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. Believe it or not, most everything discussed in this chapter is still theoretical. Neurotransmitter has yet to be measured exiting a synaptic bulb, but this is the current theory we need to know about.

Neurotransmitters (NT's) are signal molecules 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, which 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 is 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.

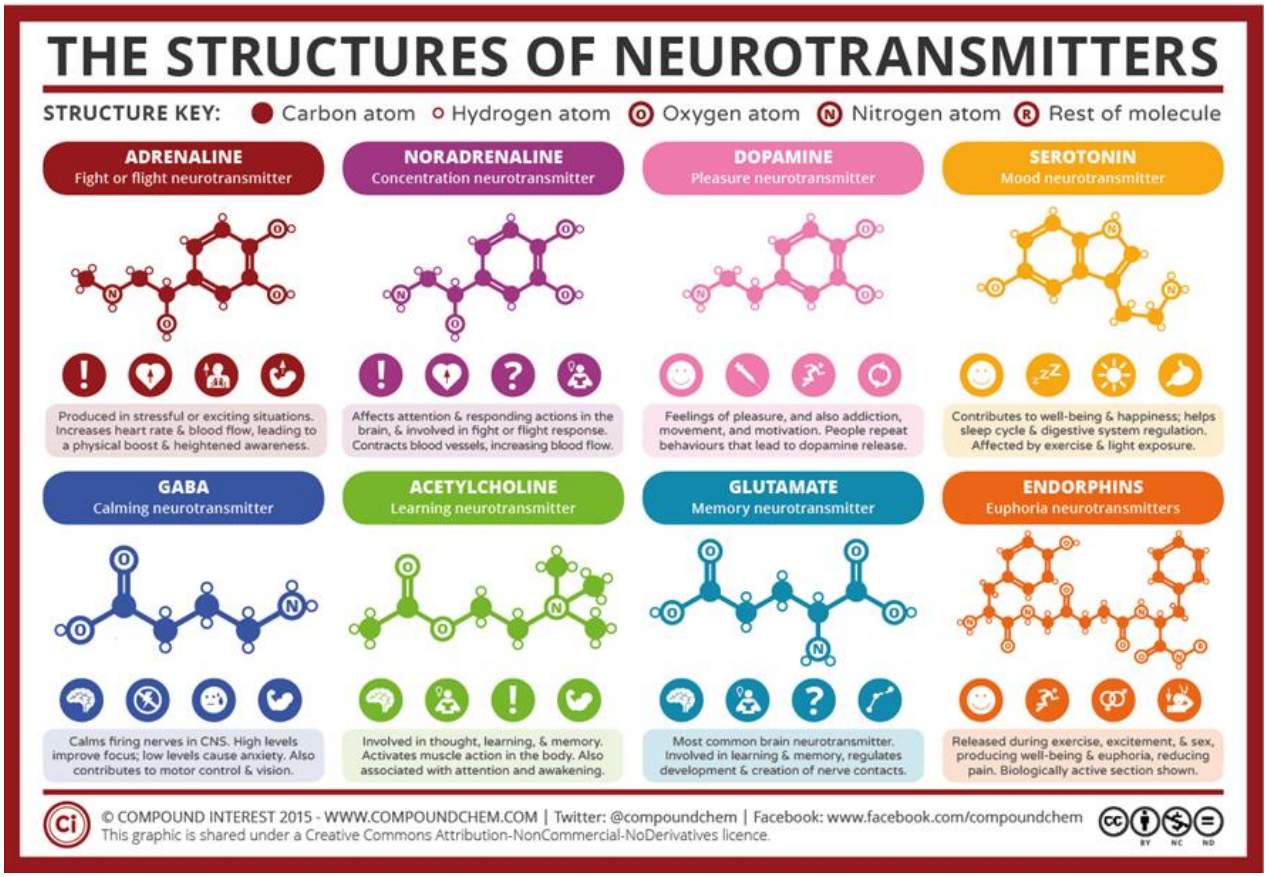
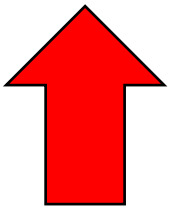


Figure 8.1 Above is the "Simple Guide to Neurotransmitters" graphic giving an overview of the most common neurotransmitters in the body and their key structural components, along with basic information about what they do in the body. This is shared from the website www.compoundchem.com/2015/07/30/neurotransmitters.

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.

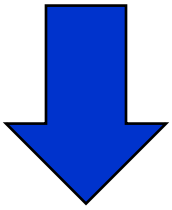
Excitatory Neurotransmitters:



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 in chapter 7 that show the RMP getting lowered, moving 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 have both excitatory and inhibitory effects. As you can see above, some neurotransmitters are listed in both categories. That is because they can cause an EPSP's or an 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 further in the text, we will have a much better understanding of why the same neurotransmitter can have various effects.

Neurotransmitters can be divided into five general categories

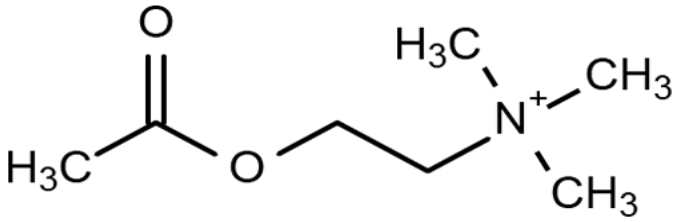
The most common way to organize and categorize neurotransmitters is by their structural, and therefore their **chemical properties**. This main reason for this is because there have been many studies on the similarities of actions and effects of neurotransmitters based on their chemical properties. As this chapter unfolds we will explore the 5 categories of neurotransmitters in the body, providing details of the exemplary neurotransmitters within each of these groups.

The Five (5) Categories of Neurotransmitters 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! This is because it is **ubiquitous** (found everywhere) and plays a vital role in 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 its name. ACh is the neurotransmitter released by somatic motor neurons at the neuromuscular junctions (NMJ) of **skeletal muscle**, and is 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 perform new roles, store additional information and new memories. The 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.

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 released by all neurons **at the ganglia** and it binds to nicotinic receptors on the postganglionic neurons (see **Fig 8.2**). It is also released by parasympathetic postganglionic neurons and binds with muscarinic receptors on effector tissue (cardiac muscle, smooth muscle and glands). The Autonomic Nervous System is fully explored in Chapter 10 of this text.

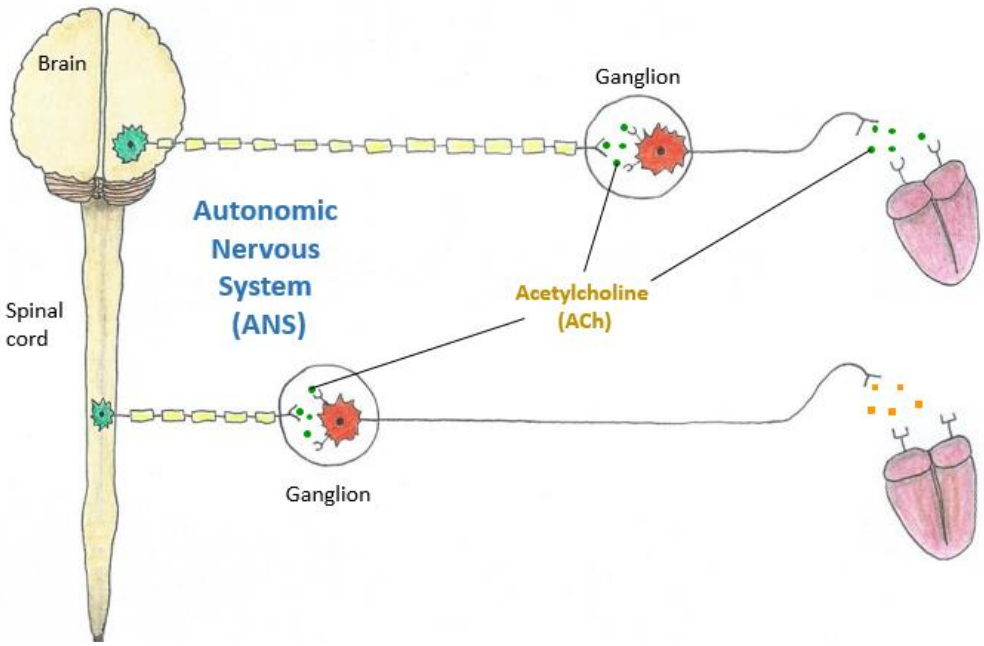


Figure 8.2 The role of acetylcholine (ACh) in both the parasympathetic and sympathetic divisions of the autonomic nervous system (ANS) is foundational. Note that ACh is released by 3 of the 4 types of neurons involved in the ANS. In addition, ACh can promote relaxation in the body via **vagus nerve**, the primary nerve for the **parasympathetic** division of the autonomic nervous system (ANS) which counteracts the "fight-or-flight" tendencies of the **sympathetic** division of the ANS.

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 anti-cholinergic drug **scopolamine** has been 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 always block other very important signaling.

How does your body make ACh?

Acetylcholine is synthesized by the enzyme **choline acetyltransferase** from the two 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 broad, 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

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 (impaired nervous system).
- Problems with word recall when speaking (memory).
- Dry mouth and eyes (impaired parasympathetic activity).
- Orthostatic hypotension (low blood pressure when moving to an upright position).

Keep this information in mind because 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. Scanning the literature, it appears that adequate levels of ACh are important to good health.

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 were fewer receptors on skeletal 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 the 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.

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 – This 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 is 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 is in **learning**. Its excitatory actions strengthen the connections between existing neurons, a process called long-term potentiation (LTP).

Inhibition of Glutamate NMDA Receptors

The importance of these **NMDA receptors** is indicated by not only all the blockers for them, but more importantly, the terrible effects produced by blocking them! The effects of the inhibition of NMDA receptors include: 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 involves significant deleterious effect to the human body that are also extremely unpleasant for individuals to experience.

To reinforce the notion that these receptors are important for brain activity, the drug **ketamine**, which is a powerful anesthetic, is an **NMDA receptor antagonist** (thus an inhibitor or blocker of Glutamate). So is **dextromethorphan**, found in cough suppressants, where it inhibits the signals that trigger the cough reflex. Keep in mind that reflexes in the body are protective and essential. When protective circuits in the body are blocked, this can lead to a denigration of that protective measure. This is not good.

Yet another NMDA blocker is the opioid **methadone**, which is used by many government programs as a 'healthy' **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 would it make sense that this would be viewed as some sort of effective treatment? It does not make any sense, except to prolong a person's drug addiction. Ultimately, none of these blockers listed above would be a good idea for anyone to take if they preferred to become or stay healthy.

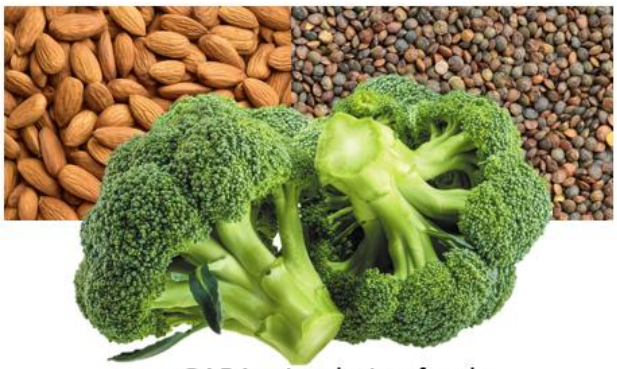
2) Aspartate – This is similar to glutamate but found mostly in the **spinal cord** for excitation (aspartic acid). It is thought to be ***the most abundant excitatory neurotransmitter in the spinal cord***. It is also known as aspartic acid. It is implicated in the physiology of **learning** and **memory** processes. In the **gonads** (testes and ovaries), 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

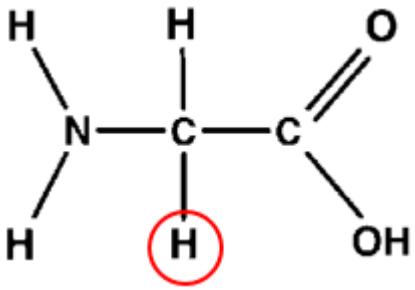
The two major classes of GABA receptors are classified as either **ionotropic $GABA_A$** (with $GABA_C$) receptors or **metabotropic $GABA_B$** receptors. As we learned from the previous section (Chapter 7), the two basic types of responses for postsynaptic cells are either ionotropic (direct opening of ion channels), or metabotropic (involving a 2nd messenger system). We can glean from this information that GABA transmission involve both ionotropic and metabotropic responses. 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 that are used to treat epilepsy often act by increasing the levels of GABA within 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 (see the **almonds**, **lentils**, **broccoli** at left), as these also have calming effects without the detrimental side effects.

4) <u>Glycine</u> - is the simplest amino acid, its R group is just H (see right), and it is ***the most common inhibitory neurotransmitter in the spinal cord.*** So, it's like the equivalent of GABA but working to calm things down in the spinal cord (instead of the brain). 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 are important in normal actions, such as **reciprocal inhibition** of antagonist muscle groups which are a critical component in creating 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. Thus, glycine levels in the body can be boosted by consuming foods that contain a lot of collagen in them. As seen in the image to the left, these foods include bone broths, poultry skin, legumes, seaweed, spinach, broccoli and many other foods that are high in protein, especially meat, eggs, fish, and dairy. There are also collagen powders that can be consumed.

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 <u>excessive excitation</u> 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. That is bad for our health. As mentioned, 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 ingredient 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 other 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

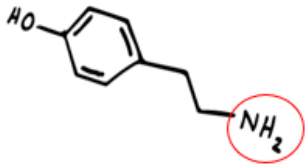
that many other animals have that would further convert the formaldehyde into the harmless **formic acid** (like what ants use to scent their trails for each other). Therefore, in humans the formaldehyde liberated remains in the body for the liver and kidneys to detoxify and remove. That takes a heavy 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 one. Refined sugar is classified as an anti-nutrient (another topic for another day), and the synthetic artificial sweeteners are toxic and no better. Select a beverage made by nature, like a tea, or Kombucha, or juice, and skip the toxic ingredients.

③ Biogenic Amines

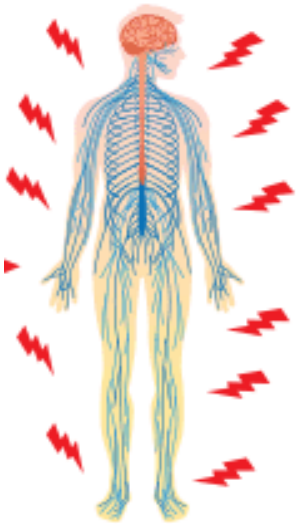
These neurotransmitters are all derived from one two amino acid, either **tryptophan**, which is an essential amino acid, or **tyrosine**, which is considered 'conditionally essential', meaning synthesis may be deleteriously impacted in special conditions, such as catabolic stress – which just means when someone has a fight-or-flight response for too long a period of time. All biogenic amines can also be referred to as *monoamines*, which are degraded by the enzyme **Monoamine Oxidase** (MAO).

The COOH groups in either amino acid are replaced by **NH_2** groups (see right).
There are two main categories of Biogenic Amines:
A) Catecholamines (derived from **tyrosine**) and,
B) Indolamines (derived from **tryptophan**).



A) Catecholamines - three (3) 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 **adrenal medulla**, which is an endocrine gland. The two adrenal glands sit on top of each kidney. The name epinephrine means above/on top of (epi); and the kidneys (nephron), thus named 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 stimulus. It is the classic "**Fight or Flight**" signal molecule.

In general, when we experience **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 "**fight or flight**" responses to any stressful or exciting situations.

Epinephrine stimulates an increase in heart rate, and it dilates airways which allows for greater air flow to the lungs. These are critical changes that ready the body for action. It also constricts most blood vessels

thereby increasing blood pressure, along with diverting blood flow away from most internal digestive organs and moving it toward skeletal muscle and the lungs. In terms of energy supply, epinephrine stimulates sugar metabolism so that glucose can be used as fuel for the body. All of these activities lead to a physical boost and heightened awareness. Stress tends to deplete our stores 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 those events are easy to remember, including the fine details. This, in part, is both epinephrine (E) and norepinephrine (NE) at work.

The Hormone Actions of Epinephrine and Norepinephrine

This will be covered in detail in the Endocrine section (Chapter12), but briefly, the adrenal medulla is the inner portion of the adrenal gland and it releases epinephrine (E) and norepinephrine (NE) into the blood stream as hormones. It is the sympathetic division of the autonomic nervous system (ANS) that is hard-wired to the adrenal medulla such that when it is activated, it stimulates the release of E (**80%**) and NE (**20%**), which promote the same physical changes on the body as E and NE do as neurotransmitters.

What is an "Epi-pen"?

If serious life-threatening reactions occur, such as a constricted airway that cause difficulty breathing, swelling of throat, tongue, and a weak, rapid pulse, etc., then it's good to have more epinephrine in the body. As we have already seen, epinephrine acts very quickly in the body to dilate the airways and increase air flow when breathing, and it stimulates the heart, thereby elevating blood pressure. It also mitigates the swelling of the face, lips, and throat, assisting in maintaining air flow. Therefore, it is very handy to have if you are allergic to something, like a **bee sting**, **drugs**, **certain foods** or other substances, and your body begins to trigger a sever reaction such as **anaphylactic shock**, also called **anaphylaxis**.

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

A device called an **Epi-pen** (seen above at right in **Fig. 8.3**) contains concentrated epinephrine within an easy-to-use injectable syringe. Other effects of anaphylaxis can include nausea, vomiting, diarrhea, dizziness, fainting or loss of consciousness. This type of Epi-pen medication can be used in emergencies to alleviate these serious reactions by delivering large amounts of epinephrine directly into the body via an intramuscular (IM) injection. This allows for immediate yet controlled high levels of epinephrine to enter the bloodstream and start reversing the effects of this extreme reaction.

What are the Most Commonly Causes of Anaphylaxis?

The most common causes of anaphylactic shock are allergic reactions to prescribed **drugs** (medications), **foods** (like peanuts, shellfish and some milk products), **insect stings** (from bees, wasps, and hornets) and contact with and **latex** substances (like latex gloves). It is food allergies that are the most prevalent trigger of anaphylaxis in children, and allergic reactions to medications are the more common trigger in adults.

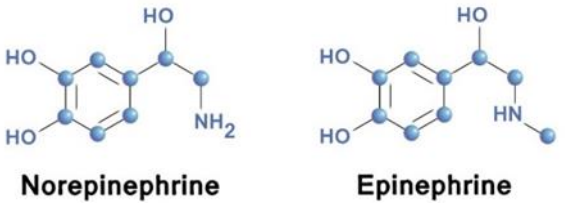
2) Norepinephrine (NE)

As a neurotransmitter, 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 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 mentioned above both NE and E are also released by the adrenal medulla, and most predominantly it is E that is released (80%).



Norepinephrine **Epinephrine**

Like epinephrine, 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.

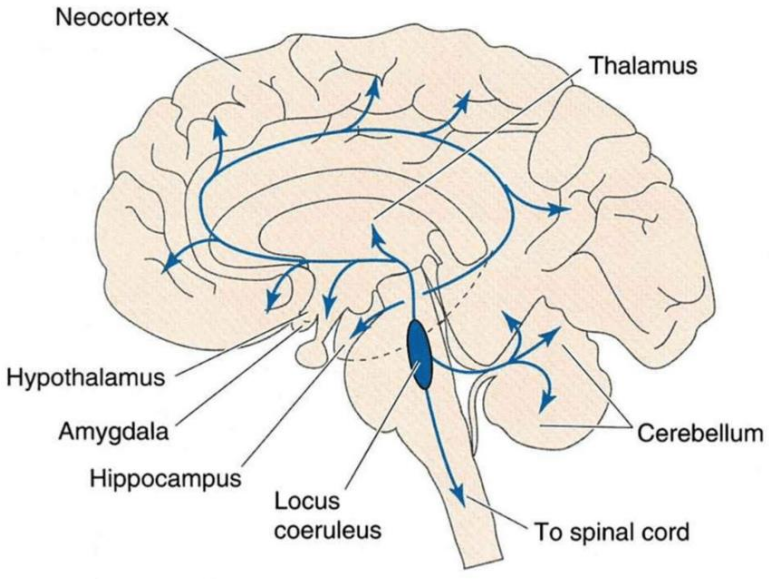


Figure 8.4 The locus coeruleus (LC) is shown as the 'blue spot' high in the brain stem. Notice how the LC has widespread projections throughout the forebrain, brainstem, cerebellum, and spinal cord, radiating out like a roundabout in the brain. This enables many regions of the brain and spinal cord to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

How Drugs Impact Norepinephrine

The high energy state of alertness 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.

Actions of 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.

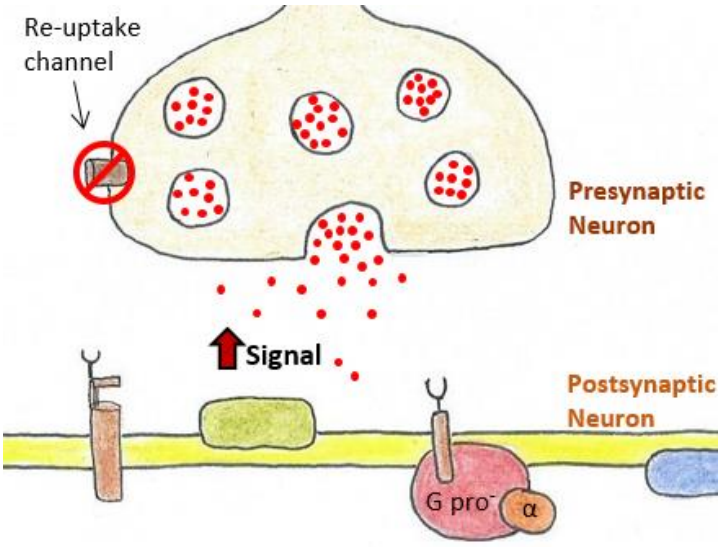


Figure 8.5 In the illustration of the synapse above, blocking the reuptake channel, with a substance like cocaine, can have the effect of increasing the signal that is delivered to the postsynaptic neuron.

Actions of Monoamine Oxidase (MAO) 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 again 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.

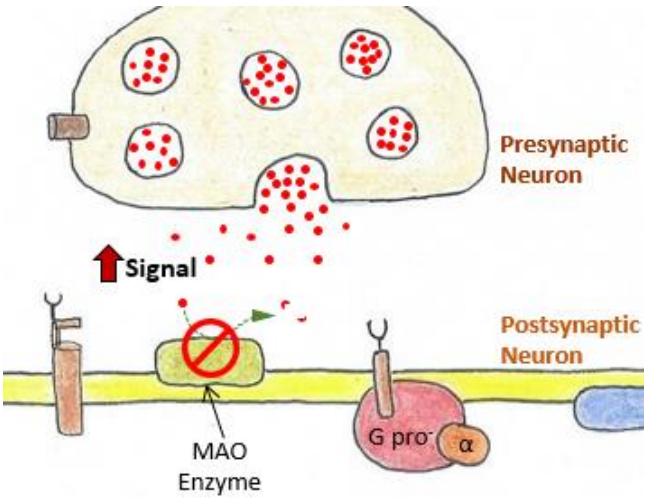


Figure 8.6 In the illustration of the synapse above, blocking the actions of the MAO enzyme that would normally degrade the neurotransmitter in the synaptic cleft will have the effect of increasing the signal that is delivered to the postsynaptic neuron because more the neurotransmitter remains in the cleft to stimulate the cell.

It is important to know that when receptors on cell membranes or within the cell are overstimulated, they will **down regulate** in response to this, that means to decrease in number. 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? The answer is ***More*** 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 a drug induced reduction of any signal molecule in the body.

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 caused the disruption of NE vesicular storage and depleted catecholamines from peripheral sympathetic nerve endings, and this had a host of very bad side effects, including severe **depression**.

Please let us not forget that the threshold 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 term means "**for which the cause is unknown**". Stop to consider this situation. There are very powerful and toxic drugs being administered, yet no one even knows why or what has caused the "problem" in the first place. It is likely that if the cause is literally totally unknown, then it may be problematic to attempt to 'treat' it with a drug, right? One thing is certain, from the drug treatment you will have depression, guaranteed, because the biogenic amines are linked to mood and emotional wellbeing, with 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 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.

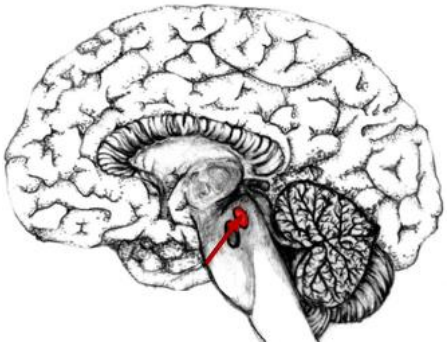
Here are some examples of Activities that can elevate E and NE naturally:

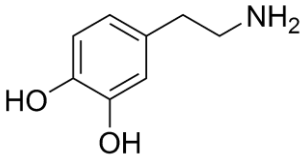
- Deep breathing exercises (there are many types).
- Praying , being grateful and meditation.
- Cold exposure, either by swimming in natural bodies of water or taking a cold shower.
- Physical exercise. Even very simple body movements generate benefits.
- Any kind of positive accomplishments. Genuine praise from others also provides a boost.
- Singing and listening or playing Music.
- Consuming coffee, tea, citrus fruits, bananas, cocoa and vanilla (just to name a few items).

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 hypothesized to play a role in **mood**, **emotional responses** and feelings of **pleasure**. Neurons that release dopamine are termed "**Dopaminergic**" neurons.

Dopamine can have effects that are both excitatory and inhibitory. It inhibits unnecessary body movements by its actions in the **substantia nigra** (see red arrow in brain image at right), it inhibits the release of prolactin, and it stimulates the secretion of growth hormone. Dopamine is also involved in memory and attention. For example, the limbic system (called the 'emotional brain') is an important brain region involved in elevation of mood and emotional responses, and emotional responses are key to learning.





The highly concentrated levels of dopamine in the substantia nigra (see above) of the midbrain are involved with voluntary motor control of skeletal muscle. The deterioration of these dopaminergic neurons in the substantia nigra can 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 thought to be 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. For example, have you ever jumped out of a plane? Some people find it exciting (see left), even though it is also somewhat terrifying.

There are many elements at play in seeking pleasure, and the dopaminergic link to reward and pleasure appears to be associated with specific behaviors or actions that can bring about thrilling sensations. Within this we can also see an association to possible **addictive behaviors**. The feelings of satisfaction caused by a euphoric release can become highly desired by a person experiencing it, and in order to re-experience these feelings a person will repeat behaviors that lead to a release again, associated with the '**pleasure center**' in the brain.

These behaviors engaged in can be balanced, or they can become unbalanced. It may involve jumping out of a plane, or other more down-to-earth activities. There are also people who find being polite and kind to others very satisfying, even thrilling! Behaviors can also include detrimental activities, such as becoming dependent on harmful drugs or medications and therefore leading to addictions.

While we're on the subject of addiction, let's define what addiction means.

Addiction is when an individual continually engages in a compulsive behavior despite the **negative impact** it has. 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 may have feelings of guilt, remorse, or feel trapped by the consequences of the seemingly unrelenting choice to continue the activity.

From the definition of addiction above, the key element is that ultimately addiction has a profound **negative** impact on the individual, and likely those around them. Some may continually engage in skydiving because it gives them a great feeling of pleasure (after some initial terror), this would not be considered an addiction if it has no harmful consequences.

One last neat thing related to the connection between what we eat and neurotransmitters in our body. 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.

Keep in mind that cocoa is not the same as chocolate. There is a big difference between chocolate that is made with **70% to 90% cocoa**, compared to the substances found in typical 'candy bars', which usually tops out at about **30% cocoa**. Not only does the chocolate in 'el cheapo' candy bars have low cocoa content, but of course the most abundant ingredient in them is **refined sugar** – and tons of it. Refined sugar is highly addictive and very destructive to human health. Therefore, if you are seeking the benefits of 'chocolate', then know they are found in the more expensive organic chocolate bars which have much higher levels of cocoa.

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**. Neurons in the brain make COMT and it is thought that it 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. Essentially 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 balance there, this then causes this region to become **hyperactive**, which is contrary to dopaminergic control there.

This may lead to **Parkinson's disease**, which is characterized by symptoms of muscle tremors, mainly at rest and also involves what is 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.

The catechol-O-methyltransferase (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

The drug **amphetamine** ("speed") 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 appears that most of the drugs and medications that elevate the mood are directly tied to elevating biogenic amines.

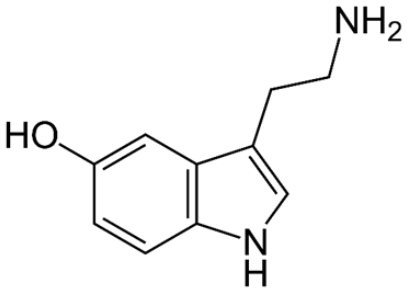
B) Indolamines

There are two main indolamines: **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 derived from the amino acid **histidine** and is famous for 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? It is now safe to scratch that theory as another long-held inaccuracy. Form an orderly queue for all the wrong things we have been encouraged to believe at various times. It's OK, that is the nature of good scientific endeavor, that we re-examine issues to test the validity of our beliefs.

This particular finding, that there is no consistent scientific conclusion about serotonin and depression, (and there are many others) is one reason I use language in this text such as 'apparently' and 'theoretically' when discussing what science believes, because the truth is often that what we were confident in and adamantly believed at one point, actually turns out to be untrue.

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 restorative 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). In fact, it is suggested there is more serotonin in your gut than in your brain. This massive amount of serotonin produced by **enteric neurons** in your gastrointestinal system should be a good indication that what we eat has a significant impact on our mood and our sense of wellbeing, since what we ingest must be triggering something related to serotonin down there. Having healthy serotonin levels is thought to help with sleeping, eating, and digesting, thus plays an important role in sleepiness, alertness, mood and body temperature. It is also secreted by platelet cells where it is associated with **wound healing**.

Serotonin is Derived from Tryptophan

As mentioned, serotonin is derived from **tryptophan**, which is an ***essential amino acid*** and must be obtained in our diet. High levels are found in nuts, cheese, and red meats. Therefore, if your diet is low in tryptophan, then your body will make lower levels of serotonin. Often is has been shown that it is the lack of adequate nutrients that can 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. Now that we know from the reference cited earlier that serotonin actually has no scientifically proven role in depression, we can perhaps view with more clarity the shocking number of "antidepressant" medications that have been tested on people for over 50 years now.

Since all biogenic amines are affected by **Monoamine Oxidase (MAO) Inhibitors**, manipulation of this MAO enzyme 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 more like a planet in space or like a **poison**. For instance, the drugs phenelzine (Nardil) and isocarboxazide (Marplan) are used to treat clinical depression. Not only can I not pronounce those drug names, I don't want to. These drugs 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 packaged into the vesicle before being released into the synaptic cleft. Thus, this revs up **sympathetic** Fight or Flight-like responses, and on the whole it sets off a bad bundle of responses called "side effects" when these drugs are consumed. These side effects include "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 destitute-looking 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 as an "*Anti-Depressant*" medication a long time ago, when it was considered the 'miracle drug'. This was before the catastrophic damage caused by their incessant use was clearly seen – by the victims at least. Conveniently, the mental health industry jumped horses, as they always do, 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 the pain and suffering of a condition. However, what occurs in reality is almost always vastly different from what the drug manufacturers predict regarding their products. This is because the use of powerful **toxic drugs** will invariably have a wide detrimental impact on the body. A poison to the body will always be poison to the body. Some may argue that the use of these drugs is better than having a person suffer the depths of depression or anxiety. Before anyone agrees with that argument, it is worth taking a look at publicly available data on this issue.

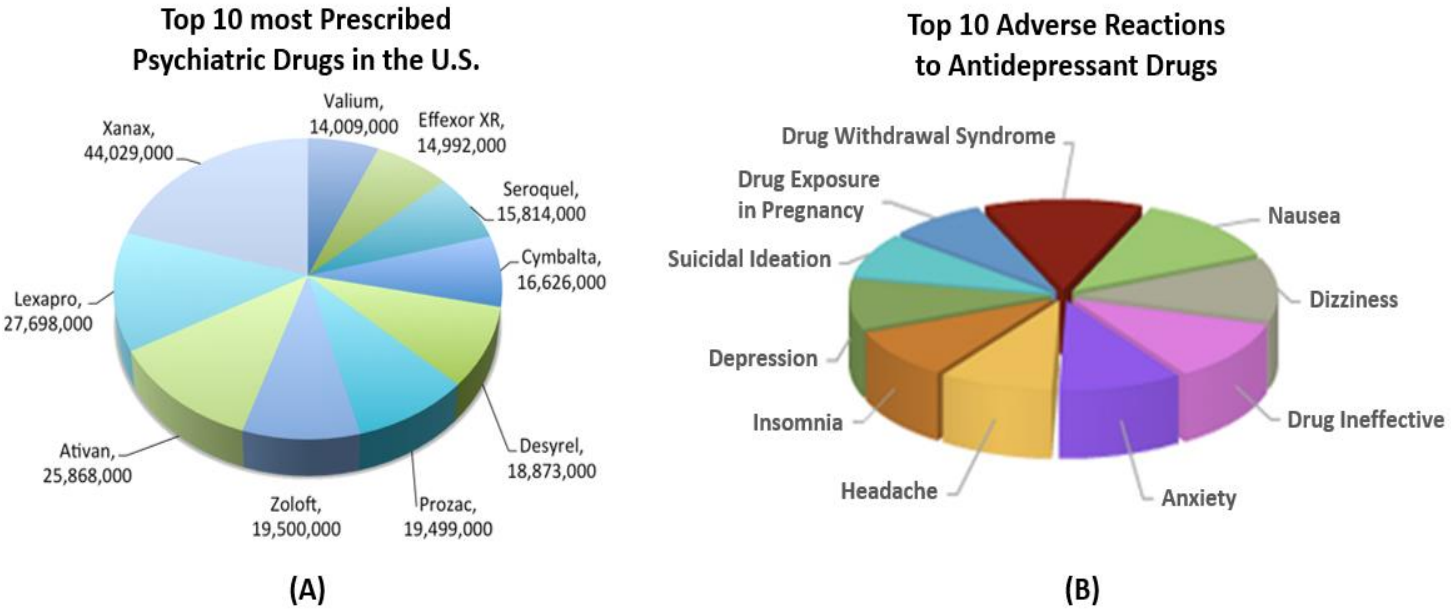


Figure 8.7 This shows the most recent data regarding **(A)** the top 10 most prescribed drugs for depression, anxiety, etc., and to the right it also shows **(B)** the top 10 most common adverse reactions or 'side effects' to all of the antidepressant and antipsychotic drugs that are prescribed in the U.S.

Notice how both of the pie charts presented in **Fig. 8.7** (above) are reminiscent of a either a crazy type of merry-go-round ride, or a disastrous type of board game. The names of the top 10 drugs in chart **(A)** are the usual shell game of hiding the names of the poisonous chemicals contained in each. The top 10 adverse reactions shown in chart **(B)** are likely more problematic than the original alleged affliction. How does it make sense that the drugs which claim to 'cure' depression can have suicidal ideation (which means thoughts that are preoccupied with death and suicide) as a major adverse reaction (side effect) of the treatment? How could this possibly be an acceptable outcome? Hopefully it seems obvious from the information openly provided that it is unwinnable for anyone who plays the game of believing these drugs will ease the core problem, let alone resolve it.

No one would argue about the pain and discomfort of debilitating depression or anxiety. However, what is worth exploring is a better way to recover from these conditions, 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 something in their life for themselves, in order to figure out 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, compared to non-self-analysis and only more toxic drugs.

For the medical field which proclaims to want to help others, here is an apparent novel idea: Try to find out what is actually bothering a person as an individual by spending time and energy talking with them to identify a possible genuine cause. Then suggest healthy actions that could augment the body' natural ability to heal itself and recover permanently, without the use of drugs. Sadly, we all understand that there is no **$** in that model, and no more lifelong customers : (The result would likely be healthy recovered people. As naive as it may sound, my vote is to work to create a health care field that makes people more healthy, not more sick. We also all know it is 100% possible to work toward that outcome.

Selective Serotonin Reuptake Inhibitors (SSRI's)

Since we have had a taste of the bitter and unpleasant history regarding the use of antidepression drugs such as MAO inhibitors on people who were suffering with depression related issues, let's now move on to take a quick look at the more recent drugs being called miracle cures. Spoiler alert: These are essentially the same drugs, just a little change up in the recipe and a new outlandish name.

The focus after the MAO inhibitor disaster became solely on **serotonin**, since the drug companies had to make an exit from any link to MAO inhibitors. Please recall, those MAO inhibitors were all also touted as miracle cures for those feeling the pain of depression and anxiety.

The medications fluoxetine (*Prozac*) and paroxetine (*Paxil*) prescribed for depression, are said to interfere with mostly 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)**. Again, it is blocking reuptake channels, only this time more specific ones. This approach will result in an increased amount of serotonin remaining in the synaptic cleft, thus serotonin activity in the CNS is said to increase.

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 medication about to appear 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 to health with no intrinsic medicinal value. In a seemingly odd maneuver, but likely realistic manner, the karmic trade-off is that the makers and prescribers of these drugs told you they were useless and toxic, so if you are senseless enough to take them anyway, knowing they are poison but blindly believing they will cure you - that is your own fault. Other options are possible rather than getting on the same old merry-go-round, 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 in various body regions until a later time when it can release them in a way that will be more protective to you. 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 engage in **fasting**, that means to deliberately abstain from eating food or drinking, 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. It might seem straightforward, aside from the extreme social and cultural pressures to constantly eat. If you give it a try, many benefits are possible. Once the digestive system is no longer busy processing all that food, it finally has the downtime to dig deep and start to release the years and years of toxins that are held deep within our tissues. This period during a fast can result in '***cleansing episodes***' and they are extremely unpleasant. Mysteriously it feels ***exactly*** like being sick. VERY SICK. As the toxins swirl around and gain access to 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 for very short periods 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**, especially important is to be in nature during this exposure. Experiencing **touch** (especially effective is **body massage**), physical **exercise**, and remembering, and recollecting **happy events** in your life. Plus of course, eating things in your diet that have high natural sources of serotonin and the precursor amino acid tryptophan.

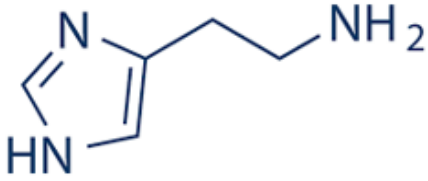
It should not have to be tested experimentally for us to know these things are true, but still, they have been tested. Just like tests have shown that babies do better in every metric when they are breast feed compared to being given formula. Again, do we really need a study to tell us this? No, we already know it.

As seen earlier, there are some examples of nutrients that can elevate E and NE naturally: Salmon, poultry, eggs, spinach, seeds, nuts and milk. These are rich in nutrients, particularly in **tryptophan**, the essential 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 of 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**. Why consume more toxins, you'll just need to take get rid of them!

5) Histamine

As stated earlier, histamine is derived from the essential amino acid **histidine**, 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 protective responses.

As we will see in later chapters, basophils are a type of granulated white blood cell (leukocyte) involved in various actions. Histamine action, in the capacity of being released from blood and tissue cells, 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 the site of tissues that might need some repair. This is part of the protective 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. The red part is an increase in local blood flow in the region due to vasodilation and the puffy part is due to the increase blood vessel permeability, which means more things flow out of the vessel and into the tissue spaces, making it more swollen.

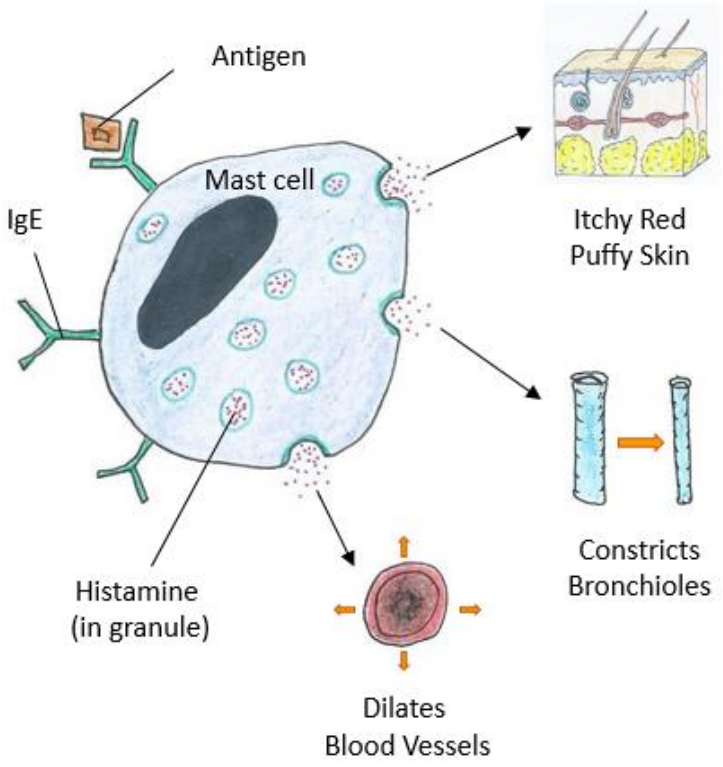


Figure 8.8 The drawing of a mast cell shows how immune IgE bind to it and then the antigens bind to the IgE causing degranulation and the release of histamine at a local area. Most common sites of histamine release: **1)** skin, gets red and puffy; **2)** bronchiole airways in the lung, constrict and 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.

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. 8.8** above). This would reduce the symptoms of puffy redness associated with these allergies. Having proper histamine levels is important for your health and wellbeing. It helps blood vessels free up body resources and lets cells to do their job. It's also vital to our digestive system.

As discussed, 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's 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

This group of 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 the pain the perception pathway. It modulates pain perception in the brain by altering cellular signaling pathways. So the **P** is for Pain. The signal of pain is not just about causing discomfort, but it's a protective measure, to warn us that tissue damage is occurring and that we should take evasive or protective action.

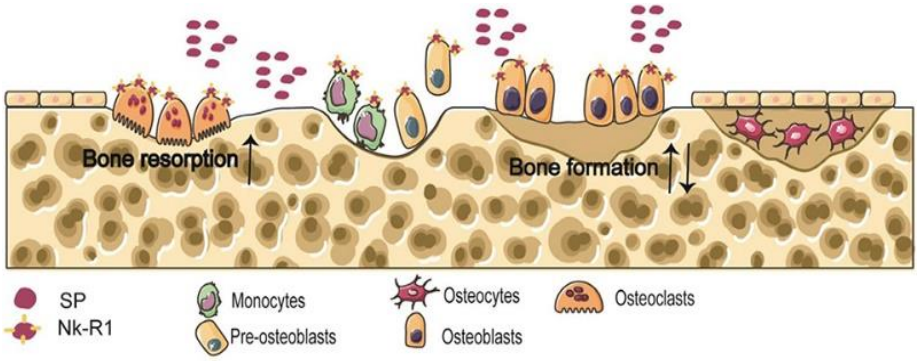


Figure 8.9 Seen in the illustration are two important bone cells, osteoclasts and osteoblasts, being stimulated by Substance P during bone repair.

Quite recently (2020), the role of Substance P (Sub P) in the regulation of **bone** and **cartilage** metabolic activity was studied (see **Fig. 8.9** above) and it was shown that Sub P binds to receptors on bone cells, thereby regulating bone and cartilage metabolism and bone fracture healing. Whoa! This recent information kind of links back to the "no pain no gain" idea, as the involvement of Substance P in healing seems to be related to a greater experience of pain, that is, the more pain we experience, the more significant the healing will be.

Shown in detail below in **Fig. 8.10** is the well-established pain transmission pathway of Sub P in terms of regulating the perception in the brain of pain in the tissue.

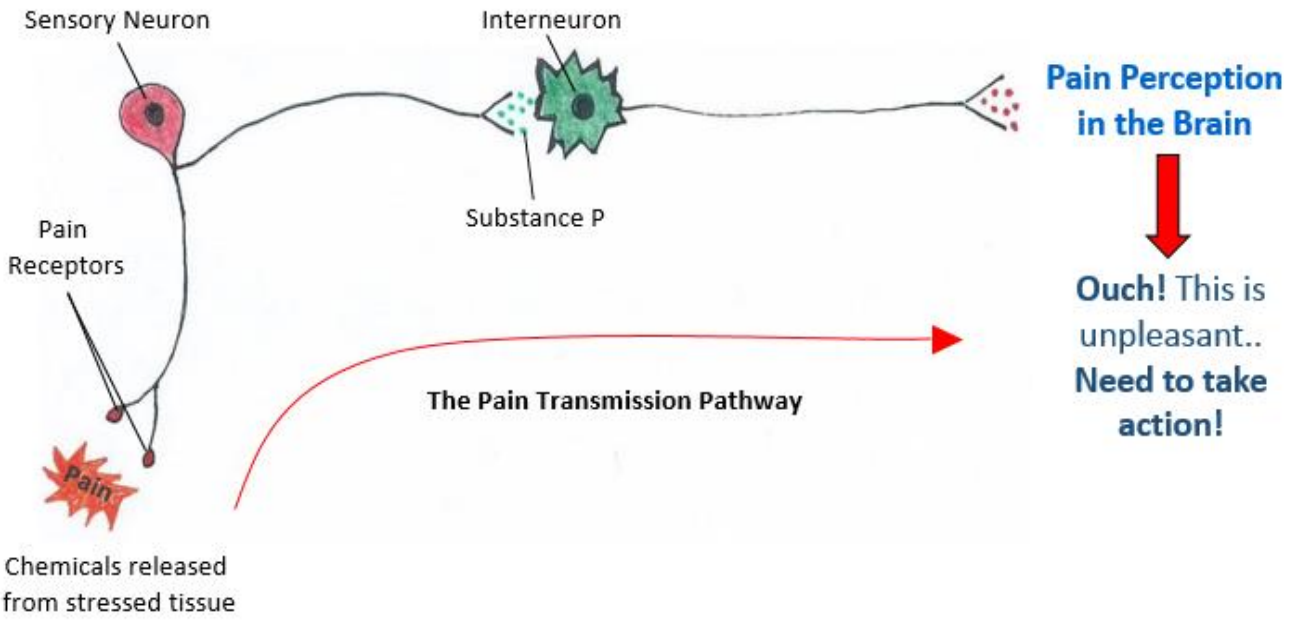
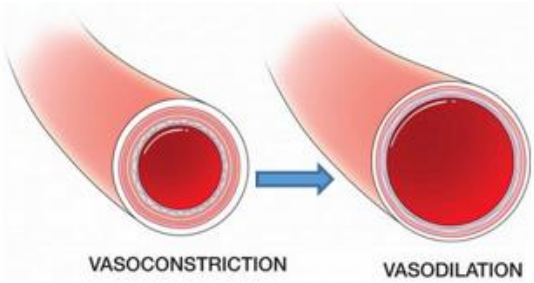


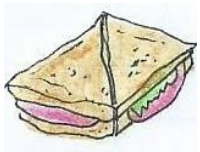
Figure 8.10 The figure above shows the pain transmission pathway and the central role of Substance P in this information loop. The stimulus is from the stressed or damaged tissues and the pain receptors (nociceptors) of sensory neurons convey this information with Substance P.

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! In simple terms, the arrival of more blood to an area means faster healing,



Although nausea and vomiting are not pleasant, again they are mechanisms designed to protect us. 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! However, if you were to eat that rotting sandwich (and please don't), then in a *very* short amount of time your body would automatically rid it 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 from 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 to any one irritant, and some may not have any such response at all.

Additionally, Substance P plays a role in **gastrointestinal** functioning, memory processing, **angiogenesis** (this term means the generation of new blood vessels), and cell growth and proliferation.

The topical application of **capsaicin** (an active component of chili peppers) can deplete substance P from local nerve endings, and by doing so relieves pain. It is like it draws out the signal molecule in like attracts like fashion. Substance P is also present in **corneal nerves** and in normal tears, which may indicate that this molecule is related to emotional sensitivity. Elevated expressions of substance P can be associated with gastrointestinal diseases such **inflammatory bowel disease.**

Enkephalins and Endorphins

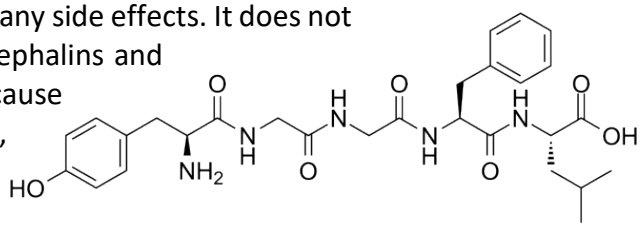
Enkephalins and endorphins are collectively known as **endogenous opiates**. The term endogenous means they are made within us. And the opiates part means they get you high. These oligopeptides are very powerful substances and are **200 times more potent** in their analgesic effects than **heroin**, **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**. The word endogenous means generated from within us. The word analgesic comes from Greek, the an- prefix meaning 'not' or without, and the -algia suffix meaning 'to feel pain'. Thus, analgesics are 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 gastrointestinal (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 the body down.

When enkephalins (see structural molecule below right) are released by cells in the **adrenal medulla** they act as **hormones** in the bloodstream and can exert their potent painkilling effects in peripheral tissue. Importantly, 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 they cannot affect brain perception if administered into the bloodstream.



As **Figure 8.11** (below) shows, opioid peptides like enkephalins have their analgesic effects by ***inhibiting substance P transmission***. However, the pain transmission pathway must be activated *first* in order for enkephalins 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 **childbirth**, as it is involved in blocking pain signals in the spinal cord during and after giving birth.

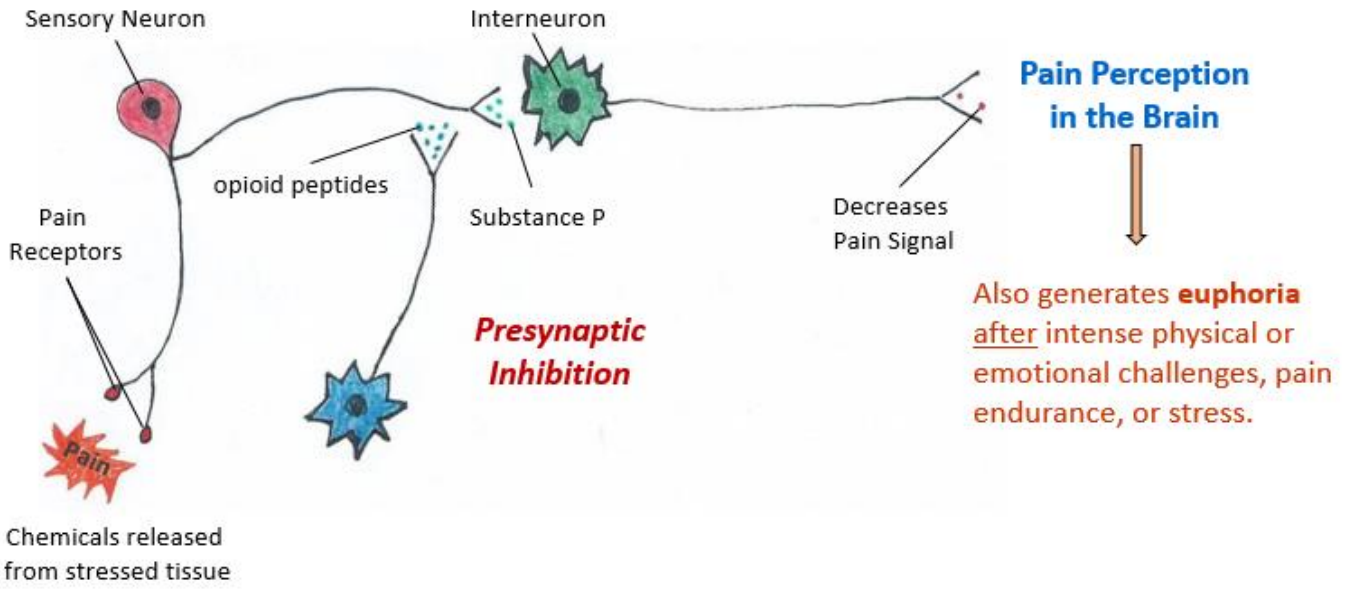


Figure 8.11 The figure above shows how opioid peptides (like enkephalins and endorphins) are involved in the presynaptic inhibition of the pain transmission pathway. They intercede before the synapse (see blue neuron) and cause less Substance P to be released (green neuron). This in turn reduces the 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 also an opioid substance produced in similar 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 certain 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 gland simultaneously during exercise, followed by a delayed release of **cortisol**. These effects combine for amazing recuperative actions (and feelings) after the physical activity ends.

These endogenous opioid peptides are similar in chemical nature to **opium** and are part of the body's natural pain relief molecules. As discussed, β-endorphins also suppress pain by blocking substance P transmission and also reduce the perception of fatigue. Endorphin release can be triggered in multiple ways to reduce pain perception. These opioid neurons engage in **pre-synaptic inhibition** of Substance P transmission (see **Fig. 8.11** 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.

Participating in **physical exercise** is great for releasing endorphins. It is linked to 'runner's high', the often discussed '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 that **walking** also promotes the release of endorphins and this contributes to producing the feelings of

relaxation and improved mood long after the walk is done. 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 vilified, so many people loved sunbathing - because it makes you feel happy and high and relaxed afterwards as well as warm and replete with vitamin D. Engaging in **good sex** releases endorphins. Good to know. Even **crying** releases endorphins! It's believed to be the deep emotional crying that can trigger this, for example from feeling emotionally vulnerable, or even possibly released when a person cries during extreme laughter.

Most people already know the sensation of feeling 'better' after an episodes of that type of crying. After all, it is recognized that there are benefits of crying, even as simple as making others feel more sympathetic towards us. In fact, an animal study showed that the magical content of female tears had the effect of reducing aggression in males! Therefore, the additional benefits that are likely to be connected to crying are that crying with or for others can bond us more closely together emotionally to each other.

Foods that Stimulate Endorphin Release

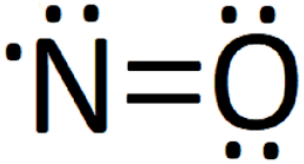
Consuming **refined sugar** releases beta-endorphins, one of the neurotransmitters in the brain that acts as a natural painkiller. It also assists in producing a sense of self-esteem and resolving anxiety – but this effect is only short lived and is quickly out-weighed by many deleterious effects all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

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: **Cocao** (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 can 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.

Nitric oxide 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 of cyclic guanosine monophosphate (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 a satisfying sexual activity. It used to be referred to as **impotence**. This condition can be a sign of a physical or psychological stress, or drug-induced imbalances (not surprising). The neurotransmitter and potent vasodilator **nitric oxide** is a physiological signal essential in the physiological process of **penile erection**, such that erectile dysfunction is related to a decrease in NO release.

Disorders that reduce NO synthesis or the release of NO in the erectile tissue are commonly associated with erectile dysfunction. The enzyme **NO synthase** (NOS) mentioned above, catalyzes the production of NO from the amino acid **L-arginine**. Therefore, one good idea is to make sure you get enough L-arginine!

A "treatment" for erectile dysfunction has been **Viagra** (called Sildenafil, another ridiculous drug name), it is a specific **phosphodiesterase** (PDE) type 5 **inhibitor** that enhances nitric oxide (NO)-mediated vasodilation in the erectile tissue (corpus cavernosum) of the penis by inhibiting cGMP breakdown. In a similar way to all the other drugs with toxic effects mentioned, the best solution for the human body is to look for a natural resolution, it is 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. Note, pot is not a miracle drug either.
- Stop drinking alcohol or using any drugs, quit them all 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 your 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 and 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!

If we want to really understand neurotransmitters, it is important to make some clear statements about the vital role that **receptors** play. Again, the same neurotransmitter can have opposing effects on tissues. How can this be? It be the receptors! The effects of ACh contracting skeletal muscle is due to nicotinic receptors, and for relaxing smooth muscle, due to muscarinic 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 Again 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. 8.12** below shows the variations in up and down regulation of surface receptors.

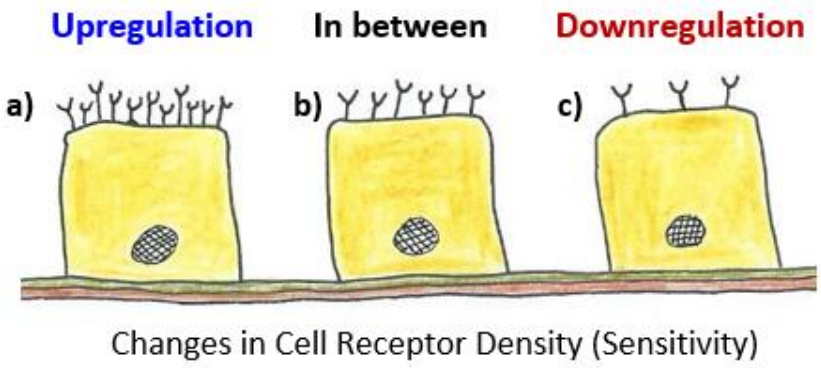


Figure 8.12 Shows the receptor density (sensitivity) changing on the cell surface, as it will always do in response to variations in levels of stimulation. In **a)** there is an upregulation of surface receptors due to a reduction of a signal molecule stimulus. In **c)** there is a downregulation of 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 require 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**!

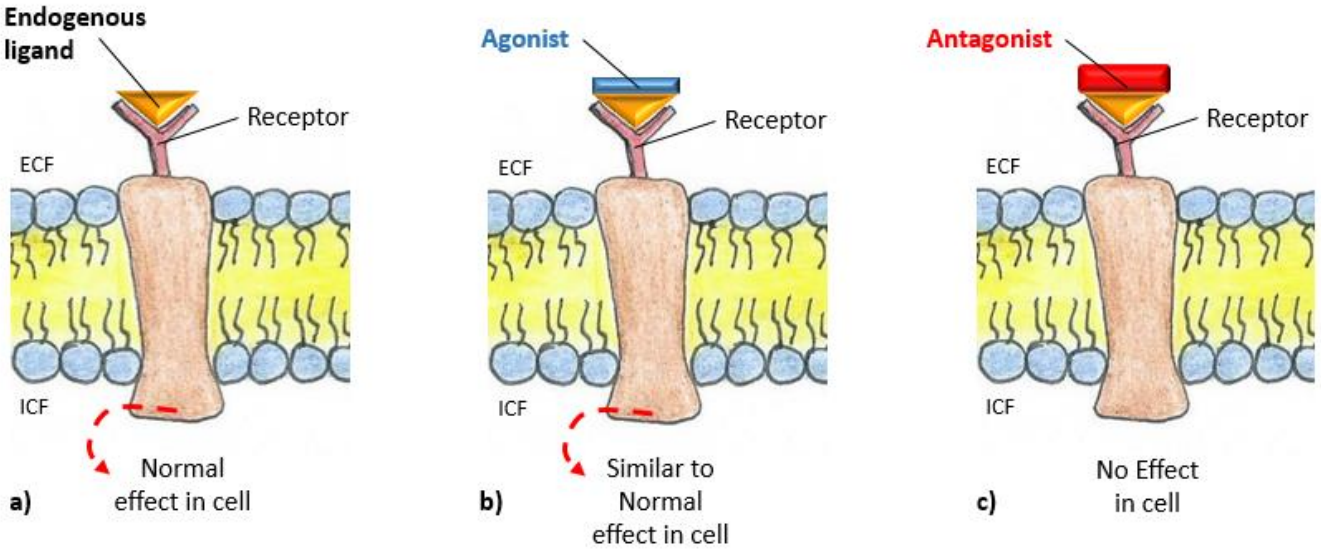


Figure 8.13 Illustrated here is the same receptor being stimulated by three different types of molecules. In **a)** the endogenous or natural ligand binds the receptor, stimulating the normal response, causing an effect in the cell. In **b)** an agonist binds to the receptor, since this molecule is similar enough to the true ligand, it stimulates a similar response caused by the endogenous ligand. In **c)** an antagonist binds the receptor, since this is molecule is close enough to the endogenous ligand it occupies the receptor, but it does not elicit a response from the cell. Because the antagonist occupies the receptors without triggering a response, it blocks the true ligand for binding and stimulating the cell, for this reason antagonists are also referred to a 'blockers'.

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. 8.13**) above.

Agonists

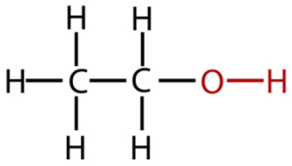
Signal molecules that bind the receptor and induce the post-receptor events that lead to a biological effect are called agonists. They act like the normal or true ligand (signal molecule), though potency may vary.

Antagonists

Signal molecules that bind the receptor and **block** the binding of the true ligand or agonist and fail to trigger the intracellular signaling events are called antagonists, inhibitors or 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 a 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 interacts with other molecules and tissues in the body.



Alcohol binds directly to **GABA, Glutamate, ACh** and **Serotonin** receptors. 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 and hazy.

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. Just from what we have learned in this chapter about neurotransmitters, we can recognize how enhancing or blocking receptors for various neurotransmitters will impact many functions of the body.

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. Often that first buzz fades very quickly and one is then left to be drunk and stuck with only the disabling effects listed above. As we know from the downregulation of overstimulated receptors, what will be needed next time is ***more alcohol*** to feel any 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 **the worst foods, drinks and ingredients** to consume for anxiety:

- Artificial colors, flavors, additives, enhancers, pesticides and preservatives.
- 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 indices.
- 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, or diacetylmorphine, is a semi-synthetic opioid because it is partially derived from the opium poppy, but further altered chemically in a laboratory.

Aspirin, or acetylsalicylic 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, or sucrose, is extracted from sugar cane and beets. It is refined, purified and concentrated (just like heroin and aspirin) into a single, unnatural, isolated component to become sugar, a drug.

Abuse of all of these drugs will harm your health and all of them can ultimately kill a person. Since there was an earlier discussion about 'antidepression' drugs, let's also take a well-known example from the **petrochemical** family and have a close look at what it is and where it comes from.

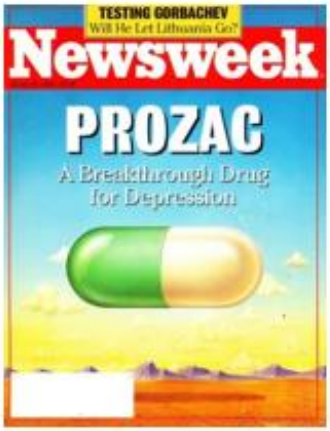
What is **PROZAC**? The active ingredient for **Prozac** is fluoxetine hydrochloride, which is said to be 'derived from' St John's wort but centrally it contains a **fluoride** derivative not found anywhere in nature. It is synthesized by reaction of p-tri-fluoromethylphenol with 3-(chloro)-N-methyl-3-phenylpropylamine in the presence of potassium carbonate to yield Fluoxetine, 3-[p-(trifluoromethyl)-phenoxy]-N-methyl-3-phenylpropylamine (7.3.6). 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, yes, depression.

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 called Prozac in the kitchen at home as a treatment for 'feeling blue'. It's not possible, thank goodness. The only entities who can make something this toxic are the big petrochemical pharmaceutical companies who want you to believe it will benefit you. They are also the ones who 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.

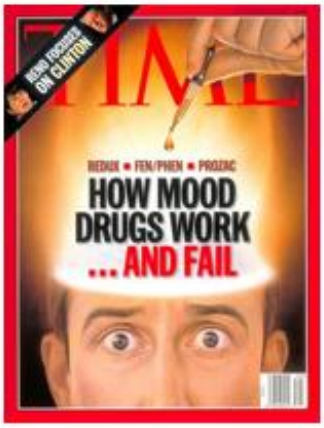
This industry actually gets people to pay them to be poisoned. Furthermore, the entire industry, which includes "healthcare", continues to promote this poison to you and your children as a 'cure' for feelings of despondency. Even though it looks like smoke and mirrors are still very effective in deceiving people, it is ending very soon! Most of us know that 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 <u>trigger suicidal thoughts and thoughts of self-harm</u>. 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 and *comments* 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 by treatment with toxic drugs. The 'drug' approach to mental, or any health, continues to 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 results in is an attempt to eliminate the expression of the symptoms, which are actually very important **stimuli** warning us of problems we need to address and resolve. Even more amazing is that these '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 complex, 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 impacts 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. 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's 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**. One 2012 study found people who consumed more folate had a lower risk of depression than those who ate less.

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, more energetic than normally"

Mushrooms - Are rich in **selenium**, an antioxidant (deficiency linked to anxiety). 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, get it from good food. **Kombucha** is a fermented mushroom tea, no wonder it's so good!

Turmeric – This is a spice composed of 95% **curcumin** (gives it the yellow-orange color), 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 neural mechanisms that releases **brain-derived neurotrophic factor** (BDNF), activating your brain stem cells to convert into new neurons, thereby improving brain health. I knew good coffee was good for you. Interestingly, 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 and produce feelings of relaxation.

Think Positively! Positive Thoughts Reduce Stress and Enhance Your Health

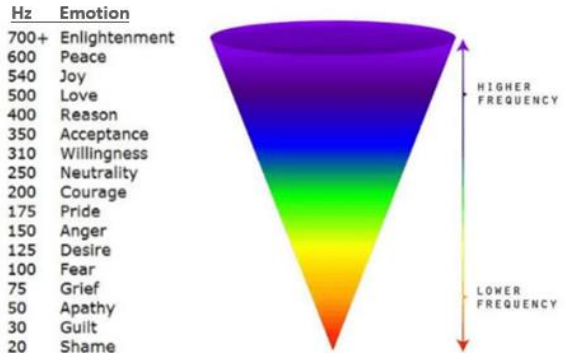
Feeling happy isn't only a matter of emotional health. Positive **thoughts** and **attitudes** are able to prompt changes in your body that strengthen your health, decrease pain and chronic disease, and provide stress relief. One study found that happiness, optimism, life satisfaction, and other positive psychological attributes are associated with a lower risk of heart disease. This should be obvious that the thoughts you think will impact all aspects of you. 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.

Acceptance does not mean just accept things you do not like, not at all. It is about accepting your uniqueness and not comparing yourself to irrelevant standards. Coupled with this is another key factor, being **grateful**. Rather than concentrate on things you lack, focus on all the things you are grateful for. Look up the vibrations of various emotions (shown below), they are measurable and have an impact.

It's been shown scientifically that happiness **alters your genetic expressions**. 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 healing responses.

In a survey of 5,000 people by the charity 'Action for Happiness', people were asked to rate themselves between 1 and 10 on 10 habits that are linked to happiness. While all 10 habits were strongly linked to overall life satisfaction, **acceptance** was the strongest predictor. In all, the survey resulted in the following "10 Keys to Happier Living," which together spell out the acronym **GREAT DREAM**:

- Giving: do things for others.
- Relating: connect with people.
- Exercising: take care of your body.
- Appreciating: notice the world around you.
- Trying out: keep learning new things.
- Direction: have goals to look forward to.
- Resilience: find ways to bounce back.
- Emotion: take a positive and kind approach.
- Acceptance: be comfortable with who you are.
- Meaning: be part of something bigger.



Recall from the first page the 2 basic kinds of happiness: **Hedonic** and **Eudaimonic**. The word origins (etymology for these two words are as follows:

> **Hedonistic** - from Greek hēdonikos "pleasurable," from hēdone "pleasure", meaning "of the nature of pleasure-seeking".
>
> **Eudaimonic/Eudemonic** - From Greek eudaimonikos "conducive to happiness," from eudaimonia "happiness," from eu "good" + daimōn "guardian, genius".

Interestingly, while both of these categories are positive emotional states associated with happiness, studies have shown that the ***physiological expressions*** they produced were not identical. Those subjects whose sense of happiness was rooted in the eudemonic category had favorable gene-expression profiles, meaning their bodies had better responses, while the hedonic well-being group produced expression profiles similar to those seen in people experiencing stress due to adversity.

A theory as to these differences is that when a person is driven by materialistic values, their happiness depends on circumstances that may or may not be within their 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 who are 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 something that can be taken away from them or can disappear at any moment.

Physiologically Relevant Tips to Become Happier

Since in the past there has been such a heavy promotion of taking drugs like the ones 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 discuss effective, proven and safe ways that people can become happier without any drugs and without any significant monetary cost.

Here are 9 Tips to Get a Quick Mood Boost

1. Get Up and Get Moving

Why not be like water? Even in a seemingly still pool it is moving! Excessive sitting and lack of exercise increase depression symptoms, while increased physical activity may alleviate such symptoms and possibly even prevent future symptoms.[2] In great contrast to that **beta endorphins** (a neuropeptide) and **anandamide** (an endogenous **cannabinoid**) known as the "bliss compound," both **increase** during and following exercise and may be partly responsible for why exercise literally makes you happy.

2. Get Outdoors and Get Grounded

Exposure to **bright natural 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 healthy sun exposure outdoors will also help you optimize your **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. In addition, other research has shown that happiness is maximized when it's 57°F outside - so keep an eye on the thermometer Cold is very stimulating! How about a cold shower to start the day? Also, whenever possible walk **barefoot on the ground**, it actually grounds you and gives you energy. 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 a friendly email. This will help you build closer bonds with others in the long run, and 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.[8] Even better, give or get a **hug** from someone. Hugging is known to lower levels of stress hormones like **cortisol** and stimulate **oxytocin**, the bonding hormone. Hugging also activates the orbitofrontal cortex in the brain which is linked to feelings of reward and compassion.

4. Complete a Task You've Been Avoiding

Procrastination and deferring, even of simple tasks, can add a bit of a strain. Often the thought or build-up to doing the aversive task (whatever it may be) is worse than actually doing it. However, completing even a simple task begins to enhance a sense of accomplishment and relief. It really makes us feel better! This usually creates momentum and allows us to move to another item on our list, which often has a very positive effect on our mood.

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 work area, maybe the kitchen counter. Habits can be changed, often very easily and quickly. It just requires you to create and engage in a new set of behaviors, ones that serve you well rather than detract from you. How about deciding to make your bed every morning, right when you get up. Do the dishes right away, don't let them build up. Go on, try one of these, start now.

6. Do a Good Deed

Helping others and doing good deeds provide a natural mood boost. Even a quick kind gesture, like letting someone go ahead of you in line at a store, is beneficial. If you have time, **volunteering** is also great for your mood; it can lower your risk of depression and anxiety and boost your psychological well-being.[11] Not only does it keep you active and on your feet, but there's a definite social aspect as well, both of which contribute to happiness. Volunteering to help others also gives a sense of purpose and can lead to a type of euphoria related to the release of feel-good hormones in your body, again like **oxytocin**, while also lowering levels of stress hormones like **cortisol**. Aside from the possible chemical high, there is also a connection with others which achieves a higher level of satisfaction.

7. Donate Something

Giving things away can help to create a positive mood, as it may help others, but it is also the letting go of things you no longer need that can make you feel lighter and happier. As the saying goes "Less is more". Similar to decluttering, letting go of 'things' can be surprisingly liberating. Giving includes material things, but we can also donate our time or skills where they're needed most.

8. Smile

Putting on a fake smile may be better than a frown, but we all know it's not genuine. However, **thinking positive thoughts** and then **smiling** as a result can make you happier. What? Yes. A genuine smile includes the facial muscles around your eyes and can actually prompt brain changes linked to increased mood. Importantly, when you smile at others, they're also more likely to smile back in return, creating an ongoing **feedback loop** that leads to more positive feeling in all of our lives. This is a great idea.

9. Learn Something New

Is there a topic or a skill you wish you knew more about? Like hot air ballooning? Playing a musical instrument? Taking up a sport? Pick something that intrigues you, something you've always wanted to know more about, or that you're **passionate** about - not something you *have to* learn. You could start by spending just a few minutes every few days reading up on it or testing out a 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 childbirth
- **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 the 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 the 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