Neurotransmitters: Their Role in the Body

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Objectives

By the end of this educational encounter, the clinician will be able to:

1. Understand how nerve impulses travel along neural pathways
2. Identify common neurotransmitters and their effect in the body
3. Explain the effect of altered concentrations of specific neurotransmitters upon the system.

The purpose of this course is to give an overview of the neurotransmitter system of the human body and increase understanding about how altered neurotransmitter concentrations affect various body organs.

Definition of a Neurotransmitter

Neurotransmitters are types of hormones in the brain that transmit information from one neuron to another. They are made by amino acids. Neurotransmitters control major body functions including movement, emotional response, and the physical ability to experience pleasure and pain. The most familiar neurotransmitters, which are thought to play a role in mood regulation, are serotonin, norepinephrine, dopamine, acetylcholine, and GABA.

In order to adequately understand the effect of neurotransmitters, we must first understand what occurs in the process of neurotransmission. We will start with an oversimplified version for better understanding and then follow up with a more detailed explaination. A nerve impulse, which is an electrical signal, travels along the neural pathway until it reaches the end. Here the electrical signal is converted to a chemical signal. This area of conversion is called a synapse. The chemical signal is called a neurotransmitter. The nerve impulse then reaches the neuron on the other side, where it once again becomes an electrical signal.

The release of a neurotransmitter is triggered by the arrival of a nerve impulse (or action potential) and occurs through an unusually rapid process of cellular secretion, also known as exocytosis. Within the presynaptic nerve terminal, vesicles containing neurotransmitter sit "docked" and ready at the synaptic membrane. Neurotransmitters are packaged into vesicles that cluster beneath the membrane on the presynaptic side of a synapse, and released into the synaptic cleft, where they bind to receptors located in the membrane on the postsynaptic side of the synapse. Release of neurotransmitters is most commonly driven by arrival of an action potential at the synapse, but may also be driven by graded electrical potentials. Also, there is often a low level of "baseline" release even in the absence of electrical stimulation.

The arriving action potential produces an influx of calcium ions through voltage-dependent, calcium-selective ion channels at the down stroke of the action potential (tail current). Calcium ions then trigger a biochemical cascade which results in vesicles releasing their contents (neurotransmitters) to the synaptic cleft within 180 microseconds of calcium entry. As calcium ions enter into the presynaptic neuron, they

bind with the proteins found within the membranes of the synaptic vesicles that allow the vesicles to "dock." Triggered by the binding of the calcium ions, the synaptic vesicle proteins begin to move apart, resulting in the creation of a fusion pore. The presence of the pore allows for the release of neurotransmitter into the synapse. The membrane added by this fusion is later retrieved by endocytosis and recycled for the formation of fresh neurotransmitter-filled vesicles.

Receptor Binding

Receptors on the opposite side of the synaptic gap bind neurotransmitter molecules and respond by opening nearby ion channels in the postsynaptic cell membrane, causing ions to rush in or out and changing the local transmembrane potential of the cell.

Often the ‘lock and key’ hypothesis is used to illustrate the interaction between a neurotransmitter and its receptor. The key (the neurotransmitter) can only unlock (activate) a lock (the receptor) if it fits perfectly into the keyhole (neurotransmitter binding site) of the lock.

Receptors and auto receptors are sensitive to the neurotransmitter concentration in the synaptic cleft. Auto receptors regulate the release of the neurotransmitter from the presynaptic neuron – when these presynaptic receptors are fully occupied, neurotransmitter production is stopped. Over sensitivity of auto receptors may be implicated in the development of depression.

Almost every neurotransmitter can bind to more than one type of receptor, and each neurotransmitter can initiate different signals at the postsynaptic neuron. This all adds to the complexity of chemical signaling. Binding of a neurotransmitter to its receptor on

the postsynaptic membrane can activate channels in the postsynaptic neuron resulting in a change in the membrane potential.

This initiates an excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic neuron and initiates an action potential. The resulting change in voltage is called a postsynaptic potential. In general, the result is excitatory, in the case of depolarizing currents, or inhibitory in the case of hyperpolarizing currents. Whether a synapse is excitatory or inhibitory depends on what type(s) of ion channel conduct the postsynaptic current display(s), which in turn is a function of the type of receptors and neurotransmitter employed at the synapse. In this way, the electrical signal or impulse is transmitted down the neuronal pathway. Once the action potential is initiated, the transmitter must then be rapidly removed from the synaptic cleft, to enable the postsynaptic cell to engage in another cycle of signal generation.

The release of a neurotransmitter from its nerve terminal is not only dependent upon the passage of an action potential, but also on the intersynaptic concentration of the transmitter. This is known as presynaptic inhibition. At certain synapses, such as noradrenergic, GABAergic, dopaminergic and serotonergic synapses, the release of the neurotransmitter may be reduced by the presence of high concentrations of the transmitter in the synaptic cleft. The release of a neurotransmitter can also be affected by a variety of other neurotransmitters; for example, stimulation of serotonin receptors on noradrenergic terminals can lead to an enhanced release of noradrenaline. Such receptors are termed heteroceptors.

Neurons and synapses occur in specific patterns in the brain, giving rise to complex neuronal circuits. This results in the specialization of different regions of the brain for different functions and allows us to integrate information such as sound, vision, smell, taste and touch. Each neurotransmitter is made by a small number of neurons whose cell bodies are clustered in specific areas of the brain. For example, noradrenaline is synthesized mainly by neurons in the brainstem, specifically in the locus coeruleus, which is situated in the pons; the cell bodies of the dopamine neurons are clustered in a few brain regions, most importantly those deep within the midbrain. However, the axons of these neurons extend throughout the brain and influence almost the entire organ.

Termination

After a neurotransmitter molecule binds to a receptor molecule, it does not stay bound forever: sooner or later it is shaken loose by random temperature-related jiggling. Once the neurotransmitter breaks loose, it can either drift away, or bind again to another receptor molecule. The pool of neurotransmitter molecules undergoing this binding-loosening cycle steadily diminishes, however. Neurotransmitter molecules are typically removed in one of two ways, depending on the type of synapse: either they are taken up by the presynaptic cell (and then processed for re-release during a later action potential), or else they are broken down by special enzymes. The time course of these "clearing" processes varies greatly for different types of synapses, ranging from a few tenths of a millisecond for the fastest, to several seconds for the slowest.

Neurotransmitters must be broken down once it reaches the post-synaptic cell to prevent further excitatory or inhibitory signal transduction. For example, acetylcholine,

(ACH) (an excitatory neurotransmitter), is broken down by acetylcholinesterase (AchE). Choline is taken up and recycled by the pre-synaptic neuron to synthesize more ACH. Other neurotransmitters such as dopamine are able to diffuse away from their targeted synaptic junctions and are eliminated from the body via the kidneys, or destroyed in the liver. Each neurotransmitter has very specific degradation pathways at regulatory points, which may be the target of the body's own regulatory system or recreational drugs.

A chemical can be classified as a neurotransmitter if it meets the following conditions:

- There are precursors and/or synthesis enzymes located in the presynaptic side of the synapse.
- The chemical is present in the presynaptic element.
- It is available in sufficient quantity in the presynaptic neuron to affect the postsynaptic neuron;
- There are postsynaptic receptors and the chemical is able to bind to them.
- A biochemical mechanism for inactivation is present.

There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides, and monoamines is sufficient for some purposes.

Approximately ten "small-molecule neurotransmitters" are known:

- Acetylcholine (ACh)
- Monoamines: norepinephrine (NE), dopamine (DA), serotonin (5-HT), melatonin
- Amino acids: glutamate, gamma aminobutyric acid (GABA), aspartate, glycine, histamine

- Purines: Adenosine, ATP, GTP, and their derivatives

In addition, over 50 neuroactive peptides have been found, and new ones are discovered on a regular basis. Many of these are "co-released" along with a small-molecule transmitter, but in some cases a peptide is the primary transmitter at a synapse.

Single ions, such as synaptically released zinc, are also considered neurotransmitters by some, as are a few gaseous molecules such as nitric oxide (NO) and carbon monoxide (CO). These are not neurotransmitters by the strict definition, however, because although they have all been shown experimentally to be released by presynaptic terminals in an activity-dependent way, they are not packaged into vesicles. Not all neurotransmitters are equally important. By far the most prevalent transmitter is glutamate, which is used at well over 90% of the synapses in the human brain. The next most prevalent is GABA, which is used at more than 90% of the synapses that don't use glutamate. Note, however, that even though other transmitters are used in far fewer synapses, they may be very important functionally: the great majority of psychoactive drugs exert their effects by altering the actions of some neurotransmitter system, and the great majority of these act through transmitters other than glutamate or GABA. Addictive drugs such as cocaine, amphetamine, and heroin, for example, exert their effects primarily on the dopamine system.

Types of Neurotransmitters

Neurotransmitters can be broadly classified into two categories; excitatory and inhibitory. Some neurotransmitters can serve both functions. Some neurotransmitters

are commonly described as "excitatory" or "inhibitory". It is important to understand what these terms mean. The only thing that a neurotransmitter does directly is to activate one or more types of receptors. The effect on the postsynaptic cell depends entirely on the properties of the receptors. It so happens that for some neurotransmitters (for example, glutamate), the most important receptors all have excitatory effects: that is, they increase the probability that the target cell will fire an action potential. For other neurotransmitters (such as GABA), the most important receptors all have inhibitory effects. There are, however, other important neurotransmitters, such as acetylcholine, for which both excitatory and inhibitory receptors exist; and there are some types of receptors that activate complex metabolic pathways in the postsynaptic cell to produce effects that cannot appropriately be called either excitatory or inhibitory.

Excitatory neurotransmitters are the nervous system's "on switches", increasing the likelihood that an excitatory signal is sent. They act like a car's accelerator, revving up the engine. Excitatory transmitters regulate many of the body's most basic functions including: thought processes, the body's fight or flight response, motor movement and higher thinking. Physiologically, the excitatory transmitters act as the body's natural stimulants, generally serving to promote alertness, energy, and activity. Without a functioning inhibitory system to put on the brakes, things can get out of control.

Inhibitory neurotransmitters are the nervous system's "off switches", decreasing the likelihood that an excitatory signal is sent. Excitation in the brain must be balanced with inhibition. Too much excitation can lead to restlessness, irritability, insomnia, and even seizures. Inhibitory transmitters regulate the activity of the excitatory neurotransmitters, much like the brakes on a car. The inhibitory system slows things down.

Physiologically, the inhibitory transmitters act as the body's natural tranquilizers, generally serving to induce sleep, promote calmness, and decrease aggression.

Excitatory neurotransmitters

- Dopamine
- Histamine
- Norepinephrine
- Epinephrine
- Glutamate
- Acetylcholine

Inhibitory neurotransmitters

- GABA
- Dopamine
- Serotonin
- Acetylcholine
- Taurine

Actions

The effects of a neurotransmitter system depend on the connections of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to.

Here are a few examples of important neurotransmitter actions:

- Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. It is also used at most synapses that are "modifiable", i.e. capable of increasing or decreasing in strength. Modifiable synapses are thought to be the main memory-storage elements in the brain.
- GABA is used at the great majority of fast inhibitory synapses in virtually every part of the brain. Many sedative/tranquilizing drugs act by enhancing the effects of GABA. Correspondingly glycine is the inhibitory transmitter in the spinal cord.
- Acetylcholine is distinguished as the transmitter at the neuromuscular junction connecting motor nerves to muscles. The paralytic arrow-poison curare acts by blocking transmission at these synapses. Acetylcholine also operates in many regions of the brain, but using different types of receptors.

Neurons expressing certain types of neurotransmitters sometimes form distinct systems, where activation of the system affects large volumes of the brain, called *volume transmission*. The major neurotransmitter systems are the noradrenaline (norepinephrine) system, the dopamine system, the serotonin system and the cholinergic system. Most other neurotransmitters, on the other hand, e.g. glutamate, GABA and glycine, are used very generally throughout the central nervous system.

Drugs targeting the neurotransmitter of such systems affects the whole system; this fact explains the mode of action of many drugs. Cocaine, for example, blocks the reentering of dopamine back into the presynaptic neuron, leaving these neurotransmitters in the synaptic gap longer. Since the dopamine is in the synapse longer, the neurotransmitter rapidly hit the receptors on the postsynaptic neuron cell, and therefore causing

happiness. Excess intake of cocaine can lead to physical addiction. The physical addiction of cocaine is when the neurotransmitters stay in the synapse so long , the body removes some receptors from the postsynaptic neuron. After the effects of the drug wear off, the person usually feels unhappy, because now the neurotransmitters are less likely to hit the receptor since the body removed many of them during the drug intake. Prozac is a selective serotonin reuptake inhibitor (SSRI), hence potentiating the effect of naturally released serotonin.

In neuroscience, neuromodulation is the process in which several classes of neurotransmitters in the nervous system regulate diverse populations of neurons (one neuron uses different neurotransmitters to connect to several neurons), as opposed to direct synaptic transmission in which one presynaptic neuron directly influences a postsynaptic partner (one neuron reaching one other neuron), neuromodulatory transmitters secreted by a small group of neurons diffuse through large areas of the nervous system, having an effect on multiple neurons. Examples of neuromodulators include dopamine, serotonin, acetylcholine, histamine and others.

A neuromodulator is a relatively new concept in the field and it can be conceptualized as a neurotransmitter that is not reabsorbed by the pre-synaptic neuron or broken down into a metabolite. Such neuromodulators end up spending a significant amount of time in the CSF (cerebrospinal fluid) and influencing (or modulating) the overall activity level of the brain. For this reason, some neurotransmitters are also considered as neuromodulators. Examples of neuromodulators in this category are serotonin and acetylcholine.

System	Origin	Targets	Effects
Noradrenaline system	locus coeruleus	adrenergic receptors in: • spinal cord • thalamus • hypothalamus • striatum • neocortex • cingulate gyrus • cingulum • hippocampus • amygdala	• arousal • reward system
Dopamine system	Lateral tegmental field dopamine pathways: • mesocortical pathway • mesolimbic pathway • nigrostriatal pathway • tuberoinfundibular pathway	• hypothalamus Dopamine receptors at pathway terminations.	motor system, reward system, cognition, endocrine, nausea
Serotonin system	caudal dorsal raphe nucleus	Serotonin receptors in: • deep cerebellar nuclei • cerebellar cortex • spinal cord	Increase (introverson), mood, satiety, body temperature and sleep, while decreasing nociception.
	rostral dorsal raphe nucleus	Serotonin receptors in: • thalamus • striatum • hypothalamus • nucleus accumbens • neocortex • cingulate gyrus • cingulum • hippocampus • amygdala	

Cholinergic system	pontomesencephalotegmental complex	(mainly) M1 receptors in: • brainstem	• learning • short-term memory • arousal • reward
	basal optic nucleus of Meynert	(mainly) M1 receptors in: • neocortex	
	medial septal nucleus	(mainly) M1 receptors in: • hippocampus • neocortex	

Noradrenaline system

The noradrenaline system consists of just 1500 neurons on each side of the brain, which is diminutive compared to the total amount of more than 100 billion neurons in the brain. Nevertheless, when activated, the system plays major roles in the brain. Noradrenaline is released from the neurons, and acts on adrenergic receptors.

Norepinephrine

Norepinephrine is an excitatory neurotransmitter that is important for attention and focus. Norepinephrine is synthesized from dopamine and is strongly associated with bringing our nervous systems into the “fight or flight” state. Norepinephrine triggers the release of hormones from the limbic section of the brain that signal other stress hormones to act in a crisis. It can raise blood pressure and increase heart rate. It can elevate the metabolic rate, body temperature and stimulate the smooth bronchial muscles to assist breathing. It is also important for forming memories.

High levels

Elevated norepinephrine activity seems to be a contributor to anxiety. In addition, brain norepinephrine turnover is increased in conditions of stress. Increased levels of norepinephrine will lead to alertness and mood elevation and increased sexual interest. However, high amounts raise blood pressure; increase heart rate, and cause anxiety, fear, panic, stress, hyperactivity, an overwhelming sense of dread, irritability, and insomnia.

Low levels

Low levels of norepinephrine are linked to lack of energy, focus, and motivation. Insufficient norepinephrine levels also contribute to depression, loss of alertness, and poor memory. Norepinephrine is a catecholamine with dual roles as a hormone and a neurotransmitter. As a stress hormone, norepinephrine affects parts of the brain where attention and responding actions are controlled. Along with epinephrine, norepinephrine also underlies the fight-or-flight response, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle.

However, when norepinephrine acts as a drug it will increase blood pressure by its prominent increasing effects on the vascular tone (due stimulation of alpha-Receptors). This increase in vascular resistance is triggering a compensatory reflex that overcomes its direct stimulatory effects on the heart. The reflex, called the baroreceptor reflex, results in a drop in heart rate called reflex bradycardia.

Norepinephrine is synthesized from dopamine by dopamine β-hydroxylase. It is released from the adrenal medulla into the blood as a hormone, and is also a

neurotransmitter in the central nervous system and sympathetic nervous system where it is released from noradrenergic neurons. The actions of norepinephrine are carried out via the binding to adrenergic receptors.

Origins

Norepinephrine is released when a host of physiological changes are activated by a stressful event. In the brain, this is caused in part by activation of an area of the brain stem called the locus ceruleus. This nucleus is the origin of most norepinephrine pathways in the brain. Noradrenergic neurons project bilaterally (send signals to both sides of the brain) from the locus ceruleus along distinct pathways to many locations, including the cerebral cortex, limbic system, and the spinal cord, forming a neurotransmitter system.

Norepinephrine is also released from postganglionic neurons of the sympathetic nervous system, to transmit the fight-or-flight response in each tissue respectively. The adrenal medulla can also be counted to such postganglionic nerve cells, although they release norepinephrine into the blood.

Norepinephrine system

The noradrenergic neurons in the brain form a neurotransmitter system, that, when activated, exerts effects on large areas of the brain. The effects are alertness and arousal, and influences on the reward system.

Anatomically, the noradrenergic neurons originate both in the locus coeruleus and the lateral tegmental field. The axons of the neurons in the locus coeruleus act on adrenergic receptors in:

- Amygdala
- Cingulate gyrus
- Cingulum
- Hippocampus
- Hypothalamus
- Neocortex
- Spinal cord
- Striatum
- Thalamus

On the other hand, axons of neurons of the lateral tegmental field act on adrenergic receptors in hypothalamus, for example. This structure explains some of the clinical uses of norepinephrine, since a modification of the system affects large areas of the brain.

Mechanism

Norepinephrine is synthesized from tyrosine as a precursor, and packed into synaptic vesicles. It performs its action by being released into the synaptic cleft, where it acts on adrenergic receptors, followed by the signal termination, either by degradation of norepinephrine, or by uptake by surrounding cells.

Receptor binding

Norepinephrine performs its actions on the target cell by binding to and activating adrenergic receptors. Unlike epinephrine, which activates all adrenergic receptors (α_1 α_2 β_1 β_2), norepinephrine activates all but β_2 receptors. The target cell expression of

different types of receptors determines the ultimate cellular effect, and thus norepinephrine has different actions on different cell types.

By indication

Norepinephrine may be used for the indications attention-deficit/hyperactivity disorder, depression and hypotension. Norepinephrine, as with other catecholamines, itself cannot cross the blood-brain barrier, so drugs such as amphetamines are necessary to increase brain levels.

Attention-deficit/hyperactivity disorder

Norepinephrine, along with dopamine, has come to be recognized as playing a large role in attention and focus. For people with ADD/ADHD, psychostimulant medications such as methylphenidate (Ritalin/Concerta), dextroamphetamine (Dexedrine), and Adderall (a mixture of dextroamphetamine and racemic amphetamine salts) are prescribed to help increase levels of norepinephrine and dopamine. Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor, and is a unique ADD/ADHD medication, as it affects only norepinephrine, rather than dopamine. As a result, Strattera has a lower abuse potential. However, it may not be as effective as the psychostimulants are with many people who have ADD/ADHD.

Depression

Differences in the norepinephrine system are implicated in depression. Serotonin-norepinephrine reuptake inhibitors are antidepressants that treat depression by increasing the amount of serotonin and norepinephrine available to postsynaptic cells in

the brain. There is some recent evidence implying that SNRIs may also increase dopamine transmission. This is because SNRIs work by inhibiting reuptake, i.e. preventing the serotonin and norepinephrine transporters from taking their respective neurotransmitters back to their storage vesicles for later use. If the norepinephrine transporter normally recycles some dopamine too, then SNRIs will also enhance dopaminergic transmission. Therefore, the antidepressant effects associated with increasing norepinephrine levels may also be partly or largely due to the concurrent increase in dopamine (particularly in the prefrontal cortex of the brain).

Tricyclic antidepressants (TCAs) increase **norepinephrine** activity as well. Most of them also increase serotonin activity, but tend to have side effects due to the nonspecific activation of histamine and acetylcholine receptors. Side effects include tiredness, increased hunger, dry mouth, and blurred vision. For this reason, they have largely been replaced by newer selective reuptake drugs such as fluoxetine (Prozac).

Hypotension

Norepinephrine is also used as a vasopressor medication (for example, brand name Levophed) for patients with critical hypotension. It is given intravenously and acts on both alpha-1 and alpha-2 adrenergic receptors to cause vasoconstriction. Its effect *in vitro* is often limited to the increasing of blood pressure through agonistic activity on alpha-1 and alpha-2 receptors and causing a resultant increase in peripheral vascular resistance. At high doses, and especially when it is combined with other vasopressors, it can lead to limb ischemia and limb death. Thus, in many nursing and paramedic schools, the phrase "Levophed'll leave them dead" is used. Norepinephrine is mainly

used to treat patients in vasodilatory shock states such as septic shock and neurogenic shock and has shown a survival benefit over dopamine.

Receptor binding modulators

Examples include alpha blockers for the α-receptors, and beta blockers for the β-receptors.

Uptake modulators

Inhibitors of uptake include:

- cocaine
- tricyclic antidepressants
    - desipramine
- phenoxybenzamine
- amphetamine

- normetanephrine
- steroid hormones
- phenoxybenzamine

Epinephrine

Epinephrine, also known as adrenaline, is an excitatory neurotransmitter. It is derived from norepinephrine and is secreted along with norepinephrine in response to fear or anger. This reaction, referred to as the “fight or flight” response, prepares the body for strenuous activity. Epinephrine regulates attentiveness, arousal, cognition, sexual

arousal, and mental focus. It is also responsible for regulating the metabolism. Epinephrine is used medicinally as a stimulant in cardiac arrest, as a vasoconstrictor in shock, as a bronchodilator and antispasmodic in bronchial asthma, and anaphylaxis.

High levels

Epinephrine levels that are too high can result in restlessness, anxiety, sleep problems, acute stress, and ADHD. Excess amounts of epinephrine can also raise the blood pressure, increase the heart rate, cause irritability and insomnia.

Low levels

Low levels of epinephrine can also contribute to weight gain, fatigue, lack of focus, decreased sexual arousal, and poor concentration.

Stress tends to deplete our store of adrenalin (epinephrine), while exercise tends to increase it.

Dopamine

Dopamine can act as both an excitatory or inhibitory neurotransmitter and functions as the brain's "feel good" neurotransmitter. It is part of the brain's reward system and creates feelings of satisfaction or pleasure when we do things we enjoy, such as eating or having sex. Drugs like cocaine, nicotine, opiates, heroin, and alcohol increase the levels of dopamine. Eating foods that taste good and having sex also stimulate an increase in dopamine levels. For this reason, many surmise that a deficient level of dopamine in the brain may be behind peoples' tendencies to use drugs, drink alcohol, smoke cigarettes, be promiscuous, gamble or overeat.

Dopamine's functions are diverse, affecting memory, motor control, and pleasure. It allows us to be alert and motivated and to feel satisfied. Dopamine is associated with positive stress states such as being in love, exercising, listening to music, and sex. Once produced, dopamine can, in turn, convert into the brain chemicals norepinephrine and epinephrine.

High levels

However, too much of a good thing can be bad for you. An increased level of dopamine in the frontal lobe of the brain contributes to the incoherent and disrupted thought processes that are characteristic of schizophrenia. Excessive levels of dopamine cause our thinking to become excited, energized, then suspicious and paranoid, as we are hyperstimulated by our environment. With low levels of dopamine, we lose the ability to focus. When dopamine levels are too high, our focus becomes narrowed and intense. High dopamine levels have been observed in patients with poor gastrointestinal function, autism, mood swings, aggression, psychosis, anxiety, hyperactivity, and children with attention disorders.

Low levels

Too little dopamine in the motor areas of the brain are responsible for Parkinson's disease, which involves uncontrollable muscle tremors. A decline in dopamine levels in the thinking areas of the brain is linked to cognitive problems (learning and memory deficits), poor concentration, difficulty initiating or completing tasks, impaired ability to "lock onto" tasks, activities, or conversations, lack of energy, lack of motivation, inability

to “feel alive”, addictions, cravings, compulsions, a loss of satisfaction in activities which previously pleased you, and slowed motor movements.

Dopamine is a hormone and neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary.

Dopamine can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, because dopamine cannot cross the blood-brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and dopa-responsive dystonia, L-DOPA (levodopa), which is the precursor of dopamine, can be given because it can cross the blood-brain barrier.

Therapeutic use

L-Dopa is used to increase dopamine levels for the treatment of Parkinson's disease and Dopa-Responsive Dystonia, since it is able to cross the blood-brain barrier, whereas dopamine itself cannot. Once levodopa has entered the central nervous system (CNS), it is metabolized to dopamine by aromatic L-amino acid decarboxylase. Pyridoxal phosphate (vitamin B6) is a required cofactor for this decarboxylation, and may be administered along with levodopa, usually as pyridoxine.

Conversion to dopamine also occurs in the peripheral tissues, i.e. outside the brain. This may be the mechanism of the adverse effects of levodopa. It is standard clinical practice to co-administer a peripheral DOPA decarboxylase inhibitor—carbidopa or benserazide—and often a catechol-O-methyl transferase (COMT) inhibitor, to prevent synthesis of dopamine in peripheral tissue. Co-administration of pyridoxine without a decarboxylase inhibitor accelerates the extracerebral decarboxylation to such an extent that it cancels out the effects of levodopa administration, a circumstance which historically caused great confusion.

Levodopa, co-administered with a peripheral DOPA decarboxylase inhibitor, has been tested as a possible treatment for restless leg syndrome (RLS) and shown "no clear picture of reduced symptoms".

Possible adverse drug reactions include:

- Hypotension, especially if the dosage is too high
- Arrhythmias, although these are uncommon
- Nausea, which is often reduced by taking the drug with food, although protein interferes with drug absorption
- Gastrointestinal bleeding
- Disturbed respiration, which is not always harmful, and can actually benefit patients with upper airway obstruction
- Hair loss
- Confusion
- Extreme emotional states, particularly anxiety, but also excessive libido
- Vivid dreams and/or fragmented sleep

- Visual and possibly auditory hallucinations
- Effects on learning; there is some evidence that it improves working memory, while impairing other complex functions
- Sleepiness and sleep attacks
- A condition similar to amphetamine psychosis.

Although there are many adverse effects associated with levodopa, particularly psychiatric ones, it has fewer than other anti-Parkinson's drugs, including anticholinergics, amantadine, and dopamine agonists.
More serious are the effects of chronic levodopa administration, which include:

- End-of-dose deterioration of function
- On/off oscillations
- Freezing during movement
- Dose failure (drug resistance)
- Dyskinesia at peak dose.
- Recent studies have demonstrated that use of L-dopa without simultanously giving proper levels of serotonin percursors depletes serotonin.

Clinicians will try to avoid these by limiting levodopa dosages as far as possible until absolutely necessary.

Toxicity

Some studies suggest a cytotoxic role in the promotion and occurrence of adverse effects associated with levodopa treatment. Other authors have attributed the observed toxic effects of levodopa in neural dopamine cell lines to enhanced formation of

quinones through increased auto-oxidation and subsequent cell death in mesencephalic cell cultures. Though levodopa is generally considered safe, some controversy surrounds use of the drug in Parkinson's Disease given some data indicating a deleterious effect on intracellular and neuronal tissue involved in the pathogenesis of the disease.

Functions in the brain

Dopamine has many functions in the brain, including important roles in behavior and cognition, motor activity, motivation and reward, inhibition of prolactin production (involved in lactation), sleep, mood, attention, and learning. Dopaminergic neurons (i.e., neurons whose primary neurotransmitter is dopamine) are present chiefly in the ventral tegmental area (VTA) of the midbrain, substantia nigra pars compacta, and arcuate nucleus of the hypothalamus.

Anatomy

Dopaminergic neurons form a neurotransmitter system which originates in substantia nigra pars compacta, ventral tegmental area (VTA), and hypothalamus. These project axons to large areas of the brain through four major pathways:

- Mesocortical pathway
- Mesolimbic pathway
- Nigrostriatal pathway
- Tuberoinfundibular pathway

This innervation explains many of the effects of activating this dopamine system. For instance, the mesolimbic pathway connects the VTA and nucleus accumbens, both are central to the brain reward system.

Cognition and frontal cortex

In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention, and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder. It has been found that D1 receptors are responsible for the cognitive-enhancing effects of dopamine. On the converse, however, anti-psychotic medications act as dopamine antagonists and are used in the treatment of positive symptoms in schizophrenia.

Regulating prolactin secretion

Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. Thus, in the context of regulating prolactin secretion, dopamine is occasionally called **prolactin-inhibiting factor** (**PIF**), **prolactin-inhibiting hormone** (**PIH**), or **prolactostatin**. Prolactin also seems to inhibit dopamine release, such as after orgasm, and is chiefly responsible for the refractory period.

Motivation and pleasure

Dopamine is commonly associated with the *pleasure system* of the brain, providing feelings of enjoyment and reinforcement to motivate a person proactively to perform certain activities. Dopamine is released (particularly in areas such as the nucleus accumbens and prefrontal cortex) by naturally rewarding experiences such as food, sex, drugs, and neutral stimuli that become associated with them. This theory is often discussed in terms of drugs such as cocaine, nicotine, and amphetamines, which seem to directly or indirectly lead to an increase of dopamine in these areas, and in relation to neurobiological theories of chemical addiction, arguing that these dopamine pathways are pathologically altered in addicted persons. Recent studies indicate that aggression may also stimulate the release of dopamine in this way.

Reuptake inhibition, expulsion

Cocaine and amphetamines inhibit the re-uptake of dopamine; however, they influence separate mechanisms of action. Cocaine is a dopamine transporter blocker that competitively inhibits dopamine uptake to increase the lifetime of dopamine and augments an overabundance of dopamine (an increase of up to 150 percent) within the parameters of the dopamine neurotransmitters.

Like cocaine, amphetamines increase the concentration of dopamine in the synaptic gap, but by a different mechanism. Amphetamines are similar in structure to dopamine, and so can enter the terminal button of the presynaptic neuron via its dopamine transporters as well as by diffusing through the neural membrane directly. By entering the presynaptic neuron, amphetamines force dopamine molecules out of their storage

vesicles and expel them into the synaptic gap by making the dopamine transporters work in reverse.

Incentive salience

Dopamine's role in experiencing pleasure has been questioned by several researchers. It has been argued that dopamine is more associated with anticipatory desire and motivation (commonly referred to as "wanting") as opposed to actual consummatory pleasure (commonly referred to as "liking").

Dopamine, learning, and reward-seeking behavior

Dopaminergic neurons of the midbrain are the main source of dopamine in the brain. Dopamine has been shown to be involved in the control of movements, the signaling of error in prediction of reward, motivation, and cognition. Cerebral dopamine depletion is the hallmark of Parkinson's disease. Other pathological states have also been associated with dopamine dysfunction, such as schizophrenia, autism, and attention deficit hyperactivity disorder in children, as well as drug abuse. Dopamine is closely associated with reward-seeking behaviors, such as approach, consumption, and addiction. Recent researches suggest that the firing of dopaminergic neurons is a motivational substance as a consequence of reward-anticipation. This hypothesis is based on the evidence that, when a reward is greater than expected, the firing of certain dopaminergic neurons increases, which consequently increases desire or motivation towards the reward.

The effects of drugs that reduce dopamine levels in humans

In humans, however, drugs that reduce dopamine activity (neuroleptics, e.g. some antipsychotics) have been shown to reduce motivation, and to cause anhedonia a.k.a. the inability to experience pleasure. Selective D2/D3 agonists pramipexole and ropinirole, used to treat Restless legs syndrome, have limited anti-anhedonic properties. Additionally, users of stimulants often have depleted dopamine levels after withdrawal from these addictive substances.

Opioid and cannabinoid transmission

Opioid and cannabinoid transmission instead of dopamine may modulate consummatory pleasure and food palatability (liking). This could explain why animals' "liking" of food is independent of brain dopamine concentration. Other consummatory pleasures, however, may be more associated with dopamine. One study found that both anticipatory and consummatory measures of sexual behavior were disrupted by DA receptor antagonists. Libido can be increased by drugs that affect dopamine, but not by drugs that affect opioid peptides or other neurotransmitters.

Sociability

Sociability is also closely tied to dopamine neurotransmission. Low D2 receptor-binding is found in people with social anxiety. Traits common to negative schizophrenia (social withdrawal, apathy, anhedonia) are thought to be related to a hyperdopaminergic state in certain areas of the brain. In instances of bipolar disorder, manic subjects can become hypersocial, as well as hypersexual. This is also credited to an increase in dopamine, because mania can be reduced by dopamine-blocking anti-psychotics.

Processing of pain

Dopamine has been demonstrated to play a role in pain processing in multiple levels of the central nervous system including the spinal cord, periaqueductal gray (PAG), thalamus, basal ganglia, insular cortex, and cingulate cortex. Accordingly, decreased levels of dopamine have been associated with painful symptoms that frequently occur in Parkinson's disease. Abnormalities in dopaminergic neurotransmission have also been demonstrated in painful clinical conditions, including burning mouth syndrome, fibromyalgia and restless legs syndrome. In general, the analgesic capacity of dopamine occurs as a result of dopamine D2 receptor activation.

Salience

Dopamine may also have a role in the salience ('noticeableness') of perceived objects and events, with potentially important stimuli such as: 1) rewarding things or 2) dangerous or threatening things seeming more noticeable or important This hypothesis argues that dopamine assists decision-making by influencing the priority, or level of desire, of such stimuli to the person concerned.

One possible mechanism of paranoid thought architecture, both in schizophrenics and in amphetamine abusers (both groups are widely hypothesized to suffer from hyperabundance of dopamine), is as follows: hyperabundance of dopamine causes widespread salience: an impression of significance attendant to statements, events, things, etc. in the immediate environment. This heightened significance can frequently be disturbing since it may have no rational basis. The individual experiencing this heightened significance may attempt to account for it, and in this way paranoid ideation begins as a theoretical structure designed to account for this disturbing impressionistic significance.

Behavior disorders

Pharmacological blockade of brain dopamine receptors increases rather than decreases drug-taking behavior. Since blocking dopamine decreases desire, the increase in drug-taking behaviour may be seen as not a chemical desire but as a deeply psychological desire to just 'feel something'.

Deficits in dopamine levels are implicated in attention-deficit hyperactivity disorder (ADHD), and stimulant medications used to successfully treat the disorder increase dopamine neurotransmitter levels, leading to decreased symptoms.

Latent inhibition and creative drive

Dopamine in the mesolimbic pathway increases general arousal and goal directed behaviors and decreases latent inhibition; all three effects increase the creative drive of idea generation. This has led to a three-factor model of creativity involving the frontal lobes, the temporal lobes, and mesolimbic dopamine.

Links to psychosis

Abnormally high dopamine action has also been strongly linked to psychosis and schizophrenia. Dopamine neurons in the mesolimbic pathway are particularly associated with these conditions. Evidence comes partly from the discovery of a class of drugs called the phenothiazines (which block D_2 dopamine receptors) that can reduce psychotic symptoms, and partly from the finding that drugs such as amphetamine and cocaine (which are known to greatly increase dopamine levels) can cause psychosis. Because of this, most modern antipsychotic medications, for example, Risperidone, are designed to block dopamine function to varying degrees.

Peripheral effects

Dopamine also has effects when administered through an IV line outside the CNS. The brand name of this preparation is known as Intropin. The effects in this form are dose dependent.

- Dosages from 2 to 5 μg/kg/min are considered the "renal dose." At this low dosage, dopamine binds D_1 receptors, dilating blood vessels, increasing blood flow to renal, mesenteric, and coronary arteries; and increasing overall renal perfusion. Dopamine therefore has a diuretic effect, potentially increasing urine output from 5 ml/kg/hr to 10 ml/kg/hr. Intermediate dosages from 5 to 10 μg/kg/min additionally have a positive inotropic and chronotropic effect through increased β_1 receptor activation. It is used in patients with shock or heart failure to increase cardiac output and blood pressure. Dopamine begins to affect the heart at the lower doses, from about 3 mcg/kg/min IV.

- High doses from 10 to 20 μg/kg/min is the "pressor" dose. This dose causes vasoconstriction, increases systemic vascular resistance, and increases blood pressure through α_1 receptor activation; but can cause the vessels in the kidneys to constrict to the point where they will become non-functional.

Serotonin (5-hydroxytryptamine**, or** 5-HT**)** is a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract of animals including humans.

Function

In the central nervous system, serotonin plays an important role as a neurotransmitter in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, appetite, and metabolism, as well as stimulating vomiting.

Serotonin has broad activities in the brain, and genetic variation in serotonin receptors and the serotonin transporter, which facilitates reuptake of serotonin into presynapses, have been implicated in neurological diseases. Drugs targeting serotonin-induced pathways are being used in the treatment of many psychiatric disorders, and one focus of clinical research is the influence of genetics on serotonin action and metabolism in psychiatric settings. In addition, serotonin is also a peripheral signal mediator. It is found extensively in the human gastrointestinal tract as about 80-90% of the body's total serotonin is found in the enterochromaffin cells in the gut.

In the blood, the major storage site is platelets, which collect serotonin for use in mediating post-injury vasoconstriction.

Recent research suggests that serotonin plays an important role in liver regeneration and acts as a mitogen (induces cell division) throughout the body.

Serotonin and SIDS

Defective signalling of serotonin in the brain may be the root cause of sudden infant death syndrome (SIDS), Italian researchers have found.

Gross anatomy

The neurons of the raphe nuclei are the principal source of 5-HT release in the brain. The raphe nuclei are neurons grouped into about nine pairs and distributed along the entire length of the brainstem, centered around the reticular formation. Axons from the neurons of the raphe nuclei form a neurotransmitter system, reaching large areas of the

brain. Axons of neurons in the *caudal* dorsal raphe nucleus terminate in the following locations:

- Deep cerebellar nuclei
- Cerebellar cortex
- Spinal cord

On the other hand, axons of neurons in the *rostral* dorsal raphe nucleus terminate in e.g.:

- Thalamus
- Striatum
- Hypothalamus
- Nucleus accumbens
- Neocortex
- Cingulate gyrus
- Cingulum
- Hippocampus
- Amygdala

Thus, activation of this serotonin system has effects on large areas of the brain.

Microanatomy

Serotonin is released from serotonergic varicosities (swellings) into the extra neuronal space, but not from synaptic terminal boutons as other neurotransmitters. Serotonin

diffuses over a relatively wide gap (>20μm) to activate 5-HT receptors located on the dendrites, cell bodies and presynaptic terminals of adjacent neurons.

Termination

Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is through the specific monoamine transporter for 5-HT, 5-HT reuptake transporter, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake including MDMA (ecstasy), amphetamine, cocaine, dextromethorphan (an antitussive), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).
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, can and do cross the blood-brain barrier. These agents are available as dietary supplements 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.

Drugs targeting the 5-HT system

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

Psychedelic drugs

The psychedelic drugs psilocin/psilocybin, DMT, mescaline, and LSD mimic the action of serotonin primarily at 5-HT_{2A} receptor. The empathogen MDMA (ecstasy) releases serotonin from synaptic vesicles of neurons.

Antidepressants

The MAOIs prevent the breakdown of monoamine neurotransmitters (including serotonin), and therefore increase concentrations of the neurotransmitter in the brain. MAOI therapy is associated with many adverse drug reactions, and patients are at risk of hypertensive emergency triggered by foods with high tyramine content and certain drugs.

Some drugs inhibit the re-uptake of serotonin, making it stay in the synapse longer. The tricyclic antidepressants (TCAs) inhibit the re-uptake of both serotonin and norepinephrine. The newer selective serotonin re-uptake inhibitors (SSRIs) have fewer side-effects and fewer interactions with other drugs.

SSRI medications have been shown to lower serotonin levels below initial level over time, despite initial increases in serotonin. This decrease in level did not rectify after the medicine was discontinued. However, the novel antidepressant Tianeptine, selective serotonin reuptake *enhancer*, has mood elevating effects. This has given evidence to the theory that serotonin is most likely used to regulate the extent or intensity of moods, and that low levels are what's associated with SSRI sexual dysfunction and/or "mood blunting" experienced by people on these medications.

Antiemetics

5-HT_3 antagonists such as ondansetron, granisetron, and tropisetron are important antiemetic agents. They are particularly important in treating the nausea and vomiting that occur during anticancer chemotherapy using cytotoxic drugs. Another application is in treatment of post-operative nausea and vomiting. Applications to the treatment of depression and other mental and psychological conditions have also been investigated with some positive results.

Pathology

If neurons that make serotonin — serotonergic neurons — are abnormal in infants, there is a risk of sudden infant death syndrome (SIDS). Low levels of serotonin may also be associated with intense spiritual experiences. Obsessive-compulsive disorder (OCD) can be a debilitating disorder with the following two anxiety-related essential features: obsessions (undesirable, recurrent, disturbing thoughts) and compulsions (repetitive or ritualized behaviors). SSRIs, and other medicines which alter serotonin levels, have been approved to be used to treat symptoms of OCD.

Serotonin syndrome

Extremely high levels of serotonin can have toxic and potentially fatal effects, causing a condition known as serotonin syndrome. In practice, such toxic levels are essentially impossible to reach through an overdose of a single anti-depressant drug, but require a combination of serotonergic agents, such as an SSRI with an MAOI. The intensity of the symptoms of serotonin syndrome vary over a wide spectrum, and the milder forms are seen even at non-toxic levels. For example, recreational doses of MDMA (ecstasy) will generally cause such symptoms but only rarely lead to true toxicity.

Serotonin

Serotonin is an inhibitory neurotransmitter involved in the regulation of mood, anxiety, libido, compulsivity, headaches, aggression, body temperature, eating disorders, social anxiety, phobias, sleep, appetite, memory and learning, cardiovascular function, muscle contraction, and endocrine regulation. Other brain neurotransmitters, such as dopamine and norepinephrine, also influence mood and arousal. However, serotonin generally has different effects.

Serotonin plays a major role in sleep and mood regulation. Proper amounts of circulating serotonin promote relaxation. Stress reduces our serotonin levels as our body uses up serotonin in an attempt to calm itself.

Low levels

Low levels of serotonin can result in depressed mood, anxiety, panic attacks, low energy, migraines, sleeping problems, obsessions or compulsions, feeling tense and irritable, craving sweets or loss of appetite, impaired memory and concentration, angry or aggressive behavior, slowed muscle movement, slowed speech, altered sleep patterns, and having a reduced interest in sex.

High levels

Excess amounts of serotonin cause sedation, a decrease in sexual drive, a sense of well-being, bliss, and of being one with the universe. However, if serotonin levels become too high they can result in Serotonin Syndrome, which can be fatal.

Serotonin Syndrome

Extremely high levels of serotonin can be toxic and possibly fatal, causing a condition known as “Serotonin Syndrome”. It is very difficult to reach these high levels by overdosing on a single antidepressant, but combining different agents known to increase levels of Serotonin, such as an SSRI and an MAOI, can result in this condition. Taking recreational Ecstasy can also have this effect, but rarely leads to toxicity. Serotonin Syndrome produces violent trembling, profuse sweating, insomnia, nausea, teeth chattering, chilling, shivering, aggressiveness, over-confidence, agitation, and malignant hyperthermia. Emergency medical treatment is required, utilizing medications that neutralize or block the action of serotonin.

Factors affecting serotonin production

Your hormones and Estrogen levels can affect serotonin levels and this may explain why some women have pre-menstrual and menopausal mood problems. Moreover, daily stress can greatly reduce your serotonin supplies.

While exercise and exposure to light may increase or stimulate serotonin levels, antidepressants can aid the brain to replenish its own supply. The most recent SSRI antidepressants, (selective serotonin reuptake inhibitors) are current drugs of choice to increase serotonin circulation.

Chronic diseases resulting from serotonin 5-HT$_{2B}$ overstimulation

In blood, serotonin stored in platelets is active wherever platelets bind, as a vasoconstrictor to stop bleeding, and also as a fibrocyte mitotic, to aid healing. Because of these effects, overdoses of serotonin, or serotonin agonist drugs, may cause acute or chronic pulmonary hypertension from pulmonary vasoconstriction, or else syndromes of

retroperitoneal fibrosis or cardiac valve fibrosis (endocardial fibrosis) from overstimulation of serotonic growth receptors on fibrocytes.

Serotonin itself may cause a syndrome of cardiac fibrosis when it is eaten in large quantities in the diet (the Matoki banana of East Africa) or when it is over-secreted by certain mid-gut carcinoid tumors. The valvular fibrosis in such cases is typically on the right side of the heart, since excess serotonin in the serum outside platelets is metabolized in the lungs, and does not reach the left circulation. Serotonergic agonist drugs in overdose in experimental animals not only cause acute (and sometimes fatal) pulmonary hypertension, but there is epidemiologic evidence that chronic use of certain of these drugs produce a chronic pulmonary hypertensive syndrome in humans. Some serotonergic agonist drugs also cause fibrosis anywhere in the body, particularly the syndrome of retroperitoneal fibrosis, as well as cardiac valve fibrosis. In the past, three groups of serotonergic drugs have been epidemiolgically linked with these syndromes. They are the serotonergic vasoconstrictive anti-migraine drugs (ergotamine and methysergide), the serotonergic appetite suppressant drugs (fenfluramine, chlorphentermine, and aminorex), and certain anti-parkinsonian dopaminergic agonists, which also stimulate serotonergic 5-HT_{2B} receptors. These include pergolide and cabergoline, but not the more dopamine-specific lisuride. As with fenfluramine, some of these drugs have been withdrawn from the market after groups taking them showed a statistical increase of one or more of the side effects described. An example is pergolide. The drug was in decreasing use since reported in 2003 to be associated with cardiac fibrosis. Two independent studies published in the New England Journal of Medicine in January 2007, implicated pergolide along with cabergoline in causing valvular heart disease. As a result of this, the FDA removed pergolide from the U.S.

market in March, 2007. (Since cabergoline is not approved in the U.S. for Parkinson's Disease, but for hyperprolactinemia, the drug remains on the market. Treatment for hyperprolactinemia requires lower doses than that for Parkinson's Disease, diminishing the risk of valvular heart disease). Because neither the amino acid L-tryptophan nor the SSRI-class antidepressants raise blood serotonin levels, they are not under suspicion to cause the syndromes described. However, since 5-hydroxytryptophan (5-HTP) does raise blood serotonin levels, it is under some of the same scrutiny as actively serotonergic drugs.

. It should be noted that serotonin, unlike its precursors 5-HTP and tryptophan, does not cross the blood–brain barrier.

Increasing serotonin levels

Serotonin levels may be increased by supplement of tryptophan. However, increasing foods rich in tryptophan (eg, meats, proteins) do not increase serotonin levels, due to competition with other amino acids. Much research has indicated that vigorous aerobic exercise improves mood, believed to be facilitated by an increase in serotonin levels. Research also suggests that eating a diet rich in whole grain carbohydrates and low in protein will increase serotonin by secreting insulin, which helps in amino acid competition. However, increasing insulin for a long period of time can sometimes onset insulin resistance, which is related to obesity, type 2 diabetes, and lower serotonin levels. It is also believed that muscles use many of the amino acids except tryptophan, allowing men to have more serotonin than women. Bright light therapy is another popular method which prevents the conversion of serotonin to melatonin. A similar effect is obtained by spending more time in natural sunlight.

Acetylcholine neurotransmitter

Acetylcholine release can be excitatory or inhibitory depending on the type of tissue and the nature of the receptor with which it interacts. Acetylcholine plays numerous roles in the nervous system. Its primary action is to stimulate the skeletal muscular system. It is the neurotransmitter used to cause voluntary muscle contraction or relaxation in the muscles.

In the brain, acetylcholine is involved in learning and memory. Acetylcholine is a small molecule transmitter that is also found in the hippocampus and prefrontal cortex. The hippocampus is responsible for memory and memory retrieval. Alzheimer's disease is associated with a lack of acetylcholine in certain regions of the brain.

The chemical compound **acetylcholine** (often abbreviated **ACh**) is a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS) in many organisms including humans. Acetylcholine is one of many neurotransmitters in the autonomic nervous system (ANS) and the only neurotransmitter used in the somatic nervous system. It is also the neurotransmitter in all autonomic ganglia.

History

Acetylcholine (ACh) was first identified in 1914 by Henry Hallett Dale for its actions on heart tissue. It was confirmed as a neurotransmitter by Otto Loewi who initially gave it the name vagusstoff because it was released from the vagus nerve. Both received the 1936 Nobel Prize in Physiology or Medicine for their work. Acetylcholine was also the first neurotransmitter to be identified.

Function

Acetylcholine has functions both in the peripheral nervous system (PNS) and in the central nervous system (CNS) as a neuromodulator. In the PNS, acetylcholine activates muscles, and is a major neurotransmitter in the autonomic nervous system. In the CNS, acetylcholine and the associated neurons form a neurotransmitter system, the cholinergic system, which tends to cause excitatory actions.

In PNS

When acetylcholine binds to acetylcholine receptors on skeletal muscle fibers, it opens ligand gated sodium channels in the cell membrane. Sodium ions then enter the muscle cell, stimulating muscle contraction. Acetylcholine, while inducing contraction of skeletal muscles, instead induces decreased contraction in cardiac muscle fibers. This distinction is attributed to differences in receptor structure between skeletal and cardiac fibers.

In CNS

In the central nervous system, ACh has a variety of effects as a neuromodulator, e.g., for plasticity and excitability. Other effects are arousal and reward. Damage to the cholinergic system in the brain has been suggested to play a role in the memory deficits associated with Alzheimer's Disease.

Myasthenia gravis

The disease myasthenia gravis, characterized by muscle weakness and fatigue, occurs when the body inappropriately produces antibodies against acetylcholine nicotinic receptors, and thus inhibits proper acetylcholine signal transmission. Over time, the

motor end plate is destroyed. Drugs that competitively inhibit acetylcholinesterase (e.g., neostigmine, physostigmine, or primarily mestinon) are effective in treating this disorder. They allow endogenously-released acetylcholine more time to interact with its respective receptor before being inactivated by acetylcholinesterase in the gap junction. Blocking, hindering or mimicking the action of acetylcholine has many uses in medicine. Drugs acting on the acetylcholine system are either agonists to the receptors, stimulating the system, or antagonists, inhibiting it.

Associated disorders

ACh Receptor Agonists are used to treat myasthenia gravis and Alzheimer's disease.

Alzheimer's disease

Since a shortage of acetylcholine in the brain has been associated with Alzheimer's disease, some drugs that inhibit acetylcholinesterase are used in the treatment of that disease.

Direct Acting

- Acetylcholine
- Bethanechol
- Carbachol
- Cevimeline
- Pilocarpine
- Suberylcholine
- Nicotine (in small doses)

Cholinesterase inhibitors

Most indirect acting ACh receptor agonists work by inhibiting the enzyme acetylcholinesterase. The resulting accumulation of acetylcholine causes continuous stimulation of the muscles, glands, and central nervous system.

They are examples of enzyme inhibitors, and increase the action of acetylcholine by delaying its degradation; some have been used as nerve agents (Sarin and VX nerve gas) or pesticides (organophosphates and the carbamates). In clinical use, they are administered to reverse the action of muscle relaxants, to treat myasthenia gravis, and to treat symptoms of Alzheimer's disease (rivastigmine, which increases cholinergic activity in the brain).

Reversible

The following substances reversibly inhibit the enzyme acetylcholinesterase (which breaks down acetylcholine), thereby increasing acetylcholine levels.

- Many medications in Alzheimer's disease
    - Donepezil
    - Galantamine
    - Rivastigmine
    - Tacrine
    - THC
- Edrophonium (differs myasthenic and cholinergic crisis)
- Neostigmine (in myasthenia gravis)
- Physostigmine (in glaucoma and anticholinergic drug overdoses)

- Pyridostigmine (in myasthenia gravis
- Carbamate insecticides (e.g., Aldicarb)
- Huperzine A

Irreversible

Semi-permanently inhibit the enzyme acetylcholinesterase.

- Echothiophate
- Isofluorophate
- Organophosphate Insecticides (Malathion, Parathion, Azinphos Methyl, Chlorpyrifos, among others)
- Organophosphate-containing nerve agents (e.g., Sarin, VX)

Victims of organophosphate-containing nerve agents commonly die of suffocation as they cannot relax their diaphragm.

Reactivation of Acetylcholine Esterase

- Pralidoxime

Antimuscarinic Agents

- Atropine
- Ipratropium
- Scopolamine
- Tiotropium

Ganglionic Blockers

- Mecamylamine
- Hexamethonium
- Nicotine (in high doses)
- Trimethaphan

Neuromuscular Blockers

- Atracurium
- Cisatracurium
- Doxacurium
- Metocurine
- Mivacurium
- Pancuronium
- Rocuronium
- Succinylcholine
- Tubocurarine
- Vecuronium
- HemiCholine

dupogimine

Release inhibitors

Botulin acts by suppressing the release of acetylcholine; where the venom from a black widow spider (alpha-latrotoxin) has the reverse effect.

- Vecuronium

- HemiCholine

dupogimine

Other / Uncategorized / Unknown

- surugatoxin
- suxamethonium

Opioid Peptides are short sequences of amino acids which mimic the effect of opiates in the brain. Opioid peptides may be produced by the body itself, for example endorphins, or be absorbed from partially digested food (casomorphins, exorphins and rubiscolins). The effect of these peptides vary, but they all resemble opiates. The opioid food peptides have lengths of typically 4-8 amino acids. The body's own opioids are generally much longer.

Brain opioid peptide systems are known to play an important role in motivation, emotion, attachment behaviour, the response to stress and pain, and the control of food intake.

Opioid food peptides

- Casomorphin (from milk)
- Gluten exorphin (from gluten)
- Gliadorphin/gluteomorphin (from gluten)
- Rubiscolin (from spinach)

Microbial opioid peptides

- Deltorphin I and II (fungal)

- Dermorphin (from an unknown microbe)

Endorphins are endogenous opioid polypeptide compounds. They are produced by the pituitary gland and the hypothalamus in vertebrates during strenuous exercise, excitement, and orgasm, and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. Endorphins work as "natural fever relievers", whose effects may be enhanced by other medications.

The term "endorphin" implies a pharmacological activity (analogous to the activity of the corticosteroid category of biochemicals) as opposed to a specific chemical formulation. It consists of two parts: *endo-* and *-orphin*; these are short forms of the words *endogenous* and *morphine,* intended to mean "a morphine like substance originating from within the body."

The term **endorphin rush** has been adopted in popular speech to refer to feelings of exhilaration brought on by pain, danger, or other forms of stress, supposedly due to the influence of endorphins. When a nerve impulse reaches the spinal cord, endorphins are released which prevent nerve cells from releasing more pain signals. Endorphins allow someone to immediately after injury feel a sense of power and control over themselves which allows them to persist with activity for an extended time.

Activity

Scientists debate whether specific activities release measurable levels of endorphins. Much of the current data comes from animal models which may not be relevant to humans. The studies that do involve humans often measure endorphin plasma levels, which do not necessarily correlate with levels in the CNS. Other studies use a blanket

opioid antagonist (usually naloxone) to indirectly measure the release of endorphins by observing the changes that occur when any endorphin activity that might be present is blocked.

Capsaicin (the active chemical in red chili peppers) also has been shown to stimulate endorphin release. Topical capsaicin has been used as a treatment for certain types of chronic pain.

Runner's high

Another widely publicized effect of endorphin production is the so-called "**runner's high**", which is said to occur when strenuous exercise takes a person over a threshold that activates endorphin production. Endorphins are released during long, continuous workouts, when the level of intensity is between moderate and high, and breathing is difficult. This also corresponds with the time that muscles use up their stored glycogen. Workouts that are most likely to produce endorphins include running, swimming, cross-country skiing, long distance rowing, bicycling, weight lifting, aerobics, or playing a sport such as soccer, basketball, rugby, lacrosse, or American football.

A study in 2003 by Georgia Tech found that runner's high might be caused by the release of another naturally produced chemical, Anandamide. Anandamide is similar to the active endocannabinoid anandamide. The authors suggest that the body produces this chemical to deal with prolonged stress and pain from strenuous exercise, similar to the original theory involving endorphins. However, the release of anandamide was not reported with the cognitive effects of the runner’s high; this suggests that anandamide release may not be significantly related to runner's high.

In 2008, researchers in Germany reported that the myth of the runner's high was not a myth but was in fact true. The participants were scanned and received psychological tests before and after a two-hour run. Data received from the study showed endorphins were produced during the exercise and were attaching themselves to areas of the brain associated with emotions (limbic and prefrontal areas).

Acupuncture

In 1999, clinical researchers reported that inserting acupuncture needles into specific body points triggers the production of endorphins. In another study, higher levels of endorphins were found in cerebrospinal fluid after patients underwent acupuncture. In addition, naloxone appeared to block acupuncture's pain-relieving effects. However, skeptics say that not all studies point to that conclusion, and that in a trial of chronic pain patients, endorphins did not produce long-lasting relief. Endorphins may be released during low levels of pain and physical stimulation when it lasts over 30 minutes. Questions remain as to whether the prolonged low level of pain stimulation as in Capsaicin, acupuncture and running or physical activity alone are the threshold that activates endorphin release.

In neuroscience, **Substance P** is a neuropeptide: a short-chain polypeptide that functions as a neurotransmitter and as a neuromodulator.It is released from the terminals of specific sensory nerves. In the central nervous system, substance P has been associated in the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity, nausea/emesis, pain and nociception.

Vomiting

The vomiting center in the brainstem contains high concentrations of substance P and its receptor, in addition to other neurotransmitters such as choline, histamine, dopamine, serotonin, and opioids. Their activation stimulates the vomiting reflex. Different emetic pathways exist, and substance P/NK1R appears to be within the final common pathway to regulate vomiting.

Substance P antagonist (SPA) aprepitant is available in the market in the treatment of chemotherapy-induced nausea / emesis.

Pain

Substance P is involved in nociception, transmitting information about tissue damage from peripheral receptors to the central nervous system to be converted to the sensation of pain. It has been theorized that it plays a part in fibromyalgia. Capsaicin has been shown to reduce the levels of Substance P probably by reducing the number of C-fibre nerves or causing these nerves to be more tolerant. Thus Capsaicin is clinically used as an analgesic and anti-inflammatory agent to relieve pain associated with arthritis and many types of neuralgia.

Stimulating cellular growth

Substance P has been shown to stimulate cellular growth in cell culture, and it was shown that Substance P could promote wound healing of non-healing ulcers in humans. It has also been shown to reverse diabetes in mice.

Vasodilation

It also has effects as a potent vasodilator. This is caused by the release of nitric oxide from the endothelium. Its release can cause hypotension.

Eczema

High levels of BDNF and Substance P have been found associated with increased itching in eczema.

Substance P in gastrointestinal infection

Entamoeba histolytica is a single-celled parasitic protozoan that infects the lower gastrointestinal tract of humans, producing symptoms of diarrhea, constipation, and abdominal pain. This protozoan was found to secrete serotonin, as well as substance P and neurotensin.

Histamine is a biogenic amine involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. It is found in virtually all animal body cells. New evidence also indicates that histamine plays an important role in chemotaxis of white blood cells. Most histamine in the body is generated in granules in mast cells or in white blood cells called basophils. Mast cells are especially numerous at sites of potential injury - the nose, mouth, and feet; internal body surfaces; and blood vessels. Non-mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter. Another important site of histamine storage and release is the enterochromaffin-like (ECL) cell of the stomach.. Histamine helps control the sleep-wake cycle and promotes the release of epinephrine and norepinephrine.

High levels

High histamine levels have been linked to obsessive-compulsive tendencies, depression, and headaches.

Low levels

Low histamine levels can contribute to paranoia, low libido, fatigue, and medication sensitivities.

The most important pathophysiologic mechanism of mast cell and basophil histamine release is immunologic. These cells, if sensitized by IgE antibodies attached to their membranes, degranulate when exposed to the appropriate antigen. Certain amines and alkaloids, including such drugs as morphine, and curare alkaloids, can displace histamine in granules and cause its release. Antibiotics like polymyxin are also found to be stimulating histamine release.

Mechanism of action

Histamine exerts its actions by combining with specific cellular histamine receptors. The four histamine receptors that have been discovered are designated H1 through H4.

Type	Location	Function
H_1 histamine receptor	Found on smooth muscle, endothelium, and central nervous system tissue	Causes vasodilation, bronchoconstriction, smooth muscle activation, separation of endothelial cells (responsible for hives), and pain and itching due to insect stings; the primary receptors involved in allergic rhinitis symptoms

		and motion sickness.
H_2 histamine receptor	Located on parietal cells	Primarily stimulate gastric acid secretion
H_3 histamine receptor	-	Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin
H_4 histamine receptor	Found primarily in the basophils and in the bone marrow. It is also found on thymus, small intestine, spleen, and colon.	Unknown physiological role.

Sleep regulation

Histamine is released as a neurotransmitter. The cell bodies of neurons which release histamine are found in the posterior hypothalamus, in various tuberomammillary nuclei. From here, these histaminergic neurons project throughout the brain, to the cortex through the medial forebrain bundle. Histaminergic action is known to modulate sleep. Classically, antihistamines (H1 histamine receptor antagonists) produce sleep. Likewise, destruction of histamine releasing neurons, or inhibition of histamine synthesis leads to an inability to maintain vigilance. Finally, H3 receptor antagonists (which stimulate histamine release) increase wakefulness.

It has been shown that histaminergic cells have the most wakefulness-related firing pattern of any neuronal type thus far recorded. They fire rapidly during waking, fire more slowly during periods of relaxation/tiredness and completely stop firing during REM and NREM (non-REM) sleep. Histaminergic cells can be recorded firing just before an animal shows signs of waking.

Sexual response

Research has shown that histamine is released as part of the human orgasm from mast cells in the genitals. If this response is lacking this may be a sign of histapenia (histamine deficiency). In such cases, a doctor may prescribe diet supplements with folic acid and niacin (which used in conjunction can increase blood histamine levels and histamine release), or L-histidine.

Schizophrenia

It has been found that about half the patients classified as suffering from schizophrenia have low histamine levels in the blood. This may be because of antipsychotics that have unwanted effect on histamine, such as quetiapine. Although, in these cases, as histamine levels were increased, their health improved.

Disorders

As an integral part of the immune system, histamine may be involved in immune system disorders and allergies.

Nomenclature

"H substance" or "substance H" are occasionally used in medical literature for histamine or a hypothetical histamine-like diffusible substance released in allergic reactions of skin and in the responses of tissue to inflammation.

Melatonin is a naturally occurring hormone found in most animals, including humans, and some other living organisms, including algae. Circulating levels vary in a daily cycle,

and melatonin is important in the regulation of the circadian rhythms of several biological functions. Many biological effects of melatonin are produced through activation of melatonin receptors, while others are due to its role as a pervasive and powerful antioxidant with a particular role in the protection of nuclear and mitochondrial DNA. The use of melatonin as a drug can entrain (synchronize) the circadian clock to environmental cycles and can have beneficial effects for treatment of certain insomnias. Its therapeutic potential may be limited by its short biological half-life, poor bioavailability, and the fact that it has numerous non-specific actions. In recent studies though, prolonged release melatonin has shown good results in treating insomnia.

In higher animals and humans, melatonin is produced by pinealocytes in the pineal gland (located in the brain) and also by the retina, lens and GI tract..

Melatonin may also be produced by a variety of peripheral cells such as bone marrow cells, lymphocytes and epithelial cells. Usually, the melatonin concentration in these cells is much higher than that found in the blood but it does not seem to be regulated by the photoperiod.

Distribution

Melatonin produced in the pineal gland acts as an endocrine hormone since it is released into the blood. By contrast, melatonin produced by the retina and the gastrointestinal (GI) tract acts as a paracrine hormone.

Circadian rhythm

In humans, melatonin is produced by the pineal gland, a gland about the size of a pea, located in the center of the brain. The melatonin signal forms part of the system that regulates the circadian cycle by chemically causing drowsiness and lowering the body temperature, but it is the central nervous system (more specifically, the suprachiasmatic nucleus) that controls the daily cycle in most components of the paracrine and endocrine systems rather than the melatonin signal (as was once postulated).

Light dependence

Production of melatonin by the pineal gland is inhibited by light and permitted by darkness. For this reason melatonin has been called "the hormone of darkness" and its onset each evening is called the Dim-Light Melatonin Onset (DLMO). Secretion of melatonin as well as its level in the blood, peaks in the middle of the night, and gradually falls during the second half of the night, with normal variations in timing according to an individual's chronotype.

Until recent history, humans in temperate climates were exposed to only about six hours of daylight in the winter. In the modern world, artificial lighting reduces darkness exposure to typically eight or fewer hours per day all year round. Even low light levels inhibit melatonin production to some extent, but over-illumination can create significant reduction in melatonin production. Since it is principally blue light that suppresses melatonin, wearing glasses that block blue light in the hours before bedtime may avoid melatonin loss. Use of blue-blocking goggles the last hours before bedtime has also been advised for people who need to adjust to an earlier bedtime, as melatonin promotes sleepiness.

Melatonin levels at night are reduced to 50% by exposure to a low-level incandescent bulb for only 39 minutes, and it has been shown that women with the brightest bathrooms have an increased risk for breast cancer.

Reduced melatonin production has been proposed as a likely factor in the significantly higher cancer rates in night workers, and the effect of modern lighting practice, including light pollution, on endogenous melatonin has been proposed as a contributory factor to the larger overall incidence of some cancers in the developed world.

Antioxidant

Besides its primary function as synchronizer of the biological clock, melatonin may exert a powerful antioxidant activity. In many lower life forms, it serves only this purpose. Melatonin is an antioxidant that easily can cross cell membranes and the blood-brain barrier.. Melatonin's antioxidant activity may reduce damage caused by some types of Parkinson's disease, may play a role in preventing cardiac arrhythmia and may increase longevity; it has been shown to increase the average life span of mice by 20% in some studies.

Immune system

While it is clear that melatonin interacts with the immune system, the details of those interactions are unclear. There have been few trials designed to judge the effectiveness of melatonin in disease treatment. Most existing data are based on small, incomplete clinical trials.. In preclinical studies, melatonin may enhance cytokine production, and by doing this counteract acquired immunodeficiences. Some studies also suggest that melatonin might be useful fighting infectious disease including viral and bacterial

infections. When taken in conjunction with calcium, it is an immunostimulator and is used as an adjuvant in some clinical protocols; conversely, the increased immune system activity may aggravate autoimmune disorders. In rheumatoid arthritis patients, melatonin production has been found increased when compared to age-matched healthy controls.

Dreaming

Many supplemental melatonin users have reported an increase in vivid dreaming. Extremely high doses of melatonin (50mg) dramatically increased REM sleep time and dream activity in both narcoleptics and those without narcolepsy. However, one factor that may influence this perception is that many over-the-counter melatonin tablets also include Vitamin B6 (pyroxidine), which is also known to be capable of producing vivid dreams. Many psychoactive drugs, such as LSD, increase melatonin synthesis. It has been suggested that nonpolar (lipid-soluble) indolic hallucinogenic drugs emulate melatonin activity in the awakened state and that both act on the same areas of the brain. It has been suggested that psychotropic drugs be readmitted in the field of scientific inquiry and therapy. If so, melatonin may be prioritized for research in this reemerging field of psychiatry.

Autism

Individuals with autism spectrum disorders (ASD) may have lower than normal levels of melatonin. A 2008 study found that unaffected parents of individuals with ASD also have lower melatonin levels, and that the deficits were associated with low activity of the ASMT gene, which encodes the last enzyme of melatonin synthesis.

Current and potential medical indications

Melatonin has been studied for the treatment of cancer, immune disorders, cardiovascular diseases, depression, seasonal affective disorder (SAD), circadian rhythm sleep disorders and sexual dysfunction.. Basic research indicates that melatonin may play a significant role in modulating the effects of drugs of abuse such as cocaine.

Learning, memory and Alzheimer's

The first published evidence that melatonin may be useful in Alzheimer's disease was the demonstration that this neurohormone prevents neuronal death caused by exposure to the amyloid beta protein, a neurotoxic substance that accumulates in the brains of patients with the disorder. Melatonin also inhibits the aggregation of the amyloid beta protein into neurotoxic microaggregates which seem to underlie the neurotoxicity of this protein, causing death of neurons and formation of neurofibrillary tangles, the other neuropathological landmark of Alzheimer's disease.

These same neurofibrillary tangles can be found in the hypothalamus in patients with Alzheimer's, adversely affecting their bodies' production of melatonin. Those Alzheimer's patients with this specific affliction often show heightened afternoon agitation, called *sundowning*, which has been shown in many studies to be effectively treated with melatonin supplements in the evening.

ADHD

Research shows that after melatonin is administered to ADHD patients, the time needed to fall asleep is significantly reduced. Furthermore, the effects of the melatonin after three months showed no change from its effects after one week of use.

Fertility

Recent research has concluded that melatonin supplementation in perimenopausal women produces a highly significant improvement in thyroid function and gonadotropin levels, as well as restoring fertility and menstruation and preventing the depression associated with the menopause. However, at the same time, some resources warn women trying to conceive not to take a melatonin supplement.

Headaches

Several clinical studies indicate that supplementation with melatonin is an effective preventive treatment for migraines and cluster headaches.

Mental disorders

Melatonin has been shown to be effective in treating one form of depression, seasonal affective disorder, and is being considered for bipolar and other disorders where circadian disturbances are involved.

Other

Some studies have shown that melatonin has potential for use in the treatment of various forms of cancer, HIV, and other viral diseases; however, further testing is necessary to confirm this. Melatonin is involved in the regulation of body weight, and may be helpful in treating obesity (especially when combined with calcium).
The primary motivation for the use of melatonin as a supplement may be as a natural aid to better sleep. Incidental benefits to health and well-being may accumulate, due to

melatonin's role as an antioxidant and its stimulation of the immune system and several components of the endocrine system.

Studies from Massachusetts Institute of Technology have said that melatonin pills sold as supplements contain three to ten times the amount needed to produce the desirable physiologic nocturnal blood melatonin level for enhancement of sleep. Dosages are designed to raise melatonin levels for several hours to enhance quality of sleep, but some studies suggest that smaller doses (for example 0.3 mg as opposed to 3 mg) are just as effective at improving sleep quality. Large doses of melatonin can even be counterproductive; in one of their subjects, 0.5 mg of melatonin was effective while 20 mg was not.

Individuals who experience orthostatic intolerance, a cardiovascular condition that results in reduced blood pressure and blood flow to the brain when a person stands, may experience a worsening of symptoms when taking melatonin supplements, a study at Penn State College of Medicine's Milton S. Hershey Medical Center suggests. Melatonin can exacerbate symptoms by reducing nerve activity in those who experience the condition, the study found.

GABA

GABA is the abbreviation for Gamma-aminobutyric acid. GABA is the major inhibitory neurotransmitter in the central nervous system and plays a major role in regulating anxiety and reducing stress. GABA has a calming effect on the brain and helps the brain filter out “background noise”. It improves mental focus while calming the nerves. GABA acts like a brake to the excitatory neurotransmitters, which can cause anxiety if the system is overstimulated. It regulates norepinephrine, adrenaline, dopamine, and

serotonin and is a significant mood modulator. The primary function of GABA is to prevent overstimulation.

High levels

Excessive GABA levels result in excessive relaxation and sedation, to the point that normal reactions are impaired.

Low levels

Insufficient GABA results in the brain being overstimulated. People with too little GABA tend to suffer from anxiety disorders and may have a predisposition to alcoholism. Low levels of GABA are associated with bipolar disorder, mania, poor impulse control, epilepsy, and seizure disorders. Since proper GABA functioning is required to induce relaxation, analgesia, and sleep, dysfunction of the GABA system is implicated in the pathophysiology of several neuropsychiatric disorders, including anxiety and depression. In 1990, a study linked lowered levels of GABA to a predisposition to alcoholism. When men of alcoholic fathers with low GABA drank a glass of vodka, their GABA levels rose to the equivalent of the control group.

Taurine

Taurine is an inhibitory neurotransmitter involved in neuromodulatory and neuroprotective actions. Supplementing with taurine can increase GABA function. By helping GABA function, taurine is an important neuromodulator for prevention of anxiety. The relevance of GABA support is to prevent overstimulation due to high levels of excitatory amino acids, such as norepinephrine and epinephrine. Therefore, taurine

and GABA constitute an important protective mechanism against excessive excitatory neurotransmitters.

Glutamate

Glutamate is a major excitatory neurotransmitter that is associated with learning and memory. It is also thought to be associated with Alzheimer's disease. Glutamate has been implicated in epileptic seizures and is a key molecule in cellular metabolism. It is also one of the major food components that provides flavor. Monosodium glutamate is a sodium salt of glutamate.

High levels

Excessive levels of glutamate are toxic to neurons and have been implicated in the development of neurological disorders such as amyotrophic lateral sclerosis and Huntington's chorea, peripheral neuropathies, chronic pain, schizophrenia, stroke, and Parkinson's disease.

Low levels

Insufficient levels of glutamate may play a role in impaired memory and learning.

Monoamines

This is a class of neurotransmitters, which includes serotonin, norepinephrine, GABA, glutamate, and dopamine. The monoamine hypothesis holds that mood disorders are caused by depletion in the levels of one or more of these neurotransmitters.

PEA

PEA is an excitatory neurotransmitter made from phenylalanine. It is important in focus and concentration.

High levels

Elevated PEA levels are observed in individuals experiencing "mind racing", sleep problems, anxiety, and schizophrenia.

Low levels

Low PEA is associated with difficulty paying attention or thinking clearly, and in depression

Conclusion

Neurotransmitters have many roles within the body that extend beyond the central nervous system. Understanding how the neurotransmission systems of the body operate, leads to greater understanding regarding the affects of drugs and medications upon the body and the manifestations of impaired neuroregulation.

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