect the activity of the neuron (closer to threshold, easier to excite).

Membrane Potential: Goldman Equation

$$V_m = \frac{RT}{F} \log \frac{P_K[K^+]_o + P_{Na}[Na^+]_o P_{Cl}[Cl^-]_o}{P_K[K^+]_i + P_{Na}[Na^+]_i P_{Cl}[Cl^-]_i}$$

NOTE:
P' = permeability

1. P = permeability
   At rest: P_K: P_{Na}: P_{Cl} = 1.0 : 0.4 : 0.45
2. Net potential movement for all ions
3. Known V_m:Can predict direction of movement of any ion

❖ *Hyperkalemia:*

- Increased extracellular K+ concentration (i.e. in blood).
- Effect: RMP becomes less negative (because of the decreased K+ flux), cell becomes easier to excite since RMP is closer to the threshold.
- Signs and symptoms:
  1- General weakness in muscle.
  2- Ascending paralysis (starts in lower limb then ascends)
  3- Cardiac arrhythmias

❖ *Hypokalemia:*

- Low concentrations of K+ outside the cell, resulting in more leakage of K+ from inside to the outside (according to the concentration gradient).
- RMP becomes more negative/less positive, therefore it gets further from the threshold = less excitable.
- Signs and symptoms:
  1- General weakness in muscles.
  2- General fatigue
  3- Motor paralysis
  4- Myopathies (muscle pain), like myotonia (due to low concentration of K+ = delay in relaxation).

Sodium level:

As we know, Sodium is not considered in the equation as its effect on RMP is almost negligible due to low conductance. However, sodium concentration can have an effect due to two factors:

1. Some neurons work even in low sodium conductance

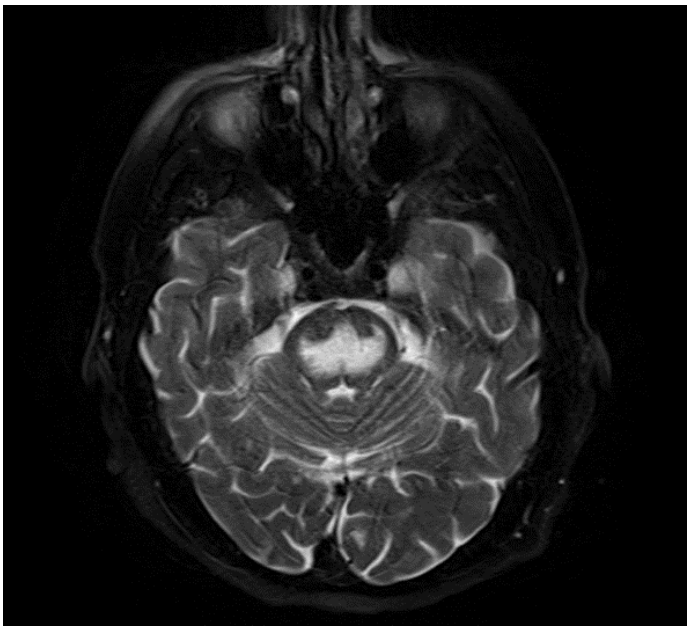
2. Water movement follows sodium movement. So, whenever sodium concentration changes, water movement will be affected resulting in either swelling or shrinkage. In both cases, RMP and movement of ions will be affected. In case of the CNS –which is surrounded by bones- the skull will press on the brain resulting in abnormalities.

❖ ***Hyponatremia:***

- Low concentration of Na+ outside the cell.
- Effect: low Na+ permeability due to the low Na+ concentration outside -> low osmolarity (hypotonic) -> water moves inside causing **swelling**.
- Signs and symptoms:
    1. weakness, lethargy, confusion, muscle cramps, nausea and vomiting.
    2. In serious conditions: coma, seizures, death.

✓ Treatment: introduce saline solution (0.9), but don't introduce it rapidly as it causes death in swelled neurons because of the presence of myelin.

Specifically speaking, rapid treatment with saline will allow axons to shrink faster than the myelin sheaths, which eventually results in demyelination and degeneration of the entire nerve. The damage is more prominent in long motor axons (from cortex to spinal cord), which leads to **osmotic demyelination syndrome (Central pontine myelinolysis).**



An MRI and an X-ray are usually done on autopsies, if it showed Central pontine myelinolysis, it is the doctors' fault. So be careful, this mistake can cost you your medical license (and the patient's life of course).

❖ *Hypernatremia:*

- High concentration of Na+ outside the cell. This results in high osmolarity (hypertonic) -> **cell shrinkage**.
- In chronic conditions, there would be shrinkage of the whole CNS, brain and brainstem descend out of foramen magnum (brain herniation).
- Signs and symptoms: nausea and vomiting, altered mental status, confusion, neuromuscular excitability and hyper-reflexia.

✓ Treatment: Slow correction by half normal saline (0.45); because rapid correction will cause rapid filling of cells leading to bursting or swelling, which eventually leads to application of high pressure on the surrounding foramen and therefore affecting blood supply, causing rupture, edema, hemorrhage, and brain damage.

The effects of Calcium changes:

Basically, Calcium doesn't have a major effect on RMP, but because it competes with Na+ on its ion channels, most (not all) of the calcium effect is on the PNS and the muscles, especially in hypocalcemia.

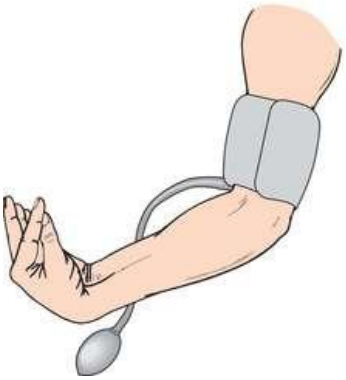
❖ *Hypercalcemia:*

- High concentration of Ca++ outside the cell -> Ca++ competes with Na+ on its channels -> less Na+ outside the cell -> less excitability.
- Signs and symptoms (on CNS): headache, anxiety and depression, Coma in serious cases, insomnia, cognitive dysfunction.

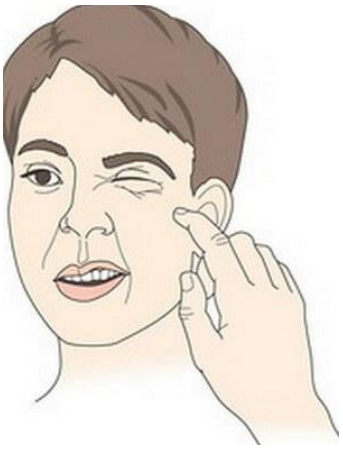
❖ *Hypocalcemia:*

- Low calcium levels outside cell.
- More and faster cell excitability especially muscles in PNS.
- Signs and symptoms: irritability, seizures, psychosis, hallucinations, tetany.
- Test of hypocalcemia:

1- **Trousseau's sign:** if we reduce ATP and O2 supply, there would be excitation of the cells (easier to excite). If we tie the patient's arm by a glove or a pressure cuff so less blood flows in the hand, this will lead to excitation and contraction of the hand muscles.



2- **Chvostek's sign:** as we said, in hypocalcemia the nerves and the muscles are easy to excite, so if the doctor taps on one of the nerves then the nerve and the corresponding muscle would be excited and it contracts. So, if the doctor taps on the corner of the cheek there would be excitation in the facial muscles.



Thank you