NEURAL TRANSMISSION, PLASTICITY, AND LEARNING

WITH EMPHASIS ON MOLECULAR STRUCTURE

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Preface

I compiled these notes while I was taking MCB 160 with Professors Bateup, Isacoff, and Ngai. However, this set of questions only covers Prof. Bateup's section, which in my opinion was by far the most interesting module since many of our lectures focused on the molecular basis of biological learning. I also wrote up notes for Prof. Ngai's section, although I did not LaTeX those. Don't be shy if you'd like those–just shoot me an email at derekwan@berkeley.edu.

My apologies if you came here looking for notes on Prof. Isacoff's section. Unfortunately his lectures have a lot of cartoons, so I found it impossible to compile any meaningful digital notes for his module.

As always, let me know if you find any mistakes. I crammed 6 lectures in one day the weekend before a CS 70 exam so half of these questions were written in panic mode, although I would like to think they're still helpful.

Chapter 1

Neurotransmitters and Neuromodulators (part 2)

1.1 Questions

1. True or false: the type of neurotransmitter determines whether a signal is excitatory or inhibitory.
2. What are the "fast" synaptic transmitters?
3. What is $GABA_AR$ selective for? What about AMPA/NMDA/kainate?
4. True or false: glutamate and GABA can be modulatory.
5. Is acetylcholine a fast excitatory neurotransmitter?
6. Acetylcholine roles in different parts of the brain?
7. Key enzymes in Ach synthesis/packing/reuptake?
8. Synthesis of monoamines?
9. How are monoamines packed/reuptaken/degraded?
10. What kind of transmitters are monoamines?
11. Dopamine functions?
12. Some dopamine pathways?
13. Dopamine neurons are most dense where?
14. What defines dopamine neurons?
15. Common target of Parkinson's disease drug?
16. Where is serotonin synthesized?
17. What is serotonin important for?
18. Some ways in which serotonin can be regulated?
19. How did people find evidence for neurotransmitter co-release? What is co-release vs co-transmission?
20. Some examples of neuropeptides?
21. Neuropeptides function?
22. How are neuropeptides created and released?

1.2 Key

1. False. The properties of the receptor and ionic composition of the post-synaptic cell determine whether a neurotransmitter is excitatory or inhibitory.
2. Gluatamate and GABA
3. $GABA_AR$ is selective for Cl^- (inhibitory, ionotropic, quick). AMPA/NMDA/kainate conduct Na^+, K^+, sometimes Ca^{2+} (these are excitatory, ionotropic glutamate receptors).
4. True. They can activate metabotropic receptors such as $GABA_B$ receptors and mGluRs (metabotropic glutamate receptors) which are GPCRs. These are examples of slow transmission.
5. Not always. Acetylcholine is fast at the NMJ but slow elsewhere.
6. Basal forebrain: acetylcholine neurons responsible for cognitive function (attention and memory).
   Brainstem: Ach nuclei mediate arousal, sleep-wake
7. (a) ChAT: choline acetyltransferase, which makes Ach (acetylates choline)
   (b) VAChT: vesicular acetylcholine transporter, which transports into vesicles using the H+ antiporter
   (c) CHT: choline transporter 1, which re-uptakes transmitters into the pre-synaptic neuron
   (d) AChE: acetylcholinesterase: hydrolyzes Ach in the cleft. Common target of Alzheimer's drugs.
8. (a) For the catecholamines:
   Tyrosine $\rightarrow$ tyrosine hydroxylase $\rightarrow$ DOPA $\rightarrow$ DOPA decarboxylase $\rightarrow$ Dopamine $\rightarrow$ Dopamin $\beta-$hydroxylase $\rightarrow$ Norepinephrine $\rightarrow$ N-methyltransferase $\rightarrow$ epinephrine
   (b) For serotonin:
   L-tryptophan $\rightarrow$ oxidation to 5-hydroxyl-L-tryptophan $\rightarrow$ decarboxylation to serotonin
   (c) For histamine: histidine gets decarboxylated.
9. (a) VMAT2: vesicle monoamine transporter, transports into vesicles
   (b) DAT/NET/SERT: Dopamine active transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT); transmitter re-uptake
   (c) MAO: Monoamine oxidase, oxidizes (break down) monoamines in the presynaptic cell
10. Neuromodulators
11. Movement, cognition, reward, motivation
12. Ventral tegmental area $\rightarrow$ mesolimbic pathway or mesocortical pathway
    Substantia nigra $\rightarrow$ nigrostriatal pathway
13. Striatum, substantia nigra pars compacta (SNc), and VTA
14. Expression of TH (tyrosine hydroylase, **the rate limiting step in DA synthesis**) and DAT.
15. L-DOPA, which is the precursor to dopamine.
16. Brainstem serotonergic nuclei: **Raphe nuclei** (RN)
17. It is important for affective behavior and mood.
18. (a) Prozac inhibits serotonin reuptake via SERT/5-HT
    (b) p-chlorophenylalanine inhibits synthesis by preventing tryptophan $\rightarrow$ 5-hydroxy tryptophan
    (c) Reserpine interferes with vesicle storage
    (d) Phenelzine inhibits MAO

19. Co-release is releasing different neurotransmitters from the same vesicles, whereas co-transmission means different neurotransmitters in separate vesicles (differentiated by different sensitivity to calcium or axon terminals are spatially segregated).
    Anyway, someone used optogenetic stimulation of dopamine neuron axon terminals. They realized there was a net outward current with V_m at 0 mV and a small inward current at -70 mV. They inhibited $GABA_AR$ and the outward current stopped, although the inward remained. Additionally inhibiting the AMPA/NMDA receptors stopped the inward current. So clearly more than one neurotransmitter was being released at the dopamine axon terminal.

20. Opioids, corticotrophin-releasing hormone, β-endorphin, oxytocin.

21. Regulate eating, sleeping, sexual behavior, stress response, pain perception

22. Neuropeptides are proteolytically cleaved from precursor proteins in the secretory pathway. They are packaged into dense core vesicles that bud off the Golgi and delivered quickly to the presynaptic terminal. **They cannot be synthesized or recycled in the axon.** They are usually **co-released** from neurons that use a small-molecule neurotransmitter.

Chapter 2

Ionotropic Receptors

2.1 Questions

1. Difference in structure between ionotropic and metabotropic receptors?
2. What determines the actions of a neurotransmitter on a post-synaptic neuron?
3. Classes of ionotropic receptors?
4. Describe the acetylcholine receptor. (4)
5. Describe the $GABA_A$ receptor. (5)
6. Describe the ionotropic glutamate receptor (3). What are some examples?
7. Describe the AMPA receptor (4)
8. Describe the AMPA receptor subunits (2)
9. Describe NMDA receptors. (5)
10. Why is the NMDA receptor called a coincidence detector?
11. Make sure you understand the IV plot on slide 17 of lecture on 10/1.
12. What is special about the GABA-A receptor subunits?
13. How do AMPA and NMDA work together?
14. True or false: AMPA and NMDA receptor subunit composition is NOT highly conserved across neurons and time.

2.2 Key

1. Ionotropic are ligand-gated ion channels. Metabotropic have 7 transmembrane spanning domains.
2. The identity of the receptor and its specific subunit composition.
3. (a) AchR, $GABA_AR$, GlyR, 5-HT_3R: 4 membrane spanning domains per subunit. In total, there are 5 subunits with 2 neurotransmitter binding sites.
   (b) Ionotropic glutamate receptors: 3 membrane spanning domains per subunit. In total, 4 subunits with 4 neurotransmitter binding sites.
4. (a) Pentamer: Two alpha, one beta, one delta, one gamma.

(b) Permeable to Na^+ and K^+, although far more permeable to inward sodium flux at resting potential.

(c) Two molecules of Ach are required for channel opening. They bind **between the alpha1/delta subunits and between the alpha2/gamma subunits.**

(d) Strongly activated by nicotine, esp nicotinic acetylcholine receptors

5. (a) Pentamer consisting of two alpha, two beta, and one gamma subunit

(b) Permeable to Cl^-

(c) GABA binding causes inward chloride current and hyperpolarization/shunting.

(d) Benzodiazepines and barbiturates positively regulate $GABA_A$-R function. Benzodiazepine and barbiturates bind in the alpha subunit.

(e) Note that this is distinct from the $GABA_B$ receptor which is metabotropic.

6. (a) Amino acid terminal domain (ATD) on top

(b) Ligand (glutamate) Binding Domain (LBD) in the middle

(c) Transmembrane domain (TMD) with subunits preM1, M1, M2, M3, M4 in the membrane. C-terminus is attached to M4 and is located within the cell.

(d) Examples include AMPA, Kainate, and NMDA receptors

7. (a) Permeable to Na^+ and K^+, sometimes calcium

(b) Glutamate binding causes inward sodium current and depolarization

(c) **Mediates the majority of fast synaptic transmission in the brain** and CNS.

(d) Note that these are distinct from mGluR's, the metabotropic analog of these glutamate receptors

8. (a) AMPA receptors are usually hetero-tetramers (4 subunits) of two or more subunits: GluA1, GluA2, GluA3, GluA4. (can also form homomers).

(b) **GluA2-containing AMPA receptors are impermeable to calcium if they have been edited. Normal is gluatmine (Q), mutated is R (arginine)**.

9. (a) Permeable to Na^+, K^+, and $\mathbf{Ca^{2+}}$ (in fact, it's HIGHLY permeable to calcium)

(b) Glycine binding is required for opening (co-agonist)

(c) Channel opening is voltage-dependent. It requires **depolarization and removal of $\mathbf{Mg^{2+}}$ block** (it's removed through depolarization)

(d) Glutamate binding causes inward sodium and calcium depolarization currents.

(e) Usually hetero-tetramers of two GluN1 (aka NR1) subunits that have glycine binding sites and GluN2 (NR2) subunits that have glutamate binding sites. GluN2 has 4 variants: GluN2A, GluN2B ... up to D.

10. It's called a coincidence detector because it requires glutamate binding AND depolarization.

11. At low membrane potentials, the inward current of sodium in channels without the Mg block is much greater than those channels with the block.

12. GABA-A receptor subunits are differentially expressed in different brain regions.

13. At resting potential, only AMPA can be activated by glutamate alone. Sodium rushes in, depolarizes the membrane, removes the Mg block on NMDA, and then NMDA lets in sodium and calcium.

14. This is true. Subunit composition differs in different neurons, undergoes developmental changes, and can be regulated by synaptic activity.

Chapter 3

Metabotropic receptors and GPCR signaling

3.1 Questions

1. Name some types of GPCRs. (9)
2. Types of G-proteins and effectors?
3. How does the muscarinic acetylcholine receptor (mAChR) work?
4. Describe the cAMP pathway of GPCRs.
5. G_s vs G_i proteins
6. True or false: ligand-bound receptors can interact with a wide variety of G proteins.
7. What does cAMP do? How is it regulated?
8. How does a single neurotransmitter exert long-term effects?
9. Describe the PLC secondary messenger cascade.
10. What types of neurotransmitters use the PLC cascade?
11. If something is modulatory, is it more likely to be ionotropic or metabotropic?

3.2 Key

1. (a) **Odorant receptors**
   (b) **Rhodopsin**
   (c) Dopamine receptors
   (d) Norepinephrine receptors
   (e) Serotonin receptors
   (f) Muscarinic acetylcholine receptors
   (g) mGluRs
   (h) $GABA_B$ receptors
   (i) Neuropeptide receptors
2. (a) cAMP system

(b) Phosphoinositol system

(c) Direct G protein-gating

3. Direct G Protein gating.

   (a) Activation by Ach causes the G protein complex to release GDP and bind to GTP.

   (b) Then it dissociates and the beta/gamma heterodimer binds to a GIRK (G protein-coupled inward-rectifier K^+ channel)

   (c) This leads to K^+ efflux and hyperpolarization of the muscle cell

   (d) This leads to decreased muscle contraction and reduced heart rate.

4. (a) Neurotransmitter binds to receptor

   (b) G-protein binds to receptor and GTP-GDP are exchanged

   (c) Alpha subunit dissociates with GTP attached

   (d) Alpha subunit binds to adenylyl cyclase and makes cAMP, which then does other things.

   (e) GTP is hydrolyzed and G-protein is reassembled.

   (f) Neurotransmitter dissociates and the cycle stops.

5. G_s make cAMP and G_i inhibit cAMP production.

6. True.

7. It activates protein kinase A (PKA). Specifically **four** cAMP molecules bind to the two regulatory subunits of PKA which liberates two catalytic subunits which are then free to phosphorylate serine or threonine residues on certain proteins.
   cAMP is regulated by phosphodiesterase and protein phosphatases. Phosphodiesterase converts cAMP to AMP (inactve) and the phosphatases de-phosphorylate the proteins.

8. After PKA is activated, it can phosphorylate a channel to modify synaptic potential. The kinase can then translocate to the nucleus and phosphorylate transcription factors that turn on gene expression for receptors and channels. Then because of the increased amount of protein, the synaptic actions are prolonged.

9. (a) Neurotransmitter activates receptor

   (b) Receptor activates G_q, a variant of G alpha

   (c) G_q-GTP activates PLC which converts PIP_2 to DAG and IP_3.

   (d) IP_3 activates IP_3 receptor on ER membrane, which causes calcium to rush into the cytoplasm

   (e) DAG + calcium co-activate PKC. Calcium also activates calmodulin and CaM kinases.

10. ACh, glutamate, or serotonin.

11. Usually we say that metabotropic/slow synaptic transmission is modulatory.

Chapter 4

Dendrites and Spines

4.1 Questions

1. What is special about dendritic spines?
2. True or false: dendritic spines can only connect to one presynaptic terminal.
3. True or false: spines and synapses can be formed and removed.
4. What is a technique by which one can measure the strength of single synapses?
5. Rank the size/shape of dendritic spines by their EPSC strengths. Why do they have different EPSC's?
6. What is the PSD?
7. What are the molecules that keep the synapse together?
8. What are TARPs?
9. What is PSD-95?
10. Which protein is responsible for the structure of the dendritic spine?
11. Which has simpler post-synaptic specialization? Inhibitory synapses or excitatory?
12. Describe the shunting effect
13. How are synaptic inputs strategically placed?

4.2 Key

1. They are the sites of excitatory synapses.
2. False: they can connect to one or more terminals, from either the same cell or from multiple cells.
3. True
4. 2-photon glutamate uncaging. It allows **spatially and temporally** precise activation of post-synaptic glutamate receptors. You can uncage by using laser light.
5. Filopedia (small to no EPSC), stubby, thin, mushroom (large EPSC). They have different AMPA receptor concentrations.
6. Post-synaptic density. It contains many proteins that provide structure and regulate synaptic signaling. There are 5600 protein copies of CaMK2, 400 PSD-95, 60 of AMPAR and NMDAR each, for example. 30 cadherin, 20 mGluRs

7. Cadherin, neurexin, neuroligin. These are synaptic adhesion molecules
8. Transmembrane AMPAR regulatory proteins. They regulate AMPA receptor trafficking and stability.
9. Post-synaptic density protein 95. It is a scaffolding protein that forms a tight structure and regulatory network in PSD. It keeps CamK2 close to the membrane, among other things.
10. F-actin.
11. Inhibitory synapses have simpler specialization.
12. If excitatory and inhibitory inputs are received at the same time, then the depolarized potential from the EPSP will increase the driving force for Cl^- and this will automatically counteract the depolarization. Alternatively, you can consider the equation $V_{EPSP} = \frac{I_{EPSP}}{g_{total}}$. Since conductance increases when the chloride channels are open, the change in voltage (depolarization) is smaller than usual.
13. Excitatory inputs are on dendritic spines. Inhibitory synapses and modulatory synapses (Ach, DA) are on dendritic shafts, the cell body, pre-synaptic terminal. Inhibitory synapses are additionally located in the axon initial segment (SIZ).

Chapter 5

Learning and Memory

5.1 Questions

1. Working memory is what type of memory? What about spatial? Habituation?
2. What is special about HM?
3. What is the main hypothesis regarding the way we learn?
4. Some concrete ways in which synaptic plasticity might occur?
5. What is required to demonstrate that plasticity has occurred? How is plasticity defined?
6. True or false: the effects of LTP can be different depending on the type of synapse.
7. Properties of LTP
8. What makes LTP a suitable mechanism for learning?
9. What hippocampal pathway is LTP associated with?
10. What is the definition of a Hebbian synapse?
11. What is responsible for LTP induction?
12. What exactly is Hebb's rule?

5.2 Key

1. Working memory is explicit and short-term. Spatial memory is explicit and long-term. Habituation is implicit and short-term.
2. We know that the hippocampus is essential for the acquisition of new explicit memories because of him. However, implicit learning and prior memories were intact.
3. Memory is stored as strengths of synaptic connections in neural circuits. Learning alters the weights of connections based on experience. Synaptic matrices transform specific input patterns (events) into specific output patterns (recall).
4. Increase in pre-synaptic release, increase in post-synaptic release, growth of new synapses between A and B.
5. The same input must produce different outputs before and after learning. Plasticity is defined as changes to the strengths of synaptic connections in response to experience and neuronal activity.

6. True. The effect of LTP at each synapse can be distinguished by its signature molecular mechanisms. Note however that LTP has been observed at all excitatory synapses in the hippocampus and in many other parts of the nervous system.

7. (a) Input specificity: only synapses that have been strongly activated will undergo LTP. No neighboring synapses will change.
   (b) Cooperativity: LTP occurs when the presynaptic cell fires a (weak) stimulus and the postsynaptic cell is already depolarized.
   (c) Associativity: Usually associated with **back-propagating signals**. Basically when the timing of a weak stimulus coincides with a strong stimulus, the strong stimulus will produce local depolarization will then cause the weak stimulus to induce LTP through cooperativity.

8. Input specificity ensures that only inputs that convey information about a given event will participate in that memory. Cooperativity ensures that only events of high significance will result in memory storage. Associativity makes it possible for coincident inputs to influence each other's strengths.

9. Schaffer collateral pathway

10. A Hebbian synapse is a synapse whose strength can be enhanced by co-activating pre- and postsynaptic partners.

11. The NMDA receptor is responsible for LTP induction. It is involved in a key form of LTP at the CA3− >CA1 synapse and in the Morris water maze learning experiment (spatial memory, since the hippocampus is important for spatial memory).

12. When a presynaptic cell repeatedly fires a postsynaptic cell, a "growth" process will occur that strengthens their connection through long-term potentiation.

Chapter 6

Molecular Basis of LTP

6.1 Questions

1. How does LTP induction occur?
2. How is post-synaptic LTP expressed?
3. How does CamKII exhibit "molecular memories"?
4. What post-synaptic changes in AMPAR expression occur during LTP?
5. What is a silent synapse?

6.2 Key

1. AMPA currents relieve the magnesium blockade on NMDA. Since NMDA is selectively permeable to calcium (and sodium and potassium) this calcium will trigger **CamK2, PKC, and tyrosine kinase Fyn** which leads to LTP induction. These active kinases can:
   (a) Phosphorylate AMPA receptors and other proteins in PSD
   (b) Cause synthesis and release of retrograde messengers that modulate pre-synaptic release probability.
2. *Post-synaptic LTP expression:* The net effect is increased trafficking, stabilization, and/or activity of AMPA receptors at the synapse, which leads to greater EPSP in response to the same stimulus.
   Post-synaptic LTP expression: The net effect is enhanced neurotransmitter release
3. CamKII has 12 subunits, each of which has a catalytic domain and auto-inhibitory domain. Binding of Ca^{2+}/calmodulin transiently displaces the inhibitory domain and activates that subunit. If a sufficient number of subunits are active in response to prolonged calcium elevation, then neighboring subunits phosphorylate each other at T286, which allows CamKII to remain active even after calcium levels have returned to baseline.

   If you mutate this auto-phosphorylation site T286, LTP is disrupted. Mutating T286A in CA1 hippocampal neurons makes the Morris water maze performance really bad because it blocks LTP and therefore spatial learning.
4. More AMPA receptors through exocytosis, then AMPAR stabilization through phosphorylation. **Stargazin** is an AMPAR binding protein which is phosphorylated and allows it to bind to PSD95, which immobilizes AMPAR at the synpase. Furthermore, GluR1 S831 subunits are phosphorylated which allows **each individual** receptor to have higher conductance.
5. A silent synapse is an NMDA-only synapse.

Chapter 7

Late-LTP and Synapse-to-Nucleus Signaling

7.1 Questions

1. Some characteristics of early LTP?
2. Some characteristics of late LTP?
3. If you feed a neuron a protein synthesis inhibitor and gene transcription inhibitor, which would cause a neuron's E-LTP to fall off faster? What about L-LTP?
4. Can LTP be induced in dendrites that have been severed from the soma?
5. What does late LTP require?
6. What is the full pathway of late LTP?
7. What happens after CREB-1 is phosphorylated?
8. What activates late response genes? What about early response genes?
9. Examples of IEGs
10. What happens if you mutate CBP?
11. What is a common application of IEGs in *in vivo* experiments?
12. How can you create a false memory?

7.2 Key

1. Early ETP is induced by one train of high frequency stimulation, and the effect lasts for a few hours. It requires protein kinase signaling (i.e., CamK2) and AMPAR trafficking but **does not require new gene transcription or protein synthesis.**
2. Late LTP is induced by multiple trains of stimuli and lasts > 3 hours. It requires **PKA signaling, gene transcription, and new protein synthesis.** L-LTP often involves structural changes to the synapse and/or the formation of new synapses.
3. E-LTP is insensitive to inhibitors of translation or transcription. For L-LTP, the protein synthesis inhibitor would cause LTP to fall off faster.

4. Yes. In L-LTP, local protein synthesis AND gene transcription both lead to changes. The local protein synthesis continues even if there is no gene transcription going on.
5. PKA signaling. Specifically, adenylyl cyclase to cAMP to PKA to CREB to gene transcription.
6. (a) Ca influx through NMDA receptors
   (b) Ca influx through voltage gated Ca channels
   (c) Ca release from the ER
   (d) Ca binds to calmodulin
   (e) Ca bound calmodulin activates a) Cam Kinases (CamK2 in the dendrites, CamK4 in the nucleus) b) Ras $->$ MAP kinase cascade (aka ERK) c) Calcium activated adenylyl cyclase $->$ PKA
   (f) Phosphorylation of CREB and other transcriptional regulators
   (g) Transcription of activity-regulated genes
7. (a) CREB binding protein (CBP) is recruited to the promoter of target genes.
   (b) CBP acetylates certain positively charged lysine residues on histones' N-terminus
   (c) Acetylation loosens binding of DNA to histones
8. Immediate early genes (IEGs) are activated by **CREB**. Late response genes are activated by ***Fos***.
9. **cfos**, Egr1 (transcription factor), BDNF (neurotrophin), Arc (cytoskeletal protein at the PSD)
10. Mutations in CBP prevent late-LTP and long-term memory
11. IEGs are the first genes activated in response to activity and so they can be used to identify recently active neurons
12. Artificially activate a population of cells that was active during contextual fear conditions

Chapter 8

Long-Term Depression and Spike Timing

8.1 Questions

1. What type of receptors are implicated in LTD?
2. What type of stimulation induces LTD?
3. What is a crucial part of the induction of NMDAR-LTD?
4. Expression of LTD is via? What is the molecular basis for this expression?
5. Explain the general phenomenon of spike-dependent plasticity.
6. Why do back propagating action potentials even exist?
7. What is the molecular basis for STDP.

8.2 Key

1. NMDA are required for LTD
2. Low-frequency stimulation
3. The activation of protein phosphatases is essential to LTD. Specifically, protein phosphatase 2A (PP-2A). Mice have trouble "unlearning" if this is mutated
4. Expression of LTD is basically just removing AMPAR from the synapse. Receptors are dephosphorylated and then endocytosed if there is low-frequency stimulation.
   The reason this happens is that low frequency stimulation causes moderate, sustained calcium influx that preferentially activates protein phosphatases (LTD). However, high frequency stimulation causes brief, large calcium influx which preferentially binds protein kinases.
5. STDP is induced by pairing a single presynaptic stimulus with the firing of AP in postsynaptic cell. The paring produces LTP if the post synaptic cell fires a few milliseconds AFTER the presynaptic cell. If the post-synaptic cell fires first, then this induces LTD.
6. They exist because the dendrites have sparse Na channels. But there are still channels that can open when the soma is stimulated.

7. LTP: the EPSP and bAP converge and cause NMDA to be super activated with lots of calcium influx. NMDARs are maximally activated when glutamate binding precedes removal of Mg block
   LTD: bAP has already decayed a little by the time the glutamate is released, generating a weaker calcium signal. Sometimes bAP even inactivates NMDARs briefly.

Chapter 9

LTP/LTD Review

9.1 Questions

1. Describe the signaling mechanisms of hippocampal mGluR-LTD.
2. Describe Fragile X Syndrome?
3. What phosphorylates FMRP and what de-phosphorylates it?
4. What does DHPG do?
5. What do we see in Fmr1 knockouts when we put DHPG in?
6. Timeline of NMDAR-dependent early LTP?
7. Timeline of NMDAR-dependent late LTP?
8. Timeline of NMDAR-dependent LTD?
9. Removing Mg first then glutamate binding produces a weaker or stronger signal then binding glutamate first and then removing Mg.
10. Knocking out which gene will disable the growth of dendritic spines?
11. How does dopamine affect spine growth? What type of receptors make this happen? How does the location of that type of receptor relate to its function?
12. What is one thing that LTD-associated spine shrinkage depends on?

9.2 Key

1. mGluR activated $->$ Removes FMRP block on Arc mRNA $->$ Synthesis of Arc protein $->$ Arc protein stimulates endocytosis of AMPA receptors
2. Fragile X is the most common cause of inherited intellectual disability among men. Autistic behaviors. It is caused by mutations resulting in silencing of Fmr1 which encodes FMRP. Without Fmr1 there is an increased number of dendritic spines.
3. S6 kinase phosphorylates it. PP2A de-phosphorylates.
4. DHPG activates mGluRs.
5. We see more exaggerated mGluR-LTD. There is less repression of Arc protein synthesis, and therefore more removal of AMPA receptors. This is detrimental to brain function.

6. (a) Coordinated pre- and post-synaptic activity (a few STDP-LTP or one LTP) OR high frequency pre-synaptic activity causes removal of Mg block and activation of NMDA receptors.
   (b) Strong activation of NMDARs produces large Ca signal
   (c) High Ca activates CamK2. CamK2 phosphorylate AMPARs and scaffolding proteins which promotes insertion, stabilization, overall increased conductance of AMPARs. **Spine can even grow in size**.
   (d) These same mechanisms can cause activation of silent synapses via insertion of AMPARs.
7. (a) Multiple high frequency trains (LTP) or many pre-post pairings (STDP-LTP). If the Ca signal from the previous question is high enough, it can cause autophosphorylation of CamK2 subunits which allows CamK2 to still be active after Ca signal has decayed
   (b) In response to large Ca signal other pathways are activated, leading to local translation at the synapse
   (c) When activity at the synapse/depolarization is high enough, then internal Ca stores in the ER and voltage-gated calcium channels are activated. Even more Ca comes in
   (d) This large Ca travels to cell body and activates **MAPK/Rsk signaling and CamK4**.
   (e) Ca activates adenylyl cyclases which produce cAMP and activate PKA.
   (f) PKA and other kinases enter nucleus and phosphorylate **CREB**. CREB binds to CBP and CRE elements in promoters of IEGs
   (g) CREB stimulates transcription of IEGs including cfos which activates transcription of other genes
   (h) mRNAs of these genes are trafficked to dendrites or made into proteins at cell body. These proteins can then be used to make new synapses.
8. (a) Evoked by prolonged low frequency stimulation or STDP-LTD. Low level activation of NMDA receptors
   (b) This weak activation produces small to medium Ca signal at synapse
   (c) Low/medium levels of Ca preferentially activate protein phosphatases including PP2A, PP1.
   (d) Phosphatases dephosphorylate AMPARs and scaffolding proteins to promote endocytosis of AMPARs from the PSD. *No further signaling events are needed to keep the synapse in a depressed state
   (e) Weakened synapses can also physically shrink and may be permanently removed.
9. Removing Mg first then glutamate binding produces a **weaker** signal. This is basically STDP-LTD
10. Blocking NMDA channels will prevent growth. CamK2, PKA and protein synthesis are also important.
11. Dopamine boosts spine growth. D1 receptors are responsible for this boost. D1R's are coupled to G_s which activate adenylyl cyclase, increase cAMP and increase PKA activity. D2R's activate G_i which inhibit AC, decrease cAMP, and decrease PKA activity.
    The D1 receptor is located on the side of the post-synaptic terminal. The hypothesis is that if there's a bunch of dopamine then some will diffuse out of the cleft and interact with the D1 receptor, signaling for growth. We don't want growth when normal stimulation occurs, so that's why the transporter is on the side.
12. NMDA receptors

Chapter 10

Homeostatic Plasticity

10.1 Questions

1. A single synapse can change strength. What's the key word associated with changes to a whole neuron or neural network?
2. When does homeostatic plasticity kick in?
3. What is the purpose of homeostatic plasticity?
4. Some ways in which you can alter homeostatic plasticity?
5. How should a graph of pA amplitude vs % mEPSCs look with reduced/increased neural activity? (x-axis going from 0 to negative amplitude pA).
6. How does synapse scaling preserve differences in synaptic weights?
7. What is a QUICK way to increase activity in a neuron?
8. What protein is crucial to homeostatic plasticity?
9. What happens to a neuron if you overexpress its Kv channels?
10. How does the SIZ change in homeostatic plasticity?

10.2 Key

1. **Homeostatic plasticity. Changes in the input/output function.** The ultimate goal is to maintain stable activity levels
2. When neurons are firing outside their preferred firing range for a long period of time.
3. Homeostatic plasticity preserves stable information transfer in neural networks.
4. (a) Number of GABA receptors
   (b) Number of AMPA receptors
   (c) Number of depolarizing ion channels
   (d) Number of hyperpolarizing channels
   (e) Pre-synaptic release probability
5. The reduced activity neuron is shifted to the right. The increased activity neuron is shifted to the left.

6. Multiplicative scaling occurs across all synapses in a neuron, which preserves differences in synaptic weights.

7. Use inhibitor of $GABA_A$ receptors to reduce inhibition. Transcription of more AMPARs might take too long.

8. Arc. Arc mRNA and protein levels jump thousands-fold in response to over-excitation. Instead of just local translation, gene expression is modulated at the nucleus level. AMPA receptors and receptor subunits are endocytosed in response to excitation.

9. The number of sodium channels increases to compensate and the neurons still fire at action potentials at close to the normal rate.

10. Distance from the soma can be increased/decreased (farther away = less excitable), length of the SIZ region can be lengthened (more length = more excitability).