There are four hormones which determine a human's happiness. 1. Endorphins 2. Dopamine 3. Serotonin 4. Oxytocin. It is important we understand these hormones, as we need all four of them to stay happy. Let's look at the first hormone the Endorphins. When we exercise, the body releases Endorphins. This hormone helps the body cope with the pain of exercising. We then enjoy exercising because these Endorphins will make us happy. Laughter is another good way of generating Endorphins. We need to spend 30 minutes exercising every day, read or watch funny stuff to get our day's dose of Endorphins. The second hormone is Dopamine. In our journey of life, we accomplish many little and big tasks, it releases various levels of Dopamine. When we get appreciated for our work at the office or at home, we feel accomplished and good, that is because it releases Dopamine. This also explains why most housewives are unhappy since they rarely get acknowledged or appreciated for their work. Once, we join work, we buy a car, a house, the latest gadgets, a new house so forth. In each instance, it releases Dopamine and we become happy. Now, do we realize why we become happy when we shop? The third hormone Serotonin is released when we act in a way that benefits others. When we transcend ourselves and give back to others or to nature or to the society, it releases Serotonin. Even, providing useful information on the internet like writing information blogs, answering people’s questions on Quora or That is because we will use our precious time to help other people via our answers or articles. The final hormone is Oxytocin is released when we become close to other human beings. When we hug our friends or family Oxytocin is released. The "Jadoo Ki Jhappi" from Munnabhai does really work. Similarly, when we shake hands or put our arms around someone's shoulders, various amounts of Oxytocin is released. So, it is simple, we have to exercise every day to get Endorphins, we have to accomplish little goals and get Dopamine, we need to be nice to others to get Serotonin and Finally hug our kids, friends, and families to get Oxytocin and we will be happy. When we are happy, we can deal with our challenges and problems better. Now, we can understand why we need to hug a child who has a bad mood. So in order to feel more and happier day by day: 1. Motivate ourselves to play and have some fun Endorphins. 2. Sharing habit through you to others, Serotonin 3. Hug your family, friends, Oxytocin. Have a Happy Life and a Joyfull.
Dopamine: Known as the “feel-good” hormone, dopamine is a neurotransmitter that’s an important part of your brain’s reward system. It’s associated with pleasurable sensations, along with learning, memory, and more.

Serotonin: This hormone and neurotransmitter helps regulate your mood as well as your sleep, appetite, digestion, learning ability, and memory.

Oxytocin: Often called the “love hormone,” oxytocin is essential for childbirth, breastfeeding, and strong parent-child bonding. It can also help promote trust, empathy, and bonding in relationships. Levels generally increase with physical affection.

Endorphins: These hormones are your body’s natural pain reliever, which your body produces in response to stress or discomfort. Levels may also increase when you engage in reward-producing activities such as eating, working out, or having sex.

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INTRODUCTION:
Overview: Hormones are the internal exudates from endocrine gland which have no duct to secrete the potent chemicals directly to the blood to improve metabolic metastasis in superfast technique. Happiness belongs to the mood and mood is cultivated by brain, so mood swing makes the human happy in feelings.

Dopamine (DA, a contraction of 3,4-dihydroxyphenethylamine) is a neuromodulatory molecule that plays several important roles in cells. It is an organic chemical of the catecholamine and phenethylamine families. Dopamine constitutes about 80% of the catecholamine content in the brain. It is an amine synthesized by removing a carboxyl group from a molecule of its precursor chemical, L-DOPA, which is synthesized in the brain and kidneys. Dopamine is also synthesized in plants and most animals. In the brain, dopamine functions as a neurotransmitter—a chemical released by neurons (nerve cells) to send signals to other nerve cells. Neurotransmitters are synthesized in specific regions of the brain, but affect many regions systemically. The brain includes several distinct dopamine pathways, one of which plays a major role in the motivational component of reward-motivated behavior. The anticipation of most types of rewards increases the level of dopamine in the brain, and many addictive drugs increase dopamine release or block its reuptake into neurons following release. Other brain dopamine pathways are involved in motor control and in controlling the release of various hormones. These pathways and cell groups form a dopamine system which is neuromodulatory. In popular culture and media, dopamine is often portrayed as the main chemical of pleasure, but the current opinion in pharmacology is that dopamine instead confers motivational salience; in other words, dopamine signals the perceived motivational prominence (i.e., the desirability or aversiveness) of an outcome, which in turn propels the organism's behavior toward or away from achieving that outcome.

Outside the central nervous system, dopamine functions primarily as a local paracrine messenger. In blood vessels, it inhibits norepinephrine release and acts as a vasodilator (at normal concentrations); in the kidneys, it increases sodium excretion and urine output; in the pancreas, it reduces insulin production; in the digestive system, it reduces gastrointestinal motility and protects intestinal mucosa; and in the immune system, it reduces the activity of lymphocytes. With the exception of the blood vessels, dopamine in each of these peripheral systems is synthesized locally and exerts its effects near the cells that release it. Several important diseases of the nervous system are associated with dysfunctions of the dopamine system, and some of the key medications used to treat them work by altering the effects of dopamine. Parkinson's disease, a degenerative condition causing tremor and motor impairment, is caused by a loss of dopamine-secreting neurons in an area of the midbrain called the substantia nigra. Its metabolic precursor L-DOPA can be manufactured; Levodopa, a pure form of L-DOPA, is the most widely used treatment for Parkinson's. There is evidence that schizophrenia involves altered levels of dopamine activity, and most antipsychotic drugs used to treat this are dopamine antagonists which reduce dopamine activity. Similar dopamine antagonist drugs are also some of the most effective anti-nausea agents. Restless legs syndrome and attention deficit hyperactivity disorder (ADHD) are associated with decreased dopamine activity. Dopaminergic stimulants can be addictive in high doses, but some are used at lower doses to treat ADHD. Dopamine itself is available as a manufactured medication for intravenous injection: although it cannot reach the brain from the bloodstream, its peripheral effects make it useful in the treatment of heart failure or shock, especially in newborn babies.[1]

Structure: A dopamine molecule consists of a catechol structure (a benzene ring with two hydroxyl side groups) with one amine group attached via an ethyl chain. As such, dopamine is the simplest possible catecholamine, a family that also includes the neurotransmitters norepinephrine and epinephrine. The presence of a benzene ring with this amine attachment makes it a substituted phenethylamine, a family that includes numerous psychoactive drugs.
Like most amines, dopamine is an organic base. As a base, it is generally protonated in acidic environments (in an acid-base reaction). The protonated form is highly water-soluble and relatively stable, but can become oxidized if exposed to oxygen or other oxidants. In basic environments, dopamine is not protonated. In this free base form, it is less water-soluble and also more highly reactive. Because of the increased stability and water-solubility of the protonated form, dopamine is supplied for chemical or pharmaceutical use as dopamine hydrochloride—that is, the hydrochloride salt that is created when dopamine is combined with hydrochloric acid. In dry form, dopamine hydrochloride is a fine powder which is white to yellow in color.

Synthesis: Dopamine is synthesized in a restricted set of cell types, mainly neurons and cells in
the medulla of the adrenal glands. The primary and minor metabolic pathways respectively are:

**Primary:** L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine

**Minor:** L-Phenylalanine → L-Tyrosine → p-Tyramine → Dopamine

The direct precursor of dopamine, L-DOPA, can be synthesized indirectly from the essential amino acid phenylalanine or directly from the non-essential amino acid tyrosine. These amino acids are found in nearly every protein and so are readily available in food, with tyrosine being the most common. Although dopamine is also found in many types of food, it is incapable of crossing the blood–brain barrier that surrounds and protects the brain. It must therefore be synthesized inside the brain to perform its neuronal activity.

L-Phenylalanine is converted into L-tyrosine by the enzyme phenylalanine hydroxylase, with molecular oxygen (O₂) and tetrahydrobiopterin as cofactors. L-Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase, with tetrahydrobiopterin, O₂, and iron (Fe²⁺) as cofactors. L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (also known as DOPA decarboxylase), with pyridoxal phosphate as the cofactor.

Dopamine itself is used as precursor in the synthesis of the neurotransmitters norepinephrine and epinephrine. Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase, with O₂ and L-ascorbic acid as cofactors. Norepinephrine is converted into epinephrine by the enzyme phenylethanolamine N-methyltransferase with S-adenosyl-L-methionine as the cofactor. Some of the cofactors also require their own synthesis. Deficiency in any required amino acid or cofactor can impair the synthesis of dopamine, norepinephrine, and epinephrine.

**Degradation:** Dopamine is broken down into inactive metabolites by a set of enzymes—monoamine oxidase (MAO), catechol-O-methyl transferase (COMT), and aldehyde dehydrogenase (ALDH), acting in sequence. Both isofoms of monoamine oxidase, MAO-A and MAO-B, effectively metabolize dopamine. Different breakdown pathways exist but the main end-product is homovanillic acid (HVA), which has no known biological activity. From the bloodstream, homovanillic acid is filtered out by the kidneys and then excreted in the urine. The two primary metabolic routes that convert dopamine into HVA are:

- Dopamine → L-DOPA → DOPAC → HVA – catalysed by MAO, ALDH, and COMT respectively
- Dopamine → 3-Methoxytyramine → HVA – catalysed by COMT and MAO+ALDH respectively

In clinical research on schizophrenia, measurements of homovanillic acid in plasma have been used to estimate levels of dopamine activity in the brain. A difficulty in this approach however, is separating the high level of plasma homovanillic acid contributed by the metabolism of norepinephrine. Although dopamine is normally broken down by an oxidoreductase enzyme, it is also susceptible to oxidation by direct reaction with oxygen, yielding quinones plus various free radicals as products. The rate of oxidation can be increased by the presence of ferric iron or other factors. Quinones and free radicals produced by autoxidation of dopamine can poison cells, and there is evidence that this mechanism may contribute to the cell loss that occurs in Parkinson’s disease and other conditions.

<table>
<thead>
<tr>
<th>Family</th>
<th>Receptor</th>
<th>Gene</th>
<th>Type</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1-like</td>
<td>D₁</td>
<td>DRD₁</td>
<td>Gₛ-coupled.</td>
<td>Increase intracellular levels of cAMP by activating adenylate cyclase.</td>
</tr>
<tr>
<td></td>
<td>D₅</td>
<td>DRD₅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2-like</td>
<td>D₂</td>
<td>DRD₂</td>
<td>Gₛ-coupled.</td>
<td>Decrease intracellular levels of cAMP by inhibiting adenylate cyclase.</td>
</tr>
<tr>
<td></td>
<td>D₃</td>
<td>DRD₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D₄</td>
<td>DRD₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAAR</td>
<td>TAAR₁</td>
<td>TAAR₁</td>
<td>Gₛ-coupled.</td>
<td>Increase intracellular levels of cAMP and intracellular calcium concentration.</td>
</tr>
</tbody>
</table>

**Table-1: Primary targets of dopamine in the human brain**
Dopamine exerts its effects by binding to and activating cell surface receptors. In humans, dopamine has a high binding affinity at dopamine receptors and human trace amine-associated receptor 1 (hTAAR1). In mammals, five subtypes of dopamine receptors have been identified, labeled from D_1 to D_5. All of them function as metabotropic, G protein-coupled receptors, meaning that they exert their effects via a complex second messenger system. These receptors can be divided into two families, known as D_1-like and D_2-like. For receptors located on neurons in the nervous system, the ultimate effect of D_1-like activation (D_1 and D_5) can be excitation (via opening of sodium channels) or inhibition (via opening of potassium channels); the ultimate effect of D_2-like activation (D_2, D_3, and D_4) is usually inhibition of the target neuron. Consequently, it is incorrect to describe dopamine itself as either excitatory or inhibitory: its effect on a target neuron depends on which types of receptors are present on the membrane of that neuron and on the internal responses of that neuron to the second messenger cAMP. D_1 receptors are the most numerous dopamine receptors in the human nervous system; D_2 receptors are next; D_3, D_4, and D_5 receptors are present at significantly lower levels.

**Storage, release, and reuptake:** Inside the brain, dopamine functions as a neurotransmitter and neuromodulator, and is controlled by a set of mechanisms common to all monoamine neurotransmitters. After synthesis, dopamine is transported from the cytosol into synaptic vesicles by a solute carrier—a vesicular monoamine transporter, VMAT2. Dopamine is stored in these vesicles until it is ejected into the synaptic cleft. In most cases, the release of dopamine occurs through a process called exocytosis which is caused by action potentials, but it can also be caused by the activity of an intracellular trace amine-associated receptor, TAAR1. TAAR1 is a high-affinity receptor for dopamine, trace amines, and certain substituted amphetamines that is located along membranes in the intracellular milieu of the presynaptic cell; activation of the receptor can regulate dopamine signalling by inducing dopamine reuptake inhibition and efflux as well as by inhibiting neuronal firing through a diverse set of mechanisms.

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**Figure-4:** Dopamine processing in a synapse. After release dopamine can either be taken up again by the presynaptic terminal, or broken down by enzymes.

- **TH:** tyrosine hydroxylase
- **DOPA:** L-DOPA
- **DAT:** dopamine transporter
- **DDC:** DOPA decarboxylase
- **VMAT:** vesicular monoamine transporter 2
- **MAO:** Monoamine oxidase
- **COMT:** Catechol-O-methyl transferase
- **HVA:** Homovanillic acid

Once in the synapse, dopamine binds to and activates dopamine receptors. These can...
be postsynaptic dopamine receptors, which are located on dendrites (the postsynaptic neuron), or presynaptic autoreceptors (e.g., the D_2sh and presynaptic D_3 receptors), which are located on the membrane of an axon terminal (the presynaptic neuron). After the postsynaptic neuron elicits an action potential, dopamine molecules quickly become unbound from their receptors. They are then absorbed back into the presynaptic cell, via reuptake mediated by the dopamine transporter or by the plasma membrane monoamine transporter. Once back in the cytosol, dopamine can either be broken down by a monoamine oxidase or repackaged into vesicles by VMAT2, making it available for future release.

In the brain the level of extracellular dopamine is modulated by two mechanisms: phasic and tonic transmission. Phasic dopamine release, like most neurotransmitter release in the nervous system, is driven directly by action potentials in the dopamine-containing cells. Tonic dopamine transmission occurs when small amounts of dopamine are released without being preceded by presynaptic action potentials. Tonic transmission is regulated by a variety of factors, including the activity of other neurons and neurotransmitter reuptake.

**Nervous system:** Inside the brain, dopamine plays important roles in executive functions, motor control, motivation, arousal, reinforcement, and reward, as well as lower-level functions including lactation, sexual gratification, and nausea. The dopaminergic cell groups and pathways make up the dopamine system which are neuromodulators.

Dopaminergic neurons (dopamine-producing nerve cells) are comparatively few in number—a total of around 400,000 in the human brain—and their cell bodies are confined in groups to a few relatively small brain areas. However their axons project to too many other brain areas, and they exert powerful effects on their targets. These dopaminergic cell groups were first mapped in 1964 by Annica Dahlström and Kjell Fuxe, who assigned them labels starting with the letter "A" (for "aminergic"). In their scheme, areas A1 through A7 contain the neurotransmitter norepinephrine, whereas A8 through A14 contain dopamine. The dopaminergic areas they identified are the substantia nigra (groups 8 and 9); the ventral tegmental area (group 10); the posterior hypothalamus (group 11); the arcuate nucleus (group 12); the zona incerta (group 13) and the periventricular nucleus (group 14).

The substantia nigra is a small midbrain area that forms a component of the basal ganglia. This has two parts—an input area called the pars compacta and an output area the pars reticulata. The dopaminergic neurons are found mainly in the pars compacta (cell group A8) and nearby (group A9). In humans, the projection of dopaminergic neurons from the substantia nigra pars compacta to the dorsal striatum, termed the nigrostriatal pathway, plays a significant role in the control of motor function and in learning.
new motor skills. These neurons are especially vulnerable to damage, and when a large number of them die, the result is a parkinsonian syndrome. The ventral tegmental area (VTA) is another midbrain area. The most prominent group of VTA dopaminergic neurons projects to the prefrontal cortex via the mesocortical pathway and another smaller group projects to the nucleus accumbens via the mesolimbic pathway. Together, these two pathways are collectively termed the mesocorticolimbic projection. The VTA also sends dopaminergic projections to the amygdala, cingulate gyrus, hippocampus, and olfactory bulb. Mesocorticolimbic neurons play a central role in reward and other aspects of motivation. Accumulating literature shows that dopamine also plays a crucial role in aversive learning through its effects on a number of brain regions.

The posterior hypothalamus has dopamine neurons that project to the spinal cord, but their function is not well established. There is some evidence that pathology in this area plays a role in restless legs syndrome, a condition in which people have difficulty sleeping due to an overwhelming compulsion to constantly move parts of the body, especially the legs. The arcuate nucleus and the periventricular nucleus of the hypothalamus have dopamine neurons that form an important projection—the tuberoinfundibular pathway which goes to the pituitary gland, where it influences the secretion of the hormone prolactin. Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus is secreted into the hypophyseal portal system of the median eminence, which supplies the pituitary gland. The prolactin cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. In the context of regulating prolactin secretion, dopamine is occasionally called prolactin-inhibiting factor, prolactin-inhibiting hormone, or prolactostatin. The zona incerta, grouped between the arcuate and periventricular nuclei, projects to several areas of the hypothalamus, and participates in the control of gonadotropin-releasing hormone, which is necessary to activate the development of the male and female reproductive systems, following puberty. An additional group of dopamine-secreting neurons is found in the retina of the eye. These neurons are amacrine cells, meaning that they have no axons. They release dopamine into the extracellular medium, and are specifically active during daylight hours, becoming silent at night. This retinal dopamine acts to enhance the activity of cone cells in the retina while suppressing rod cells—the result is to increase sensitivity to color and contrast during bright light conditions, at the cost of reduced sensitivity when the light is dim.[2]

**Basal ganglia:** The largest and most important sources of dopamine in the vertebrate brain are the substantia nigra and ventral tegmental area. These structures are closely related to each other and functionally similar in many respects. Both are components of the mid brain. The largest component of the basal ganglia is the striatum. The substantia nigra sends a dopaminergic projection to the dorsal striatum, while the ventral tegmental area sends a similar type of dopaminergic projection to the ventral striatum.
Progress in understanding the functions of the basal ganglia has been slow. The most popular hypotheses, broadly stated, propose that the basal ganglia play a central role in action selection. The action selection theory in its simplest form proposes that when a person or animal is in a situation where several behaviors are possible, activity in the basal ganglia determines which of them is executed, by releasing that response from inhibition while continuing to inhibit other motor systems that if activated would generate competing behaviors. Thus the basal ganglia, in this concept, are responsible for initiating behaviors, but not for determining the details of how they are carried out. In other words, they essentially form a decision-making system. The basal ganglia can be divided into several sectors, and each is involved in controlling particular types of actions. The ventral sector of the basal ganglia (containing the ventral striatum and ventral tegmental area) operates at the highest level of the hierarchy, selecting actions at the whole-organism level. The dorsal sectors (containing the dorsal striatum and substantia nigra) operate at lower levels, selecting the specific muscles and movements that are used to implement a given behavior pattern.

Dopamine contributes to the action selection process in at least two important ways. First, it sets the "threshold" for initiating actions. The higher the level of dopamine activity, the lower the impetus required to evoke a given behavior. As a consequence, high levels of dopamine lead to high levels of motor activity and impulsive behavior; low levels of dopamine lead to torpor and slowed reactions. Parkinson's disease, in which dopamine levels in the substantia nigra circuit are greatly reduced, is characterized by stiffness and difficulty initiating movement—however, when people with the disease are confronted with strong stimuli such as a serious threat, their reactions can be as vigorous as those of a healthy person. In the opposite direction, drugs that increase dopamine release, such as cocaine or amphetamine, can produce heightened levels of activity, including, at the extreme, psychomotor agitation and stereotyped movements.

The second important effect of dopamine is as a "teaching" signal. When an action is followed by an increase in dopamine activity, the basal ganglia circuit is altered in a way that makes the same response easier to evoke when similar situations arise in the future. This is a form of operant conditioning, in which dopamine plays the role of a reward signal. **Dopamine Reward:** In the language used to discuss the reward system, reward is the attractive and motivational property of a stimulus that induces appetitive behavior (also known as approach behavior) and consummatory behavior. A rewarding stimulus is one that can induce the organism to approach it and choose to consume it. Pleasure,
learning (e.g., classical and operant conditioning), and approach behavior are the three main functions of reward. As an aspect of reward, pleasure provides a definition of reward; however, while all pleasurable stimuli are rewarding, not all rewarding stimuli are pleasurable (e.g., extrinsic rewards like money). The motivational or desirable aspect of rewarding stimuli is reflected by the approach behavior that they induce, whereas the pleasure from intrinsic rewards results from consuming them after acquiring them.

![Dopaminergic reward structures](image)

**Figure-7: Illustration of dopaminergic reward structures**

A neuropsychological model which distinguishes these two components of an intrinsically rewarding stimulus is the incentive salience model, where "wanting" or desire (less commonly, "seeking") corresponds to appetitive or approach behavior while "liking" or pleasure corresponds to consummatory behavior. In human drug addicts, "wanting" becomes dissociated with "liking" as the desire to use an addictive drug increase, while the pleasure obtained from consuming it decreases due to drug tolerance.

Within the brain, dopamine functions partly as a global reward signal. An initial dopamine response to a rewarding stimulus encodes information about the salience, value, and context of a reward. In the context of reward-related learning, dopamine also functions as a reward prediction error signal, that is, the degree to which the value of a reward is unexpected. According to this hypothesis proposed by Montague, Dayan, and Sejnowski, rewards that are expected do not produce a second phasic dopamine
response in certain dopaminergic cells, but rewards that are unexpected, or greater than expected, produce a short-lasting increase in synaptic dopamine, whereas the omission of an expected reward actually causes dopamine release to drop below its background level. The "prediction error" hypothesis has drawn particular interest from computational neuroscientists, because an influential computational-learning method known as temporal difference learning makes heavy use of a signal that encodes prediction error. This confluence of theory and data has led to a fertile interaction between neuroscientists and computer scientists interested in machine learning. Evidence from microelectrode recordings from the brains of animals shows that dopamine neurons in the ventral tegmental area (VTA) and substantia nigra are strongly activated by a wide variety of rewarding events. These reward–responsive dopamine neurons in the VTA and substantia nigra are crucial for reward-related cognition and serve as the central component of the reward system. The function of dopamine varies in each axonal projection from the VTA and substantia nigra; for example, the VTA–nucleus accumbens shell projection assigns incentive salience ("want") to rewarding stimuli and its associated cues, the VTA–prefrontal cortex projection updates the value of different goals in accordance with their incentive salience, the VTA–amygdala and VTA–hippocampus projections mediate the consolidation of reward-related memories, and both the VTA–nucleus accumbens core and substantia nigra–dorsal striatum pathways are involved in learning motor responses that facilitate the acquisition of rewarding stimuli. Some activity within the VTA dopaminergic projections appears to be associated with reward prediction as well.

Pleasure: While dopamine has a central role in causing "wanting," associated with the appetitive or approach behavioral responses to rewarding stimuli, detailed studies have shown that dopamine cannot simply be equated with hedonic "liking" or pleasure, as reflected in the consummatory behavioral response. Dopamine neurotransmission is involved in some but not all aspects of pleasure-related cognition, since pleasure centers have been identified both within the dopamine system (i.e., nucleus accumbens shell) and outside the dopamine system (i.e., ventral pallidum and parabrachial nucleus). For example, direct electrical stimulation of dopamine pathways, using electrodes implanted in the brain, is experienced as pleasurable, and many types of animals are willing to work to obtain it. Antipsychotic drugs reduce dopamine levels and tend to cause anhedonia, a diminished ability to experience pleasure. Many types of pleasurable experiences—such as sex, eating, and playing video games— increase dopamine release. All addictive drugs directly or indirectly affect dopamine neurotransmission in the nucleus accumbens; these drugs increase drug "wanting," leading to compulsive drug use, when repeatedly taken in high doses, presumably through the sensitization of incentive-salience. Drugs that increase synaptic dopamine concentrations include psychostimulants such as methamphetamine and cocaine. These produce increases in "wanting" behaviors, but do not greatly alter expressions of pleasure or change levels of satiation. However, opiate drugs such as heroin and morphine produce increases in expressions of "liking" and "wanting" behaviors. Moreover, animals in which the ventral tegmental dopamine system has been rendered inactive do not seek food, and will starve to death if left to themselves, but if food is placed in their mouths they will consume it and show expressions indicative of pleasure.

A clinical study from January 2019 that assessed the effect of a dopamine precursor (levodopa), dopamine antagonist (risperidone), and a placebo on reward responses to music – including the degree of pleasure experienced during musical chills, as measured by changes in electrodermal activity as well as subjective ratings – found that the manipulation of dopamine neurotransmission bidirectionally regulates pleasure cognition (specifically, the hedonic impact of music) in human subjects. This research demonstrated that increased dopamine neurotransmission acts as a sinea qua non condition for pleasurable hedonic reactions to music in humans.

Outside the nervous system: Dopamine does not cross the blood–brain barrier, so its synthesis and functions in peripheral areas are to a large degree independent of its synthesis and functions in the brain. A substantial amount of dopamine circulates in the bloodstream, but its functions there are not entirely clear. Dopamine is found in blood plasma at levels comparable to those of epinephrine, but in humans, over 95% of the dopamine in the plasma is in the form of dopamine sulfate, a conjugate produced by the
enzyme sulfotransferase 1A3/1A4 acting on free dopamine. The bulk of this dopamine sulfate is produced in the mesentery that surrounds parts of the digestive system. The production of dopamine sulfate is thought to be a mechanism for detoxifying dopamine that is ingested as food or produced by the digestive process—levels in the plasma typically rise more than fifty-fold after a meal. Dopamine sulfate has no known biological functions and is excreted in urine. The relatively small quantity of unconjugated dopamine in the bloodstream may be produced by the sympathetic nervous system, the digestive system, or possibly other organs. It may act on dopamine receptors in peripheral tissues, or be metabolized, or be converted to norepinephrine by the enzyme dopamine beta hydroxylase, which is released into the bloodstream by the adrenal medulla. Some dopamine receptors are located in the walls of arteries, where they act as a vasodilator and an inhibitor of norepinephrine release. These responses might be activated by dopamine released from the carotid body under conditions of low oxygen, but whether arterial dopamine receptors perform other biologically useful functions is not known.

Beyond its role in modulating blood flow, there are several peripheral systems in which dopamine circulates within a limited area and performs an exocrine or paracrine function. The peripheral systems in which dopamine plays an important role include the immune system, the kidneys and the pancreas.

**Immune system:** In the immune system dopamine acts upon receptors present on immune cells, especially lymphocytes. Dopamine can also affect immune cells in the spleen, bone marrow, and circulatory system. In addition, dopamine can be synthesized and released by immune cells themselves. The main effect of dopamine on lymphocytes is to reduce their activation level. The functional significance of this system is unclear, but it affords a possible route for interactions between the nervous system and immune system, and may be relevant to some autoimmune disorders. Here’s a look at what you can do to help produce more of these natural mood boosters.\[^3\]

**Oxytocin:** Oxytocin (Oxt or OT) is a peptide hormone and neuropeptide normally produced in the hypothalamus and released by the posterior pituitary. It plays a role in social bonding, reproduction, childbirth, and the period after childbirth. Oxytocin is released into the bloodstream as a hormone in response to sexual activity and during labour. It is also available in pharmaceutical form. In either form, Oxytocin stimulates uterine contractions to speed up the process of childbirth. In its natural form, it also plays a role in bonding with the baby and milk production. Production and secretion of Oxytocin is controlled by a positive feedback mechanism, where its initial release stimulates production and release of further Oxytocin. For example, when Oxytocin is released during a contraction of the uterus at the start of childbirth, this stimulates production and release of more Oxytocin and an increase in the intensity and frequency of contractions. This process compounds in intensity and frequency and continues until the triggering activity ceases. A similar process takes place during lactation and during sexual activity. Oxytocin is derived by enzymatic splitting from the peptide precursor encoded by the human OXT gene. The deduced structure of the active nonapeptide is: Cys – Tyr – Ile – Gln – Asn – Cys – Pro – Leu – Gly – NH₂, or CYIQNCPLG-NH₂

**Figure-8: Oxytocin Structure**

**Biochemistry:** Oestrogen has been found to increase the secretion of Oxytocin and to increase the expression of its receptor, the Oxytocin receptor, in the brain. In women, a single dose of estradiol has
been found to be sufficient to increase circulating Oxytocin concentrations.

**Biosynthesis:** The oxytocin peptide is synthesized as an inactive precursor protein from the OXT gene. This precursor protein also includes the oxytocin carrier protein neurophysin I. The inactive precursor protein is progressively hydrolysed into smaller fragments (one of which is neurophysin I) via a series of enzymes. The last hydrolysis that releases the active oxytocin nonapeptide is catalyzed by peptidylglycine alpha-amidating monooxygenase (PAM).

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The activity of the PAM enzyme system is dependent upon vitamin C (ascorbate), which is a necessary vitamin cofactor. By chance, sodium ascorbate by itself was found to stimulate the production of Oxytocin from ovarian tissue over a range of concentrations in a dose-dependent manner. Many of the same tissues (e.g. ovaries, testes, eyes, adrenals, placenta, thymus, and pancreas) where PAM (and oxytocin by default) is found are also known to store higher concentrations of vitamin C. Oxytocin is known to be metabolized by the oxytocinase, leucyl/cystinyl aminopeptidase. Other oxytocinases are also known to exist. Amastatin, bestatin (ubenimex), leupeptin, and puromycin have been found to inhibit the enzymatic degradation of oxytocin, though they also inhibit the degradation of
various other peptides, such as vasopressin, met-enkephalin, and dynorphin A.

**Neural sources:** In the hypothalamus, Oxytocin is made in magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei, and is stored in Herring bodies at the axon terminals in the posterior pituitary. It is then released into the blood from the posterior lobe (neurohypophysis) of the pituitary gland. These axons (likely, but dendrites have not been ruled out) have collaterals that innervate neurons in the nucleus accumbens, a brain structure where oxytocin receptors are expressed. The endocrine effects of hormonal oxytocin and the cognitive or behavioral effects of oxytocin neuropeptides are thought to be coordinated through its common release through these collaterals. Oxytocin is also produced by some neurons in the paraventricular nucleus that project to other parts of the brain and to the spinal cord. Depending on the species, oxytocin receptor-expressing cells are located in other areas, including the amygdala and bed nucleus of the stria terminalis. In the pituitary gland, oxytocin is packaged in large, dense-core vesicles, where it is bound to neurophysin I as shown in the inset of the figure; neurophysin is a large peptide fragment of the larger precursor protein molecule from which oxytocin is derived by enzymatic cleavage. Secretion of oxytocin from the neurosecretory nerve endings is regulated by the electrical activity of the oxytocin cells in the hypothalamus. These cells generate action potentials that propagate down axons to the nerve endings in the pituitary; the endings contain large numbers of oxytocin-containing vesicles, which are released by exocytosis when the nerve terminals are depolarized.

**Non-neural sources:** Endogenous oxytocin concentrations in the brain have been found to be as much as 1000-fold higher than peripheral levels. Outside the brain, Oxytocin-containing cells have been identified in several diverse tissues, including in females in the corpus luteum and the placenta; in males in the testicles' interstitial cells of Leydig; and in both sexes in the retina, the adrenal medulla, the thymus and the pancreas. The finding of significant amounts of this classically "neurohypophysial" hormone outside the central nervous system raises many questions regarding its possible importance in these diverse tissues.

**Male:** The Leydig cells in some species have been shown to possess the biosynthetic machinery to manufacture testicular Oxytocin de novo, to be specific, in rats (which can synthesize vitamin C endogenously), and in guinea pigs, which, like humans, require an exogenous source of vitamin C (ascorbate) in their diets.

**Female:** Oxytocin is synthesized by corpora lutea of several species, including ruminants and primates. Along with estrogen, it is involved in inducing the endometrial synthesis of prostaglandin F2α to cause regression of the corpus luteum.

**Evolution:** Virtually all vertebrates have an Oxytocin-like nonapeptide hormone that supports reproductive functions and a vasopressin-like nonapeptide hormone involved in water regulation. The two genes are usually located close to each other (less than 15,000 bases apart) on the same chromosome, and are transcribed in opposite directions (however, in fugu, the homologs are further apart and transcribed in the same direction). The two genes are believed to result from a gene duplication event; the ancestral gene is estimated to be about 500 million years old and is found in cyclostomata (modern members of the Agnatha).

**Biological function:** Oxytocin has peripheral (hormonal) actions, and also has actions in the brain. Its actions are mediated by specific Oxytocin receptors. The Oxytocin receptor is a G-protein-coupled receptor, OT-R, which requires magnesium and cholesterol and is expressed in myometrial cells. It belongs to the rhodopsin-type (class I) group of G-protein-coupled receptors. Studies have looked at oxytocin's role in various behaviors, including orgasm, social recognition, pair bonding, anxiety, in-group bias, situational lack of honesty, autism, and maternal behaviors. Oxytocin is believed to have a significant role in social learning. There are indicators that Oxytocin may help to decrease noise in the brain's
auditory system, increase perception of social cues and support more targeted social behavior. It may also enhance reward responses. However, its effects may be influenced by context, such as the presence of familiar or unfamiliar individuals.

Physiological: The peripheral actions of Oxytocin mainly reflect secretion from the pituitary gland. The behavioral effects of Oxytocin are thought to reflect release from centrally projecting Oxytocin neurons, different from those that project to the pituitary gland, or that are collaterals from them. Oxytocin receptors are expressed by neurons in many parts of the brain and spinal cord, including the amygdala, ventromedial hypothalamus, septum, nucleus accumbens, and brainstem, although the distribution differs markedly between species. Furthermore, the distribution of these receptors changes during development and has been observed to change after parturition in the montane vole.

Milk ejection reflex/Letdown reflex: It is found in lactating (breastfeeding) mothers, Oxytocin acts at the mammary glands, causing milk to be 'let down' into lactiferous ducts, from where it can be excreted via the nipple. Suckling by the infant at the nipple is relayed by spinal nerves to the hypothalamus. The stimulation causes neurons that make Oxytocin to fire action potentials in intermittent bursts; these bursts result in the secretion of pulses of Oxytocin from the neurosecretory nerve terminals of the pituitary gland.

Uterine contraction: important for cervical dilation before birth, Oxytocin causes contractions during the second and third stages of labor. Oxytocin release during breastfeeding causes mild but often painful contractions during the first few weeks of lactation. This also serves to assist the uterus in clotting the placental attachment point postpartum. However, in knockout mice lacking the Oxytocin receptor, reproductive behavior and parturition are normal.

In male rats, Oxytocin may induce erections. A burst of Oxytocin is released during ejaculation in several species, including human males; its suggested function is to stimulate contractions of the reproductive tract, aiding sperm release. Human sexual response: Oxytocin levels in plasma rise during sexual stimulation and orgasm. At least two uncontrolled studies have found increases in plasma Oxytocin at orgasm – in both men and women. Plasma Oxytocin levels are increased around the time of self-stimulated orgasm and are still higher than baseline when measured five minutes after self-arousal. The authors of one of these studies speculated that oxytocin's effects on muscle contractibility may facilitate sperm and egg transport. In a study measuring Oxytocin serum levels in women before and after sexual stimulation, the author suggests it serves an important role in sexual arousal. This study found genital tract stimulation resulted in increased Oxytocin immediately after orgasm. Another study reported increases of Oxytocin during sexual arousal could be in response to nipple/areola, genital, and/or genital tract stimulation as confirmed in other mammals. Murphy et al. (1987), studying men, found that plasma Oxytocin levels remain unchanged during sexual arousal, but that levels increase sharply after ejaculation, returning to baseline levels within 30 minutes. In contrast, vasopressin was increased during arousal but returned to baseline at the time of ejaculation. The study concludes that (in males) vasopressin is secreted during arousal, while Oxytocin is only secreted after ejaculation. A more recent study of men found an increase in plasma Oxytocin immediately after orgasm, but only in a portion of their sample that did not reach statistical significance. The authors noted these changes "may simply reflect contractile properties on reproductive tissue". Due to its similarity to vasopressin, it can reduce the excretion of urine slightly, and so it can be classified as an antidiuretic. In several species, Oxytocin can stimulate sodium excretion from the kidneys (natriuresis), and, in humans, high doses can result in low sodium levels (hyponatremia).

Cardiac effects: Oxytocin and Oxytocin receptors are also found in the heart in some rodents, and the hormone may play a role in the embryonal development of the heart by promoting cardiomyocyte differentiation. However, the absence of either Oxytocin or its receptor in knockout mice has not been
reported to produce cardiac insufficiencies. Modulation of hypothalamic-pituitary-adrenal axis activity: Oxytocin, under certain circumstances, indirectly inhibits release of adrenocorticotropic hormone and cortisol and, in those situations, may be considered an antagonist of vasopressin. Preparing fetal neurons for delivery (in rats): crossing the placenta, maternal Oxytocin reaches the fetal brain and induces a switch in the action of neurotransmitter GABA from excitatory to inhibitory on fetal cortical neurons. This silences the fetal brain for the period of delivery and reduces its vulnerability to hypoxic damage.

Feeding: A 2012 paper suggested that oxytocin neurons in the para-ventricular hypothalamus in the brain may play a key role in suppressing appetite under normal conditions and that other hypothalamic neurons may trigger eating via inhibition of these oxytocin neurons. This population of oxytocin neurons is absent in Prader-Willi syndrome, a genetic disorder that leads to uncontrollable feeding and obesity, and may play a key role in its Pathophysiology. Research on the oxytocin-related neuropeptide asterotocin in starfish also showed that in echinoderms, the chemical induces muscle relaxation, and in starfish specifically caused the organisms to evert their stomach and react as though feeding on prey, even when none were present.

Autism: Oxytocin has been implicated in the etiology of autism, with one report suggesting autism is correlated to a mutation on the oxytocin receptor gene (OXTR). Studies involving Caucasian, Finnish and Chinese Han families provide support for the relationship of OXTR with autism. Autism may also be associated with an aberrant methylation of OXTR.

Bonding: In the prairie vole, oxytocin released into the brain of the female during sexual activity is important for forming a pair bond with her sexual partner. Vasopressin appears to have a similar effect in males. Oxytocin has a role in social behaviors in many species, so it likely also does in humans. In a 2003 study, both humans and dog oxytocin levels in the blood rose after a five to 24 minute petting session. This possibly plays a role in the emotional bonding between humans and dogs.

Maternal behaviour: Female rats given oxytocin antagonists after giving birth do not exhibit typical maternal behavior. By contrast, virgin female sheep show maternal behavior toward foreign lambs upon cerebrospinal fluid infusion of oxytocin, which they would not do otherwise. Oxytocin is involved in the initiation of human maternal behavior, not its maintenance; for example, it is higher in mothers after they interact with unfamiliar children rather than their own.

Human in-group bonding: Oxytocin can increase positive attitudes, such as bonding, toward individuals with similar characteristics, who then become classified as “in-group” members, whereas individuals who are dissimilar become classified as "out-group" members. Race can be used as an example of in-group and out-group tendencies because society often categorizes individuals into groups based on race (Caucasian, African American, Latino, etc.). One study that examined race and empathy found that participants receiving nasally administered Oxytocin had stronger reactions to pictures of in-group members making pained faces than to pictures of out-group members with the same expression. Moreover, individuals of one race may be more inclined to help individuals of the same race than individuals of another race when they are experiencing pain. Oxytocin has also been implicated in lying when lying would prove beneficial to other in-group members. In a study where such a relationship was examined, it was found that when individuals were administered oxytocin, rates of dishonesty in the participants' responses increased for their in-group members when a beneficial outcome for their group was expected. Both of these examples show the tendency of individuals to act in ways that benefit those considered to be members of their social group, or in-group. Further, oxytocin influences the responses of individuals in a particular group to those of another group. The in-group bias is evident in smaller groups; however, it can also be extended to groups as large as one's entire country leading toward a tendency of strong national zeal. A study done in the Netherlands
showed that Oxytocin increased the in-group favouritism of their nation while decreasing acceptance of members of other ethnicities and foreigners. People also show more affection for their country's flag while remaining indifferent to other cultural objects when exposed to oxytocin. It has thus been hypothesized that this hormone may be a factor in xenophobic tendencies secondary to this effect. Thus, oxytocin appears to affect individuals at an international level where the in-group becomes a specific "home" country and the out-group grows to include all other countries.\cite{4}

**Drug interaction:** According to several studies in animals, oxytocin inhibits the development of tolerance to various addictive drugs (opiates, cocaine, alcohol), and reduces withdrawal symptoms. MDMA (ecstasy) may increase feelings of love, empathy, and connection to others by stimulating oxytocin activity primarily via activation of serotonin 5-HT1A receptors, if initial studies in animals apply to humans. The anxiolytic drug buspirone may produce some of its effects via 5-HT1A receptor-induced oxytocin stimulation as well.

**Addiction vulnerability:** Concentrations of endogenous oxytocin can impact the effects of various drugs and one's susceptibility to substance use disorders, with higher concentrations associated with lower susceptibility. The status of the endogenous oxytocin system can enhance or reduce susceptibility to addiction through its bidirectional interaction with numerous systems, including the dopamine system, the hypothalamic–pituitary–adrenal axis and the immune system. Individual differences in the endogenous oxytocin system based on genetic predisposition, gender and environmental influences, may therefore affect addiction vulnerability. Oxytocin may be related to the place conditioning behaviors observed in habitual drug abusers.

**Fear and anxiety:** Oxytocin is typically remembered for the effect it has on prosocial behaviors, such as its role in facilitating trust and attachment between individuals. However, oxytocin has a more complex role than solely enhancing prosocial behaviors. There is consensus that oxytocin modulates fear and anxiety; that is, it does not directly elicit fear or anxiety. Two dominant theories explain the role of oxytocin in fear and anxiety. One theory states that oxytocin increases approach/avoidance to certain social stimuli and the second theory states that oxytocin increases the salience of certain social stimuli, causing the animal or human to pay closer attention to socially relevant stimuli.
Nasally administered oxytocin has been reported to reduce fear, possibly by inhibiting the amygdala (which is thought to be responsible for fear responses). Indeed, studies in rodents have shown oxytocin can efficiently inhibit fear responses by activating an inhibitory circuit within the amygdala. Some researchers have argued oxytocin has a general enhancing effect on all social emotions, since intranasal administration of oxytocin also increases envy and Schadenfreude. Individuals who receive an intranasal dose of oxytocin identify facial expressions of disgust more quickly than individuals who do not receive oxytocin. Facial expressions of disgust are evolutionarily linked to the idea of contagion. Thus, oxytocin increases the salience of cues that imply contamination, which leads to a faster response because these cues are especially relevant for survival. In another study, after administration of oxytocin, individuals displayed an enhanced ability to recognize expressions of fear compared to the individuals who received the placebo. Oxytocin modulates fear responses by enhancing the maintenance of social memories. Rats that are genetically modified to have a surplus of oxytocin receptors display a greater fear response to a previously conditioned stressor. Oxytocin enhances the aversive social memory, leading the rat to display a greater fear response when the aversive stimulus is encountered again.

**Mood and depression:** Oxytocin produces antidepressant-like effects in animal models of depression, and a deficit of it may be involved in the pathophysiology of depression in humans. The antidepressant-like effects of oxytocin are not blocked by a selective antagonist of the oxytocin receptor, suggesting that these effects are not mediated by the oxytocin receptor. In accordance, unlike oxytocin, the selective non-peptide oxytocin receptor agonist WAY-267,464 does not produce antidepressant-like effects, at least in the tail suspension test. In contrast to WAY-267,464, carbetocin, a close analogue of oxytocin and peptide oxytocin receptor agonist, notably does produce antidepressant-like effects in animals. As such, the antidepressant-like effects of oxytocin may be mediated by modulation of a different target, perhaps the vasopressin V1A receptor where oxytocin is known to weakly bind as an agonist. Oxytocin mediates the antidepressant-like effects of sexual activity. A drug for sexual dysfunction, sildenafil enhances electrically evoked oxytocin release from the pituitary gland. In accordance, it may have promise as an antidepressant.

**Sex differences:** It has been shown that oxytocin differentially affects males and females. Females who are administered oxytocin are overall faster in responding to socially relevant stimuli than males who received oxytocin. Additionally, after the administration of oxytocin, females show increased amygdala activity in response to threatening scenes; however, males do not show increased amygdala activation. This phenomenon can be explained by looking at the role of gonadal hormones, specifically estrogen, which modulate the enhanced threat processing seen in females. Estrogen has been shown...
to stimulate the release of oxytocin from the hypothalamus and promote receptor binding in the amygdala. It has also been shown that testosterone directly suppresses oxytocin in mice. This has been hypothesized to have evolutionary significance. With oxytocin suppressed, activities such as hunting and attacking invaders would be less mentally difficult as oxytocin is strongly associated with empathy.

Social: Affecting generosity by increasing empathy during perspective taking: In a neuroeconomics experiment, intranasal oxytocin increased generosity in the Ultimatum Game by 80%, but had no effect in the Dictator Game that measures altruism. Perspective-taking is not required in the Dictator Game, but the researchers in this experiment explicitly induced perspective-taking in the Ultimatum Game by not identifying to participants into which role they would be placed. Serious methodological questions have arisen, however, with regard to the role of oxytocin in trust and generosity. Empathy in healthy males has been shown to be increased after intranasal oxytocin This is most likely due to the effect of oxytocin in enhancing eye gaze. There is some discussion about which aspect of empathy oxytocin might alter – for example, cognitive vs. emotional empathy. While studying wild chimpanzees, it was noted that after a chimpanzee shared food with a non-kin related chimpanzee, the subjects' levels of oxytocin increased, as measured through their urine. In comparison to other cooperative activities between chimpanzees that were monitored including grooming, food sharing generated higher levels of oxytocin. This comparatively higher level of oxytocin after food sharing parallels the increased level of oxytocin in nursing mothers, sharing nutrients with their kin.

Trust is increased by oxytocin. Disclosure of emotional events is a sign of trust in humans. When recounting a negative event, humans who receive intranasal oxytocin share more emotional details and stories with more emotional significance. Humans also find faces more trustworthy after receiving intranasal oxytocin. In a study, participants who received intranasal oxytocin viewed photographs of human faces with neutral expressions and found them to be more trustworthy than those who did not receive oxytocin. This may be because oxytocin reduces the fear of social betrayal in humans. Even after experiencing social alienation by being excluded from a conversation, humans who received oxytocin scored higher in trust on the Revised NEO Personality Inventory. Moreover, in a risky investment game, experimental subjects given nasally administered oxytocin displayed "the highest level of trust" twice as often as the control group. Subjects who were told they were interacting with a computer showed no such reaction, leading to the conclusion that oxytocin was not merely affecting risk aversion. When there is a reason to be distrustful, such as experiencing betrayal, differing reactions are associated with oxytocin receptor gene (OXTR) differences. Those with the CT haplotype experience a stronger reaction, in the form of anger, to betrayal.

Romantic attachment: In some studies, high levels of plasma oxytocin have been correlated with romantic attachment. For example, if a couple is separated for a long period of time, anxiety can increase due to the lack of physical affection. Oxytocin may aid romantically attached couples by decreasing their feelings of anxiety when they are separated.

Group-serving dishonesty/deception: In a carefully controlled study exploring the biological roots of immoral behavior, oxytocin was shown to promote dishonesty when the outcome favored the group to which an individual belonged instead of just the individual. Oxytocin affects social distance between adult males and females, and may be responsible at least in part for romantic attraction and subsequent monogamous pair bonding. An oxytocin nasal spray caused men in a monogamous relationship, but not single men, to increase the distance between themselves and an attractive woman during a first encounter by 10 to 15 centimeters. The researchers suggested that oxytocin may help promote fidelity within monogamous relationships. For this reason, it is sometimes referred to as the "bonding hormone". There is some evidence that oxytocin promotes ethnocentric behavior, incorporating the trust and empathy of in-groups with their suspicion and rejection of outsiders. Furthermore, genetic differences in the oxytocin receptor gene (OXTR) have been associated with maladaptive social traits such as aggressive behavior.[5]

Social behavior and wound healing: Oxytocin is also thought to modulate inflammation by decreasing certain cytokines. Thus, the increased release in oxytocin following positive social interactions has the
potential to improve wound healing. A study by Marazziti and colleagues used heterosexual couples to investigate this possibility. They found increases in plasma oxytocin following a social interaction were correlated with faster wound healing. They hypothesized this was due to oxytocin reducing inflammation, thus allowing the wound to heal more quickly. This study provides preliminary evidence that positive social interactions may directly influence aspects of health. According to a study published in 2014, silencing of oxytocin receptor interneurons in the medial prefrontal cortex (mPFC) of female mice resulted in loss of social interest in male mice during the sexually receptive phase of the estrous cycle. Oxytocin evokes feelings of contentment, reductions in anxiety, and feelings of calmness and security when in the company of the mate. This suggests oxytocin may be important for the inhibition of the brain regions associated with behavioral control, fear, and anxiety, thus allowing orgasm to occur. Research has also demonstrated that oxytocin can decrease anxiety and protect against stress, particularly in combination with social support. It is found, that endocannabinoid signaling mediates oxytocin-driven social reward. According to a study published in 2008, its results pointed to how a lack of oxytocin in mice saw a abnormalities in emotional behavior. Another study in conducted in 2014, saw similar results with a variation in the oxytocin receptor is connected with dopamine transporter and how levels of oxytocin are dependent on the levels of dopamine transporter levels. One study explored the effects of low levels of oxytocin and the other on possible explanation of what affects oxytocin receptors. As a lack of social skills and proper emotional behavior are common signs of Autism, low levels of oxytocin could become a new sign for individuals that fall into the Autism Spectrum.

**Chemistry:** Oxytocin is a peptide of nine amino acids (a nonapeptide) in the sequence cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-amide (Cys – Tyr – Ile – Gln – Asn – Cys – Pro – Leu – Gly – NH₂, or CYIQNCPLG-NH₂); its C-terminus has been converted to a primary amide and a disulfide bridge joins the cysteine moieties. Oxytocin has a molecular mass of 1007 Da, and one international unit (IU) of oxytocin is the equivalent of 1.68 μg of pure peptide.
exists as a reduced straight-chain (non-cyclic) dithiol nonapeptide called oxytoceine. It has been theorized that oxytoceine may act as a free radical scavenger, as donating an electron to a free radical allows oxytoceine to be re-oxidized to oxytocin via the dehydroascorbate / ascorbate redox couple. Recent advances in analytical instrumental techniques highlighted the importance of liquid chromatography (LC) coupled with mass spectrometry (MS) for measuring oxytocin levels in various samples derived from biological sources. Most of these studies optimized the oxytocin quantification in electrospray ionization (ESI) positive mode, using [M+H]+ as the parent ion at mass-to-charge ratio (m/z) 1007.4 and the fragment ions as diagnostic peaks at m/z 991.0, m/z 723.2 and m/z 504.2. These important ion selections paved the way for the development of current methods of oxytocin quantification using MS instrumentation.

The structure of oxytocin is very similar to that of vasopressin. Both are nonapeptides with a single disulfide bridge, differing only by two substitutions in the amino acid sequence (differences from oxytocin bolded for clarity):

\[
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Oxytocin and vasopressin were isolated and their total synthesis reported in 1954, work for which Vincent du Vigneaud was awarded the 1955 Nobel Prize in Chemistry with the citation: "for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone." Oxytocin and vasopressin are the only known hormones released by the human posterior pituitary gland to act at a distance. However, oxytocin neurons make other peptides, including corticotropin-releasing hormone and dynorphin, for example that act locally. The magnocellular neurosecretory cells that make oxytocin are adjacent to magnocellular neurosecretory cells that make vasopressin. These are large neuroendocrine neurons which are excitable and can generate action potentials.

**Figure-13: Oxytocin & Vasopressin**

**Endorphins** (contracted from **endogenous morphine**) are chemical signals in the brain that block the perception of pain and increase feelings of wellbeing. They are produced and stored in an area of the brain known as the pituitary gland. The class of endorphins consists of three endogenous opioid peptides: \(\alpha\)-endorphin, \(\beta\)-endorphin, and \(\gamma\)-endorphin. The endorphins are all synthesized from the precursor protein, proopiomelanocortin, and all contain a Met-enkephalin motif at their N-terminus: Tyr-Gly-Gly-Phe-Met. \(\alpha\)-endorphin and \(\gamma\)-endorphin result from proteolytic cleavage of \(\beta\)-endorphin between the Thr(16)-Leu(17) residues and Leu(17)-Phe(18) respectively. \(\alpha\)-endorphin has the shortest sequence, and \(\beta\)-endorphin has the longest sequence.\[^{[6]}\]
α-endorphin and γ-endorphin are primarily found in the anterior and intermediate pituitary. While β-endorphin is studied for its opioid activity, α-endorphin and γ-endorphin both lack affinity for opiate receptors and thus do not affect the body in the same way that β-endorphin does. Some studies have characterized α-endorphin activity as similar to that of psychostimulants and γ-endorphin activity to that neuroleptics separately.

### Table 2: Endorphin amino acid sequence

<table>
<thead>
<tr>
<th>Name</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-OH</td>
</tr>
<tr>
<td>β-endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Glu</td>
</tr>
<tr>
<td>γ-endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-OH</td>
</tr>
</tbody>
</table>

**Synthesis:** Endorphin precursors are primarily produced in the pituitary gland. All three types of endorphins are fragments of the precursor protein proopiomelanocortin (POMC). At the trans-Golgi network, POMC binds to a membrane-bound protein, carboxypeptidase E (CPE). CPE facilitates POMC transport into immature budding vesicles. In mammals, pro-peptide convertase 1 (PC1) cleaves POMC into adrenocorticotropic (ACTH) and beta-lipotropin (β-LPH). β-LP:H, a pituitary hormone with little opiate activity, is then continually fragmented into different peptides, including α-endorphin, β-endorphin, and γ-endorphin. Peptide convertase 2 (PC2) is responsible for cleaving β-LPH into β-endorphin and γ-lipotropin. Formation of α-endorphin and γ-endorphin results from proteolytic cleavage of β-endorphin. Regulation of α-endorphin and γ-endorphin increases endorphin production within inflammatory tissues, resulting in an analgesic effect; the stimulation of sympathetic nerves by electro-acupuncture is believed to be the cause of its analgesic effects.

**Mechanism of action:** Endorphins are released from the pituitary gland, typically in response to pain, and can act in both the central nervous system (CNS) and the peripheral nervous system (PNS). In the PNS, β-endorphin is the primary endorphin released from the pituitary gland. Endorphins inhibit transmission of pain signals by binding μ-receptors of peripheral nerves, which block their release of neurotransmitter substance P. The mechanism in the CNS is similar but works by blocking a different neurotransmitter: gamma-aminobutyric acid (GABA). In turn, inhibition of GABA increases the production and release of dopamine, a neurotransmitter associated with reward learning.

**Functions:** Endorphins play a major role in the body's inhibitory response to pain. Research has demonstrated that meditation by trained individuals can be used to trigger endorphin release. Laughter may also stimulate endorphin...
production and elevate one's pain threshold. Endorphin production can be triggered by vigorous aerobic exercise. The release of β-endorphin has been postulated to contribute to the phenomenon known as a "runner's high." However, several studies have supported the hypothesis that the runner's high is due to the release of endocannabinoids rather than that of endorphins. Endorphins may contribute to the positive effect of exercise on anxiety and depression. The same phenomenon may also play a role in exercise addiction. Regular intense exercise may cause the brain to downregulate the production of endorphins in periods of rest to maintain homeostasis, causing a person to exercise more intensely in order to receive the same feeling.

Serotonin: Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter. Its biological function is complex and multifaceted, modulating mood, cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction. Approximately 90% of the serotonin that the body produces is in the intestinal tract. Biochemically, the indoleamine molecule derives from the amino acid tryptophan, via the (rate-limiting) hydroxylation of the 5 position on the ring (forming the intermediate 5-hydroxytryptophan), and then decarboxylation to produce serotonin. Serotonin is primarily found in the enteric nervous system located in the gastrointestinal tract (GI tract). However, it is also produced in the central nervous system (CNS), specifically in the raphe nuclei located in the brainstem, Merkel cells located in the skin, pulmonary neuroendocrine cells and taste receptor cells in the tongue. Additionally, serotonin is stored in blood platelets and is released during agitation and vasoconstriction, where it then acts as an agonist to other platelets. Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the GI tract, where it regulates intestinal movements. About 8% is found in platelets and 1–2% in the CNS. The serotonin is secreted luminally and basolaterally, which leads to increased serotonin uptake by circulating platelets and activation after stimulation, which gives increased stimulation of myenteric neurons and gastrointestinal motility. The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions. These include the regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning. Several classes of antidepressants, such as the SSRIs and the SNRIs among others, interfere with the normal reabsorption of serotonin after it is done with the transmission of the signal, therefore augmenting the neurotransmitter levels in the synapses.

Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they release serotonin, where it can serve as a vasoconstrictor or a vasodilator while regulating hemostasis and blood clotting. In high concentrations, serotonin acts as a vasoconstrictor by contracting endothelial smooth muscle directly or by potentiating the effects of other vasoconstrictors (e.g. angiotensin II, norepinephrine). The vasoconstrictive property is mostly seen in pathologic states affecting the endothelium – such as atherosclerosis or chronic hypertension. In physiologic states, vasodilation occurs through the serotonin mediated release of nitric oxide from endothelial cells. Additionally, it inhibits the release of norepinephrine from adrenergic nerves. Serotonin is also a growth factor for some types of cells, which may give it a role in wound healing. There are various serotonin receptors. Serotonin is metabolized mainly to 5-HIAA, chiefly by the liver. Metabolism involves first oxidation by monoamine oxidase to the corresponding aldehyde. The rate-limiting step is hydride transfer from serotonin to the flavin cofactor. There follows oxidation by aldehyde dehydrogenase to 5-HIAA, the indole acetic-acid derivative. The latter is then excreted by the kidneys.[7]
Besides mammals, serotonin is found in all bilateral animals including worms and insects, as well as in fungi and in plants. Serotonin's presence in insect venoms and plant spines serves to cause pain, which is a side-effect of serotonin injection. Serotonin is produced by pathogenic amoebae, and its effect in the human gut is diarrhea. Its widespread presence in many seeds and fruits may serve to stimulate the digestive tract into expelling the seeds.

**Biological role:** Serotonin is involved in numerous physiological processes, including sleep, thermoregulation, learning and memory, pain, (social) behavior, sex, feeding, motor activity, biological rhythms and possibly others. In less complex animals, such as some invertebrates, serotonin regulates feeding and other processes. In plants serotonin synthesis seems to be associated with stress signals.

**Cellular effects:** Serotonin primarily acts through its receptors and its effects depend on which cells and tissues express these receptors.

**Receptors:** The 5-HT receptors, the receptors for serotonin, are located on the cell membrane of nerve cells and other cell types in animals, and mediate the effects of serotonin as the endogenous ligand and of a broad range of pharmaceutical and psychedelic drugs. Except for the 5-HT3 receptor, a ligand-gated ion channel, all other 5-HT receptors are G-protein-coupled receptors (also called seven-transmembrane, or heptahelical receptors) that activate an intracellular second messenger cascade.

**Termination:** Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is accomplished through the specific monoamine transporter for 5-HT, SERT, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake, including cocaine, dextromethorphan (an antitussive), tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). A 2006 study conducted by the University of Washington suggested that a newly discovered monoamine transporter, known as PMAT, may account for "a significant percentage of 5-HT clearance". Contrasting with the high-affinity SERT, the PMAT has been identified as a low-affinity transporter, with an apparent $K_m$ of 114 micromoles/L for serotonin; approximately 230 times higher than that of SERT. However, the PMAT, despite its relatively low serotonergic affinity, has a considerably higher transport 'capacity' than SERT, "resulting in roughly comparable uptake efficiencies to SERT in heterologous expression systems." The study also suggests some SSRIs, such as fluoxetine and sertraline anti-depressants, inhibit PMAT but at IC$_{50}$ values which surpass the therapeutic plasma concentrations by up to four orders of magnitude. Therefore, SSRI monotherapy is "ineffective" in PMAT inhibition. At present, no known pharmaceuticals are known to appreciably inhibit PMAT at normal therapeutic doses. The PMAT also suggestively transports dopamine and norepinephrine, albeit at K$_m$ values even higher than that of 5-HT (330–15,000 μmoles/L).

**Serotonylation:** Serotonin can also signal through a nonreceptor mechanism called serotonylation, in which serotonin modifies proteins. This process underlies serotonin's effects upon platelet-forming cells (thrombocytes) in which it links to the modification of signaling enzymes called GTPases that then trigger the release of vesicle contents by exocytosis. A similar process underlies the pancreatic release of insulin. The effects of serotonin upon vascular smooth muscle tone – the biological function after which serotonin was originally named – depend upon the serotonylation of proteins involved in the contractile apparatus of muscle cells.

**Nervous system:** The neurons of the raphe nuclei are the principal source of 5-HT release in the brain. There are nine raphe nuclei, designated B1–B9, which contain the majority of serotonin-containing neurons (some scientists chose to group the nuclei raphes lineares into one nucleus), all of which are located along the midline of the brainstem, and centered on the reticular formation. Axons from the neurons of the raphe nuclei form a neurotransmitter system reaching almost every part of the central nervous system. Axons of neurons in the lower raphe nuclei terminate in the cerebellum and spinal cord, while the axons of the higher nuclei spread out in the entire brain.
Ultrastructure and function: The serotonin nuclei may also be divided into two main groups, the rostral and caudal containing three and four nuclei respectively. The rostral group consists of the caudal linear nuclei (B8), the dorsal raphe nuclei (B6 and B7) and the median raphe nuclei (B5, B8 and B9), that project into multiple cortical and subcortical structures. The caudal group consists of the nucleus raphe magnus (B3), raphe obscurus nucleus (B2), raphe pallidus nucleus (B1), and lateral medullary reticular formation, that project into the brainstem.[8]

The serotonergic pathway is involved in sensorimotor function, with pathways projecting both into cortical (Dorsal and Median Raphe Nuclei), subcortical, and spinal areas involved in motor activity. Pharmacological manipulation suggests that serotonergic activity increases with motor activity while firing rates of serotonergic neurons increase with intense visual stimuli. Animal models suggest that kainate signaling negatively regulates serotonin actions in the retina, with possible implications for the control of the visual system. The descending projections form a pathway that inhibits pain called the "descending inhibitory pathway" that may be relevant to a disorder such as fibromyalgia, migraine, and other pain disorders, and the efficacy of antidepressants in them.

Serotonergic projections from the caudal nuclei are involved in regulating mood and emotion, and hypo- or hyper-serotonergic states may be involved in depression and sickness behavior.

Microanatomy: Serotonin is released into the synapse, or space between neurons, and diffuses over a relatively wide gap (>20 nm) to activate 5-HT receptors located on the dendrites, cell bodies, and presynaptic terminals of adjacent neurons. When humans smell food, dopamine is released to increase the appetite. But, unlike in worms, serotonin does not increase anticipatory behaviour in humans; instead, the serotonin released while consuming activates 5-HT2C receptors on dopamine-producing cells. This halts their dopamine release, and thereby serotonin decreases appetite. Drugs that block 5-HT2C receptors make the body unable to recognize when it is no longer hungry or otherwise in need of nutrients, and are associated with weight gain, especially in people with a low number of receptors. The expression of 5-HT2C receptors in the hippocampus follows a diurnal rhythm, just as the serotonin release in the ventromedial nucleus, which is characterized by a peak at morning when the motivation to eat is strongest.[9]

In macaques, alpha males have twice the level of serotonin in the brain as subordinate males and females (measured by the concentration of 5-HIAA in the cerebrospinal fluid (CSF)). Dominance status and CSF serotonin levels appear to be positively correlated. When dominant males were removed from
such groups, subordinate males begin competing for dominance. Once new dominance hierarchies were established, serotonin levels of the new dominant individuals also increased to double those in subordinate males and females. The reason why serotonin levels are only high in dominant males, but not dominant females has not yet been established. In humans, levels of 5-HT₁\textsubscript{A} receptor inhibition in the brain show negative correlation with aggression, and a mutation in the gene that codes for the 5-HT₂\textsubscript{A} receptor may double the risk of suicide for those with that genotype. Serotonin in the brain is not usually degraded after use, but is collected by serotonergic neurons by serotonin transporters on their cell surfaces. Studies have revealed nearly 10% of total variance in anxiety-related personality depends on variations in the description of where, when and how many serotonin transporters the neurons should deploy.

**Psychological influences:** Serotonin has been implicated in cognition, mood, anxiety and psychosis, but strong clarity has not been achieved.

**Autism spectrum disorder (ASD):** In regards to research for neurotransmitters and effects on patients with Autism Spectrum Disorder (ASD), 5-HT has been studied the most in terms of research efforts and investigations. As noted, 5-HT signaling does facilitate many neural processes including that of neurogenesis, cell migration and survival, synaptogenesis, and synaptic plasticity. It was noted that 45% of tested ASD subjects contained high levels of 5-HT in their blood. In addition, investigations performed on ASD-like animal models reported that hyperserotonemia significantly reduced the motivation for social interest through inhibition of separation distress, which could be related in the ASD patients that have social impairments.

**Pharmacology:** Several classes of drugs target the 5-HT system, including some antidepressants, antipsychotics, anxiolytics, antiepileptics, and antimigraine drugs, as well as, the psychedelic drugs and empathogens.

**Mechanism of action:** At rest, serotonin is stored within the vesicles of presynaptic neurons. When stimulated by nerve impulses, serotonin is released as a neurotransmitter into the synapse, reversibly binding to the postsynaptic receptor to induce a nerve impulse on the postsynaptic neuron. Serotonin can also bind to auto-receptors on the presynaptic neuron to regulate the synthesis and release of serotonin. Normally serotonin is taken back into the presynaptic neuron to stop its action, then reused or broken down by monoamine oxidase.

**Methyl-tryptamines and hallucinogens:** Several plants contain serotonin together with a family of related tryptamines that are methylated at the amino (NH\(_2\)) and (OH) groups, are N-oxides, or miss the OH group. These compounds do reach the brain, although some portion of them are metabolized by monoamine oxidase enzymes (mainly MAO-A) in the liver. Examples are plants from the genus Anadenanthera that are used in the hallucinogenic yopo snuff. These compounds are widely present in the leaves of many plants, and may serve as deterrents for animal ingestion. Serotonin occurs in several mushrooms of the genus Panaeolus.

**Mood:** We can describe mood not as specific to an emotional status, but as associated with a relatively long-lasting emotional state. Serotonin's association with mood is most known for various forms of depression and bipolar disorders in humans. Disorders caused by serotonergic activity potentially contribute to the many symptoms of major depression, such as overall mood, activity, suicidal thoughts and sexual and cognitive dysfunction. Selective serotonin reuptake inhibitors (SSRI's) are a class of drugs demonstrated to be an effective treatment in major depressive disorder and are the most prescribed class of antidepressants. SSRI's function is to block the reuptake of serotonin, making more serotonin available to absorb by the receiving neuron. Animals have been studied for decades in order to understand depressive behavior among species. One of the most familiar studies, the forced swimming test (FST), was performed to measure potential antidepressant activity. Rats were placed in an inescapable container of water, at which point time spent immobile and number of active behaviors (such as splashing or climbing) were compared before and after a panel of anti-depressant drugs were administered. Antidepressants that selectively inhibit NE reuptake were shown to reduce immobility and selectively increase climbing without affecting swimming. However, results of the SSRI's also show reduced immobility but increased swimming without affecting climbing. This study demonstrated the importance of behavioral tests for antidepressants, as they can detect...
drugs with an effect on core behavior along with behavioral components of species.

**Growth and reproduction:** In the nematode C. elegans, artificial depletion of serotonin or the increase of octopamine cues behavior typical of a low-food environment: C. elegans becomes more active, and mating and egg-laying are suppressed, while the opposite occurs if serotonin is increased or octopamine is decreased in this animal. Serotonin is necessary for normal nematode male mating behavior, and the inclination to leave food to search for a mate. The serotonergic signaling used to adapt the worm's behavior to fast changes in the environment affects insulin-like signaling and the TGF beta signaling pathway, which control long-term adaption. In the fruit fly insulin both regulates blood sugar as well as acting as a growth factor. Thus, in the fruit fly, serotonergic neurons regulate the adult body size by affecting insulin secretion. Serotonin has also been identified as the trigger for swarm behavior in locusts. In humans, though insulin regulates blood sugar and IGF regulates growth, serotonin controls the release of both hormones, modulating insulin release from the beta cells in the pancreas through serotonylation of GTPase signaling proteins. Exposure to SSRIs during pregnancy reduces fetal growth. Genetically altered C. elegans worms that lack serotonin have an increased reproductive lifespan, may become obese, and sometimes present with arrested development at a dormant larval state.[11]

**Biosynthesis:**
**Aging and age-related phenotypes:** Serotonin is known to regulate aging, learning and memory. The first evidence comes from the study of longevity in *C. elegans*. During early phase of aging the level of serotonin increases, which alters locomotory behaviors and associative memory. The effect is restored by mutations and drugs (including mianserin and methiothepin) that inhibit serotonin receptors. The observation does not contradict with the notion that the serotonin level goes down in mammals and humans, which is typically seen in late but not early phase of aging.

**Biochemical mechanisms:** In animals including humans, serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes, tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (DDC), and the coenzyme pyridoxal phosphate. The TPH-mediated reaction is the rate-limiting step in the pathway. TPH has been shown to exist in two forms: TPH1, found in several tissues, and TPH2, which is a neuron-specific isoform. Serotonin can be synthesized from tryptophan in the lab using *Aspergillus niger* and *Psilocybe coprophila* as catalysts. The first phase to 5-hydroxytryptophan would require letting tryptophan sit in ethanol and water for 7 days, then mixing in enough HCl (or other acid) to bring the pH to 3, and then adding NaOH to make a pH of 13 for 1 hour. *Asperigillus Niger* would be the catalyst for this first phase. The second phase to synthesizing tryptophan itself from the 5-hydroxytryptophan intermediate would require adding ethanol and water, and letting sit for 30 days this time. The next two steps would be the same as the first phase: adding HCl to make the pH = 3, and then adding NaOH to make the pH very basic at 13 for 1 hour. *Aspergillus Niger* would be the catalyst for the reaction. Serotonin taken orally does not pass into the serotonergic pathways of the central nervous system, because it does not cross the blood–brain barrier. However, tryptophan and its metabolite 5-hydroxytryptophan (5-HTP), from which serotonin is synthesized, do cross the blood–brain barrier. These agents are available as dietary supplements and in various foods, and may be effective serotonergic agents. One product of serotonin breakdown is 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. Serotonin and 5-HIAA are sometimes produced in excess amounts by certain tumors or cancers, and levels of these substances may be measured in the urine to test for these tumors.[12]

**Analytical chemistry:** Indium tin oxide is recommended for the electrode material in electrochemical investigation of concentrations produced, detected, or consumed by microbes. A laser desorption ionization mass spectrometry technique was developed by Bertazzo et al. 1994 to measure the molecular weight of both natural and synthetic serotonin.

**How to boost Happy Hormone Level:** Looking to boost your serotonin level? Spending time outdoors, in sunlight, is a great way to do this. According to research, exposure to ultraviolet (UV) radiation from the sun can increase the production of serotonin. You can try spending about 15 minutes outside a few times a week. Try exploring a new neighbourhood or park if you’re tired of the same old sights. Just be aware that UV exposure can also increase the risk of skin cancer, so don’t forget sunscreen!

**Make time for exercise:** Exercise has multiple physical health benefits. It can also have a positive impact on emotional well-being. If you’ve heard of a “runner’s high,” you might already know about the link between exercise and endorphin release. But exercise doesn’t just work on endorphins. Regular physical activity can also increase your dopamine and serotonin levels, making it a great option to boost your happy hormones.

**Maximize your workout**
To see even more benefits from exercise:

**Include a few friends:** A small 2017 study of medical students found evidence to suggest group exercise offers more significant benefits than solo exercise.

**Get some sun:** Move your workout outdoors to maximize your serotonin boost.

**Time it:** Aim for at least 30 minutes of aerobic exercise at a time. Any amount of physical activity has health benefits, but research Trusted Source associates higher-intensity workouts with a greater release of endorphins.

**Laugh with a friend:** Who hasn’t heard the old saying, “Laughter is the best medicine?” Of course, laughter won’t treat ongoing health issues. But it can help relieve feelings of anxiety or stress, and
improve a low mood by boosting dopamine and endorphin levels. According to a small 2017 study looking at 12 young men, social laughter triggered endorphin release. Research supports this finding.

So, share that funny video, dust off your joke book, or watch a comedy special with a friend or partner. An added bonus? Bonding over something hilarious with a loved one might even trigger oxytocin release.

**Cook (and enjoy) a favourite meal with a loved one:** This tip could — in theory — boost all four of your happy hormones. The enjoyment you get from eating something delicious can trigger the release of dopamine along with endorphins. Sharing the meal with someone you love, and bonding over meal preparation, can boost oxytocin levels. Certain foods can also have an impact on hormone levels, so note the following when meal planning for a happy hormone boost:

- **Spicy foods** may trigger endorphin release
- **Yogurt, beans, eggs, meats with low-fat content, and almonds** are just a few foods linked to dopamine release
- **Foods high in tryptophan** have been linked to increased serotonin levels
- **Foods containing probiotics**, such as yogurt, kimchi, and sauerkraut, can influence the release of hormones

**Try supplements:** There are several supplements that may help increase your happy hormone levels. Here are just a few to consider: Tyrosine (dopamine production), Green tea and green tea extract (dopamine and serotonin), Probiotics (serotonin and dopamine production), Tryptophan (serotonin)

Experts studying the effects of supplements have found varied results. Many studies involved animals only, so more research is needed to help support the benefits of supplements for humans. Supplements may be helpful, but some aren’t recommended for people with certain health conditions. They can also interact with certain medications, so talk to a healthcare provider before you try them. If you do take any supplements, read all package instructions and stick to the recommended dose, since some can have negative effects at high doses.[13]

**Listen to music (or make some):** Music can give more than one of your happy hormones a boost. Listening to instrumental music, especially music that gives you chills, can increase dopamine production in your brain. But if you enjoy music, simply listening to any music you enjoy may help put you in a good mood. This positive change in your mood can increase serotonin production. You may also experience an endorphin release while performing music, especially in a large group. For example, a 2016 study found that choir members experienced increased endorphin release during rehearsals.

**Meditate:** If you’re familiar with meditation, you might already know of its many wellness benefits — from improving sleep to reducing stress. Research links many of meditation’s benefits to increased dopamine production during the practice. Not sure how to start? It’s not as hard as you might think.
think. You don’t even need to sit still, though it can help when you’re first starting out.

Try it
To get started with meditation:
Choose a quiet, comfortable place to sit.
Get comfortable, whether that’s standing, sitting, or lying down.
Let all your thoughts — positive or negative — rise and pass you by.
As thoughts come up, try not to judge them, cling to them, or push them away. Simply acknowledge them.
Start out by doing this for 5 minutes and work your way up to longer sessions over time.

Plan a romantic evening: Oxytocin’s reputation as the “love hormone” is well earned. Simply being attracted to someone can lead to the production of oxytocin. But physical affection, including kissing, cuddling, or having sex, also contributes to oxytocin production. Just spending time with someone you care about can also help boost oxytocin production. This can help increase closeness and positive relationship feelings, making you feel happy, blissful, or even euphoric. If you really want to feel those happy hormones, note that dancing and sex both lead to endorphin release, while orgasm triggers dopamine release. You can also share a glass of wine with your partner for an added endorphin boost.

Pet your dog: If you have a dog, giving your furry friend some affection is a great way to boost oxytocin levels for you and your dog. According to research Pet owner's oxytocin, dog owners as well as their dogs see an increase in oxytocin when interacting. Even if you don’t own a dog, you might also experience an oxytocin boost when you see a dog you know and like.
If you’re a dog lover, this might happen when you get a chance to pet any dog at all. So, find your favourite canine and give it a good ear scratch or lap cuddle.

Get a good night’s sleep
- Not getting enough quality sleep can affect your health in multiple ways.
- For one, it can contribute to an imbalance of hormones, particularly dopamine, in your body. This can have a negative impact on your mood as well as your physical health.
- Setting aside 7 to 9 hours each night for sleep can help restore the balance of hormones in your body, which will likely help you feel better.
- If you find it difficult to get a good night’s sleep, try:
  - Going to bed and getting up around the same time every day
  - Creating a quiet, restful sleeping environment (try reducing light, noise, and screens)
  - Decreasing caffeine intake, especially in the afternoon and evening

Manage stress
- It’s normal to experience some stress from time to time. But living with regular stress or dealing with highly stressful life events can cause drops in dopamine and serotonin production. This can negatively affect your health and mood, making it harder to deal with stress.
- If you’re under a lot of stress, the American Psychological Association recommends:
  - Taking a brief break from the source of stress
  - Laughter
  - Taking 20 minutes for a walk, run, bike ride, or other physical activity
  - meditation
  - social interaction
  - Any of these approaches may help relieve your stress while also boosting your levels of serotonin, dopamine, and even endorphins.

GET A MASSAGE:
If you enjoy a massage, here’s one more reason to get one: massage can boost all four of your happy hormones. According to studies, massage boosts endorphins. Older research found that massage also increases serotonin and dopamine. You can get these benefits from a massage by a licensed massage therapist, but you can also get a massage from a partner for some extra oxytocin.

TAKEAWAY:
Serotonin, dopamine, endorphins, and oxytocin help promote happiness and pleasure while reducing depression and anxiety. You can give these feel-good hormones a natural boost with some simple activities. If you’re having difficulty regulating your mood, talk with a healthcare provider, who can recommend therapies or treatments that may help.

CONCLUSION:
Happy hormone axes typify complex feedback systems in which two or more model variables (e.g., secretion and clearance) are required to account for the
nonlinear behaviour of the system output (neurohormone concentrations over time). For example, episodic fluctuations in blood concentrations of a neurohormone are controlled jointly by neurohormone secretory event frequency, amplitude, duration, and waveform, as well as by neurohormone disappearance rates from the blood. In addition, a variable admixture of basal and pulsatile neurohormone release may further determine circulating effectors concentrations. A major complicating factor is the extent to which model parameters (e.g., secretory burst frequency, basal secretion rate, neurohormone half-life, and secretory event amplitude, mass, and/or duration) are highly correlated, as such parameter correlations make it difficult to determine unique model values to characterize any particular set of observed data. For example, a quantitative model of admixed pulsatile and basal neurohormone secretion and removal may require simultaneous estimation of both basal and pulsatile neurohormone secretory rates with or without concomitant estimates of neurohormone half-life. However, in relation to any particular data set, any given estimate of the basal secretory rate has a strong statistical dependency on the half-life estimate, and vice versa. Such parameter correlations are expected to challenge nonlinear least-squares methods of parameter estimation in at least two respects: (a) the determination of unique solutions to multiparameter model estimates and (b) the valid estimation of statistical confidence intervals that define the precision of parameter estimates whether considered alone or jointly.

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Five pharma stalwarts are very happy to publish [HAPPY HORMONES] in UGC approved journal! Hormones are the internal exudates from endocrine gland which have no duct to secrete the potent chemicals directly to the blood to improve metabolic metastasis in superfast technique. Happiness belongs to the mood and mood is cultivated by brain, so mood swing makes the human happy in feelings. Dr. R. Badmanaban [Professor & Principal], Kushal Nandi [MPharm scholar in Pharmaceutical Chemistry], Dr. Dhrubo Jyoti Sen [Professor & Head of the Department of Pharmaceutical Chemistry], Dr. Kishor Dholwani [Professor of Pharmacognosy & Principal], Dr. Rajesh Dodiya [Associate Professor of Pharmacognosy] & Dr. Dhananjoy Saha [Deputy Director, Directorate of Technical Education]. All the chemistry wizards have tried to give perfect shape to the article by giving extraordinary outputs.

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