Neuropsychopharmacology Notebook

Neurotransmitters

Neurotransmitters have low molecular weight and are usually amines or amino acids
Amines include

- Monoamines
  - Serotonin
  - Dopamine
  - Norepinephrine or epinephrine
- Acetylcholine
- Histamine

Amino Acids

- GABA
- Glutamate
- Orexins a and b

Monoamines require energy for the transport of them, through a sodium pump. Presynaptic reuptake transporters are a major method of an in activation for serotonin and gaba

Constitutive activity is a signal transduction when no agonist or inverse agonist is bound to the receptor.

Classical Neurotransmission: occurs when asymmetric, presynaptic to postsynaptic A neurotransmitter begins with electrical process, sends impulses from one part of the cell to another part of the same cell via other axons electrical impulses do not jump directly to other neurons.

Communication between neurotransmitters at synapses are chemical. Electrical impulses in the first neuron is converted to a chemical signal at the synapse between first and second neuron in a process known as excitation secretion coupling. This is the first stage of neuro transmission.

Communication with neurons is electrical, but communication between neurons *is chemical*

Retrograde Neurotransmission: (bottom to the top)

- post synaptic can talk back to presynaptic.
- Can make post sematic side make nitric oxide (gas in your brain) which goes to presynaptic.
- Cannabinoid receptors make endocannabinoids send to presynaptic and regulate neurotransmission
- MGM

Volume neurotransmission: It is without a synapse or non synaptic. when a type of neuro talks to multiple receptors. “cell phone”. Chemical puff that stimulates all receptor sites in a certain radius. Ex. Dopamine in the prefrontal cortex

Receptors that are presynaptic, neurotransmitters can leak out of the presynaptic area, without a synapse, there are receptors for it.

Signal Transduction cascades
Passes from one to the other

- First messenger ->
- second messenger (can be an ion, they go into the cell)->
- third messenger (kinase, or phosphatase or calcineurin) ->
    - put phosphate on critical proteins
    - wake up ligand gated ion channel, regulatory enzymes, voltage channel
- fourth messenger (ex. Phosphoprotein, will be phospholated or de-phospholated)

As sodium flows into the presynaptic nerve through NA channels and the axon membrane, the electrical charge of the axon potential moves along the axon until it reaches this presynaptic nerve terminal, where it also opens calcium channels. As calcium flows into the presynaptic nerve terminal, it causes synaptic vesicles.

Anchor to the inner membrane to spill into their chemical contents, into the synapse signal, transduction, cascades. They are communication from genome of presynaptic neuron to the genome of the post-synaptic neuron. And back from the genome of the post-synaptic neuron to the genome of the presynaptic neuron.

So cascades have to do have to be involved with genomes or genetic.

Four families that signal transduction cascades

- G-protein (allows you to form second messengers
    - G protein link system include the neurotransmitter, the Gprotein link neurotransmitter receptor, a G protein and an enzyme
- Ion channel linked neurotransmitters (works through calcium) allows gene expression
- Hormone nuclear receptor complex
- Growth factors (ex. Ketamine causes neurotropic factors, creates neurons in 20 min, or psychedelics which sprouts neurons)

Gene activation

- Protein kinase may go into the cell nucleus, and can invade the gene
- Transcription factor turns on enhancer or promoter which turns on the gene. The direct role of transcription factors as to what it influences gene transmission
    - Turn on with protein kinase send it a phosphate
    - RNA polymerase activated, then gene activated
- Early genes activate the late genes
- sixth messenger.
    - Activate the late gene
        - Growth factor
        - Enzyme
        - Receptor

Epigenetics

- A heritable trait that results from a change in gene expression
- Activation or silencing of normal genes at the same time.
- Methyl group on DNA will make it quite
    - Methyl group makes histone quiet
- Histone is a type of protein which wraps around DNA. This activate or silence
- Acetylated histone can turn on a gene

- Demethylation can activate a gene
- Chromatin is the name of the wrapped around DNA and histone

RNA
DNA is the gene, transcription leads to RNA, then proteins are made
DNA to RNA to RNA interferences are small shRNA, exportin can interfer with protein creation
Dicer breaks RNA apart, then RISC make it so the RNA cannot make a protein

The five molecular targets of psychotropic drugs

- Twelve transmembrane region transporter 30% of psychotropics
    - Presynaptic neuro presynaptic terminal
        - Serotonin transporter (SERT)
            - Can also transport ecstasy (MDMA)
        - Norepinephrine transporter (NET)
            - Can also transport dopamine, epinephrine, and amphetamine
        - Dopamine transporter (DAT)
            - Can also transport norepinephrine, epinephrine, amphetamine
        - GABA transporter (GAT)
        - Glycine transporter (GlyT)
        - Excitatory amino acid transporter (EAAT)
    - Inside the cell
        - Vesicular monoamine transporter (5HT, NE, DA, HA).
        - Vesicular acetylcholine transporter (Ach)
        - Vesicular inhibitory amino acid transporter (GABA)
        - Vesicular glutamate transporter (glutamate)
- Seven-transmembrane region G-protein linked 30% psychotropic drugs

Key G-Protein-Linked Receptors Directly Targeted by Psychotropic Drugs

Neurotransmitter	Receptor subtype directly targeted	Pharmacological action	Therapeutic action
Norepinephrine	Alpha 2	Antagonist	Antidepressant
		Agonist	Improved cognition and behavioral disturbance in ADHD
	Alpha 1	Antagonist	Improved sleep (nightmares) Improved agitation in Alzheimer's disease Side effects of orthostatic hypotension and possibly sedation
GABA	GABA-B	Agonist	Cataplexy Sleepiness in narcolepsy Possible enhanced slow-wave sleep Pain reduction in chronic pain and fibromyalgia Possible utility for alcohol use disorder and alcohol withdrawal
Melatonin	MT1	Agonist	Improvement of insomnia and circadian rhythms
	MT2	Agonist	Improvement of insomnia and circadian rhythms
Histamine	H1	Antagonist	Therapeutic effect for anxiety and insomnia Side effects of weight gain and sedation
	H3	Antagonist or inverse agonist	Improvement of daytime sleepiness

Key G-Protein-Linked Receptors Directly Targeted by Psychotropic Drugs

Neurotransmitter	Receptor subtype directly targeted	Pharmacological action	Therapeutic action
Dopamine	D2	Antagonist or partial agonist	Antipsychotic; antimanic
Serotonin	5HT2A	Antagonist or inverse agonist	Antipsychotic actions in Parkinson's disease psychosis Antipsychotic actions in dementia-related psychosis Reduced drug-induced parkinsonism Possible reduction of negative symptoms in schizophrenia Possible mood stabilizing & antidepressant actions in bipolar disorder Improve insomnia and anxiety
		Agonist	Psychotomimetic actions Experimental treatment of refractory depression and other disorders, especially accompanying psychotherapy
	5HT1B/1D	Antagonist or partial agonist	Possible procognitive and antidepressant actions
	5HT2C	Antagonist	Antidepressant
	5HT6	?	?
	5HT7	Antagonist	Possible procognitive and antidepressant actions
	5HT1A	Partial agonist	Reduced drug-induced parkinsonism Anxiolytic Booster of antidepressant actions of SSRIs/SNRIs

Key G-Protein-Linked Receptors Directly Targeted by Psychotropic Drugs

Neurotransmitter	Receptor subtype directly targeted	Pharmacological action	Therapeutic action
Acetylcholine	M1	Agonist	Procognitive and antipsychotic
		Antagonist	Side effects of sedation and memory disturbance
	M4	Agonist	Antipsychotic
	M2/3	Antagonist	Side effects of dry mouth, blurred vision, constipation, urinary retention May contribute to metabolic dysregulation (dyslipidemia and diabetes)
	M5	?	?
Orexin	OX1 OX2	Antagonist	Therapeutic effect for insomnia

- Enzymes 10% of psychotropic drugs
  - After a substrate binds to an enzyme, it is turned into a product which is then released from the enzyme
  - Ex. GSK-3 a possible target for lithium and other mood stabilizers
  - Lithium blocks the ability of the cells to kill themselves.
  - CYP450 cytochromes, lives in the gut and liver. This is the way the body degrades drugs.
- Four transmembrane region ligand gated ion channels 20% of psychotropic drugs
  - Agonist causes the channel to open more frequently
    - stop responding to an Agonist with three certain particular situations when the agonist stops binding to it, when the receptor becomes desensitized, and when the receptor becomes inactivated
  - The known receptor sites for ligand-gated ion channels are both inside and outside the cell.
  - Ligand is a neurotransmitter that ties to a gate next to an ion channel

Key ligand-Gated Ion Channels Directly Targeted by Psychotropic Drugs

Neurotransmitter	Receptor subtype directly targeted	Pharmacological action	Therapeutic action
Acetylcholine	α4β2-nicotinic receptors	Partial agonist	Smoking cessation
GABA	GABA-A benzodiazepine receptors	Full agonist, phasic inhibition	Anxiolytic
	GABA-A non-benzodiazepine PAM sites	Full agonist, phasic inhibition	Improves insomnia
	GABA-A neurosteroid sites (benzodiazepine insensitive)	Full agonist, tonic inhibition	Post-partum depression Rapid-acting antidepressant Anesthetic
Glutamate	NMDA NAM channels sites/Mg^{2+} sites	Antagonist	Procognitive in Alzheimer disease
	NMDA open channel sites	Antagonist	Dissociative hallucinogen Anesthetic Pseudobulbar affect Agitation in Alzheimer disease Rapid-acting antidepressant Treatment-resistant depression
Serotonin	5HT3	Antagonist	Procognitive Antidepressant Reduce chemotherapy-induced emesis

  - Pentameric ligand-gated ion channel

4 Transmembrane Regions, 5 Subunits

Neurotransmitter	Receptor Subtype
Acetylcholine	Nicotinic receptors (e.g., α7-nicotinic receptors; α4β2-nicotinic receptors)
GABA	GABA-A receptors (e.g., α1 subunits; γ subunits; δ subunits)
Glycine	Strychnine-sensitive glycine receptors
Serotonin	5HT3 receptors

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  - Tetrameric Ligand-gated ion channels

3 Transmembrane Regions, 1 Re-entrant Loop, 4 Subunits

Neurotransmitter	Receptor Subtype
Glutamate	AMPA (e.g., GluR1–4 subunits)
	KAINATE (e.g., GluR5–7, KA1–2 subunits)
	NMDA (e.g., NMDAR1, NMDAR2A–D, NMDAR3A subunits)

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    - Positive allosteric modulator PAM will keep the channel open. Ex. Benzodiazepines
    - Negative allosteric modulation
        - Both are only possible present in the presence of a neurotransmitters
- Six transmembrane voltage gated ion channels 10% of drugs
- Excitation coupling
    - Voltage sensitive sodium channel
        - Sodium always flows into the cell
        - Amino acids between channels 5 and 6 are filtered to only let sodium
        - You need four copies
        - Pore inactivator connects III and IV allows you to shut the channel fast for sodium
    - Voltage sensitive calcium channel
        - Voltmeter 4 detects charge
        - Amino acids between channels 5 and 6 are filtered to only let calcium
        - You need four copies
        -

Antagonists: of ion channels, reversed the action of agonists. They bring the receptor back to the resting.
Inverse agonist does the opposite of an agonist.

Signal Propagation from presynaptic postsynaptic neuron, a nerve impulse is generated a neuron A and the action potential is sent along the axon via voltage sensitive sodium channels until it reaches Voltage sensitive calcium channels, linked to synaptic vesicles full of neurotransmitters in the axon terminal. Opening of the voltage sensitive calcium channel causing calcium influx. Causes neurotransmitter release into the synapse arrival of a neurotransmitter of post synaptic receptors on the Dendrite of neuron B triggers depolarization of the membrane in that neuron and consequently post synaptic signal propagation.

Partial agonist: In the absence of a fill agonist they increase transductions. In the presence of a full agonist they will turn down the strength of various downstream signals.

The alpha 2 delta subunit of voltage-sensitive calcium channels is believed to help regulate opening and closing of the voltage-sensitive calcium channel. Propagation of an action potential to the axon terminal is mediated by voltage-sensitive sodium channels. Influx of sodium through voltage-sensitive sodium channels at the axon terminal leads to opening of voltage-sensitive calcium channels, also at the axon terminal. Influx of calcium through the open voltage sensitive calcium channels leads to docking of synaptic vesicles and secretion of neurotransmitter into the synapse.