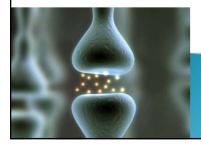
NEUROTRANSMITTERS

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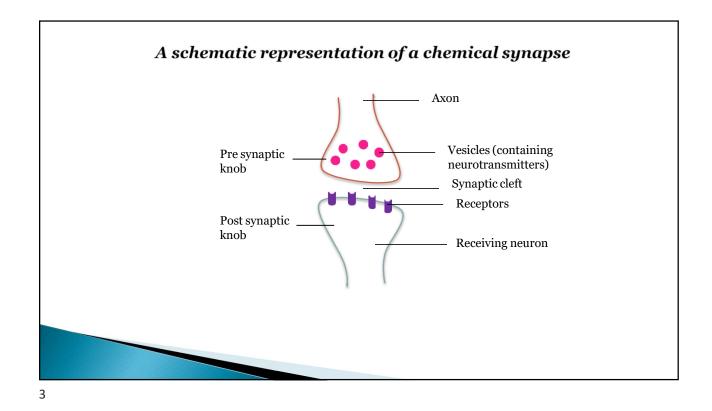


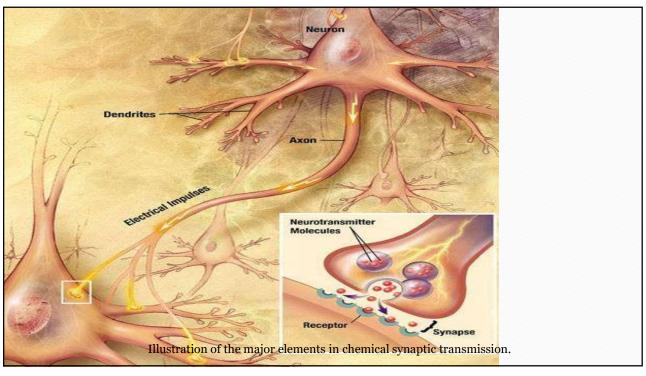
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INTRODUCTION

- $\ \square$ Neurotransmitters are chemical messengers that transmit signals from a neuron to a target cell across a <u>synapse</u>.
- ☐ Target cell may be a neuron or some other kind of cell like a muscle or gland cell.
- □ Necessary for rapid communication in synapse.
- □ Neurotransmitters are packaged into **synaptic vesicles** presynaptic side of a synapse.







PROPERTIES OF NEUROTRANSMITTERS

- Synthesized in the presynaptic neuron
- 2) Localized to vesicles in the presynaptic neuron
- 3) Released from the presynaptic neuron under physiological condition
- 4) Rapidly removed from the synaptic cleft by uptake or degradation
- 5) Presence of receptor on the post-synaptic neuron.
- 6) Binding to the receptor elicits a biological response

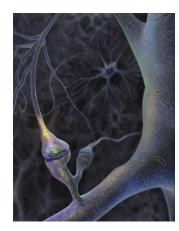
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Neurotransmitter Physiology

- In mammals, true electrical synapses are very rare.
- They exist only where completely synchronous activity of neurons having a common action is required.
- Examples include neurons for breathing and neurons for eye movements called saccades
- A saccade is a rapid, conjugate, eye movement that shifts the center of gaze from one part of the visual field to another. Saccades are mainly used for orienting gaze towards an object of interest. Saccades may be horizontal, vertical, or oblique.

Neurotransmission

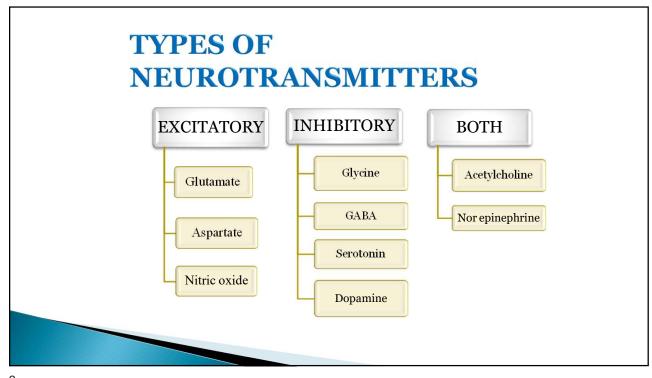
- Most synaptic connections in humans are modulated by neurotransmitters.
- Neurotransmitters can be excitatory or inhibitory.



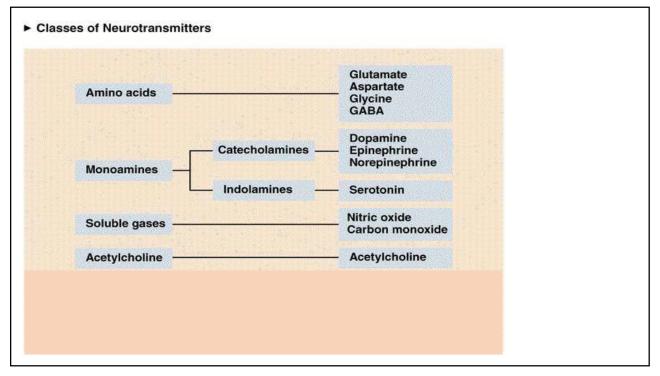
7

Types of Neurotransmitters

- Neurotransmitters are broken up into 4 main groups
 - 1. Amino Acid
 - 2. Biogenic Amines
 - 3. Neuropeptides
 - 4. Gaseous



9



SUPERSTARS?

 Superstar neurotransmitters (NT) get the most attention, dopamine, serotonin etc.

80% Neurotransmission:

- GLUTAMATE 60% most important daily NT for alertness.
- GABA 20%
- Depletion of Glutamate can lead to low GABA. Depletion can come from stress, overtraining, glutamine deficiency.

11

GLUTAMATE

- GLUTAMINE demand driven
- A physiological way to reduce circulating glutamine levels is through exercise
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7114859/#:~:text=A cute%20and%20Long%2DTerm%20Exercise,glutamine%20levels%20is%2 0through%20exercise
- Glutamine, beans, fish, eggs, nuts, soya, kefir, dark leafy veg, meats
- Fasting, dieting can deplete glutamine glutamate GABA
- Body Builders often emphasize BCAA, neglecting glutamine. Serious exercise depletes glutamine
- GI Resolve 30 days will increase alertness and energy, besides gut healing

GLUTAMATE

- GLUTAMINE WEIGHT LOSS
- https://www.healthline.com/nutrition/l-glutamine-weightloss#effectiveness
- 6-week study in 66 people with type 2 diabetes found that taking 30 grams of glutamine powder daily improved multiple risk factors for heart disease and reduced both **belly and body fat**.
- Similarly, a 2-week study using the same amount of glutamine observed decreased waist circumference, a marker for belly fat, in 39 people with overweight or obesity.
- In another small study, 6 women who took glutamine supplements for 4 weeks experienced significant reductions in body weight and **belly fat** without making other dietary or lifestyle changes.
- MECHANISM?
- Microbiome, Inflammation, Immune system, Improves blood sugar control, enhances insulin sensitivity

13

GLUTAMATE TO GABA conversion

- GABA function as NT, it has structure of amino acid so it's called AANT
- Synthesis mostly in brain but also in pancreas
- ▶ GABA is synthesized from the precursor glutamate by the enzyme glutamate decarboxylase, an enzyme which uses vitamin B6 (pyridoxine) as a cofactor.
- MSG
- Mg and B6 crucial for Glutamate to GABA conversion. Most people deficient in both.

GABA

- Besides the nervous system, GABA is also produced at relatively high levels in the insulin-producing beta cells (β -cells) of the pancreas. The β -cells secrete GABA along with insulin and the GABA binds to GABA receptors on the neighboring islet alpha cells (α -cells) and inhibits them from secreting glucagon (which would counteract insulin's effects).
- GABA can promote the replication and survival of β -cells and also promote the conversion of α -cells to β -cells, which may lead to new treatments for diabetes.
- Alongside GABAergic mechanisms, GABA has also been detected in other peripheral tissues including intestines, stomach, fallopian tubes, uterus, ovaries, testicles, kidneys, urinary bladder, the lungs and liver, albeit at much lower levels than in neurons or β-cells

15

GABA

- Administration of GABA can suppress inflammatory immune responses and promote "regulatory" immune responses, such that GABA administration has been shown to inhibit autoimmune diseases.
- AUTOIMMUNE Type 1 diabetes, immune system attacks and destroy insulin-secreting pancreatic beta cells and the pancreas stops producing insulin
- dysfunctional β cells can recover in patients with T2D with proper management, such as diet, exercise,... can be restored to normal function through the removal of excess fat in the cells
- Exercise, fat loss, GABA... restoration of beta cells

GABA - LIVER, MICROBIOME

- **▶ LIVER**
- Over the past 40 years it has become evident that the mammalian liver contains high concentrations of GABA
- Our results showed that preemptive treatment with GABA protected against severe acute liver injury in mice via GABA-mediated STAT3 signaling.
- Recent studies show that the metabolites produced by the gut microbiota also include some neurotransmitters such as glutamate, GABA, serotonin, and dopamine. Metabolites of the colonic fermentation of carbohydrates by the microbiota, such as acetate, can cross the blood-brain barrier and be incorporated into the GABA metabolic cycle, preferentially in the hypothalamus

17

GABA - OPTIMIZATION

- SN vs PSN balance. Meditation, Prayer, transcendental thinking
- Exercise increases: Dopamine (DA), noradrenaline (NE), and serotonin (5-HT), GABA
- Intense exercise increases levels of two common neurotransmitters -- glutamate and gamma-aminobutyric acid, or GABA -- that are responsible for chemical messaging within the brain.
- ▶ The Journal of Neuroscience, 2016
- https://www.sciencedaily.com/releases/2016/02/160225101241 htm#:~:text=Intense%20exercise%20increases%20levels%20of,ch emical%20messaging%20within%20the%20brain

GABA OPTIMIZATION

Neurotransmitters: Elusive glutamate receptors

Current Biology, Volume 4, Issue 1, 1 January 1994,

Mapping neurotransmitter systems to the structural and functional organization of the human neocortex, 27 October 2022

- Neurotransmitter receptors support the propagation of signals in the human brain. How receptor systems are situated within macro-scale neuroanatomy and how they shape emergent function remain poorly understood, and there exists no comprehensive atlas of receptors.
- https://www.nature.com/articles/s41593-022-01186-3#author-information

19

GABA B3, ADAPTOGENS

- Adaptogens: BioAshwagandha, ADHS, Balanced B8
- Research indicates that niacinamide and inositol enhance the effects of GABA
- Niacinamide's potent role in alleviating anxiety with its benzodiazepine-like properties: A case report
- June 2004, Journal of Orthomolecular Medicine 19(2):104-110
- Niacinamide possess benzodiazepine-like effects, 38, 39 which stimulate the GABA system and theoretically would reduce seizure activity.

GABA - INOSITOL

- Inositol helps boost serotonin and dopamine receptor density. Improving the effectiveness of serotonin, GABA, glutamate and dopamine neurotransmitters in your brain. Neurotransmitters: Inositol improves the effectiveness of major neurotransmitters in your brain.
- Neurobiology and Applications of Inositol in Psychiatry: A Narrative Review
- It has been suggested that the therapeutic activity of inositol may be related to the modulation of serotonin and/or norepinephrine receptors

21

GABA RECEPTOR

- GABA binds to GABA receptor
- Benzodiazapines and alcohol very high affinity for the GABA receptor they can cause addictions. Rx and alcohol disrupt the Sleep architecture so you don't get a lot of deep sleep on these drugs.
- > VHP Valerian binds to GABA receptors without addiction
- GABA needed during the day as well

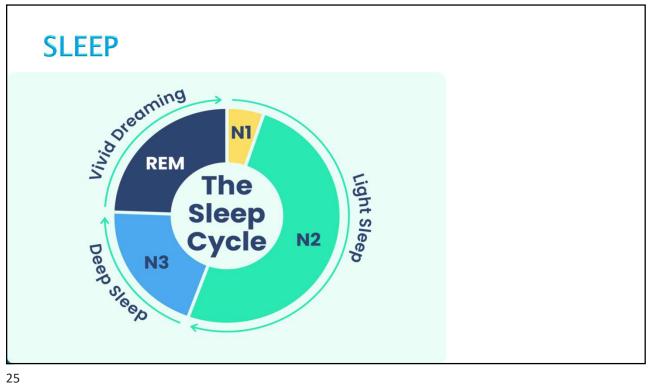
DOPAMINE - GABA

- DOPAMINE INHIBITS GABA
- Dopamine Directly Modulates GABA-A Receptors
- Paul Hoerbelt, Tara A. Lindsley and Mark W. Fleck
- Journal of Neuroscience 25 February 2015
- Our results suggest that dopamine may directly inhibit GABAa receptors that are both immediately adjacent to dopamine release sites in the striatum and activated by tonic GABA.
- Dopamine-Screen time?
- https://www.jneurosci.org/content/35/8/3525#:~:text=Our% 20results%20suggest%20that%20dopamine,and%20activated% 20by%20tonic%20GABA

23

OTHER SUPERHERO NT

- **DOPAMINE**
- **EPINEPHRINE**
- **SEROTONIN**
- **ACETYLCHOLINE**



SLEEP			
Sleep Stages	Type of Sleep	Other Names	Normal Length
Stage 1	NREM	N1	1–7 minutes
Stage 2	NREM	N2	10-25 minutes
Stage 3	NREM	N3, slow-wave sleep (SWS), delta sleep, deep sleep	20-40 minutes
Stage 4	REM	REM Sleep	10-60 minutes



27

SLEEP

- Research says that early birds are happier, more punctual, do better in school, and share more conservative morals. Night owls are more impulsive, angry, and likely to become cyberbullies; they have shoddier diets and, most critically, are worse at kicking soccer balls.
- The researchers also found an association between morning people and a higher life satisfaction.
- https://psycnet.apa.org/doiLanding?doi=10.1037%2Fa0027071
- https://link.springer.com/article/10.1007/s12144-014-9246-1
- https://www.cambridge.org/core/journals/europeanpsychiatry/article/abs/novelty-seekers-and-impulsive-subjectsare-low-in-morningness/9A3BABD26BBB290E77E1A510D952994E

SLEEP

- Cell Press journal "Rapid and Reversible Control of Human Metabolism by Individual Sleep States".
- https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01373-5
- Study examines REM sleep, which is associated with dreaming and high emotional content dream vs slow wave sleep, which tends to be more focused on physical repair of the body, more mundane dreams, and how those different states of mind during sleep relate to different aspects of metabolism.
- Conclusion: sleep states regulate more than 50%, of all metabolite features detected in human breath.
- We can determine if we are metabolizing more lipids or carbohydrate based on the contents of our breath. This is true during waking and during sleep.

29

SLEEP

- Study measured close to 2000 metabolites in breath, every 10 seconds across the entire night's sleep.
- There are major pathways related to lipid metabolism.
- The switch from sleep to wakefulness reduces fatty acid oxidation. While you are asleep, you're oxidating more fatty acids. And as you wake up, that becomes less the case.
- There's a switch in slow wave sleep that increases fatty acid oxidation. Transition from rapid eye movement sleep to other aspects of sleep brings about TCA cycle – tricarboxylic acid cycle. If you're sleep deprived, even by an hour or so, you're going to get far less rapid eye movement sleep

SLEEP

- SECOND STUDY published in 2019 "Resetting the Late Timing of 'Night Owls' Has a Positive Impact on Mental Health and Performance."
- https://pubmed.ncbi.nlm.nih.gov/31202686/ Sleep Med., 2019 Aug:60:236-247
- It was human study, a randomized control trial.
- ▶ They used non-pharmacological, practical interventions in a real world setting.
- They used targeted light exposure, consistent sleep, wake times, fixed meal times, controlled caffeine intake and exercise.
- Outcome showed significant improvements in terms of mood and far less depression and stress.

31

A FEW MORE UNUSUAL TWISTS

- 1. EPINEPHRINE IS MADE FROM DOPAMINE: Dopamine is hydroxylated to give norepinephrine by dopamine beta-hydroxylase. In the adrenal medulla and in a few brain regions, norepinephrine is converted to epinephrine by the enzyme phenylethanolamine N-methyltransferase https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/epinephrine
- 2. In spite of their significant differences, there are strong links between the serotonin and dopamine systems, both structurally and in function.
- a) Both dopamine and serotonin are neurotransmitters with positive associations.
- b) They are also neuromodulators... unlike other neurotransmitters, they are able to communicate with many neurons that are near and far away from the dopamine or serotonin release site.
- c) As neuromodulators, they send signals that last longer than the signals of other neurotransmitters.

ACETYLCHOLINE

- Involved in states of focus, memory and learning
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2659740/
- Essential for brain plasticity, ability to change and learn more quickly.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6673455/ The Journal of neuroscience, Dec 2007
- https://www.nature.com/articles/s41598-018-27393-2 "Acetylcholine-modulated plasticity in reward-driven navigation: a computational study" Scientific Reports June 2018
- Ach to communicates signals between neurons in the central nervous system (CNS) and the peripheral nervous system (PNS)
- Essential in the neocortex to learn simple tasks of discrimination.
- https://www.ncbi.nlm.nih.gov/books/NBK557825/

33

24 HR PHASES

- → 0-9 PHASE I from the time you wake up until about nine hours later, the neuromodulators, dopamine and epinephrine, tend to be at their highest levels
- ▶ 9–16 PHASE II Dopamine, Epinephrine subside, Serotonin rises
- ▶ 17-24 PHASE III ORGANIZED CHAOS incredible peaks and drops in acetylcholine, dopamine and serotonin.

24 HR PHASES

- Acetylcholine (Ach) is under control more in terms of what we happen to be doing at any given moment, whether or not we're focusing or not focusing,
- ACh is used at the nerve to muscle synapse. The contraction of muscle fibers is exerted through the release of acetylcholine.
- Ach is at its strongest both during REM (rapid eye movement) sleep and while you are awake. It seems to help your brain keep information gathered while you are awake. It then sets that information as you sleep. So if you study or learn new information in the hours before bed, "sleeping on it" can help you remember it.
- https://www.hopkinsmedicine.org/health/conditions-and-diseases/sleepwake-

35

OTHER CONNECTIONS

- When testosterone goes up, dopamine goes up and sometimes even vice versa. When dopamine goes up, testosterone go up.
- CORTISOL UP EPINEPHRINE UP
- Oxytocin or prolactin are increased, SEROTONIN UP
- PROLACTIN REDUCES DOPAMINE. After childbirth. Prolactin up, serotonin up
- We can't draw a direct link between any one hormone system and acetylcholine.

OTHER CONNECTIONS

- > SUNLIGHT INCREASES HORMONES. Hormones affect neurotransmitters
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4335177/
- Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Frontiers in neuroscience. 2007
- "Skin exposure to UVB light induces a skin-brain-gonad axis and sexual behavior" Cell Reports, August 2021
- https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01013-5
- SKIN IS ENDOCRINE ORGAN, hormone secreting hormones are controlling those neuromodulators
- DOPAMINE AND SEROTONIN BOTH UP
- "When your skin absorbs sunlight and produces vitamin D, that cycle triggers the production of dopamine as well as serotonin, meaning time in the sun can boost your dopamine levels. A 2018 study found that vitamin D may protect dopaminergic neurons against neuroinflammation and oxidative stress." Mar 12, 2021
- https://davisphinneyfoundation.org/sunlight-and-parkinsons/

37

OTHER CONNECTIONS

- Dopamine is not only about pleasure. Dopamine is about motivation, craving and pursuit... career, to mate, food, goals, things we don't have. Athletes experience this.
- Serotonin is associated with a feeling of satiety of having enough of what we already have. Now when serotonin is very, very high, people can even be sedate. They can be completely amotivated, no motivation to seek out things like food or sex or work or et cetera. Whereas when serotonin levels are very low, people can actually exhibit agitation and high levels of stress.

SUMMARY

- ▶ 1. DOPAMINE motivation, drive and pursuit and to some extent, focus.
- ▶ 2. EPINEPHRINE, NOREPINEPHRINE energy of having a forward center of mass, mentally and or physically.
- ▶ 3. SEROTONIN peaceful, content, sated state of being.
- → 4. ACETYLCHOLINE focus in particular focus as it relates to learning and encoding new information. Brain plasticity.

39

DOPAMINE

- SUNLIGHT increases levels of genes related to thyroid hormone and actually increases certain dopamine receptors. Sunlight exposure can actually increase the amount of so-called DRD4.
- Essential roles of dopamine D4 receptors and the type 1 adenylyl cyclase in photic control of cyclic AMP in photoreceptor cells
- https://pubmed.ncbi.nlm.nih.gov/19166506/ Journal of neurochemistry, April 2009
- DRD4 is under photic control. Get sunlight exposure to your eyes and it needs to be in the early part of the day.

DOPAMINE

- D2, D3 TYROSINE 15 MINUTES Cheese effect (tyrosine and tyramine) Too much can cause headaches in some people
- > O3, PROBIOTICS, GREEN TEA, exercise, Mucuna Pruriens (Dopatropic) can increase it
- ▶ INCREASING EPINEPHRINE increases D2, D3.
- ▶ B vitamins, especially B6 Phosphate
- HABENULA
- Involved in regulation of monoamines, such as dopamine and serotonin. The habenular nuclei are involved in pain processing, reproductive behavior, nutrition, sleep-wake cycles, stress responses, and learning.
- Activated by bright light, such as phone screens.
- Habenula-Induced Inhibition of Midbrain Dopamine Neurons Is Diminished by Lesions of the Rostromedial Tegmental Nucleus, Journal of Neurscience Jan 2017
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5214632/

41

EPINEPHRINE (Adrenaline) – Alertness

- Released both in the brain and the body.
- > BBB (blood brain barrier) prevents the epinephrine released
- from adrenal glands to enter brain.
- ▶ Brain has a separate site locus coeruleus. This is a collection of neurons in the back of the brain.
- The locus coeruleus (LC), or 'blue spot', is a small nucleus located deep in the brainstem that provides the far-reaching noradrenergic neurotransmitter system of the brain.
- Upon input of locus coeruleus eyelids are wide open,
- If PUPILS are really big and eyes are really wide open, It's a sign there is a lot of adrenaline in the system
- EXERCISE and cold shower increases epinephrine

ACETHYLCHOLINE – Attention/Learning

- Acetylcholine is released in the basal forebrain from two sites: the basal nucleus of Meynert and the medial septal nucleus.
- Ach important for the so-called fidelity of information coming in through our eyes, our ears, our nose, et cetera.
- We are constantly being bombarded with sensory information through all of our various senses and acetylcholine has the ability to increase the extent to which visual information or just visual and auditory information would make it through to our consciousness whereas all the other types of sensory information that are coming in are filtered out.

43

ACETHYLCHOLINE - Attention/Learning

- **FOCUS**
- ACh triggers immediate and **long-lasting changes** in the way that those circuits work even when acetylcholine is not being deployed. This is a part of neuroplasticity; it affects that neural circuits literally change.
- Nicotine, Alpha GPC, Huperzine increase ACh
- ▶ Foods: Beef liver is the most potent source of choline. EGGS
- TMAO (Trimethylamine N-Oxide) can impair ACh
- Allicin reduces TMAO and thus protects Ach: "Allicin exhibits inhibitory activity against acetylcholinesterase and butyrylcholinesterase enzymes, which are responsible for the breakdown of acetylcholine, a neurotransmitter involved in cognition"
- https://www.sciencedirect.com/science/article/pii/S2667142523000696

ACETHYLCHOLINE

- Behavior to Increase Focus & Acetylcholine:
- Staring at a particular distant visual target at the same distance for 30 to 60 seconds, narrowing in a very deliberate way your visual field, and then moving into a focused work. That behavioral practice of narrowing your visual aperture will increase the amount of acetylcholine transmission in particular neural circuits that will then make it easier to focus.
- Alzheimer's age-related cognitive decline andADHD are connected with low Ach
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3164006/

45

SEROTONIN

- Prosocial behaviors such as holding hands, cuddling, cooperation, and affiliation increases serotonin
- Receiving, not giving GRATITUDE, is what has the most potent effects on increasing serotonin and activity of the brain circuits that involve serotonin
- Observing others giving and receiving gratitude is immensely powerful for evoking serotonin – LONG LASTING

•

SEROTONIN

- Exposure to outdoor sunlight, exercise. eating foods that contain a substance known as tryptophan (such as nuts, eggs, cheese, red meat, turkey, salmon, tofu and pineapple)
- Myo-inositol can have the effect of increasing serotonin and other neurochemicals - improves sleep, reduces anxiety, bipolar.
 Stomach discomfort
- ▶ High serotonin is not desirable either: reduced appetite, reduced libido, increased lethargy, et cetera.

47

ALCOHOL & NEUROTRANSMITTERS





It enhances the effects of the GABA,

which is an inhibitory neurotransmitter.

- Enhancing an inhibitor make things sluggish.
- The neuron activity is diminished-sedative effects of alcohol.

Alcohol inhibits glutamate receptor function.

 This causes discoordination, slurred speech, staggering, memory disruption, and blackout.

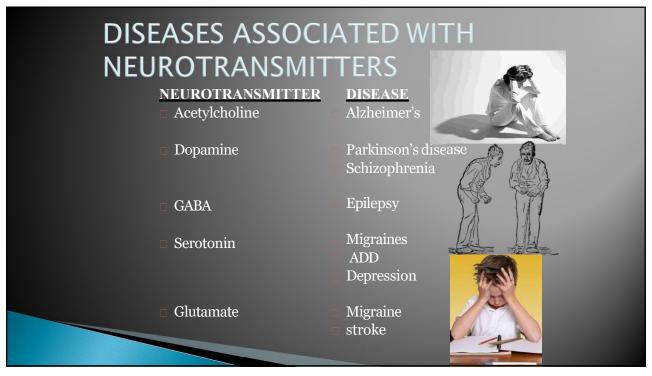
Alcohol raises dopamine levels.

This leads to excitement, pleasure and later addiction.

NICOTINE & NEUROTRANSMITTERS

- □ Nicotine **imitates the action of ACh** & binds to ACh receptor.
- □ Like acetylcholine, nicotine leads to a burst of receptor activity.
- □ Nicotine activates cholinergic neurons in many different regions throughout your brain simultaneously.
- ☐ This stimulation leads to:
 - Increased release of glutamate.
 - Stimulation of cholinergic neurons promotes the release of dopamine. The production of dopamine causes feelings of reward and pleasure.

49



SUPPORTING NUTRIENTS

- Mg Zyme 2 x 2 F or ActiMag 1 scoop a day
- ▶ B6 Phosphate 1-2 F
- ▶ Balanced B8 1 tsp anytime
- ▶ Tyrosine 1-2 E morning or noon (not late at night)
- Taurine 2-4 day or night, but at night assists sleep
- MSM 5 daily anytime. Combine together with:
- ▶ Mo Zyme Forte 1-2 daily
- ▶ Phosphatidyl Serine 1-2 E
- ▶ Phospatidyl Choline 1-2 F
- VHP 2x2 É
- ▶ Curcum Rx 2-4 daily anytime
- ▶ Biomega liquid 1 tsp or Biomega 1000 2 daily F
- ▶ IAG 1-2 tbsp E
- ▶ BioDoph7 1x2 E