CNS communication mechanism

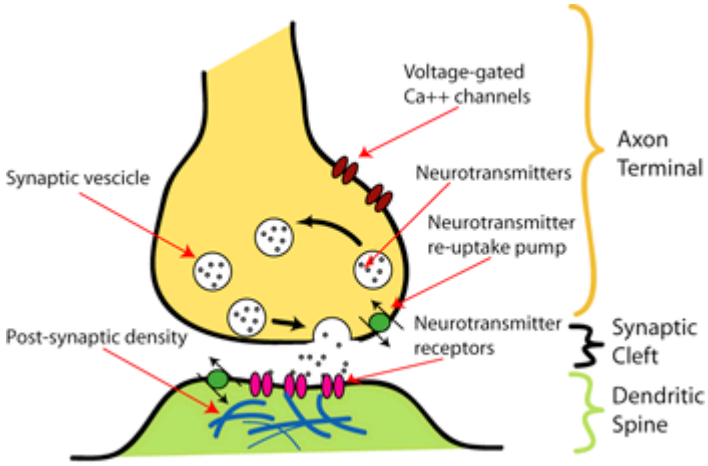
Synapses

There are a few things to understand about the terminal region of the neurons. Action Potentials (AP –reversal of membrane potential– Neuron membrane currents are positive and directed outward if carried by positive ions) cannot turn around and re-propagate in the opposite direction it came from. This happens due to the refractory period. As we know Axons conduct electric impulses away from the neuron, and at the end of these axons there are boutons, which are filled with vesicles. The membrane of these boutons contains voltage-gated Ca^{++} channels, which open when depolarized by AP currents.

Incoming AP can trigger these Voltage-gated Ca^{++} channels, which opens, allowing Ca^{++} to diffuse into the synaptic bouton. Note that the concentration gradient of Ca^{++} is much higher on the outside of the cell, because it is sequestered in the glycocalyx (glycocalyx is a network of polysaccharides that project from cellular surfaces). This influx of Ca^{++} triggers several other reactions, which result in a vesicle exocytosis (commonly 'kiss & run' type). These vesicles contain a neurotransmitter, which is released into the extracellular fluid. This vesicle release is a probabilistic event; where 1 AP has a 10-90% (depending on the type of neuron that is releasing the vesicle) chance of releasing 1 vesicle. So it is possible that an AP will arrive in a bouton but nothing will happen. The distance between the bouton and the adjacent cell is a normal distance of 200 Å, however what makes this region special, is the presence of a membrane that contain a high densities of *protein receptors*. The two membranes are called presynaptic boutons and postsynaptic membrane, which compose a synapse, the mean of chemical communication between adjacent neurons.

Just for clarification, exocytosis is defined as a biological cell process, in which there is a release of a substance into the extra cellular fluid. It's the opposite of endocytosis. Vesicles that contain the substances to be released are transported to the plasmalemma and fuse with it. The machinery that initiates the exocytosis is a whole assembly of proteins named SNARE (Soluble NFS Attachment Receptor) proteins, which interact with the vesicles, which has to already be in position, lined up with the latent fusion pore (structure on the outside of the boutons). The Calcium changes the shape of the SNARE complex due to the synaptotagmin, which is a calcium sensor found in these structures. The vesicles dock and are pulled right into the fusion pores, so that

the contents of the vesicle can diffuse into this neuron. This is a kiss and run type of exocytosis, where the vesicle pulls away quickly, reconstituting its membrane with some of its contents.



Some muscle cells and neurons and glia may be linked by gap junctions, in other words, membranes of two of these cells could be separated by an intervening space of 35Å, compared to the normal distance of 200 Å between membranes. There is nothing special about the value 35 Å, but this smaller gap is used as a pathway for impulses to travel in the nervous system. These gaps are known as electrotopic synapses or gap junctions. These gaps are bridged by proteins, known as connexins that are like tubes between the two cells. This allows several small ions and even action potentials to go right through the membranes. These types of junctions appear in cells that work together.

Post-Synaptic Receptors

Once the vesicle contents are released into the synaptic cleft the transmitter agent rapidly diffuses across and binds to specific receptor sites on a receptor protein embedded in the postsynaptic membrane. Vesicle release is quantitatively proportional to the degree of membrane depolarization or the amount of Ca^{++}, which enters the bouton. Movement across the synaptic cleft (200 Å wide) is by simple diffusion. The transmitter GABA, for example, is electrically neutral at physiological pH, so that diffusion is unimpaired by electrostatic interaction. This process usually takes less than 0.5ms. Upon the binding of the transmitter, there is a change in the shape of the receptor protein and this change in shape has two possible effects: *ionotropic* or *metabotropic*.

In the Ionotropic effect, the binding of the ligand (neurotransmitter) opens up an ion channel (pore) in the receptor protein, which allows specific ions to diffuse through this channel. Now again there are two possibilities, we can allow a number of small cations to diffuse through the channel, such as Na^+, K^+ together. This generates a small depolarizing potential, because the equilibrium potential for Na^+ is +50mV and for K^+ is –90mV, but if both of them are diffusing together the equilibrium Potential would be about 20mV, which is fairly depolarized compared to the rest of the membrane potential (-70mV). Therefore we call this an Excitatory Post-Synaptic Potential (EPSP). The other case the ion channel could be specific for Cl^- ion or K^+ ion all by itself. So if it is specific for K^+ it has a hyperpolarizing effect, called Inhibitory Post-Synaptic Potential (IPSP), taking the membrane resting potential away from threshold, making it harder to excite. The equilibrium potential for Cl^- is -70mV, which is very close to the resting potential, so opening a Cl^- channel doesn't cause any change to the resting potential, but it helps to hold it at –70mV, preventing a depolarization of the membrane. If there are EPSPs on the vicinity, they will be cancelled. These are the possibilities for producing post-synaptic potentials, and they will last as long as the transmitter is bound to the specific receptor, and that is about 20-40 ms (much longer than action potentials). At the end of this period all the transmitters will have been removed. The resulting Ionotropic effects are determined by the receptor protein, and not determined by the chemical transmitter, which can have several different effects. These effects can be inhibitory, excitatory or even be a metabotropic effect.

These PSPs are generated in unexcitable membranes (does not have high density of Na voltage-gated channels) of neuronal dendrites and cell bodies of the post-synaptic neurons. After the transmission of this PSP, the nearest excitable membrane is the initial segment of the axon. So in order to generate this next action potential, the PSP currents must passively spread through the membrane to the beginning of the axon. However, the individual PSPs are very small (1mV or less) and only last for 30-40ms, therefore they cannot depolarize the initial segment of the axon to threshold. The solution for this problem is a summation of many PSPs that will be able to trigger a new AP. In order for this to happen, a current of at least 20mV needs to arrive at the initial segment. From the cable properties of the membrane, we know that some of the voltage generated at the synapse will be lost on the way there, which will require even more PSPs to be generated in order to get threshold potentials. From studies, it has been determined that between 30 and 50 simultaneous EPSPs are necessary.

Something to consider when studying PSPs, is that usually EPSPs tend to be located in the region of the dendrites, and IPSPs are preferentially located on the cell body. The implications of this configuration are that IPSPs are variably produced in positions that interfere with the transmission of the EPSPs currents. They basically can short-circuit these depolarizing currents, so that they don't get to the initial segment. This is a very strategic position to prevent any excitation in the initial segment.

Types of PSP Summations

There are two types of post-synaptic summation. There are the Spatial Summations, where you would have a number of synchronous EPSPs in the dentritic tree. Around 10 to 30 PSPs (max. 1.5mV each), each generated at a different synapse, can create a sufficiently strong depolarization at the initial site to create an AP. The other strategy is the Temporal Summation, where you need a small amount of active synapses, but each one generating EPSPs at a very rapid frequency. Since an EPSP has duration of about 30-40ms and action potentials can occur several times in that period, so that each successive AP can generate a new EPSP on the post-synaptic membrane, which piles on top of the already existing ones giving you a staircase summation. In reality it is usually a mix of the two types of summation that triggers an AP.

Synapses on dendritic tree are usually within 0.4λ of the axonomal initial segment. However, this electronic distance isn't always a fact, research indicates that in some cases the first AP is created in the first node of Ranvier. On average 50% of the EPSP amplitude reaches the initial segment, but it only takes very few IPSPs to short circuit these currents, due to their location in the soma.

When summated PSPs achieve threshold, an impulse is triggered, and if summated PSPs remain above threshold, this should be signaled by continued spike (AP) generation. However, holding the membrane potential above threshold causes an inactivation unless you lower the potential. The mechanism that brings the potential down below threshold is the afterhyperpolarizations, where the voltage-gated K channels come in play, bringing the potential down for a few milliseconds. So there will be a continuous generation of spikes as long as you have the summated PSPs keeping their summated voltages above threshold. At these spike train-generating sites, you must have V-G K channels. The frequency of these spikes will be determined by how large the amplitudes of these depolarizations are, which determines how fast you drive the membrane potential up to threshold after hyperpolarization. These after

hyperpolarizations are not responsible for the refractory period, they are actually there to get right of it.

Ionotropic Receptors

Ionotropic receptors have a limited number of ligands, which are: Acetylcholine (ACh – nicotinic receptor), glutamate (usually excitatory), GABA (usually inhibitory), glycine (usually inhibitory) and Seratonin. Also note that the receptor is what determines which type of action the transmitter will have.

Inhibition can be both pre-synaptic and post-synaptic. The difference is that in pre-synaptic the inhibition is occuring on the bouton rather than in the post-synaptic membrane. In this case GABA is usually the transmitter, or glycine, and the synapse is made onto a bouton, the release of GABA opens GABA-gated Cl^- channels. Depolarizing currents in the bouton cause an influx of Cl^-, which restores the resting potential. This weakening of the depolarizing currents, prevent the opening of V-G Ca^{++} channels and exocytosis of vesicles. This mechanism is widely used in the spinal chord and the brain to terminate action potentials.

Metabotropic effects

There are a series of effects that can originate from metabotropic effects. When the ligand (transmitter agent) binds to the post-synaptic receptor, instead of opening an ion channel, there is an activation of an enzyme, usually via G-protein coupling. This enzyme can increase or decrease the production of 2^{nd} messenger molecules. These are one of cAMP, cGMP or InP_3 throughout the body. 2^{nd} messengers activate other enzymes, such as phosphokinases (kinases), which phosphorylate ionotropic receptors. They can also modulate ion currents (ionotropic synapses), facilitating or preventing these currents, without necessarily having to influence ion channels at all, the effect can be internal on the metabolism of the post synaptic cell. These can actually affect the nucleus and the transcription of specific genes of the nucleus, such that the production of certain proteins are enhanced, specifically receptor proteins or specific transmission agents. What we need to remember here is that the metabotropic effects don't need to have any direct influence on membrane potentials post-synaptically. When it does it arrives slowly, because its gradual, its modulating membrane channels, increasing/decreasing their availability. They act through channels that are essentially ionotropic, so we should think of the metabotropic activity as modulating effects, either

enhancing or suppressing ionotropic receptors. Metabotropic influences are much longer lasting, since it goes through these second messengers, activating enzymes. There are many transmitter agents that can act in metabotropic receptors, including all of the compounds that acted with the ionotropic receptors, but most commonly small peptides, catecholamines, serotonin, purines (ATP) and free radicals such as NO and CO, which are both gases acting on metabotropic receptors, but they fall in the gaseous transmitter category.

Transmitter Removal

Transmitters are removed from the synapse within 40ms in general. There are two main mechanisms to remove transmitters: either breaking the transmitter down with an enzyme, used in some cases; but in most cases the transmitters are removed by a transport mechanism. Transporters in the membranes of the pre-synaptic cells, surrounding glial cells (astrocytes), or the post-synaptic membrane, which just take transmitter back to the cytosol to be re-used in a vesicle. All surrounding membranes have transporters (anti-porters) to get rid of transmitter agents.

- Leonardo Silenieks