# Synaptic Transmission

## Excitatory or Inhibitory Receptors in the Postsynaptic Membrane

Some postsynaptic receptors, when activated, cause excitation of the postsynaptic neuron, and others cause inhibition. The importance of having inhibitory as well as excitatory types of receptors is that this gives an additional dimension to nervous function, allowing restraint of nervous action as well as excitation.

The different molecular and membrane mechanisms used by the different receptors to cause excitation or inhibition include the following:

- **Excitation**:
  1. Opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell, raising the intracellular membrane potential in the positive direction up toward the threshold level for excitation. It is by far the most widely used means for causing excitation.
  2. Depressed conduction through chloride or potassium channels, or both. This decreases the diffusion of negatively charged chloride ions to the inside of the postsynaptic neuron or decreases the diffusion of positively charged potassium ions to the outside. The ultimate effect is to make the internal membrane potential more positive than normal → excitatory.
  3. Various changes in the internal metabolism of the postsynaptic neuron to excite cell activity or, in some instances, to increase the number of excitatory membrane receptors or decrease the number of inhibitory membrane receptors.
- **Inhibition**:
  1. Opening of chloride ion channels through the postsynaptic neuronal membrane → rapid diffusion of negatively charged chloride ions from outside the postsynaptic neuron to the inside, thereby carrying negative charges inward and increasing the negativity inside, which is inhibitory.
  2. Increase in conductance of potassium ions out of the neuron. This allows positive ions to diffuse to the exterior, which causes increased negativity inside the neuron → this is inhibitory.
  3. Activation of receptor enzymes that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

## Electrolyte potentials

- Resting potential of the soma: −65 mV
- Potential of $Na^+$: +61 mV. The sodium ions that leak to the interior are immediately pumped back to the exterior by the Na/K ATPase pump, thus maintaining the −65mV negative potential inside the neuron.
- Potential of $K^+$: −86 mV. There is a net tendency for potassium ions to diffuse to the outside of the neuron, but this is opposed by continual pumping of these potassium ions back to the interior by the Na/K-ATPase pump.
- Potential of $Cl^-$: −70 mV. There is a net tendency for chloride ions to diffuse very slightly to the interior of the neuron, but those few who do leak are pumped back to the exterior, most probably by a chloride-pump.

The electrical potential is uniform inside the soma due to:

- Highly conductive intracellular fluid, which can passively maintain electrotonic conduction without resistance.
- The diameter of the soma is large (unlike dendrites), thus resistance is kept virtually zero.

The uniformity of the potential inside the soma is valid as far as no action potential is occurring. It is an important property because it allows summation of various electrical potentials until they reach the action hillock (initial segment of axon), from where the Action Potential can be elicited and propagated.

## Neuromuscular Transmission

Neuromuscular junctions are specific chemical synapses. The synapses between the axons of motor neurons and skeletal muscle fibers (also known as "motor end-plates") have been the first synapses studied. They possess all common characteristics of the CNS synapses.

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### Function

The steps that take place when the action potential is conducted to the muscle fiber are:

1. The depolarization caused by an action potential transiently opens voltage-gated $Ca^{2+}$ channels and increases the calcium conductance. $Ca^{2+}$ flows down its electrochemical potential gradient into the axon terminal at a high rate.
2. The increase of free $Ca^{2+}$ concentration is short-lived, because $Ca^{2+}$-binding proteins and $Ca^{2+}$ pumps (e.g. Na/Ca anti-porter) rapidly take up and remove the $Ca^{2+}$, respectively. In this way the terminal is ready to

transmit another signal in a very short time.
3. The influx of $Ca^{2+}$ triggers an interaction of contractile proteins (synapsin I = actin-like protein), attached to the presynaptic membrane, with synaptic vesicles. Vesicles fuse with the presynaptic membrane and discharge their contents into the synaptic cleft (exocytosis).
4. The exocytosis is restricted to specialized regions known as **active zones** (or release sites), exactly opposite the receptors on the postsynaptic cell. The membrane of the discharged synaptic vesicles is subsequently retrieved from the presynaptic plasma membrane by endocytosis.
5. An axon terminal at a neuromuscular junction typically releases a few hundred of its many thousands of synaptic vesicles in a response to a single action potential.
6. The time required for calcium channels to open in response to depolarization is the major component of synaptic delay.
7. The conversion of the chemical signal into an electrical signal is achieved by ligand-gated ion channels in the postsynaptic membrane. When transmitter binds to the receptor proteins, they change their conformation – open the ion channel → membrane potential is altered. If the shift of membrane potential is large enough, it causes the voltage-gated channels to open → action potential is triggered.
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Unlike voltage-gated ion channels, the ligand-gated ion channels are relatively insensitive to the membrane potential. They cannot by themselves produce an all-or-non, self-amplifying excitation. Instead they produce an electrical change that is graded according to the intensity and duration of the external chemical signal, according to how much transmitter is released into the synaptic cleft and how long it stays there. This feature is important for the integration properties of the signal by neurons.

Postsynaptic ligand-gated channels have enzyme-like specificity for a particular ligand → they respond only to one neurotransmitter (the one released from the presynaptic terminal), with other transmitters having no effect. In their role as channels, they are characterized by different ion selectivity (to $K^+$, $Cl^-$, nonselective to cations but exclude anions) → the ion selectivity determines the character of the postsynaptic response.

The channels in the skeletal muscle cell membrane gated by acetylcholine (acetylcholine receptors) have several discrete alternative conformations. Upon binding acetylcholine the channel jumps from closed to an open state and then stays open, with the ligand bound, for a randomly variable length of time (average about 1 ms, depending on temperature and the species). In the open conformation the channel is indiscriminately permeable to small cations including $Na^+$, $K^+$, and $Ca^{2+}$, but impermeable to anions. Since there is little selectivity among these cations, their relative contributions to the current through the channel depend chiefly on their concentrations and on the electrochemical driving forces:

- If the muscle cell membrane is at its resting potential, the net driving force for $K^+$ is near zero, because the voltage gradient (negative inside) nearly balances the $K^+$ concentration gradient.
- For $Na^+$, the voltage gradient and the concentration gradient both act in the same direction to drive $Na^+$ into the cell. Similarly some $Ca^{2+}$ ions contribute to the total inward current.

In order for the post-synaptic excitation to be accurately controlled by the pattern of signals sent from the presynaptic terminal, it must be switched off very rapidly when the presynaptic cell falls quiet. This is achieved by the removal of the acetylcholine from the synaptic cleft and it takes a few hundred microseconds:

1. Acetylcholine disperses by diffusion.
2. Acetylcholine is hydrolyzed by acetylcholinesterase to acetate and choline.

## CNS Synapses

The fast chemical synapses in the CNS also employ ligand-gated channels and are constructed on the same principles. Only few neurotransmitters can mediate such rapid signaling:

1. acetylcholine – excitatory;
2. γ-aminobutyric acid (GABA) – inhibitory;
3. glycine – inhibitory;
4. glutamate (aspartate, ATP?) – excitatory.

Acetylcholine opens a cation channel and so depolarizes the cell toward the threshold for firing an action potential – excitatory synapses. Also glutamate acts on a similar type of receptors – the major excitatory transmitter in the CNS. Aspartate acts on the same receptors (NMDA) as glutamate; ATP serves as a fast excitatory transmitter at synapses of certain types of smooth muscle.

Receptors to which GABA and glycine bind are linked to channels that, when open, admit small negative ions (chiefly $Cl^-$), but are impermeable to positive ions:

- The concentration of $Cl^-$ is much higher outside the cell than inside.
- The equilibrium potential for $Cl^-$ is close to normal resting potential or even more negative.

Thus, the opening of $Cl^-$ channels tends to hold the membrane potential at its resting value or even at a hyperpolarized value, making it more difficult to depolarize the membrane and to excite the cell. GABA and glycine are the major transmitters that mediate fast inhibition.

For a single transmitter, several types of receptors often exist:

- Acetylcholine channel linked receptors – excitatory effect (skeletal muscle) – nicotinic receptors .
- Acetylcholine non-channel linked receptors – both excitatory and inhibitory effects, slower action (heart muscle cell) – muscarinic receptors (5 Subtypes, $M_4$ and $M_5$ in CNS).

## Synapses as major targets for drug action

- Curare and α-bungarotoxin – antagonists of nicotinic receptors.
- Atropine – antagonist of muscarinic receptors.
- Barbiturate, benzodiazepines – agonists of GABA (tranquilizers, antiepileptics, hypnotics).
- Physostigmine – reversible inhibitors of acetylcholinesterase (relieve the weakness of patients suffering from myasthenia gravis → shortage of functional ACh receptors), organophosphates – insecticides, weapons (irreversible inhibitors).
- Strychnine – antagonist to glycine receptors – blocks the action of glycine (→ muscle spasms, convulsions, death).
- L-DOPA (dihydroxyphenylalanine) – precursor of dopamine (treatment in Parkinson's disease).
- Naloxone (morphine derivate) – inhibitor of opioid receptors (used as an antidote in opioid intoxication).

## Fatigue of Synapse

When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the postsynaptic neuron is at first very great, but the firing rate becomes progressively less in succeeding milliseconds or seconds. This is called fatigue of synaptic transmission.

Fatigue is an exceedingly important characteristic of synaptic function because when areas of the nervous system become overexcited, fatigue causes them to lose this excess excitability after awhile. For example, fatigue is probably the most important means by which the excess excitability of the brain during an epileptic seizure is finally subdued so that the seizure ceases. Thus, the development of fatigue is a **protective mechanism against excess neuronal activity**.

The mechanism of fatigue is mainly exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals. The excitatory terminals on many neurons can store enough excitatory transmitter to cause only about 10,000 action potentials, and the transmitter can be exhausted in only a few seconds to a few minutes of rapid stimulation. Part of the fatigue process probably results from two other factors as well:

1. Progressive inactivation of many of the postsynaptic membrane receptors.
2. Slow development of abnormal concentrations of ions inside the postsynaptic neuronal cell.

## Effect of Acidosis or Alkalosis on Synaptic Transmission

Normally, alkalosis lncreasesowers neuronal excitability (pH: 7.4 → 7.8). Alkalosis causes $H^+$ to move out from the cells and $K^+$ to move in to the cell, leading to hypokalemia. This leads to a higher concentration gradient between intracellular and extracellular $K^+$ leading to more $K^+$ exiting the cell through leakage channels leading to hyperpolarization of the cell. This means that a greater than normal stimulus is required to reach the threshold and thus elicit a subsequent action potential.

Conversely, acidosis iecreasesncreases neuronal activity (pH: 7.4 → 7.0). Acidosis causes $H^+$ to move into the cells and $K^+$ to move out from the cell, leading to hyperkalemia. This lead to a lower concentration gradient between intracellular extracellular $K^+$, leading to less $K^+$ exiting the cell through leakage channels leading to relative depolarization of the cell. This means that a weaker than normal stimulus is required to reach the threshold for eliciting a subsequent action potential. For a transient period, the cells can be more easily depolarized. However, this causes **some** of the $Na^+$-VGCs to activate (but their number is not enough to elicit depolarization and subsequent action potential), causing them to enter in a refractory mode. This eventually leads decrease in excitability of the cell (e.g.: slowing of conduction in cardiac muscle that can lead to ventricular fibrillation or asystole).

## Effect of Hypoxia on Synaptic Transmission

Neuronal excitability is also highly dependent on an adequate supply of oxygen. Cessation of oxygen for only a few seconds can cause complete un-excitability of some neurons. Most anesthetics increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system. Their lipid-solubility, allows them to modify post-synaptic cell membranes into making them less responsive to excitatory agents.

## Synaptic Delay

The synaptic delay is the minimal period for all the events occurring in a single cycle at a synapse to take place. It is at least 0.5 ms. These steps are:

1. Discharge of the transmitter substance by the presynaptic terminal.
2. Diffusion of the transmitter to the postsynaptic neuronal membrane.
3. Action of the transmitter on the membrane receptor.

4. Action of the receptor to increase the membrane permeability.
5. Inward diffusion of sodium to raise the excitatory postsynaptic potential to a high enough level to elicit an action potential.
6. From the measure of delay time, one can then estimate the number of series neurons in the circuit.

# Links

## Related articles

- Inhibitory Neuronal Circuits
- Dendrite
- Axon
- Synapse
- Neuromuscular Transmission
- Membrane Potentials
- Transformation of Synaptic Input into Action Potential

## Sources

- Lecture Notes: Prof. MUDr. Jaroslav Pokorný DrSc.

## Bibliography


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## Further reading