Integration Activity of Neurons

Transformation of a Synaptic Input Into Action Potential

Read this article before proceeding below: [[Transformation of Synaptic Input into Action Potential].

The role of synaptic input in formation of a neuronal response

Synaptic inputs that are located close to the trigger zone (axon hillock), are more effective in depolarizing and hyperpolarizing it than synaptic inputs of equal strength located further away. To overcome such disadvantage, peripheral synapses group together (multiple inputs from a single source) or they elicit various forms of dendritic spike potentials. From the point of further information processing, location of synapses is often decisive. Excitatory and inhibitory synapses can be located at various strategic points:

- at soma or directly at the axon hillock;
- at the nodes of Ranvier;
- close to the axon terminals;
- at the dendritic bifurcations at the necks of dendritic spines.

Such strategic positioning enables to more effectively inhibit or facilitate the conductance of postsynaptic potentials (detonators or permissive synapses), than synapses located at less important points (which end up being considered as stimulatory or modulatory synapses).

Synapses at which a dendrite delivers a stimulus to another cell play a large part in communication between neurons that lie close together. Over small distances (several millimeters or less), electrical signals can be propagated passively (electrotonically), spreading from postsynaptic sites on the dendritic membrane where they are received, to presynaptic sites on the same dendritic membrane, where they control the transmitter release. Such neurons sometimes do not even possess an axon and do not conduct action potentials. In some cells, where the dendritic tree is large, separate parts of it can behave as more or less independent pathways for communication and for information processing. In other words, it behaves as mediator where it collectively processes (summates) and relays the signals between dendrites. Furthermore, the presence of voltage-gated ion channels in the dendritic membrane might enable the dendrites to conduct action potentials, consequently having a single neuron that can behave as a highly complex computational device.

Non-Channel-linked Receptors and Synaptic Modulation

Synapses with channel-linked receptors show immediate effects of a neurotransmitter, at defined location of transmission.

Non-channel-linked receptors allow for slow, complex, long-lasting effects, often spatially diffuse and acting on many cells, essentially comprising neuromodulation. The non-channel-linked receptors act by the same molecular mechanisms as the receptors for hormones and local chemical mediators:

- Catalytic receptors: directly phosphorylate proteins inside the cell.
- G-protein-linked receptors - activation of GTP-binding regulatory protein, which activates or inactivates a membrane-bound enzyme (adenylate-cyclase → cAMP → protein kinase C → intracellular Ca^{2+} release) or regulates directly an ion channel.

More than 50 neurotransmitters have been identified that act on non-channel-linked receptors. Some of them also bind to channel-linked receptors (such as acetylcholine).

The response, mediated by the non-channel-linked receptors takes typically hundreds of milliseconds or longer, usually because a series of enzymatic reactions must intervene between the initial signal and the ultimate response. One of the most important neuromodulators are monoamines.

Drugs designed to interfere with the synthesis, uptake, breakdown, or interact with particular subclasses of monoamine receptors have been proved to be valuable in the treatment of psychiatric and neurological diseases (Examples include: schizophrenia - blocking dopamine receptors, Parkinson's disease - increase in concentration of dopamine, severe depression - increase in concentration of norepinephrine or serotonin).

The neuropeptides are the largest family of neuromodulators. They appear to be particularly important in regulating feeling and drives, such as pain, pleasure, hunger, thirst, and sex. Neuropeptides are often secreted together with a non-peptide neurotransmitter.

The Role of Synaptic Plasticity in Memory

Neurotransmitters and neuromodulators released at synapses, besides relaying transient electrical signals, can also alter concentrations of intracellular messenger molecules, which activate enzymatic cascades that bring about lasting changes in the efficacy of synaptic transmission. However, several major mechanisms are yet unknown in

regards to how do these changes endure for weeks, months, or a lifetime in the face of the normal turnover of cell constituents.

Physiologically, memories are caused by changes in the capability of synaptic transmission from one neuron to the next as a result of previous neural activity. These changes cause new pathways to develop for transmission of signals through the neural circuits of the brain (i.e.: memory traces). Once they are established, they can be activated to reproduce the memories.

The repetitive use of a synapse might enhance the efficacy of that synapse if the discharge of the postsynaptic cell is correlated with a particular input signal. This means that **conjunction of postsynaptic firing and the presynaptic input would be the requirement for strengthening specific connections**. This hypothetical construct has only recently found concrete support in the studies of the mechanism underlying long-term potentiation.

Experiments in animals have shown that high-frequency (100–200 Hz) tetanic stimulation of Ia afferent fibers for several seconds was followed by an enduring increase in the ventral root responses to subsequent Ia volleys. The duration of this potentiation depends on the duration of the tetanus (the effect of 7 min. tetanus lasts for almost 15 mins, whereas a tetanus of 20 mins caused enhancement lasting up to 2 hours). Posttetanic potentiation (PTP) that lasts for hours might be a possible mechanism for short-term memory, though its dependence on prolonged bursts of synchronous high-frequency stimulation of afferents has no clear counterpart in learning paradigms. PTP seems to be an entirely presynaptic phenomenon that results of an activity-dependent calcium accumulation in presynaptic terminal, which leads to an increased transmitter release.

The ability of a cell to respond to a stimulus and the nature of that response are determined by the various voltage- and transmitter-dependent conductances in its membrane. Thus, the two possible synaptic mechanisms just described must somehow result from changes in post- and presynaptic membrane conductances:

1. Pre-synaptically: conductance changes in the presynaptic terminal could alter the duration and/or amplitude of the action potential invading the terminal → affecting the coupling between the action potential and the release of neurotransmitter.

1. Post-synaptically: at the postsynaptic site, additional or new receptors could be formed or receptors could be redistributed (as in the denervation supersensitivity, potassium conductance could decrease).

Most of the above changes are based on changes of activity of proteins (channels, protein kinases, etc). The synthesis of new proteins, initiated by the transcription of previously dormant DNA sequences may also change the nature of neuronal membrane, thus altering both pre- and postsynaptic function – result of activity of various second messengers (cyclic nucleotide, calmodulin, calcium).

Classical Conditioning

Classical conditioning is a type of conditioning discovered by Ivan Pavlov (1927). [1] It is also known as Pavlovian, respondent conditioning, Pavlovian reinforcement.

Classical conditioning describes a behavioural response which is elicited when triggered by an otherwise neutral stimulus (the conditional stimulus), that has been linked to an unconditional stimulus, which normally evokes a clear, immediate and reflexive response.

Examples

1. Classic example described as discovered by Pavlov:
    - Unconditioned stimulus: meat powder
    - Unconditioned (i.e.: reflex, innate) response: dogs begin to salivate
    - Conditioned (neutral) stimulus: the presence of the lab technician
    - When the conditioned and unconditioned stimulus are combined (occur simultaneously), that is when the lab technician was bringing the meat powder to the dogs, the dogs eventually **learned** that the lab technician is associated with food. Eventually, the mere *presence* of the lab technician (neutral, conditioned stimulus), evoked salivation by the dogs (a conditioned response).
2. Gill withdrawal reflex:
    - A conditioned reflex response is established by presenting a conditioned stimulus (CS), which itself elicits a little response, followed immediately by an unconditioned stimulus (UCS) which itself elicits a clear response.
    - After repeated pairing of the CS and USC, the CS delivered alone produces a clear response.
    - Classical conditioning occurs only if there is a predictable temporal relation between the CS and UCS.
3. In aplysia (a sea hare):
    - CS - stimulation of the mantle shelf is paired with UCS; stimulation of the tail, which alone produce an enlarged EPSP, later on an additional stimulation of the mantle shelf produce an enlarged EPSP.
    - The facilitatory action of serotonin released from interneurons by tail stimulation is enhanced if the mantle sensory afferent is active just before serotonin is released from the tail interneurons. Activity in the mantle afferent allows some calcium to enter the terminal, Ca^{2+} in turn, acts through calmodulin to increase adenylate cyclase activity so that the serotonergic input due to tail stimulation produces more cAMP → Ca^{2+} entry during action potential.
    - In the mantle sensory neuron, activated adenylate cyclase leads to cellular events associated with tail stimulation being more effective → coordinated activity in both the pre- and postsynaptic elements appears to strengthen (or facilitate) the synaptic effect.

Role of receptors

G-protein-linked receptor can enable a transient signal to cause a persistent change in the electrical properties of a synapse and hence the behavior of the animal. The phosphorylation of G_S channels represents a form of short-term memory, easily erased by the action of phosphoprotein phosphates (dephosphorylation of G_S channels) and limited by the finite lifetime of the G_S-channel proteins. The mechanism of the long-term memory that follows repeated signal processing is not known, but it requires new RNA and protein synthesis and seems to involve changes in the structure as well as the chemistry of the presynaptic terminals. cAMP and A-kinase seem to mediate these changes too, presumably by phosphorylation other proteins which are able to alter the pattern of gene expression.

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You can join the authors (https://www.wikilectures.eu/index.php?title=Integration_Activity_of_Neurons&action=history) and it. You can discuss the changes at discussion.

Long-Term Potentiation

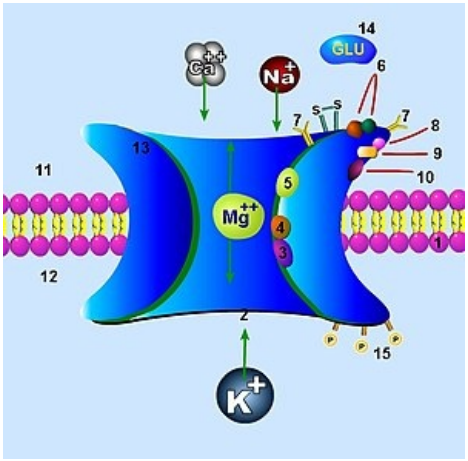
Definition: "*Long-term potentiation (LTP) occurs on any occasion when a presynaptic cell fires (once or more) at a time when the postsynaptic membrane is strongly depolarized (either through recent repetitive firing of the same presynaptic cell or by other means).*"[2]

NMDA Channels

Most of the depolarizing current for excitatory PSP (Post-synaptic potential) is carried in the ordinary way by ligand-gated ion channels that bind glutamate. During LTP development, a second distinct subclass of channel-linked glutamate receptors - NMDA receptors (named so because they are selectively activated by the artificial glutamate analog N-methyl-D-aspartate). The NMDA-receptor channels are doubly-gated, opening only when two conditions are satisfied simultaneously:

1. The membrane must be strongly depolarized (the channels are subjected to a peculiar form of voltage gating that depends on extracellular Mg^{2+})
2. The neurotransmitter glutamate must be bound to the receptor (on the contrary, when NMDA-receptors are blocked with a specific inhibitor, LTP does not occur, even though ordinary synaptic transmission continues)

An animal treated with an NMDA inhibitor fails to learn/remember information of the type thought to depend on the hippocampus (declarative/reflexive type), but behaves almost normally otherwise.



NMDA receptor

NMDA channels, when opened, are highly permeable to Ca^{2+}, which acts as an intracellular messenger, triggering the local changes responsible for long-term potentiation. On the contrary, LTP is prevented when Ca^{2+} levels are held artificially low in the postsynaptic cell (by injecting EDTA into it) and can be induced by transiently raising extracellular Ca^{2+} levels artificially high. The nature of the long-term changes triggered by Ca^{2+} is uncertain, but they are thought to involve structural alterations in the synapse.

The entry of calcium (after successful activation of NMDA-receptor channel) triggers number of events:

1. Protease activation → results in cytoskeletal (morphological) changes, such as change in the shape of dendritic spines.
2. Lipase activation → breakdown of fats → arachidonic acid formation → arachidonic acid exits the postsynaptic cell and bind on the presynaptic membrane → promoting even more glutamate release → thus behaving as a retrograde messenger.
3. Production of second messengers:
    1. IP3 (inositol triphosphate):
        1. Stimulates release of calcium from intra-synaptosomal stores →
        2. Ca^{2+}-calmodulin complex activates the Ca^{2+}-calmodulin-depended kinase → cAMP production → cAMP activates cAMP–depended kinases by phosphorylating them → the activated kinases phosphorylate and activate transcription factors.
    2. Diacylglycerol (DAG) as second messengers →
        1. Activation of Protein Kinase C →
        2. Further activation of transcription factors that enable serotinin and acetylcholine-enhanced neuronal excitation associated with memory tasks.[3]

Memory Consolidation

For memory consolidation, this process requires certain time: 5-10 minutes for minimal consolidation, 1 hour for stronger consolidation. This can occur by the rehearsal technique (as proven by psychological studies):

- Brain has a natural tendency to rehearse newfound information

- Rehearsal causes the mind to accelerate the process of consolidation
- Progressively over time, more and more information is fixed in memory spaces.
- This explains why a person can better remember in depth information on a single subject, rather than superficial information on vast amounts of different subjects.
- This also explains why a person who is wide awake can consolidate memories better than a person who experiences mental fatigue.

Links

Related articles

References

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Sources

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

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