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There are 17 questions.
Point values for each are given; 100 points total.
Equations given on the last pages.

1. (6 points) Attribute the following properties or characteristics to axons (A), dendrites (D), both (B), or neither (N).

Multiple in number	___ D	Acute angle branching	___ D
Usually myelinated	___ A	Uniform diameter	___ A
Originates from the cell body	___ B	Microtubule cytoskeleton	___ B
Has protein synthetic machinery	___ B	Action potential propagation	___ B

2. (6 points) Name three functions of neuroglia

1.

2.

3.

(a) Mechanical support (b) Guidance for migration and axonal growth (c) Growth factor secretion (d) Segregate receptive surfaces/synapses (e) Removal of ions (K⁺) from extracellular space (e) Removal of neurotransmitters (f) Regulation of blood vessel diameter (f) Antigen presentation to T-cells (g) Regulate metabolite exchanges with neurons and perivascular space (h) Proliferate in response to injury

3. (6 points) Name three differences in the electron microscopic appearance between GABAergic and Glutamatergic synapses in the CNS:

	GABAergic	Glutamatergic
1.		
2.		
3.		

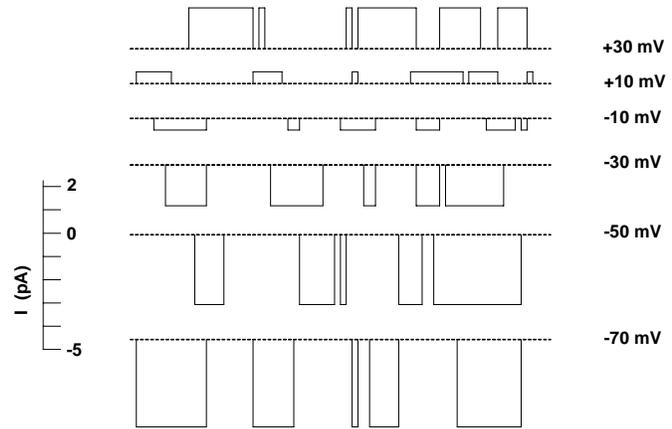
Vesicles tend to be round and clear (Glu) while they can be flattened (GABA).
Width of the postsynaptic density (GABA is thin, Glu is thick).
Cleft is large (Glu) or small (GABA)
Glu preferentially occur on spines; GABA preferentially occur on shaft of dendrite

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4. (8 points) You are recording from a newly-discovered type of neuron to determine its physiological properties. You first record from a patch of membrane that has one or a few of a particular type of ion channel. The individual records at different membrane potentials look like this:



a. Does this channel appear to be voltage-gated? If so, in what way? **No.:**

b. The experimental solutions were these:

extracellular:

150 mM KGluconate, 10 mM NaCl, (Gluconate is a large impermeant anion)

intracellular:

150 mM KCl, 1 mM MgCl₂

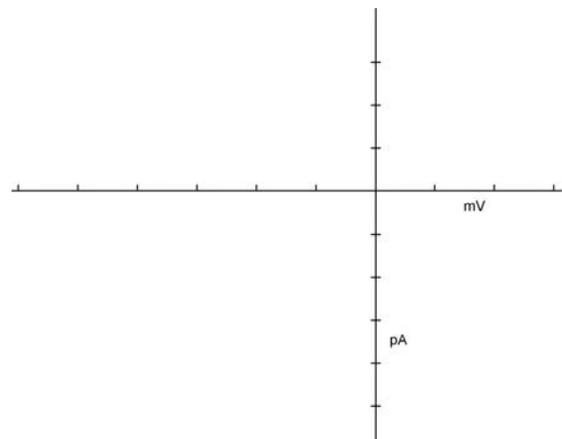
Which ion(s) do you think carries this current? Why?

K⁺ (since $E_{rev\ K^+} = 0mV$), and Na⁺ is only present in the pipette (E_{rev} extremely low). Ca²⁺ will be chelated.

c. Draw the I-V relationship for this channel, adding scale numbers

Reverses at zero.

Line with slope corresponding to conductance of 60 nS (below). -3pA at -50mV, -1.8pA at -30mV, etc.



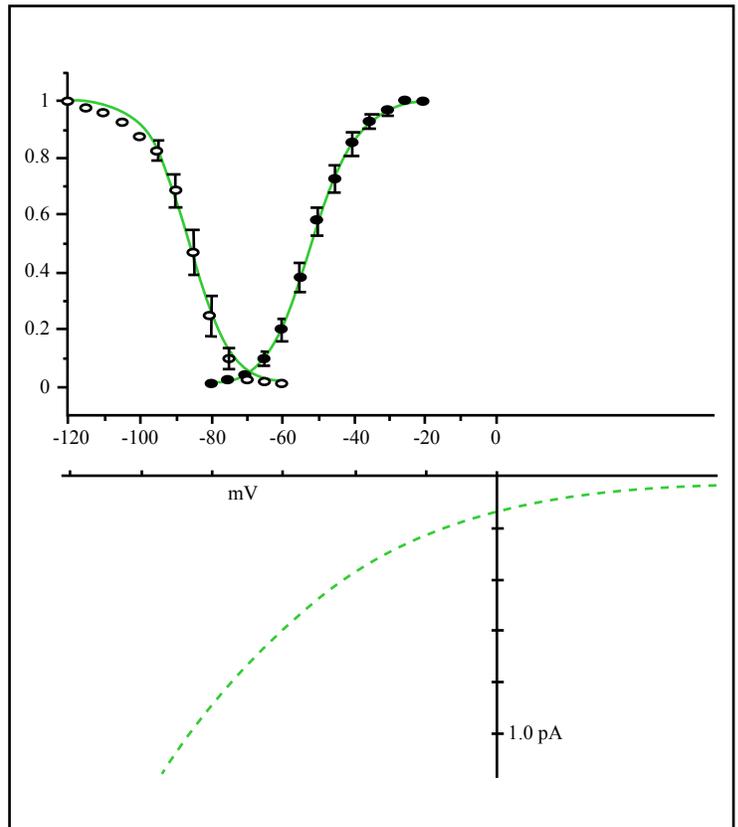
d. What is the single-channel conductance of this channel type?

G = 60pS

e. Going to larger voltages, you find that the channel passes less current above +30 mV and none above +45. To try to understand this, you replace the MgCl_2 in the intracellular solution with CaCl_2 . Now the single-channel current increases linearly at higher voltages. What prevented current flow through this channel before? Why can current flow now?

Could be block by Mg^{2+} (similar to NMDAR). Similar to an inward rectifier GIRK with +30mV where rectification starts.

5. (7 points) One type of channel that we did not discuss very much, either in lecture or section, is the T-type voltage-gated calcium channel. So named because of its *tiny* conductance and *transient* current, this channel type is important for rebound firing in thalamic relay neurons. After a cursory literature search, you glean the following salient pieces of information regarding voltage dependence of activation and inactivation (upper) and the open-channel I(V) curve (lower). You have also found that the current activates with a time constant of ~ 0.5 ms and inactivates with a time constant of ~ 30 ms.



- a. With a patch-clamp setup, you record from a SINGLE T-type calcium channel, holding at -100 mV and stepping to -20 mV for 15 ms. Draw a representative record for the current through a single channel as a function of time (including 5ms before and after the voltage step).

Single channel recording at -100mV will start out at 0pA. No current since the activation gates are almost all shut at -100mV (activation gates 0%, though inactivation gates are about 90% open – per upper graph). Then, after pulsing to -20mV, activation gates rapidly open (activation gates 100%, with a 0.5ms timecourse – meaning about 63% chance of opening within 0.5 ms). When open, peak current is -0.2pA (per lower graph at -20mV). However, the channel may inactivate (steady state inactivation gate of 0%, but pulse is only 15ms long, and the timeconstant is 30ms – so close to half will inactivate during this time. Single channel records also fluctuate between open and closed states randomly (so the trace looks square wave like).

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- b. After blocking all the other channel types in the cell, you record in WHOLE-CELL mode, holding at -100 mV and stepping to -20 mV for 100 ms. Assuming your cell has ~1000 T-type calcium channels, draw the expected current *using an appropriate scale*.

Like the single channel recording, at -100mV will start out at 0pA. No current since the activation gates are almost all shut at -100mV (activation gates 0%, though inactivation gates are 90% open – per upper graph).

Then, after pulsing to -20mV, activation gates rapidly open (activation gates 100%). Peak current at -20mV (if all channels open) is $-0.2\text{pA per channel} \times 1000 = -200\text{pA}$. In order to calculate a peak, I arbitrarily picked 2ms after the pulse (four time constants for activation, but hardly any inactivation) and computed:

Activation gates: $1.00 \times (1 - e^{-2/0.5}) = 1.00 \times (1 - e^{-4}) = 1.00 \times (0.98) = 0.98$

Inactivation gates: $0.9 \times (e^{-2/30}) = 0.85$

Thus, about 0.80 of the channels are open (0.85×0.98), giving a peak current of -160pA at 2ms. (Other short times may yield different answers).

However, over 100ms of the pulse, inactivation gates close:

Activation gates: $1.00 \times (1 - e^{-100/0.5}) = 1.00$

Inactivation gates: $0.9 \times (e^{-100/30}) = 0.036$

So, only 0.036 of the channels are open (about 36 channels), with a current of -7.2pA .

After we return to -100mV, peak current is $-1.2\text{pA per channel} \times 1000 = -1200\text{pA}$. Since we determined that at 100ms, all activation gates were open (100%), but most inactivation gates were closed (about 3.6%), this is an instantaneous increase in the driving force, and we see a tail of current reflecting this: $0.036 \times -1200\text{pA} = -43.2\text{pA}$.

The tail rapidly decays, as now at -100mV, steady state activation gates are not open (0.00) and they approach this with a timecourse of 0.5 ms (so almost all closed at 2ms).

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6. (5 points). Increasing the resting potassium conductance of an excitable neuron would:
(circle true statements)

- a. decrease the peak voltage of the action potential
- b. speed the repolarization phase of the action potential
- c. decrease the refractory period duration
- d. decrease the threshold potential for eliciting an action potential
- e. increase the membrane time constant

7. (7 points) For each of the following physiologic differences,

- (1) indicate whether the change would SPEED, SLOW or NOT AFFECT the velocity of action potential propagation down an axon and,
- (2) give a physiologic mechanism by which such a change or difference could arise.

A. Increased membrane resistance at rest

SPEED. Elimination of K⁺ leak channels.

B. Increased membrane capacitance

SLOW. Decreased myelination, perhaps secondary to a demyelinating disease.

C. Increased peak voltage-gated sodium channel conductance

SPEED. More sodium channels, or different type of sodium channel with greater single channel conductance.

D. Increased axial resistance

SLOW. Shrink the axon in diameter. Could also say changing the resistivity of cytoplasm.

8. (7 points) Attribute the following properties to an electrical synapse (E), a chemical synapse (C), both (B), or neither (N):

- Allows for communication between neurons ___ B
- No synaptic delay ___ E
- Requires connexins ___ E
- Calcium-triggered neurotransmitter release ___ C
- Unidirectional ___ C/N (retrograde messages)
- Metabolically expensive ___ C
- Can amplify signal ___ C

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9. (8 points) We discussed several mechanisms by which the strength of synapses can be changed. List three presynaptic and three postsynaptic mechanisms by which the strength of a synapse can be increased, and explain (briefly!) why.

PRESYNAPTIC:

- increased number of Ca^{2+} channels
- change in voltage dependence of Ca^{2+} channels
- increased number of vesicles
- increased transmitter per vesicle
- residual Ca^{2+} (as during facilitation)

POSTSYNAPTIC:

- increased number of receptors or type: new AMPARs at silent synapse
- different kind of receptor with higher conductance
- increased conductance of receptors (phosphorylation, etc)
- changes in the electrotonic “shape” of the input structure
(widening of a spine neck)
- changes in desensitization (Flip-Flop),
- changes in receptor affinity (if not saturated),
- kinetic changes (NMDA decay timecourse),
- closed leakage channels in postsynaptic membrane

10. (3 points) What are three differences between AMPA and NMDA receptors?

AMPA

NMDA

1.

2.

3.

Mg sensitivity or IV curve differences. Kinetics of closing (NMDA is slow). Affinity for Glu (high for NMDAR). Desensitization (fast for AMPAR). RNA editing in AMPAR/ Ca^{2+} permeability in general. Developmental changes in expression of subunits. Developmental changes in ratio (AMPARs later when originally synapses silent).

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11. (6 points) Tetanus toxin is a bacterial exotoxin discussed in class produced by *Clostridium tetani*. Please describe

- a. its target in the synapse and the location of that target
synaptobrevin, associated with vesicles
- b. its effect on the target
cleaves it (specific protease)
- c. its effect on the synapse
prevents vesicle release
- d. Intoxication with botulinum and tetanus toxins cause very different clinical pictures. Briefly describe the symptoms of each and the basis for differences:

Botulinum: Flaccid paralysis with loss of muscle tone, etc. (tropism for motoneurons thus no firing)

Tetanus toxins: Tetanic paralysis, with arched back, muscle contraction, grimace, etc. Tropism for inhibitory interneurons in the spinal cord (thus increased excitation of motoneurons)

12. (4 points) Name the ions to which each of the following receptors is normally permeable, and whether activation of the receptor is usually excitatory or inhibitory

- a. AMPA receptor (Na, K, sometimes Ca; excitatory)
- b. GABA_A receptor (Cl⁻; inhibitory)
- c. nACh receptor (Na, K; excitatory)
- d. NMDA receptor (Na, K, Ca; excitatory)

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13. (5 points) The following are symptoms or signs consistent with demyelinating peripheral neuropathy (circle all that apply):

- a. Hyporeflexia on physical exam
- b. Stocking glove distribution of sensory loss in extremities
- c. Muscular appearance with accentuated muscle definition
- d. Burning sensation or pain in extremities
- e. Gait abnormalities

14. (6 points) In the inherited disease hyperkalemic periodic paralysis, elevated serum potassium produces (by a mechanism that is not completely understood) failure of inactivation in the voltage-activated sodium channels of skeletal muscle. Three characteristics are surprising:

1. only a few percent of the muscle sodium channels have failed inactivation at any given time
2. the disease is dominantly inherited
3. the same mutation can cause myotonia (sustained muscle contraction) and paralysis (no muscle contraction), sometimes as different phases of the same attack.

Explain how characteristic 1 is compatible with and explains the other two characteristics.

If only a few percent need to function abnormally to produce the disease, then half the sodium channels could be normal in a heterozygote and a small fraction of the mutant channels could produce enough abnormal inactivation. The symptoms are produced by the steady sodium influx through the non-inactivating channels causing depolarization of the muscle membrane. A moderate amount of depolarization causes sustained firing and constraction. A larger degree of depolarization (paradoxically) inactivates all the normal sodium channels, to prevent action potentials and to cause paralysis.

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15. (5 points) Please match each description below with the single best diagnosis:

__b__ A child experiences involuntary repetitive movement of his arm without losing awareness

__d__ The patient describes seeing lights flashing, then begins to stare off into space while smacking her lips

__b__ A 30 year old woman is often overcome with a sensation of an intense odor of burning rubber

__a__ A teacher notices one of her students is often staring into space with a blank face while rapidly blinking her eyes, then quickly resumes normal activity

__e__ Repeated “drop” episodes with sudden loss of postural muscle tone

diagnosis:

- a. absence seizure
- b. simple partial seizure
- c. tonic seizure
- d. complex partial seizure
- e. atonic seizure
- f. generalized tonic-clonic seizure

16. (6 points) Barbiturates and benzodiazepines are both prescribed to treat seizures.

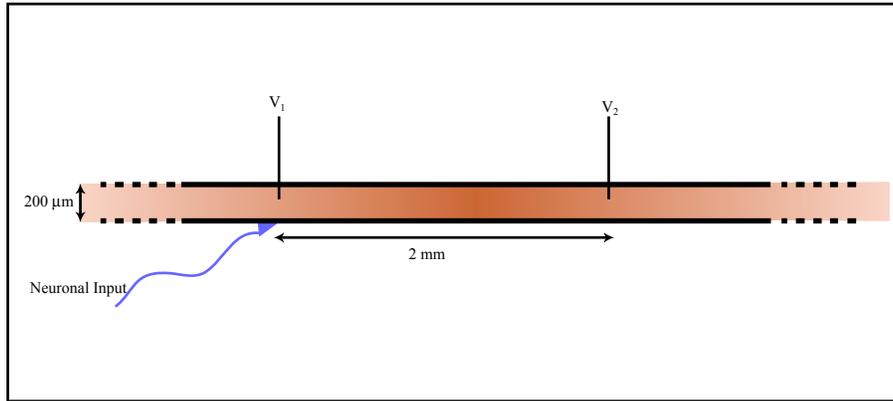
a. Identify their target(s), how they affects their target(s), and how this effect acts to reduce seizures.

Both classes of drugs increase the response of GABA_A chloride channels to GABA, resulting in overall increased inhibitory signaling in the brain. This would result in decreased excitability of neurons and prevent epileptogenesis by shifting the balance of activity in the brain more towards inhibition.

b. Why are benzodiazepines considered safer drugs than barbiturates?

Benzodiazepines increase the affinity of the GABA_A receptor for GABA and so can potentiate inhibition, if inhibitory inputs are active. Barbiturates increase the rate constant for opening and so at high concentrations can activate it directly and cause a lethal inhibition.

17. (5 points) Assume that the following infinitely long dendrite has no active conductances.



Assuming a membrane resistance per unit length of fiber of 1000 ohm-mm, and an axial resistance per unit length of fiber of 40 ohm/mm, what is the length constant of the fiber?

$$\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{1000}{40}} = 5\text{mm}$$

Given the length constant calculated above, if we apply 10 mV at V_1 , what voltage will we record at V_2 ?

$$V_2 = 10 * \exp(-2/5) \\ = 6.7 \text{ mV}$$

Next, instead of introducing the 10 mV depolarization via our electrode, we stimulate the nerve fiber input depicted with a single shock. At V_1 we record a peak depolarization (EPSP) of 10 mV in the fiber, but at V_2 the depolarization is less than we calculated above. What's the source of this discrepancy?

For signals that occur in real (not infinite) time, you have to take into account the membrane capacitance. The depolarization will be spread out in time and consequently smaller in amplitude.

Some Constants and Equations

electron charge	$e = 1.6 \times 10^{-19}$ coul	
gas constant	$R = 8.31$ J/mol-K ⁰	
Faraday	$F = 96485$ coul/mol	
therefore	$RT/zF = 25.4$ mV	if $z=1$ and $T=22^{\circ}\text{C}$
permittivity of free space	$\epsilon_0 = 8.85 \times 10^{-12}$ coul ² /J-m	or Farad/m
Avogadro's number	$N_A = 6.02 \times 10^{23}$ mol ⁻¹	
Resistance	$R = V/I$	ohms=volts / amperes
Conductance	$G = 1/R = I/V$	Siemens=amperes / volts
Resistance in series	$R_T = R_1 + R_2 + R_3 + \dots$	
Resistance in parallel	$1/R_T = 1/R_1 + 1/R_2 + 1/R_3 + \dots$	
Capacitance of parallel plates in vacuum	$C = \epsilon_0 A/d$	Farads = permittivity * area / separation
		for lipid: $\epsilon \sim 2.1 \epsilon_0$; $d \sim 2$ nm
		so $C \sim 1 \mu\text{F}/\text{cm}^2$
Charge	$Q = C V$	coulombs = Farads * volts
Capacitance in series	$1/C_T = 1/C_1 + 1/C_2 + 1/C_3 + \dots$	
Capacitance in parallel	$C_T = C_1 + C_2 + C_3 + \dots$	
Membrane capacitance	$C_m \sim 1 \mu\text{F}/\text{cm}^2 = 0.01$ pF/ μm^2	
Nernst potential for an ion X	$E_X = \frac{RT}{zF} \ln \frac{[X_o]}{[X_i]}$	

Goldman equation for reversal potential with several permeabilities

$$V_{rev} = \frac{RT}{F} \ln \left[\frac{P_K [K_o] + P_{Na} [Na_o] + P_{Cl} [Cl_i]}{P_K [K_i] + P_{Na} [Na_i] + P_{Cl} [Cl_o]} \right]$$

Time constant of a membrane $\tau = R_m C_m$

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Length constant of a fiber $\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{aR_m}{2R_i}}$

note: r_i , r_m and c_m are per unit length of fiber; they have units of ohm/cm, ohm-cm and farad/cm, respectively. To put it in terms of bulk properties of membranes, the dimensions of the fiber must be considered, so

$$r_i = \frac{R_i}{\pi a^2}, \quad r_m = \frac{R_m}{2\pi a}, \quad \text{and} \quad c_m = C_m 2\pi a$$

where a is fiber radius, R_i is in ohm-cm, R_m is in ohm-cm², and C_m is in F/cm².

Conduction velocity of a fiber $v \propto \sqrt{\frac{aD}{2R_i C_m}}$ (very roughly)

where a is radius and D is channel density.