1. Acetylcholine is released during a period of about 1ms after an AP arrives in the presynaptic bouton, but no LHRH peptide is release. However, a burst of APs does release LHRH and release persists for many ms. Explain why acetylcholine is release so rapidly and for such a short time, while LHRH requires more APs and is released over a longer period of time.

Ach is release from clear vesicles that are docked at the plasma membrane and can thus fuse immediately, while LHRH is released from dense core vesicles that are located away from the membrane and so their fusion is delayed by the time it takes them to reach the plasma membrane.

ACh release ends quickly because the low Ca++ affinity of the Ca++ sensor on the clear vesicles (synaptotagmin) means that Ca++ is only bound (and fusion triggered) as long as the voltage-gated Ca++ channels located nearby are open (during the AP).

Dense core vesicles have a higher affinity for Ca++ sensor which is activated by the summed (accumulated) Ca++ from several APs. Affinity is high enough so that even after Ca++ channels close the sensor remains activated and release continues until Ca++ is pumped out of the cell.

2. Italy’s prime minister disappears from public view for a week and reappears looking younger. Speculations abound: was it surgery or Botox? A few weeks later the wrinkles around the eyes return. It must have been botox (Botulitus Neurotoxin), a protease that cuts syntaxin in the neuromuscular junction. Explain the effect and the normal location and function of Syntaxin.

Syntaxin is a T-SNARE in the plasma membrane of the presynaptic nerve terminal (bouton) Along with another T-SNARE, snap-25, it interacts tightly with a V-SNARE called VAMP which is located in the membrane of secretory vesicles.

The SNARE complex docks the synaptic vesicle to the plasma membrane at the active zone preparing vesicles for rapid fusion (and, perhaps, contributing energy to the fusion process... not necessary, but acceptable). Cleaving syntaxin blocks vesicle docking and thus transmitter release, resulting in relaxation of the muscle.

3. Loss of myelin produces paralysis. Why? Describe what myelin is and what is its function. Explain how it works and use equivalent circuit diagrams to show the effect of myelin loss.

Myelin is a multi-layered wrapping of glial membrane around an axon. It raises the axonal membrane Rm (By making it harder for ions to leak out of the axon and into the bulk extracellular solution) and lowers Cm (by increasing the effective thickness of the membrane).

The loss of myelin decreases Rm, thus increasing Leak of ions out of the cell so that less charge travels axially. Thus reducing the length constant.
Since Na+ channels are located far apart in the Nodes of Ranvier if the length constant becomes too short the AP will not reach the next node and the conduction will fail.

Equiv. circuit diagram showing at least two RC circuits connected by an Ra which lowered Rm resulting in less axial current

4. A neuron has a resting potential of -70 mV with the usual ionic gradients (E_k = -100 mV, E_cl = -70 mV, E_na = +60 mV, E_ca = +150) and typical leak channels, voltage-gated channels and SK-type Ca++ activated K+ channels. Explain the direction changes in Membrane potential of the following events:

a. Presynaptic axons release LHRH which activate a GPCR in the neuron and Closes K+ channels
depolarization. K+ channels open at rest are closed reducing outward current, moving V_m away from E_k

b. another group of presynaptic axons release glycine onto the neuron and open Cl- selective Gly receptors.

GlyRs open, but no change in voltage since V_m = E_cl
c. A third set of axons release glutamate leading to depolarization.

Draw the responses you’d expect for activation of metabotropic and ionotropic receptors and explain the differences.

Fast AMPAR EPSP. These are ligand-gated channels which open quickly whey they bind glutamate and close quickly when glutamate concentration drops.

Slow mGluR response due to either closure of K+ channel or opening of Na+ permeant channel. Response is delayed by postsynaptic second messenger cascade and persists for some time until second messenger system is turned off.

Suggest two experiments to distinguish if the EPSP is caused by AMPA and NMDA receptors.

1. specific blockers
2. Dependence on Mg++ out and voltage
3. Dose response.

5. An AP is initiated at the SIZ of the axon. It travels in two directions: back into the dendrite where it decrements and down the axon toward the nerve terminal without decrement.
a) Explain the decrement in the dendrite
The density of Na+ channels in the dendrite is too low to sustain active AP propagation, and for this reason, back-propagation is decremental.
b) When the protease trypsin is injected into the axon, the AP becomes a little longer in duration and the AP reflects when it reaches the nerve terminal and is conducted back from the terminal toward the cell body. Propose a mechanistic explanation for this effect using a sketch of the membrane topology and functional domains of the channel type that is responsible.

*The protease cleaves the Na+ channel inactivation ball. This has two effects:
1. The AP is broadened because the Na+ channels now are shut only by repolarization due to K+ current and not by inactivation
2. Normally APs do not reflect because the axon is refractory, but removal of inactivation eliminates this refractoriness.*

*Topology model showing 4 domain channel with ball between domains III and IV.*

6. Two action potentials separated by 5 ms occur in an excitatory presynaptic axon. The interval is shorter than the time constant of the dendrite, and short enough so that the second action potential arrives when residual Ca++ is still high from the first action potential. Draw the EPSPs and explain why the second one is more likely to reach threshold

*EPSPs summate (interval shorter than time constant) so that the second EPSP adds to the first and gets closer to threshold.*

*Second EPSP is facilitated (larger than the first) due to residual Ca++ activation of CaMKII, which phosphorylates synapsin on the vesicle membrane which lets go of actin and lets vesicle mobilize, dock and participate in release, thus increasing number of vesicles fusing.*