# Section Two: Chapter 8: Neurotransmitters

Now we venture into what we think we know regarding how (by what mechanism) the body actually sends signals. Our lives are much more than chemicals, but in this chapter the focus is on chemical signaling.

**Neurotransmitters** (NT's) are signal molecules that seem to be released from neurons as a form of communication. There are believed to be about 60 known neurotransmitters. They can function as **excitatory** or **inhibitory** substances, but this can change depending on the location of neuron and type of effector (target) cell it acts on. For example, Acetylcholine (ACh) contracts skeletal muscle and the same ACh relaxes smooth muscle! How can the same neurotransmitter have contrasting effects on various tissues? The answers lies in the ***type of receptor*** on the target tissue. The specific type of receptor on the tissue will determine how the tissue responds to various signal molecules.

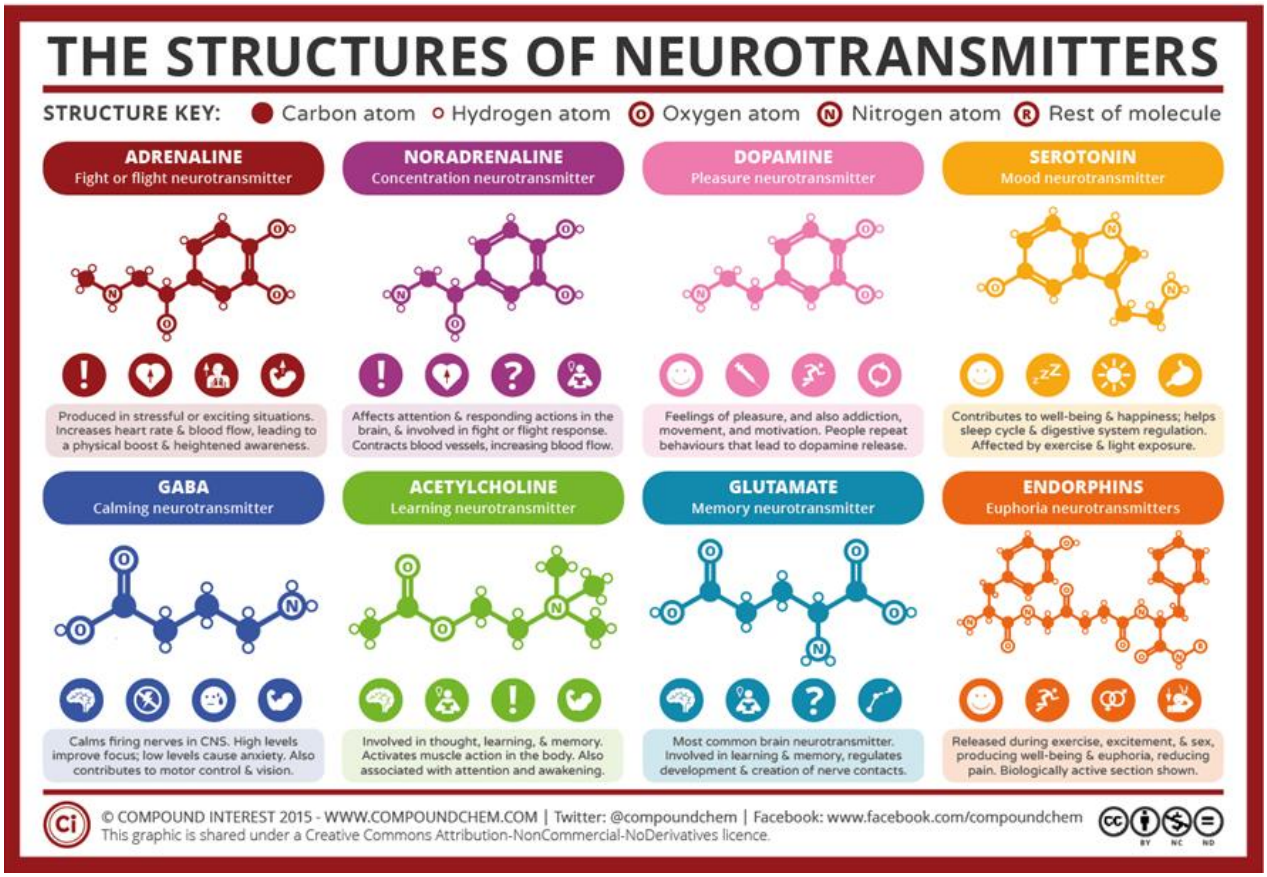
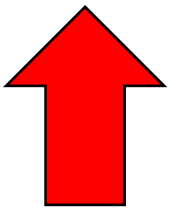



**Figure 8.1** Above is the "Simple Guide to Neurotransmitters" graphic giving an overview of the most common neurotransmitters in the body and their key structural components. Also provided is some basic information about what they do and their connections to other parts of the body.
This is shared from the website www.compoundchem.com/2015/07/30/neurotransmitters.

## Classifications of Neurotransmitters

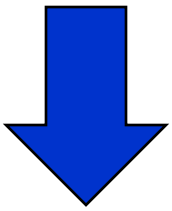
There are many ways to classify neurotransmitters and we need to be familiar with a few key ways that these signal molecules can be organized. We will see that some neurotransmitters can be **excitatory** or **Inhibitory**, they also fall into broad categories depending on their **chemical nature**. The mode of action of neurotransmitters can vary, and sometimes it is relevant to consider the location in the body in order to understand which neurotransmitters may dominate and the multitude of effects they may have.

**Excitatory Neurotransmitters**:



These types of neurotransmitters have **excitatory effects** on other neurons or the effector tissue they innervate. Succinctly, this means they increase the likelihood that the neuron receiving this signal will fire an action potential or respond. At a synapse (with another neuron), an excitatory neurotransmitter causes a **depolarization** of the post-synaptic membrane, this pushes the membrane up, to become more positive, thus it's termed an **excitatory postsynaptic potential** (EPSP) because it increases the prospect that the effected neuron will fire an action potential. Think of the graphs shown in chapter 7 where the RMP became elevated and got closer to threshold. This was "excitation" of the membrane. For other effector tissue (like glands or muscle) it will stimulate action or activity. Some of the major excitatory neurotransmitters include **glutamate**, **epinephrine**, **norepinephrine**, **acetylcholine** and **dopamine**.

**Inhibitory Neurotransmitters**:



These types of neurotransmitters have **inhibitory effects** on other neurons or the effector tissue they innervate. Succinctly, this means they decrease the likelihood that the neuron receiving this signal will fire an action potential or yield a response. At a synapse (with another neuron), an inhibitory neurotransmitter causes a **hyperpolarization** of the post-synaptic membrane, this pulls the membrane down, to become more negative, thus it's termed an **inhibitory postsynaptic potential** (IPSP) because it decreases the prospect that the effected neuron will fire an action potential. Again recall the graphs that show the RMP getting lowered, moving it further away from threshold. This was "inhibition" of the membrane. For other effector tissue it will inhibit action or activity. Some of the major inhibitory neurotransmitters include **serotonin**, **gamma-aminobutyric acid** (GABA), **acetylcholine** and **dopamine**.

Some neurotransmitters can be have both excitatory and inhibitory effects. As you can see above, some neurotransmitters are listed in both categories. That is because they can cause EPSP's or IPSP's, but this depends on the location of neuron (or other cell), and importantly, depends on the specific type of **receptors** on the target cell that it acts on. Neurotransmitters that have both excitatory and inhibitory effects include acetylcholine and dopamine. When we take a closer look at receptors ahead, we will have a much better understanding of why the same neurotransmitter can have various effects.

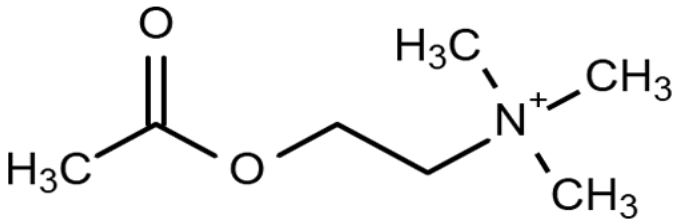
## Neurotransmitters can be divided into five categories

The most common way to organized and categorize neurotransmitters is by their structural, and therefore chemical, properties. This is mostly because there have been many studies on the similarities of actions and effects of neurotransmitters based on their chemical properties. As this chapter unfolds we will examine five categories of neurotransmitters in the body, providing details of the exemplary neurotransmitters within each of these groups. The five (5) categories are as follows:

1. **Acetylcholine (ACh)**
2. **Amino Acids**
3. **Biogenic Amines**
4. **Neuropeptides**
5. **Soluble Gases (Nitric Oxide)**

## ① ACh

Acetylcholine (ACh) is a single molecule that is in a class all by itself, that is how important it is! It **ubiquitous** (found everywhere) and plays a vital role voluntary and automatic control as well as memory, and learning. Its chemical structure is fairly simple (see below).




Acetylcholine has the honor or being the first neurotransmitter to ever be identified in the brain (in 1914). It is released by neurons in the **central nervous system** (CNS) and many neurons in the **peripheral nervous system** (PNS). Neurons that release ACh are termed "**Cholinergic**" neurons, after the *choline* part of the name. ACh is thee neurotransmitter released by somatic motor neurons in the neuromuscular junctions (NMJ) of **skeletal muscle**, and also immensely involved in the **autonomic nervous system** (see **Fig. 8.2**)

### ACh Actions

It has been established that ACh plays a large variety of roles throughout the brain, and is most commonly associated with **memory** and **learning**. In fact, there is a requirement to have enough acetylcholine in the brain to form memories. For the physiological concepts we will be focusing on, ACh plays a role in **voluntary motor control**, '**automatic**' control, **memory**, regulation of **attention**, **learning** and **sleeping**.

It is worth mentioning that ACh is also involved in **synaptic plasticity**. This is a dynamic process in the brain which allows brain cells to preform new roles, store additional information and new memories. Levels of ACh have even been shown to rise during rapid eye movement (REM) sleep, the phase thought to be the critical stage of sleep when humans may reorganize new information and memories. More recent studies suggest acetylcholine also helps you stay awake, alert and focused.

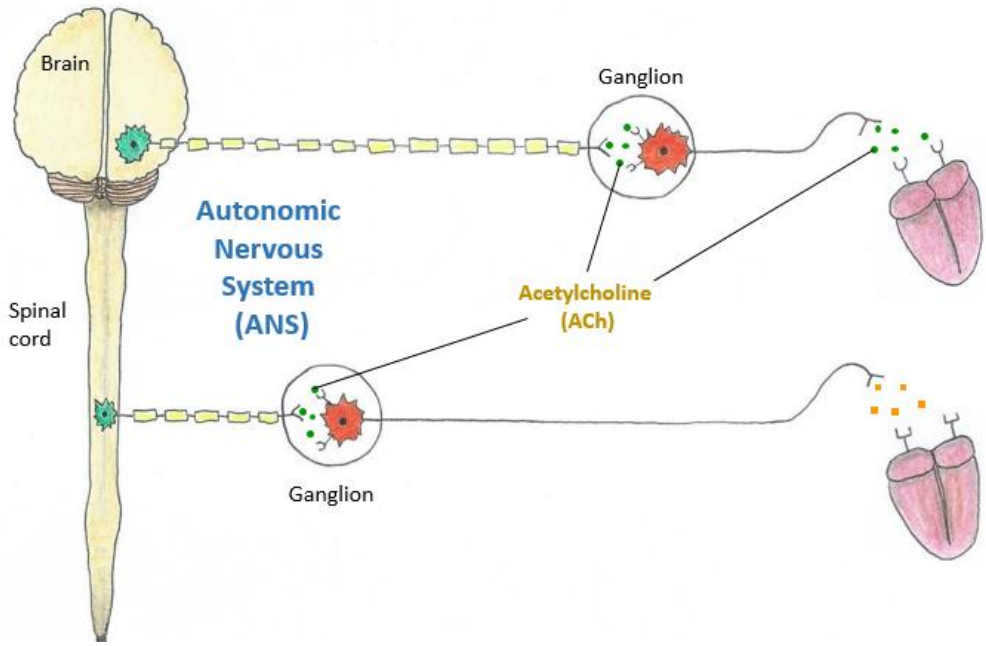



**Figure 8.2** The role of acetylcholine (ACh) in both divisions (parasympathetic and sympathetic) of the autonomic nervous system (ANS) is foundational. Note that ACh is release by 3 of the 4 types of neurons involved in the ANS.

In addition, ACh can promote relaxation in the body by stimulating the **vagus nerve**, this is the primary nerve for the **parasympathetic** division of the autonomic nervous system (ANS) and counteracts the "fight-or-flight" tendencies of the **sympathetic** division of the ANS.

In the peripheral nervous system (PNS), ACh is the sole neurotransmitter used by the **Somatic Nervous System** (SNS). At the neuromuscular junctions (NMJ), ACh binds to **nicotinic receptors** (see below) on skeletal muscle and causes excitation (contraction) of skeletal muscle.

In the **Autonomic Nervous System** (ANS), ACh is release by all neurons **at the ganglia** and binds to nicotinic receptors on postganglionic neurons. It is also released by parasympathetic postganglionic neurons and binds with muscarinic receptors on effector tissue (cardiac muscle, smooth muscle and glands).

### What Receptors do ACh Bind to?

ACh binds to two types of receptors, **nicotinic** and **muscarinic** (see chapter 10 for more details). As a consequence, these are called '**Cholinergic**' receptors denoting the importance of choline as a part of acetylcholine, discussed below.

In general terms, **nicotinic receptors are always excitatory**, meaning that when these receptors are stimulated they make the target membrane depolarize and cause an EPSP or excite the membrane.

For the most part, **muscarinic receptors are generally inhibitory**, in that when these receptors are stimulated they make the target membrane hyperpolarize and cause an IPSP or inhibit the membrane.

### Drugs that Block ACh

The anticholinergic drug **scopolamine** has been was used as a drug for motion sickness and postoperative nausea and vomiting. It is also sometimes used before surgery to decrease saliva production. The effects of using scopolamine are very unpleasant, including dry mouth, drowsiness, dizziness, decreased sweating, and constipation. It is also known to impair learning and memory in both humans and animals. Wherever possible at all, skip using these drugs as they also block other very important signaling.

### How does your body make ACh?

Acetylcholine is synthesized by the enzyme **choline acetyltransferase** from the compounds **choline** and **acetyl-CoA**. The choline part is an *essential nutrient*, this means our body cannot make its own choline and therefore we must get it in our **diet**. Since choline is a building block of acetylcholine, foods that have a naturally high choline content are important to include in a board, eclectic and healthy diet.

Food high in **choline** include: Whole eggs, yeast extract, meats and fish, fermented soy, seeds, nuts and whole grains.

Whole eggs

Yeast extract

Seeds and nuts

Studies in laboratory research suggests that consuming foods or supplements rich in **choline** may **elevate levels of acetylcholine in the brain**, having the potential of fortifying neurons there. Choline is not a vitamin but is often grouped with the water-soluble vitamin B complex due to its similarities.

### What if we are Lacking ACh?

Without enough choline, it is possible to be lacking in acetylcholine. As we shall see shortly, without ACh, muscles cannot contract and many other areas of body function are adversely affected. Some of the major symptoms of acetylcholine deficiency are:

- Constipation and gastroparesis (paralysis of the stomach).
- Low muscle tone (skeletal muscle).
- Memory and learning difficulties.
- Problems with word recall when speaking.
- Dry mouth and eyes.
- Orthostatic hypotension (low blood pressure when moving to an upright position).

Keeping this information in mind, as a few simple additions to the diet (shown above in eggs, yeast extract and nuts and seeds) could easily address any choline deficiency.

Another significant link of choline deficiency is with **Alzheimer's disease** and **dementia**, as people with these conditions often have low acetylcholine levels. With an estimated 90% loss of acetylcholine in brains of patients with Alzheimer's disease. Studies have indicated that children with **autism** may also lack acetylcholine in their brain, which can contribute to intellectual impairment. Increasing acetylcholine can improve cognitive and social symptoms associated with autism. It's also been found that patients with relapsing-remitting **multiple sclerosis** have lower acetylcholine levels.

### Myasthenia Gravis

The condition called **myasthenia gravis** (MG) is also related to ACh but is associated with the ability of ACh to bind to nicotinic receptors. MG is a condition characterized by the destruction of nicotinic receptors on skeletal muscle. As will be seen in discussions of skeletal muscle physiology in chapter 13, if there are fewer receptors on this muscle tissue, this would lead to reduced transmission of nerve impulses at the motor end plate of the neuromuscular junction. The outcome would be **weakness** and **fatigability** of skeletal muscle, in other words muscle strength is reduced. Look up the etymology of the words *myasthenia gravis* and it should provide a good link to its meaning.

In the technical sense, the weakness of voluntary skeletal muscle in this condition is caused by the reduction in ACh effectiveness after repeated stimulation. Symptoms of can range from mild to severe. Including: weakness in the arms, legs, hands, fingers, or neck. Difficulties with mastication (chewing) and dysphagia (difficulty or discomfort swallowing) indicate weakness of pharyngeal and laryngeal muscles.

## ② Amino Acids

Interestingly, the good old building blocks of proteins, **amino acids**, are very versatile and can act as neurotransmitters. If an amino acid is able to act as a signal molecule across that synapse, then it qualifies a neurotransmitter. There are many examples, but we will cover four well established amino acid neurotransmitters: **Glutamate**; **Aspartate**; **GABA**; and **Glycine**. These neurotransmitters fall into excitatory and inhibitory categories, the first two are excitatory and the last two are inhibitory

## Excitatory Amino Acids

**1) Glutamate** - accounts for approximately 75% of all excitatory transmission in the brain, so it is ***the most common excitatory neurotransmitter in the brain*.** It is also called glutamic acid. It's released in the **cerebral cortex** and **brain stem** and is involved in cognitive functions, such as learning and memory. It also regulates brain development and the creation of nerve contacts involved in neural networking.

If glutamate present in abnormally high concentration in the brain, for example when monosodium glutamate (MSG) is ingested in high quantities (as shown in animal studies), glutamate can be toxic to neurons due to over-exciting other neurons. Therefore anything that is introduced and overstimulates excitatory neurons can act as an 'excitotoxin' and cause damage to nervous tissue.

**Important Glutamate Receptors**

There are several types of ionotropic glutamate receptors and three of them are ligand-gated ion channels: **1)** N-methyl-D-aspartate (**NMDA**) receptors; **2)** α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (**AMPA**) receptors; **3)** and kainate receptors.

The **NMDA** and **AMPA** receptors are the most common and well described, and both are non-selective ligand-gated ion channels, which mainly allow the passage of $Na^+$ and $K^+$. They differ in that only $Na^+$ and $K^+$ passage occurs in AMPA receptors, whereas in NMDA receptors, $Ca^{2+}$ influx also occurs in addition to $Na^+$ and $K^+$. The NMDA receptors are found on post-synaptic membranes and play a crucial role in regulating a wide variety of neurological functions including **breathing**, **locomotion**, and **learning** and **memory formation**,

Glutamate also has a critical role in **neuroplasticity**, which is the nervous system's ability to change, adapt and modify its structure and function in response to experience and use. It used to be thought there was no such thing as neuroplasticity, but it is now widely observed and showcases the body's resilience. Balanced glutamate transmission is central for effective **neural circuitry** specifically for synaptic plasticity, which is the ability to strengthen or weaken signaling between neurons over time in order to shape learning and memory. Thus one of glutamate's roles in **learning**. Its excitatory actions strengthen the connections between existing neurons, a process called long-term potentiation (LTP).

Inhibition of Glutamate NMDA receptors include effects such as hallucinations, paranoid delusions, confusion, difficulty concentrating, agitation, alterations in mood, nightmares, catatonia, ataxia (a lack of muscle control or coordination in voluntary body movements), anesthesia, and learning and memory deficits. In other words, actively blocking these receptors is not a good idea, as it is usually very disturbing to human physiology and an unpleasant experience.

To reinforce this notion, some prominent NMDA receptor **antagonists** (inhibitors or blockers) include the drugs **ketamine**, which is a powerful anesthetic, and **dextromethorphan**, found in a cough suppressants where it inhibits the signals that trigger the cough reflex. Keep in mind that reflexes in the body are protective and essential. Another blocker is the opioid **methadone**, which is used by many government programs as a heroin substitute for those addicted to heroin. Ask why anyone would want to replace one highly addictive one drug with another highly addictive of drug that has many detrimental side effects? How could it be perceived that this would be some sort of effective treatment? It does not make any sense, except to prolong a person's drug addiction. None of these substances listed above would be a good idea for anyone to take if one preferred to become or stay healthy.

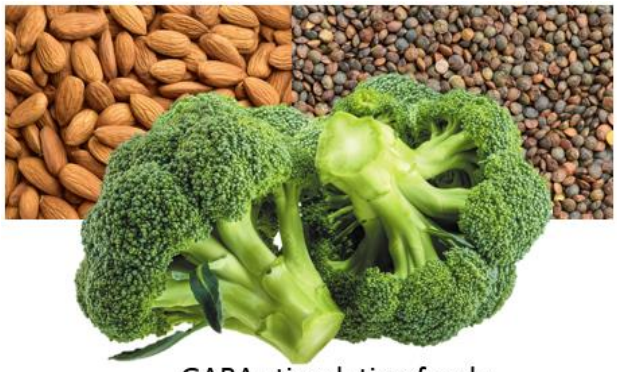
**2) Aspartate** - similar to glutamate but found mostly in the **spinal cord** for excitation (aspartic acid). It is thought to be the most abundant excitatory neurotransmitter in the spinal cord. It is also known as aspartic acid. It is implicated in the physiology of **learning** and **memory** processes. In the **gonads**, it plays a crucial role in **sex hormone synthesis**. It is like the excitatory counterpart to glycine (which is inhibitory) because aspartate is primarily localized to the ventral spinal cord, and also like glycine, aspartate opens ion channels and is inactivated by reabsorption into the presynaptic membrane.

## Inhibitory Amino Acids

**3) GABA** - Gamma Amino Butyric Acid (GABA) is **the most common inhibitory neurotransmitter in the brain**. Released in the **thalamus**, **hypothalamus**, **cerebellum**, **occipital lobe**, **limbic system** and **retina**. As the most common inhibitory neurotransmitter in the brain its primary role is to inhibit the firing of nerves in the CNS and as a consequence it acts to **calm** neural processing. Almonds are high in GABA and can be calming! Increased GABA levels improve mental focus and relaxation, whilst low levels can cause anxiety, and have also been linked with epilepsy. GABA also contributes to motor control and vision.

### GABA Receptors

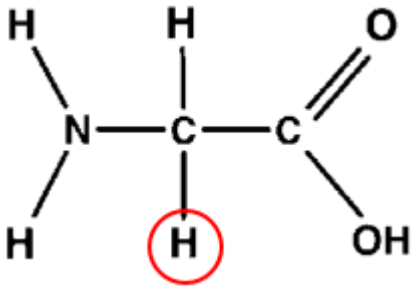
The two major classes of GABA receptors are classified as either **ionotropic $GABA_A$** (with $GABA_C$) receptors or **metabotropic $GABA_B$** receptors. There are significant $GABA_A$ receptors found in the **limbic system** which is an important region of the brain for processing emotional memories and personal feelings.



GABA stimulating foods

Drugs to treat epilepsy often act by increasing levels of GABA in the brain. **Benzodiazepines** (valium) are **GABA agonists**, meaning they act to stimulate GABA receptors and illicit similar responses to GABA (the true ligand) and help calm down those with anxiety. However, becoming addicted to valium poses a significant health problem. Therefore, a much better solution would be to eat foods that stimulate GABA (**almonds**, **lentils**, **broccoli**), as this also has a calming effect without detrimental side effects.

**4) Glycine** - is the simplest amino acid, its R group is just H (see right)




Glycine is the most common **inhibitory** neurotransmitter in the **spinal cord**. So it's like the equivalent of GABA in the brain but working to calm things down in the spinal cord. It is also released in the **brain** and **retina**. Glycinergic synapses are well-established in the regulation of **locomotion**, this makes sense because inhibitory signals such as ***reciprocal inhibition*** of antagonist muscle groups are a critical component in body movement. These neurons are major contributors to the regulation of neuronal excitability that is, toning it down. These neurons also control fluctuations in the sensory information between the periphery and the CNS, and operate in other motor activities like **respiration** or **vocalization**.

Note that glycine is the main amino acid in the fiber **collagen**, which is the most abundant fiber in the human body, replete in connective tissue of the skin, bone, ligaments, tendons and cartilage. The glycine

levels in the body can be boosted by consuming collagen, which can be attained in bone broths, poultry skin, legumes, seaweed, spinach, and many other foods that are high in protein (meat, egos, fish, or dairy).

## Be Cautious of Excessive amounts of specific Amino Acids that act as Neurotransmitters

Like so many other realms in human physiology, deficiencies and excesses can be problematic. The amino acids that act as neurotransmitters provide a good example of what can be detrimental about excessive amounts of these, especially if they lead to excessive excitation within the nervous system.

Glutamate acts as an **excitatory** neurotransmitter in our bodies. The flavor enhancer monosodium glutamate (**MSG**) has **glutamate** in it. Aspartate also acts as an excitatory neurotransmitter. The artificial sweetener *aspartame* is a synthetic molecule involving synthetic bonds between the two amino acids of **phenylalanine** and **aspartate**.

Here is a brief examination of the possible connection between both of these **excitatory** neurotransmitters and the overstimulation of regions of the nervous system. If overstimulation is excessive, this class of chemicals can cause a firing of impulses in nervous tissue at such a rapid rate that they become completely exhausted and depleted, which can in turn cause these neurons to deteriorate and die. Chemicals which act this way are called '**excitotoxins'**.

### Monosodium Glutamate (MSG)

Some may not appear to be affected by MSG or aspartame in what they consume, however, over the decades there has been documentation of a significant catalog of health concerns. The effects can seem as benign as headaches, but most who experience migraines are often debilitated by them. Other effects, though rare, are serious enough to have caused the food industry to label these ingredients prominently, or so we thought! There is a reason food manufactures use MSG as a flavor enhancer, that's because most people can't stop eating processed foods that contain MSG. Many favorite savory snack foods will have MSG in it, even though the ingredients label may not specifically list MSG. How can that be? There are many other names used for essentially the same active elements, and processed snack makers apparently wish to lull people into a false sense of relief when they read an ingredient label without MGS on it. However, the **Truth in Labeling** organization provides lists of the **hidden names for MSG** so people can now be on the lookout for a whole lot more ingredients to avoid. Foods always contain MSG when these words are on the label:

**Table 8.1** A list of various names for MSG that are used in packaged food ingredient labels.

| MSG | Gelatin | Calcium Caseinate |
|---|---|---|
| Monosodium glutamate | Hydrolyzed Vegetable Protein (HVP) | Textured Protein |
| Monopotassium glutamate | Hydrolyzed Plant Protein (HPP) | Yeast Extract |
| Glutamate | Autolyzed Plant Protein | Yeast food or nutrient |
| Glutamic Acid | Sodium Caseinate | Autolyzed Yeast |

By the 1950's baby food companies had already increased their focus on taste, adding sugar, salt and **MSG** to their formulas based on animal trials. It was found that if foods and beverages containing high amounts of glutamate and aspartate were consumed regularly, the nervous system would be effected and parts of the brain that are specifically targeted by excitotoxins are the **hypothalamus** and the **temporal lobe**. As we will see, these brain centers control behavior, emotions, sleep cycles, olfaction, hearing and detoxing. Therefore it is to our benefit to not poison those regions of our nervous system. Note, the added MSG was quietly removed from baby formulas once the potential dangers were recognized by consumers. However, one can only guess it was replaced with the same-same but with a different name.

### Aspartame - the Artificial Sweetener

As a quick example of how what we eat can be altered by our regular physiological pathways in the body that are normally used all the time, let's take the artificial sweetener 'aspartame' and see how the body normally responds to it.

The weak synthetic esterification bond between the two naturally occurring amino acids **phenylalanine** and **aspartate** that make the artificial '**aspartame'** is easily broken at temperatures above about 80° F. The breaking of this synthetic bond liberates **methanol**; this type of alcohol is toxic, the kind that you should not drink because it can make you go blind. See the bottle of methanol to the right, note the skull and cross bones label as a tip off to its toxicity.


In an attempt to protect the body, the enzyme **alcohol dehydrogenase** (remember that one?) acts on this methanol and converts it to **formaldehyde**, which is highly **cytotoxic** (cell killing). It turns out that humans lack the enzyme that many other animals have that would further convert the formaldehyde into the harmless **formic acid** (like what ants use to scent their trails for each other). Therefore, in humans the formaldehyde liberated remains in the body for the liver and kidneys to detoxify and remove. That takes a heavy toll on your hard working organs and causes other significant damage in other tissues.

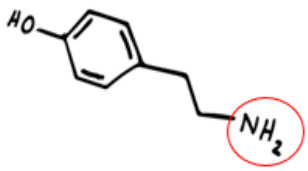
**Should it be Diet Soda or Regular? Which is best?**

That is essentially the same as asking yourself if you'd like to be hit on the foot with a sledgehammer or a baseball bat. Mmm… Baseball bat? Nah, make it neither. Refined sugar is an anti-nutrient (another topic for another day), and the synthetic artificial sweeteners are toxic and really no better. Select a beverage made by nature, like a tea, or Kombucha, or juice, and skip the toxic ingredients.

## ③ Biogenic Amines

These neurotransmitters are all derived from either the amino acid **tryptophan**, which is an essential amino acid, or **tyrosine**, which is considered 'conditionally essential', meaning synthesis may be deleteriously impacted in special conditions, such as catabolic stress – which just means when someone has a fight-or-flight response for too long a period of time.

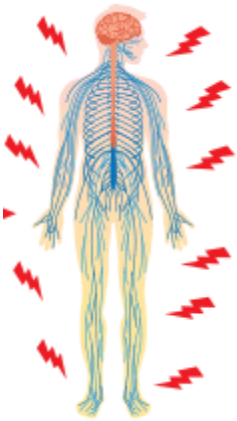
The COOH groups in the amino acid are replaced by **$NH_2$** groups (see right). There are two main categories of Biogenic Amines, they are **A) Catecholamines** (derived from **tyrosine**) and **B) Indolamines** (derived from **tryptophan**). All of these can also be referred to as ***monoamines***, which are degraded by the enzyme **Monoamine Oxidase** (MAO).



**A) <u>Catecholamines</u>** - three main catecholamines: Epinephrine (E), Norepinephrine (NE) and Dopamine.

**1) Epinephrine** (E)

Epinephrine used to be called **adrenaline**, and most people are familiar with the notion of some event or circumstance that "gets the adrenaline pumping", right? The release of epinephrine or norepinephrine as a neurotransmitter or a hormone prepares the body for **excitement** and **action**.



Primarily epinephrine is released as a **hormone** from the endocrine gland the **adrenal medulla**. There are two adrenals glands, one sitting on top of each kidney. The name epinephrine means above/on top of (epi); and the kidneys (nephrine) in relation to the location of the adrenal glands that sit on each kidney. As we will see in the renal section, the nephron is the function unit of the kidneys.

Epinephrine is released in response to something that is perceived as exciting, alarming, stressful or scary. Its purpose is to prepare the body for how to react to this stimuli. It is the classic "**Fight or Flight**" signal molecule. In general, when we experienced anger we fight, and when we experience fear we flee! When these strong emotions such as **anger** or **fear** cause epinephrine to be released into the bloodstream as a hormone, it is highly effective in preparing the body for stressful or exciting situations. It stimulates an increase in heart rate, and dilates airways allowing for greater air flow. It contracts most blood vessels thereby increasing blood pressure and it also diverts blood flow to the skeletal muscles and oxygen to the lungs. It stimulates sugar metabolism. All of these lead to a physical boost and heightened awareness. Stress tends to deplete our store of adrenalin, while exercise tends to increase it.

In terms of its role as a neurotransmitter, epinephrine is released in the **thalamus**, **hypothalamus** and **spinal cord**. Chemically and functionally it is very similar to the effects of Norepinephrine. It is important for forming memories. Think of how events in your life that have been incredibly exciting or stressful, and how most often they are easy events to remember, including fine details. This, in part, is both epinephrine (E) and norepinephrine (NE) at work.

### What is an "Epi-pen"?

The substance epinephrine acts quickly to dilate the airways and increase airflow when breathing, and it stimulates the heart, elevates blood pressure that is dropping, and mitigates swelling of the face, lips, and throat. Therefore, it is very handy to have if you are <u>allergic</u> to something, like a bee sting, drugs, foods or other substances and begin to trigger a sever reaction such as **anaphylactic shock**. A device called an **Epi-pen** seen at right in **Fig. 8.3** contains concentrated epinephrine within an easy to use injectable syringe.

**Figure 8.3** Examples of epi-pens for injectable epinephrine are shown.

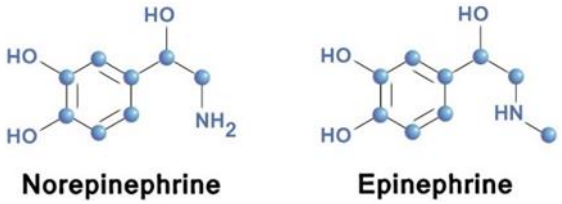
Serious life threatening reactions can occur, such as constricted airways causing difficulty breathing, swelling of throat, tongue, and a weak, rapid pulse. Plus nausea, vomiting, diarrhea, dizziness, fainting or loss of consciousness. This medication can be used in emergencies to alleviate these serious reactions by delivering epinephrine directly into the body via intramuscular (IM) injection. This allows for an immediate

yet controlled large amount of epinephrine to enter the bloodstream and start reversing the effects of the extreme reaction.

**2) Norepinephrine** (NE)

Norepinephrine is released by most **sympathetic** postganglionic nerve fibers of the autonomic nervous system (ANS). It is also released in the **cerebral cortex**, **hypothalamus**, **brain stem**, **cerebellum** and **spinal cord**. It has an important role in mood, dreaming, wakefulness and alertness levels. As discussed above, norepinephrine and epinephrine this used to be called noradrenaline and adrenaline respectively. That is why neurons that release norepinephrine (NE) or epinephrine (E) are termed "**Adrenergic**" neurons. Both NE and E bind to alpha (α) and beta (β) receptors, which are called *adrenergic receptors*. There are several subtypes for each of these receptors which is fully explored in the ANS chapter 10.

For the most part, NE is an excitatory or stimulatory neurotransmitter, typically elevating **mood** and **alertness**.




As it turns out, both NE and E are also released by the adrenal medulla, when it is stimulated by the Sympathetic division of the ANS. Most predominantly it is E that is released (**80%**) and to a much lesser degree NE (**20%**).

Norepinephrine is released when a host of physiological changes are activated by a perceived **stressful event**. In the central nervous system this is caused in part by activation of an area of the brain stem called the **locus coeruleus**. This is the principal site and the origin of most norepinephrine pathways in the brain. In Latin locus means 'place, location or spot' and coeruleus means 'dark or sky blue', so together it means "blue spot". Looking at the mid-sagittal section of the brain in **Figure 8.4** below, notice how the core of the norepinephrine pathways are highly integrated into all of the other brain regions.

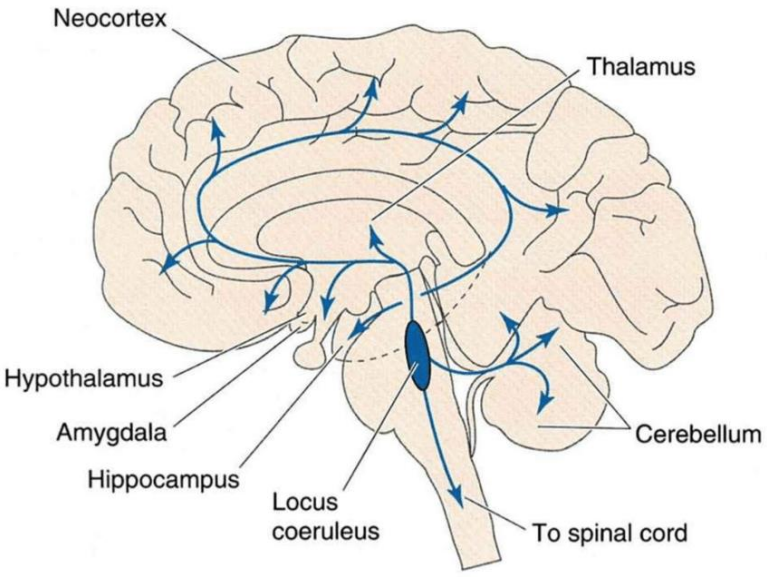



**Figure 8.4** The locus coeruleus (LC) is shown as the 'blue spot' high in the brain stem. Notice how the LC has widespread projections throughout the forebrain, brainstem, cerebellum, and spinal cord, radiating out like a roundabout in the brain. This enables many regions of the brain and spinal cord to become activated simultaneously and quickly, receiving input from a wide range of sources.

## How Drugs Impact Norepinephrine

The high energy state of alert that the release of NE causes in the body can be augmented or blocked by drugs, be they prescribed medications or other drugs. Below are some relevant examples.

### Cocaine

The highly addictive drug ***cocaine*** has its effects in the body when it interferes with NE and dopamine transmission in the brain. Cocaine acts to block the reuptake of both NE and dopamine that would normally go back into adrenergic or dopaminergic neurons that released them. Since the re-uptake mechanism is one way to clear up the synaptic cleft, when this is blocked it causes an increase in the amount of NE that lingers in the synaptic cleft, thus increasing the stimulatory effects on the target cell. See the drawing of the synapse to the right in **Fig. 8.5**. This elevated NE accounts for the super 'alert' state experienced for most who are on cocaine, and the elevated dopamine enhances the perceived pleasure of the experience.

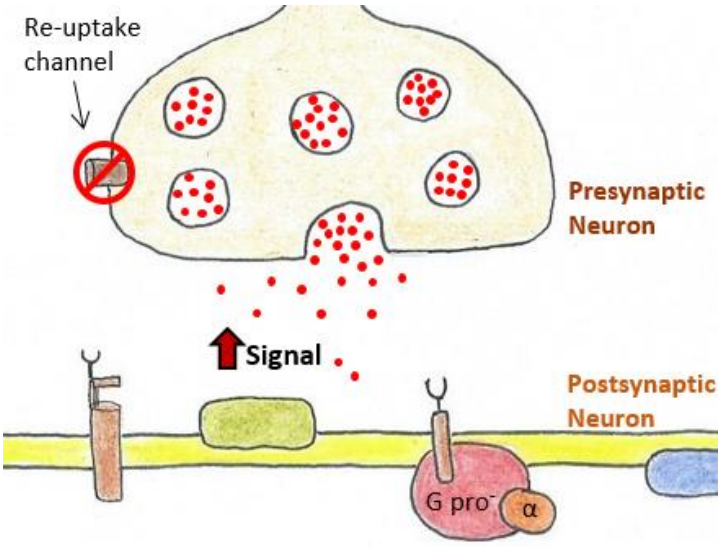



**Figure 8.5** In the illustration of the synapse above, blocking the reuptake channel with a substance like cocaine, can have the effect of increasing the signal that is delivered to the postsynaptic neuron.

### Monoamine Oxidase Inhibitors

There are also drugs that inhibit the effects of the degradative enzyme **Monoamine Oxidase** (MAO), they are called ***Monoamine Oxidase Inhibitors***, or MAO Inhibitors. They exert their effects by inhibiting the degradative MAO enzyme, and in this way the normal reduction of NE stimulating the post-synaptic membrane cannot occur. This has the effect of increasing the amount of NE that remains in the synaptic cleft, as well as increasing the amount of NE that is packaged into the vesicle before being released into the synaptic cleft. The net result is overstimulation by NE on its target tissue. This is shown in the drawing of the synapse to the left in **Fig. 8.6**., where taking out the action of the degradative MAO enzyme will increase the amount of neurotransmitter that can linger in the synaptic cleft.

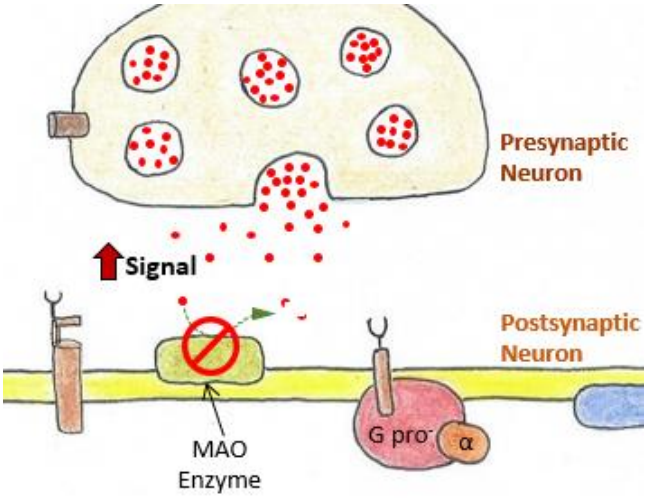



**Figure 8.6** In the illustration of the synapse above, blocking the actions of the MAO enzyme that would normally degrade the neurotransmitter can increase the signal that is delivered to the postsynaptic neuron.

It is important to know that when overstimulated, receptors on cell membranes or within the cell, will **down regulate** in response to this, and the immediate consequence is a **decreased sensitivity** of the tissue to the same level of stimulation the next time. The question then is, what will be required to get the same

effect as the first time? ***More*** of the stimulation! This can incite the classic cycle of *addiction* - as person will need more and more of the substance (drug or activity) since they are becoming less and less sensitive to the effects of it and they continue to use it. As we will see toward the end of this chapter in the section about the 'up' and 'down' regulation of receptors, the effects of elevated NE and thus a boost in mood and alertness is short lived due to the adaptation of the receptors. As will also be outlined in much greater detail later, this also applies to any deficiencies or drug induced reduction of any signal molecule.

**The Habituated use of "Medications"**

There is probably a medication for everything, but the question is, does there need to be? Because E and NE are so vital in maintaining a high level of activity and alertness in the body, their effects on the body are the targets of many drugs prescribed in medical interventions. For example, some medications that act to reduce the amount biogenic amine action in the body are used for high blood pressure (**hypertension**). The now banned adrenergic blocking drug **reserpine** was for 'moderate' hypertension. Apparently it causes the disruption of NE vesicular storage and depletes catecholamines from peripheral sympathetic nerve endings. However, it had a host of very bad side effects, including **depression**. And let us not forget that the numbers used to label a person with hypertension have been incessantly lowered and lowered over the past 50 years such that basically everyone can be diagnosed with hypertension. Added to that, **90%** of the diagnoses of hypertension is **idiopathic** – this terms means "**for which the cause is unknown**". Consider that powerful and toxic drugs are administered and yet no one even knows why or what has caused the "problem" in the first place. It is likely that there was no problem, till the 'treatment' for the cure started, for a problem that is not even known in terms of any cause. But don't worry, you'll have depression guaranteed because the biogenic amines are central to mood and emotional wellbeing, and there is a consistent link to clinical depression in those who experience a drug induced lowering of these neurotransmitters.

### Increasing Epinephrine and Norepinephrine Naturally

Elevated levels of E and NE and are not bad, there are many positive attributes to having elevated stores and levels of E and NE in the body that are generated naturally, compared to the significant spikes in these substances when an individual is undergoing a traumatically stressful event. There are some simple ways to elevate E and NE in the body in a healthy balanced way without trauma. This will allow an individual to be alert, energetic and experience an elevated mood and not move the body into the fight or flight state.

**Here are some examples of activates that can elevate E and NE naturally:**

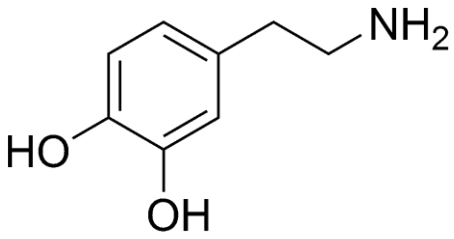
- Deep breathing exercises. There are many types.
- Praying and meditation.
- Cold exposure, either by swimming in natural bodies of water or taking a cold shower.
- Physical exercise. Even very simple body movements generate benefits.
- Any kind of positive accomplishments.
- Music listening or playing.
- Consuming coffee, tea, citrus fruits, bananas, cocoa and vanilla.

**3) Dopamine**

This neurotransmitter plays several important roles in the CNS and the body. Dopamine is integral to the voluntary control of **body movements** and is also well known as a key neurotransmitter related to **mood**, **emotional responses** and feelings of **pleasure**.

Dopamine has effects that are both excitatory and inhibitory. It inhibits unnecessary movements in the **substantia nigra**, inhibits the release of prolactin, and stimulates the secretion of growth hormone. Dopamine is also involved in memory and attention. For example, the limbic system (which is called the 'emotional brain') is an important brain region that is involved in elevation of mood and emotional responses, and emotional responses are key to learning.

There are highly concentrated levels of dopamine in the substantia nigra of the midbrain where it is involved with voluntary motor control. Neurons that release dopamine are termed "**Dopaminergic**" neurons. A deterioration of dopaminergic neurons in the substantia nigra lead to Parkinson's disease (see below).




### Happiness and Motivation

In the brain, dopamine is released by the cerebral cortex, hypothalamus and the limbic system. It is also released by the retina of the eye. Higher levels of dopamine can lead to feelings of euphoria, bliss, and enhanced motivation and concentration. Therefore, exposure to substances and activities that increase dopamine can become highly sought after by many people.

### The Pleasure Center

Dopamine is naturally involved in the elevation of mood and emotionally rewarding responses. In the brain it is also integrated into the perceptions of reward and motivation. Many studies have suggested it is closely associated with feelings of pleasure and satisfaction. Regardless of what molecule may or may not be involved, we understand that when we engage in an activity that we enjoy, it promotes feelings of satisfaction and often a desire to repeat the activity to some degree.

Have you ever jumped out of a plain? Some people find it exciting (see left), even though it is also somewhat terrifying. There are many elements at play, but the dopaminergic link to reward and pleasure appears to be associated with specific behaviors or actions that can bring about thrilling sensations. In this we can also see an association to possible **addictive activities**. The feelings of satisfaction caused by dopamine release can become highly desired by a person experiencing it. In order to satisfy this, a person will repeat behaviors that lead to the release of dopamine again, as it is associated with the '**pleasure center**' in the brain. These behaviors that are engaged in can be balanced, or they can become unbalanced. It may involve jumping out of planes. There are people who find that being polite and kind to others in very satisfying. It can also include detrimental activities such as becoming dependent on drug or medication addictions.

It has been hypothesized that the consumption of **cocoa** increases dopamine transmission, and this may be part of the reason why eating **chocolate** may lead some to feeling good. However, there is a big difference between chocolate that is **70% to 90% cocoa** and the substances found in typical 'candy bars'. The chocolate in el cheapo candy bars tops out at about **30% cocoa** and of course the most abundant ingredient in them is refined sugar – which is highly addictive and very destructive. Therefore, if you are seeking the benefits of 'chocolate', then they are found in the more expensive bars that have much higher levels of cocoa.

While we're on the subject, let's define addition:

**Addiction** is when an individual continually engages in a compulsive behavior despite the **negative impact** it has, and this behavior hampers their ability to remain mentally and physically healthy and functional. The person may find the behavior rewarding while engaged in it, but often later feels guilt, remorse, or trapped by the consequences of the seemingly unrelenting choice.

Since dopamine transmission has also been linked to reward (or 'pleasure') centers in the brain and has been associated with addictive behavior, it is important to apply terms appropriately. From the definition of addiction above, the key element is that ultimately it has a profound **negative** impact on the individual. Some may continually engage in skydiving because it gives them a great feeling of pleasure (after some initial terror), this would not considered an addiction if it has no harmful consequences.

**Another Degradative Enzyme just for Catecholamines**

There is another enzyme, **catechol-O-methyltransferase** (**COMT**) that is specifically involved in the degradation of the **catecholamine** neurotransmitters **epinephrine**, **norepinephrine** and **dopamine**. Nerve cells in the brain make the membrane-bound catechol-O-methyltransferase (MB-COMT), and it is thought that the shorter COMT plays an important role in dopamine metabolism by modulating extracellular levels of dopamine.

### Parkinson's disease

The **substantia nigra** is part of the **basal ganglia**, which is a group nerve cell clusters located deep within the cerebral hemispheres, specifically in the midbrain. In Latin substantia nigra means 'black substance', this is because it looks dark due to being deeply pigmented. It contains dopaminergic neurons that normally prohibits excessive activity in these basal ganglia motor centers. It keeps things calm.
However, it appears that degeneration of dopaminergic neurons in the substantia nigra for whatever reason can cause a disproportionate amount of ACh to dopamine, this then causes this region to become **hyperactive**, which is contrary to dopaminergic control here.

This may lead to **Parkinson's disease**, which is characterized by symptoms of muscle tremors, mainly at rest and described as 'pill rolling' tremors in the hands. Other consequences may include limb rigidity, shuffling gait and balance problems, along with **bradykinesia** (slowness in body movement). The molecule **L-Dopa** is a precursor to dopamine and used as a medication for Parkinson's disease as it can pass through the blood brain barrier, whereas dopamine cannot. It's also postulated that too much Dopamine activity is involved in schizophrenia.

The COMT enzyme has been applied in various treatments to manage the metabolism of an assortment of catechol drugs that are used to treat hypertension, asthma, and Parkinson disease.

### Drugs that impact Dopamine and other Neurotransmitters

**Amphetamine** ("speed") is a drug that is thought to work by causing an augmented release of the norepinephrine, dopamine and serotonin. This is thought to occur by stimulating a greater release of these neurotransmitters from the synaptic end bulb, as well as reducing the reuptake mechanisms at the synapse, and inhibiting MOA degradation of these neurotransmitters. All of these occurrences increase the presence of these neurotransmitters at the synapse and therefore are thought to intensify the effects of these neurotransmitters on the central nervous system. It looks like we can see a pattern developing

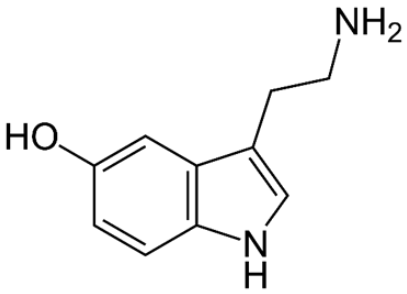
here. Most of the drugs and medication that elevate the mood are directly tied to elevating biogenic amines.

**B) Indolamines**

There are two main indolamines: There is **Serotonin**, also known as 5-hydroxytryptophan (**5-HT**) and **Histamine**. Serotonin is derived from the essential amino acid **tryptophan**, as the 5-hydroxytryptophan name tells us. Histamine is famous in its inflammatory role when released from **mast cells** and **basophils** but in this section we will also touch on its role as a neurotransmitter.

**4) Serotonin**

Serotonin is the same molecule as 5-hydroxytryptamine, also abbreviated as **5-HT**, and this is another very important monoamine neurotransmitter. Its physiological function is complex and multifaceted, modulating **mood**, **cognition**, **reward**, **learning**, **memory**, and is involved in numerous physiological processes such as **vomiting** and **vasoconstriction**. Serotonin has always been thought to be a key hormone that stabilizes our mood, feelings of well-being, and happiness, and that a lack of it causes depression. However, recent findings may surprise many.




A peer reviewed article published in **Nature: Molecular Psychiatry in July 2022** (Moncrieff, et al.) examined the serotonin theory of depression by engaging in a massive systemic review of the scientific evidence. Its conclusion: **There was no consistent evidence of their being any associated between serotonin and depression. None**. Depression was not correlated to activity, amount present, or the absence of serotonin. Effectively there is no support in the scientific literature for serotonin being related to depression, yet how long have we all been so confident in that apparent association? So it is now safe the scratch that theory as another long held inaccuracy. Form an orderly queue for all the wrong things we have been encouraged to believe by various brainiacs. This finding (and there are many others) is one reason why I use language in this text such as 'apparently' and 'theoretically' when discussing what science 'believes', because the truth is often that what we believe turns out to be false.

What appears to be accurate is that serotonin is found all over the body, so it must be doing something! It seems to enable brain cells and other nervous system cells to communicate with each other. Steady balanced serotonin levels also appear to help with sleeping, eating, and digestion.

Serotonin is closely related to hormone **melatonin**, this is because the hormone melatonin, which is released by the **pineal gland** for inducing sleep and regulating circadian rhythm of the body, is derived from serotonin! In fact, serotonin is also released by the pineal gland and its levels are related to getting adequate sleep, as it has become very clear that adequate restorative sleep is directly related to a balanced mood and good health. To remain in good health, good sleep is fundamental.

**Serotonin Release in the Body**

The locations that serotonin is released from are in the **hypothalamus**, **limbic system**, **cerebellum**, the **spinal cord**, and the retina of that eye. Serotonin is present at high levels in the **pineal gland** during the day, increasing further at night in the absence of melatonin formation. It is believed to play a role in sleepiness, alertness, mood and thermoregulation. In addition, serotonin is also found in abundance in your **gut** (digestion system). This massive amounts of serotonin that can be produced by **enteric neurons**

should be a good indication that what we eat has a significant impact on mood and a sense of wellbeing, since what we ingest must be triggering something related to serotonin down there. It is a natural mood stabilizer, it helps with sleeping, eating, and digesting, thus plays an important role in sleepiness, alertness, mood and thermoregulation. It is also secreted by platelet cells where it is associated with **wound healing**.

**Serotonin Derived from Tryptophan**

Serotonin is derived from the amino acid **tryptophan**. Tryptophan is an ***essential amino acid*** and must be obtained in your diet (found in nuts, cheese, and red meat). Therefore if your diet is low in tryptophan, then your body will make lower levels of serotonin. This can be associated with and result in anxiety or depression.

**"Antidepressant" Medications and the Consequences**

Since it has widely been theorized that serotonin is a stabilizer for mood, emotional well-being, and happiness, it's been a prime target for medications that propose to treat depression and anxiety. Know that we know from the reference above that serotonin has no proven role in depression we can perhaps view with more clarity all of the horrific "antidepressant" medications that have been tested on people for over 50 years now. Since all biogenic amines are affected by **Monoamine Oxidase (MAO) Inhibitors** this appeared to be another way to modulate serotonin levels. There are other pharmaceutical examples of attempting to manipulate biogenic amine levels, and they all have odd and unnatural names that sound like **poison**. For instance the drugs phenelzine (Nardil) and isocarboxazide (Marplan) are also used to treat clinical depression. Not only can I not pronounce those drug names, I don't want to. These have an effect of increasing the amount of NE in the synaptic cleft (see **Fig. 8.6** previously), as well as increasing the amount of NE that is packages into the vesicle before being released into the synaptic cleft.

The effects of these drugs that elevate the NE response tend to be seen in the sympathetic division of the ANS, so a whole set of bad responses ("side effects") can occur, such as "dry mouth", elevated heart rate, and increased blood pressure. At least the doctors who prescribe these drugs should now know what is causing the hypertension in their patients.

**The Lesser Known History of MAO Inhibitors**

If you have ever seen an older homeless person erratically walking down the street, riddled with body ticks and spasms while they look deranged and emotionally devastated, have sympathy for them. It is highly likely they were placed on MOA inhibitor "*Anti-Depressants*" a long time ago, when it was considered the 'miracle drug', before the catastrophic damage caused by their incessant use was clearly seen – by the victims at least. Conveniently, the mental health industry jumped horses to a new 'miracle drug' wherein Prozac et al. were ushered in to take the place of the highly toxic MAO inhibitors.

In theory, it may seem like tinkering with this area or that pathway in the body might be a good idea, if it can alleviate pain and suffering. However, what occurs in reality is almost always vastly different from what the manufacturers predict regarding their products, because the use of powerful **toxic drugs** can only have a wide detrimental impact on the body. A poison to the body will always be poison. Some will say that the use of these drugs is better than having a person suffer the depths of depression or anxiety. No one would argue about the pain and discomfort of debilitating depression, but what is worth exploring is a better way to recover since clearly hopping from one drug to the next has never been a viable solution. A deeper issue about depression is that it is a signal to the individual to examine for themselves what it is that might be troubling them. If a person is prepared to be honest (at least with themselves) this approach in combination with help from others can have a much more positive impact on their health.

For the medical field which proclaims to want to help others, here is an apparent novel idea: Find out what is actually wrong with a person by spending time and energy talking with them to identify a genuine cause. Then suggest healthy actions that would augment the body' natural ability to heal itself. We should all understand that there is no **$** in that model, only healthy recovered people.

**Selective Serotonin Reuptake Inhibitors (SSRI's)**
Some medications prescribed for depression, such as fluoxetine (*Prozac*) and paroxetine (*Paxil*), interfere with serotonin transmission in the brain. Both of these drugs prevent reuptake of serotonin by presynaptic neurons. When first introduced, this represented a new class of antidepressants called ***selective serotonin reuptake inhibitors*** **(SSRIs)**. This approach results in an increased amount of serotonin remaining in the synaptic cleft, thus serotonin-dependent activity in the CNS increases.

The effects of SSRI's are analogous with the effects of **cocaine** for NE neurons (see **Fig. 8.5**), in that it floods the normal receptors in an **unnatural** and **unhealthy** way. The SSRIs were hailed as the new wonder drug to replace the now universally recognized failure of MAO inhibitors, as SSRI's were more specific and only targeted serotonergic synapses. It's the same old story though, and it is basically another magic trick. These SSRI's have very serious, significant adverse effects, as will any other new type of medications just on the horizon. The receptors will 'down-regulate' and the wonder drug will lose its sheen in about 6 weeks. In the section "What are Drugs?" below it was shown in **1997** by Time Magazine that Prozac et al. Mood Drugs were a FAILURE! It's like that saying "hidden in plain sight", all you have to do is start looking and it is easy to find out that all of these drugs are known to be damaging with no intrinsic medicinal value. The karmic trade-off is that the makers and prescribers of these told you they were useless, so if you are senseless enough to take them and believe they will cure you - that is your own fault. Other options are possible, why not at least explore them.

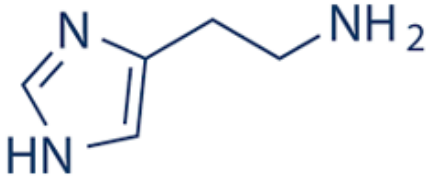
**Fasting to Remove Toxins and Other Benefits**
Here is a clue: The body will always reject what is **unnatural** and **toxic**, and this will always be done in an effort to help the entire body. Often the body will store away toxins until a later time when it can release them in a way that may be more protective. However, the body needs 'down-time' to be able to do serious house-cleaning, just like most of us will need some time off in order to clean out the garage. One way to give your body time to focus on cleaning is to **fast**, that means to deliberately abstain from eating food or drink, usually except for water. It sounds simple enough, but if anyone has ever fasted for at least 3 days, most know it is not easy. Aside from the extreme social and cultural pressures to eat constantly, once the digestive system is no longer busy processing all that food, it finally has the down-time to dig deep and start to release the years and years of toxins that are held deep within our tissues. This results in '***cleansing episodes***' and mysteriously it feels ***exactly*** like being sick. VERY SICK. As the toxins swirl around in your bloodstream it will feel terrible, but as long as you can get them out of your body via the natural elimination processes you will benefit dramatically. Fasting is not for the faint hearted and if a person has never fasted before, start easy and safely with juice fasting, it is way more feasible to begin with.

**Non-Drug ways to boost Serotonin**
By many accounts, there are four main ways to boost serotonin activity, and they are … ready? Maybe write these down: Exposure to natural **sunlight**, experiencing **touch**, especially effective is **body massage**, physical **exercise**, and remembering, and recollecting **happy events** in your life. It should not have to be tested experimentally for us to know these things to be true, but they have been tested. Just like tests have shown that babies do better in every metric when they are breast feed compared to being given formula. Again, do we really need a study to tell us this? No, we already know it.

Here are some examples of activates that can elevate E and NE naturally: Salmon, poultry, eggs, spinach, seeds, nuts and milk. These are rich in nutrients, particularly in **tryptophan**, the amino acid which is **required from the diet to make serotonin**. Also, pineapple, bananas, kiwi and plums all contain high amounts of serotonin, which can provide a natural boost in mood. We can see a pattern in the types natural foods that elevate all of the neurotransmitters discussed so far. They are all **whole foods** (not refined or processed) and have **no artificial ingredients** like phony colors, preservatives, additives, flavor enhancers, and other **toxins**.


**5) Histamine**

Histamine is derived from the essential amino acid **histidine**, it's produced by decarboxylation via L-histidine decarboxylase. In general, it has generally **excitatory** effects on target neurons, but oddly it has been suggested that histamine neurons may also release the inhibitory neurotransmitter GABA, this would make them GABAergic neurons though, interesting! In the CNS, histamine as a neurotransmitter is released by the **hypothalamus**, and within the brain it acts via three receptors: **$H_1$**, **$H_2$**, and **$H_3$** receptors. It facilitates the state of wakefulness in the conscious mind, and it is believed that its activity is required to sustain wakefulness, alertness, and reaction time.




It is likely that histamine is more familiar to most as an **inflammatory** molecule released by **mast cell** and **basophils** where it acts as a **paracrine** (local) modulator for immunological responses. In this capacity, histamine is a potent mediator in many physiological processes in the body. For example, histamine is a **potent vasodilator** and increases vessel **permeability** allowing an increase in blood flow and delivery of white blood cells to attack pathogens. This is part of the immune response the body has to perceived dangers. This action of histamine is what is responsible for an area becoming red and *puffy* and causing local heat. Those who suffer from seasonal allergies are said to have a hypersensitivity to harmless substances and initiate a considerable release of histamine when it is not really necessary. These people might take "**anti-histamines**" in order to alleviate the over-reaction by mast cells which release too much histamine (see **Fig. 8.7** below). This would reduce the symptoms of puffy redness associated with these allergies. As you can see, having proper histamine levels is important for your health and wellbeing. It helps blood vessels free up immune system cells to do their job. It's also key to our digestive system.

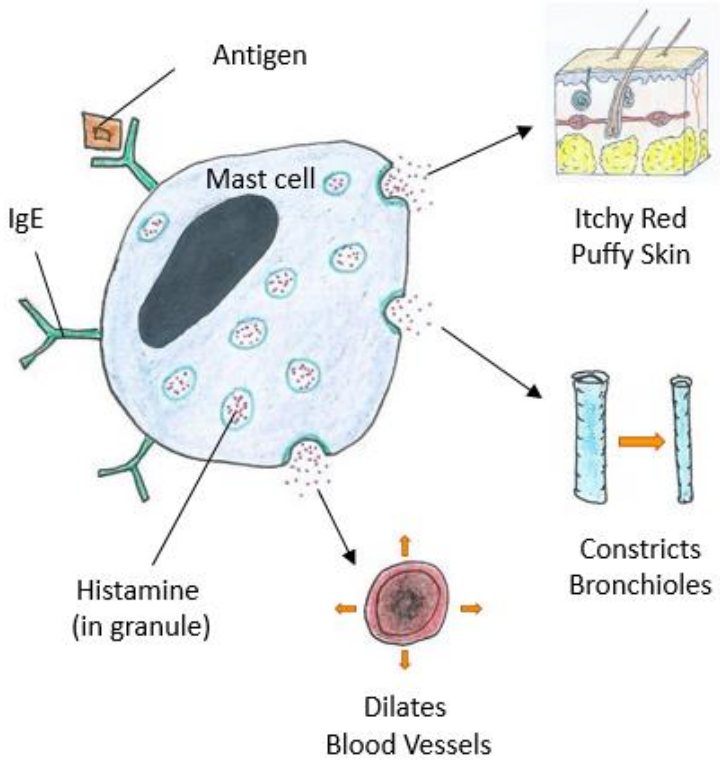



**Figure 8.7** The drawing of a mast cell shows how immune IgE bind to it and then the antigens bind to the IgE causing degranulation and the release of histamine at a local area. Most common sites of histamine release: **1)** skin, gets red and puffy; **2)** bronchiole airways in the lung, constrict and decrease airflow; and **3**) blood vessels, which dilates (become larger) delivering more blood, increasing white blood cells but also makes the area more red and warmer.

If a person has high histamine levels, this can lead to an allergic reaction due to a histamine response. It could also lead to other potentially serious health issues. Keep in mind that **histamine is not bad!** It helps the body in many ways, when it is in balance. Our main focus at this juncture was to note that histamine acts as a neurotransmitter in the central nervous system (CNS). Interestingly, it is also a component of gastric acid in the stomach that aids in normal digestive activities.

## ④ Neuropeptides

These neurotransmitter's can be from 2 to 40 amino acids in length. There are many neuropeptide but we will limit our discussion to three: **Substance P**, **Enkephalins** and **β-Endorphins**.

### 1) Substance P

This neuropeptide is released by neurons of the basal nuclei, midbrain, cerebral cortex and hypothalamus. This is a very important neurotransmitter for mediation of **pain transmission** and pain perception pathway. It modulates pain perception by altering cellular signaling pathways. The **P** is for Pain. The signal of pain is not just about causing discomfort, but it is a protective measure, to warn you that tissue damage is occur and to take evasive/protective action.

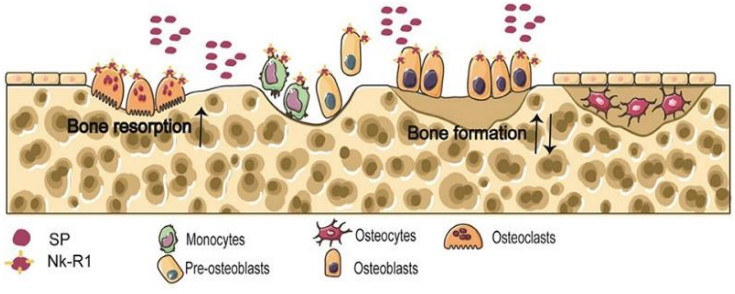



**Figure 8.8** Seen here are bone cells osteoclasts and osteoblasts being stimulated by Substance P during bone repair.

Quite recently (2020), the role of Substance P (Sub P) in the regulation of **bone** and **cartilage** metabolic activity was studied (see **Fig. 8.8** above) and it was shown that Sub P binds to receptors on bone cells, thereby regulating bone and cartilage metabolism and fracture healing. It kind of links back to "no pain no gain" with the involvement of Substance P in healing. Shown in detail below in **Fig. 8.9** is the well-established pain transmission pathway of Sub P in terms of regulating the perception of pain.

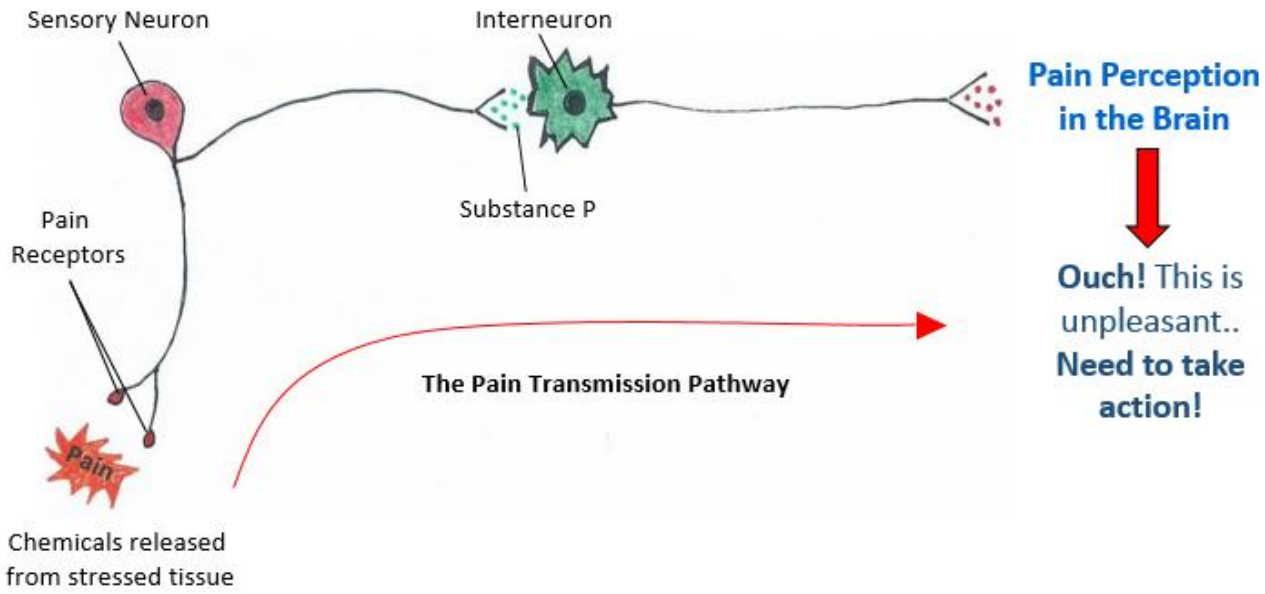
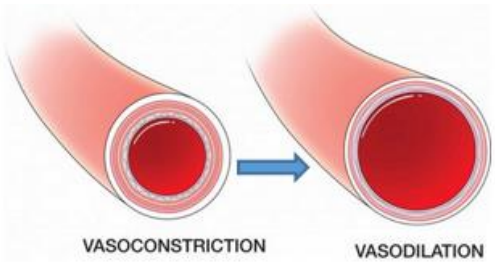


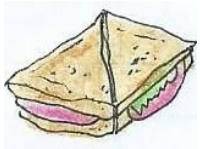

**Figure 8.9** The figure above shows the pain transmission pathway and the central role of Substance P in this information loop. The stimulus is from the stressed or damaged tissues and the pain receptors (nociceptors) of sensory neurons convey this information with Substance P.

Substance P (Sub P) also causes **vasodilation** (see vessels below right) and is a trigger for **nausea** and **vomiting**. Just like its role in the pain transmission pathway, again here it is protective. Localized vasodilation causes an increase in blood flow to that region, which allows for a greater number of white blood cells to arrive more quickly, ready to deal with any situation!




Although nausea and vomiting are not pleasant, again they are mechanisms designed to protect you. These responses are automatically triggered when the body detects dangerous substances or substantial toxins within the body.

**<u>Protective Measures</u>**:



For example, take a hypothetical sandwich (see left) and leave it out in the sun for a week. Yes, it is going to rot and become full of toxins made by the bacteria and other critters eating it and loving it! If you were to eat that rotting sandwich however (and please don't), in a *very* short time your body would automatically rid that from you in order to protect itself – often the fastest and most effective way to do that is to **vomit** it out! This response is also a very common effect of drinking alcohol, it is a toxin after all. The moment your body has too much of the toxin, look out! We also know from experience that individuals have different

levels of tolerance for various toxins, most notably due to previous exposure and the development of tolerance to it. Therefore not everyone will have the same ***ejection*** response, and some may not have any such response at all.

Additionally, Sub P plays a role in **gastrointestinal** functioning, memory processing, **angiogenesis** (this is the generation of new blood vessels), and cell growth and proliferation. Topical **capsaicin** (an active component of chili peppers) can deplete substance P from local nerve endings to relieve pain. Substance P is also present in **corneal nerves** and in normal tears, which may indicate that this molecule is related to sensitivity. Elevated expression of substance P is associated with gastrointestinal diseases such **inflammatory bowel disease.**

### Enkephalins and Endorphins

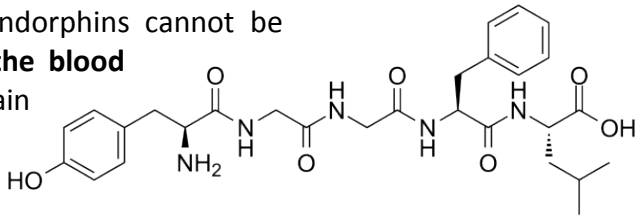
Enkephalins and endorphins are collectively known as **endogenous opiates**. The term endogenous means they are made within us. And the opiates part means they get you high. These oligopeptides are very powerful substances, and are **200 times more potent** in their analgesic effects than heroine, morphine or opium. Wow, impressive. And we make them.

**2) Enkephalins**

Enkephalins are small peptides that can serve as neurotransmitters in the brain and also act as hormones when released into the periphery and act as powerful natural endogenous **analgesics** ('pain killers'). In the CNS, this analgesic is released in **hypothalamus**, **limbic system**, **pituitary gland** and pain pathways of the **spinal cord**. Importantly, and like many other key neurotransmitters it is also found in nerve endings of the G.I. tract.

The mechanism of action of enkephalins it to **attenuate substance P release** in the dorsal horn of the spinal cord and inhibit afferent pain fibers. Enkephalins are opiates and these **inhibit** transmission at **sympathetic** and **locus coeruleus** synapses in the basal ganglia. As we've seen, those are two critical centers for the release of NE in the brain and periphery respectively. Therefore, enkephalins act to reduce NE transmission and thus calm things down.

When enkephalins (see structural molecule below right) are released by cells in the **adrenal medulla** they act **hormones** in the bloodstream and can exert their potent painkilling effects in peripheral tissue. Enkephalins, unlike morphine, have few, if any side effects. It does not have the abuse potential of opiate alkaloids. Both enkephalins and endorphins cannot be employed therapeutically because they **do not cross the blood brain barrier** (BBB), therefore cannot affect brain perception if administered into the bloodstream.




As **Figure 8.10** below shows, opioid peptides like enkephalins act as analgesics by ***inhibiting substance P transmission***. However, the pain transmission pathway must be activated *first* in order for it to respond. The term 'pain killer' implies that you must feel some discomfort and pain first before you get relief! For example, levels of enkephalins increase significantly during **child birth**, as it is involved in blocking pain signals in the spinal cord during and after giving birth.

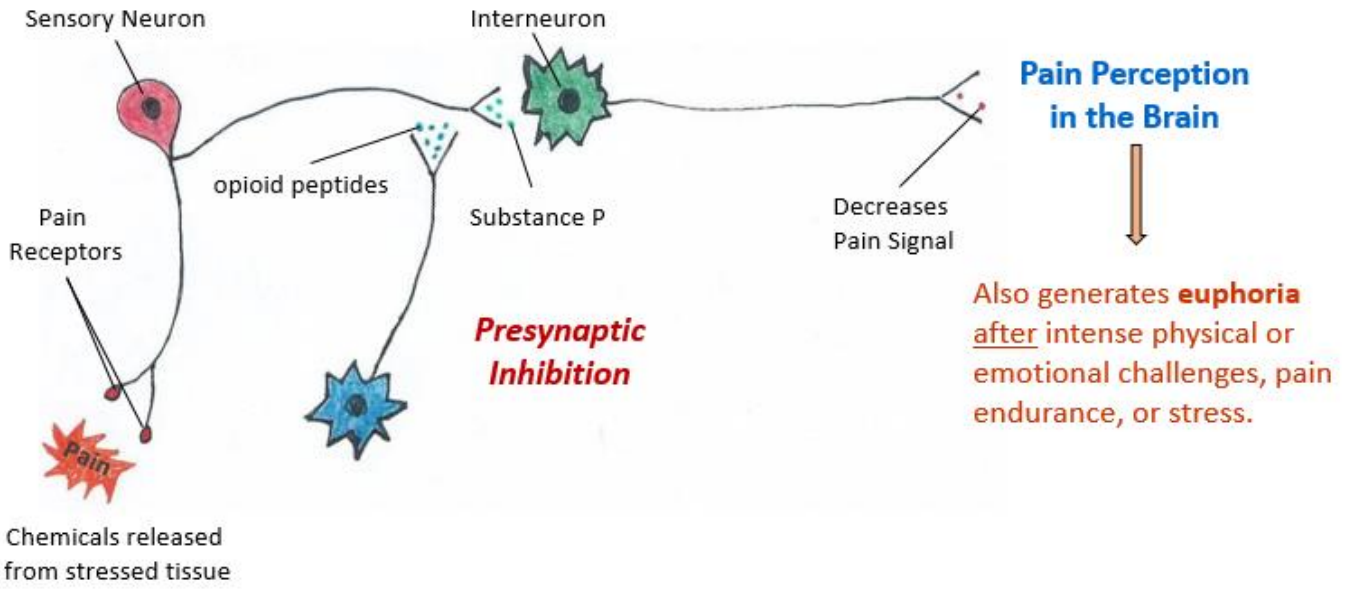



**Figure 8.10** The figure above shows how opioid peptides (like enkephalins and endorphins) are involved in the presynaptic inhibition of the pain transmission pathway. They intercede before the synapse (see blue neuron) and cause less Substance P to be released (green neuron). This in turn reduces the intensity of the other signal molecules, reducing the perception of pain. Additionally, the opioid peptides stimulate reward and pleasure centers in the brain that generates feelings of euphoria after the stressor is endured.

### 3) β-Endorphins

The β-endorphins are an opioid substance produced in parts of the brain, including the **hypothalamus,** the **amygdala**, and the **pituitary gland** (where it can be released as a hormone). When released within the brain it goes into the cerebrospinal fluid (CSF) for dispersion. It **blocks the sensation of pain**, importantly, it's produced and released in response to intense pain, strenuous exercise or types of stress. This neurotransmitter is also found in the G.I. tract. For exercise buffs, β-endorphin and enkephalins are released together with **adrenocorticotropic hormone** (ACTH) from the anterior pituitary simultaneously during exercise, followed by a delayed release of **cortisol**.

These opioid peptides are similar in chemical nature to **opium** and are part of the body's natural pain relief molecules. β-endorphins also suppress pain by blocking substance P transmission and also reduce the perception of fatigue. The release of endorphins can be triggered in multiple ways and it acts by reducing pain perception in the brain. These neurons engage in **pre-synaptic inhibition** of Substance P transmission (see **Fig. 8.10** above).

### What Triggers Endorphin Release

As described earlier, endorphins are released in response to pain or stress. A variety of studies have found that they are also released during other activities. Here are some examples.

**Exercise** is great for releasing endorphins. It is linked to 'runner's high', the often euphoric feeling experienced by individuals after an endurance run. Interestingly it is not just running or other intense physical activities which trigger the release of endorphins, but research shows **walking** also promotes the release of endorphins and this contributes to producing the feelings of relaxation and improved mood after a walk. It was noted that the walk does not have to be a fast paced one to have the benefits of relieving stress.

**Sunbathing** stimulates β-Endorphin release. That is why, before sun exposure was overly vilified, so many people loved sunbathing - because it makes you feel happy and relaxed afterwards as well as warm and replete with vitamin D. Engaging in **good sex** releases endorphins. **Crying** even releases endorphins! It's believed to be the deep emotional crying that can trigger this, feeling emotionally vulnerable, or it's even possibly released when a person cries during laughter. Most people know the sensation of feeling 'better' after these episodes of crying. After all it is recognized that there are benefits of crying, even as simple as making others feel more sympathetic towards us. The other benefits that may be connected to crying could be that crying with or for others can bond us more closely together emotionally.

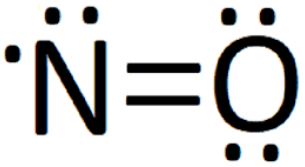
### Foods that Stimulate Endorphin Release

Consuming **refined sugar** releases beta-endorphins, one of the neurotransmitters in the brain that acts as a natural painkiller. It also assists in producing a sense of self-esteem and resolving anxiety – but this effect is only short lived and is quickly out-weighed by many deleterious effects all over the body. Therefore although eating a sugary snack may alleviate feelings of anxiousness temporarily, it literally feeds into a *sugar addition*, which is real and wide-spread. Sugar and refined carbohydrates also release the neurotransmitter and hormone **serotonin** in the brain, which enhances mood in the same way antidepressants and anti-anxiety drugs do. It is strongly advised to avoid this sugar medication too.

In contrast to the cheap, degraded and highly addictive sugary and synthetic snacks, there are several great whole foods that encourage the release of endorphins in the brain. They include: **Cacao** (this is not the same as chocolate), **vanilla beans**, **strawberries**, **oranges**, **grapes**, **ginseng**, **turmeric** (and other spices), **animal proteins**, **nuts** and **seeds**. These can produce similar feelings of euphoria and reduce anxiety in the body but also provide an abundance of other extremely beneficial elements for good health, such as minerals and vitamins, which are always stripped out of processed foods (including sugar). In addition, these real foods may contain antioxidants, and other elements that may not have been identified yet in terms of its specific molecular structure, but are special substances (like **salvestrols**) that are exceptionally good for the body.

## ⑤ Soluble Gases

The best known soluble gas neurotransmitter is **Nitric Oxide** (NO), and therefore this will be our main focus in this category. Nitric oxide is widespread and made by almost every cell type in the body. It is one of the most important molecules for blood vessel health because it is a powerful **vasodilator**, meaning it makes blood vessels larger by relaxing the inner smooth muscle within the blood vessel wall, causing the vessels to widen. This is how NO increases blood flow and lowers blood pressure. The role of NO on the cardiovascular system cannot be overstated, as it works to dilate blood vessels and this can have an enormous impact on blood pressure and flow in the body.



As a neurotransmitter, NO works as a **retrograde neurotransmitter in synapses**, what this means is that it diffuses from the postsynaptic neuron and travels "backwards" across the synaptic cleft to where it activates receptors on the presynaptic neuron. Pretty clever huh! NO allows greater blood flow to the brain and has important roles in intracellular signaling in neurons related to neuronal metabolism and dendrite growth.

Nitric oxide is produced at **excitatory** synapses and has its effects on the body in several ways. NO can diffuse and act on presynaptic or postsynaptic targets. For example, when **glutamate** is released from the

presynaptic terminal it causes them to open and permit $Ca^{2+}$ influx which activates **calmodulin**, which then binds to and activates the enzyme **nitric oxide synthase** (NOS). This NOS catalyzes the production of **nitric oxide** from L-arginine. NO helps modulate **vascular tone** (contracting the smooth muscle in blood vessels), regulate **insulin** secretion, **airway tone**, and **peristalsis**, (wave-like movements in the gut) and is involved in **angiogenesis** and **neural development**.

In terms of mood, in conjunction with the anti-anxiety effect of **GABA**, nitric oxide (NO) causes the brain to release **norepinephrine** which inhibits pain signaling throughout the body. NO is also generated in synapses in the CNS upon activation of N-methyl-D-aspartate (**NMDA**) receptors and exerts its effects by changing the levels cGMP within the cells (related to excitatory glutamate transmission).

**Erectile Dysfunction and Nitric Oxide**

The broad definition for **erectile dysfunction** (ED) is the inability of a man to maintain an erection sufficient for satisfying sexual activity. It used to be referred to as **impotence**. This condition can be a sign of a physical or psychological stress, or hardly surprising, drug induced imbalances. The neurotransmitter and potent vasodilator **nitric oxide** is a physiological signal essential in the physiological process of **penile erection**. Disorders that reduce NO synthesis or NO release in the erectile tissue are commonly associated with erectile dysfunction. The enzyme **NO synthase** mentioned above, (NOS) catalyzes production of NO from the amino acid **L-arginine**. So fellas, make sure you get enough L-arginine!

A "treatment" for erectile dysfunction has been **Viagra** (or Sildenafil - and by the way what another ridiculous name) and it is a specific **phosphodiesterase** type 5 (PDE 5) **inhibitor** that enhances nitric oxide (NO)-mediated vasodilation in the erectile tissue of the penis the corpus cavernosum by inhibiting cyclic guanosine monophosphate breakdown. As for all the other toxic drugs mentioned, the best solution for the human body is to look for a much better remedy than using any of these drugs.

**Some other steps to implement Improved Sexual Function**:

- Stop smoking (any substance), quit as soon as possible. Pot is not a miracle drug either.
- Stop drinking alcohol or using drugs, quit as soon as possible.
- Lose excess weight, carrying excessive weight worsens erectile dysfunction.
- Always engage in healthy physical activity every day if possible.
- Work through relationship issues and be honest, especially with yourself.

## 5 Ways to Increase Nitric Oxide Naturally

There are a number of ways to increase NO naturally, especially by consuming very specific and interesting nutrients. For example, **apple cider vinegar** works by inhibiting the enzymes that cause the constriction of blood vessels and increase nitric oxide, which relaxes them thereby lowering blood pressure. As usual, exercise will also get the blood flowing which will then generate NO.


Other interesting things to consume to increase NO levels: Vegetables high in nitrates; increase your intake of antioxidants; **beet juice**, this is one of the best sources of nitrates in any food, which converts to nitric oxide in your body. Try red spinach juice, celery, and arugula juice too.

## It's the Receptors!

As we want to really understand neurotransmitters, it is important to make some clear statements about the vital role that **receptors** play. As we have seen, the same neurotransmitter can have opposing effects on tissues, e.g., the effects of ACh on skeletal muscle and smooth muscle are different. How can this be? It be the receptors!

The effects of any signal molecule, including neurotransmitters will be dependent on the specific type of receptor they bind. Also remember that the cell responds and adapts to changes in signals, and this changes the intensity of the effect on the target tissue.

### Upregulation and Downregulation – let's mention this now!

In terms of all the drugs and other addictive substances discussed, a key element to the sensitivity of a target cell for any signal molecule is **receptor density**. Receptors in the tissue or on the plasma membrane of cells are there to receive signals and allow the cell to respond. In relation to our discussion of neurotransmitters, the more receptors a cell has for that specific molecule, the more strongly the cell will respond to it.

Receptors levels can be fine-tuned and changed. It can be increased (**upregulated**) if the signal is too faint or diminished, or it can be decreased (**downregulated**), if the signal is too strong or overwhelming. The illustration in **Fig. 8.11** below shows the variations in up and down regulation of surface receptors.

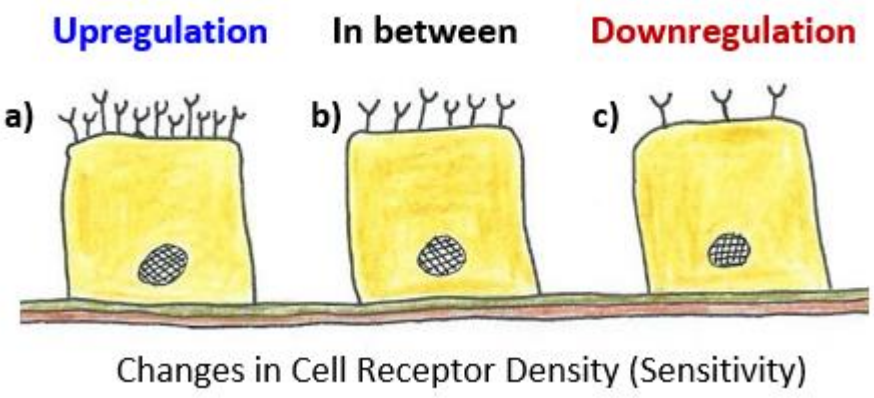



**Figure 8.11** Shows the receptor density (sensitivity) changing on the cell surface, as it will always do in response to variations in levels of stimulation. In **a)** there is an upregulation of surface receptors due to a reduction of a signal molecule stimulus. In **c)** there is a downregulation of surface receptors due to overstimulation by the signal molecule. The cell in **b)** is in a transient state in between **a)** and **c)** and the direction it will move will be influenced by the amount of the ligand (signal molecule) present.

- **Upregulation** of receptors is when the cell increases receptor density in response to a stimulus.
- **Downregulation** of receptors is when a cell decreases receptor density in response to a stimulus.

The changes in the receptor density of target cells is a great example of a negative feedback mechanism in action in the body. The **upregulation** of receptors can '**super-sensitize**' cells. This can be seen after a prolonged absence of the ligand. The cells generate more surface receptors and will therefore become more sensitive to the elusive, reclusive molecule. When the ligand is re-introduced, there will be an elevated sensitivity to even small amounts of it. A useful example might be a person who drinks coffee

every day who decides to stop drinking any coffee for a month. When after a month of no coffee stimulation they then begin to drink coffee again, their body will be much more sensitive to even a small cup of coffee! The up and down regulation of receptors is the main reason why 'drugs' do not work long.

In contrast, the **downregulation** of receptors occurs after chronic exposure to an excessive amount of a ligand, for instance a hormone or neurotransmitter that is released repeatedly, or in very high concentrations. The consequence is that the cell become will become '**desensitized'** to that substance and will required a greater amount of it in order to evoke a similar response to the previous stimulus. This is the hallmark of 'addiction', as the addictive practice continues 'more' stimulus is required for less and less response. Imagine if the coffee drinker from above now drinks 10 cups each day! Ahhh, your body will want to tone down that type of stimulation by decreasing receptor sensitivity. As we will see in later sections, the extremely common and totally reversible disease state of **Diabetes Mellitus Type 2** is all about **receptor downregulation** from overstimulation of the body's cells with **Glucose**!

**Agonists** and **Antagonists**: Some substances are known as agonists because they function by increasing the effects of specific neurotransmitters, while other substances are referred to as antagonists because they act to block the effects of a neurotransmitter. See **Fig. 8.12** below.

**Agonists**
Signal molecules that bind the receptor and induce the post-receptor events that lead to a biological effect. They act like the normal or true ligand (signal molecule), though potency may vary.

**Antagonists**
Signal molecules that bind the receptor and **block** binding of the true ligand or agonist, and fail to trigger intracellular signaling events.

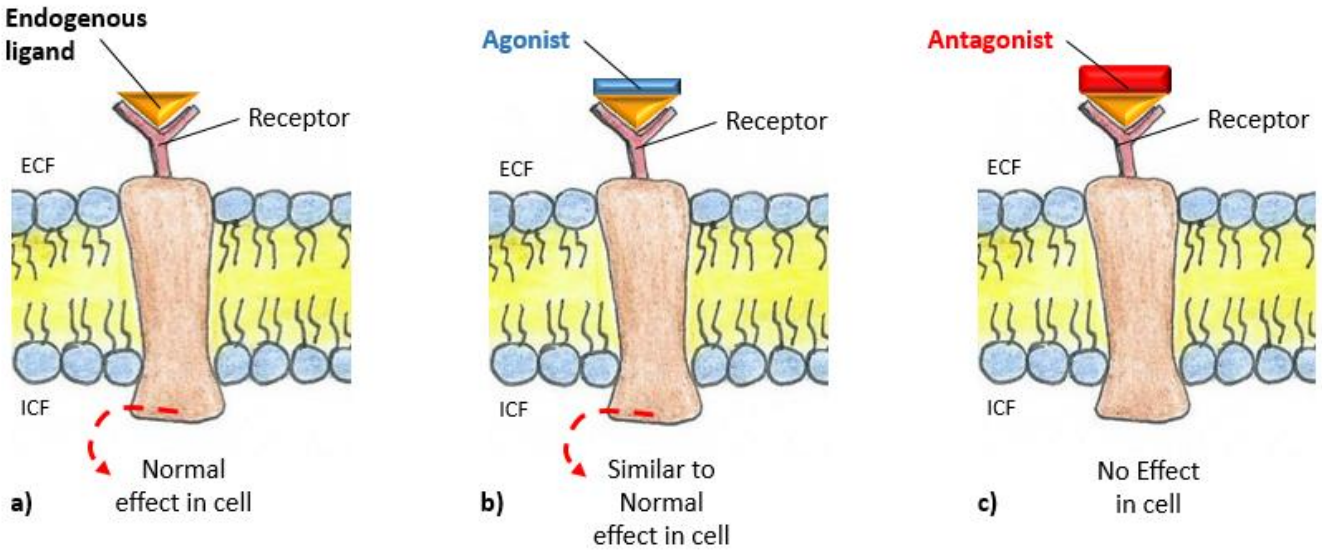
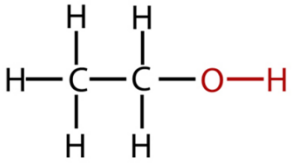



**Figure 8.12** Illustrated is the same receptor being stimulated by three different types of molecules. In **a)** the endogenous or natural ligand is binding to the receptor. This stimulates the normal response that causes an effect in the cell. In **b)** there is an agonist binding to the receptor. This is molecule has a binding site that is similar enough to the true ligand molecule that it stimulates a similar response caused by the endogenous ligand. In **c)** there is an antagonist binding to the receptor. This is molecule is close enough to the endogenous ligand to bind the receptor, but not close enough to its structure to elicit a response from the cell. Because the antagonist is occupying the receptors and not triggering a response, it is also blocking the true ligand for binding and stimulating the cell, for this reason antagonists are also referred to a 'blockers'.

## Alcohol, Neurotransmitters and Receptors

Here is some information about alcohol and its effects on neurotransmitters. Everyone's tolerance for alcohol is different, so people respond very differently to drinking even small amounts of it. Even for those with high tolerance, there are consequences of excessive alcohol intake. The most well-known alcohol consumed by people drinking alcoholic beverages is ethyl alcohol or **ethanol**. The chemical structure of ethanol is $C_2H_5OH$. It's that OH group (see structure below) that interact with other molecules and tissues in the body.



Alcohol binds directly to **GABA, Glutamate, ACh** and **Serotonin** receptors. So yeah, look out! Alcohol enhances the effects of GABA, and as we now know GABA is an **inhibitory** neurotransmitter, this means alcohol enhances this inhibition and contributes to making neural processing very sluggish.

Alcohol inhibits glutamate receptor function. Since glutamate is **excitatory**, inhibition of this causes more shutting down of the central nervous system processing. With the addition of the interference of ACh transmission, all of this leads to a **lack of coordination of body movement**, including lack of gait (walking) control, slurred speech, disruptions in memory, and even blackouts.

Interestingly, certain centers in the brain are stimulated to release **dopamine** after drinking alcohol, which is responsible for the 'buzz' or the high feeling experienced soon after drinking it. This can lead to the perception of pleasure, and excitement from drinking and may lead to the formation of a pattern of drinking to get that feeling again. And as we know from the downregulation of overstimulated receptors, what will be needed next time is ***more alcohol*** to feel that same level of buzz.

It is understandable that people want to feel good, but alcohol has severe limitations in that realm.

One way of feeling better is to avoid feeling anxious or on edge. That may seem obvious, but it is important to know that there are certain types of food and beverages that really should be avoided in order to reduce these troubling emotional states.

Here are **10 of the worst foods, drinks and ingredients** to consume for anxiety:

- Cakes, cookies, candy and pies.
- Sugary drinks.
- Processed meats, cheese and ready-made meals (think frozen 'diet' meals).
- Energy drinks and highly caffeinated coffee or tea.
- Alcohol.
- Fruit and vegetable smoothies with high glycemic indexes.
- Gluten.
- Artificial sweeteners.

## What are Drugs?

By definition, a **drug** is a substance (medicine, narcotic, legal, illegal) which has a **physiological effect** when ingested or otherwise introduced into the body. That is all that a drug is, and any medicine or poison can be called a drug. Think of heroin, aspirin, or sugar. All have physiological effects when introduced into the body, thus all are drugs.

**Heroin**, diacetylmorphine, is a semi-synthetic opioid because it is partially derived from the opium poppy, but further altered chemically in a laboratory.

**Aspirin**, acetylsalicyclic acid, is derived from salicin found naturally in the bark of the white willow and slippery elm trees (and other plants). Like heroin, a specific component is isolated, modified and concentrated to create this drug.

**Sugar**, sucrose, is extracted from sugar cane and beets. It is refined, purified and concentrated (just like heroin and aspirin) into a single, un-natural, isolated component to become a drug.

Abuse of all of these drugs will harm your health and all of them can ultimately kill a person.

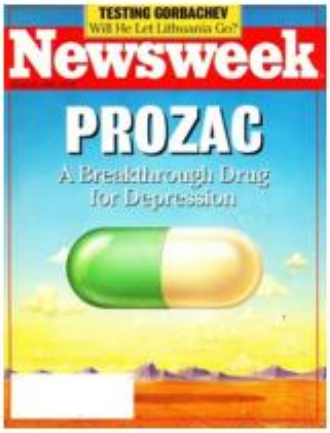
Let's take it to the next level and now examine drugs infused with **petrochemicals**.


What is **PROZAC**? The active ingredient for **Prozac** is fluoxetine hydrochloride, which is said to be 'derived from' St John's wort but centrally it contains a **fluoride** derivative not found anywhere in nature. It is synthesized by reaction of p-tri-fluoromethylphenol with 3-(chloro)-N-methyl-3-phenylpropylamine in the presence of potassium carbonate to yield Fluoxetine, 3-[p-(trifluoromethyl)-phenoxy]-N-methyl-3-phenylpropylamine (7.3.6). Well that was clear as mud. But wait, there's more. The non-medicinal ingredients are benzyl alcohol, butyl paraben, carboxymethylcellulose sodium, edetate calcium disodium, F D & C Blue (dyes). None of those non-medicinal ingredients are good for normal human physiology either. Get this, many of the artificial dyes are linked to… depression.

So as we can recognize from the information above, Prozac is one long series of synthetic chemicals that are found **nowhere in nature**.

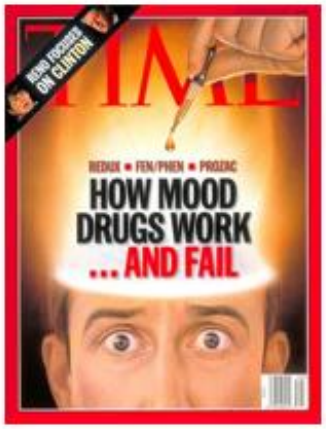
Ask yourself, can anyone make this 'medicine' at home? In the same way a person could make a cup of **slippery elm bark tea**, which contains a natural and whole source of acetyl salicylic acid? The answer is no, nobody can make this cozy little home-spun remedy for 'feeling blue' in the kitchen at home. It's not possible, thank goodness. The only ones who can make something this toxic are the big petrochemical pharmaceutical companies. They are also the only ones with enough money to fund billion dollar promotional campaigns that will go to great lengths to have as many people as possible believe that the answer to any of their problems is to take a pill for it. Smoke and mirrors are still very effective. This industry actually gets people to pay money to be poisoned. Furthermore, the entire industry, which includes the "health-care" industry has managed to get away with continuing to promote this poison to you and your children as a 'cure' for feelings of despondency. The cure for those feelings will **never** be in the form of a pill.

Take a quick look at the history of this drug that many proclaimed was a miracle in a pill. The primarily pandering articles and reports were dutifully published (see below) when the new wonder drug was first introduced in 1990. Throughout the 1990's the marketing of antidepressant drugs continued, but inevitably the truth is always revealed, even by the very entities that pushed the lies so vehemently. Below it can be seen that in less than one decade it was publicly acknowledged that the "Breakthrough drug for depression" Prozac was a big **FAILURE**.




**1990**: The miracle wonder drug, a 'breakthrough' for Depression. Note, there is never any claim that this can cure it, or anything else.


**1992**: Drugs for the treatment of mental illness have never actually worked, nor can they ever address the cause of depression.




**1997**: Now publicly conceding these drugs 'FAIL', yet still promoting the non-proven 'alternation in brain chemistry' theory for mood changes.

To complete this story, if you Google this: **Why was Prozac taken off the market?** You will find this:

> It was banned after research showed it could trigger suicidal thoughts and thoughts of self-harm. The drug's maker, GlaxoSmithKline, disagreed with the Government's decision at the time, saying it would "limit the choices" available to doctors to treat depression. **Dec 10, 2003**.
>
> Manufacturer Teva Pharmaceuticals has issued a voluntary nationwide recall of fluoxetine (Prozac), used to treat depression, obsessive-compulsive disorder, and panic attacks. The generic Prozac was recalled due to **abnormal testing results** (*whatever that means*). **Feb 21, 2018.**

***Emphasis*** added.

Don't worry, a dizzying parade of other antidepressants with equally nonsensical and outlandish names have already filled that void, as they continue to make great strides in claiming to 'improve' the mental health of people with toxic drugs. The 'drug' approach to mental or any health continues to just make no sense, this is because it is not addressing the underlying **cause** of the problem. The practice of symptomatic medicine is to 'treat' the **symptoms**. All this means is an attempt to eliminate the expression of the symptoms, which are important **stimuli** warning us of problems we need to resolve, and even more amazing is that 'symptoms' such as inflammation, headache, increases mucous, fever, etc., are actually all a part of the healing process! Such that stopping them from occurring literally means stopping the healing from occurring.

## Lessons from Homeostasis

After starting and completing just one section of human physiology, hopefully it is clear that the body is very complicated and that the introduction of a drug to treat symptom 'X' (not the cause by the way) is almost guaranteed to have some unwanted, undesirable impact on other systems of the body.

A primary lesson we can learn from examining some of the mechanisms of homeostasis is that **the body is fully capable of regulating itself**, to perfection in fact. So the first order of business, where possible, is to get out of the way and try not to interfere with the natural reparative capabilities of the body. In addition, if you can provide some of the great building blocks to your body, it will be better equipped to do all of the things it can. On the rudimentary level this means consuming good, whole, nutrient rich food, clean vibrant water, and all of the essential vitamins and minerals. On another level it also about the way your **think** and **feel**, as this has an enormous impact on the physiology of your body.

### Did You Know You Can Boost Your Mood with Your Diet?

What you eat or don't eat can have a significant impact on your mood. Hopefully this has become self-evident. While excess sugar has been linked to depression, certain foods are linked to positive emotions.

**Vegetables, Especially Leafy Greens -** Dark leafy greens like spinach are rich in **folate**, which helps your body produce mood-regulating neurotransmitters, including **serotonin** and **dopamine**. One 2012 study found people who consumed the most folate had a lower risk of depression than those who ate the least.

Research from the University of Otago found that eating fruits and vegetables of any sort (except fruit juice and dried fruit) helped young adults calm their nerves. Researcher found: "On days when people ate more fruits and vegetables, they reported feeling calmer, happier, and more energetic than they normally did."

**Mushrooms –** From the veggie section (no the other kind) are rich in **selenium**, an antioxidant (deficiency linked to anxiety). **Kombucha** is a fermented mushroom tea, no wonder it's so good! Mushrooms are also a great source of **vitamin D**, which supports healthy mood. The best option to optimize your vitamin D levels is **regular sun exposure**; if that's not possible, a vitamin $D_3$ supplement may be necessary.

**Turmeric -** This is a spice, 95% composed of **curcumin** (gives it the yellow-orange color), it is a powerful anti-inflammatory, has neuroprotective properties and may enhance mood and possibly help with depression.

**Cocoa (Dark Chocolate) -** Like exercise, cocoa may trigger your brain to produce the "bliss compound" **anandamide**. It also contains other chemicals that prolong the "feel-good" aspects of anandamide and trigger **dopamine** release. Note: 'dark chocolate' requires at least **70% cocoa** – and ideally has zero refined sugar. Drinking 1.5 ounces daily made subjects feel calmer, thus has anti-anxiety effects.

**Organic Black Coffee -** Research has shown that coffee triggers a mechanism in your brain that releases **brain-derived neurotrophic factor** (BDNF), which activates your brain stem cells to convert into new neurons, thereby improving your brain health. I knew good coffee was good for you. Interestingly enough, research also suggests that low BDNF levels may play a significant role in depression and that increasing neurogenesis has an antidepressant effect. One Harvard study even found women who drink four or more cups of coffee a day have a 20% lower risk of depression than those who drank little or none.

**Green Tea -** Green tea contains **theanine**, an amino acid that crosses the blood-brain barrier and has beneficial psychoactive properties. Theanine increases levels of **gamma-aminobutyric acid** (GABA), **serotonin**, **dopamine**, and alpha wave activity, and may reduce mental and physical stress, anxiety, and produce feelings of relaxation.

## Think Positive! Positive Thoughts Reduce Stress and Enhance Your Immune System

Feeling happy isn't only a matter of emotional health. Positive **thoughts** and **attitudes** are able to prompt changes in your body that strengthen your immune system, decrease pain and chronic disease, and provide stress relief. One study found, for instance, that happiness, optimism, life satisfaction, and other positive psychological attributes are associated with a lower risk of heart disease.

It's even been scientifically shown that happiness can **alter your genes**! A team of researchers at UCLA showed that people with a deep sense of happiness and well-being had lower levels of inflammatory gene expression and stronger antiviral and antibody responses. The field of **Epigenetics** has demonstrated that no one is 'doomed' by their genes, because they can be changed. Sufficient **vitamins** and **minerals** play a very important part in this.

Interestingly, if you're wondering how to maintain a state of happiness in the long run, **self-acceptance** appears to be one of the most important factors that can produce a more consistent sense of happiness.

**There are 2 basic Kinds of Happiness and they can Produce Different Health Results**

- **Hedonic** – characterized by happiness gleaned from pleasurable experiences, including exciting things (like sex, thrill-seeking, shopping, consuming) and can be associated with material possessions.

- **Eudaimonic** – this form of happiness comes from activities that bring you a greater sense of purpose, life meaning, or self-actualization (and realization).

Interestingly, while both of these categories are positive emotional states associated with happiness, in studies, the ***gene expressions*** they produced were not identical. Those subjects whose sense of happiness was rooted in the eudemonic category had favorable gene-expression profiles, while the hedonic well-being produced gene profiles similar to those seen in people experiencing stress due to adversity. This relates back to **epigenetics**.

It has been theorized as to why these differences are, it is that when you're driven by materialistic values, your happiness depends on circumstances that may or may not be within your control. If you run into adversity, it can cause a great deal of stress because it impedes your perceived ability to be happy. On the other hand, those driven by a sense of "purpose" are largely buffered against the uncertainty that comes with adversity, and their happiness is not dependent on having or experiencing anything in particular that can at any moment be taken away.

### Physiologically Relevant Tips to Become Happier

Since in the past there has been such a heavy promotion of taking drugs like the one mentioned above to address the feelings of depression, anxiety and despair, let's devote some time and energy in the tail end

of the neurotransmitter section to effective, proven safe ways that people can become happier without any drugs and without any significant monetary coast.

**Here are 9 Tips to Get a Quick Mood Boost**

**1. Get Up and Get Moving**

Excessive sitting and lack of exercise increase depression symptoms, while increased physical activity typically alleviates these symptoms. Also **beta endorphins** and **anandamide** (AEA), an endogenous **cannabinoid** known as the "bliss compound," both increase during and following exercise and may be partly responsible for why exercise makes you happy.

**2. Get Outdoors**

Exposure to **bright outdoor light** is crucial for a **positive mood**, in part because regular exposure to sunlight helps to enhance your mood and energy through the release of **endorphins**. Getting sun exposure outdoors also optimizes **vitamin D** levels. Vitamin D deficiency has long been associated with seasonal affective disorder (**SAD**), as well as chronic depression. One study found that it takes just 20 minutes outdoors to make most people happier, while other research showed that happiness is maximized when it's 57$^{o}$F outside — so keep an eye on the thermometer. Being cold can be very stimulating. If you can't get outdoors, at least open your shades and let the sunshine in. A brighter living or work area will help to boost your mood.

**3. Reach Out to Others**

Call a friend or even send an email, build closer bonds with others. Strong social ties are a key for well-being. One study even found that **relationships** are worth more than $100,000 in terms of life satisfaction, while actual changes in income buy very little happiness. Even better, give or get a **hug**. ***Hugging is known to lower levels of stress hormones like cortisol***. Do not be afraid of catching anything but appreciate! Hugging also activates the **orbitofrontal cortex** in your brain, which is linked to feelings of reward and compassion, and involves the bonding hormone **oxytocin**.

**4. Complete a Task You've Been Avoiding**

Often, the build-up to doing the aversive task is worse than actually doing it. And once you've crossed it off your to-do list, you'll feel a sense of accomplishment and relief. It really makes you feel better!

**5. Organize and De-clutter**

A cluttered, disorganized environment can lead to **inner discord**. Set your timer for 10 minutes and tackle one spot that you wish were more clear of clutter, like your desk or maybe the kitchen counter. Do it now!

**6. Do a Good Deed**

Helping others and doing good deeds provide a natural mood boost. Even a quick good deed, like letting someone go ahead of you in line at the grocery store, is beneficial, but if you have more time volunteering is also great for your mood. **Volunteering** can lower your risk of depression and anxiety, and even boost your psychological well-being. Volunteering to help others also gives you a sense of purpose and can even lead to a so-called "helper's high," which may occur because doing good releases feel-good hormones like **oxytocin** in your body while lowering levels of stress hormones like **cortisol**.

**7. Donate Something**

Along the lines of doing a good deed, giving things away can help to create a positive environment. This includes material things and alternatively you can donate your time or skills where they're needed most.

**8. Smile**

Putting on a fake smile can worsen your mood, but **thinking positive thoughts** and then **smiling** as a result can make you happier. A genuine smile includes the facial muscles around your eyes, and can actually prompt brain changes linked to increased mood. When you smile at others, they're also more likely to smile back in return, creating an ongoing **feedback loop** that may lead to more positivity in your life.

**9. Learn Something New**

Is there a topic you wish you knew more about? Like deep sea diving? Pick something that intrigues you or something you're **passionate about** — not something you have to learn. You could start by spending even just a few minutes every few days reading up on your newfound passion.

## Review Questions for Chapter 8: Neurotransmitters

**1.** If a receptor is *adrenergic*, this means that:

- **a)** it is always an inhibitory receptor
- **b)** ACh binds to it
- **c)** NE and E bind to it
- **d)** It is found only in the brain
- **e)** a and c

**2.** Which of the following statements about ACh is *false*?

- **a)** Skeletal muscles contain nicotinic ACh receptors.
- **b)** The heart contains muscarinic ACh receptors.
- **c)** Stimulation of nicotinic receptors results in the production of EPSP's.
- **d)** The choline precursor from the diet can be obtained from whole eggs, meats and fish.
- **e)** G-proteins are needed to open the ions channels for nicotinic receptors.

**3.** The effect of GABA on a postsynaptic neuron is:

- **a)** All-or-none action potential
- **b)** Hyperpolarization of the membrane
- **c)** Repolarization of the membrane
- **d)** Depolarization of the membrane
- **e)** Excitation of the membrane

**4.** What are the roles for the neurotransmitter Substance P in the nervous system?

- **a)** It causes vasodilation and is a trigger for nausea and vomiting.
- **b)** It is for the transmission of pain perception.
- **c)** It is biogenic amine for pain transmission.
- **d)** a and b
- **e)** a and c

**5.** Which of these statements about **β-Endorphins** is accurate?

- **a)** it acts by pre-synaptic inhibition on Substance P
- **b)** it's released during child birth
- **c)** it blocks Substance P after it is released
- **d)** it is an amino acid neurotransmitter

**6.** For nitric oxide (NO), what functions is it involved in as discussed in this section?

**a)** It causes vasoconstriction of blood vessels.
**b)** Disorders that reduce NO synthesis or NO release can lead to erectile dysfunction.
**c)** It blocks NMDA receptors and causes arrhythmias.
**d)** Too much NO leads to erectile dysfunction.
**e)** Slowly it is converted to $CO_2$ and signals the lungs to increase breathing rate.

**7.** The monoamines include all of the following neurotransmitters except:

**a)** serotonin
**b)** norepinephrine
**c)** dopamine
**d)** GABA
**e)** histamine

**8.** Which of the following statements about catecholamines is ***false***?

**a)** They include epinephrine, norepinephrine and dopamine.
**b)** They are inactivated by monoamine oxidase.
**c)** Their effects are increased by action of the enzyme catechol-o-methyltransferase.
**d)** They are inactivated by re-uptake into the presynaptic.
**e)** They may stimulate the production of cAMP in the postsynaptic membrane.

**9.** If the drug Benzodiazepine (valium) calms people down, then which of these are true?

**1.** it's a GABA agonist **2.** it's a GABA antagonist **3.** it's a substance P antagonist
**4.** it blocks glutamate **5.** it's a glutamate agonist **6.** It hyperpolarizes the postsynaptic membrane

**a)** 4 and 3
**b)** 1 and 6
**c)** 1 only
**d)** 5 and 1
**e)** 2 only

**10.** In an excitatory cholinergic synapse:

**a)** ACh binds to ligand-gated ion channels.
**b)** The postsynaptic neuron is hyperpolarized.
**c)** An IPSP will occur.
**d)** A second messenger system, such as cAMP, is activated.
**e)** ACh is removed from the synapse by reuptake rather than by enzymatic degradation.

*Answers in Appendix B*