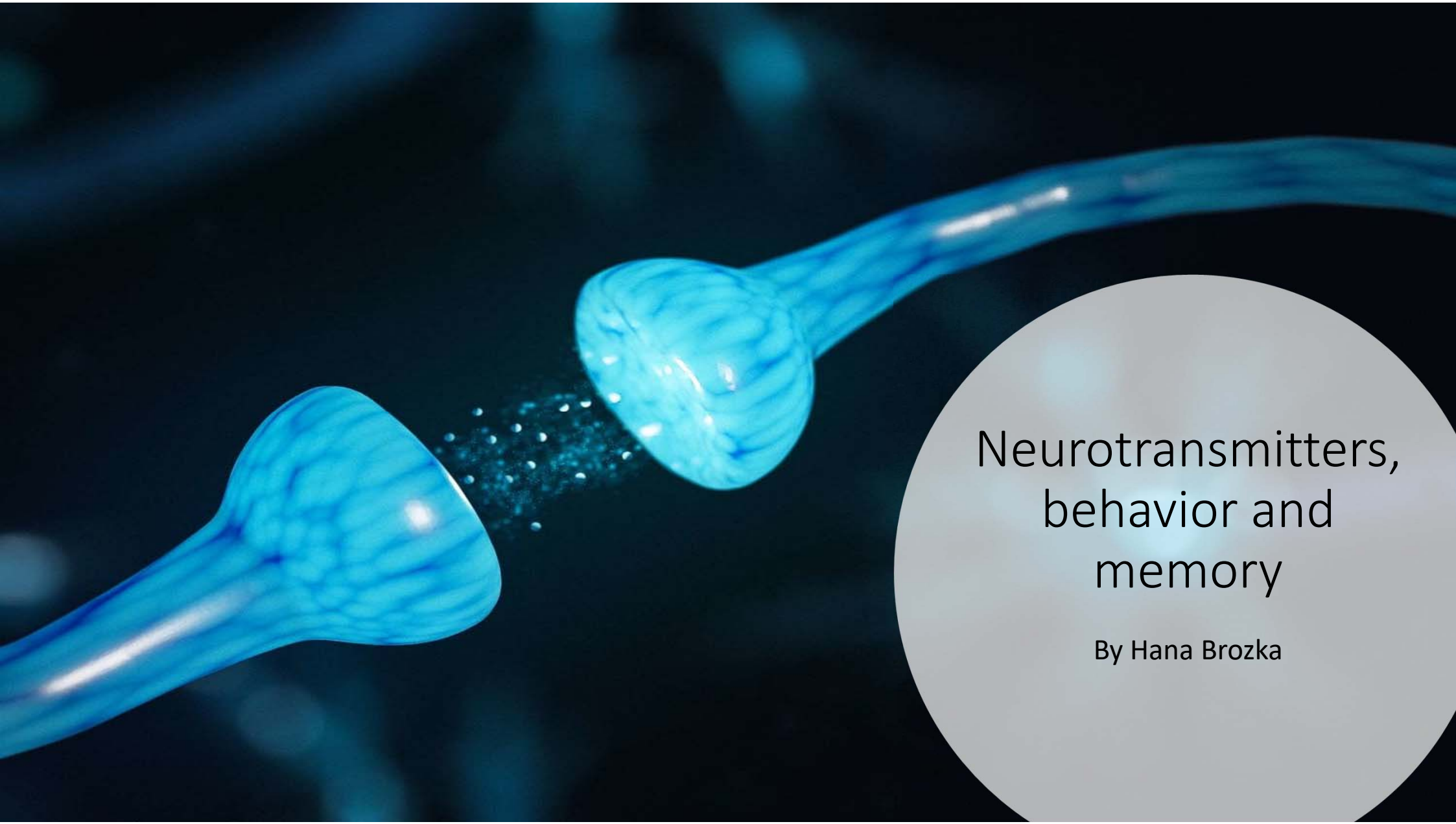


Neurotransmitters, behavior and memory

By Hana Brozka

Neurotransmitters and neuromodulators

- Chemical communication between neurons
- Neurotransmitter: neuron to neuron communication
- Neuromodulators: one neuron affects many other neurons
- Transfer of signal across synapse within CNS (but also outside: neuromuscular junction)
- Specific chemicals are released and bind to specific receptors
- Chemically heterogenous:
  - ester (acetylcholine)
  - monoamines (serotonin, melatonin, histamine)
  - catecholamines (dopamine, norepineprine),
  - amino acids (glutamate, GABA, glycine)
  - peptides (substance P, enkephalin, vasopressin)

We can interfere with this type of information transfer using drugs

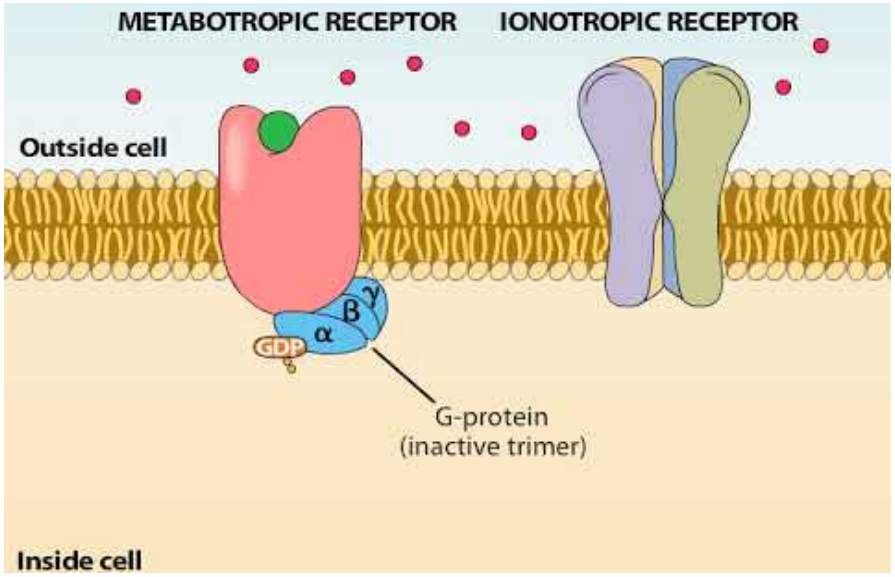
Neurotransmitter criteria

1. Transmitter must be present in the vesicles of presynaptic terminals
2. Sufficient quantity of transmitter must be released from the presynaptic nerve terminal concomitantly with nerve activity
3. Effect of experimental application of the transmitter should mimic the effect of stimulating the presynaptic nerve
4. If avaliable, specific agonists and antagonists should activate and block, respectively, the fuction of neurotrasmitter
5. There should be a mechanism present - reuptake or enzymatic degradation – that terminates action of the transmitter

Transmitters that do not meet the 'traditional' critteria (NO, retrograde diffusion increases neurotransmitter release from presynaptic terminal directly activates gunanylyl cyclase; d-serine: released from astorcytes, modulate NMDA function; canabinoids: retrograde signalling)

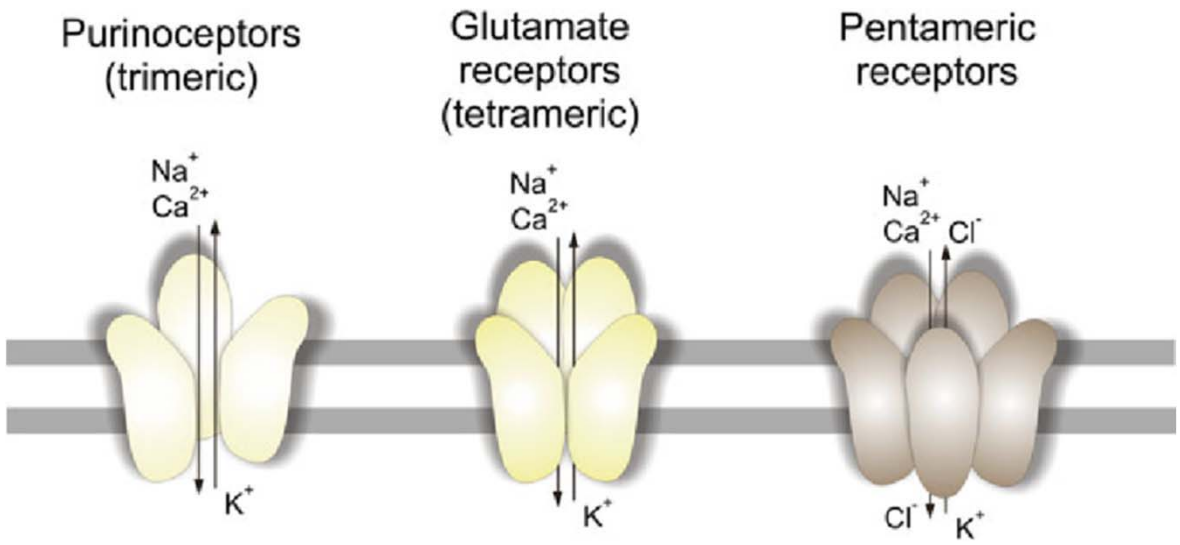
Neurotransmitter receptors

- Ionotrophic and metabotrophic
- Ionotropic
  - Receptor contains a ion channel
  - Directly affects membrane potential
- Metabotropic
  - Induces changes within neuron via G-protein
  - Slower effect
- With own enzymatic activity
  - Tyrosine kinase receptors



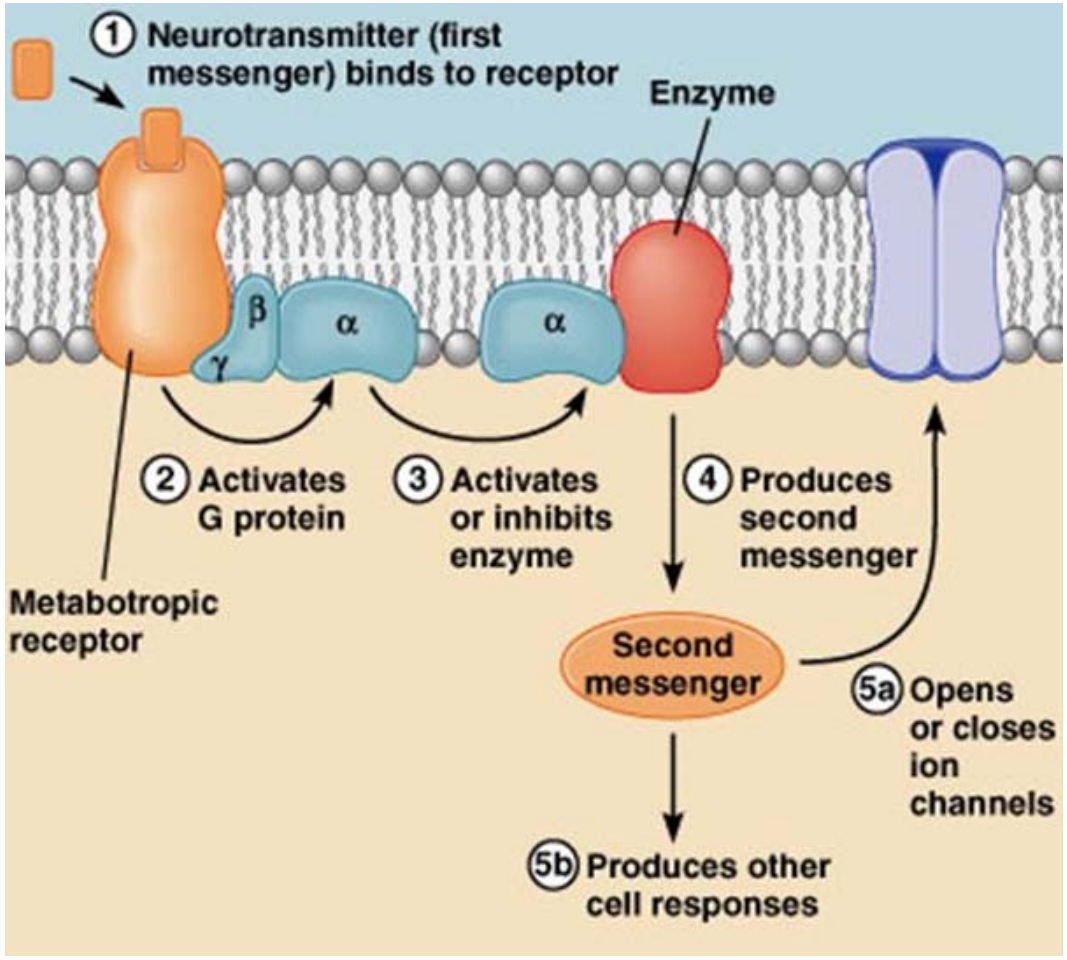
Ionotropic receptors

- Ligand regulated channels
- Binding of ligand induces conformation change
- Selective for certain anions and cations
- Trimers (ATP), tetramers (glutamate), pentamers (acetylcholine)
- Several binding sites



Metabotropic receptors

- G protein coupled receptors (GPCR)
- Binding of ligand activates signaling cascades by activating G-protein
- Inhibit (Gi) or activate (Gs) adenyl cyclase
- Gq: phospholipase C activation produces DAG and IP3
- End result: modulate ion channel opening probability, thus modulating cell excitability
- Neuromodulators are usually GPCR

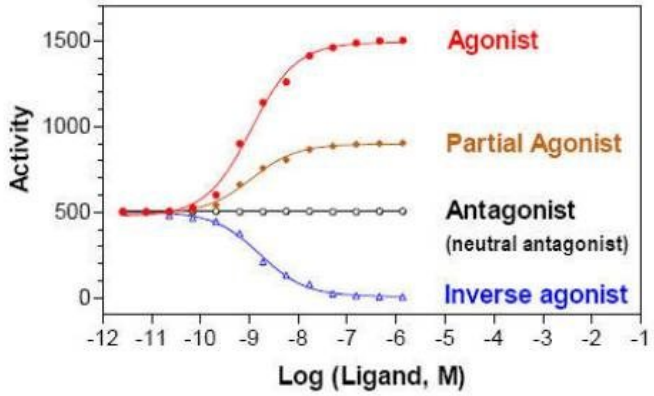


Receptor localization

- Synaptic
  - Postsynaptic
  - Presynaptic (includes autoreceptors)
- Extrasynaptic
  - Neuromodulators
- Intracellular
  - Neurostereoids (released from astrocytes)
  - Cortisol (from periphery)
  - NO (from proximal neurons)

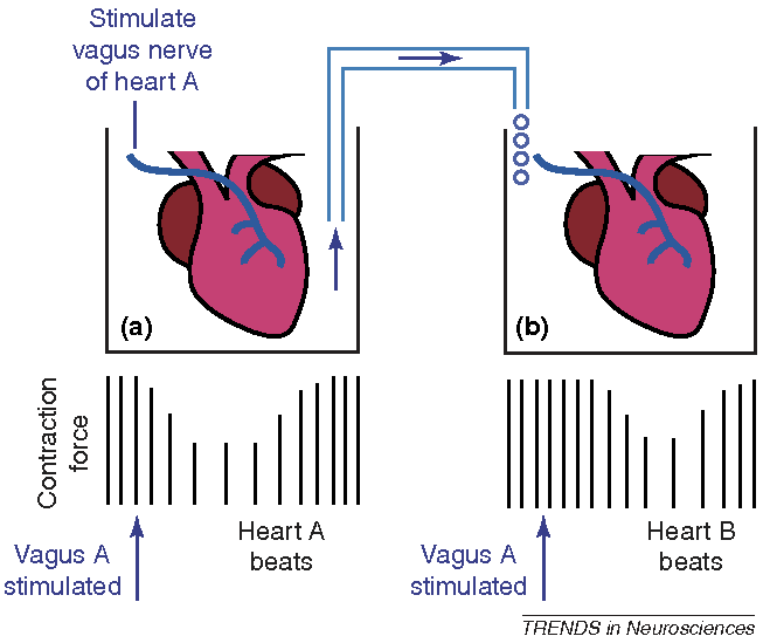
Classification of receptor ligands

- Agonist
  - Induces same response as natural ligand on the effector neurons
    - Full
    - Partial (lower effectivity)
    - Inverse agonist (opposite physiological response)
- Antagonist
  - Does not affect receptor activity
  - Competitive (binds the same spot as natural ligand)
  - Non-competitive (different binding spot; allosteric antagonist)
- Allosteric modulators (modify response to agonist)



Acetylcholine

- First neurotransmitter to be discovered = validation of idea of chemical neurotransmission
- Frog heart (Otto von Loewi, 1921)
- 2 hearts
- One stimulated by the vagus nerve = decrease heartbeat
- Liquid from stimulated heart is transferred to unstimulated heart
- The heartbeat of the other one slows down as well
- Some chemical must have been released into the liquid from the vagus = acetylcholine



Acetylcholine

- 2 types of receptors: nicotinic (nAchR) and muscarinic (mAchR)
- Nicotininc
  - Ionotropic, excitatory
  - Agonist: nicotine, carbachol (eye drops); Antoagonist: turbocurarine (arrow poison)
- Muscarinic
  - Metabotropic (G protein coupled)
  - Agonist: muscarine (mushrooms) ; antagonist: atropine (decrease saliva production during surgeries), scopolamine (treats motion sickness and nausea)
- Degraded by Acetylcholine esterase (AchE): inhibitors of AchE are insecticides (organophosphates) and nerve gas (sarin), but also drugs for Alzheimer's disease (donepezil)
- Botulotoxin inhibits release och Ach - muscle paralisis

Acetylcholine

- Myasthenia gravis, Alzhaimer’s disease
- Myasthemia gravis
  - Antibodies against nicotinic Ach receptors
  - Reoccurring muscle weakness
  - Usually affects eyelids, chewing muscles, facial muscles, but can progress
  - Ach agonists improve symptoms
- Alzheimer's disease
  - Decrease concentration of Ach
  - However, drugs that increase Ach often do not help
  - Probably a symptom, not a cause
  - Amyloid decreases acetylcholine production *in vitro*

Acetylcholine

- Ach is one of the main neurotransmitters modulating hippocampal function
- Increased supports theta activity (memory formation, communication with rest of the brain) and supresses sharp wave ripples (important for memory recollection)
- This is in line with Ach being released when external attention is needed: introspection is inhibited while memory encoding is supported
- In sleep Ach levels are very low: sharp wave ripples increase. In sleep, sharp wave ripples are important for memory transfer from hippocampus to cortex

Acetylcholine

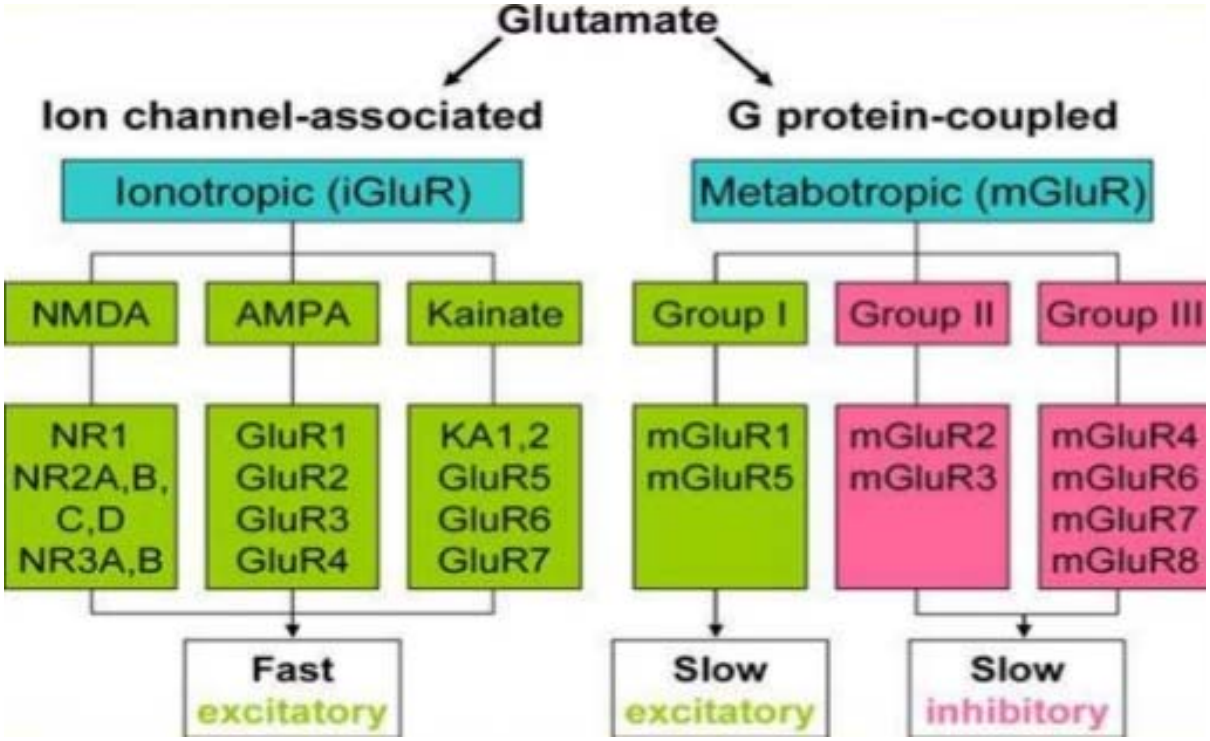
- Important in memory formation
- In memory consolidation during sleep low levels of Ach are needed
- Better choligenic drug timing in patients with AD

Glutamate

- Most common excitatory neurotransmitter in CNS
- Stored in synaptic vesicles, when released interacts with glutamate receptors
- Excitatory amino acid transporter (EAAT) removes glutamate from extrasynaptic space
- Extracellular glutamate concentrations must be kept low, otherwise risk of excitotoxic damage increases
- Glutamate stimulates increase of intracellular calcium via NMDA receptors (and AMPA receptors on inhibitory GABA releasing interneurons)
- Too much Ca2+ activates apoptotic cascades

Glutamate - receptors

- Ionotropic and metabotropic receptors
- Ionotropic
  - NMDA
  - AMPA
  - Kainate
- Metabotropic
  - mGlu1-8



Glutamate - schizophrenia

- Schizophrenia
- Hypofunction of NMDA receptors
- NMDA antagonists - such as MK-801, Ketamine, Phencyclidine (PCP) evoke states very similar to psychosis of schizophrenia patients
- Reduced expression of NMDA subunit NR1 in prefrontal cortex of schizophrenia patients
- The NMDA receptor hypofunction appear to be specific to parvalbumin interneurons. These are less stimulated by neurons and inhibitory tone is reduced, resulting in disinhibition of neurons, leading potentially network wide disinhibition, and increased oxidative stress
- Many other theories of schizophrenia (eg. dopamine theory, oxidative stress…they are not mutually exclusive..but we do understand etiology of schizophrenia yet)

Gamma-AminoButyric Acid (GABA)

- Main inhibitory neurotransmitter in CNS
- (in brainstem, spinal cord, retina: glycine takes up the role of GABA)
- Maintains excitatory-inhibitory balance
- GABAergic neurons: interneurons (calbindin, somatostatin, parvalbumin,…)
- Maintain neuronal oscilations (measured by EEG)
  - Connected by gap junctions - interneurons can fire together and inhibit whole network (by GABA release). Release of interneuronal inhibition allows neurons to fire coordinately at the same time
  - Parvalbumin positive interneurons (PV is a calcium binding protein) maintain gamma oscillations = important in information transfer and memory formation
  - Back to schizophrenia: in schizophrenia, baseline gamma is slightly higher, but there is no task related increase as in healthy people

Gamma-AminoButyric Acid (GABA) receptors

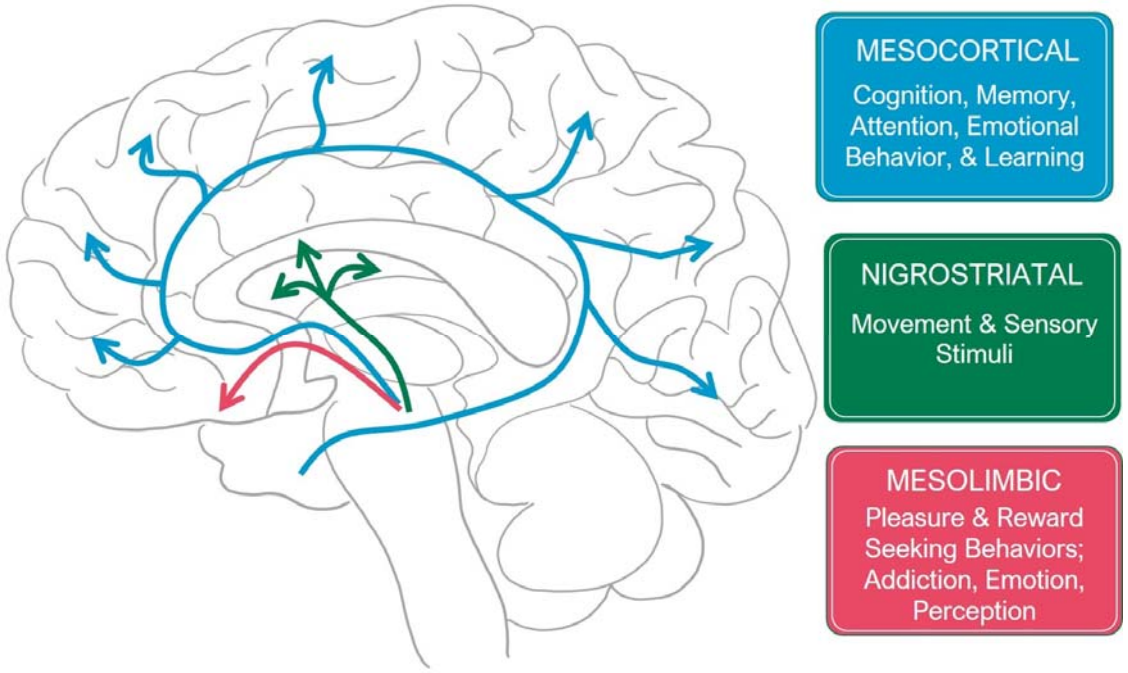
- **GABA A** receptors
  - Ionotropic, Cl- channels
  - Mostly on interneurons
  - Antagonists: bicuculine, picrotoxine (models of epilepsy);
  - Agonist: muscimol (experimental inactivation of brain regions)
  - Binds benzodiazepines, alcohol
- **GABA B** receptors
  - Metabotropic
  - Agonist: baclofen (treatment of spasms, epilepsy);
  - Antagonists do not induce spasms, potential pro-cognitive drugs
- **GABA C**
  - Ionotropic, Cl- channels
  - Insensitive to bicuculine, picrotoxine and baclofen. Otherwise similar to GABA A

Gamma-AminoButyric Acid (GABA)

- Important commonly used agonists: barbiturates, benzodiazepines and alcohol
- Benzodiazepines: increase frequency of channel opening GABA A
- Most GABA A receptors are in limbic system, which explains benzo anxiolytic effects
- Also hypnotics - target alpha 1 isoform of GABA A subunit, which are expressed in wake promoting regions od the brain (such as reticular formation)
- Barbiturates: increase time when GABA A channel is open – that is why they are more dangerous (when someone commits suicide by overdose with pills it is usually barbiturates E.g. Marylin Monroe)
- Overdose: respiratory depression. Lethal and terapheutic doses are very close (narrow therapeutic index)
- Alcohol:
  - Enhance GABA transmission (+ allosteric modulator of GABA A) - relaxed mood and behavior
  - Non-selectively disrupting lipid bilayer (potential effect of many anesthesias)
  - Antagonist of NMDA receptors - blackout

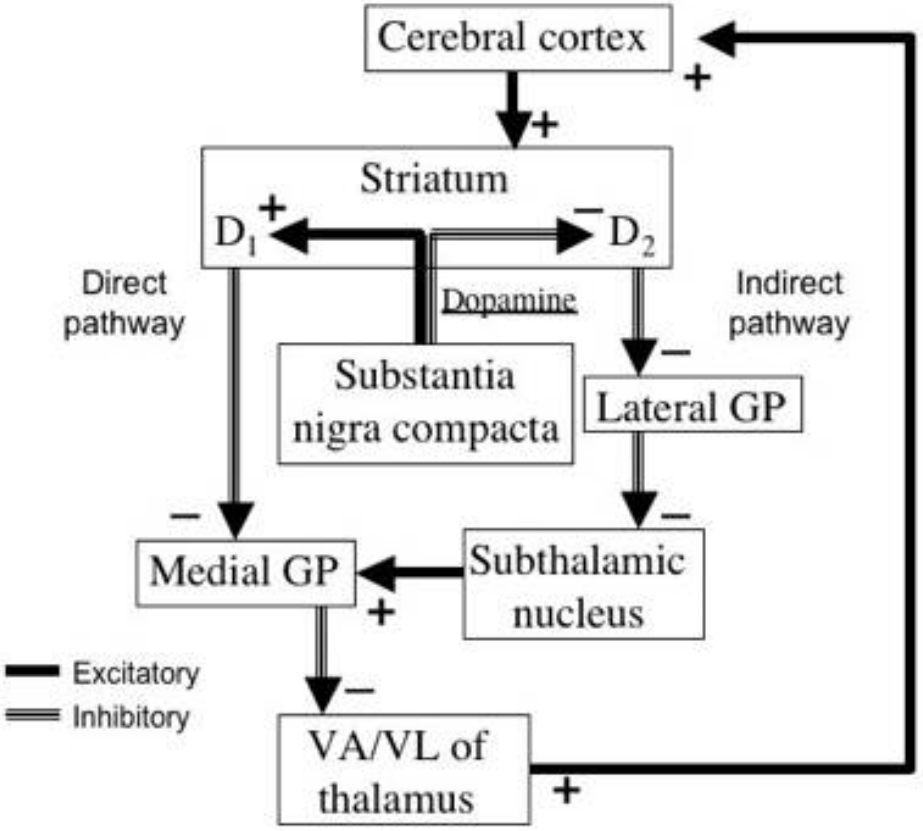
Dopamine

- Neuromodulator
- Projects from brainstem nuclei to whole brain
- Four pathways
- Nigrostriatal
  - Substantia nigra (SN) to striatum
  - Motoric coordination
  - Impaired in Parkinson's disease
- Mesolimbic
  - VTA to nucleus accumbens, hippocmapus and amygdala
  - Reward pathway
  - Addiction
- Mesocortical
  - VTA to prefrontal cortex and other cortical areas
  - Cognitive control, motivation, emotion
  - Altered in schizophrenia
- Tuberoinfundibular pathway
  - Nucleus arcuatus to pituitary gland
  - Prolactin secretion



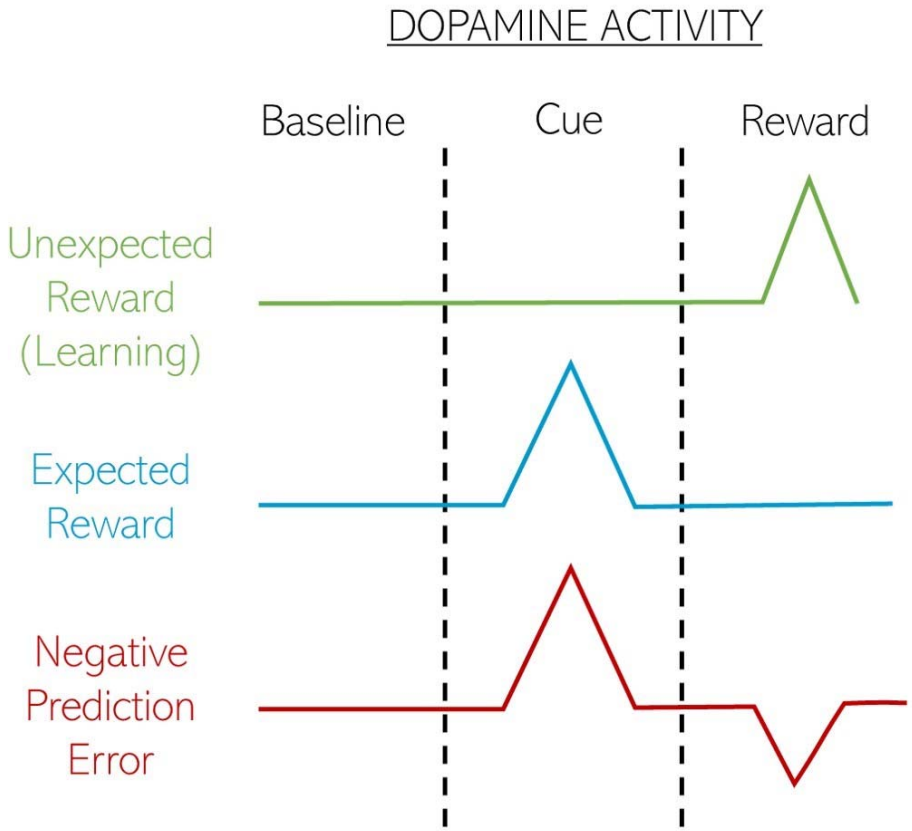
Dopamine

- Receptors
  - D1 like and D2 like receptors
  - D1 like
    - D1 and D5
    - Activate adenylcyclase (increase cAMP)
  - D2 like
    - D2, D3 and D4
    - Inhibit adenyl cyclase (decrease cAMP)
- Generation of habitual movement by basal ganglia (nigrostriatal pathway)
- cortico striatal thalamic loop - direct and indirect pathways
- D1 are expressed in direct pathway – movement facilitation
- D2 are expressed in indirect pathway - movement inhibition (default)



Dopamine - reward system

- Mesolimbic pathway (VTA-NAc): reward prediction error
- Unexpected reward, or better than expected reward increases dopamine release
- When cue predicts the reward, dopamine is released on a cue (because cue is unexpected).
- If the reward is the same as usual no more dopamine is released
- When reward is smaller than expected, dopamine release is shut down



Dopamine - gambling

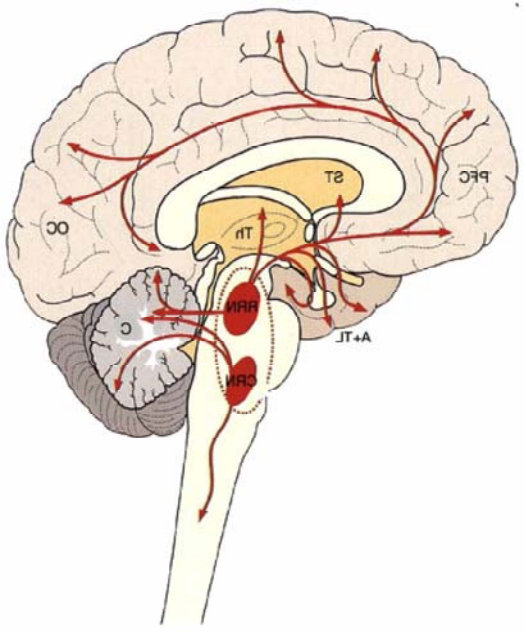
- It is not about reward
- It is about expected reward (you do not feel overjoyed when you get chocolate bar from wending machine every time, as expected)
- When you receive reward only half of the time, the expectancy of reward is lower (50%) therefore receiving a reward always increases dopamine and reinforces the behavior
- B.F. Skinner devised this type of reinformcement now called variable ratio schedule. When administered once behavior is established it is very difficult to extinguish it.
- News feeds, likes, dating apps…

Dopamine - schizophrenia

- *Positive symptoms*
  - Positive symptoms include delusions and hallucinations, linked to aberrant salience (everything in environment is 'important'). These symptoms are most recognisable during periods of acute psychosis.
- *Cognitive symptoms*
  - Impairments in learning, memory, attention and executive functioning. These symptoms get worse with each psychosis episode
- *Negative symptoms:*
  - Negative symptoms include blunting of affect (lacking emotional expression), avolition (deficits in motivation) and social withdrawal.
- Increased dopamine synthesis capacity (measured by radiolabelled L-DOPA uptake)
- Increased dopamine in associative striatum - in line with mis-attribution of salience (this is a main symptom of schizophrenia: patients gives more importance to not important things, such as coincidences)
- Antipsychotics are usually D2 antagonists

Serotonin

- neuromodulator
- Produced by raphe nuclei in the brain stem
- Projects to the whole brain (dorsal and medial raphe)
- Mostly metabotropic receptors, one ionotropic
  - 5-HT1 decreases cAMP (autoreceptors)
  - 5-HT2 increases IP3 and DAG
  - 5-HT3 ion channel (Na+, K+)
  - 5-HT4 increases cAMP
  - 5-HT5 decreases cAMP
  - 5-HT6 increases cAMP
  - 5-HT7 increases cAMP



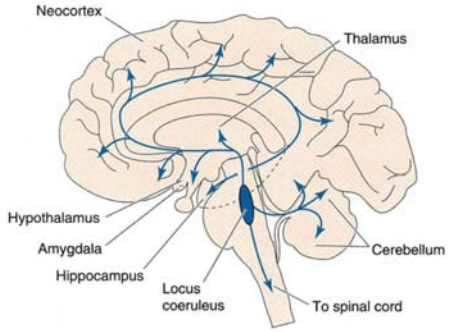
Serotonin

- Dubbed a hormone of happiness, however, not much is known about serotonin function
- The only link with ‘happiness’ - effectiveness of antidepressants in depressed patients
- However antidepressant do not only block serotonin release (SSRI) but have many different potential targets (effect on adult neurogenesis in hippocampus, changes in tryptophan metabolism in the liver)
- Umbrela analysis of metaanalyses shown that there is no link between serotonin and depression (at least how levels of serotonin are often measured: from blood and inferred from gene variants)
- NMDA antagonists, such as ketamine, produce much more robust antidepressive effects than antidepressants (and with no delay)

Serotonin

- Mice that do not synthetize any serotonin (TPH2 knock out animals) do not display any overt abnormalities (no depression, just agression)
- However, more pups die - model of sudden infant death
- Adult mice have all serotonin receptors in place despite lack of serotonin, and whole serotonin system is fully developed
- Increased agression and compulsive behavior is observed, but not depressive behaviors
- In humans, depleting tryptophan increases depressive synmptoms only in depressive individuals, no effect on healthy individuals

Norepineprine



- neuromodulator
- Noradrenaline (latin) = norepineprine (greek)
- Released from the nucleus coeruleus
- Receptors: alfa1 (Gq), alfa2 (Gi), beta1 (Gs), beta3 (Gs)
- Alfa agonists - sedative effects, used to deepen anesthesia during surgeries, xylazine, inhibit norepinephrine release
- Beta antagonists - used to treat migrane
- Mediates arousal, alertnes and readiness for action (very correlated with activity of peripheral sympathetic system)
- Lowest during sleep (no activity during REM sleep)

Norepineprine – memory consolidation

- Memory reconsolidation is beta1 dependent
- Memory reconsolidation - every time memory is retrieved it is potentially maleable to change
- Every time memory is retrieved it has to be ‘saved again’ - reconsolidated
- (that is why memories can change over time and why people remember same things differently)
- Reconsolidation requires activation of beta1 receptors, their blockade results in failure to reconsolidate and the memory is lost
- Propranolol (beta 1 antagonist) can erase memories that are reactivated = treatment for post traumatic stress disorder and phobias
- https://aeon.co/videos/can-you-cure-a-phobia-by-medically-rewriting-the-original-fear-memory

Thank you for the attention!