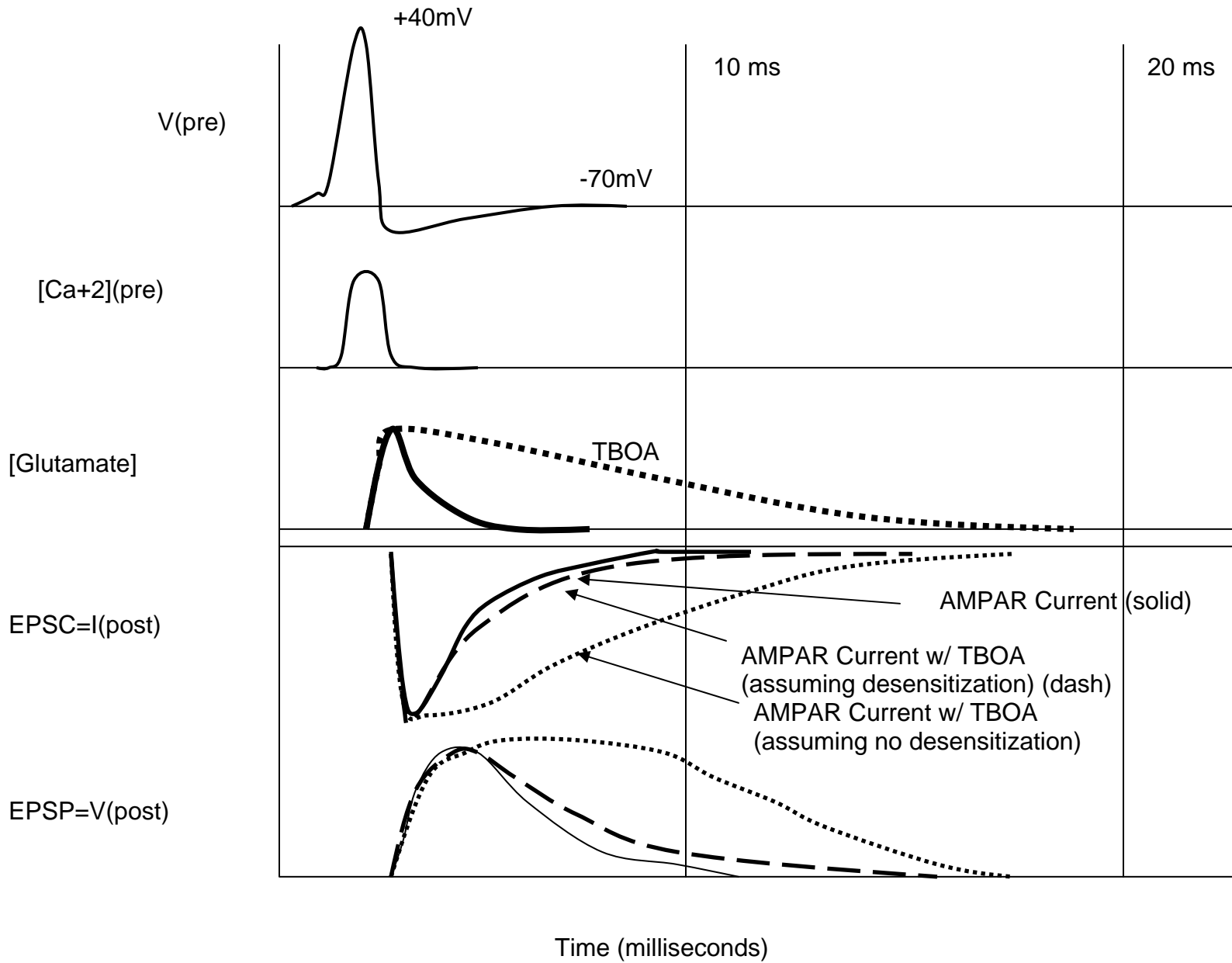


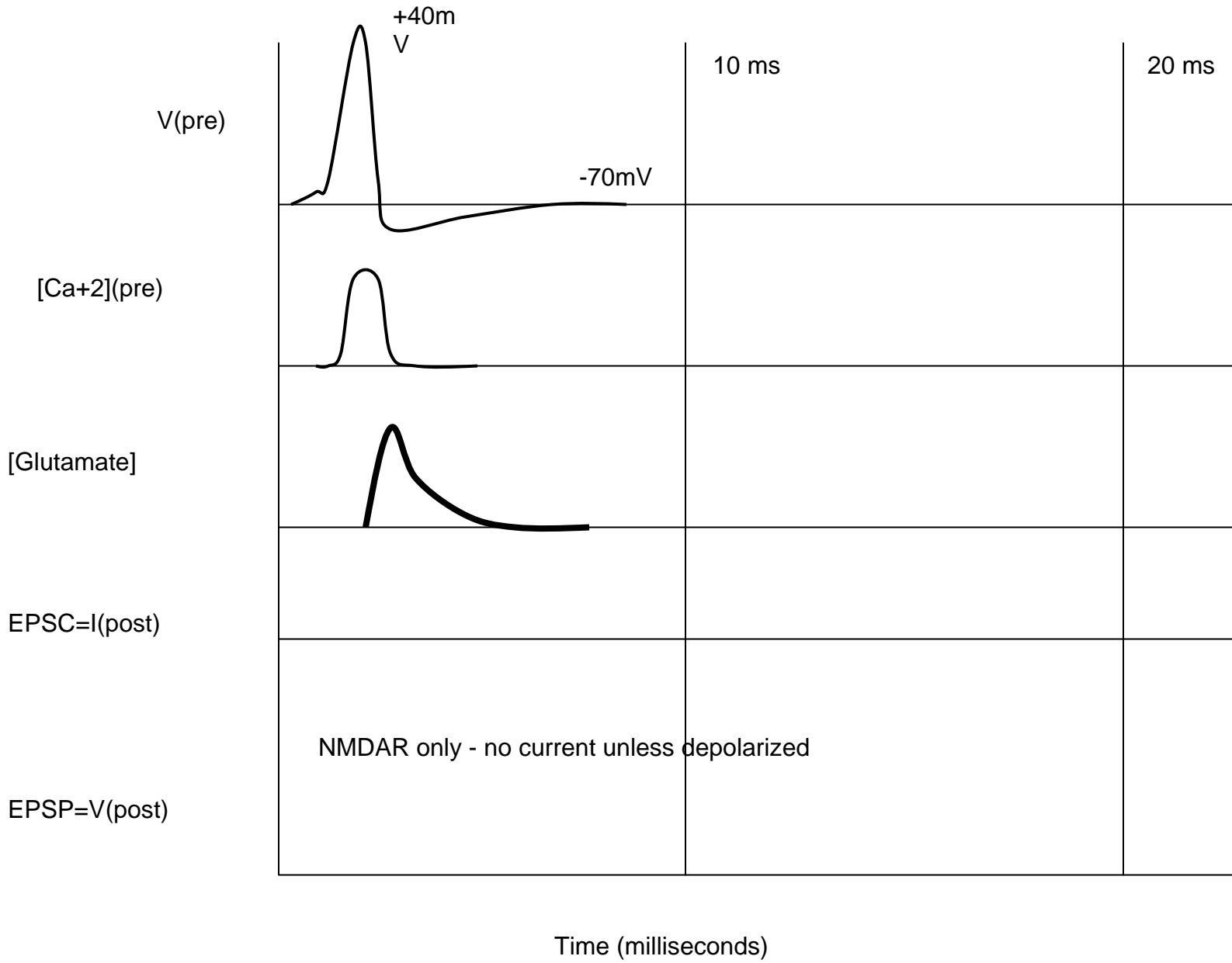
HST 131/ Neuro 200
18 September 05

Problem Set 3 - Answers

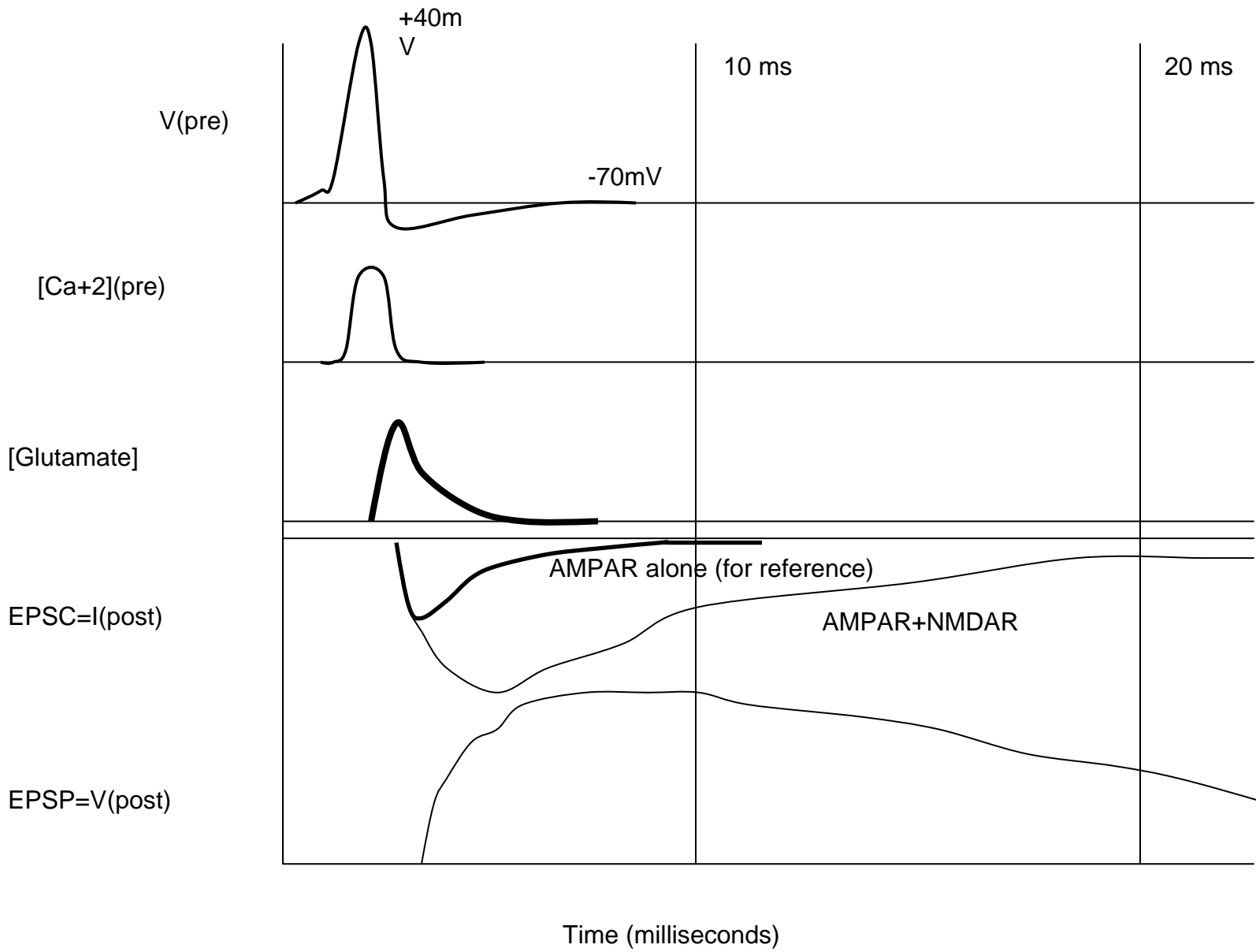
Explanation in text below graphs.



Now consider NMDAR only:



Now consider NMDAR and AMPAR:



Timing:

-The presynaptic action potential takes less than 1 ms at mammalian temperatures.

-The entry of Ca^{++} is delayed by about 100 μs (can be as short at 60 μs), and is also about 0.5 ms in duration. Although Ca^{++} concentration in the presynaptic terminal as a whole stays somewhat elevated for a while, the concentration near the Ca^{++} channels, that is, at the vesicle release site, is high for less than 1 ms, and during that time the vesicles available for release fuse and dump their contents.

-Glutamate increases in the cleft very rapidly (200 μs delay time or more for a monosynaptic delay). Then glutamate rapidly diffuses away or is taken up by glutamate transporters. In the illustration for TBOA, glutamate reuptake by glutamate transporters is blocked, and all removal is due to diffusion.

-The excitatory postsynaptic current rises once AMPA receptors (AMPA receptors) bind glutamate. AMPARs turn on and off faster than NMDARs, accounting for the short transient. We show the current as negative (inward) since the postsynaptic cell will be resting at -70mV. AMPAR current will roughly follow the glutamate in the cleft, and so lengthening of the current will be observed under conditions (such as TBOA) that keep glutamate around longer. In addition, AMPARs *desensitize* (close in the presence of agonist) and so postsynaptic current (epsc) is reduced below what might be expected if the glutamate concentration were the sole determinant of current. AMPAR actually desensitizes to a relatively large extent, such that the effect of extending glutamate exposure does not greatly increase the amount of synaptic current (think of Dr. Schwarz's lecture on the Flip and Flop variants of AMPAR and the current timecourse). Desensitization makes this part of the question quite tough. AMPAR currents can decay with a time constant (τ) as rapid as 2 milliseconds, while NMDAR currents can decay much more slowly ($\tau = 50\text{-}200$ ms)

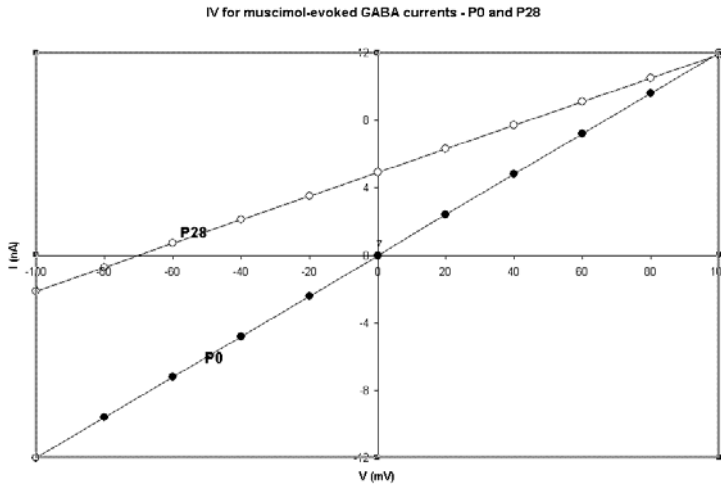
-The excitatory postsynaptic potential (epsp) reflects changes due to the synaptic current, with a lag inserted to account for capacitance. In this example, we do not show an active response (firing of an action potential), though we do show the effect of leak currents. (Without any leak, the cell would not sit at -70mV, nor would it return there after excitation.) TBOA also lengthens the epsp, even with AMPAR desensitization.

When we assume that there are only NMDAR receptors, there is no postsynaptic current unless the cell is already depolarized. This is due to the voltage-dependent magnesium block discussed in lecture. With no epsc, there is also no epsp.

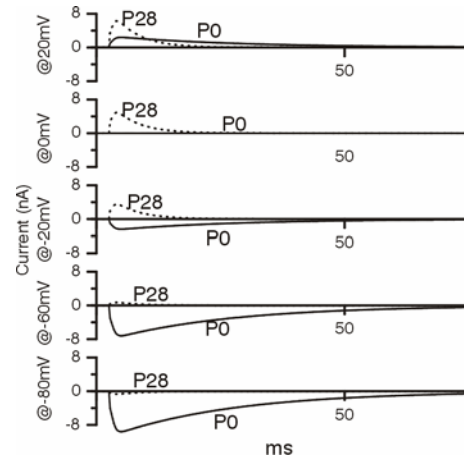
Consider the situation with AMPARs *and* NMDARs: Current through AMPARs flows as before, depolarizing the postsynaptic cell and now allowing current to flow through the NMDARs. This current is larger (NMDAR have larger conductance, and we assume here a similar number of channels) and lasts longer (slower decay τ).

2) In this case, we make the simplifying assumption that the Cl⁻ current can be approximated by $I = g(V_m - V_{rev})$.

2a)



2b)



For 2b, assume the rise time is fast and that current decays with the slow (P0) or fast time course given in the question. The peak current at various voltages is determined by reference to 2a.

2c) At P0, the GABA current has an amplitude of ~ -6 nA at -50 mV membrane potential. (Excitatory, Depolarizing). (Solve $I = g(V_m - V_{rev})$ for the appropriate reversal potential and conductance.)

At P28, the GABA current has an amplitude of $\sim +1.4$ nA (Inhibitory, Hyperpolarizing)

2d) At P0:

$$E_{GABA} = 0mV$$

$$0mV = -25.4 \ln\left(\frac{120}{x_1}\right)$$

$$x_1 = 120mM = [Cl]_{i1}$$

At P28:

$$E_{GABA} = -70mV$$

$$-70mV = -25.4 \ln\left(\frac{120}{x_2}\right)$$

$$x_2 = 7.6mM = [Cl]_{i2}$$

Possible mechanisms for accounting for the change in internal concentrations:

-A Cl⁻ influx pump @ P0

-downregulation of the Cl⁻ influx pump, upregulation of a Cl⁻ efflux pump during development.

The negative internal charge is primarily made up by membrane-impermeant organic anions at later points in development.

- 2e) Mechanisms that might explain the conductance change include:
- number of channels inserted in membrane
 - the decreased concentration of intracellular chloride
 - change in subunit composition of GABA_A channels
 - phosphorylation state
 - RNA editing

Mechanisms that might explain the change in the time constant include

- change in subunit composition of GABA_A channels
- phosphorylation state
- RNA editing

3a) One pulse produces an EPSP of sufficient magnitude to evoke an action potential (AP). If the postsynaptic cell is stimulated by two pulses, the second pulse occurs during the absolute refractory period and thus does not evoke a second AP. If five pulses are delivered, the cumulative EPSP is large enough to reach threshold during the relative refractory period and thus a second AP is evoked.

b) The amplitude is simply a function of Ohm's Law, $V=IR$. The magnitude of the voltage change will be the product of the postsynaptic current and the membrane resistance of the postsynaptic cell. Of course, the postsynaptic current will decrease as the depolarization brings the membrane closer to the reversal potential for the receptor channels.

The time course of the voltage change will depend on the membrane time constant, which is the product of the membrane resistance and the membrane capacitance. Of course, the synaptic conductance will decrease the membrane resistance to some extent and slightly speed the time constant.

For five pulses there is a temporal summation of the response to a single pulse. Again, the amplitude depends on $V=IR$. However, for each subsequent pulse, the current and the resistance are slightly smaller, thus ΔV is smaller. (This question is not intended to explore the role of facilitation or depression in synaptic transmission.)

c) The current does not mimic the conductance exactly. There is a slight increase in conductance with successive pulses because the second pulse occurs when channels from the first haven't completely closed. However, as V_M becomes more depolarized, closer to V_{Rev} for the postsynaptic conductance, the current decreases. Changing G_{leak} alters the magnitude of the EPSP. It also changes the amount of depolarization and the magnitude of this effect. That is, a larger G_{leak} reduces the depolarization caused by each epsc, so that there is less depolarization, so that subsequent epscs are closer in amplitude to the first.