Neurotransmitters
D.HAMMOUDI.MD
1. Action potential reaches presynaptic terminal.

2. Depolarization of presynaptic terminal opens ion channels allowing calcium ($\text{Ca}^{2+}$) into cell.

3. $\text{Ca}^{2+}$ triggers release of neurotransmitter from vesicles.

4. Neurotransmitter binds to receptor sites on postsynaptic membrane.

5. Opening and closing of ion channels cause change in postsynaptic membrane potential.

6. Action potential propagates through next cell.

7. Neurotransmitter is inactivated or transported back into presynaptic terminal.
CRITERIA

• NT found in axon terminals
• NT released by action potentials
• Synthesis identified
• External application mimic normal Response
• Pharmacology same for normal and externally applied NT ~
Lock & Key Model

- NT binds to receptor
  NT = key
  Receptor = lock
- Receptor changes shape
determines if EPSP or IPSP
receptor subtypes
- NOT NT ~
- ligand binds to receptor
- activation: + or -
• Same NT can bind to different -R
• different part of NT ~
Specificity of drugs

Drug A

Receptor A

NT

Receptor B

Drug B
Neurotransmitter synthesis pathways:

**Phenylalanine** --> Tyrosine --> L-Dopa --> Dopamine --> Norepinephrine

Tryptophan --> 5-Hydroxytryptophan (5-HTP) --> Serotonin (5-Hydroxytryptamine)

Choline + Acetyl-CoA --> Acetylcholine

Glutamic acid --> GABA (gamma-amino-butyric-acid)

---

**Serotonin**
**Synthesis and metabolism**

\[
\text{tryptophan} \overset{a.}{\rightarrow} \text{5 hydroxytryptophan} \overset{b.}{\rightarrow} \text{serotonin (5HT)}
\]

a. tryptophan hydroxylase
b. l-aromatic acid decarboxylase

---

substrate availability is rate limiting step
tryptophan hydroxylase is rate limiting enzyme

---

\[
\text{serotonin (5HT)} \overset{a.}{\rightarrow} \overset{b.}{\rightarrow} \text{5HIAA (5hydroxyindolacetic acid)}
\]

a. MAO
b. Aldehyde dehydroxylase
Catecholamines (dopamine and norepinephrine)

synthesis and metabolism

Tyrosine → dopa

phenylalanine

tyrosine hydroxylase
pterin cofactor
rate limiting step

dopa decarboxylase (pyridoxal cofactor)

dopa → dopamine beta hydroxylase (copper containing enzyme)
(Ascorbate and O2 req.)
norepinephrine

PNMT (SAM) → epinephrine
(occurs in periphery not CNS)

epinephrine

The genetic disorder phenylketonuria (PKU) is the inability to metabolize phenylalanine.

• Individuals with this disorder are known as "phenylketonurics" and must regulate their intake of phenylalanine.

• A (rare) "variant form" of phenylketonuria called hyperphenylalaninemia is caused by the inability to synthesize a coenzyme called biopterin, which can be supplemented.

• Pregnant women with hyperphenylalaninemia may show similar symptoms of the disorder (high levels of phenylalanine in blood) but these indicators will usually disappear at the end of gestation.

• Individuals who cannot metabolize phenylalanine must monitor their intake of protein to control the buildup of phenylalanine as their bodies convert protein into its component amino acids.
**Neurotransmitters**
- Acetylcholine (Ach)
- Dopamine (DA)
- Histamine
- Norepinephrine (NE)
- Epinephrine
- Serotonin (5HT)

**Peptides**
- Gamma Aminobutyric Acid (GABA)
- Glutamate
- Aspartate
- Glycine

**Neuropeptides**
- Insulin
- Betaendorphin
- Neuropeptide Y
- Calcitonin
Neurotransmitters found in the nervous system

EXCITATORY

• Acetylcholine
• Aspartate
• Dopamine
• Histamine
• Norepinephrine
• Epinephrine
• Glutamate
• Serotonin

INHIBITORY

• GABA
• Glycine
## Major Neurotransmitters in the Body

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Role in the Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>A neurotransmitter used by the spinal cord neurons to control muscles and by many neurons in the brain to regulate memory. In most instances, acetylcholine is excitatory.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>The neurotransmitter that produces feelings of pleasure when released by the brain reward system. Dopamine has multiple functions depending on where in the brain it acts. It is usually inhibitory.</td>
</tr>
<tr>
<td>GABA (gamma-aminobutyric acid)</td>
<td>The major inhibitory neurotransmitter in the brain.</td>
</tr>
<tr>
<td>Glutamate</td>
<td>The most common excitatory neurotransmitter in the brain.</td>
</tr>
<tr>
<td>Glycine</td>
<td>A neurotransmitter used mainly by neurons in the spinal cord. It probably always acts as an inhibitory neurotransmitter.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Norepinephrine acts as a neurotransmitter and a hormone. In the peripheral nervous system, it is part of the flight-or-flight response. In the brain, it acts as a neurotransmitter regulating normal brain processes. Norepinephrine is usually excitatory, but is inhibitory in a few brain areas.</td>
</tr>
<tr>
<td>Serotonin</td>
<td>A neurotransmitter involved in many functions including mood, appetite, and sensory perception. In the spinal cord, serotonin is inhibitory in pain pathways.</td>
</tr>
<tr>
<td>Neurotransmitter Molecule</td>
<td>Derived From</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Choline</td>
</tr>
<tr>
<td>Serotonin 5-Hydroxytryptamine (5-HT)</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>GABA</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Histamine</td>
<td>Histidine</td>
</tr>
<tr>
<td>Epinephrine synthesis pathway</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Norpinephrine synthesis pathway</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Dopamine synthesis pathway</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Nitric oxide, NO</td>
<td>Arginine</td>
</tr>
</tbody>
</table>
Neurotransmitter Criteria

Neuroscientists have set up a few guidelines or criteria to prove that a chemical is really a neurotransmitter. Not all of the neurotransmitters that you have heard about may actually meet every one of these criteria.

<table>
<thead>
<tr>
<th>The chemical must be produced within a neuron.</th>
<th>The chemical must be found within a neuron.</th>
<th>When a neuron is stimulated (depolarized), a neuron must release the chemical.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
<td><img src="image2.png" alt="Diagram" /></td>
<td><img src="image3.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When a chemical is released, it must act on a post-synaptic receptor and cause a biological effect.</th>
<th>After a chemical is released, it must be inactivated. Inactivation can be through a reuptake mechanism or by an enzyme that stops the action of the chemical.</th>
<th>If the chemical is applied on the post-synaptic membrane, it should have the same effect as when it is released by a neuron.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4.png" alt="Diagram" /></td>
<td><img src="image5.png" alt="Diagram" /></td>
<td><img src="image6.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>
Acetylcholine

1. synthesis and metabolism
   \[ \text{Choline} + \text{Acetyl CoA} \xrightarrow{\text{CAT}} \text{actetylcholine} \]
   CAT-Choline acetyl transferase
   marker enzyme for Ach neurons

   \[ \text{acetylcholine} \xrightarrow{\text{cholinesterase}} \text{Choline and acetate} \]
   terminates effect at the receptor

2. Central anatomy-interneurons of striatum
   pedunculopontine nucleus-projects to thalamus
   nucleus basalis-projects to cortex
Types of NT

Acetylcholine (ACh)

1. this NT has 2 types of receptors

   A. nicotinic receptors:
      a. agonist: is nicotine
      b. antagonist: is curare

   B. muscarinic receptors:
      a. agonist: is muscarine
      b. antagonist: in atropine (deadly nightshade)

2. deactivated by acetylcholinesterase (AChE) & choline is reused

3. physostigmine: inhibits AChE (agonist) but is reversible.

4. botulinum toxin prevents the release of ACH from the terminal button (antagonist)

5. black widow spider venom causes ACH terminals to release ACH (agonist)
The nicotinic acetylcholine receptor is one of the main mediators of neurotransmission. This receptor is activated by the binding of two acetylcholine molecules. As a ligand gated ion channel it permits the movement of positively charged ions from the synaptic cleft into the cytoplasm.
Amanita muscaria, the mushroom from which muscarine was isolated.

• **Muscarinic receptors**, or mAChRs, are acetylcholine receptors that form G protein-receptor complexes in the cell membranes of certain neurons and other cells.

• They play several roles, including acting as the main end-receptor **stimulated by acetylcholine released from postganglionic fibers in the parasympathetic nervous system.**
South American Indian
Preparing Curare
Both botulinum toxin (BoTx) and black widow spider venom (b.w.s.v.) cause a presynaptic block of neuromuscular transmission but each has a different mode of action. BoTx impairs the release of acetylcholine (ACh) from motor nerve terminals and causes prolonged paralysis of skeletal muscle. Recovery from paralysis is slow and associated with sprouting of axons from nerve terminals and formation of new motor end-plates.
Acetylcholine - ACh

- Most abundant NT in Peripheral N.S.
  - also found in Central N.S.
- Precursor = choline nutrient
- Degraded by acetylcholinesterase - AChE
  - Membrane bound - pre- & postsynaptic
- Nicotinic receptor - ionotrophic
- Muscarinic receptor - metabotropic ~
Ach - Distribution

- Peripheral N.S.
- Excites somatic muscle
- **Autonomic NS**
  - Ganglia
  - Parasympathetic NS
  - Neuroeffector junction

Central N.S. - widespread
  - Hippocampus
  - Hypothalamus
Cholinergic Agonists

• **Direct**
  – Muscarine
  – Nicotine
  – small doses

• **Indirect**
  – AChE Inhibitors ~
AChE inhibitors

• Physostigmine
• Organophosphates - irreversible
  – DFP
  – Soman & Sarin
  – Malathion*
• Agonist or Antagonist?
  indirect agonist
Cholinergic Antagonists

• **Direct**
  - **Nicotinic** - Curare
  - **Muscarinic** - Atropine
    - Scopolamine

• **Indirect**
  - Botulinum Toxin
  - Black Widow Spider Venom ~
ACh

Botulinum toxin

BWSV

Curare

Atropine

AChE

AChE

NM AChEBWSV

Curare

Atropine

AChE
**Monoamines**

neurotransmitters and neuromodulators
All monoamines work thru metabotropic receptors
All monoamines are derived from aromatic amino acids like phenylalanine, tyrosine, tryptophan, and the thyroid hormones by the action of aromatic amino acid decarboxylase enzymes.

**Monoamine oxidase (MAO) & catechol-O-methyltransferase (COMT)** deactivate these. Monoamine oxidase A (MAOA) is an enzyme involved in the metabolism of the monoamines, eg 5-HT and noradrenaline.

1. The drug reserpine prevents the storage of the monoamines

**Types of monoamines:**

I. Indolamines:

**Serotonin (5-HT)**

A. produced in the raphe nuclei in the midline of the pons & medulla

B. the drug parachlorophenylalanine (PCPA) blocks tryptophan hydroxylase & prevents the synthesis of 5-HT (an antagonist)

C. iproniazid block MAO (agonists)
MONOAMINES EXAMPLES

Histamine (His/H is Diamine)

Catecholamines:
  • Dopamine (DA)
  • Noradrenaline (NA) (Norepinephrine, NE)
  • Adrenaline (Epinephrine)

Tryptamines:
  • Serotonin (5-HT)
  • Melatonin

Trace amines:
  • β-Phenylethylamine (PEA, β-PEA)
  • Tyramine
  • Tryptamine
Monoamines

Catecholamines

- **Dopamine - DA**
  - Dopaminergic

- **Norepinephrine - NE**
  - Noradrenergic

- **Epinephrine - E**
  - Adrenergic ~

Indolamines

- **Serotonin - 5-HT**
  - Serotonergic
Monoamines

Terminated by...
  • reuptake
  • monoamine oxidase - MAO
  • catechol-O-methyltranferase - COMT
  • also in liver

  • Reserpine ---> leaky vesicles
depletes monoamines ~
Monoamines

MAO

Reserpine

COMT

A

MAO

COMT

Monoamines
Indirect Monoamine Agonists

• **MAOIs**
  - Iproniazid

• **Reuptake blockers**
  - Tricyclic antidepressants
    • Imipramine
    • Desipramine

*Cocaine & Amphetamine*
Catecholamines:

The amino acid tyrosine is the precursor
NT is released thru axononal varicosities: swellings on the axon

1. **Norepinephrine (NE) noradrenalin**
   A. in the CNS this is produced in the locus ceruleus (nucleus in midbrain) &
      is distributed through out the CNS

2. **Epinephrine (E) adrenaline**
   A. works at the same receptors as NE
   B. stimulates the sympathetic nervous system
   C. ephedrine: alpha & beta receptor agonist
   D. propranolol: beta receptor blocker has antihypertensive effects

3 **Dopamine (DA)**
   A. produced in substantia nigra & ventral tegmental area (midbrain) & sent to
      the cortex, limbic system, hypothalamus, & basal ganglia
   B. implicated in movement disorders e.g., in Parkinson's disease (L-DOPA)
   C. cocaine and amphetamine work by preventing reuptake
   D. apomorphine: stimulates only autoreceptors (an antagonist)
Dopamine

- Only in central nervous system
  mostly inhibitory systems

Controls arousal levels and motor control in many parts of the brain. When levels are severely depleted in Parkinson's disease, patients are unable to move voluntarily. LSD and other hallucinogenic drugs are thought to work on the dopamine system.

- Reward
- Schizophrenia
- Movement
  - Nigrostriatal Pathway
- At least 5 DA-R types: $D_1$, $D_2$, $D_3$ etc.
Dopaminergic Drugs

• Agonist
  – L-dopa

• Antagonists
  – Chlorpromazine
    • $D_1$
  – Haloperidol
    • $D_2$
Dopamine Synthesis

Tyrosine $\rightarrow$ DOPA $\rightarrow$ DA

**tyrosine hydroxylase**

DOPA decarboxylase
Norepinephrine

- **Peripheral N.S.**
  - Sympathetic neuroeffector junction
  - Adrenal glands
- **Central N.S.**
  - Hypothalamus
  - Locus coeruleus
- **Alpha & Beta receptor subtypes**
  - $\text{NE}_\alpha$ & $\text{NE}_\beta$
Noradrenergic Drugs

• Agonists
  – Mescaline
  – Ephedrine

• Antagonist
  – Propranalol -
  – beta receptors ~
Norepinephrine Synthesis

Tyrosine $\rightarrow$ DOPA $\rightarrow$ DA $\rightarrow$ NE

- tyrosine hydroxylase
- DOPA decarboxylase
- dopamine $\beta$ hydroxylase
Serotonin

- NOT a catecholamine
- Peripheral
  - 98% in blood & smooth muscle
- Central N.S.
  - Raphe nucleus
  - Hypothalamus
- R subtypes: $5HT_1$ & $5HT_2$ ~
Serotonin

- Appetite
- Sleep
- Sex Drive
- Attention
- Pain
Serotonin Nerve Pathways in the Brain

Raphe nucleus
Sertonergic Drugs

• Agonists
  – **SSRIs**
    • Selective Serotonin Reuptake Inhibitors
  – **Buspirone**
  – MDMA
    • **Ecstacy**
Serotonin Synthesis

Tryptophan → 5-HTP → 5-HT

- Tryptophan hydroxylase
- 5-HTP decarboxylase
Gamma-aminobutyric acid

- **GABA** - GABAergic
- **Major NT in brain inhibitory system**
- Receptor subtypes
  - \( \text{GABA}_A \) - controls Cl- channel
  - \( \text{GABA}_B \) - controls K+ channel
- Precursor = glutamate ~
Neuropeptide

- Substance P - pain signaling
- Endorphins - analgesia, euphoria ~
Endorphins

Enkephalins and Endorphins

These are opioids that, like the drugs heroine and morphine, modulate pain, reduce stress etc. They may be involved in the mechanisms of physical dependence.

• **Opioids**
  - Dynorphin
  - met-enkephalin
  - leu-enkephalin
  - Beta-endorphin

• **Agonists**
  - morphine
  - heroin
  - codeine

• **Antagonists**
  - naloxone
  - naltrexone ~
Other NTs

• Excitatory amino acids
  – Glutamate & Aspartate

• Histamine
  – Inflammatory Response

• Nitric Oxide - It’s a gas

• Anandamide
Glutamate

- The brain's major excitatory neurotransmitter,
- vital for forging the links between neurons that are the basis of learning and long-term memory.
Neurotransmitter deficiency over 60 condition are related

- Depression
- Anxiety
- Panic Attacks
- Insomnia/Sleep disorders
- Premenstrual Tension
- Fibromyalgia
- Obesity
- Anorexia
- Bulimia
- “Hypoglycemia”
- Chronic pain states
- Migraines
- ADD/ADHD
Three Drugs (of many) which affect Neurotransmission

Methamphetamine

Nicotine

Alcohol
Methamphetamine alters Dopamine transmission in two ways:

1. Enters dopamine vesicles in axon terminal causing release of NT
2. Blocks dopamine transporters from pumping dopamine back into the transmitting neuron

More dopamine in the Synaptic Cleft causes neurons to fire more often than normal resulting in a euphoric feeling
1. After the drug wears off, **dopamine** levels drop, and the user “crashes”. The euphoric feeling will not return until the user takes more **methamphetamine**

2. Long-term use of methamphetamine causes dopamine axons to wither and die.

3. Note that **cocaine** also blocks **dopamine** transporters, thus it works in a similar manner.
•**Nicotine** binds to the *presynaptic* receptors exciting the neuron to fire more action potentials causing an *increase* in *dopamine* release.

•**Nicotine** also affects neurons by *increasing* the number of synaptic vesicles released.
How does alcohol affect synapses?

- Alcohol has multiple effects on neurons. It alters neuron membranes, ion channels, enzymes, and receptors.

- It **binds directly to receptors** for acetylcholine, serotonin, and gamma aminobutyric acid (GABA), and glutamate.

- We will focus on GABA and its receptor.
Alcohol and the GABA Receptor

• When alcohol enters the brain, it binds to **GABA** receptors and amplifies the **hyperpolarization** effect of **GABA**.
• The neuron activity is further diminished
• This accounts for some of the **sedative affects** of alcohol
The Adolescent Brain and Alcohol

- The brain goes through dynamic change during adolescence, and alcohol can seriously damage long- and short-term growth processes.
- Frontal lobe development and the refinement of pathways and connections continue until age 16, and a high rate of energy is used as the brain matures until age 20.
- Damage from alcohol at this time can be long-term and irreversible.
The Adolescent Brain (cont.)

• In addition, short-term or moderate drinking impairs learning and memory far more in youth than adults.

• Adolescents need only drink half as much as adults to suffer the same negative effects.

• To see an animation of GABA receptors and the influence of alcohol, http://www.thirteen.org/closetohome/animation/gaba-anim-main.html
# Drugs That Influence Neurotransmitters

<table>
<thead>
<tr>
<th>Change in Neurotransmission</th>
<th>Effect on Neurotransmitter release or availability</th>
<th>Drug that acts this way</th>
</tr>
</thead>
<tbody>
<tr>
<td>increase the number of impulses</td>
<td>increased neurotransmitter release</td>
<td>nicotine, alcohol, opiates</td>
</tr>
<tr>
<td>release neurotransmitter from vesicles with or without impulses</td>
<td>increased neurotransmitter release</td>
<td>amphetamines, methamphetamines</td>
</tr>
<tr>
<td>release more neurotransmitter in response to an impulse</td>
<td>increased neurotransmitter release</td>
<td>nicotine</td>
</tr>
<tr>
<td>block reuptake</td>
<td>more neurotransmitter present in synaptic cleft</td>
<td>cocaine, amphetamine</td>
</tr>
<tr>
<td>produce less neurotransmitter</td>
<td>less neurotransmitter in synaptic cleft</td>
<td>probably does not work this way</td>
</tr>
<tr>
<td>prevent vesicles from releasing neurotransmitter</td>
<td>less neurotransmitter released</td>
<td>No drug example</td>
</tr>
<tr>
<td>block receptor with another molecule</td>
<td>no change in the amount of neurotransmitter released, or neurotransmitter cannot bind to its receptor on postsynaptic neuron</td>
<td>LSD, caffeine</td>
</tr>
</tbody>
</table>

NIH Publication No. 00-4871
**Intoxication** vs. **Withdrawal**

**Disinhibition**, **Sedation**, **Loss of Balance**

**Hypertension**, **Memory disruption**

**Sedation**, **Euphoria**

**Mood Elevation**

**GABA**

**Epinephrine**

**L-glutamic Acid**

**Serotonin**

**Dopamine**

**Anxiety**, **Insomnia**, **Seizures**

**Hypertension**, **Tachycardia**

**Delirium**, **Seizures**

**Insomnia**, **Mood Disorder**

**Dysphoria**
**Acetylcholine deficiency**

**Acetylcholine deficiency signs/symptoms:**
- Difficulty remembering names and faces after meeting people
- Difficulty remembering people’s birthdays and numbers
- Difficulty remembering lists, directions or instructions
- Forgetting common facts
- Trouble understanding spoken or written language
- Forget where I put things (e.g. keys)
- Making simple mistakes at work
- Slowed and confused thinking
- Difficulty finding the right words before speaking
- Disorientation
- Prefer to do things alone than in groups / social withdrawal
- Rarely feel passionate
- Feel despair and lack joy
- Lost some of my creativity
- Lack imagination
- Dry mouth

Acetylcholine levels may be low due to a combination of genetic and acquired reasons. Acetylcholine can be raised effectively using either nutrient based therapies or medications.

**Factors which reduce acetylcholine levels:**
- Choline (precursor) deficiency
- B1 & B5 deficiency
- Chronic stress
- Inadequate sleep
- Elevated blood sugar/insulin resistance
- Mercury, lead, aluminium, PCB’s, fertilizers, pesticides and EMF exposure
- Over-methylation
Clinical Aspects of ACh Systems

Alzheimer's disease

loss of ACh neurons in the basal nucleus of Meynert

Aricept—ACh agonist
**Dopamine deficiency**

**Dopamine deficiency signs/symptoms:***
- Physically fatigued easily
- Sleep too much and trouble getting out of bed
- Reduced ability to feel pleasure
- Flat, bored, apathetic
- Low drive, motivation & enthusiasm
- Depressed
- Difficulty getting through a task even when interesting to me
- Procrastinator/little urgency
- Shy/introvert
- Mentally fatigued easily
- Difficulty paying attention and concentrating
- Slow thinker and/or slow to learn new ideas
- Put on weight easily
- Crave uppers (e.g. caffeine/sugar/nicotine/diet soft drinks/cocaine/amphetamines)
- Use these improve energy/motivation/mood
- Prone to addictions (e.g. alcohol)/addictive personality
- Light headedness
- Reduced libido and/or impotence
- Family history of depression/alcoholism/ADD

Dopamine levels may be low due to a combination of genetic and acquired reasons. Dopamine can be raised effectively using either nutrient based therapies or medications. Dopamine is synthesized form the amino acid tyrosine.

**Factors which reduce dopamine levels:**
- **Chronic stress**
- Inadequate sleep
- Hypothyroidism
- Lead, arsenic and cadmium exposure
- Under-methylation
- **Tyrosine (precursor) deficiency**
- Magnesium, iron, zinc & vitamins B3/B6/C/D deficiency
- **Excess copper levels**
- Genetic dopamine receptor abnormalities
- Chronic opioid, alcohol & marijuana use
- Adrenal insufficiency
- **Glutathione deficiency**
- **Parkinson's Disease**
- Influenza
- **Estrogen deficiency**
- Human growth hormone deficiency
**Endorphin deficiency**

**Endorphin deficiency signs/symptoms:**
- Very emotionally sensitive
- Cry easily
- Emotional pain really gets to you
- Find it hard to get through losses or grieving
- Difficulty experiencing pleasure
- Been through a lot of physical or emotional pain
- Overly responsible or time urgent
- Low pain tolerance
- Chronic pain (e.g. back aches, neck aches)
- Physical pain really gets to you
- Use alcohol/chocolate/carbs for relaxation, numbing, or comfort
- Use codeine, methadone, darvon, heroin
  - Have had difficulty stopping one of these

Endorphin levels may be low due to a combination of genetic and acquired reasons. Endorphins can be raised effectively using either nutrient based therapies or medications.

**Factors which reduce endorphin levels:**
- Chronic stress
- Chronic pain
- Chronic GABA deficiency
- Chronic opioid and alcohol use
- Chronic inflammation
- Genetic endorphin deficiency
**GABA deficiency**

**GABA deficiency signs/symptoms:**
- Anxious/nervous/jumpy/'on edge'
- Feel panicky/panic attacks
- Feel stressed/pressured/overwhelmed
- Have trouble relaxing/loosening up
- Low stress tolerance
- Body tends to be tense/stiff/uptight
- Butterflies in stomach
- Lump in throat
- Trembling/twitching/shaking
- Sweaty, clammy hands
- Sleep problems
  - Valium/xanax/avitan/GABA relax you
  - Use alcohol/food/cigarettes to relax
  - Heart palpitations and fast pulse
- History of having seizures
- Family history of anxiety or panic attacks

GABA is our relaxing (anti-anxiety) neurotransmitter which is raised by valium.

GABA levels may be low due to a combination of genetic and acquired reasons.

GABA can be raised effectively using either nutrient based therapies or medications. GABA is synthesized from the amino acid glutamine.

**Factors which reduce GABA levels:**
- Glutamaine (precursor) deficiency
- B1, B6, zinc, manganese & iron deficiency
- Chronic stress

**Chronic pain**
- Inadequate sleep
- Progesterone deficiency
- Mercury and lead exposure
- Alcohol withdrawal

**Caffeine excess**
- Excessive electromagnetic radiation

**Excessive loud noise exposure**
Serotonin deficiency
Serotonin deficiency signs/symptoms:
- Depressed
- Nervous/anxious
- Worrier
- Fears/phobias
- Negative/pessimistic
- Irritable/impatient/edgy
- Obsessive compulsive tendency
- Think about the same things over & over again
- Self destructive or suicidal thoughts/plans
- Low self esteem/confidence
- Rage/anger/explosive behavior/assaultive
- Sleep problems/light sleeper
- Feel worse in & dislike dark weather
- Crave sugar/carbohydrates/alcohol/marijuana
  - Use these substances to improve mood & relax
- Chronic pain (e.g. headaches, backaches, fibromyalgia)
- PMS
- Antidepressants or 5-HTP improve mood
- Family history of depression/anxiety/OCD/eating disorders

Serotonin levels may be low due to a combination of genetic and acquired reasons. Serotonin can be raised effectively using either nutrient based therapies or medications. Serotonin is synthesized from the amino acid tryptophan.

Factors which reduce serotonin levels:
- Stress
- PCB’s, pesticides and plastic chemicals exposure
- Under-methylation
- Inadequate sunlight exposure
- Tryptophan (precursor) deficiency
- Iron, calcium, magnesium, zinc, B3, B6, folate & vitamin C deficiency
- Inadequate sleep
- Glutathione deficiency
- Chronic infections
- Food allergies
- Genetic serotonin receptor abnormalities
- Chronic opioid, alcohol, amphetamine & marijuana use
- Human growth hormone deficiency
- Progesterone deficiency
- Impaired blood flow to brain
- Insulin resistance or deficiency
“How do the levels of serotonin and catecholamine neurotransmitters get to such critically low levels?” There are several explanations.

The first is that neurotransmitter depletion is nutritionally based. Neurotransmitters are made from amino acids that must be obtained in the diet. In addition, amino acids, vitamins and minerals eaten in food are required for the creation of the neurotransmitters.

If the diet is deficient, neurotransmitter deficiency develops.

There are multiple medications that have shown to cause depletion of serotonin and/or catecholamine in the urine. as Prozac, Paxil, Zoloft

These are the medications prescribed to increase the activity of serotonin in the brain such as Prozac, Paxil, Zoloft, etc.

Apparently as a result of increasing the brain level of serotonin, the body increases the metabolism of serotonin and thus the levels slowly decline because these medications do nothing to increase the level, they just re-circulate the already low level.

Caffeine, ephedrine, ephedra and other stimulants including Ritalin, chocolate, etc. also seem to reduce the effectiveness of neurotransmitters thereby creating a resistance to neurotransmitters.

Phentermine (of the Phen-Fen diet) actually cause long-term damage to the receptor so that in order to get the effect of serotonin, you have to have an even higher level. This is why so many people gain even more weight after stopping Phen-Fen.
Sensory overload. The brain is bombarded by sounds, rapid visual effects from television, movies, electronic monitors flickering faster than the eye can detect, radio waves, fluorescent artificial light, etc.

All of this requires the brain to modulate this sensory bombardment so that you can stay focused on the task in front of you. Brain overload means that you have to literally calm yourself down.

Rapid lifestyle, stress, over work, etc. may also contribute.

Since the largest source of neurotransmitters is the gastrointestinal tract, dysfunction as discussed above could be a major contributory component. This would include congestive bowel toxicity, candidal/yeast overgrowth conditions, increased intestinal permeability (leaky gut syndrome)

It has been suggested that several SSRI medications deplete 40-60% of the serotonin receptors in the brain. It is also reported that receptors in the liver, kidneys, and colon are also damaged by SSRIs.
ingestion of various food allergens or sensitivities, inhalation or ingestion of various chemicals, chemical sensitivities, rapid changes in hormone levels, rapid changes in barometric pressure, head cold or sinus congestion, rapid changes in blood sugars, dehydration, inadequate exposure to sunlight (hence the excessive conversion of serotonin to melatonin), and hepatobiliary dysfunction. These remarks may be based on the precipitation of migraines, to always be related to serotonin imbalance.
Symptoms seen in complex appetite (misnamed “hypoglycemia”)

<table>
<thead>
<tr>
<th>Tremor</th>
<th>Headaches</th>
<th>Lightheadedness</th>
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<tbody>
<tr>
<td>Dizziness</td>
<td>Sweating</td>
<td>Irritability</td>
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<tr>
<td>Nausea</td>
<td>Anxiety</td>
<td>Disorientation</td>
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<tr>
<td>Goose bump skin</td>
<td>Feeling of uneasiness</td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>
Figure 2. Tryptophan metabolism.
<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Postsynaptic effect</th>
<th>Derived from</th>
<th>Site of synthesis</th>
<th>Postsynaptic receptor</th>
<th>Fate</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acetyl choline (Ach)</td>
<td>Excitatory</td>
<td>Acetyl co-A + Choline</td>
<td>Cholinergic nerve endings Cholinergic pathways of brainstem</td>
<td>1. Nicotinic 2. Muscarinic</td>
<td>Broken by acetyl cholinesterase</td>
<td>Cognitive functions e.g. memory Peripheral action e.g. cardiovascular system</td>
</tr>
<tr>
<td>2. Catecholamines i. Epinephrine (adrenaline)</td>
<td>Excitatory in some but inhibitory in other</td>
<td>Tyrosine produced in liver from phenylalanine</td>
<td>Adrenal medulla and some CNS cells</td>
<td>Excites both alpha α &amp; beta β receptors</td>
<td>1. Catabolized to inactive product through COMT &amp; MAO in liver 2. Reuptake into adrenergic nerve endings 3. Diffusion away from nerve endings to body fluid</td>
<td>For details refer ANS. e.g. fight or flight, on heart, BP, gastrointestinal activity etc. Norepinephrine controls attention &amp; arousal.</td>
</tr>
<tr>
<td>ii. Norepinephrine</td>
<td>Excitatory</td>
<td>Tyrosine, found in pons. Reticular formation, locus coeruleus, thalamus, mid-brain</td>
<td>Begins inside axoplasm of adrenergic nerve ending is completed inside the secretary vesicles</td>
<td>α₁, α₂, β₁, β₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iii. Dopamine</td>
<td>Excitatory</td>
<td>Tyrosine</td>
<td>CNS, concentrated in basal ganglia and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and tubero-hypophyseal pathway</td>
<td>D₁ to D₅ receptor</td>
<td>Same as above</td>
<td>Decreased dopamine in parkinson’s disease. Increased dopamine concentration causes schizophrenia</td>
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<tr>
<td>3. serotonin (5HT)</td>
<td>Excitatory</td>
<td>Tryptophan</td>
<td>CNS, Gut (chromaffin cells) Platelets &amp; retina</td>
<td>5-HT\textsubscript{1} to 5-HT\textsubscript{7}</td>
<td>Inactivated by MAO to form 5-hydroxyindoleacetic acid(5-HIAA) in pineal body it is converted to melatonin</td>
<td>Mood control, sleep, pain feeling, temperature, BP, &amp; hormonal activity</td>
</tr>
<tr>
<td>4. Histamine</td>
<td>Excitatory</td>
<td>Histidine</td>
<td>Hypothalamus</td>
<td>Three types (H_{1}), (H_{2}), (H_{3}) receptors found in peripheral tissues &amp; the brain</td>
<td>Enzyme diamine oxidase (histaminase) cause breakdown</td>
<td>Arousal, pain threshold, blood pressure, blood flow control, gut secretion, allergic reaction (involved in sensation of itch)</td>
</tr>
<tr>
<td>5. Glutamate</td>
<td>Excitatory 75% of excitatory transmission in the brain</td>
<td>By reductive amination of Kreb’s cycle intermediate (\alpha)–ketoglutarate.</td>
<td>Brain &amp; spinal cord e.g. hippocampus</td>
<td>Ionotropic and metabotropic receptors. Three types of ionotropic receptors e.g. NMDA, AMPA and kainate receptors.</td>
<td>It is cleared from the brain ECF by Na\textsuperscript{+} dependent uptake system in neurons and neuroglia.</td>
<td>Long term potentiation involved in memory and learning by causing Ca\textsuperscript{++} influx.</td>
</tr>
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<tr>
<td><strong>6. Aspartate</strong></td>
<td>Excitatory</td>
<td>Acidic amines</td>
<td>Spinal cord</td>
<td>Spinal cord</td>
<td></td>
<td>Aspartate &amp; Glycine form an excitatory / inhibitory pair in the ventral spinal cord</td>
</tr>
<tr>
<td><strong>7. Gama amino butyric acid (GABA)</strong></td>
<td>Major inhibitory mediator</td>
<td>Decarboxylation of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron.</td>
<td>CNS</td>
<td>GABA – A increases the Cl⁻ conductance, GABA – B is metabotropic works with G – protein GABA transaminase catalyzes. GABA – C found exclusively in the retina.</td>
<td>Metabolized by transamination to succinate in the citric acid cycle.</td>
<td>GABA – A causes hyperpolarization (inhibition) Anxiolytic drugs like benzodiazepine cause increase in Cl⁻ entry into the cell &amp; cause soothing effects. GABA – B cause increase conductance of K⁺ into the cell.</td>
</tr>
<tr>
<td><strong>8. Glycine</strong></td>
<td>Inhibitory</td>
<td>Is simple amino acid having amino group and a carboxyl group attached to a carbon atom</td>
<td>Spinal cord</td>
<td>Glycine receptor makes postsynaptic membrane more permeable to Cl⁻ ion.</td>
<td>Deactivated in the synapse by simple process of reabsorption by active transport back into the presynaptic membrane</td>
<td>Glycine is inhibitory transmitted found in the ventral spinal cord. It is inhibitory transmitter to Renshaw cells.</td>
</tr>
</tbody>
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