EPSP & IPSP AND THEIR CLINICAL IMPLICATIONS

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Introduction:

At the neuromuscular junction, synaptic action increases the probability that an action potential will occur in the postsynaptic muscle cell; indeed, the large amplitude of the EPP ensures that an action potential always is triggered. Whether a postsynaptic response is an EPSP or an IPSP depends on the type of channel that is coupled to the receptor, and on the concentration of permeant ions inside and outside the cell. As an example of inhibitory postsynaptic action, consider a neuronal synapse that uses GABA as its transmitter. At such synapses, the GABA receptors typically open channels that are selectively permeable to Cl^-. When these channels open, negatively charged chloride ions can flow across the membrane.

Mechanism of Post Synaptic Potential (PSP):

Acetylcholine release in the central nervous system (CNS) has an important role in attention, recall, and memory formation. A significant portion of acetylcholine's effect likely results from the modulation of GABAergic inhibitory interneurons, which have crucial roles in controlling excitatory inputs, synaptic integration, rhythmic coordination of principal neurons, and outputs in the hippocampus. Acetylcholine affects interneuron function in large part by altering their membrane potential via muscarinic and nicotinic receptor activation. [1]

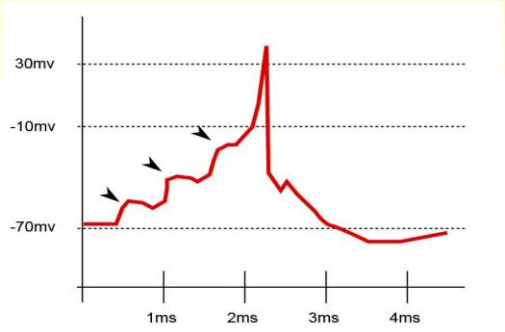

Fig 1: The summation of these three EPSPs generates an action potential.

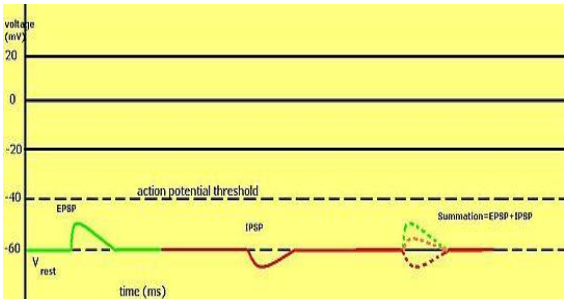

Fig 2: Sodium ion flow inward is responsible for the generation of an EPSP.

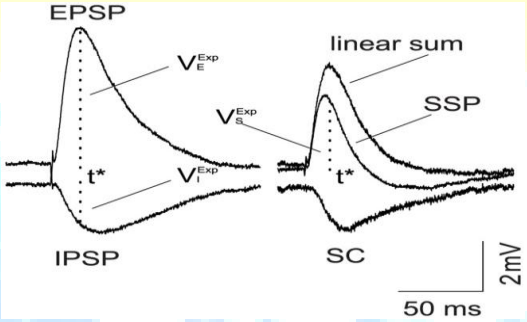

Fig 3: Experimental measurement of EPSP, IPSP and SSP.

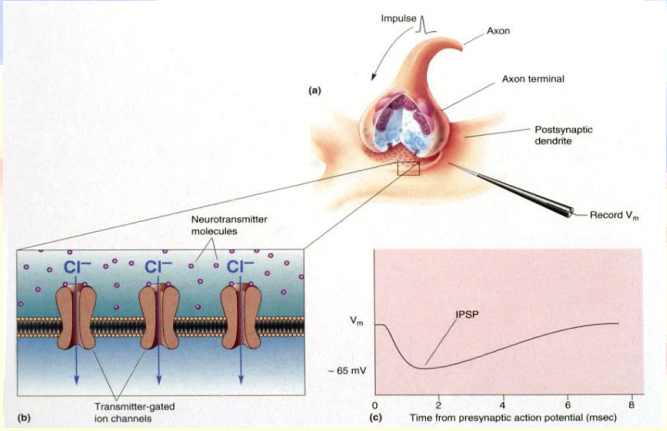

Fig 4. Chloride ion and IPSP

Electrophysiology & neurochemistry of PSP:

Simple temporal summation of postsynaptic potentials occurs in smaller neurons, whereas in larger neurons larger numbers of synapses and ionotropic receptors as well as a longer distance from the synapse to the soma enables the prolongation of interactions between neurons (Fig 1 & 2).

The time when EPSP reaches its peak value is denoted by t^*. V_E^{Exp} and V_I^{Exp} represent the amplitude of EPSP and IPSP at time t^*, respectively. V_S^{Exp} represents the amplitude of SSP at time t^*. SC is the difference between the SSP and the linear sum of the individual EPSP and IPSP measured under separate excitatory and inhibitory inputs. [2] When the excitatory input and the inhibitory input are elicited simultaneously, the response amplitude measured at the soma is found to be smaller than that of the linear sum (Fig 3).

Chloride ion flow inward is usually responsible for the generation of an IPSP. Post-synaptic membrane may receive an excitatory post-synaptic potential (EPSP) and become depolarized or Post-synaptic membrane may receive an inhibitory post-synaptic potential (IPSP) and become hyperpolarized or both multiple excitatory and inhibitory inputs onto dendrites and the soma summate (Fig 4).

An excitatory postsynaptic potentials (EPSP) is a temporary depolarization of postsynaptic membrane caused by the flow of positively charged ions into the postsynaptic cell as a result of opening of ligand-sensitive channels. An EPSP is received when an excitatory presynaptic cell, connected to the dendrite, fires an action potential. The EPSP signal is propagated down the dendrite and is summed with other inputs at the axon hilllock. The EPSP increases the neurons membrane potential. When the membrane potential reaches threshold the cell will produce an action potential and send the information down the axon to communicate with postsynaptic cells. The strength of the EPSP depends on the distance from the soma. The signal degrades across the dendrite such that the more proximal connections have more of an influence.[3]

An inhibitory postsynaptic potentials (IPSP) is a temporary hyperpolarization of postsynaptic membrane caused by the flow of negatively charged ions into the postsynaptic cell. An IPSP is received when an inhibitory presynaptic cell, connected to the dendrite, fires an action potential. The IPSP signal is propagated down the dendrite and is summed with other inputs at the axon hilllock. The IPSP decreases the neurons membrane potential and makes more unlikely for an action potential to occur. A postsynaptic cell typically has less inhibitory connections but the connections are closer to the soma. The proximity of the inhibitory connections produces a stronger signal such that fewer IPSPs are needed to cancel out the effect of EPSPs.

The membrane potential and spiking rate are dependent on a cells biophysical mechanism and the interaction of the cells internal and external voltage. Hodgkin and Huxley (1952) have introduced a standard model to describe the dynamics of cell's membrane potential. That model, described in terms of differential equations, tends to be computationally slow. Over the years, several other simplified spiking models have been designed. Although the later models are faster, they are less accurate than the Hodgkin and Huxley model. In this demonstration the Izhikevich resonate-and-fire model is used. This spiking model is used because it is faster than quadratic firing models and more biologically accurate than integrate and fire models.[4]

Synaptic potentials in the post synaptic membrane may be classified as either EPSP (excitatory post synaptic potential), or IPSP (inhibitory post synaptic potential). The determining factor in this classification scheme is the ion that the postsynaptic membrane becomes more permeable to. If the neurotransmitter binds to a receptor that lets in an ion that causes a DEpolarization (i.e. sodium) then that event is labeled as an EPSP, as it pushes the neuron toward threshold. On the other hand if the ion that experiences an increase in conductance is one that causes a Hyperpolarization of the membrane (i.e. chlorine) then it is considered an IPSP. This is because it makes it harder for the neuron to achieve threshold, it has an inhibitory effect. These polarization events occur at sites on the neuron that contain the appropriate neurotransmitter receptor, either on the cell body or the dendritic membrane.

An excitatory postsynaptic potential (EPSP) is a temporary depolarization of postsynaptic membrane potential caused by the flow of positively charged ions into the postsynaptic cell. A postsynaptic potential is defined as excitatory if it makes it easier for the neuron to fire an action potential.

They are the opposite of inhibitory postsynaptic potentials (IPSPs), which usually result from the flow of negative ions into the cell. An Inhibitory Postsynaptic Potential (commonly abbreviated as IPSP) is the change in membrane voltage of a postsynaptic neuron which results from synaptic activation of inhibitory neurotransmitter receptors.

A postsynaptic potential is considered inhibitory when the resulting change in membrane voltage makes it more difficult for the cell to fire an action potential, lowering the firing rate of the neuron.

Integration of IPSP & EPSP: Dendritic integration of excitatory and inhibitory inputs is critical for neuronal computation, but the underlying rules remain to be elucidated. Based on realistic modeling and experiments in rat hippocampal slices, it is derived a simple arithmetic rule for spatial summation of concurrent excitatory glutamatergic inputs (*E*) and inhibitory GABAergic inputs (*I*). Neural information processing depends critically on the summation of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) at the dendrite, a process that determines the change in the somatic membrane potential and the pattern of neuronal spiking. Rall proposed that the summation of EPSPs is sublinear for inputs at the same dendritic branch, but linear for those at different branches. Measurements in hippocampal CA1 pyramidal neurons. [5]

EPSP vs IPSP: There are more than 20 neurotransmitters at CNS synapses all of which open certain synapses; there are 3 different types of synapses:

1. excitatory – produce excitatory postsynaptic responses (EPSPs), they are depolarizing and typically increase gNa or decrease gK and sum up to cause an action potential; e.g. glutamate
2. inhibitory synapses – produce inhibitory postsynaptic potentials (IPSPs), they are generally hyperpolarizing and typically increase gCl or gK; e.g. GABA.
    i) opening a Cl channel puts a small hole near the soma and the opened Cl channel shunts out the capacitance current of Na killing the summed EPSPs
    ii) as the membrane becomes increasingly depolarized, EPSP decreases and IPSP increases
3. modulatory synapses – modulate the actions of other transmitters, may be depolarizing or hyperpolarizing and often act on second messenger systems; e.g. norephinephrine

When the membrane potential reaches 0, EPSP disappears because of a decreased tendency for Na to enter the cell and an increased tendency for K to leave the cell; when the membrane potential is positive, EPSP changes direction and when the membrane potential reaches –80 mV, IPSP changes direction.

Key Points

- Postsynaptic potentials are graded changes in the membrane potential of a postsynaptic synapse.
- Spatial summation occurs when postsynaptic potentials at nearby synapses are summed.
- Temporal summation occurs when postsynaptic potentials that are close together in time are summed.
- Excitatory postsynaptic potentials (EPSP) bring the neuron's potential closer to its firing threshold.
- Inhibitory postsynaptic potentials (IPSP) change the charge across the membrane to be further from the firing threshold.
- Neuromodulation occurs when a group of neurons releases neuromodulators which can affect the excitability of multiple target neurons simultaneously.
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Clinical implications of EPSP & IPSP:

The antennal lobe (AL) of insects constitutes the first synaptic relay and processing center of olfactory information, received from olfactory sensory neurons located on the antennae. Complex synaptic connectivity between olfactory neurons of the AL ultimately determines the spatial and temporal tuning profile of (output) projection neurons to odors.[6]

Dopamine D_4 receptor (D_4R), which is strongly linked to neuropsychiatric disorders, such as attention-deficit hyperactivity disorder and schizophrenia, is highly expressed in pyramidal neurons and GABAergic interneurons in prefrontal cortex (PFC). D_4R activation also induced distinct effects in both types of PFC neurons on spontaneous excitatory and inhibitory postsynaptic currents, which drive the generation of sAP. Moreover, dopamine substantially decreased sAP frequency in PFC pyramidal neurons, but markedly increased sAP frequency in PV+ interneurons, and both effects were partially mediated by D_4R activation. [7]

A combination of voltage imaging and electrophysiological experiments reveal that GABAergic feedforward and feedback inhibition is unaffected by carbamazepine and additional commonly used Na(+) channel-acting anticonvulsants, both in control and epileptic animals.[8]

Sensory thalamic ventral posterior medial and lateral geniculate nuclei followed cortical active states with major inhibitory and weak tonic-like "modulator" EPSPs. In these nuclei,

sharp-rising, large-amplitude EPSPs ("drivers") were not modulated by cortical slow waves, suggesting their origin in ascending pathways. The thalamic active states in other investigated nuclei were composed of depolarization: some revealing "driver"- and "modulator"-like EPSPs, others showing "modulator"-like EPSPs only.[9]

The sensory experience may have distinct functional consequences in normal versus deprived sensory cortices, and that experience-dependent BDNF expression controls the plasticity of inhibitory synaptic transmission particularly when recovering vision during the critical period. [10]

The functional consequences of metabolic and oxidative stress in fast-spiking interneurons can be observed in aging, ischemia, Alzheimer's disease, schizophrenia and other brain diseases. [11]

A hallmark feature of Ca(2+)/calmodulin (CaM)-dependent protein kinase II (CaMKII) is generation of autonomous (Ca(2+)-independent) activity by T286 autophosphorylation. The CaMKII-induced enhancement of synaptic strength in rat hippocampal neurons required both autonomous activity and further stimulation. The Synaptic strength was decreased by CaMKIIα knockdown and rescued by reexpression, but not by mutants impaired for autonomy (T286A) or binding to NMDA-type glutamate receptor subunit 2B. [12]

During neural development in animals, GABAergic and glycinergic neurons are first excitatory, and then become inhibitory in the mature state. This developmental shift is due mainly to strong expression of the cation-chloride K-Cl cotransporter 2 (KCC2) and down-regulation of Na-K-Cl cotransporter 1 (NKCC1) during maturation. [13]

Conclusions:

The interaction between excitatory and inhibitory inputs is critical to neuronal signal processing. The neuronal plasticity depends on activity of somatic (mainly non-synaptic) NMDA receptors (NMDARs). In contrast, the same repetitive stimulation induced the LTP of excitatory inputs in strongly activated MCs (MC2) that require activity of synaptic NMDARs. [14,15]

It's not scientists that "use" temporal and spatial summation; it's neurons that do. The EPSP's and IPSP's decrement from the time and point of initiation is due to the cable (passive) properties of the membrane. This results largely from the leakiness (conductance). When two inputs occur at different times or different points on the postsynaptic cell, it doesn't matter

whether they are dying out because of the time or space considerations – all that's important is the degree of de- or hyperpolarization available to summate, and thus bring the axon hillock closer to or farther from threshold.

In neuroscience, an excitatory postsynaptic potential (EPSP) is a temporary depolarization of postsynaptic membrane potential caused by the flow of positively charged ions into the postsynaptic cell as a result of opening of ligand-gated ion channels. They are the opposite of inhibitory postsynaptic potentials (IPSPs), which usually result from the flow of negative ions into the cell or positive ions out of the cell. An inhibitory postsynaptic potential (IPSP) is a kind of synaptic potential that makes a postsynaptic neuron less likely to generate an action potential. They can take place at all chemical synapses, which use the secretion of neurotransmitters to create cell to cell signaling.

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