T. G. SEVERINA

PHYSIOLOGY OF EXCITABLE TISSUES

Minsk BSMU 2024

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КАФЕДРА НОРМАЛЬНОЙ ФИЗИОЛОГИИ

Т. Г. СЕВЕРИНА

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Р е ц е н з е н т ы: д-р мед. наук, проф., зав. каф. патологической физиологии Белорусского государственного медицинского университета Ф. И. Висмонт; каф. физиологии человека и животных Белорусского государственного университета

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Содержит материалы курса нормальной физиологии, необходимые для подготовки к практическим занятиям и коллоквиуму по разделу «Физиология возбудимых тканей». Особое внимание уделено подробному объяснению механизмов электрической сигнализации в организме — процессов генерации и передачи импульсов от клетки к клетке, мышечного сокращения, взаимодействия нейронов в центральной нервной системе. Значительное количество иллюстраций и схем облегчает понимание сложного материала и способствует его более глубокому усвоению.

Предназначено для студентов 1–2-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке по специальности «Лечебное дело» и «Стоматология».

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Section 1
BIOLOGICAL POTENTIALS

ELECTRICAL SIGNALING.
LAWS OF RESPONSE OF EXCITABLE TISSUES

Electrical signaling is a type of fast transfer of information that developed in evolution later as compared to chemical signaling. This type of communication is used by cells of the **excitable** tissues.

The main excitable tissues are **nervous** and **muscle** tissues. These tissues react to stimulation by a specific response such as excitation. Generally, excitation of cells is a change of their membrane potential. The manifestation of excitation for nervous cells is the generation of an **impulse**, or Action Potential that can be transmitted from one neuron to another one, or to a muscle cell. For muscle cells, excitation is manifested by their **contraction**.

Additionally, some **endocrine cells** can be stimulated by impulses from nervous cells, and these endocrine cells in response to impulses begin their **secretion**.

Before the main processes underlying cell excitation were discovered, the response characteristics of excitable tissue were studied in laboratory conditions. In these studies, a number of ***excitable tissues laws*** was established.

There are two different types of excitable tissue response to increasing force of stimulation. For both these cases, tissues are stimulated by electrodes with increasing current strength. Very weak stimulation of the skeletal muscle does not produce a response until a particular level of stimulation force is reached (this level then is called the threshold force, or simply the ***threshold***). After reaching the threshold, stimulation with increasing force results in muscle contractions of progressively increasing degree (amplitude) of muscle shortening, which means stronger muscle contractions. This is formulated as **law of force** (Fig. 1.1):

- The higher the **force** of **stimulation**, the higher the **amplitude** (force) of muscle **contraction** (until a certain reasonable limit, as the force of contraction cannot increase endlessly).

The other type of response is obtained when nervous cells or a heart muscle are stimulated. A ***subthreshold*** stimulation force does not produce any response, as in case of the law of force. However, with the ***threshold*** and higher force, response is full size.

It is a generation of an action potential by a neuron, or normal contraction of the heart, and this response is standard, with a constant amplitude. A further increase of stimulation force does not bring an increase in the action potential amplitude or force of the heart contraction. This is formulated as **law "All or None"** (Fig. 1.2):

- Before reaching the threshold, stimulation with increasing force does not produce a response (**"none"**); the threshold force produces response that remains standard (**"all"**) when force of stimulation increases above threshold.

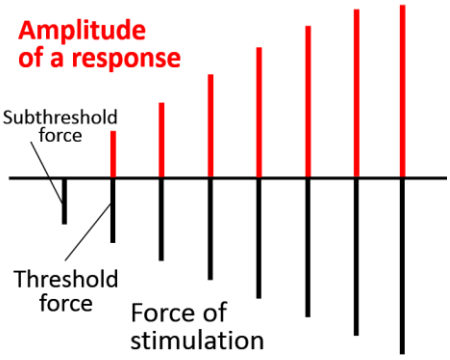


Fig. 1.1. Law of force

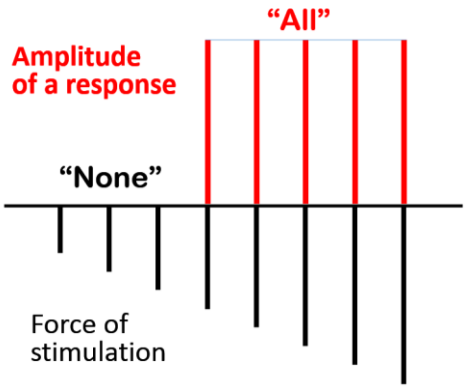


Fig. 1.2. Law "All or None"

To understand fully, why neuron, heart and skeletal muscle follow different laws of excitation, it is necessary to take into account differences in connection between cells in skeletal muscle and the heart, and to know the properties of the action potential. Therefore, an explanation is given after consideration of action potential features.

There are some more laws of excitable tissues response. **Law of duration** of stimulation states that the higher duration of stimulation is, the higher the amplitude of response is (similarly to the law of force). When stimulation force increases gradually, it is also important, how quickly it increases. Velocity of the force increase is called the ***gradient of force***. Correspondingly, there is a **law of gradient of force**, which states that higher gradient of force (faster increase in stimulation force) produces earlier and higher response.

RESTING MEMBRANE POTENTIAL

Before considering of the process of impulses generation by excitable tissue cells, it is necessary to understand the state of the membranes of these cells at rest. All excitable cells membranes at rest are charged negatively inside and positively at their outer surface. This charge of the membrane is called the resting membrane potential.

Resting membrane potential is the **potential difference** across the cell membrane (between its inner and outer sides, or between the cytoplasm and the interstitial fluid surrounding the cell) that exists at the membrane of the excitable cell in its resting state. For considering of the mechanism of resting membrane potential formation and maintaining it is necessary to recall the structure of the membrane.

The membrane of the excitable cell, as well as all biological membranes, consists of two layers of phospholipids facing each other with their hydrocarbon tails (nonpolar and therefore hydrophobic). Polar (and therefore hydrophilic) parts of the phospholipid molecules are directed to the membrane surface. There are proteins on the surface of the membrane; proteins are spaced irregularly floating in the phospholipid sea. Some of them are **integral proteins**, which span all membrane layers. These proteins form the membrane channels, pumps, carriers, and receptors.

The membrane is freely permeable for ***water***, O_2, CO_2 and ***lipophilic*** substances as they are soluble in the membrane phospholipids. The membrane is impermeable

for hydrophilic substances insoluble in lipids. As ions are charged particles, they are hydrophilic and not able to pass directly through the membrane phospholipid layers. They can pass only through the membrane **channels**. The **membrane permeability** for different ions is unequal (**selective permeability**). It is determined by the number of open channels for the ion, which are available at a given moment.

Now it is necessary to introduce the structure and types of the ion channels.

Ion channels of the membrane are divided into 2 fundamentally different groups:

I. ***Non-gated*** channels (leakage channels) which do not have gates. At first it was believed that they are the "holes" in the membrane which appear in case of increase of the distance between the phospholipid molecules of the membrane. Therefore, these channels were believed to have no protein walls. Lately non-gated channels with protein walls were found in some bacteria. Regardless of the presence or absence of protein walls, the leakage channels definitely do not have gates, and are always open. They are selectively permeable mainly for potassium (K^+) ions. Through these channels potassium ions *leak* — go *out of the cell*. That is why these channels are referred to as **leakage channels**.

II. ***Gated channels*** possess gates and therefore are the channels, which may be in the closed state and under certain conditions — in the open state. These channel in turn are divided into 3 groups by the difference in the mechanism of their gates opening (Fig. 1.3):

1. ***Voltage-gated*** channels, which open under certain change of the membrane's charge (potential), usually **depolarization**.

2. ***Ligand-gated*** channels, which open when certain substance (**ligand**) binds to the protein forming the channel.

3. ***Mechanically gated*** channels present in some mechanoreceptors. They are open by a certain mechanical action (mechanical pressure, or deviation of stereocilia in a certain direction etc.).

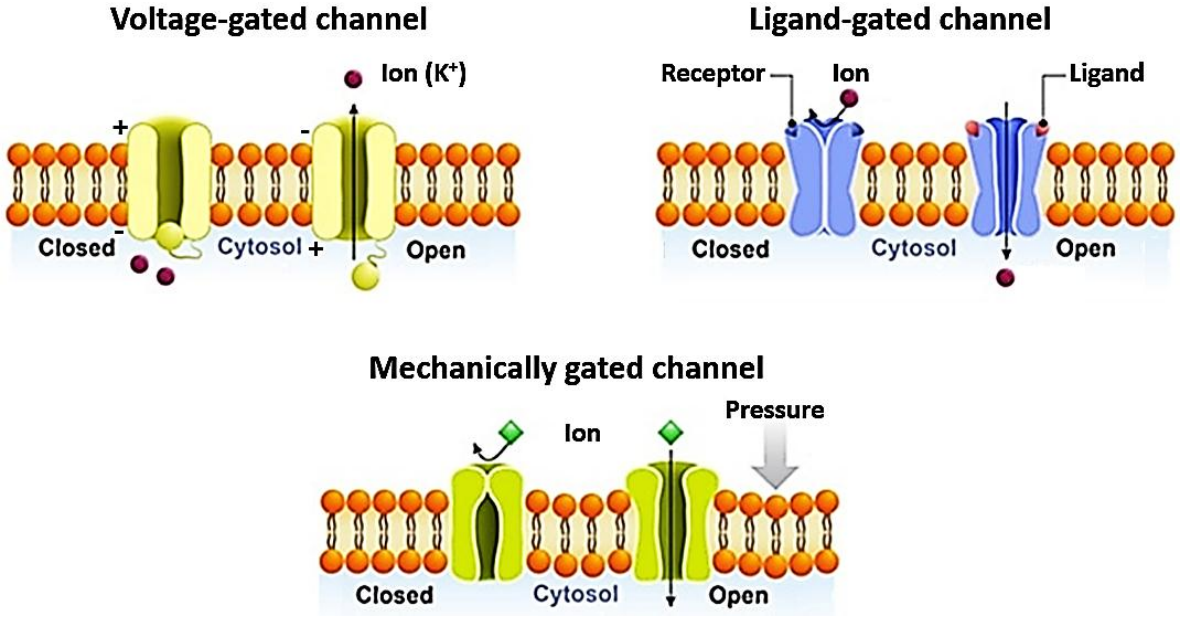


Fig. 1.3. Types of gated ion channels

For our consideration of the electrical signaling, the main channels are **voltage-gated** ones. At rest, these membrane channels are closed as a rule. The main channels for the **resting** membrane potential of the excitable cell are the **potassium leakage channels**, which are always open and consequently are open at rest.

Open channels just ***permit*** the ion diffusion across the membrane. For the directed ion diffusion, the force for ions transfer should be present. This is the **ion *concentration difference*** that is the ***driving force*** for the **ion diffusion** through open channels. The ion diffusion is directly proportional to the ion concentration difference (**D ~ ΔC**). The ion concentration differences can be deduced from the table below.

Table 1.1

The ion concentrations most important for the resting potential formation

Ions	Inside the cell	Outside the cell
K^+	**140** mmol/l	**4.5** mmol/l
Na^+	**12** mmol/l	**142** mmol/l

The concentration gradients exist either for the potassium ions or for the sodium ions. However, the membrane permeability (**P**) for **potassium ions** is much higher than for sodium:

$$\mathbf{P_{K+} : P_{Na+} = 1 : 0.04}$$

Leakage channels are well permeable for potassium (that is why they are called potassium channels) and 25 times less permeable to sodium (**1 : 0.04 = 25**). According to some sources, this difference is even higher, up to 100 times.

The differences of the ion **concentrations** and of the membrane **permeability** are the basis of the resting potential ***formation*** and ***maintaining*** it at a constant level.

Due to the open leakage channels availability, potassium ions diffuse outside the cell down their concentration gradient. Each K^+ ion that goes out creates one positive charge outside and one uncompensated negative charge inside the cell. At the inner side of the membrane K^+ ions are bound mainly to the anion groups of proteins (Fig. 1.4), for example, to the carboxylic groups: $–COO^-K^+$. Potassium ions dissociate from the carboxylic groups and leave the cell down their concentration gradient, whereas large protein molecules with their negatively charged carboxylic groups remain inside the cell. Therefore, **outflow of the K^+ ions** results in the **negative charge** predominance inside the cell. However, why does K^+ outflow not continue until K^+ concentrations inside and outside the cell become equal? That is because K^+ ions outflow itself creates the force that opposes further K^+ outflow. The higher the negative charge inside the cell is, the higher the force is that opposes positively charged K^+ ions outflow from the cell. Thus, there are **two oppositely directed forces** acting on **K^+ ions**: ***concentration gradient*** makes K^+ ions go out from the cell, and the ***electrical driving force,*** which is created by the difference of the charges inside and outside of the cell, makes K^+ ions go into the cell (Fig. 1.4). Normally these two oppositely directed forces are equal, and there are the stable **dynamic equilibrium** between the amount of K^+ ions leaving the cell and the amount of K^+ ions entering the cell per time unit. With a constant ion concentration difference and a constant membrane permeability for ions, this dynamic equilibrium is

established at the same constant charge of the membrane — this is a **constant *resting membrane potential***. This membrane potential can be calculated using the **Nernst equation**. Potassium equilibrium potential calculated with the Nernst equation is –85 mV; that is somewhat higher (more negative) than the actual resting potential. The difference between actual and calculated resting potential values is due to the membrane permeability to ions other than K^+, and primarily Na^+ (sodium) ions. Membrane permeability to Na^+ is much less than to K^+, but it is not zero, so a certain amount of Na^+ ions enters the cell down the sodium concentration gradient. Due to these positively charged Na^+ ions, the negative charge inside the cell is decreased. Resting membrane potential may be influenced by the other ions – Cl^-, Ca^{2+}, but the basis of the potential is created by K^+ ions, i.e. the resting membrane potential is the "*potassium potential*".

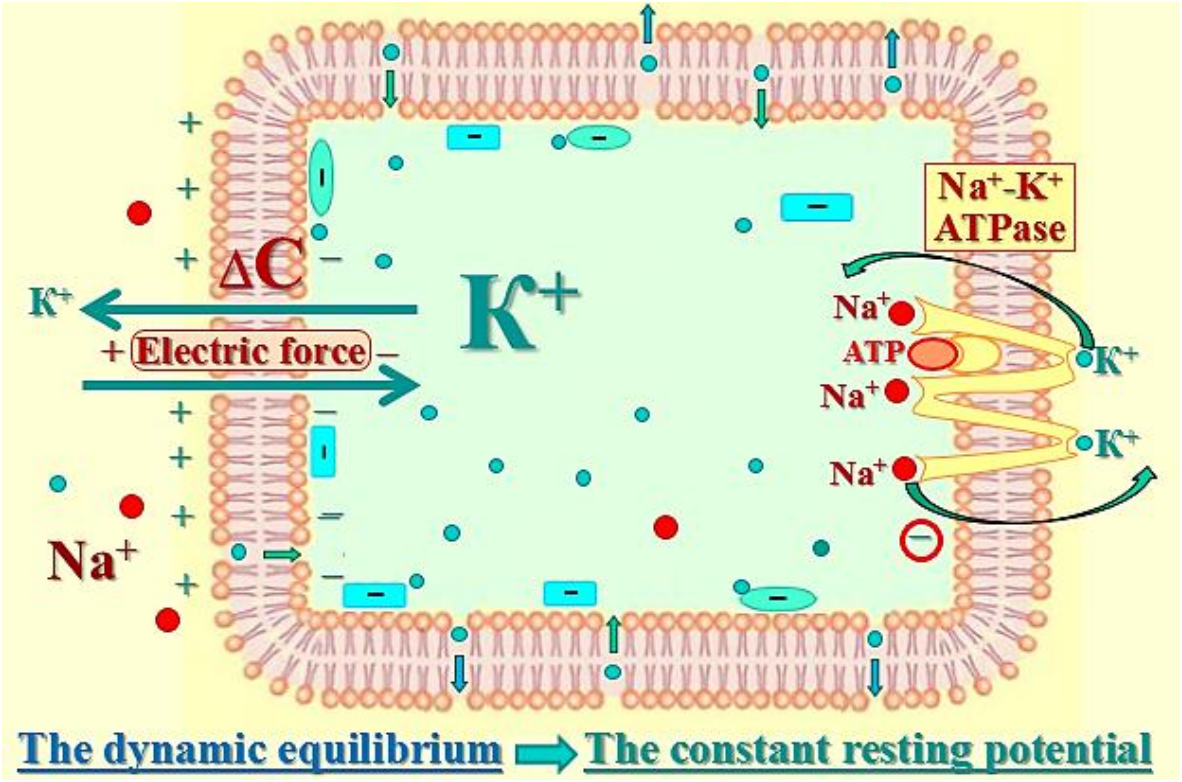


Fig. 1.4. The mechanism of formation of the resting membrane potential

The actual values of the resting membrane potentials of different types of the excitable cells may vary, but the average resting potentials are:

– of **neurons**: **–60 mV** (–70 mV),

– of **muscle cells** (skeletal muscle): **–90 mV**.

In spite of the fact that the influx of Na^+ ions to the cell is relatively small, after a certain period of time membrane potential could decrease. However, this does not occur due to the presence of a special molecular device in the cell membrane. This is the **Na^+-K^+ pump,** or **Na^+-K^+ ATPase**. This is a membrane integral protein having an ATPase center. There are 2 binding sites for K^+ ions in the outer part of the pump (on the outer surface of the cell) and 3 binding sites for Na^+ ions in the inner part of the pump (inside the cell). After the breakdown of the ATP molecule into ADP and

phosphate, the energy liberation results in conformational changes in the pump protein and the transfer of 2 K^+ ions inside the cell and 3 Na^+ ions outside the cell. The Na^+-K^+ pump operates with ***energy expenditure*** and ***against*** **a concentration gradient**; this is a case of **primary active transport**. After each cycle of the pump functioning, Na^+ ions are pumped outside, K^+ ions are pumped back inside, and the negative charge inside the cell increases; therefore, the pump is *electrogenic* and contributes to the negative resting potential maintaining. The pump contribution to the resting potential value is small; however, when there is a lack of ATP in the cell, the pump is slowed down, and the resting potential decreases (becomes less negative).

The resting potential ***decrease*** from its normal value (a decrease of the negative charge on the inner side of the membrane) is referred to as **depolarization**. An ***increase*** of the resting potential value (increase of the negative charge) is referred to as **hyperpolarization** (Fig. 1.5).

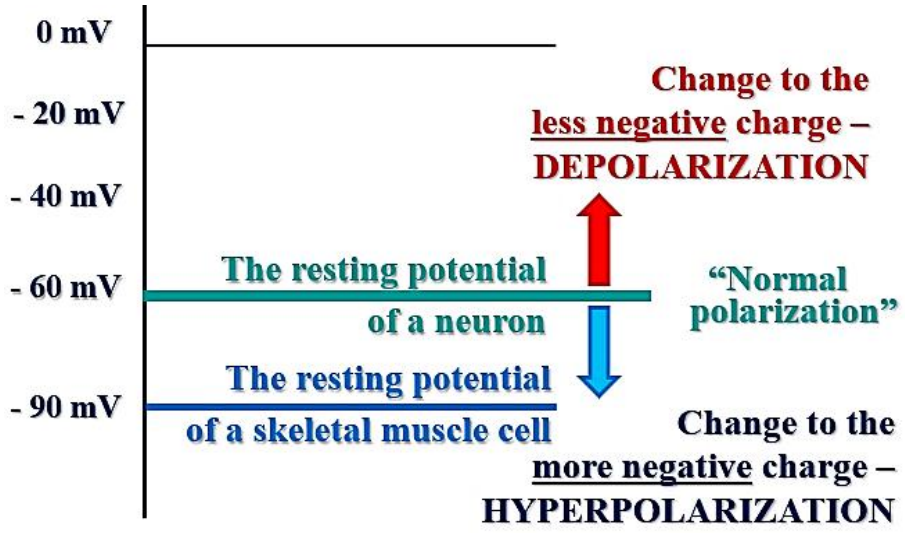


Fig. 1.5. Depolarization and hyperpolarization

Thus, the **main factors** that determine the resting potential value are:

I. ΔC_{K+} — K^+ ions concentration difference between inside and outside the cell.

II. P_{K+} — membrane permeability, firstly to the K^+ ions.

III. **Na^+-K^+ pump** activity.

All these three factors determine the resting potential value in the **direct proportion**. The higher K^+ concentration difference, the higher (more negative) the resting potential. The K^+ **concentration gradient** can be changed mainly due to variability of K^+ concentration in the blood plasma (and therefore in the whole extracellular fluid). When ***plasma K^+ concentration*** **increases**, the gradient ***decreases***, and the resting potential ***decreases*** too (Fig. 1.6). When ***plasma K^+ concentration*** **decreases**, the gradient ***increases***, and the resting potential ***increases*** too (Fig. 1.7).

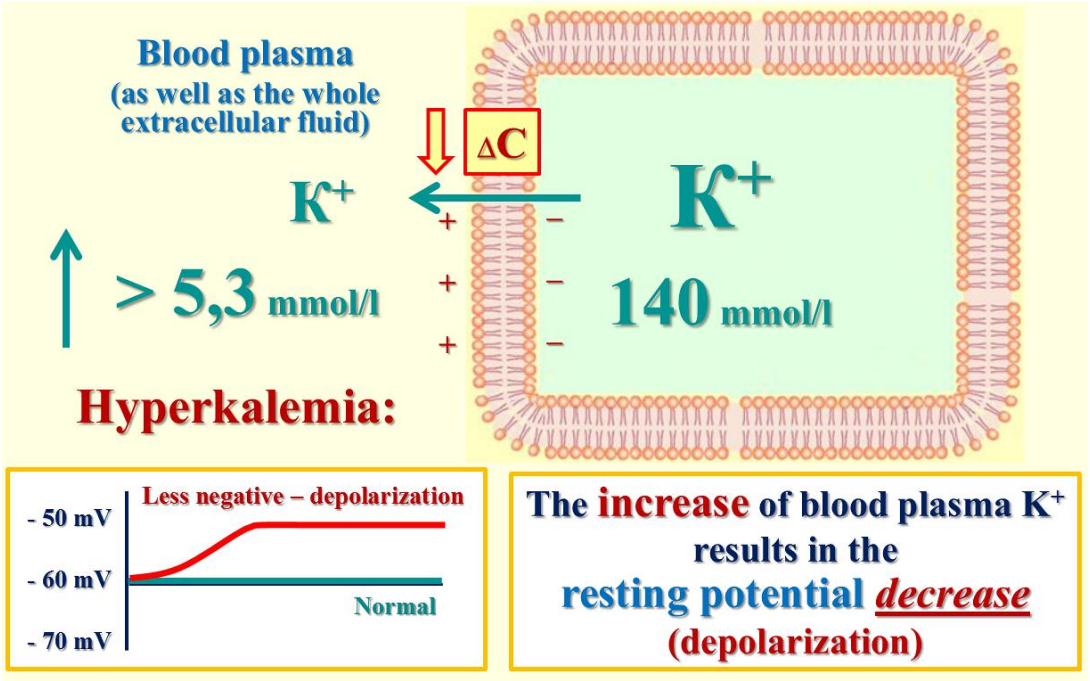


Fig. 1.6. Influence of hyperkalemia on the resting membrane potential

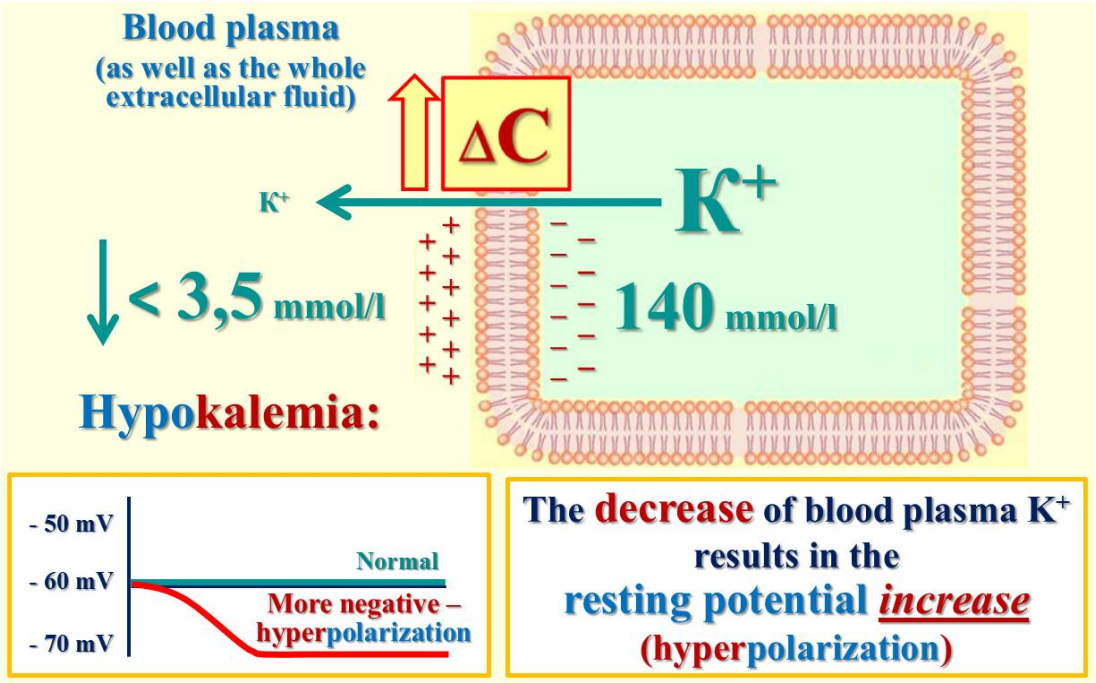


Fig. 1.7. Influence of hypokalemia on the resting membrane potential

Further, the higher the membrane **permeability** to K^+, the higher the K^+ outflow, as well as the negative charge inside the cell, i.e. resting potential. And finally, the higher the Na^+-K^+ **pump activity**, the higher the resting membrane potential.

I. $\uparrow \Delta C_{K+} \Rightarrow \uparrow$ **Resting Potential value.**

II. $\uparrow P_{K+} \Rightarrow \uparrow$ **Resting Potential value.**

III. $\uparrow Na^+–K^+$ **pump activity** $\Rightarrow \uparrow$ **Resting Potential value.**

The opposite is also true: when any of these three factors decreases, the resting potential decreases.

Depolarization of the membrane brings the membrane potential ***closer*** to a certain level of potential that is necessary to excite the membrane. This level is called the **threshold**, or *critical level* of depolarization; it is about **–45 mV** (from –40 to –50 mV) on average. Then, due to depolarization, it becomes easier to cause excitation of the membrane, which corresponds to a **higher excitability** of the membrane.

Hyperpolarization of the membrane moves membrane potential ***away*** from the **threshold** of depolarization. As a result, it is necessary to use ***stronger*** stimulation in order to cause membrane excitation; this corresponds to a **lower excitability** of the membrane.

ACTION POTENTIAL

Action potential is a fast oscillation of the membrane potential that consists of rapid depolarization followed by repolarization of membrane. Generation of an action potential is a manifestation of cell excitation.

Prior to the considering the action potential generation it is necessary to have an idea what is the purpose it serves. Action potential (AP), or nervous impulse, is an information unit, the standard basic unit of the brain's language. All the variety of information received by the central nervous system (CNS) from the external and internal environment, all the variety of the controlling commands sent by the brain to the peripheral organs, and the main interaction processes between neurons of CNS are made of the alternation of impulses and pauses between impulses. Patterns of impulses are the way to transfer the information. For example, increase of the frequency of action potentials sent from skin tactile receptors is perceived by the CNS as the increase in the force of mechanical pressing action on the skin.

To achieve maximum information per time unit, the AP must meet the following requirements: it must be short and require minimal energy (***time saving*** and ***energy saving***). AP entirely meets these requirements.

To generate the AP, the presence of ***voltage-gated*** channels for **sodium** and **potassium** is necessary in the membrane. At rest, both channels are **closed**.

1. *Fast voltage-gated Na^+ channels* have two gates (Fig. 1.8). ***Activation*** gates are located at the outer side of the membrane; in the resting state of the membrane, they are closed. ***Inactivation*** gates are located at the inner side of the membrane; and in the resting state of the membrane they are open. Under depolarization that is enough to reach the threshold of depolarization or above, the conformation of the gate proteins is changed in such a way that activation gates open and inactivation gates close; but the inactivation gates closure is slower. As a result, for the short period when the outer gates are *already open* and the inner gates are *not closed yet*, the channel becomes ***opened***. During this time, Na^+ ions can pass through the open channels that are selectively permeable for Na^+. The period of time during which channels are open is very short, about a few ten thousandths of a second. That is why channels are called ***fast***. There are a large number of such channels in the membrane of an excitable cell.

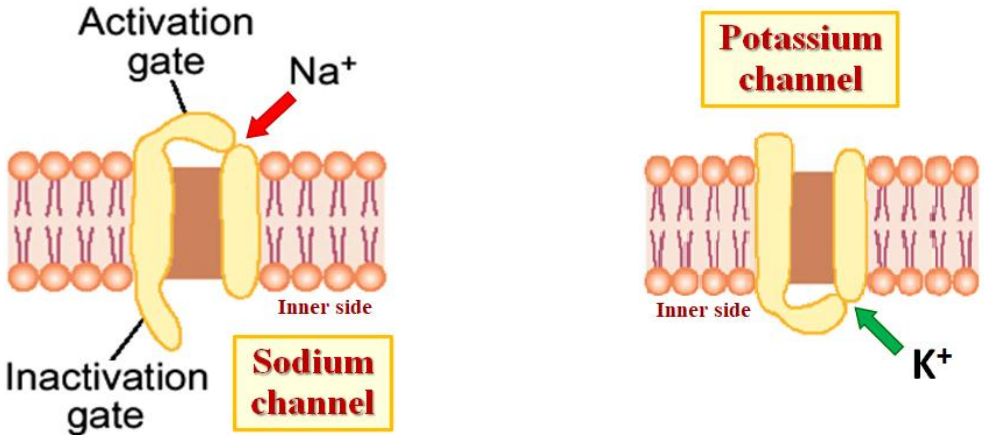


Fig. 1.8. The resting state of the two main channels for action potential (from Guyton & Hall, 14 ed., 2021, modified)

2. *Voltage-gated K^+ channels* have only one gate, which is closed at rest. Under depolarization K^+ channels open as the sodium channels do. However, their opening occurs much slower and is achieved when the sodium channels are already closed.

This sequence of gates opening and closure creates that fast and short change of the membrane potential that constitutes an action potential. Generally, AP consists of the 2 main opposite phases: a rapid change in the charge of the inner side of the membrane to positive, due to the influx of Na^+ ions (**depolarization**), and then a return to the resting potential due to the outflow of K^+ ions (**repolarization**). It is enough just to open and close the channels for the ions shifts; ions pass through open channels down their **concentration gradients**. Thus, the energy expenditure for AP generation is minimized; it is necessary just to maintain the Na^+ and K^+ concentration gradients inside and outside the cell. It is for these processes of gradients maintaining by pumps functioning that mostly the energy is spent on in the CNS and in the whole body.

The normal stimulus for AP generation is depolarization (usually caused by a nerve impulse sent from a receptor or from another neuron). After the *threshold depolarization*, the following events occur:

1. Activation gates of ***Na^+ channels*** opening which results in the Na^+ influx to the cell down the concentration gradient. Positively charged Na^+ ions change the potential of the membrane inner side from its resting level (–60 mV) to approximately +30 mV. This AP phase is called ***depolarization***.

After the very short time there occurs:

2. Closure of the inactivation gates of Na^+ channels resulting in the Na^+ influx termination. This moment corresponds to the peak (highest point) of the AP.

By that moment there occurs:

3. Potassium channels opening that results in the outward current of K^+ ions, and therefore the outflow of the positive charge from the cell until the resting potential is restored — ***repolarization*** phase.

The successive opening and closure of sodium and potassium channels is shown in the Fig. 1.9.

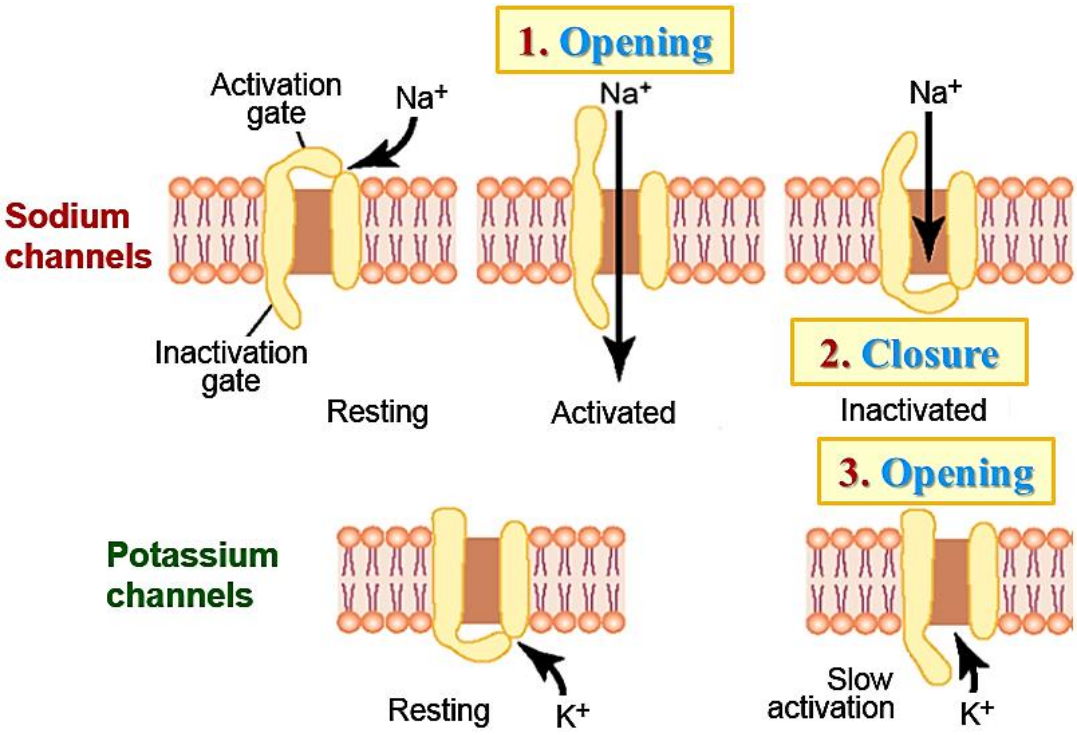


Fig. 1.9. Sequence of Na^+ and K^+ channels opening and closure during action potential generation (modified from Guyton & Hall, 14 ed., 2021)

In many neurons, the potassium channels remain open for some time after repolarization, and the continuing K^+ outward current down the concentration gradient creates the ***hyperpolarization*** phase. During this phase, the charge of the inner side of the membrane becomes more negative than at the resting potential level. After the closure of K^+ channels membrane, potential returns to its resting level.

Thus, action potential consists of three phases (Fig. 1.10):

1. ***Depolarization***.
2. ***Repolarization***.
3. ***Hyperpolarization***.

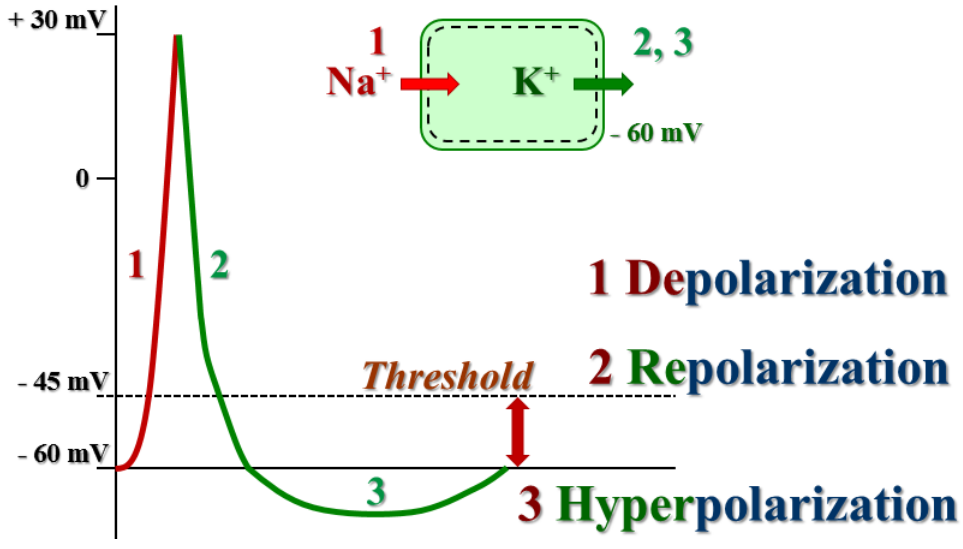


Fig. 1.10. Action Potential figure

During the depolarization phase Na^+-K^+ pump is switched off. After the end of depolarization, the pump is switched on again and restores the ion concentration gradients. There are no considerable changes of ion concentrations gradients even after generation a great number of action potentials.

The **threshold level** for AP generation is about from –40 to –50 mV (**–45 mV** on the average). The ***difference*** between the resting potential and threshold levels (that is the second meaning of the **threshold**) is about 15 mV (between –60 and –45 mV).

The initial depolarization causes the opening of a certain number of Na^+ channels. Inward current of Na^+ into the cell results in an increase of the depolarization level. If the initial depolarization is weak and opens just a few Na^+ channels, then Na^+ influx to the cell is insufficient to cause depolarization higher than the initial one. In this case, depolarization fades away without reaching threshold; AP is not generated. ***Threshold depolarization*** opens the number of Na^+ channels enough for the *closed circle* formation:

$$\text{Depolarization} \Rightarrow Na^+ \text{ channels opening}$$
$$\Uparrow \qquad\qquad \Downarrow$$
$$\text{Influx of } Na^+ \text{ to the cell}$$

Due to the formation of such a circle after reaching a threshold level, the depolarization is increased avalanche-like, and all the fast voltage-gated Na^+ channels of the membrane at the threshold level open almost instantly.

EXCITABILITY ALTERATION DURING ACTION POTENTIAL

The excitability of the membrane is determined primarily by the number of channels able to open under depolarization (1), as well as the value of the depolarization threshold, which is the difference between the membrane potential and the threshold level (2). In case of membrane depolarization, the excitability increases; in case of hyperpolarization — vice versa. However, after the Na^+ channels opening excitability abruptly decreases to zero level (Fig. 1.11).

Open channels cannot respond to depolarization by their new opening. Thus, as soon as all Na^+ channels are open, the membrane becomes refractory (non-excitable). Inactivated sodium channels (the state that corresponds to the peak of the action potential) also cannot open. Only reactivated channels can open. Channels **reactivation** occurs by the successive closure of the activation gates and opening of the inactivation gates. This process of restoration of the initial protein conformation requires restoring the negative charge of the inner side of a membrane.

Therefore, during the main part of the action potential, the excitability of the membrane depends on the state of its sodium channels, and at the end of the action potential, when all the Na^+ channels are reactivated, the excitability depends only on the threshold. The correspondence of the state of sodium channels to the phases of the action potential is shown at the Fig. 1.12.

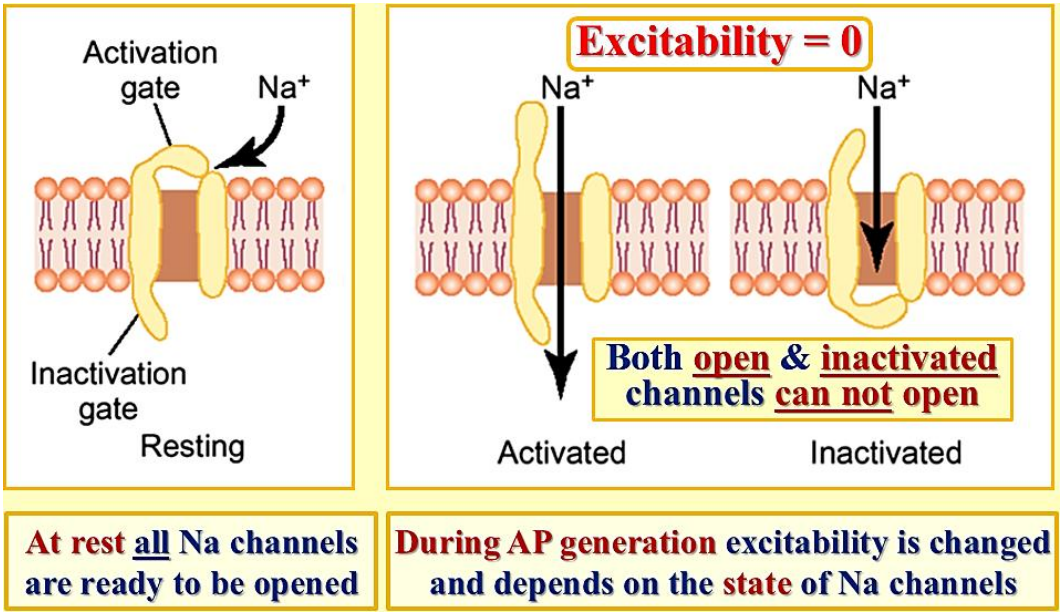


Fig. 1.11. The state of Na^+ channels determines membrane excitability

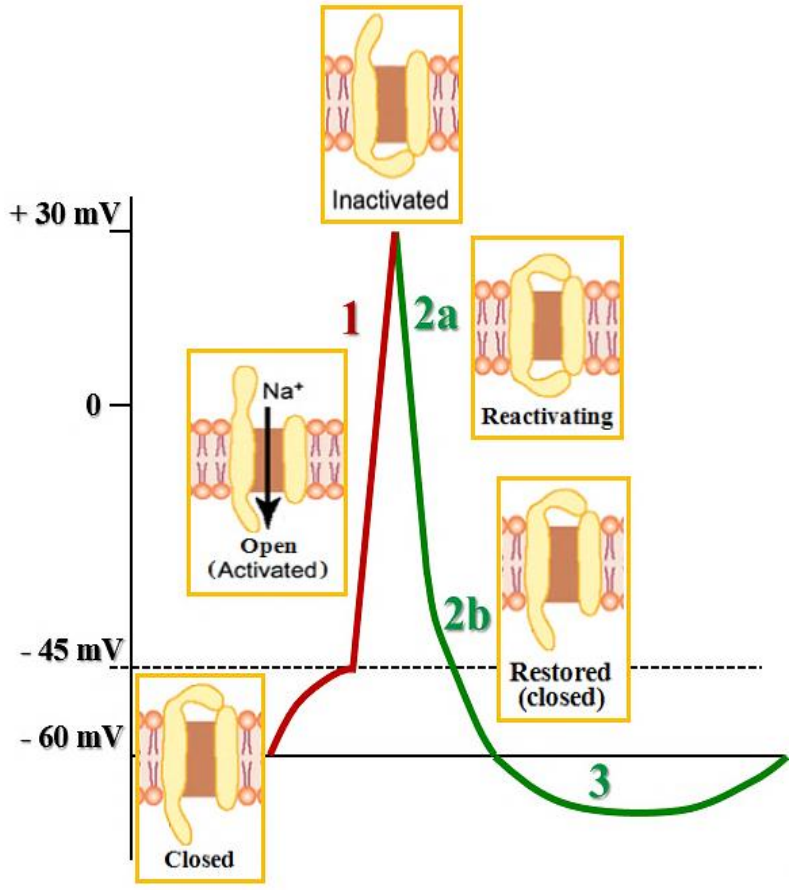


Fig. 1.12. The state of Na channels during action potential

Initially, all Na^+ channels are closed, with their activation gates closed, and inactivation gates open. Starting from the threshold, all of these channels open, thus making membrane unable to respond to new stimuli for a short time. For the whole depolarization phase (1) including the peak point, when channels become inactivated, the membrane is not excitable. Then, during the first part of repolarization (2a), the reactivation process begins, first with the activation gate closing, then the inactivation gates opening inside. The restoration of channels occurs very quickly, but not exactly simultaneously. Thus, at first a small part of channels is reactivated, then more, and very soon, before the end of repolarization (2b), all the channels are restored (reactivated).

PHASES OF EXCITABILITY

Thus, from the moment of all Na^+ channels opening (starting from the threshold level), the membrane excitability falls to zero. This absence of excitability is referred to as **absolute refractory period** (absolute absence of response). During this period AP cannot be elicited, no matter how strong the stimulus is. The absolute refractory period lasts until the beginning of repolarization and reactivation of a certain number of Na^+ channels. From this moment, the membrane excitability is still low, but not zero. This period is referred to as the **relative refractory period**. At the end of repolarization when all Na^+ channels have already been restored and membrane potential is close to the threshold (until reaching the resting potential), the membrane excitability for a short period becomes even higher than normal; this is called **supernormal excitability**. During the ***hyperpolarization,*** the excitability is lowered (**subnormal excitability**) since the difference between the membrane potential and the threshold level is higher than at rest, and stronger than normal stimulation is required to generate AP. Normal excitability is restored after hyperpolarization is finished, and the membrane potential returns back to its resting level. The graph of the excitability, in correspondence with the action potential phases, along with their characteristics, is shown in the Fig. 1.13.

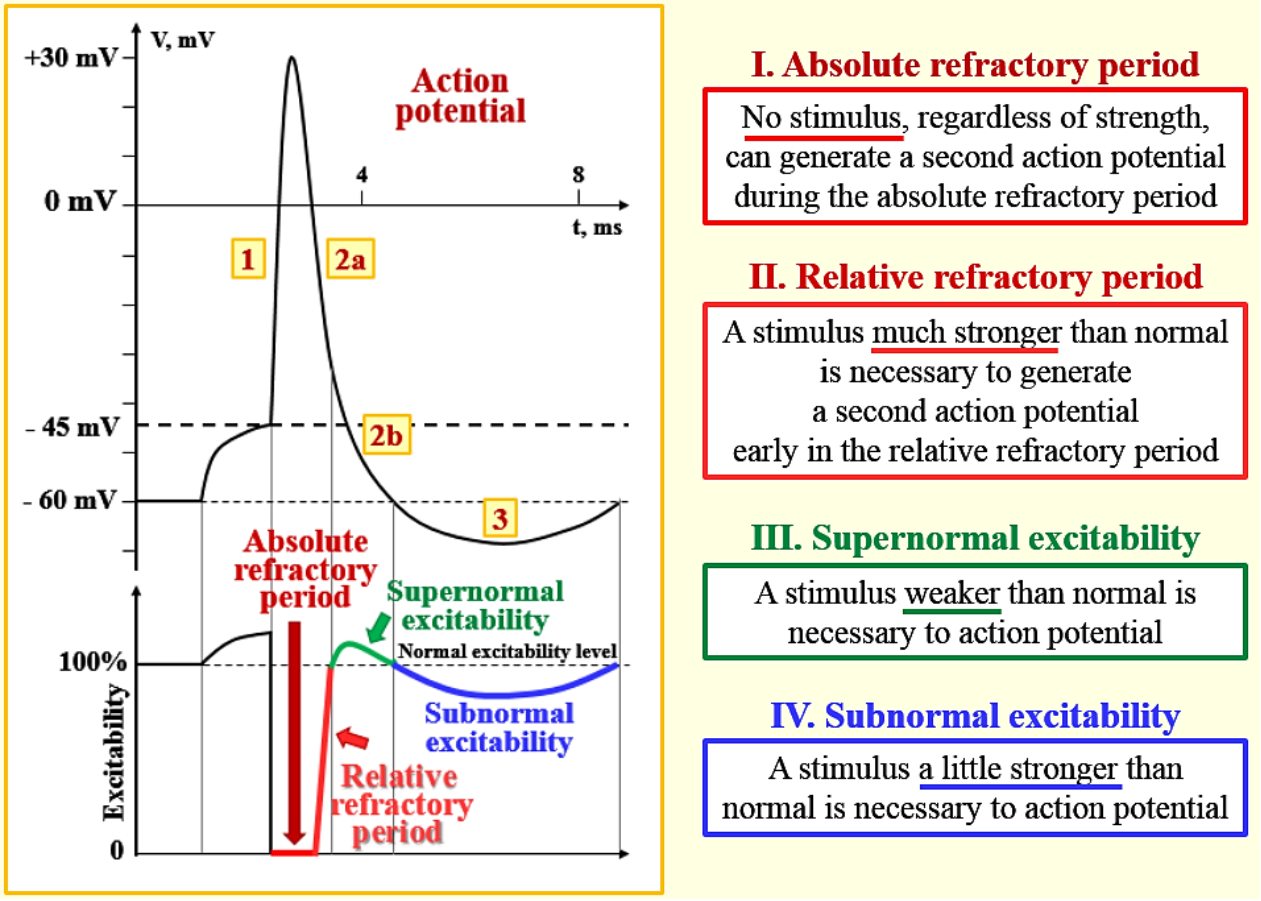


Fig. 1.13. Excitability phases, in parallel with action potential phases

To summarize, we can see that the AP meets the basic requirements for an information unit. Due to the ***fast*** opening and closing of the channels gates, the period of complete loss of excitability — absolute refractory period — lasts about one millisecond or less. It allows the membrane to generate impulses with a high rate for the transfer of *maximum amount of information per time unit*. The shorter the absolute refractory period, the higher the maximal possible rate of impulses. The maximal rate of impulses generated by neurons can reach 800 and even more action potentials per second. ***Energy*** during action potentials generation is spent only on the operation of pumps, for maintaining of the **ion concentration gradients** necessary for the passive ion movement through open channels. Therefore, the action potential is and energy-saving and time-saving unit of information transfer in the central nervous system.

COMPARISON OF ACTION POTENTIAL AND OTHER POTENTIALS

The most important difference of the action potential from all other potentials occurring in the nervous system is its subjecting to the All-or-none law. All other potentials, which are going to be considered in next sections, are subject to the Law of force. These potentials include the Receptor Potential, Excitatory and Inhibitory Postsynaptic Potentials, and the postsynaptic potential in the neuromuscular junction — the End Plate Potential. All these potentials are not intended for the conduction to long distances, and their propagation along the membrane occurs with a decrease in its amplitude, or *damping*. As will be considered in the Section 2, action potential conduction occurs by its repetitive generation along nerve fibers and, therefore, without any decrease in its amplitude, regardless of the length of the fiber. And, since the action potential follows the All-or-None law, it is impossible to summate such potential. At the moment of one AP generation, the membrane in not excitable, and there is no response to new stimulation. When the excitability is restored, new stimulation causes the same AP of standard amplitude, i.e. there is no summation. The other potentials can be summated, and new stimulation before the end of such potentials produces adding of the potential amplitude. The main differences between action potential and other potentials are given in the table below.

Table 1.2

Action Potential and other potentials comparison

Action Potential	**Receptor potential, postsynaptic potentials**
All-or-none law	Law of **force**
Propagation **without damping**	Propagation with **damping** (decrease in amplitude)
No summation	Able for summation

Section 2
RECEPTORS. NERVE FIBERS. SYNAPSE

RECEPTORS

The primary source of action potentials generation in the nervous system is mainly the sensory cell, the **receptor**. Sensory cells are ***pseudounipolar*** (or ***bipolar***) ***afferent neurons*** or ***specialized sensory cells*** that contact afferent neurons. Receptors transform action of various external and internal stimuli into nervous impulses, which can be sent to the central nervous system. Stimulation results in a change in the potential of the nerve ending or sensory cell membrane that is referred to as the **receptor potential**. Receptor potential amplitude depends on the force of stimulation. This means that the receptor potentials change according to the ***law of force***: the higher the stimulus strength is, the higher the receptor potential amplitude becomes. Receptor potential in turn causes action potential generation in the nearest part of the membrane, which has voltage-gated Na and K channels, or excites the sensory neuron that contacts the receptor, by releasing a specific substance. Receptor potential is an example of ***analog encoding*** (or *amplitude* encoding), as the amplitude of the receptor potential changes ***analogically*** to the amplitude (force) of stimulus. However, the amplitude of action potentials is constant and cannot be changed, as action potential responds according to the ***all-or-none law***. Therefore, the information on the force of stimulation is encoded by the **frequency** of action potentials transmitted to the central nervous system (Fig. 2.1). The higher the stimulus strength, the higher action potentials frequency. This is the example of a **discrete** (or *frequency*) encoding.

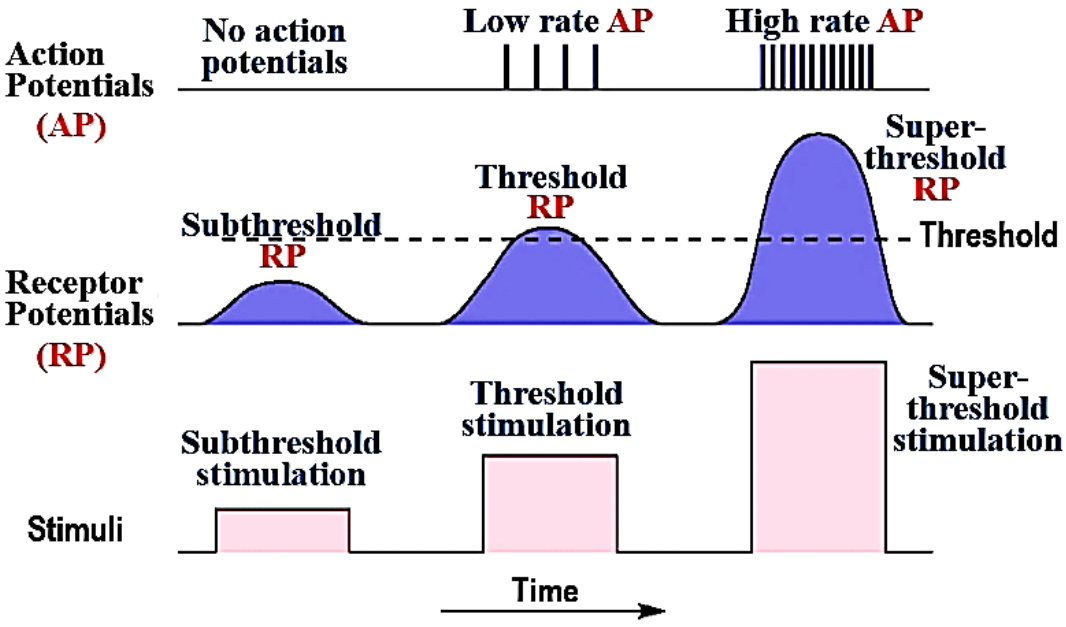


Fig. 2.1. Generation of Receptor Potentials and Action Potentials in response to stimulation with increasing force

Adaptation of receptors consists in the decrease in the receptor potential amplitude, and therefore in the rate of impulses sent from the receptor, under action of the stimulus of a constant strength (Fig. 2.2). Ability of receptors to adaptation is different. Some receptors adapt slowly, the others adapt fast. For example, **fast adapting** receptors are tactile receptors, which produce depolarization only in the beginning of stimulation. Thus, such receptors provide information mainly on the beginning and the end of stimulation. Some receptors must not change their response to stimulation as they monitor important factors of the internal environment of the body. These receptors are **non-adapting** (or very slow adapting). The examples are osmoreceptors, receptors of O_2 and CO_2 pressure in blood, and others.

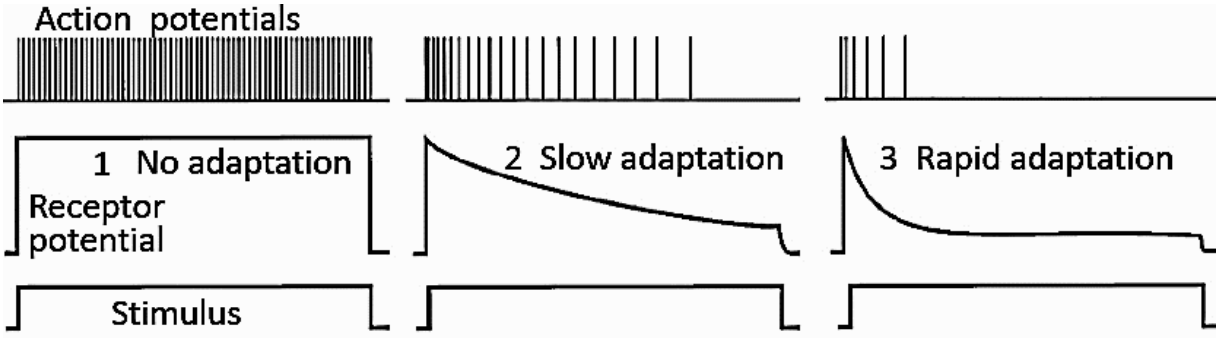


Fig. 2.2. Response of non-adapting (1), slow adapting (2), and fast adapting receptors (3) to stimulation of a constant strength

NERVE FIBERS

Every neuron has many processes of its body, or **soma**. There are many **dendrites** and only one **axon** among them. Dendrites serve for the input of impulses, and the axon is used for the output — for sending the information to the next excitable cell. Nerve fibers include dendrites and axons of neurons; axons joined together form ***nerve trunks***. Action potential is generated in the **initial segment** of axon, or *axon hillock*, and then it propagates along the axon to its ending. In sensory pseudounipolar neurons, the action potential is generated near their receptor ending, in the fiber membrane that contains voltage-gated Na and K channels. Then the action potential propagates along the peripheral fiber, the dendrite, to the neurons body and then along the central part of the fiber, the axon, towards its ending.

There are ***two different types*** of nerve fibers. The thinnest nerve fibers are **unmyelinated**, as Schwann cells, which wrap fibers around, do not form multiple layers around the fiber that is necessary to form a *myelin sheath*. Action potential propagation along unmyelinated fibers is achieved by the successive repeated generation of the action potential in every point of a membrane along the axon. There are **local currents** arising between the depolarized initial segment of axon and the adjacent part of the axon membrane, which is still at its resting potential (Fig. 2.3). Local currents arise due to charges difference: the inner side of the depolarized part of membrane is positively charged, and the inner side of

the nearest resting part of membrane is negatively charged; on the surface of the fiber, charges are correspondingly positive and negative. Between these opposite charges, local currents arise, directed from positive charge to negative charge. These local currents are circular, with opposite directions on the outer and inner sides of the membrane. They depolarize the adjacent part of the membrane and cause the opening of the **voltage-gated Na channels**. When the threshold level of the membrane potential is achieved, all channels open, and action potential is generated in this part of the membrane. Now local currents arise between this part of membrane (already depolarized) and the next adjacent part of the membrane. **Repeated generation** of action potentials along the axon results in ***non-decremental*** AP propagation (propagation without a decrease in the potential amplitude). Unmyelinated nerve fibers (**type C** according to the nerve fibers classification) are present in the autonomic nervous system; in particular, they are sympathetic postganglionic fibers. Their conduction velocity is about **0.5–3 m/sec**.

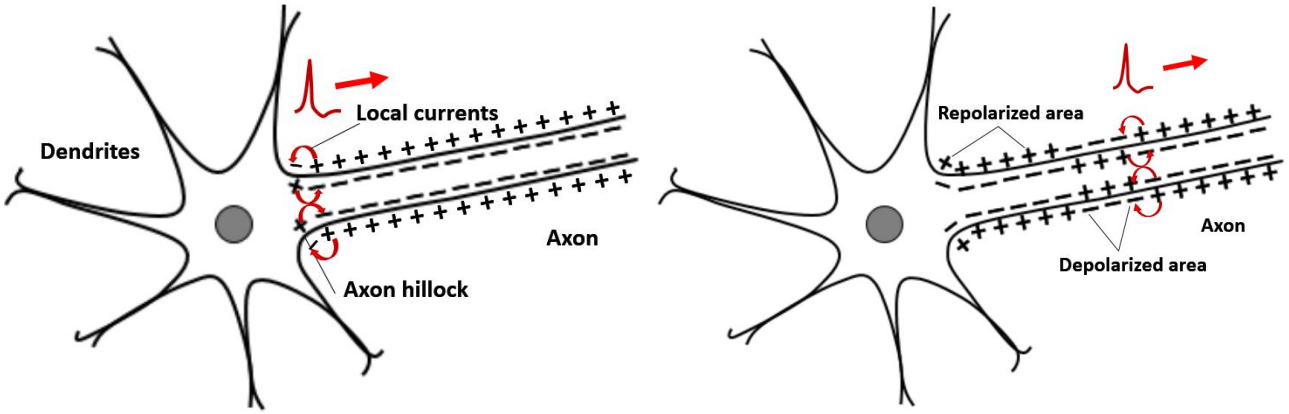


Fig. 2.3. Action Potential generation and propagation along the unmyelinated nerve fiber

Myelinated nerve fibers have a regularly spaced covering, myelin sheath, which is formed by **Schwann cells** (in the peripheral nervous system) or by **oligodendrocytes** (in the central nervous system). Schwann cell (or oligodendrocyte's process) has a flattened shape and wraps itself ***many times*** around the axon; a thin space of Schwann cells interior is filled with **myelin**, a lipid substance that has good insulating properties. The axon membrane under the myelin sheath is not excitable; however, between every two successive Schwann cells along the axon there are small areas, which are not covered by the myelin sheath. These uninsulated areas are called **nodes of Ranvier** (Fig. 2.4). They are only 2 to 3 micrometers in length, but they are extremely rich in voltage-gated Na channels, and this is the place where action potentials are generated during nervous impulses propagation. In the thickest myelinated nerve fibers, the distance between the successive nodes of Ranvier is as long as 1–2 mm. This is a long distance but nevertheless local currents arise between the depolarized node of Ranvier and the next non-depolarized one; these local currents cause the opening of **voltage-gated Na channels** of the next node, Na ions enter the axon interior and depolarize the membrane to the threshold level (Fig. 2.5). After this, the action potential is

generated in this node of Ranvier, and new local currents begin to depolarize the next node. Therefore, in myelinated nerve fibers action potential conduction is ***non-decremental*** too, as action potentials are generated again in each node of Ranvier. This way of action potential conduction is called **"saltatory"** conduction, as excitation moves down the axons as if by big "jumps" (*salto*) over the parts of the axon covered by myelin sheath. It makes it possible to conduct impulses with the **high velocity** up to 120 m/sec. The other advantage of salutatory conduction in myelinated nerve fibers is the **energy saving**. Little energy is required to reestablish the initial Na^+ and K^+ concentration differences after each action potential since just a small part (nodes) of the axon membrane is depolarized. Myelinated nerve fibers (types **A** and **B**) are present in the somatic nervous system; the thinnest among them (type **B**) are parasympathetic nerve fibers having conduction velocity about **3–5 m/sec**. The thickest myelinated fibers (type **Aα**) are motor nerve fibers that come from the motor neurons and innervate skeletal muscles; their conduction velocity is highest and equals to **70–120 m/sec**.

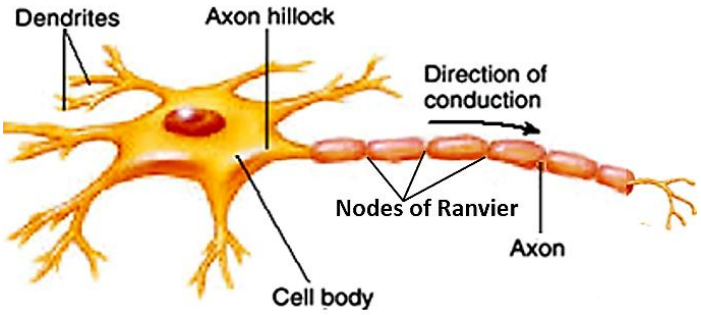


Fig. 2.4. Neuron with myelinated nerve fiber (from S. I. Fox. 14 ed. 2016)

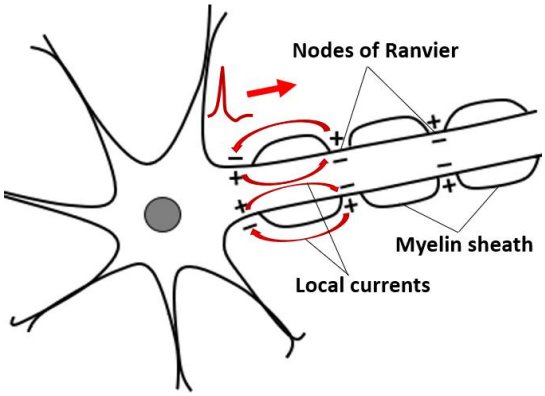


Fig. 2.5. Action Potential generation and propagation along the myelinated nerve fiber

Nerve fibers classification is given below. From type A to the type C fibers, the velocity of impulses conduction decreases, as well as fibers diameter. Motor neuron axons are the thickest and fastest nerve fibers, while sympathetic nerve fibers (postganglionic), type C fibers, are the thinnest and slowest.

Table 2.1

Classification of nerve fibers

Types of fibers	Classes of fibers	Conduction velocity	Characteristics
Myelinated	Type A alpha	70–120 m/s	Motor nerve fibers mainly
	A beta	40–70 m/s	Sensory nerve fibers
	A gamma	15–40 m/s	
	A delta	5–15 m/s	
	Type B	3–18 m/s	Autonomic nerve fibers
Unmyelinated	Type C	0.5–3 m/s	Autonomic (sympathetic) nerves

AXONAL TRANSPORT

Inside the axons, there is a set of longitudinal microtubules that serve as tracks for axonal transport of vesicles containing various substances, or cellular organelles. Axonal transport is performed by proteins that use ATP energy to change their conformation, which results in step-by-step movement along microtubules inside the axon. Transport in the axon that goes from the body of a neuron towards the end of the axon (to the synapse) is ***anterograde*** (directed forward). This transport is performed by the protein ***kinesin***. Velocity of anterograde transport is up to **0.5 m/day**. Transport directed from the end of an axon (from a synapse) to the neuron's body is retrograde (directed back). Such transport is provided by the protein ***dynein***, together with the cofactor *dynactin*. Velocity of this type of transport is approximately twice slower than of the anterograde transport. Axonal transport proteins are shown at the Fig. 2.6.

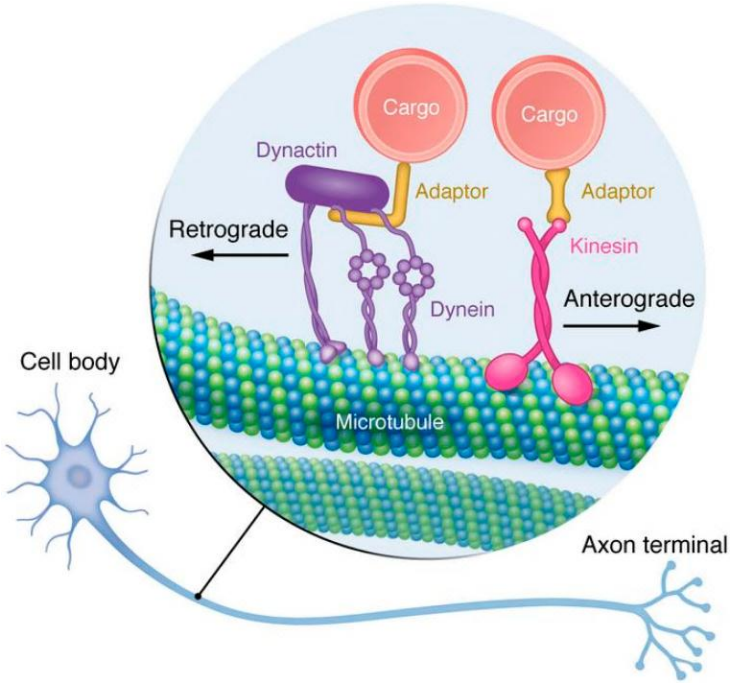


Fig. 2.6. Axonal transport proteins carrying cargo vesicles along microtubules (from: Disruption of axonal transport in neurodegeneration / S. H. Berth, T. E. Lloyd // J. Clin. Invest. 2023. 133 (11))

LOCAL ANESTHETICS

The main role in action potential conduction belongs to the fast sodium voltage-gated channels. If these channels do not open, action potentials do not occur. Thus, blockade of the nerve conduction can be achieved by blocking **voltage-gated Na channels** of the axon (or receptor) membrane. Substances that produce this effect are called **local anesthetics**. These substances, such as *procaine* and *tetracaine*, block opening of the activation gates of sodium channels in nerve fibers, thereby blocking excitation conduction and turning off local sensitivity. Anesthetics are widely used in medical practice to stop pain sensitivity.

SYNAPSE

The human brain contains at least 100 billion neurons, and the performance of complex brain functions is based primarily on communication between them. Such communication is made possible by synapses. Synapse is a special contact between the axon of a neuron and the membrane of the other excitable cell. It can be another neuron or a muscle cell as well. Two different types of synapses can be distinguished on the basis of their mechanism of transmission: ***electrical*** and **chemical** ones. Electrical synapses are a minority in the nervous system. In electrical synapses, the current flows through gap junctions, which are specialized membrane channels connecting two cells. Most of our synapses are chemical. Signal transmission from cell to cell in these synapses occurs by means of a chemical substance, the **neurotransmitter**.

There are many other classifications of synapses. Synapses are divided into the ***central*** and ***peripheral***; ***excitatory*** and ***inhibitory***. Depending on the site of contact, synapses are divided into ***axosomatic***, ***axodendritic***, and ***axo-axonic*** (Fig. 2.7). Also, according to the kind of neurotransmitter, synapses are called **cholinergic** (using acetylcholine as a neurotransmitter), **adrenergic** (using noradrenaline or adrenaline as a neurotransmitter), ***histaminergic***, ***GABA-ergic*** and so on.

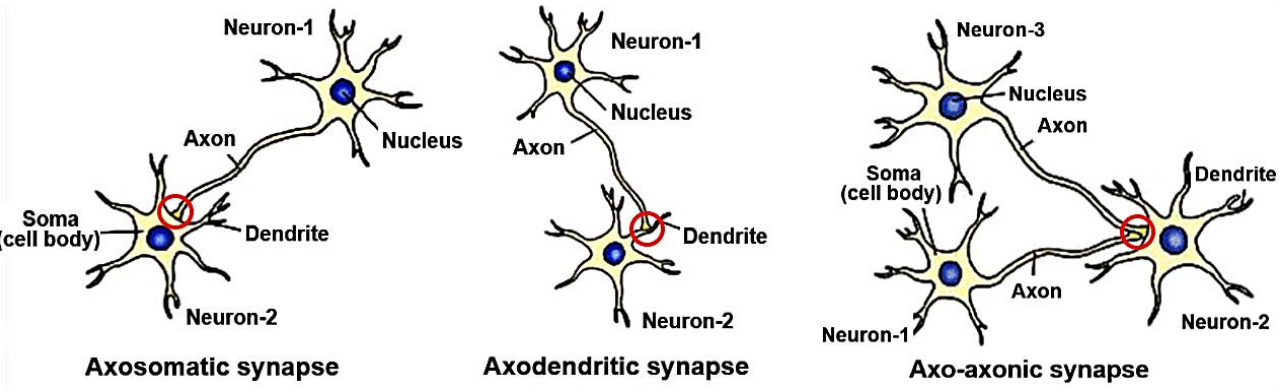


Fig. 2.7. Types of synapses with different sites of a contact between neurons

In general, the process of signal transmission in chemical synapse can be described as follows: nervous impulse (action potential) causes the release of a neurotransmitter; molecules of the neurotransmitter reach the membrane of the postsynaptic cell, bind to specific receptors and change the membrane permeability resulting in the membrane depolarization. This in turn causes action potential generation on the postsynaptic cell membrane (or increases the probability of an action potential generation).

Before considering this process in detail, it is necessary to know the structure of the synapse (Fig. 2.8). The main parts of each synapse include presynaptic terminal with **presynaptic membrane** (**1**), **synaptic cleft** (**2**), and **postsynaptic membrane** (**3**) — the thickened part of the postsynaptic cell membrane faced to the presynaptic terminal. The synaptic cleft is a gap about 20 nm that separates

the presynaptic and postsynaptic membranes. A nervous impulse cannot be transmitted through such a distance simply by electrical way.

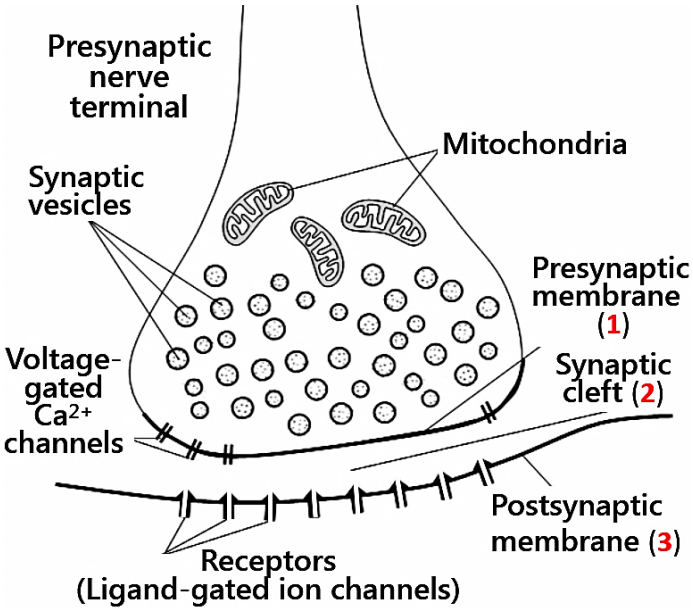


Fig. 2.8. Main structures of the synapse

Near the synapse area, axon terminal loses its myelin sheath and forms *the terminal button*, or **presynaptic terminal**. The presynaptic terminal contains a large number of **synaptic vesicles** with neurotransmitter molecules. Vesicles are mainly produced in the soma and are carried to the terminal button by fast ATP-dependent **anterograde transport** by **kinesin**. Some vesicles (only the small ones) are produced from recycled material in the terminal button by the *cisternae*, a collection of membranes similar to the Golgi apparatus. As excitation conduction through the synapse requires energy, the presynaptic terminal contains numerous **mitochondria**.

The process of neurotransmitter release requires **calcium** ions. The presynaptic membrane has **voltage-gated calcium channels**, which open when the membrane is depolarized by an action potential coming down the axon. There are no voltage-gated sodium and potassium channels in the presynaptic membrane; it is passively depolarized by action potential. Through opened channels, **Ca ions** rush into the presynaptic terminal down its electrochemical gradient.

Calcium triggers the neurotransmitter release, the process that is called **exocytosis** (Fig. 2.9). In the presynaptic terminal, many vesicles are already prepared for this process: they are **docked** against the presynaptic membrane by attaching clusters of **protein molecules** in their membrane to clusters of proteins in the presynaptic membrane. **Calcium** ions entering the terminal button bind to these protein molecules. It makes the segments of the protein clusters move apart, producing a **fusion pore** — a hole through both membranes that enables them to fuse together, forming the so-called **Ω-figures**. Thus, only when Ca ions enter do the synaptic vesicles fuse with the presynaptic membrane and empty their contents into the synaptic cleft. Calcium channels stay open only during depolarization. When

repolarization occurs, the channels close, exocytosis stops, and the **calcium pump** quickly transports Ca from the presynaptic terminal.

There are many special **synaptic proteins** that take part in docking and fusion of vesicles with the presynaptic membrane. The **main proteins** include the following:

Vesicle membrane proteins: **synaptobrevin; synaptotagmin**.

Presynaptic membrane proteins: **syntaxin, SNAP-25**.

Synaptobrevin / syntaxin and SNAP-25 (the so-called *SNARE* proteins) form a macromolecular complex that spans the two membranes bringing them into close apposition. **Docked vesicles** are ready to fuse with presynaptic membrane. When Ca^{2+} ions enter the presynaptic terminal, they bind to **synaptotagmin** and cause a change in synaptotagmin conformation and its binding to other proteins (SNARE). It results in the fusion of vesicle and presynaptic membranes, and the **release** of neurotransmitter.

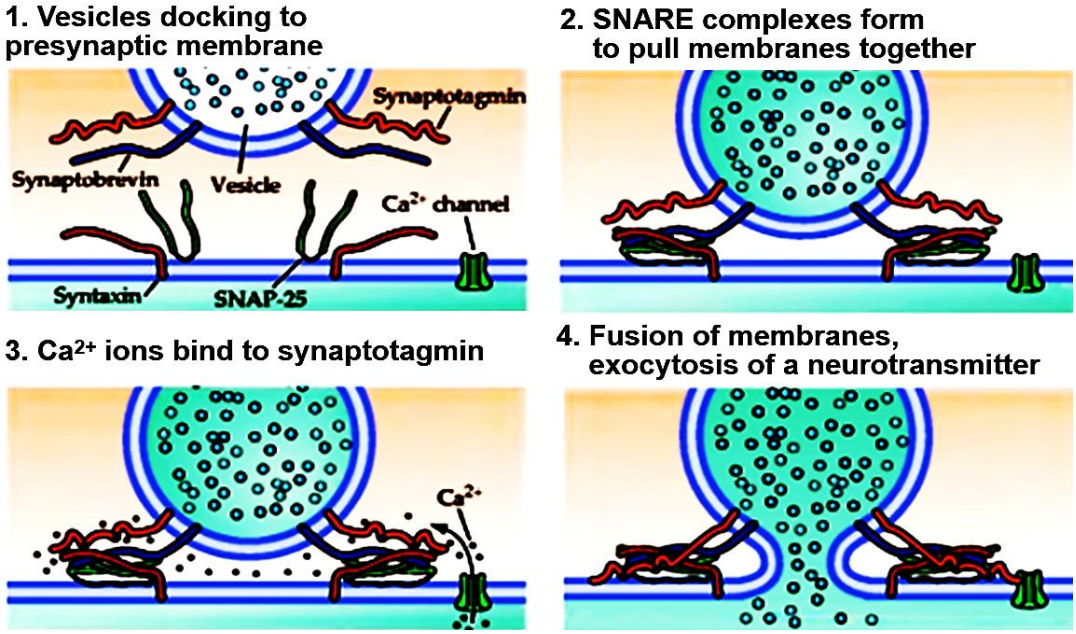


Fig. 2.9. Mechanism of the synaptic release of a neurotransmitter (from Neuroscience / ed. by D. Purves [et al.], 6 ed., 2018)

Presynaptic membrane recycling process

At the point of junction between the axon and the terminal button, little buds of membrane are **pinched off** into the cytoplasm by pinocytosis, and then **move to the cisternae** and fuse with them. These new synaptic vesicles **break off** the cisternae, then **filled** with neurotransmitter, receive appropriate **proteins insertion** to the membrane and are transported toward the presynaptic membrane. The recycling process takes approximately **one minute**.

The whole process of synaptic transmission is to be considered using the example of a synapse between a **motor neuron** and a **skeletal muscle cell**, the ***neuromuscular junction***, or *motor end plate* (Fig. 2.10). The neurotransmitter of neuromuscular junction (NMJ) is **acetylcholine** (ACh). This is the most widespread neurotransmitter in the body, as it is used also in other kinds of synapses, including the synapses of the central nervous system and autonomic nervous system.

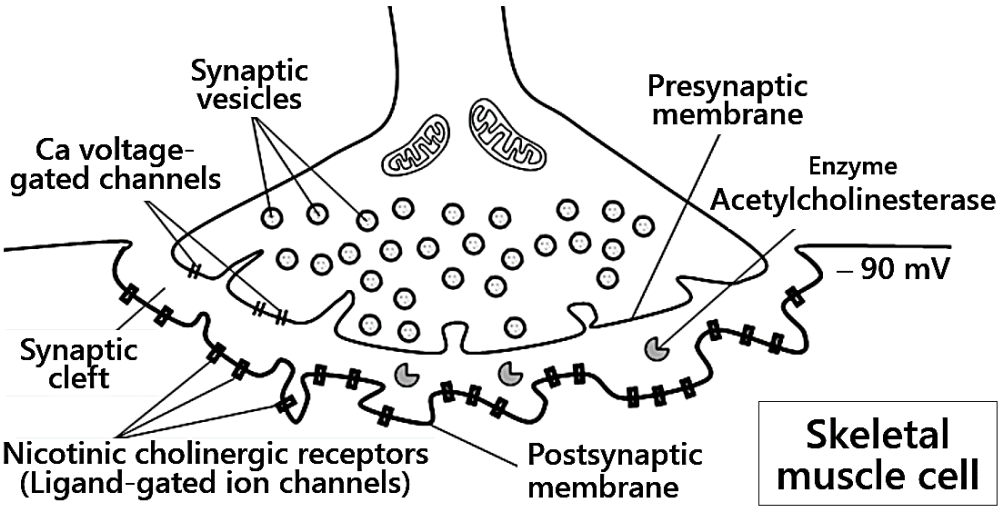


Fig. 2.10. Structure of the neuromuscular junction

The synaptic cleft of cholinergic synapse contains **acetylcholinesterase**, an enzyme that rapidly inactivates ACh by breaking it down into ***acetate*** and ***choline***. However, at first large quantities of ACh molecules diffuse across the cleft and **bind to the receptors** of the postsynaptic membrane.

The postsynaptic membrane does not have voltage-gated channels at all (as it is a chemical synapse!). The postsynaptic membrane of the neuromuscular junction contains **ligand-gated channels**, which are **nicotinic cholinoreceptors** (N-ChR), as distinct from the *muscarinic* ones (M-ChR) of autonomic nervous system. Binding of ACh to the external parts of the receptor protein subunits causes conformational change that **opens** the channel. Channels are ***non-selective*** as they are permeable for both $\mathbf{Na^+}$ and $\mathbf{K^+}$. However, the influx of Na^+ is **higher** than K^+ outflow, since sodium enters the cell down both a ***concentration*** and an ***electrochemical*** gradients, and potassium goes out only due to a ***concentration*** gradient; the negative charge inside the cell **opposes** the efflux of K^+. Thus, the predominant Na^+ influx results in **depolarization** of the postsynaptic membrane. The amount of ACh released from one vesicle (1 "***quantum***") causes a depolarization of about 1–2 mV, which is called the ***Miniature Postsynaptic Potential***. It is a very little depolarization, which cannot result in AP transmission. But each AP causes **many vesicles** to release their content, therefore many channels open and produce depolarization sufficient for signal transmission. Due to the **folds** of the postsynaptic membrane, which represent one of the **distinct *structural* characteristics** of NMJ, the area of the membrane and number of channels available for opening upon ACh release are great. This is one of the major **distinct *functional* characteristics** of NMJ that **one Action Potential is enough** for the NMJ to transmit a signal and generate an Action Potential on the muscle cell membrane. In ***central*** synapses between neurons of the central nervous system, at least ***two Action Potentials*** arriving successively or simultaneously to the postsynaptic cell are necessary to achieve excitation of the postsynaptic cell; a single impulse just increases the probability of postsynaptic Action Potential generation.

Depolarization of the postsynaptic membrane for all kinds of excitatory synapses is referred to as **Excitatory Postsynaptic Potential** (**EPsP**). There is a particular term for NMJ: **End Plate Potential** (**EPP**). The amplitude of the EPP (degree of depolarization) depends on the number of open channels, which depends on the amount of ACh molecules released, which in turn is determined by the rate of impulses that come to the synapse. One can see that this potential (EPsP or EPP) is subjected to the **law of force**, not to the "all-or-nothing" law. This is entirely different from the Action Potential, which is standard in its amplitude.

Depolarization of the postsynaptic membrane (EPP) creates **local currents** between the **postsynaptic membrane** and not yet depolarized adjacent parts of the **muscle cell membrane,** where **voltage-gated Na and K** channels are present. These local currents open Na channels, Na^+ ions enter and depolarize the membrane to the threshold level, and finally an **Action Potential** is generated on the **muscle cell membrane** ***around the synapse area***. Thus, the transmission of the impulse through the synapse is completed. The transmitted impulse (Action Potential) then propagates along the muscle fiber and causes muscle contraction.

Depolarization of the postsynaptic membrane stops when ACh molecules become **detached** from the receptors, and channels close. This detachment occurs only when concentration of ACh molecules in the synaptic cleft **decreases**, which happens due to breaking it down by **acetylcholinesterase**. Thus, acetylcholinesterase function is to provide for readiness of the synapse to the next impulse transmission.

In contrast to the fast voltage-gated sodium channels, which close automatically in a fraction of a second, by closure of their inactivation gates, ligand-gated channels stay open as long as the ligand remains attached to the channel. Thus, the whole process completion includes breaking down acetylcholine molecules in the synaptic cleft by acetylcholinesterase. Cholinesterase starts to work immediately after the neurotransmitter release, but at first the number of acetylcholine molecules is great, and many of them bind and open channels, thus producing impulses conduction. Then, very quickly, the concentration of acetylcholine in the synaptic cleft decreases, the molecules bound to the receptors (channels) get detached themselves, and undergo breaking down by acetylcholinesterase as well. Channels close, and become ready to open in response to the next impulse.

Now, there is summarizing of all the processes included in the excitation conduction through the NMJ, from action potential coming to the synapse from a motor neuron to the action potential generated on the muscle cell membrane:

1. **Depolarization** of the presynaptic membrane.
2. Opening of **voltage-gated Ca^{2+}** channels in the presynaptic membrane.
3. **Entry of Ca^{2+}** into the presynaptic terminal from the synaptic cleft (from the extracellular fluid), down its concentration gradient.
4. **Ca^{2+} ions binding** to the specific synaptic proteins (possibly, to synaptotagmin), that causes conformational changes of these proteins. and
5. **Fusion** of vesicular membrane with the presynaptic membrane.
6. **Release** of the neurotransmitter (acetylcholine) through the fusion pore to the synaptic cleft (exocytosis of the vesicles content).

7. Diffusion of acetylcholine molecules to the postsynaptic membrane, their **binding to nicotinic cholinergic receptors** of the membrane, which are ligand-gated channels.

8. **Opening of ligand-gated channels** by acetylcholine molecules (their ligands).

9. Entry of Na^+ ions and outflow of K^+ ions through the channels, with **predominant Na^+ entry** (Na^+ entry > K^+ outflow).

10. Depolarization of the postsynaptic membrane (**End Plate Potential**, type of the Excitatory Postsynaptic Potential for NMJ).

11. Formation of **local circular currents** between the depolarized postsynaptic membrane and adjacent areas of the muscle cell membrane (sarcolemma) that are in their resting state (–90 mV).

12. Depolarization of the **nearest to the synapse parts** of sarcolemma up to the threshold, opening of **voltage-gated Na^+ channels, generation of an Action Potential** on the sarcolemma, and its conduction along the skeletal muscle fiber, similarly to conduction along unmyelinated nerve fibers.

Action Potential is conducted. However, one more point should be included.

13. By this moment, **acetylcholinesterase** has completed breaking down ACh molecules in the synaptic cleft, causing ligand-gated channels to close, and thus making the synapse ready to conduct next impulses.

Normally skeletal muscle fibers are stimulated by high frequency impulses from motor neurons. These impulses cause Ca ions release from the sarcoplasmic reticulum into the sarcoplasm and interaction of muscle proteins that leads to muscle contraction.

PROPERTIES OF SYNAPSES. DRUGS AFFECTING SYNAPTIC TRANSMISSION

Obviously, the synapse uses only **one-way conduction**, from the presynaptic membrane to the postsynaptic one. One of the basic synapse properties is the conduction **delay**. The minimal duration of conduction through the synapse is about 0.5 millisecond (the ***synaptic delay***). Due to this property, the rate of action potentials conducted through synapses may differ from the stimulation rate. If the rate of action potentials exceeds the maximal rate of synaptic transmission, the rate of AP output from the synapse **decreases** (property of **rhythm transformation**). Another important property is the **fatigue** of synapses. With repeated stimulation of excitatory synapses at a high frequency, the firing rate of the postsynaptic neuron is also high at first, but then gradually **decreases**. Synapses have the **highest ability** to fatigue development in comparison to both nerve fibers and muscle cells. One more property of synapses is their high sensitivity to **hypoxia** and acidosis/alkalosis. Synapses also are **sensitive to various drugs** that can affect the process of synaptic conduction.

Many drug substances are known to affect the synaptic transmission (Fig. 2.11). The main ways of NMJ blockade include: block of neurotransmitter release from the presynaptic terminal; inhibition of acetylcholinesterase; and blockade of receptors of the postsynaptic membrane.

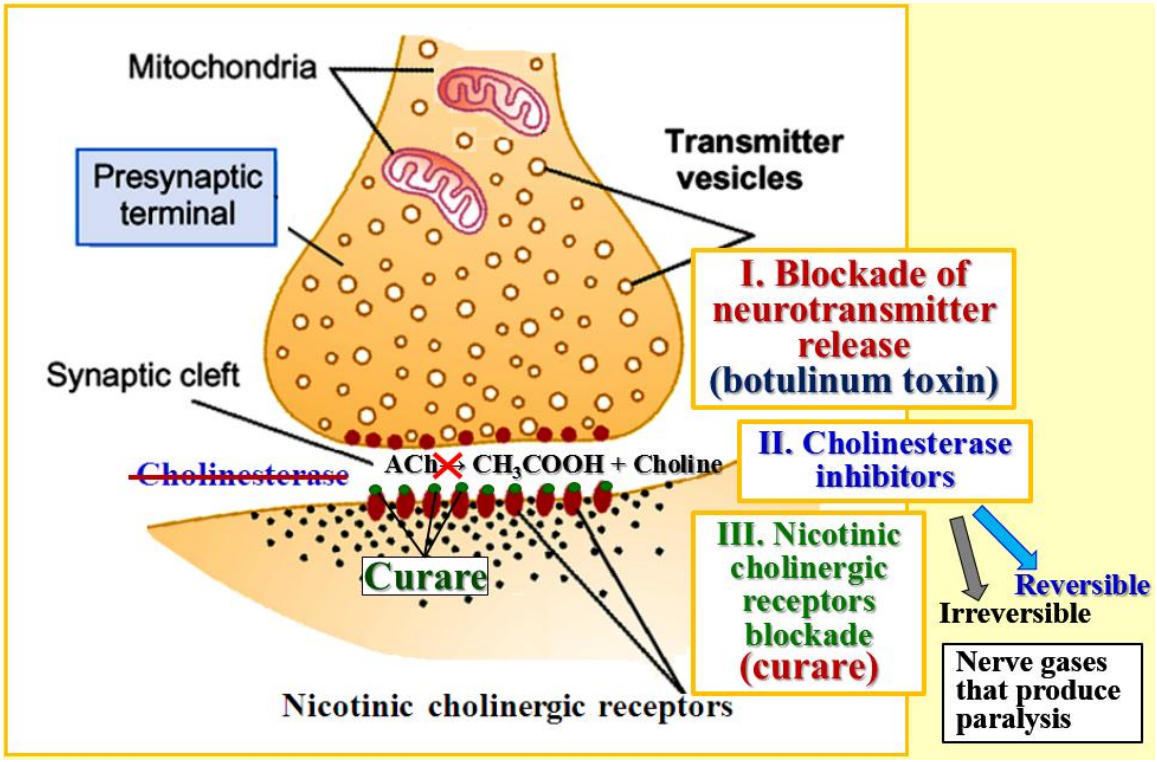


Fig. 2.11. The main ways of neuromuscular junction blockade

For example, **botulinum toxins** prevent neurotransmitter release by destroying synaptic proteins necessary for exocytosis (synaptobrevin and others), and therefore block synapses. These toxins are produced by the anaerobic bacteria Clostridium botulinum, which can develop in spoiled canned food. Ingestion of such food can cause severe poisoning and death. However, botulinum toxin is used as a medication to manage and treat a number of therapeutic and cosmetic problems. Medicinal uses include spastic disorders, cervical dystonia, and chronic migraine; it is also used for cosmetic purposes to relax facial muscles and reduce wrinkles (a drug known as Botox). It is used in injections into the muscle, in order to reduce or stop impulses conduction from neurons. One injection can effectively decrease neuromuscular conduction and relax muscles for several months.

Acetylcholinesterase inhibitors prevent ACh breaking down, so that ACh molecules remain attached to the receptors, and ligand-gated channels of the postsynaptic membrane remain open. It results in persistent ***stable depolarization*** of postsynaptic membrane. At first, a number of impulses is easily conducted through NMJ; thus, initially convulsions may occur. But then, since repolarization of the area around synapse does not occur, inactivation gates of Na channels remain closed; this means **inactivation** of Na channels of the postsynaptic cell membrane near synapse. As a result, excitation conduction through the synapse stops (synapse blockade). This mechanism is characteristic for the ***irreversible*** inhibitors — substances that are used for purposes far from medicine. These are chemical warfare agents, or **nerve gases**, that have been used in military actions since the First World War. By affecting neuromuscular synapses, these substances can cause skeletal muscle twitching, seizures, coma and death. Additionally, they greatly increase parasympathetic

autonomic effects. Other irreversible acetylcholinesterase inhibitors are **organophosphorus compounds**, insecticides, which effectively kill insects.

Reversible acetylcholinesterase inhibitors (proserin, neostigmine and others) are used in medicine to treat a number of diseases when it is necessary to facilitate impulses conduction through synapses by prolonging the action of ACh. Main indication for the use of these drugs is myasthenia gravis, a disease characterized by severe muscle weakness due to very poor excitation conduction through NMJ. Other indications include Alzheimer's disease and some other neurodegenerative conditions when these drugs may help to improve communication between neurons.

Another mechanism of the synapse (NMJ) blockade is blocking of **nicotinic cholinergic receptors** of the **postsynaptic membrane**. A poisonous substance derived from certain tropical South American trees, ***curare***, binds to nicotinic receptors instead of acetylcholine but does not open the channels (non-depolarizing action). When impulses are sent to the synapse, neurotransmitter molecules cannot bind to receptors and open channels, as curare occupies their binding sites on receptor molecules, thereby blocking impulses conduction by neuromuscular junctions and causing skeletal muscular paralysis (complete loss of voluntary movements). The indigenous peoples of Central and South America knew about the properties of curare and used it as a paralyzing agent for hunting. They dipped the arrow tips into a plant preparation, and even a minor injury caused by such an arrow made the animal too weak to escape.

Curare derivatives, contemporary curare-like compounds such as tubocurarine chloride and others are used in anesthesiology as **muscle relaxants**, in combination with general anesthesia (under control of artificial lung ventilation). By blocking neuromuscular junctions, these drugs prevent muscle contractions during surgical manipulations. As these drugs act on muscle cells rather than neurons, they do not have a toxicity to the nervous system as the central anesthesia may have. The duration of muscle relaxants effect can be various, depending on the required duration of surgery.

It must be understood that any substance that is able to block the synapses between motor neuron and muscle fibers, in its ultimate effect produces total paralysis of the skeletal muscles. This means inability to move, and not only that. Skeletal muscles include our respiratory muscles, the diaphragm and the external intercostal muscles. Therefore, full NMJ blockade involves paralysis of the respiratory muscles, respiratory arrest. This blockade does not stop heart contractions, or contractions of the smooth muscles. However, absence of respiration within a few minutes leads to death.

Section 3
PHYSIOLOGY OF MUSCLES

SKELETAL MUSCLE STRUCTURE AND FUNCTION

There are **three types** of muscle tissue: **skeletal**, **cardiac**, and **smooth** muscle tissue (Fig. 3.1). Both skeletal and cardiac muscles have ***visible striation*** due to their regular arrangement of proteins filaments. Skeletal muscle fibers contain multiple peripheral nuclei, whereas branching cardiac cells have single central nucleus. Smooth muscle cells are spindle-shaped cells with one central nucleus. They lack visible striation. Both cardiac and smooth muscle are under involuntary control, and only skeletal muscles are under ***voluntary*** control.

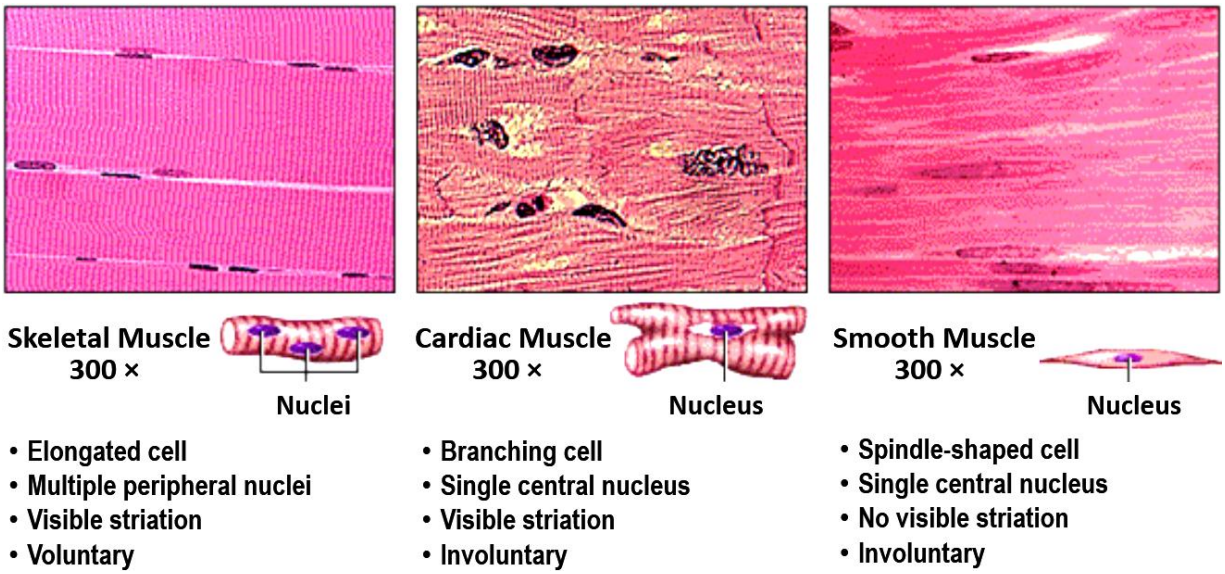


Fig. 3.1. Three types of muscle tissue cells and their main features
(from Interactive Physiology. Muscular module / by M. J. Branstrom)

The main properties of skeletal muscle tissue are ***excitability***, the ability for ***conduction*** of action potentials along its membrane, and the specific muscle tissue ability ***to contract***. The excitability of muscle tissue is **lower** than that of the nervous tissue. One of explanation of this can be a comparison of the excitation threshold for nervous and muscle tissue. The threshold level for excitation of nervous and muscle cells membranes is the same, about –45 mV (–40 – –50 mV). The resting potential of a neuron is about –60mV, and that of a skeletal muscle cell is –90mV. Thus, the minimal force required to achieve the muscle cell excitation is higher than that of a neuron, and the excitability is lower. The velocity of action potential **conduction** along muscle fiber membrane is about 3–5 m/sec.

For understanding of the ability of a muscle to contract, it is necessary to consider its **structure**. The **whole** skeletal muscle consists of the **fascicles**, which are composed by the **muscle fibers**, or muscle cells (Fig. 3.2). Muscle cells have a cylindrical shape. Their nuclei are located peripherally, on the surface of the cylinder. Muscle fibers consist of **myofibrils**. Also, they contain a special

extensive reticulum that surrounds each myofibril of the muscle fiber, called the **sarcoplasmic reticulum**. This reticular structure is a reservoir for **Ca^{2+} ions** storage. Ca ions are necessary for muscle contraction. The peripheral parts of the sarcoplasmic reticulum are sac-like **terminal cisternae** that are in contact with the transverse tubules, or **T-tubules**, which perform conduction of action potentials from the surface of the muscle cell to its interior. One T-tubule and two adjacent terminal cisternae contacting the tubule form a ***triad***. Due to the ***contacts*** between T-tubules and the sarcoplasmic reticulum cisternae membranes, an action potential propagating along the muscle fiber membrane (sarcolemma) is conducted to the T-tubules and then causes the opening of **voltage-gated Ca channels** in the sarcoplasmic reticulum. It occurs through the **ryanodine receptors** (named after a plant alkaloid that can bind to the receptor and open Ca channel). Calcium ions concentration in the reticulum is about 10000 times higher than in the sarcoplasm (skeletal muscle cell cytoplasm). Therefore, Ca channels opening results in the ***release*** of large quantities of **Ca^{2+}** ions stored within the reticulum (down the concentration gradient). The released Ca ions trigger muscle contraction due to their interaction with the **myofilaments proteins** that compose the myofibrils.

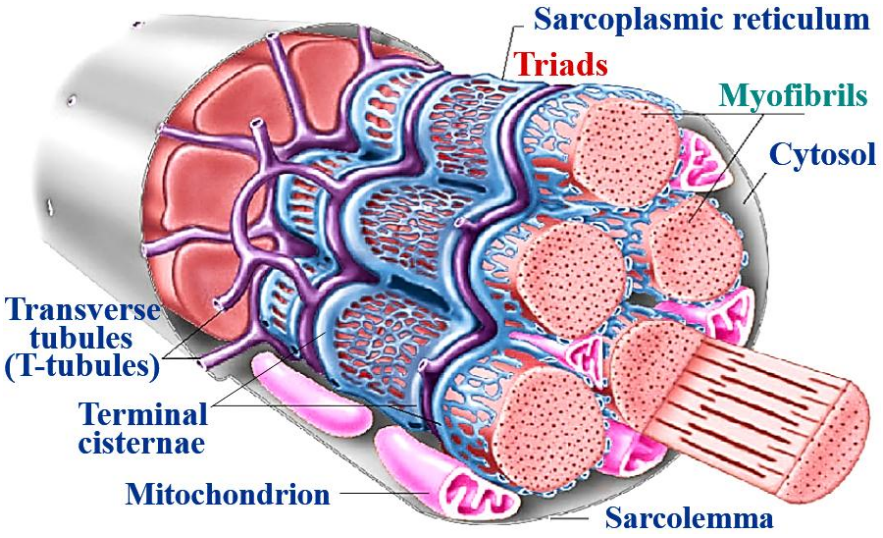


Fig. 3.2. Skeletal muscle fiber (cell) (from Human Physiology / Vander. 15 ed. 2019)

There are **thick** and **thin** filaments partially overlapping in the myofibril. Thick filaments are called **myosin filaments**, as they are composed of myosin protein molecules (about 200 molecules per one thick filament). Each myosin molecule looks like a golf club with ***two heads*** and a long ***tail*** (Fig. 3.3). Either heads (or ***cross bridges***) of myosin molecule have **two binding sites**: one for the **actin** (main protein of the thin filaments) and the other for ATP molecule. Myosin heads have the ability to **hydrolyze** the **ATP** molecule to ADP and P_i (inorganic phosphate). The energy released causes a specific change of myosin molecule conformation — myosin heads flexing movement, which is called a **power stroke** for muscle contraction.

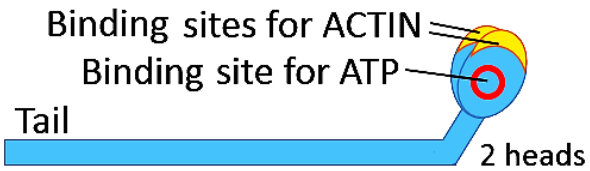


Fig. 3.3. Myosin molecule structure

Thin, or **actin filaments** are composed of three proteins: **actin**, **tropomyosin,** and **troponin** (Fig. 3.4). The major component, actin, has globular subunits arranged in two twisted helical chains. Each subunit possesses a binding site for myosin cross bridge. The regulatory protein **tropomyosin** entwines around the actin chains. When Ca ions concentration in muscle cell cytoplasm is low (about 10^{-8}–10^{-7} M), tropomyosin covers the binding sites on actin subunits and prevents myosin cross bridges binding to actin. To expose binding sites for myosin on actin molecules, the tropomyosin molecule must be moved aside. This is performed by a third molecular complex called **troponin**. Troponin is attached and spaced periodically along the tropomyosin strand. Troponin consists of three subunits, one of which is attached to actin, the other — to tropomyosin, and the third one is **C**-subunit (**C**a-binding). Depolarization of the sarcoplasmic reticulum cisternae membranes, caused by an action potential, opens calcium channels, and **calcium ions** are released from the sarcoplasmic reticulum and bind to the **C**-subunit of troponin. This causes a conformational change in tropomyosin-troponin complex resulting in tropomyosin movement along the thin filament thus making **binding sites** on actin exposed.

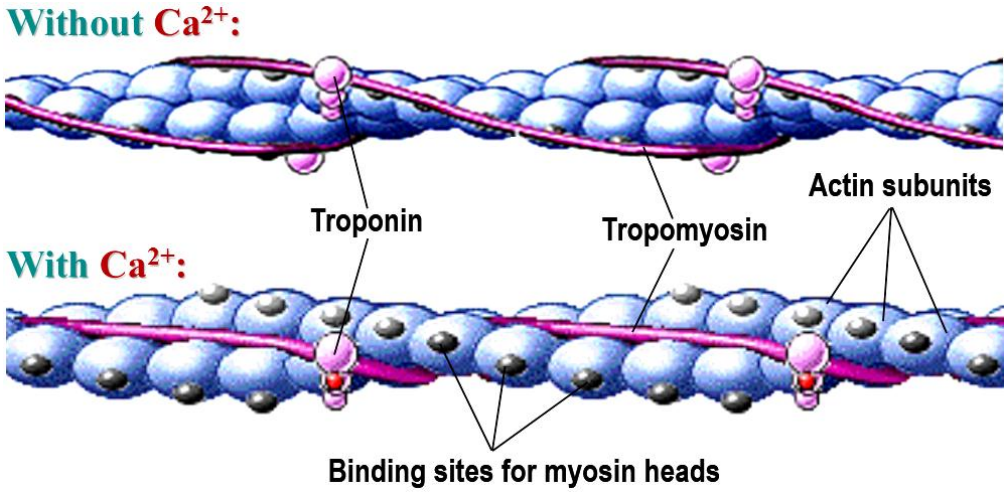


Fig. 3.4. Actin filaments structure without and with Ca ions
(from Interactive Physiology. Muscular module)

Thick and thin myofilaments form light (**I band**) and dark (**A band**) alternating bands (Fig. 3.5) along the myofibril. These dark and light bands create the transverse **striation** of skeletal muscle. Thin myofilaments are attached to a special protein disc called Z-disc (or **Z-line** at the plane cross-sections). Thick filaments are located between thin filaments; in the middle they are attached to the disk structure that forms the **M-line**. The repeating portion of myofibril between two Z-lines is called a **sarcomere**.

The light I band is made by thin filaments only, with Z-line in the middle. The dark, A band, consists of both thick and thin filaments overlapping each other. In the central part of A band there is lighter **H zone** where only myosin filaments are present.

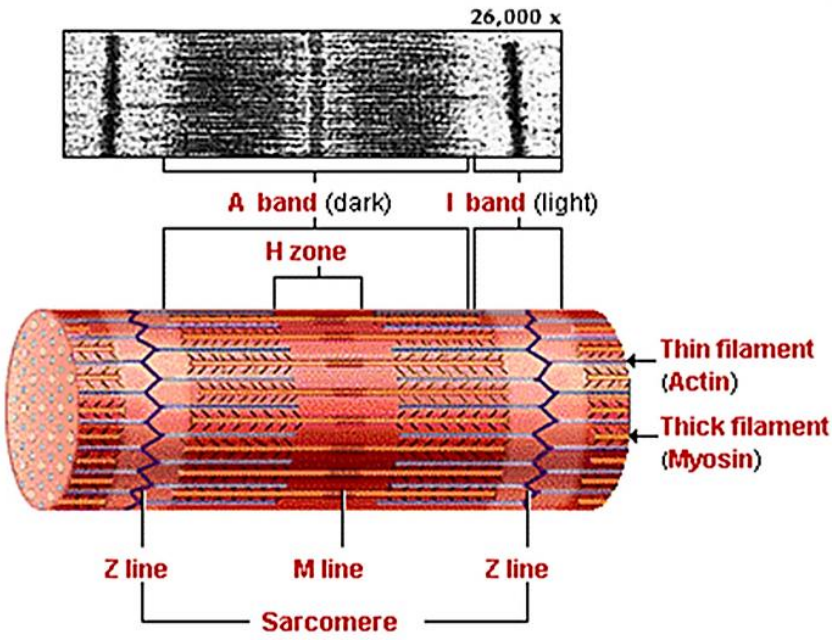


Fig. 3.5. Structure of the sarcomere (from Interactive Physiology. Muscular module)

Figure 3.6 shows composition of the sarcomere with its thin actin and thick myosin filaments. The actin filaments are directly attached to Z-lines, while the myosin filaments are held together by the M-line (not shown at the picture) in the middle of the sarcomere. Additional fixation of myosin filaments is made by the structural protein **titin** that connects the ends of the myosin filaments to Z-lines. Due to this fixation, the myosin filaments are arranged precisely in parallel to each other and to the actin filaments, which is important for easy ***sliding*** of the filaments along each other (Fig. 3.7). This sliding movement of myofilaments is the essence of the contraction process.

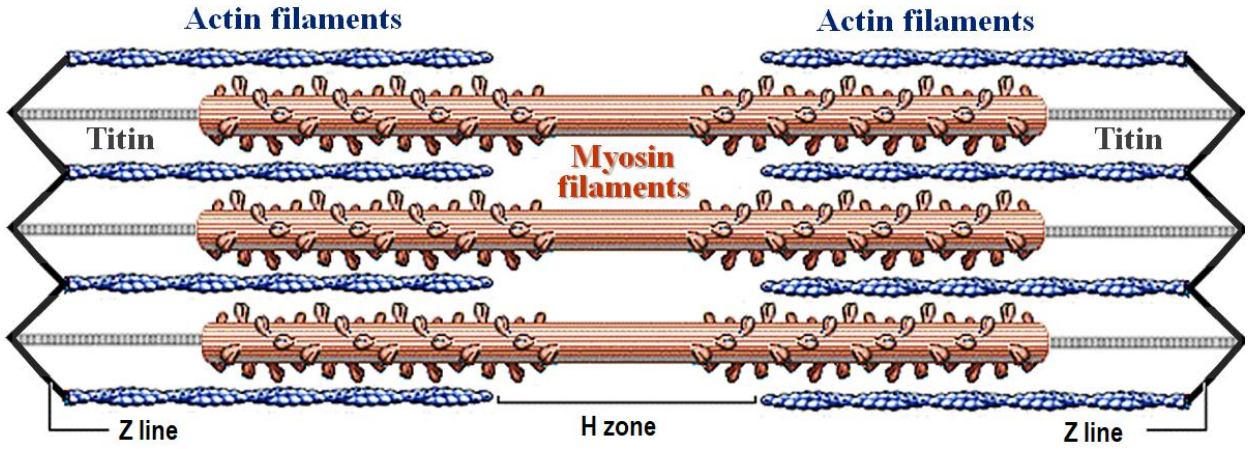


Fig. 3.6. Sarcomere and the myofilaments arrangement
(from Interactive Physiology. Muscular module; modified)

Mechanism of skeletal muscle contraction: *theory of sliding filaments.*

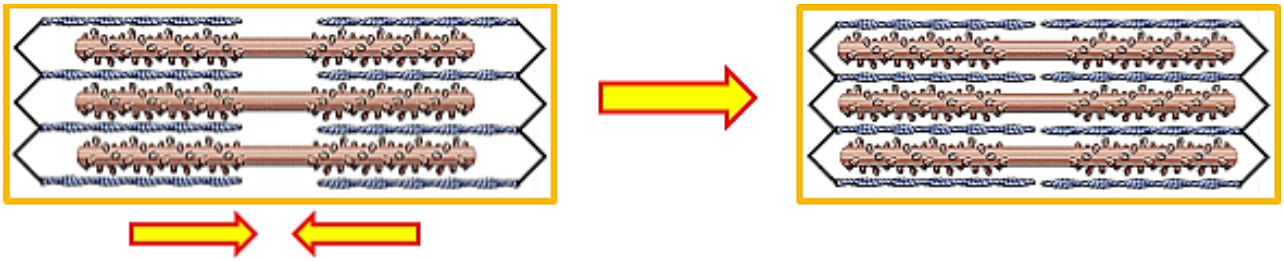


Fig. 3.7. Shortening of sarcomere due to sliding of filaments

The basis for muscle contraction is the successive connecting and disconnecting of **actin** and **myosin** resulting in steady **sliding** of the thin actin filaments along the thick ones. The whole process is a repeating sequence of events which is referred to as the **single cross bridge cycle**. Before considering this cycle, it is necessary to recall the state of muscle cells before they are stimulated by the action potential from a motor neuron. Before stimulation of the muscle fibers, their myosin cross bridges are already *energized*. This means that ATP is already hydrolyzed to ADP and P_i, and the conformation of myosin molecules provides its readiness to connect to actin binding sides, which still are not available without Ca ions. After the **action potential** coming down the axon to the muscle fibers, depolarization of muscle cell membrane occurs, including the T-tubules. This **opens Ca channels** of the sarcoplasmic reticulum (SR), and the **cross bridge cycling** starts.

A **single cross bridge cycle** includes the following events:

1. Ca ions release from SR, binding to the C-subunit of **troponin**, **exposure** of binding sites on actin.

2. Binding of myosin to actin.

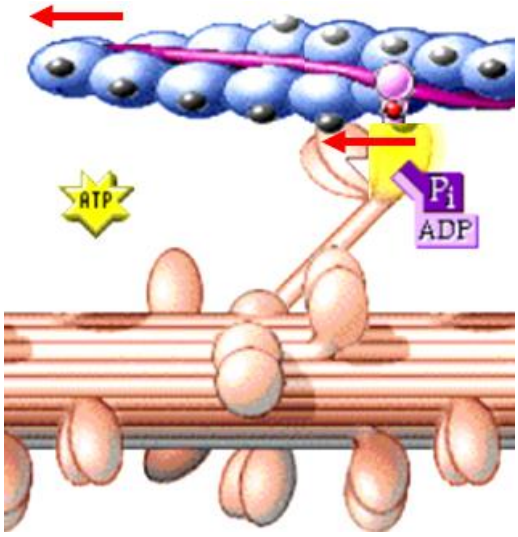


Fig. 3.8. Power stroke of a myosin head (from Interactive Physiology, Muscular module)

3. Flexing of myosin molecules heads (**power stroke** of the cross bridges; Fig. 3.8) that causes **sliding** of the thin filaments along myosin ones from both sides to the center of the sarcomeres, and **shortening** of myofibrils. Detachment of ADP and P_i.

4. Binding of a **new ATP molecule** to the cross bridge, which results in the cross bridge **disconnecting** from actin.

5. ATP hydrolysis, which leads to **re-energizing** and **repositioning** of the cross bridge (the energy of this ATP molecule is to be used for the next cycle).

6. Transports of **calcium ions back** into the sarcoplasmic reticulum by **calcium pump** (ATP-ase).

During muscle contraction, these stages are **repeated many times per second** until muscle stimulation by motor neuron ceases, and calcium is pumped back into

the sarcoplasmic reticulum. Myosin heads (cross bridges) are connected and disconnected to actin **in turn**. The **multiple cross bridge cycle** is the successive connecting and disconnecting of many myosin heads to actin, resulting **in steady sliding** of the thin actin filaments along thick ones.

Relaxation of the muscle occurs after a **decrease of Ca ions** concentration caused by the **pumping** Ca back to the sarcoplasmic reticulum. Restoration of the initial muscle length is achieved due to the **elasticity** of muscle cell proteins.

Evidently, **Ca ions** play a key role in the mechanism of muscle contraction. Calcium ions intermediate between membrane depolarization (action potential) and myofilaments sliding that results in muscle contraction, or between ***electrical*** and ***mechanical*** processes. This function of Ca ions is called the **excitation-contraction coupling**. If after the action potential there is no release of Ca ions, contraction is impossible. On the contrary, an increase in sarcoplasmic Ca concentration without an action potential can cause muscle contraction. For example, in case of intramuscular injection of $CaCl_2$ solution (which must be injected **only** intravenously), Ca concentration in muscle cells in the site of injection increases, and it results in a strong contraction of damaged by injection muscle fibers, and their subsequent **necrosis**.

An important condition for muscle contraction is the **ATP availability**. ATP is produced in muscles by two different ways: anaerobic glycolysis and oxidative phosphorylation. **Glycolysis** does not require oxygen and provides quick output of 2 ATP molecules per one molecule of glucose. However, it works for a rather short time, and then the pyruvic acid formed from glucose starts to be converted into lactic acid that decreases muscle performance. **Oxidative phosphorylation** requires oxygen and takes longer time to produce ATP, but it can be used for a much longer period, and it produces up to 38 ATP molecules per one molecule of glucose.

WHITE AND RED MUSCLE FIBERS COMPARATIVE CHARACTERISTICS

On a basis of the difference in their biochemical processes, muscle fibers are differentiated into two main types, fast (white) and slow (red) fibers. **Fast** (***white***) muscle fibers are larger and have lower blood supply. They possess a large number of glycolytic enzymes for the rapid ATP production. They are able to ***strong*** but ***short*** contractions. The skeletal muscles involved in our movements contain predominantly white muscle fibers. **Slow** (***red***) muscle fibers are red in color due to the high content of **myoglobin**, which is an additional source of O_2, and they have a higher blood supply. They are smaller in size, contain a large number of mitochondria and produce ATP by oxidative phosphorylation. The muscles composed mainly of this type of fibers are capable of rather ***slow*** but ***prolonged*** contractions. The deep muscles of the trunk, involved in maintaining the body posture, consist mainly of red muscle fibers. Usually muscles are composed of both type of muscle fibers, with predomination of one type.

The most important features of the two types of muscle fibers are given in the table below. There is also a mixed type of fibers, which are fast oxidative-glycolytic (red). Their properties are intermediate between white and red fibers, and they develop medium force.

Table 3.1

The main properties of white and red muscle fibers

White muscle fibers	Red muscle fibers
Large diameter	About $^1/_2$ of white fibers diameter
Light in color due to reduced myoglobin	Dark in color due to myoglobin
Surrounded by few capillaries	Surrounded by many capillaries
Relatively few mitochondria	Numerous mitochondria
High glycogen content	Low glycogen content
Synthesize ATP mainly by ***glycolysis***	Synthesize ATP mainly by ***oxidative phosphorylation***
Develop fatigue fast	Fatigue resistant
Suited for fast & strong but not prolonged contractions	Suited for slow but sustained contractions

WHOLE MUSCLE CONTRACTION

Single muscle cells (fibers) respond to stimulation in an **all-or-none** fashion. When the muscle fiber is stimulated by an action potential, it contracts. Without impulses, it is relaxed. Thus, it follows the same law as Action Potential itself. The **whole muscle** responds according to the **law of force** as it shows variations in tension, or force of contraction. The reason for this difference is involving into contraction smaller of larger number of muscle fibers present in the muscle. Stronger stimulation involves greater number of muscle fiber into excitation and contraction; therefore, the muscle develops greater tension (force) of contraction.

Whole muscle contraction normally is produced by series of action potentials from motor neurons. Single muscle contraction experimentally caused by one nervous impulse is called a **muscle twitch**. Each muscle twitch is divided into **3 periods**: **latent** period, periods of **contraction** and **relaxation** (Fig. 3.9).

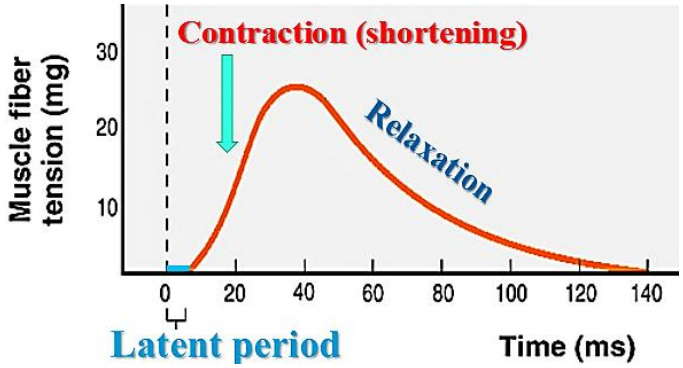


Fig. 3.9. Single muscle twitch three periods

The latent period lasts from the moment of stimulation until the beginning of muscle shortening; during this period action potential propagates along

the sarcolemma and T-tubules, causing Ca channels opening and Ca ions release. The period of muscle shortening starts after Ca release. During this period muscle length decreases. During the relaxation period, the initial length of the muscle is restored again.

Muscle fibers are joined into motor units due to their innervation by a motor neuron. A **motor unit** is a whole group of muscle fibers innervated by single motor neuron, together with that motor neuron. One motor neuron of the spinal cord innervates about ***several hundred*** muscle fibers on average. In some large muscles, the motor units include up to several thousand fibers, while in the muscles that perform the most precise movements, the motor units are small and may consist of just a few muscle fibers. The **number** and **size** of motor units determine the **force** and **precision** of muscle contraction: ***higher number*** and ***smaller size*** of motor unit are necessary for muscles performing **small precise** movements; ***fewer number*** and ***larger size*** of motor unit are necessary for muscles that perform **large strong** movements. Such large and strong movements are performed, for example, by the large thigh muscle, the *quadriceps femoris* muscle. An example of muscles that make precise small movements are the muscles of the fingers and, in particular, the ocular muscles involved into the fastest movements of the body, the eye movements.

SKELETAL MUSCLE ACTION POTENTIAL, EXCITABILITY & CONTRACTION

Skeletal muscle contraction can last for a long time, depending on the need. As it was already mentioned, our normal muscle contractions are caused by action potentials sent from motor neurons at a high rate. Therefore, normally we have *summational* contractions, and not single muscle twitches. The basis for the contraction summation is the much longer duration of the contraction (muscle twitch) as compared to the action potential duration. The skeletal muscle action potential is very short (Fig. 3.10). It consists of only two phases: depolarization due to entry of Na^+ ions, and repolarization due to K^+ ions outflow from the cell. Correspondingly, the absolute refractory period, when the membrane (sarcolemma) is not excitable, is also very short; it lasts within the latent period, and is almost ended by the beginning of muscle contraction. So, from the very beginning of contraction, muscle fibers are ready to respond to the next impulse, and to release a new portion of Ca^{2+} ions. Higher Ca^{2+} ions level in the sarcoplasm results in the higher force of contraction.

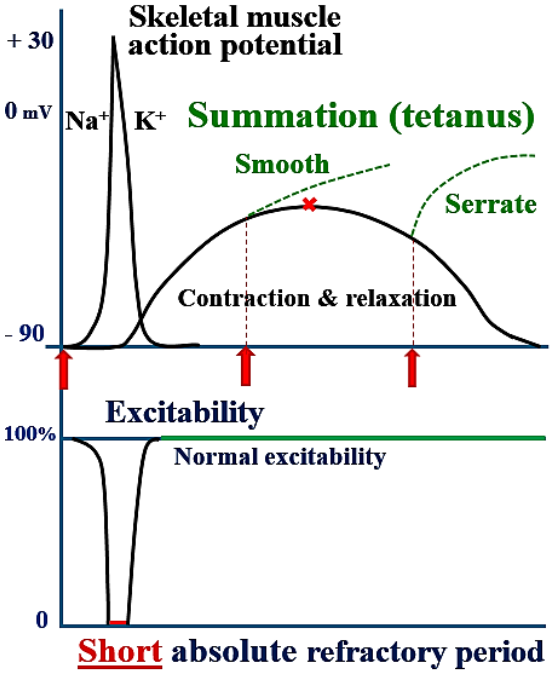
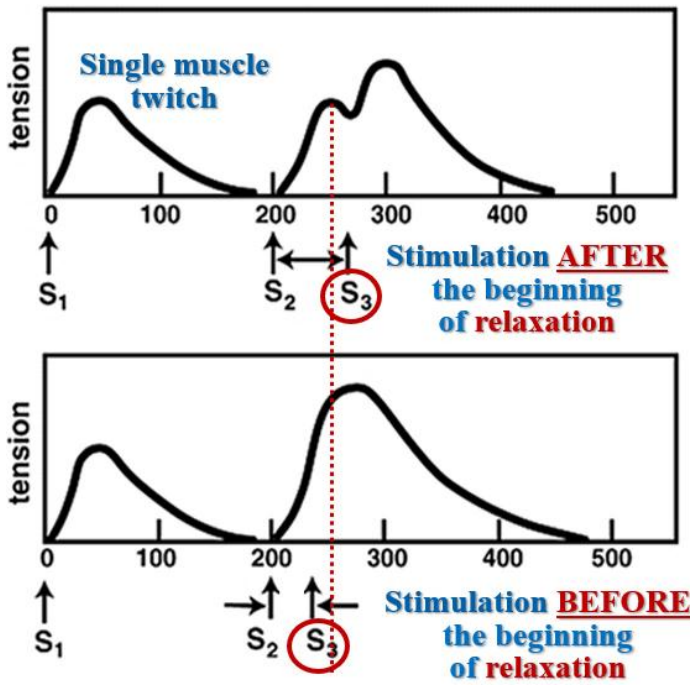


Fig. 3.10. Skeletal muscle cell excitation, excitability & contraction

Stimulation of the muscle when each subsequent impulse comes before the contraction is completed produces **summation of contraction** that is called ***tetanus***. There are two types of tetanus (Fig. 3.11).



- **Incomplete (serrate) tetanus**

(S — stimulus)

- **Complete (smooth) tetanus**

Fig. 3.11. Types of skeletal muscle contraction summation

Incomplete (serrate) tetanus. This type of summation is achieved when the next impulse arrives during ***muscle relaxation*** period. Relaxation that normally occurs due to a decrease in Ca level, then stops, and a new contraction follows, with a higher amplitude. The second contraction develops higher tension due to the **higher level of Ca ions**, which are released from the sarcoplasmic reticulum in addition to the ions that are not fully pumped back after the first release. Incomplete tetanus record appears as a serrate line. Contractions are followed by relaxations, then before each relaxation is completed, a new contraction begins, and so on. This type of contraction can be obtained experimentally, while our normal muscle contractions are of the following type, which is achieved at a higher frequency of stimulation.

Complete (smooth) tetanus. Smooth tetanus is achieved when the next impulse comes during muscle contraction period. In this case, muscle continues to contract without relaxation, and develops higher tension proportionally to the rate of muscle stimulation, until a maximal tension is reached. The main reason for higher tension is the same, the higher level of Ca ions released from sarcoplasmic reticulum. There is no time enough to pump Ca back during the interval between impulses, and Ca concentration progressively increases. Thus, Ca ions concentration in the sarcoplasm is the key factor that determines the force of muscle contraction when stimulation frequency increases.

FACTORS FOR FORCE (TENSION) OF MUSCLE CONTRACTION

The same muscle may develop stronger or weaker contractions. There are a number of factors that determine the force, or ***tension*** of muscle contraction.

One of the **factors** that **determine the force** of muscle contraction is the **number of muscle motor units (1)** participating in the contraction. The greater proportion of muscle motor units involved in contraction, the greater the force of muscle contraction.

Another factor that influences the tension of muscle contraction is the **frequency of stimulation (2)** by nervous impulses. The increase of frequency provides a temporal **summation** of contractions and increases muscle tension until reaching maximal force.

A recording of the skeletal muscle response to ***increasing rate of stimulation*** is shown at the Fig. 3.12. At a lower frequency of stimulation, the muscle responds with single muscle twitches, then relaxation becomes incomplete as summation of the serrate type begins. From a certain level of impulses frequency, the next impulses start to come before relaxation begins, and the summation becomes complete. This is a smooth tetanus, a usual mode of muscles contraction. After reaching maximal force of contraction (*optimum*), further increase in stimulation frequency decreases the force of muscle contraction, and the muscle relaxes despite the continuing increase in stimulation frequency (exhaustion).

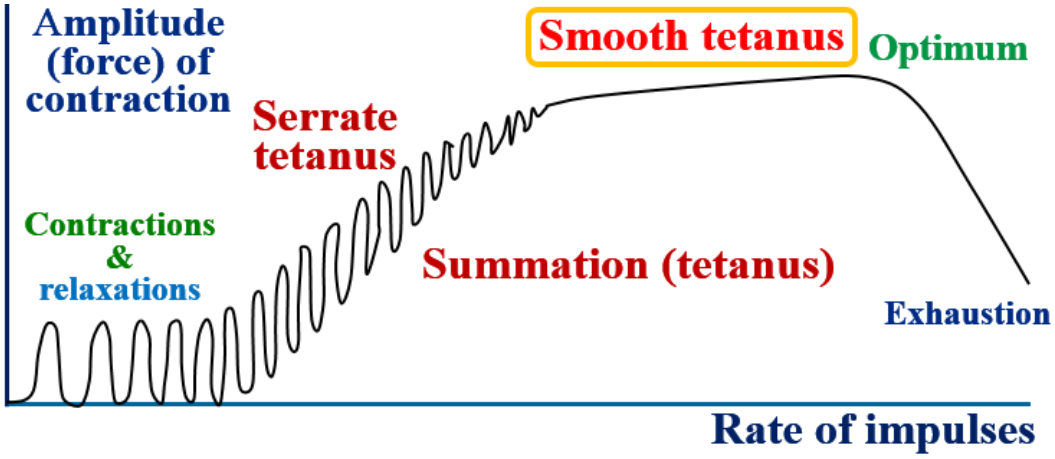


Fig. 3.12. Skeletal muscle response to stimulation with increasing rate

The third factor for muscle tension is the **degree of muscle stretching (3)** before contraction. Skeletal muscle **stretching** before contraction results in the **increase** of tension developed during muscle contraction. When the muscle is stretched for about **45–50 %** of its initial length (optimal) before stimulation, the maximal force of contraction is achieved (Fig. 3.13). This degree of stretching provides the ***optimal positioning*** of actin and myosin filaments in sarcomeres. Further stretching of the muscle (more than 50 % of the initial lengths, ***overstretching***) results in the decreased muscle tension due to smaller number of cross bridges able to bind to actin, as the thin filaments are pulled away from the region of myosin cross bridges.

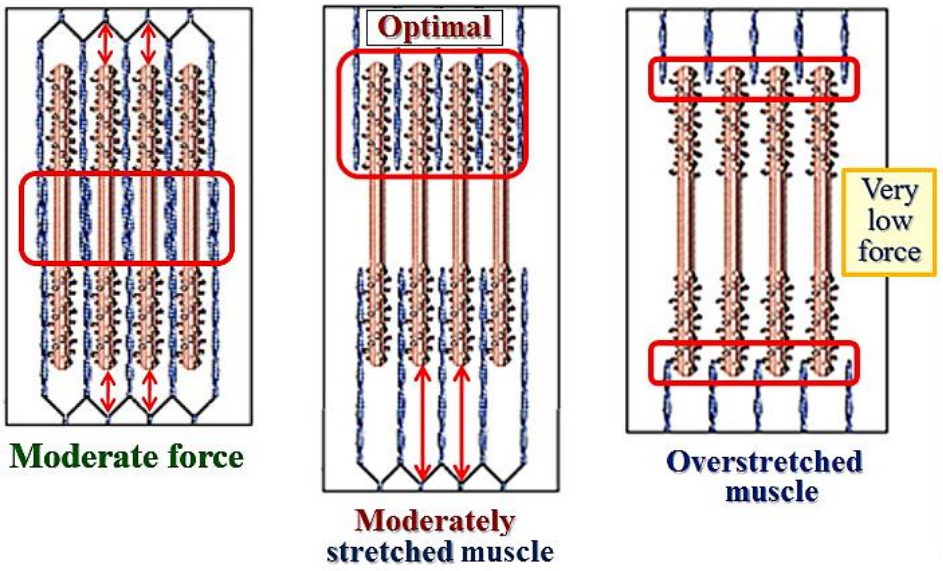


Fig. 3.13. Stretching of the sarcomere and its influence on the force of contraction (from Interactive Physiology. Muscular module; modified)

The **resting state** of the muscle usually **is not a state of full relaxation**. The muscle is not visibly shortened, but a certain level of tension is developed in its fibers. This normal resting state is **muscle tone**. In can be lower or higher, but it is always present. The muscle tone is achieved by *unsynchronized* contractions and relaxations of motor units in the muscle. At any moment, the percentage of contracted fibers is small, and the whole muscle in not shortened, but maintains a certain degree of tension. Muscle tone is produced by impulses sent from the spinal cord motor neurons. When the motor nerves of a muscle are damaged (cut), the muscle becomes flaccid and unresponsive, its muscle tone and voluntary control are lost (muscle paralysis).

SMOOTH MUSCLE

Smooth muscles have some ***distinctive properties*** compared to skeletal muscles. First, their contraction can be caused by **various stimuli**, not by nervous impulses only. Some smooth muscle cells have the ability to **auto-excitation**. The **resting potential** of smooth muscle cells is about **–50 – –60 mV**. One of the most important characteristics of smooth muscle contraction is its dependence on the **extracellular Ca^{2+}** ions influx into the cell since the plasma membrane of smooth muscle cell contains **Ca channels**, both ***voltage- and ligand-gated.***

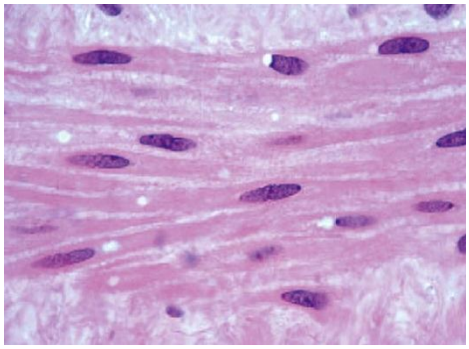


Fig. 3.14. Smooth muscle tissue (from S. I. Fox. 14 ed. 2016)

Smooth muscle cells are spindle-shaped, with a single central nucleus in the thicker middle portion of the cell, and thin sharp ends (Fig. 3.14). There are no visible striation and voluntary control in smooth muscles.

Smooth muscle is composed of much smaller and shorter fibers compared to skeletal muscle. Smooth muscles vary in size, structural organization, and functions, but generally, they can be divided into ***two major types*: multi-unit** and **unitary** (or single-unit) smooth muscles (Fig. 3.15).

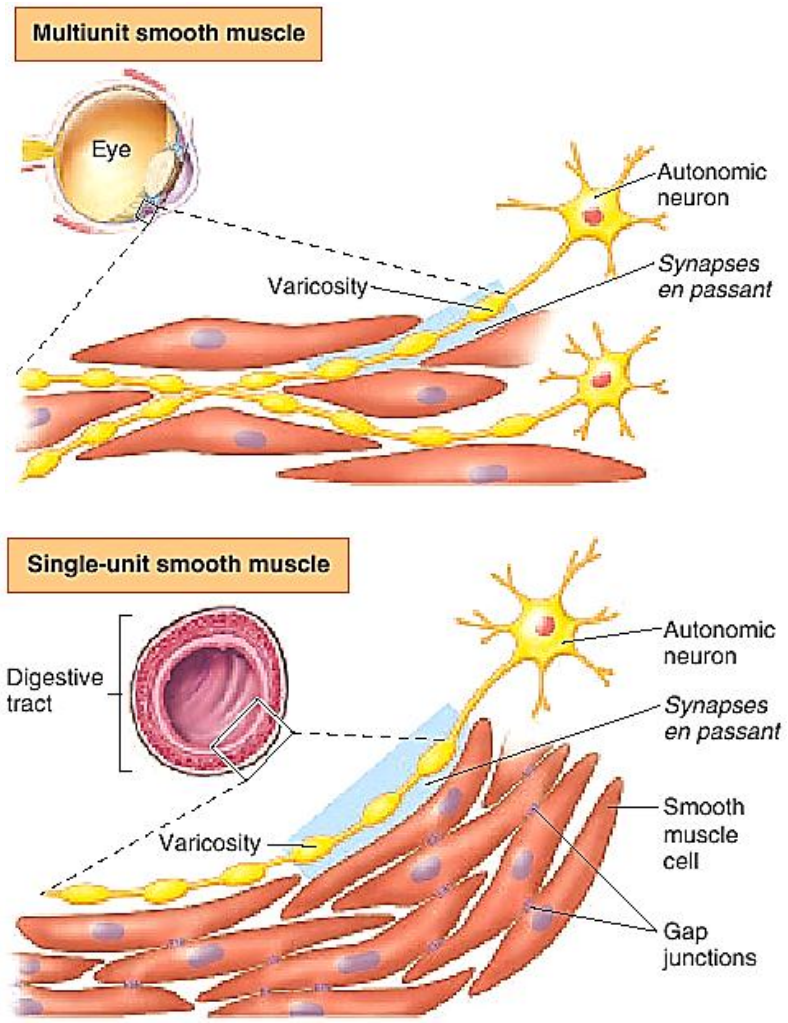


Fig. 3.15. Multi-unit and unitary smooth muscles (from S. I. Fox. 14 ed. 2016)

Multi-unit smooth muscle is composed of separate smooth muscle fibers. Each fiber can contract independently of the others and often is innervated by an individual nerve ending, as occurs for skeletal muscle fibers. This type of smooth muscle is not very common; just a few types of it are present in the body. **Examples** of multi-unit smooth muscle are the *ciliary muscle* of the eye, and the *iris muscle* of the eye.

Unitary smooth muscle is called this way because its fibers contract together as a single unit. The fibers are usually arranged in bundles, and their cell membranes are adherent to one another. The cell membranes are connected by numerous **gap junctions** through which ions can flow freely from one muscle cell to the next so that action potentials can be passed from one fiber to another and cause the muscle fibers to contract together. This type of smooth muscle is also known as ***syncytial*** muscle. This type of smooth muscle prevails in the body and is present in the walls of the visceral organs, including the intestines, bile ducts, blood vessels and others.

There are many similar features in the contraction of smooth and skeletal muscles. Smooth muscles consist of actin and myosin filaments too. However, there are many **distinctive features** of smooth muscle structure. They contain much **less myosin** (the ratio of thin to thick filaments is about 16 to 1). The arrangements of filaments is not as regular as in skeletal muscle, therefore smooth muscle has **no visible striation**. Thin filaments of smooth muscle cells are quite long. They attach either to regions of the plasma membrane of smooth muscle cells or to cytoplasmic protein structures called **dense bodies,** which are analogous to the Z discs of striated muscle (Fig. 3.16). The endoplasmic **reticulum** of smooth muscles is **less developed** than that of skeletal muscles, and Ca^{2+} released from the reticulum participates only in the initial phase of smooth muscle contraction. Smooth muscle contractions are maintained by **extracellular Ca^{2+}** diffusing into the smooth muscle cell through its plasma membrane. This Ca^{2+} enters mainly through voltage-gated Ca^{2+} channels in the plasma membrane. The opening of these channels depends on level of membrane depolarization. The greater the depolarization, the **more Ca^{2+}** enter the cell and the **stronger** is the smooth muscle contraction.

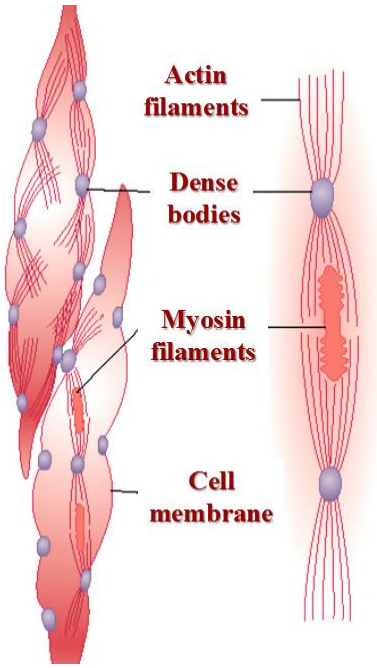


Fig. 3.16. Smooth muscle cells (from S. I. Fox. 14 ed. 2016)

The other way of the cytoplasmic Ca^{2+} concentration increase in the smooth muscle cell is the **action of the neurotransmitter** on the receptors of the cell plasma membrane. Neural control of skeletal muscles differs significantly from that of smooth muscles. Each skeletal muscle fiber has only one synapse with a somatic nerve fiber, and the receptors for the neurotransmitter are located only on the postsynaptic membrane of the neuromuscular junction. By contrast, the entire surface of smooth muscle cells contains **receptor** proteins for a neurotransmitter. The regions of autonomic fiber that release neurotransmitters appear as bulges, or *varicosities*, and the neurotransmitters released from these varicosities stimulate a number of smooth muscle cells. Since there are numerous varicosities along the autonomic nerve ending, they form synapses "in passing" — or *synapses en passant* — with smooth muscle cells (see Fig. 3.15).

Smooth muscle cells have a double innervation by sympathetic and parasympathetic divisions of the autonomic nervous system (Fig. 3.17).

Therefore, neurotransmitters that cause smooth muscle contraction can be either acetylcholine and norepinephrine. They act through their correspondent receptors, cholinergic and adrenergic ones. Usually the sympathetic and parasympathetic effects on the same smooth muscle are opposite. However, in different muscles each of the two neurotransmitters may produce opposite effects, due to the activation of different type of receptors. In order to produce **muscle contraction**, receptors activate the same **effector enzyme.** This is **Phospholipase C** (Fig. 3.18), which splits phospholipid phosphatidyl inositol, with formation of the two second messengers,

inositol triphosphate (**IP_3**) and **diacylglycerol** (**DAG**). **Inositol triphosphate** opens **Ca^{2+} ion channels** in the membrane of the endoplasmic reticulum in smooth muscle cells. It results in **Ca^{2+} ions release** to the cytoplasm and increase in **Ca^{2+} ions** intracellular concentration**.** The other second messenger, **diacylglycerol**, activates **Proteinkinase C**, which phosphorylates a number of intracellular proteins, also contributing the muscle contraction.

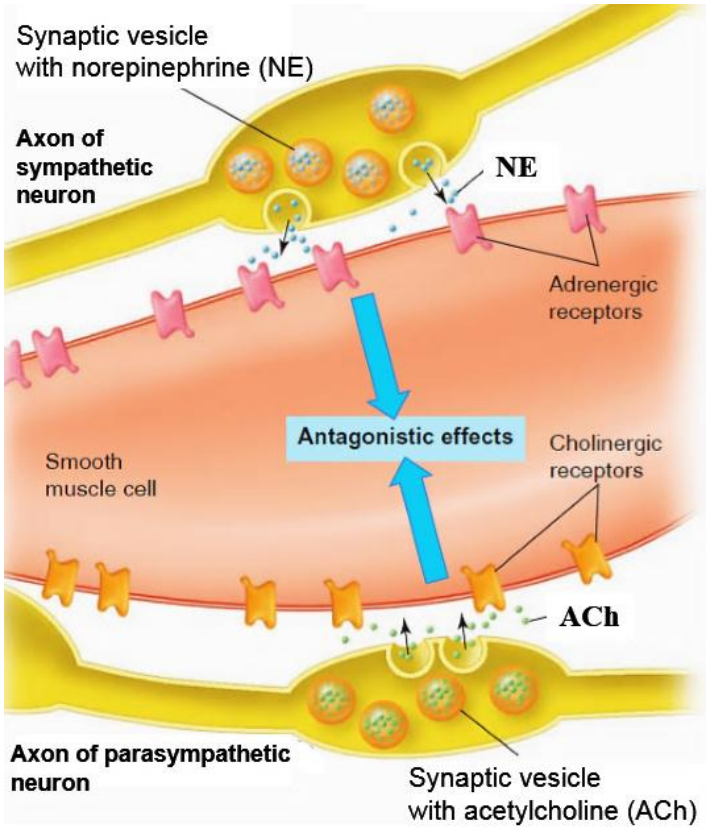


Fig. 3.17. Double innervation of a smooth muscle cell (from S. I. Fox. 14 ed. 2016)

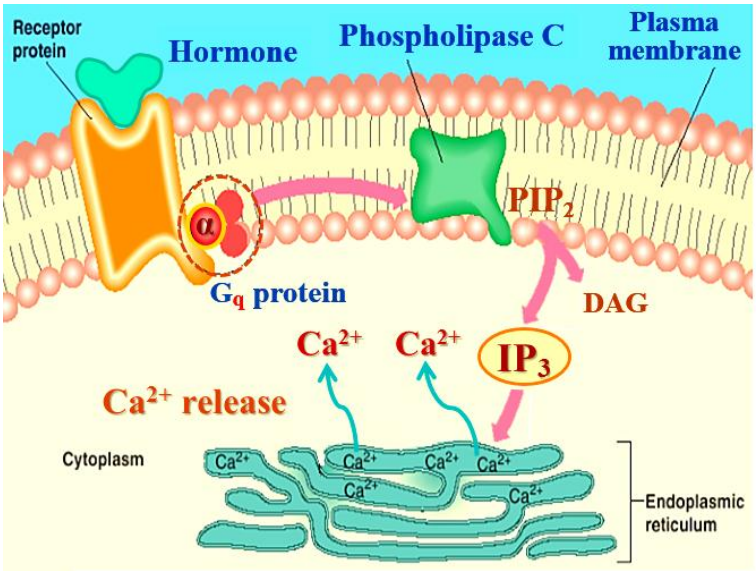


Fig. 3.18. Mechanism of smooth muscle contraction activation by Phospholipase C — IP_3 pathway (from S. I. Fox. 14 ed. 2016)

The third way to **increase Ca^{2+} concentration** in smooth muscle is by **stretching**. Stretching of the cell plasma membrane increases the number of **non-gated (leakage) channels** permeable for Ca ions. As a result, Ca ions leak inside the cells down the concentration gradient (influx of Ca ions). The greater the degree of stretching, the greater the influx of Ca through the leakage channels. Calcium ions entering the cell contribute to a further increase in the level of Ca in the cytoplasm due to the opening of Ca-Ca channels in the endoplasmic reticulum. These channels are ligand-gated, and their ligands are Ca ions, which bind to the reticulum channels from their outer side (from the cell cytoplasm). As a result, Ca concentration in the cell cytoplasm rises, and it increases the force of smooth muscle contraction. All ways of Ca ions entry into the smooth muscle cell are shown at the Fig. 3.19.

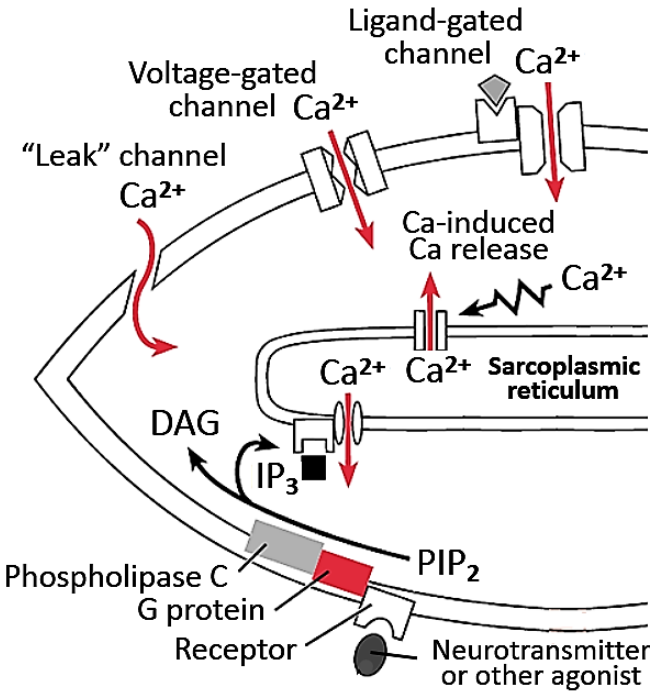


Fig. 3.19. Ways of Ca ions entry into the smooth muscle cell (from Medical Physiology / Rhoades, Tanner. 2nd ed. 2003)

Thus, there are at least **3 main ways to increase Ca^{2+} concentration** in smooth muscle:

1) Muscle cell membrane **depolarization** and opening of **voltage-gated Ca channels** that allow Ca ions entry to the cell;

2) Release of **neurotransmitters**, which activate receptors that act through **phospholipase C activation** and production of **inositol triphosphate**, a ligand that opens ligand-gated **Ca^{2+} ion channels** in the endoplasmic reticulum membrane in smooth muscle;

3) Stretching of smooth muscle that causes the formation of permeable for Ca ions **leakage channels** in the plasma membrane of smooth muscle cell.

All these three ways lead to an increase in intracellular Ca, followed by the same **sequence of events** ending in smooth muscle contraction. This sequence is as follows. First, **Ca ions** bind to a specific cytoplasmic protein called **calmodulin**, which is structurally similar to troponin. In contrast to the striated muscles, there is no troponin in smooth muscle cells. The **calmodulin-Ca^{2+} complex** thus formed combines with and activates **myosin light-chain kinase (MLCK),** an enzyme that catalyzes the **phosphorylation** (addition of phosphate groups) of myosin light chains, a component of myosin **cross bridges**. In smooth muscle, unlike striated muscle, phosphorylation of myosin cross bridges is a necessary condition that permits them to bind to actin and thereby produce a contraction. Unlike striated muscle cells, which produce *all-or-none* action potentials, smooth muscle cells can produce *graded* depolarization that is conducted from cell to cell, and can contract without producing

action potentials. The greater the **depolarization** of the smooth muscle cell, the more **Ca^{2+}** enters the cell, and the greater number of **MLCK** enzymes is activated. With more MLCK enzymes activated, more cross bridges become **phosphorylated** and **able to bind** to actin. In this way, stronger depolarization of smooth muscle cells leads to their **stronger contraction**.

Thus, from an **increase in Ca ions** concentration in the cell cytoplasm, **the smooth muscle contraction mechanism** includes the following events (Fig. 3.20):

1. Binding of Ca ions to the regulatory protein **calmodulin** resulting in the **Ca-calmodulin complex** formation.

2. Activation of the enzyme **myosin light-chain kinase (MLCK)** by the **Ca-calmodulin complex**.

3. Phosphorylation of myosin light chains, a component of myosin **cross bridges**, which enables myosin heads **to bind to actin** filaments.

4. Binding of myosin heads **to actin** filaments, followed by a power stroke (flexing movement of heads), resulting in the muscle **contraction**.

Relaxation of the smooth muscle occurs due to the **closing of Ca^{2+}** channels and the **lowering** of the cytoplasmic Ca^{2+} concentration, mainly by active transport. There are two types of calcium pumps in smooth muscle cells (Fig. 3.21): **Ca pump** of the **cell membrane** that pumps Ca ions out to the extracellular fluid, and **Ca pump** in the endoplasmic **reticulum** membrane that transports Ca ions back to the reticulum. In addition, the plasma membrane of smooth muscle cells contains a Ca^{+}/Na^{+} exchanger that does not use ATP.

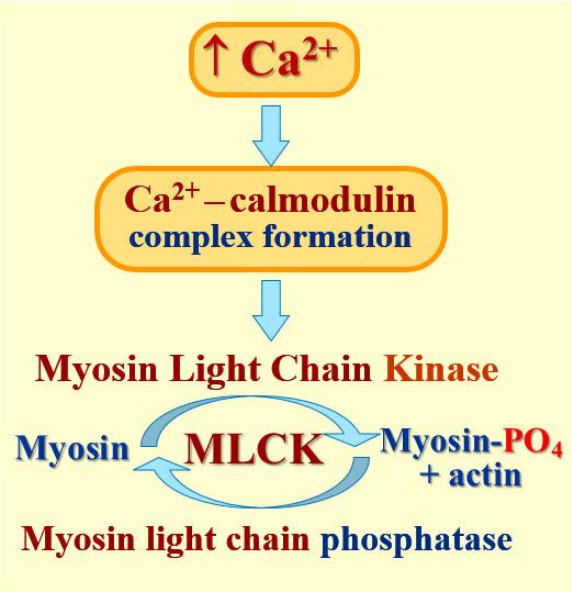


Fig. 3.20. Final mechanism of smooth muscle contraction

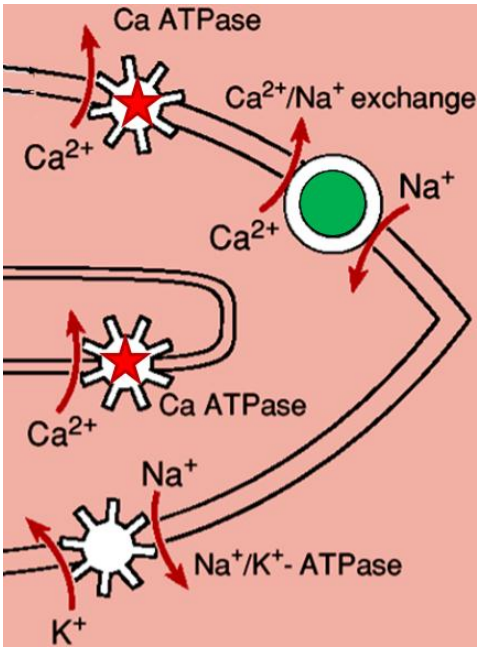


Fig. 3.21. Ca ions removing from smooth muscle cell (from Medical Physiology / Rhoades, Tanner. 2nd ed. 2003)

When Ca concentration decreases, calmodulin loses Ca and dissociates from the myosin light-chain kinase, thereby inactivating this enzyme. The other enzyme, myosin phosphatase, then removes the phosphate groups that have been added to

the myosin heads by MLCK. **Dephosphorylation** prevents myosin cross bridges from binding to actin, and another power stroke does not occur.

The velocity of myosin cross-bridges interaction with actin in smooth muscle is **much slower** in smooth muscle than in skeletal muscle. This cycling frequency is as little as 1/10 to 1/300 that in skeletal muscle. Due to this, the ***fraction of time*** that the cross-bridges remain attached to the actin filaments is much longer in smooth muscle as compared to the skeletal one. This attachment duration is the main factor that determines the **force of contraction.** Thus, smooth muscle contractions are strong enough, compared to the skeletal muscle contractions. Regardless of the duration of a single cross-bridge cycle, only **one ATP molecule** is required for each cycle. Consequently, much **less energy** (1/10 to 1/300) per time unit is required to maintain the same tension of contraction in smooth muscle as in skeletal muscle. That is why smooth muscle is able to prolonged contraction with low ATP consumption.

As can be seen from the described above mechanisms of smooth muscle contraction, there are many ways of this contraction activation. One of the most important mechanisms is the binding of various hormones or neurotransmitters to receptors available in the membrane of smooth muscle cells. Generally, when a hormone activates the receptor coupled with G_q protein and, correspondingly, Phospholipase C enzyme activation occurs, this is followed by IP_3 formation, Ca ions release from the reticulum, and an increase in muscle contraction force. This effect is characteristic for hormones such as noradrenaline and adrenaline (through α_1 adrenergic receptors), angiotensin II, vasopressin (antidiuretic hormone), oxytocin, and for local factors such as endothelins. Hormones that bind to receptors, which activate the enzymes adenylate cyclase or guanylate cyclase, produce the opposite effects. The formation of the cAMP or cGMP results in smooth muscle relaxation. For example, activation of β_2 adrenergic receptors by adrenaline produces dilation of the bronchi and coronary vessels through cAMP formation.

COMPARISON OF SKELETAL AND SMOOTH MUSCLE

Table 3.1

Characteristic	Skeletal muscle	Smooth muscle
Innervation	Somatic	Autonomic
Visible striation	Yes	No
Electrical coupling of cells	No	Yes, gap junctions
T-tubules system	Yes	No
Troponin	Yes	No
Sarcoplasmic reticulum	++++	+
Source of Ca ions	Sarcoplasmic reticulum	ECF and reticulum
Role of Ca ions	Exposure of actin binding sites	Initiation of myosin heads phosphorylation
Speed of contraction	Fast	Slow
Energy consumption	High	Low
Auto-excitation	No	Yes (possible for some cells)
Effect of nerve stimulation	Excitation	Excitation or inhibition
Hormone regulation	No	Yes
Activation by stretching	No	Yes

Section 4
GENERAL PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM. INHIBITION IN THE CNS. PRINCIPLES OF THE CNS ACTIVITY COORDINATION

The whole nervous system is morphologically divided into the **central nervous system** (CNS) and the **peripheral** nervous system. The CNS includes the brain and the spinal cord, while all the nerves outgoing from the central nervous system compose the peripheral nervous system. Functionally, the nervous system can be divided into the **somatic** nervous system that innervates skeletal muscle, and the **autonomic nervous system** (ANS) that controls internal organs, glands, smooth muscle and other cells.

Functions of the CNS include the following:

• **Sensory** function that consists in perception of various stimuli of the external and internal environment, and transformation of these stimuli into nervous impulses.

• **Conduction** function that provides conduction of signals carrying information to the nervous centers of the brain for further analysis of information.

• **Control & regulation** of the function of cells, tissues and organs of the body, which is based on analysis of all perceived information.

• **Integration** function that ensures interaction and integration of the functioning of all structures of the body.

• **Behavior** control function provides the humans with a choice of the way of behavior that contributes to homeostasis maintaining, the survival of the body, and meeting the social requirements.

A **neuron** is a structural and functional unit of the CNS. Up to 10^{11}–10^{12} neurons form the central nervous system. Each neuron consists of a neuron soma, or body, that contains the neuron nucleus, and a number of processes. Among the processes there is only one axon, which serves to send impulses outgoing from the neuron. All other processes are dendrites that serve for the input of information to the neuron. Dendrites form numerous branches thus greatly increasing the surface area available for synapses that connect many neurons to any given neuron.

There are two main types of neurons (Fig. 4.1). ***Afferent*** (sensory) neurons are ***pseudounipolar*** neurons located in the spinal ganglia. Initially they send out one process extending from the cell, but just nearly the soma of the neuron it divides into two branches, one peripheral, dendrite, and one central that is axon. Impulses are generated at the peripheral (receptor) end of the dendrite and conducted from the periphery to the neuron body, and then through the axon. ***Central*** neurons are ***multipolar*** as they have numerous dendrites projecting from their body, and a single axon. Impulses are conducted along the axon from the initial segment of axon, or **axon hillock**, where impulses are generated, to the peripheral end of the axon where it forms numerous branches and synapses on the bodies and dendrites of other neurons or other excitable cells — muscle or endocrine gland cells. Central neurons are divided into ***interneurons*** and efferent (***motor***) neurons.

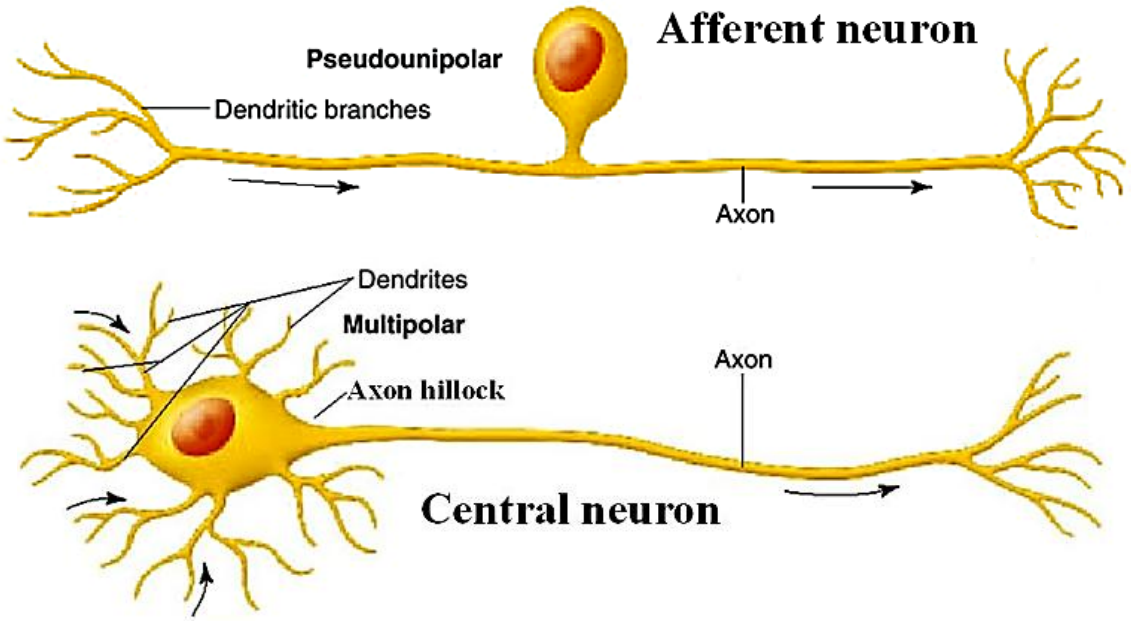


Fig. 4.1. Pseudounipolar sensory neuron and multipolar central neuron (from S. I. Fox. 14 ed. 2016)

Another type of cells that form the central nervous system tissue, other than neurons, is neuroglia. **Neuroglia** cells **functions** are the following:

- **Support** function is providing mechanical support of neurons.
- **Nutrition** supply to neurons (neuroglia cell can provide for neurons nutritional substances, such as pyruvic acid).
- **Protective** and **reparative** function.
- Formation of **myelin sheath** (insulation) around axons of neurons.
- **Growth factors** production for nervous fibers.
- Participation in **blood-brain barrier** formation.
- Regulation of brain interstitial fluid **ionic composition** (neuroglia can remove **K^+ ions excess**, and thereby prevent an abnormal increase of neurons excitability).
- **Replacement** of brain neuronal tissue defects due to **proliferation**.

Neurons are associated into **neural networks**. Neural networks formation is based on the following main principles (Fig. 4.2).

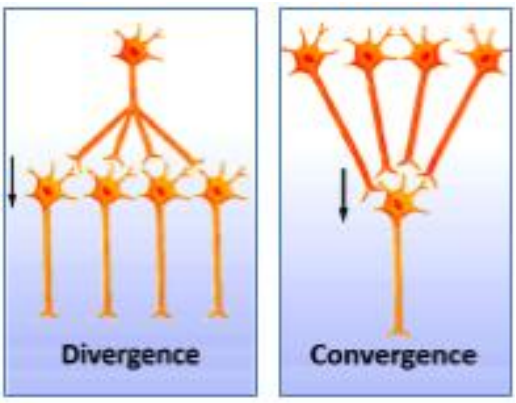


Fig. 4.2. Divergence and convergence

Divergence, which is the branching of neuron axon terminals resulting in numerous synaptic contacts of one neuron with many other neurons.

Convergence that is establishing synaptic contacts from many different neurons to one neuron.

Basic types of neural networks:

1. Hierarchical.
2. Divergent.
3. Local.

Hierarchical neural networks are all afferent (sensory) and efferent (motor) neural conduction pathways (ascending and descending tracts). All these pathways are ***multi-level*** and ***multi-channel*** as their numerous parallel fibers pass from neurons of one level to another, higher or lower, providing precise incoming or outgoing information for the next level and, finally, to higher structures of the CNS (cerebral cortex, for the ascending pathways) or to lower structures (for the descending pathways).

Divergent neural networks are nonspecific integrating pathways that, as their name suggests, become more and more divergent so that the activation of a certain limited number of neurons initially results in stimulation of a great number of neurons.

For example, the ***reticular formation*** of the brainstem forms an ascending divergent network that nonselectively stimulates practically all cerebral cortex.

Local networks have one main feature: they form a ***closed loop*** in which excitation once generated can circulate for a long time (this phenomenon is called reverberation of excitation). Therefore, one of the function of local networks is the longterm maintenance of excitation circulation (Fig. 4.3). The other kind of such networks is a short chain that is formed by a motor neuron of the spinal cord and an inhibitory cell called ***Renshaw*** cell. Within the ventral horns of the spinal cord, a motor neuron sends a branch of its axon to the inhibitory Renshaw cell, and this cell sends its axon back to the same motor neuron (recurrent inhibition). This type of local network serves for ***prevention*** of ***over-excitation*** of motor neurons and, finally, ***exhaustion*** of the muscle innervated by these neurons, since the inhibitory effect of the Renshaw cell on the motor neuron becomes pronounced only when the activity of that neuron is very high (Fig. 4.4).

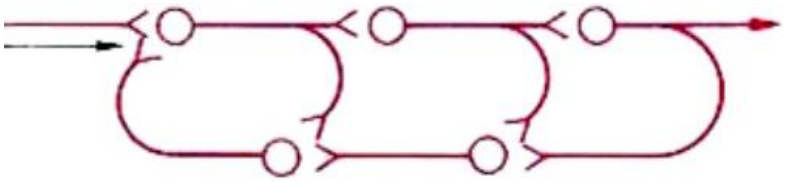


Fig. 4.3. Local circular neuronal chain that provides reverberation of excitation

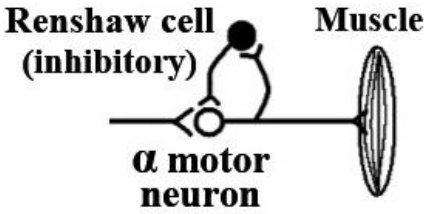


Fig. 4.4. Motor neuron — Renshaw cell neuronal chain

MORPHOLOGICAL & FUNCTIONAL PROPERTIES OF CENTRAL SYNAPSES

Table 4.1

Central (interneuronal) synapse	Neuromuscular junction
Neurons have up to 20 000 synapses on their surface	There is just one synapse on the muscle cell
Synapses on neurons are both excitatory and inhibitory	Synapses on muscle cells are always excitatory
Neurotransmitters are various	Neurotransmitter is always acetylcholine
Single Excitatory Postsynaptic Potential is NOT enough for AP generation	Single End Plate Potential is enough for AP generation

REFLEX ACTIVITY OF THE CNS

Reflex is a stereotype reaction of the body to stimulation of sensory receptors that is performed with **the participation of the CNS**.

There are many **classifications** of reflexes:

- Based on the reflex arc structure: monosynaptic, polysynaptic.
- Based on the type of receptors: exteroceptive, interoceptive, proprioceptive.
- Based on the localization of the central part: spinal (in the spinal cord), bulbar (medulla), mesencephalic (midbrain), diencephalic etc.
- Based on the effector type: somatic or autonomic.
- Based on the mechanism of formation: unconditioned and conditioned.

The structure of a typical reflex arc includes an ***afferent*** part, a ***central*** part, and an ***efferent*** part. The afferent part of a reflex arc is composed by a receptor (or receptor nerve ending) and an afferent neuron located in the spinal ganglion. The central part consists of one or many interneurons. The efferent part is composed by efferent (motor) neuron that sends its axon to muscle fibers or other excitable cells (Fig. 4.5).

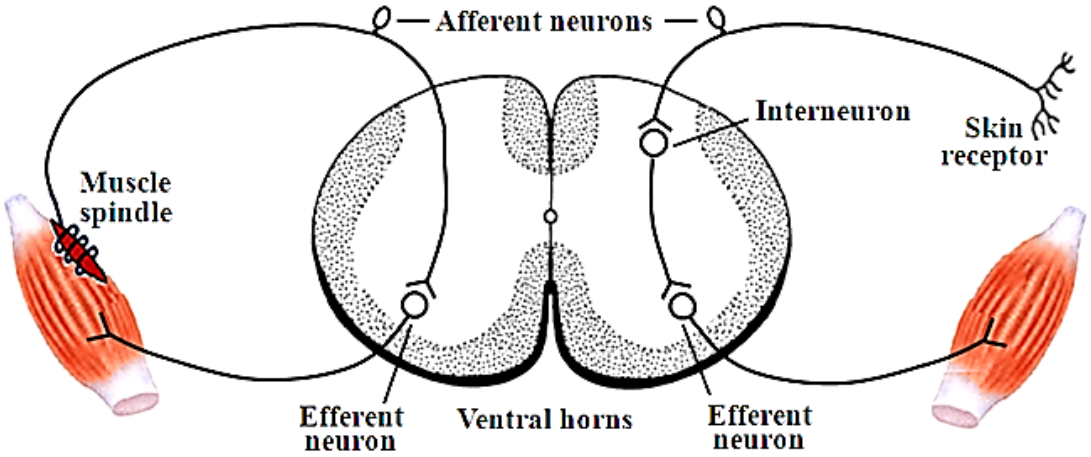


Fig. 4.5. Reflex arcs of monosynaptic and 2-synaptic reflexes

The shortest reflex arc of a ***monosynaptic reflex*** has no interneurons; it is formed by two neurons only, afferent and efferent. Thus, there is only one central synapse between these two neurons; therefore it is a monosynaptic reflex. Such reflexes are the fastest, as central synaptic conduction occurs there only once. Other types of reflexes that have at least two central synapses are called ***polysynaptic***. The simplest polysynaptic reflex arc contains one interneuron located usually in the dorsal horns of the spinal cord. Interneurons in the reflex arcs can be numerous as many reflexes are complex.

To evaluate the result of a reflex, information about the reflex execution must be provided to the CNS. Such information is provided by the reflex **feedback**. Feedback is the information on the result of a reflex sent from the effector's own sensory receptors (proprioceptors) (Fig. 4.6). For example, in motor reflexes that cause muscle contraction, feedback consists of a change in the rate of muscle stretch receptors impulses sent back to the motor neuron (i.e., feedback in this case goes

along the afferent part of the monosynaptic reflex arc). Feedback provides control of the reflex reaction effectiveness, and is used for the reflex response correction if necessary.

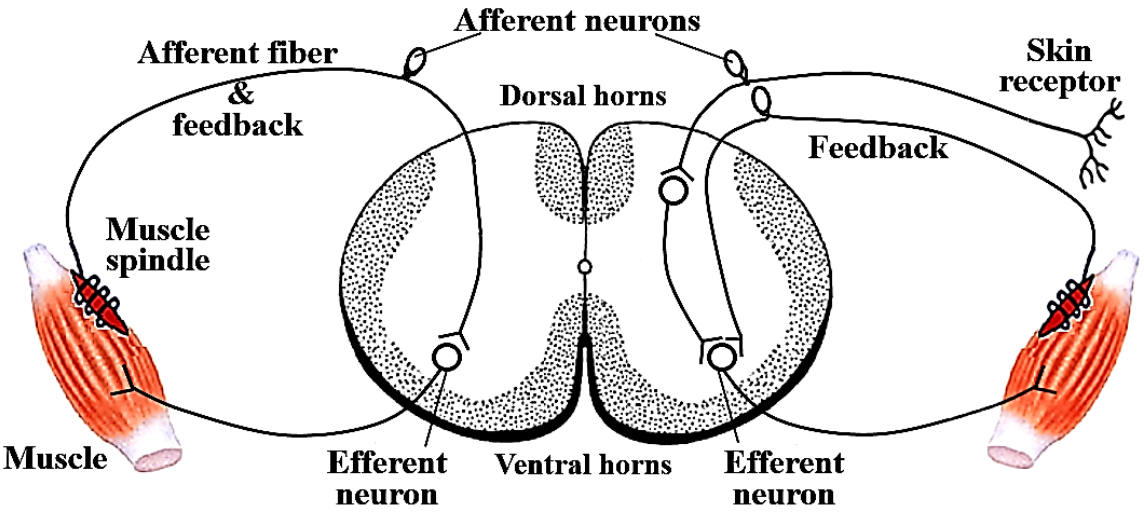


Fig. 4.6. Feedback in monosynaptic and two-synaptic reflex arcs

INHIBITION IN THE CNS

Inhibition is an independent nervous process that is caused by excitation and appears as a decrease or termination of the other excitation.

Classification of inhibition types. Inhibition in the CNS is divided into two types, primary and secondary inhibition (Fig. 4.7).

PRIMARY inhibition occurs with the participation of specific ***inhibitory neurons***, and with the use of specific inhibitory synapses, in contrast to ***secondary*** inhibition, which does not use any inhibitory structures. Primary inhibition develops on the postsynaptic membrane of inhibitory synapses. It is manifested by **hyperpolarization** of the postsynaptic cell membrane.

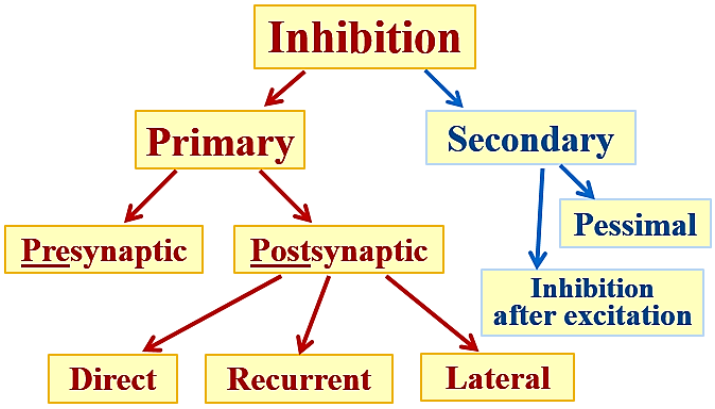


Fig. 4.7. Types of inhibition in the CNS

Inhibition develops due to the action of inhibitory neurotransmitters (for example, GABA and glycin). These transmitters bind to postsynaptic membrane receptors that are ligand-gated channels, open postsynaptic membrane channels for K^+ or Cl^- ions, and cause **K^+ efflux** or **Cl^- influx** from/to the cell (Fig. 4.8). Both cases result in the postsynaptic membrane hyperpolarization, or **Inhibitory Postsynaptic Potential (IPSP)** (Fig. 4.9). The threshold force required for the membrane excitation becomes higher, and the excitability of the postsynaptic cell decreases, which is a manifestation of the cell inhibition.

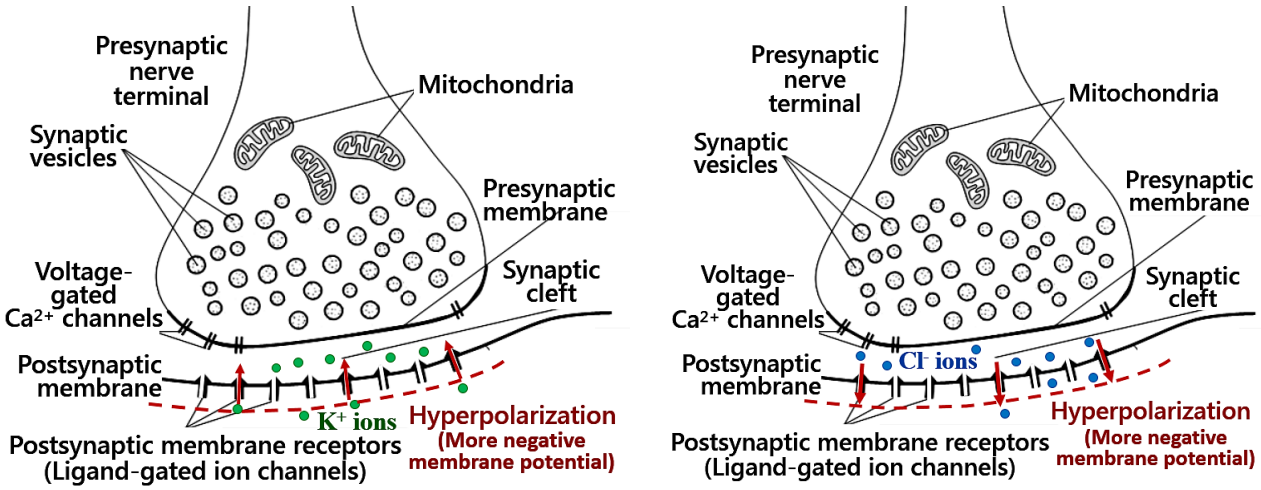


Fig. 4.8. Hyperpolarization due to opening of K^+ channels (left) or Cl^- channels (right)

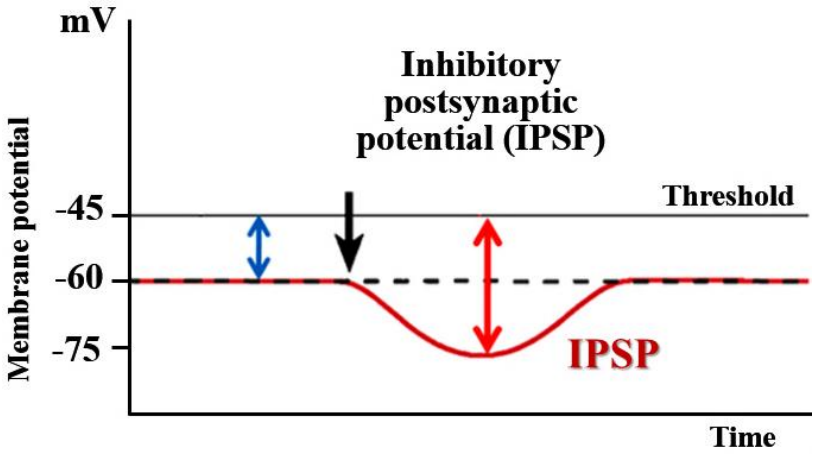


Fig. 4.9. Inhibitory postsynaptic potential, IPSP (hyperpolarization)

TYPES OF PRIMARY POSTSYNAPTIC INHIBITION

Direct inhibition occurs when one inhibitory neuron is inserted into a chain of the excitatory neurons (Fig. 4.10). When an inhibitory neuron is excited, the next neuron and the entire further part of the chain of neurons become inhibited.

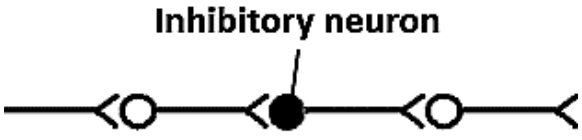


Fig. 4.10. Neuronal chain with a direct inhibition

Reciprocal inhibition is a more complex type of the **direct** inhibition. This type of inhibition allows a specific structure to be inhibited simultaneously with the stimulation of a structure that has an antagonistic function (Fig. 4.11). For example, activation of motor neurons of a muscle occurs at the same time with inhibition of antagonistic muscle motor neurons, through activation of inhibitory neurons in the spinal cord. Due to that, a contraction of a flexor muscle occurs while

the extensor muscle becomes relaxed, and vice versa. Reciprocal inhibition is involved in many processes that require control of structures that perform opposite functions.

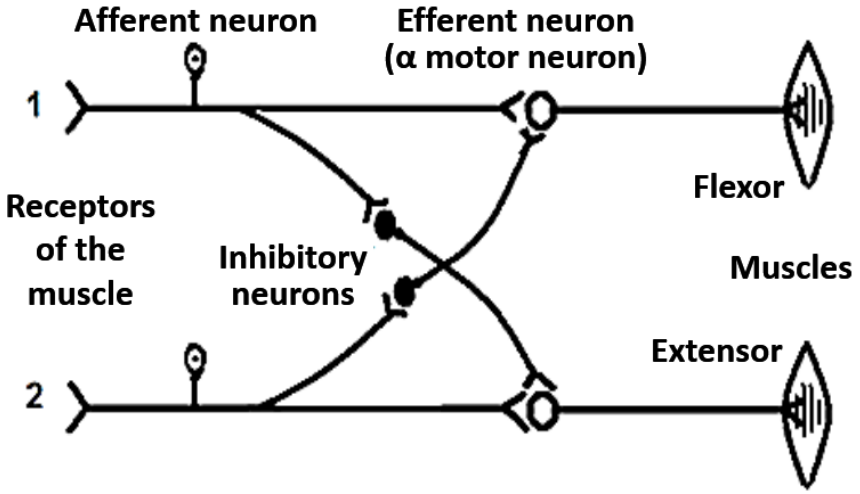


Fig. 4.11. Reciprocal inhibition of motor neurons of antagonist muscles

Lateral inhibition is a complex mutual inhibition of neurons located in the same layer of cells (Fig. 4.12). This type of inhibition is observed in sensory systems, for example, in ***retina***. Each neuron stimulates inhibitory cells (*horizontal* and *amacrine* cells), which inhibit neighboring cells located laterally to this neuron. Function of lateral inhibition in the visual system is to make images in the retina sharper. In the tactile sensory system, it contributes to precise localization of sensation.

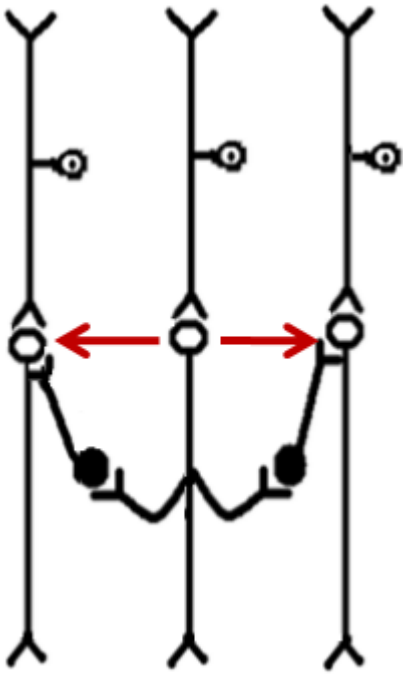


Fig. 4.12. Lateral inhibition

Recurrent inhibition occurs due to Renshaw cells in the spinal cord, which inhibit motor neurons activity. The scheme of this type of inhibition is presented in Fig. 4.4. When neuronal activity is low or moderate, the inhibitory effect of Renshaw cell on motor neurons is insignificant, since motor neurons receive a large number of excitatory impulses through their numerous synapses. However, when impulses rate of the motor neurons becomes very high, this proportionately more and more significantly stimulates Renshaw cells, and their inhibitory effect on motor neurons becomes pronounced. As a result, it prevents extremely high motor neurons activity that can cause muscle exhaustion. Thus, the function of the recurrent inhibition is to limit the maximal activity of motor neurons, thus preventing their over-excitation, and protecting skeletal muscles from depletion of reserves and exhaustion.

PRIMARY PRESYNAPTIC INHIBITION

Primary presynaptic inhibition occurs in **axo-axonic** synapses (Fig. 4.13). Terminal button A forms an inhibitory axo-axonic synapse on the presynaptic membrane of the excitatory synapse between terminal button B and the dendritic spine. When terminal button A and the axo-axonic synapse are not active, terminal button B activity causes release of a neurotransmitter and excitation of the dendritic spine. However, when terminal button A releases its neurotransmitter, GABA, it produces a **stable depolarization** of the postsynaptic membrane of the axo-axonic synapse (that is the presynaptic membrane of the excitatory synapse). Mechanism of this effect is quite complex; since its descriptions in different sources are contradictory, it is not going to be considered. Nevertheless, eventually, this ***stable*** depolarization caused by axo-axonic synapse activation reduces release of the neurotransmitter from the excitatory synapse (terminal button B), and brings inhibition of the postsynaptic cell of the excitatory synapse (the dendritic spine of this cell is seen at the picture).

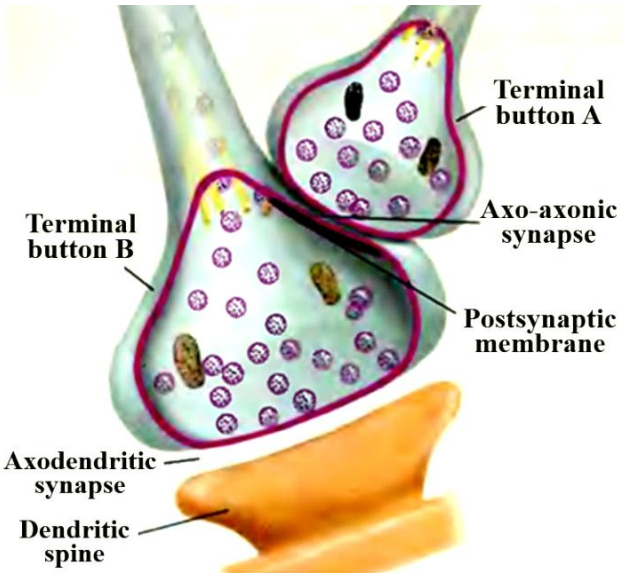


Fig. 4.13. Presynaptic inhibition in axo-axonic synapse (from N. Carlson. Physiology of Behavior. 11 ed. 2013)

SECONDARY INHIBITION

Secondary inhibition develops in common excitatory neurons ***without*** any inhibitory structures. It does not involve inhibitory neurons, synapses, or inhibitory neurotransmitters. Under certain conditions, this type of inhibition can occur in the excitatory chains of neurons. There are two types of secondary inhibition.

Pessimal inhibition is rather rare type of inhibition that can develop when the rate of impulses exciting a neuron becomes extremely high. Then the amount of released neurotransmitter becomes so large that the channels of the postsynaptic membrane remain open for a long time. In this case, **stable depolarization** of the postsynaptic membrane of the neuron develops, the conduction of impulses is blocked, and the neuron becomes inhibited. This type of inhibition provides protection of the neuron from over-excitation.

Inhibition after excitation is the other type of secondary inhibition**.** It occurs in those neurons that have a long ***hyperpolarization phase*** of the action potential. This hyperpolarization is similar to IPSP, Inhibitory Postsynaptic Potential (Fig. 4.14). However, in contrast to the IPSP, hyperpolarization is produced without inhibitory synapses and neurotransmitters, simply as a result of stimulation of the neuron. After

each excitation, such neurons are inhibited for a certain time. To excite them, a force greater than the initial threshold force is required, as shown in the figure by red arrows. An increase in threshold force means a decrease in excitability, that is, inhibition.

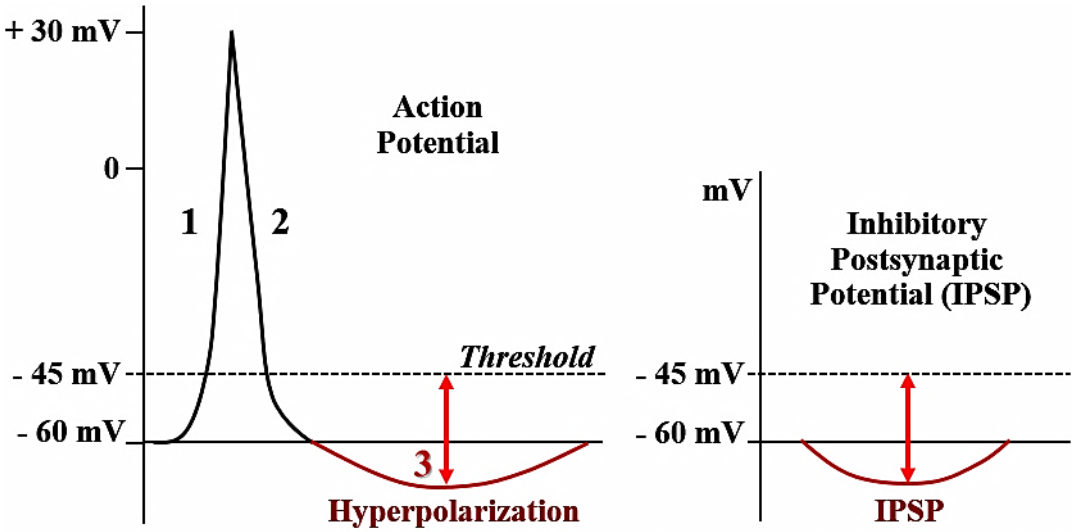


Fig. 4.14. Comparison of the hyperpolarization phase of the Action Potential with the Inhibitory Postsynaptic Potential (IPSP)

PRINCIPLES OF COORDINATION IN THE CNS

Coordination means the simultaneous control and regulation of numerous body functions, ensuring their integration. Basic principles of coordination in the Central Nervous System are:

1. Divergence & **2.** Convergence — provide interconnection between neurons.

3. Reciprocal inhibition (control of the activity of antagonistic structures).

4. Common final pathway principle (example: motor neurons which are the efferent part of many different reflex arcs with different afferent parts, and are the final common pathway for many reflexes).

5. Feedback principle (information to be sent from effectors back to CNS).

6. The principle of **dominance**.

• **Dominance** is the state of the nerve center that controls the most important function of the organism at given moment. There are many important body functions, but the state of dominance of the nerve center provides preferential execution of the **most important** at the moment function. The center in the state of dominance at the moment becomes the main one in the CNS.

This is achieved due to the following ***properties*** of the dominant center:

– High excitability;

– Persistence of excitation;

– Summation of excitation;

– Reinforcement (support) even by weak sensory input;

– Suppression (inhibition) of other nerve centers.

NERVE CENTERS, THEIR FUNCTIONS AND PROPERTIES

Nerve center is an association of neurons located in various parts of the CNS and performing a certain reflex reaction or regulation of ***a certain function***. Since nerve centers consist of many neural chains, an important feature of nerve centers is a large number of synapses that ensure the interaction of neurons by conducting impulses from one neuron to another. The **properties** of nerve centers are determined by this presence of a great number of synapses, and these properties partially are the same as **synapses** properties. The main **properties of nerve centers** are given below.

- **One-way** conduction of excitation (due to synapses).
- Central delay (total time of impulses conduction through central synapses).
- **Low excitability** and **lability,** because of many synaptic conductions that limit maximal possible rate of impulses. ***Lability*** is assessed by the maximal rate of impulses that can be transmitted in accordance with the stimulation frequency.
- **Transformation of the rhythm** of excitation (usually with a decrease in the rate of impulses).
- **Summation** of excitation on the neuron membrane: ***spatial*** (summation of impulses coming to different synapses at the same time) and ***temporal*** (summation of impulses coming to the same synapse sequentially, with a short time interval).
- **Afterdischarge** (prolonged circulation of impulses within the nerve center after the end of the impulses input; it occurs due to local closed loops of neurons).
- **Nerve centers *tone*** (a certain basic level of activity, expressed as a rate of outgoing impulses sent from the nerve center; the tone of the nerve center directly depends on the total income of excitatory impulses, so that the level of impulses ***input*** determines the level of impulses ***output*** from the center).
- Rapid **fatigability** (due to one of the main properties of synapses).
- Plasticity (the ability to ***adjust*** the nerve center activity to provide regulation of a specific body function).
- **High metabolic rate** and high sensitivity to **hypoxia**.

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CONTENT

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