ejpmr, 2022, 9(5), 526-576

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A BRIEF DISCUSSION ABOUT NEUROHORMONES

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Article Received on 11/03/2022 **Article Revised on 21/04/2022** **Article Accepted on 01/05/2022**

ABSTRACT

A **neurohormone** is any hormone produced and released by neuroendocrine cells (also called neurosecretory cells) into the blood. By definition of being hormones, they are secreted into the circulation for systemic effect, but they can also have a role of neurotransmitter or other roles such as autocrine (self) or paracrine (local) messenger. The hypothalamus releasing hormones are neurohypophysial hormones in specialized hypothalamic neurons which extend to the median eminence and posterior pituitary. The adrenal medulla produces adrenomedullary hormones in chromaffin cells, cells which are very similar in structure to post-synaptic sympathetic neurons, even though they are not neurons they are derivatives of the neural crest. Enterochromaffin and enterochromaffin-like cells, both being enteroendocrine cells, are also considered neuroendocrine cells due to their structural and functional similarity to chromaffin cells, although they are not derivatives of the neural crest. Other neuroendocrine cells are scattered throughout the body. Neurohormones are released by neurosecretory cells.

KEYWORDS: Oxytocin, Vassopressin, Neural Secretion, Metabolism, Pressure Management.

Releasing hormones also known as hypophysiotropic or hypothalamic hormones are synthesized by different kinds of specialized neurons in the hypothalamus. They are then transported along neuronal axons to their axon terminals forming the bulk of the median eminence, where they are stored and released into the hypophyseal portal system. They then rapidly reach the anterior pituitary where they exert their hormonal action. The residual hormones pass into the systemic circulation where they are diluted, degraded and have comparatively little effects. The synthesis, control, and release of those hormones is co-regulated by hormonal, local and synaptic signals (neurotransmitters). The neurons secreting various hormones have been found to discharge impulses in burst, causing a pulsatile release which is more efficient than a continuous release. Hypophysiotropic hormones include.

Thyrotropin-releasing hormone

Thyrotropin-releasing hormone (**TRH**) is a hypophysiotropic hormone produced by neurons in the hypothalamus that stimulates the release of thyroid-stimulating hormone (TSH) and prolactin from the anterior pituitary.

TRH has been used clinically for the treatment of spinocerebellar degeneration and disturbance of consciousness in humans. Its pharmaceutical form is called **protirelin** (INN) (/proʊˈtaɪrɪlɪn/).

Synthesis and Release

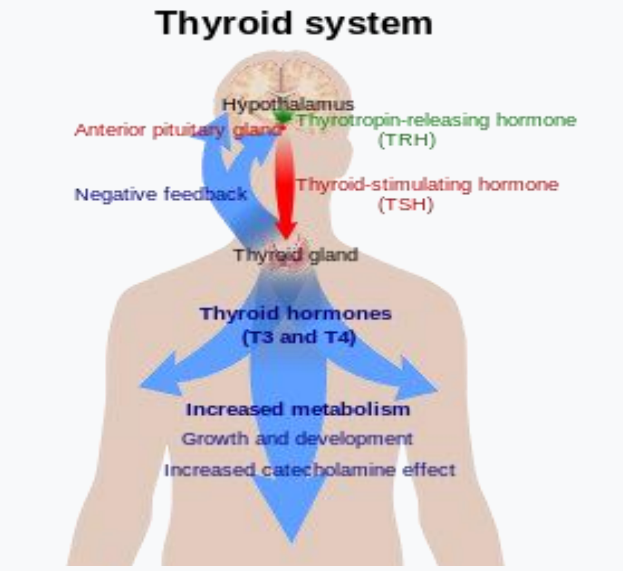

Figure-1: The hypothalamic-pituitary-thyroid axis. TRH can be seen in green.

TRH is synthesized within parvocellular neurons of the paraventricular nucleus of the hypothalamus. It is translated as a 242-amino acid precursor polypeptide that contains 6 copies of the sequence -Gln-His-Pro-Gly-, flanked by Lys-Arg or Arg-Arg sequences.

To produce the mature form, a series of enzymes are required. First, a protease cleaves to the C-terminal side of the flanking Lys-Arg or Arg-Arg. Second, a carboxypeptidase removes the Lys/Arg residues leaving Gly as the C-terminal residue. Then, this Gly is converted into an amide residue by a series of enzymes collectively known as peptidylglycine-alpha-amidating monooxygenase. Concurrently with these processing steps, the N-terminal Gln (glutamine) is converted into pyroglutamate (a cyclic residue). These multiple steps produce 6 copies of the mature TRH molecule per precursor molecule for human TRH (5 for mouse TRH).

TRH synthesizing neurons of the paraventricular nucleus project to the medial portion of the external layer of the median eminence. Following secretion at the median eminence, TRH travels to the anterior pituitary via the hypophyseal portal system where it binds to the TRH receptor stimulating the release of thyroid-stimulating hormone from thyrotropes and prolactin from lactotropes. The half-life of TRH in the blood is approximately 6 minutes.

Structure

TRH is a tripeptide, with an amino acid sequence of pyroglutamyl-histidyl-proline amide.

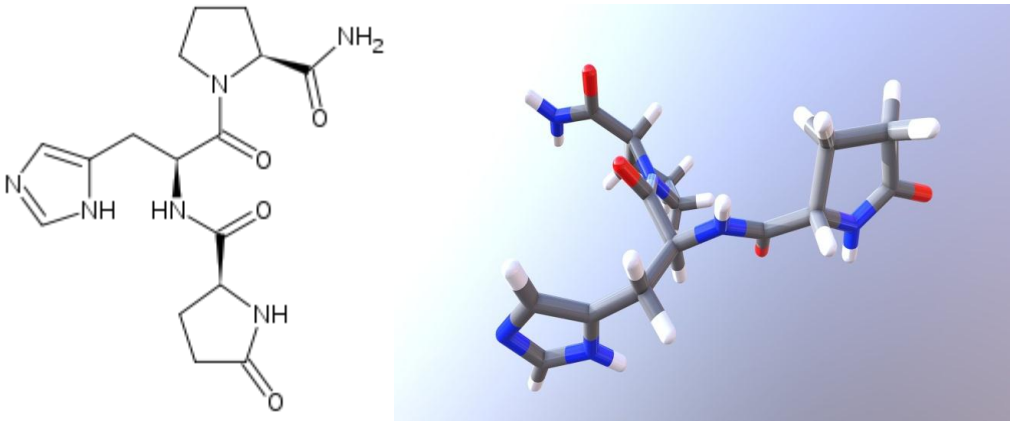

Figure-2: TRH chemical and 3D structure.

Clinical significance

TRH is used clinically by intravenous injection (brand name Relefact TRH) to test the response of the anterior pituitary gland; this procedure is known as a TRH test. This is done as diagnostic test of thyroid disorders such as secondary hypothyroidism and in acromegaly.

TRH has anti-depressant and anti-suicidal properties, and in 2012 the U.S. Army awarded a research grant to develop a TRH nasal spray in order to prevent suicide amongst its ranks.

TRH has been shown in mice to be an anti-aging agent with a broad spectrum of activities that, because of their actions, suggest that TRH has a fundamental role in the regulation of metabolic and hormonal functions.

Side effects

Side effects after intravenous TRH administration are minimal. Nausea, flushing, urinary urgency, and mild rise in blood pressure have been reported. After intrathecal administration, shaking, sweating, shivering, restlessness, and mild rise in blood pressure were observed.

Corticotropin-releasing hormone

Corticotropin-releasing hormone (**CRH**) (also known as **corticotropin-releasing factor** (**CRF**) or **corticoliberin**; corticotropin may also be spelled **corticotrophin**) is a peptide hormone involved in the stress response. It is a releasing hormone that belongs to corticotropin-releasing factor family. In humans, it is encoded by the *CRH* gene. Its main function is the stimulation of the pituitary synthesis of ACTH, as part of the HPA Axis.[1]

Corticotropin-releasing hormone (CRH) is a 41-amino acid peptide derived from a 196-amino acid preprohormone. CRH is secreted by the paraventricular nucleus (PVN) of the hypothalamus in response to stress. Increased CRH production has been observed to be associated with Alzheimer's disease and major depression, and autosomal recessive hypothalamic corticotropin deficiency has multiple and potentially fatal metabolic consequences including hypoglycaemia.

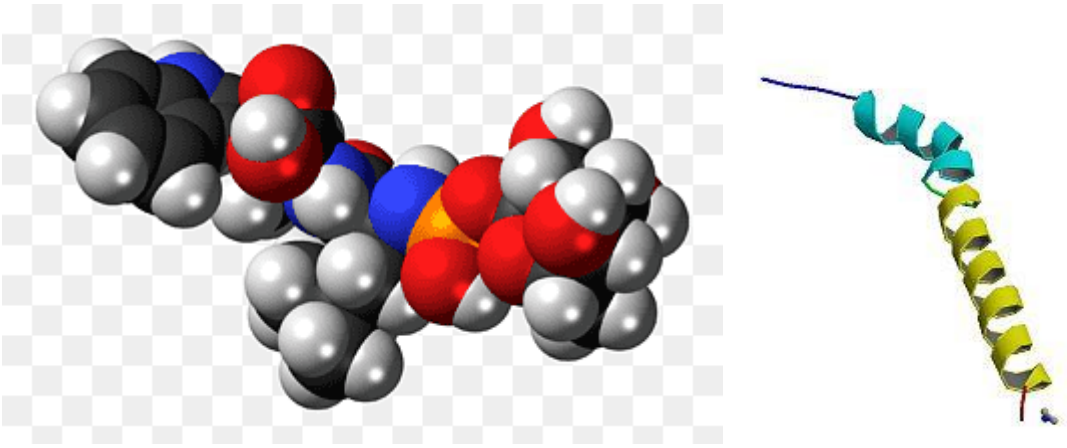

Figure-3: CRH Structure.

In addition to being produced in the hypothalamus, CRH is also synthesized in peripheral tissues, such as T lymphocytes, and is highly expressed in the placenta. In the placenta, CRH is a marker that determines the length of gestation and the timing of parturition and delivery. A rapid increase in circulating levels of CRH occurs at the onset of parturition, suggesting that, in addition to its metabolic functions, CRH may act as a trigger for parturition.

A recombinant version for diagnostics is called corticorelin (INN).

Hormonal actions

CRH is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRH to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete adrenocorticotropic hormone (ACTH) and other biologically-active substances (β-endorphin). ACTH stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

In the short term, CRH can suppress appetite, increase subjective feelings of anxiety, and perform other functions like boosting attention. Although the distal action of CRH is immunosuppressant via the action of cortisol, CRH itself can actually heighten inflammation, a process being investigated in multiple sclerosis research.

Psychopharmacology

The CRH-1 receptor antagonist pexacerfont is currently under investigation for the treatment of generalized anxiety disorder. Another CRH-1 antagonist antalarmin has been researched in animal studies for the treatment of anxiety, depression and other conditions, but no human trials with this compound have been carried out.

Also, abnormally high levels of CRH have been found in the cerebrospinal fluid of people who have committed suicide.

Recent research has linked the activation of the CRH1 receptor with the euphoric feelings that accompany alcohol consumption. A CRH1 receptor antagonist developed by Pfizer, CP-154,526 is under investigation for the potential treatment of alcoholism.

Alpha-helical CRH-(9–41) acts as a CRH antagonist.

Role in parturition

CRH is also synthesized by the placenta and seems to determine the duration of pregnancy.

Levels rise towards the end of pregnancy just before birth and current theory suggests three roles of CRH in parturition

- Increases levels of dehydroepiandrosterone (DHEA) directly by action on the fetal adrenal gland, and indirectly via the mother's pituitary gland. DHEA has a role in preparing for and stimulating cervical contractions.
- Increases prostaglandin availability in uteroplacental tissues. Prostaglandins activate cervical contractions.
- Prior to parturition it may have a role inhibiting contractions, through increasing cAMP levels in the myometrium.
- In culture, trophoblast CRH is inhibited by progesterone, which remains high throughout pregnancy. Its release is stimulated by glucocorticoids and catecholamines, which increase prior to parturition lifting this progesterone block.

Structure

The 41-amino acid sequence of CRH was first discovered in sheep by Vale *et al.* in 1981. Its full sequence is:

- SQEPPISLDLTFHLLREVLEMTKADQLAQQAH SNRKLLDIA

The rat and human peptides are identical and differ from the ovine sequence only by 7 amino acids.

- S**E**EPPISLDLTFHLLREVLEM**AR**A**E**QLAQQAH SNRKL**ME**I**I**

Role in non-mammalian vertebrates

In mammals, studies suggest that CRH has no significant thyrotropic effect. However, in representatives of all non-mammalian vertebrates, it has been found that, in addition to its corticotropic function, CRH has a potent thyrotropic function, acting with TRH to control the thyroid axis (TRH has been found to be less potent than CRH in some species).

Interactions

Corticotropin-releasing hormone has been shown to interact with its receptors corticotropin-releasing hormone receptor 1 (CRFR1) and corticotropin-releasing hormone 2 (CRFR2) in order to induce its effects. Injection of CRF into the rodent paraventricular nucleus of the hypothalamus (PVN) can increase CRFR1 expression, with increased expression leading to depression-like behaviors. Sex differences have also been observed with respect to both CRF and the receptors that it interacts with. CRFR1 has been shown to exist at higher levels in the female nucleus accumbens, olfactory tubercle, and rostral anteroventral periventricular nucleus (AVPV) when compared to males, while male voles show increased levels of CRFR2 in the bed nucleus of the stria terminalis compared to females.

Growth hormone–releasing hormone

Growth hormone–releasing hormone (**GHRH**), also known as **somatocrinin** or by several other names in its endogenous forms and as somatorelin (INN) in its pharmaceutical form, is a releasing hormone of growth hormone (GH). It is a 44-amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus.

GHRH first appears in the human hypothalamus between 18 and 29 weeks of gestation, which corresponds to the start of production of growth hormone and other somatotropes in foetuses.

Nomenclature

- **Endogenous**
  - somatocrinin
  - somatoliberin
  - growth hormone–releasing hormone (GHRH or GH-RH; HGNC symbol is GHRH)
  - growth hormone–releasing factor (GHRF or GRF)
  - somatotropin-releasing hormone (SRH)
  - somatotropin-releasing factor (SRF)
- **Pharmaceutical**
  - somatorelin (INN)

Origin

GHRH is released from neurosecretory nerve terminals of these arcuate neurons, and is carried by the hypothalamo-hypophyseal portal system to the anterior pituitary gland, where it stimulates growth hormone (GH) secretion by stimulating the growth hormone-releasing hormone receptor. GHRH is released in a pulsatile manner, stimulating similar pulsatile release of GH. In addition, GHRH also promotes slow-wave sleep directly. Growth hormone is required for normal postnatal growth, bone growth, regulatory effects on protein, carbohydrate, and lipid metabolism.

Effect

GHRH stimulates GH production and release by binding to the GHRH receptor (GHRHR) on cells in the anterior pituitary.

Receptor

The GHRHR is a member of the secretin family of G protein-coupled receptors, and is located on chromosome 7 in humans. This protein is transmembranous with seven folds, and its molecular weight is approximately 44 kD.

Signal transduction

GHRH binding to GHRHR results in increased GH production mainly by the cAMP-dependent pathway, but also by the phospholipase C pathway (IP_3/DAG pathway), and other minor pathways.

The cAMP-dependent pathway is initiated by the binding of GHRH to its receptor, causing receptor conformation that activates G_s alpha subunit of the closely associated G-Protein complex on the intracellular side. This results in stimulation of membrane-bound adenylyl cyclase and increased intracellular cyclic adenosine monophosphate (cAMP). cAMP binds to and activates the regulatory subunits of protein kinase A (PKA), allowing the free catalytic subunits to translocate to the nucleus and phosphorylate the transcription factor cAMP response element-binding protein (CREB). Phosphorylated CREB, together with its coactivators, p300 and CREB-binding protein (CBP) enhances the transcription of GH by binding to CREs cAMP-response elements in the promoter region of the GH gene. It also increases transcription of the GHRHR gene, providing positive feedback.

In the phospholipase C pathway, GHRH stimulates phospholipase C (PLC) through the βγ-complex of heterotrimeric G-proteins. PLC activation produces both diacylglycerol (DAG) and inositol triphosphate (IP_3), the latter leading to release of intracellular Ca^{2+} from the endoplasmic reticulum, increasing cytosolic Ca^{2+} concentration, resulting in vesicle fusion and release of secretory vesicles containing premade growth hormone.

Some Ca^{2+} influx is also a direct action of cAMP, which is distinct from the usual *cAMP-dependent pathway* of activating *protein kinase A*.

Activation of GHRHRs by GHRH also conveys opening of Na+ channels by phosphatidylinositol 4,5-bisphosphate, causing cell depolarization. The resultant change in the intracellular voltage opens a voltage-dependent calcium channel, resulting in vesicle fusion and release of GH.

Relationship of GHRH and somatostatin

The actions of GHRH are opposed by somatostatin (growth-hormone-inhibiting hormone). Somatostatin is released from neurosecretory nerve terminals of periventricular somatostatin neurons, and is carried by the hypothalamo-hypophyseal portal circulation to the anterior pituitary where it inhibits GH secretion. Somatostatin and GHRH are secreted in alternation, giving rise to the markedly pulsatile secretion of GH.

Other functions

GHRH expression has been demonstrated in peripheral cells and tissues outside its main site in the hypothalamus, for example, in the pancreas, epithelial mucosa of the gastrointestinal tract and, pathologically, in tumour cells.

Sequence

The amino acid sequence (44 long) of human GHRH is:
HO - Tyr - Ala - Asp - Ala - Ile - Phe - Thr - Asn - Ser - Tyr - Arg - Lys - Val - Leu - Gly - Gln - Leu - Ser - Ala - Arg - Lys - Leu - Leu - Gln - Asp - Ile - Met - Ser - Arg - Gln - Gln - Gly - Glu - Ser - Asn - Gln - Glu - Arg - Gly - Ala - Arg - Ala - Arg - Leu - NH_2

Analogs

Growth-hormone-releasing hormone is the lead compound for a number of structural and functional analogs, such as Pro-Pro-hGHRH(1-44)-Gly-Gly-Cys, CJC-1293 and CJC-1295.

Many GHRH analogs remain primarily research chemicals, although some have specific applications. Sermorelin, a functional peptide fragment of GHRH, has been used in the diagnosis of deficiencies in growth hormone secretion. Tesamorelin, under the trade name Egrifta, received U.S. Food and Drug Administration approval in 2010 for the treatment of lipodystrophy in HIV patients under highly active antiretroviral therapy, and, in 2011, was investigated for effects on certain cognitive tests in the elderly. As a category, the use of GHRH analogs by professional athletes may be prohibited by restrictions on doping in sport because they act as growth hormone secretagogues.

Somatostatin

Somatostatin, also known as **growth hormone-inhibiting hormone** (**GHIH**) or by several other names, is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Somatostatin inhibits insulin and glucagon secretion.

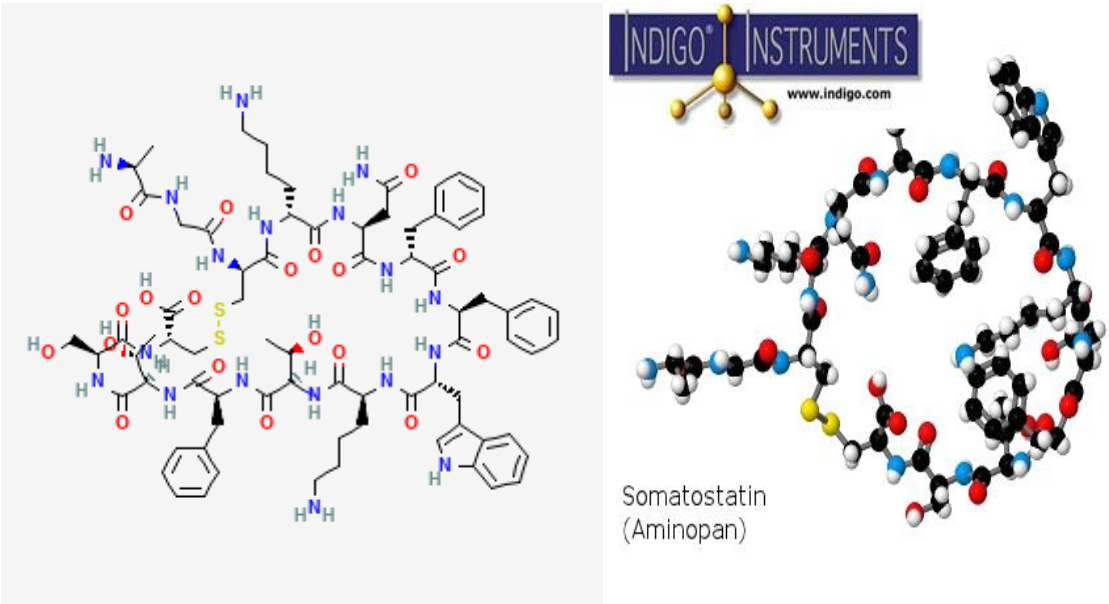

Figure-4: Somatostatin Structures.

Somatostatin has two active forms produced by the alternative cleavage of a single preproprotein: one consisting of 14 amino acids (shown in info box to right), the other consisting of 28 amino acids.

Among the vertebrates, there exist six different somatostatin genes that have been named *SS1*, *SS2*, *SS3*, *SS4*, *SS5* and *SS6*. Zebrafish have all six. The six different genes, along with the five different somatostatin receptors, allow somatostatin to possess a large range of functions. Humans have only one somatostatin gene, *SST*.

Nomenclature

Synonyms of "somatostatin" include

- Growth hormone–inhibiting hormone (GHIH)
- Growth hormone release–inhibiting hormone (GHRIH)
- Somatotropin release–inhibiting factor (SRIF)
- Somatotropin release–inhibiting hormone (SRIH)

Production

Digestive system

Somatostatin is secreted by delta cells at several locations in the digestive system, namely the pyloric antrum, the duodenum and the pancreatic islets.

Somatostatin released in the pyloric antrum travels via the portal venous system to the heart, then enters the systemic circulation to reach the locations where it will exert its inhibitory effects. In addition, somatostatin release from delta cells can act in a paracrine manner.

In the stomach, somatostatin acts directly on the acid-producing parietal cells via a G-protein coupled receptor (which inhibits adenylate cyclase, thus effectively antagonising the stimulatory effect of histamine) to reduce acid secretion. Somatostatin can also indirectly decrease stomach acid production by preventing the release of other hormones, including gastrin and histamine which effectively slows down the digestive process.

Brain

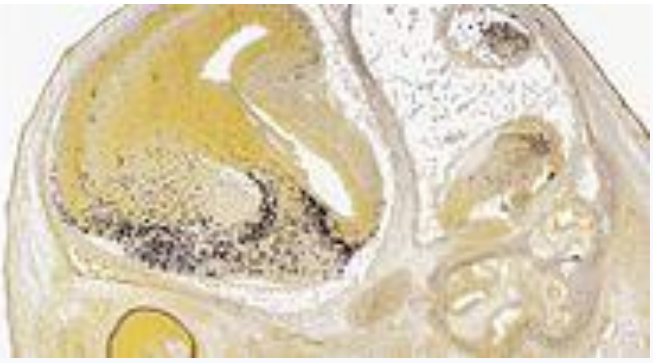

Figure-5: Sst is expressed in interneurons in the telencephalon of the embryonic day 15.5 mouse. Allen Brain Atlases.

Figure-6: Sst expression in the adult mouse. Allen Brain Atlases

Somatostatin is produced by neuroendocrine neurons of the ventromedial nucleus of the hypothalamus. These neurons project to the median eminence, where somatostatin is released from neurosecretory nerve endings into the hypothalamohypophysial system through neuron axons. Somatostatin is then carried to the anterior pituitary gland, where it inhibits the secretion of growth hormone from somatotrope cells. The somatostatin neurons in the periventricular nucleus mediate negative feedback effects of growth hormone on its own release; the somatostatin neurons respond to high circulating concentrations of growth hormone and somatomedins by increasing the release of somatostatin, so reducing the rate of secretion of growth hormone.

Somatostatin is also produced by several other populations that project centrally, i.e., to other areas of the brain, and somatostatin receptors are expressed at many different sites in the brain. In particular, populations of somatostatin neurons occur in the arcuate nucleus, the hippocampus, and the brainstem nucleus of the solitary tract.

Functions

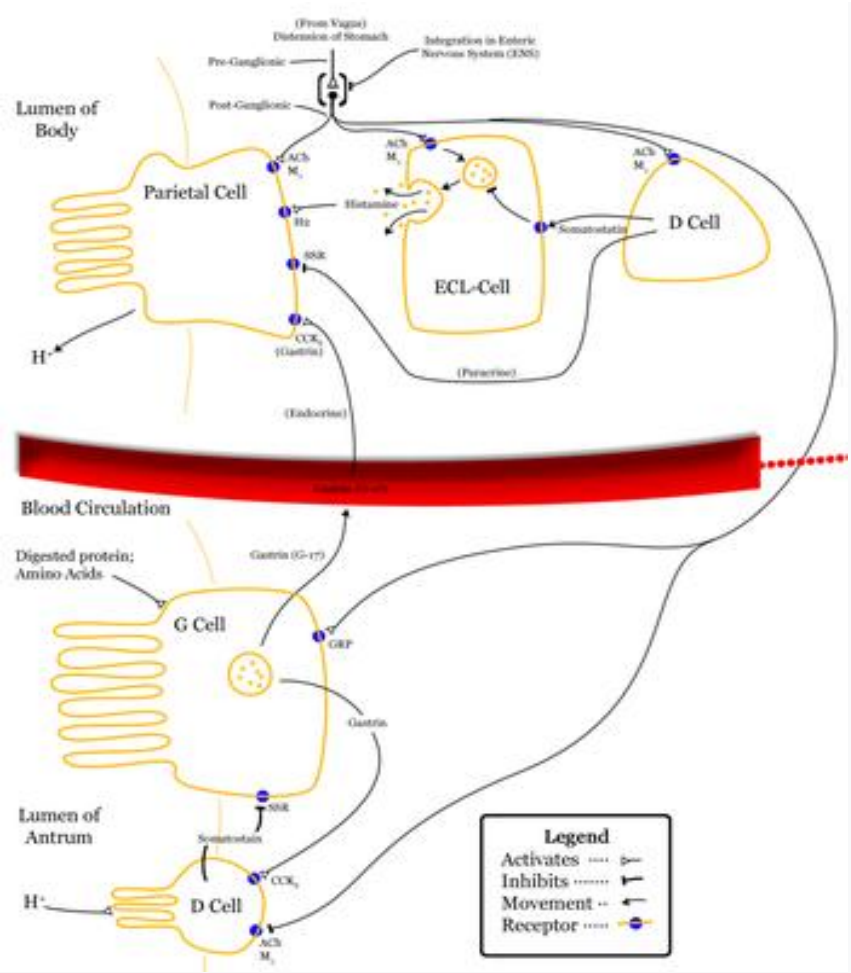

Figure-7: D cell is visible at upper right, and somatostatin is represented by middle arrow pointing left.

Anterior pituitary

In the anterior pituitary gland, the effects of somatostatin are:

- Inhibiting the release of growth hormone (GH) (thus opposing the effects of growth hormone–releasing hormone (GHRH))
- Inhibiting the release of thyroid-stimulating hormone (TSH)
- Inhibiting adenylyl cyclase in parietal cells
- Inhibiting the release of prolactin (PRL)

Gastrointestinal system

- Somatostatin is homologous with cortistatin (see somatostatin family) and suppresses the release of gastrointestinal hormones
- Decreases the rate of gastric emptying, and reduces smooth muscle contractions and blood flow within the intestine
- Suppresses the release of pancreatic hormones
- Somatostatin release is triggered by the beta cell peptide urocortin3 (Ucn3) to inhibit insulin release.
- Inhibits the release of glucagon
- Suppresses the exocrine secretory action of the pancreas

Synthetic substitutes

Octreotide (brand name Sandostatin, Novartis Pharmaceuticals) is an octapeptide that mimics natural somatostatin pharmacologically, though is a more potent inhibitor of growth hormone, glucagon, and insulin than the natural hormone, and has a much longer half-life (about 90 minutes, compared to 2–3 minutes for somatostatin). Since it is absorbed poorly from the gut, it is administered parenterally (subcutaneously, intramuscularly, or intravenously). It is indicated for symptomatic treatment of carcinoid syndrome and acromegaly. It is also finding increased use in polycystic diseases of the liver and kidney.

Lanreotide (Somatuline, Ipsen Pharmaceuticals) is a medication used in the management of acromegaly and symptoms caused by neuroendocrine tumors, most notably carcinoid syndrome. It is a long-acting analog of somatostatin, like octreotide. It is available in several countries, including the United Kingdom, Australia, and Canada, and was approved for sale in the United States by the Food and Drug Administration on August 30, 2007.

Pasireotide, sold under the brand name Signifor, is an orphan drug approved in the United States and the

European Union for the treatment of Cushing's disease in patients who fail or are ineligible for surgical therapy. It was developed by Novartis. Pasireotide is somatostatin analog with a 40-fold increased affinity to somatostatin receptor 5 compared to other somatostatin analogs.

Evolutionary history

Six somatostatin genes have been discovered in vertebrates. The current proposed history as to how these six genes arose is based on the three whole-genome duplication events that took place in vertebrate evolution along with local duplications in teleost fish. An ancestral somatostatin gene was duplicated during the first whole-genome duplication event (1R) to create *SS1* and *SS2*. These two genes were duplicated during the second whole-genome duplication event (2R) to create four new somatostatin genes:*SS1, SS2, SS3*, and one gene that was lost during the evolution of vertebrates. Tetrapods retained *SS1* (also known as *SS-14* and *SS-28*) and *SS2* (also known as cortistatin) after the split in the Sarcopterygii and Actinopterygii lineage split. In teleost fish, *SS1, SS2*, and *SS3* were duplicated during the third whole-genome duplication event (3R) to create *SS1, SS2, SS4, SS5*, and two genes that were lost during the evolution of teleost fish. *SS1* and *SS2* went through local duplications to give rise to *SS6* and *SS3*.

Gonadotropin-releasing hormone

Gonadotropin-releasing hormone (**GnRH**) is a releasing hormone responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. GnRH is a tropic peptide hormone synthesized and released from GnRH neurons within the hypothalamus. The peptide belongs to gonadotropin-releasing hormone family. It constitutes the initial step in the hypothalamic–pituitary–gonadal axis.

Structure

The identity of GnRH was clarified by the 1977 Nobel Laureates Roger Guillemin and Andrew V. Schally.

pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

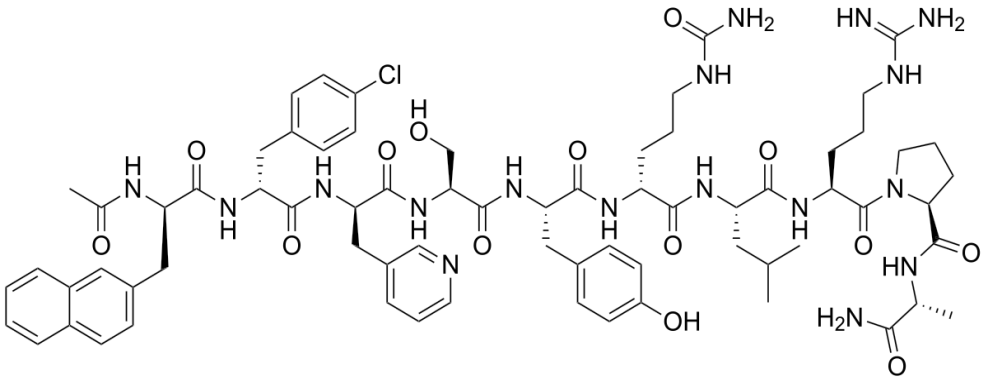

Figure-8: GnRH Structure.

As is standard for peptide representation, the sequence is given from amino terminus to carboxyl terminus; also standard is omission of the designation of chirality, with assumption that all amino acids are in their L- form. The abbreviations are the standard abbreviations for the corresponding proteinogenic amino acids, except for *pyroGlu*, which refers to pyroglutamic acid, a derivative of glutamic acid. The *NH2* at the carboxyl terminus indicates that rather than terminating as a free carboxylate, it terminates as a carboxamide.

Synthesis

The gene, *GNRH1*, for the GnRH precursor is located on chromosome 8. In mammals, the linear decapeptide end-product is synthesized from an 89-amino acid preprohormone in the preoptic anterior hypothalamus. It is the target of various regulatory mechanisms of the hypothalamic–pituitary–gonadal axis, such as being inhibited by increased estrogen levels in the body.

Function

GnRH is secreted in the hypophysial portal bloodstream at the median eminence. The portal blood carries the GnRH to the pituitary gland, which contains the gonadotrope cells, where GnRH activates its own receptor, gonadotropin-releasing hormone receptor (GnRHR), a seven-transmembrane G-protein-coupled receptor that stimulates the beta isoform of Phosphoinositide phospholipase C, which goes on to mobilize calcium and protein kinase C. This results in the activation of proteins involved in the synthesis and secretion of the gonadotropins LH and FSH. GnRH is degraded by proteolysis within a few minutes.

GnRH activity is very low during childhood, and is activated at puberty or adolescence. During the reproductive years, pulse activity is critical for successful reproductive function as controlled by feedback loops. However, once a pregnancy is established, GnRH activity is not required. Pulsatile activity can be disrupted by hypothalamic-pituitary disease, either dysfunction (i.e., hypothalamic suppression) or organic lesions (trauma, tumor). Elevated prolactin levels decrease GnRH activity. In contrast, hyperinsulinemia increases pulse activity leading to disorderly LH and FSH activity, as seen in polycystic ovary syndrome (PCOS). GnRH formation is congenitally absent in Kallmann syndrome.

Control of FSH and LH

At the pituitary, GnRH stimulates the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These processes are controlled by the size and frequency of GnRH pulses, as well as by feedback from androgens and estrogens. Low-frequency GnRH pulses are required for FSH release, whereas high-frequency GnRH pulses stimulate LH pulses in a one-to-one manner.

There are differences in GnRH secretion between females and males. In males, GnRH is secreted in pulses at a constant frequency; however, in females, the frequency of the pulses varies during the menstrual cycle, and there is a large surge of GnRH just before ovulation.

GnRH secretion is pulsatile in all vertebrates, and is necessary for correct reproductive function. Thus, a single hormone, GnRH1, controls a complex process of follicular growth, ovulation, and corpus luteum maintenance in the female, and spermatogenesis in the male.

Neurohormone

GnRH is considered a neurohormone, a hormone produced in a specific neural cell and released at its neural terminal. A key area for production of GnRH is the preoptic area of the hypothalamus, which contains most of the GnRH-secreting neurons. GnRH neurons originate in the nose and migrate into the brain, where they are scattered throughout the medial septum and hypothalamus and connected by very long >1-millimeter-long dendrites. These bundle together so they receive shared synaptic input, a process that allows them to synchronize their GnRH release.

The GnRH neurons are regulated by many different afferent neurons, using several different transmitters (including norepinephrine, GABA, glutamate). For instance, dopamine appears to stimulate LH release (through GnRH) in estrogen-progesterone-primed females; dopamine may inhibit LH release in ovariectomized females, Kisspeptin appears to be an important regulator of GnRH release. GnRH release can also be regulated by estrogen. It has been reported that there are kisspeptin-producing neurons that also express estrogen receptor alpha.

Other organs

GnRH is found in organs outside of the hypothalamus and pituitary, and its role in other life processes is poorly understood. For instance, there is likely to be a role for GnRH1 in the placenta and in the gonads. GnRH and GnRH receptors are also found in cancers of the breast, ovary, prostate, and endometrium.

Effects of behavior

GnRH production/release is one of the few confirmed examples of behavior influencing hormones, rather than the other way around. Cichlid fish that become socially dominant in turn experience an upregulation of GnRH secretion whereas cichlid fish that are socially subordinate have a down regulation of GnRH secretion. Besides secretion, the social environment as well as their behavior affects the size of GnRH neurons. Specifically, males that are more territorial have larger GnRH neurons than males that are less territorial. Differences are also seen in females, with brooding females having smaller GnRH neurons than either spawning or control females. These examples suggest that GnRH is a socially regulated hormone.

Medical uses

Natural GnRH was previously prescribed as gonadorelin hydrochloride (Factrel) and gonadorelin diacetate tetrahydrate (Cystorelin) for use in treating human diseases. Modifications of the decapeptide structure of GnRH to increase half life have led to GnRH1 analog medications that either stimulate (GnRH1 agonists) or suppress (GnRH antagonists) the gonadotropins. These synthetic analogs have replaced the natural hormone in clinical use.

Its analogue leuprorelin is used for continuous infusion, to treat breast cancer, endometriosis, prostate cancer, and following research in the 1980s by researchers, including Dr. Florence Comite of Yale University, it was used to treat precocious puberty.

A Cochrane Review is available which investigates whether GnRH analogues, given before or alongside chemotherapy, could prevent damage to women's ovaries caused by chemotherapy. GnRH agonists appear to be effective in protecting the ovaries during chemotherapy, in terms of menstruation recovery or maintenance, premature ovarian failure and ovulation.

Animal sexual behavior

GnRH activity influences a variety of sexual behaviors. Increased levels of GnRH facilitate sexual displays and behavior in females. GnRH injections enhance copulation solicitation (a type of courtship display) in white-crowned sparrows. In mammals, GnRH injections facilitate sexual behavior of female display behaviors as shown with the musk shrew's (*Suncus murinus*) reduced latency in displaying rump presents and tail wagging towards males.

An elevation of GnRH raises males' testosterone capacity beyond a male's natural testosterone level. Injections of GnRH in male birds immediately after an aggressive territorial encounter results in higher testosterone levels than is observed naturally during an aggressive territorial encounter.

A compromised GnRH system has adverse effects on reproductive physiology and maternal behavior. In comparison to female mice with a normal GnRH system, female mice with a 30% decrease in GnRH neurons are

poor caregivers to their offspring. These mice are more likely to leave their pups scattered rather than grouped together, and will take significantly longer to retrieve their pups.

Veterinary use

The natural hormone is also used in veterinary medicine as a treatment for cattle with cystic ovarian disease. The synthetic analogue deslorelin is used in veterinary reproductive control through a sustained-release implant.

Other names

As with many hormones, GnRH has been called by various names in the medical literature over the decades since its existence was first inferred. They are as follows:

- Gonadotropin-releasing factor (GnRF, GRF); Gonadotropin-releasing hormone (GnRH, GRH)
- Follicle-stimulating hormone-releasing factor (FRF, FSH-RF); Follicle-stimulating hormone-releasing hormone (FRH, FSH-RH)
- Luteinizing hormone-releasing factor (LRF, LHRF); Luteinizing hormone-releasing hormone (LRH, LHRH)
- Follicle-stimulating hormone and luteinizing hormone–releasing factor (FSH/LH-RF); Follicle-stimulating hormone and luteinizing hormone-releasing hormone (FSH/LH-RH)
- Luteinizing hormone and follicle-stimulating hormone–releasing factor (LH/FSH-RF); Luteinizing hormone and follicle-stimulating hormone-releasing hormone (LH/FSH-RH)
- Gonadorelin (INN for pharmaceutical form)
- Gonadoliberin

Dopamine

Dopamine (**DA**, a contraction of **3,4-dihydroxyphenethylamine**) is a neuromodulatory molecule that plays several important roles in cells. It is an organic chemical of the catecholamine and phenethylamine families. Dopamine constitutes about 80% of the catecholamine content in the brain. It is an amine synthesized by removing a carboxyl group from a molecule of its precursor chemical, L-DOPA, which is synthesized in the brain and kidneys. Dopamine is also synthesized in plants and most animals. In the brain, dopamine functions as a neurotransmitter—a chemical released by neurons (nerve cells) to send signals to other nerve cells. Neurotransmitters are synthesized in specific regions of the brain, but affect many regions systemically. The brain includes several distinct dopamine pathways, one of which plays a major role in the motivational component of reward-motivated behavior. The anticipation of most types of rewards increases the level of dopamine in the brain, and many addictive drugs increase dopamine release or block its reuptake into neurons following release. Other brain dopamine pathways are involved in motor control and in controlling the release of various hormones. These pathways and cell groups form a dopamine system which is neuromodulatory.[2]

In popular culture and media, dopamine is often portrayed as the main chemical of pleasure, but the current opinion in pharmacology is that dopamine instead confers motivational salience; in other words, dopamine signals the perceived motivational prominence (i.e., the desirability or aversiveness) of an outcome, which in turn propels the organism's behavior toward or away from achieving that outcome.

Outside the central nervous system, dopamine functions primarily as a local paracrine messenger. In blood vessels, it inhibits norepinephrine release and acts as a vasodilator (at normal concentrations); in the kidneys, it increases sodium excretion and urine output; in the pancreas, it reduces insulin production; in the digestive system, it reduces gastrointestinal motility and protects intestinal mucosa; and in the immune system, it reduces the activity of lymphocytes. With the exception of the blood vessels, dopamine in each of these peripheral systems is synthesized locally and exerts its effects near the cells that release it.

Several important diseases of the nervous system are associated with dysfunctions of the dopamine system, and some of the key medications used to treat them work by altering the effects of dopamine. Parkinson's disease, a degenerative condition causing tremor and motor impairment, is caused by a loss of dopamine-secreting neurons in an area of the midbrain called the substantia nigra. Its metabolic precursor L-DOPA can be manufactured; *Levodopa*, a pure form of L-DOPA, is the most widely used treatment for Parkinson's. There is evidence that schizophrenia involves altered levels of dopamine activity, and most antipsychotic drugs used to treat this are dopamine antagonists which reduce dopamine activity. Similar dopamine antagonist drugs are also some of the most effective anti-nausea agents. Restless legs syndrome and attention deficit hyperactivity disorder (ADHD) are associated with decreased dopamine activity. Dopaminergic stimulants can be addictive in high doses, but some are used at lower doses to treat ADHD. Dopamine itself is available as a manufactured medication for intravenous injection: although it cannot reach the brain from the bloodstream, its peripheral effects make it useful in the treatment of heart failure or shock, especially in newborn babies.

Structure

A dopamine molecule consists of a catechol structure (a benzene ring with two hydroxyl side groups) with one amine group attached via an ethyl chain. As such, dopamine is the simplest possible catecholamine, a family that also includes the neurotransmitters norepinephrine and epinephrine. The presence of a benzene ring with this amine attachment makes it a substituted phenethylamine, a family that includes numerous psychoactive drugs.

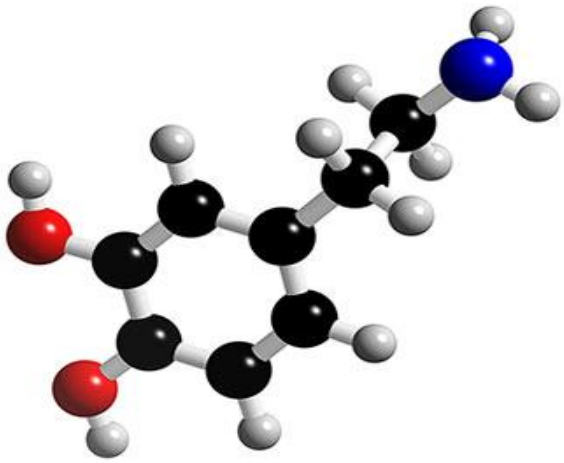

Figure-9: Dopamine 3D Structure.

Like most amines, dopamine is an organic base. As a base, it is generally protonated in acidic environments (in an acid-base reaction). The protonated form is highly water-soluble and relatively stable, but can become oxidized if exposed to oxygen or other oxidants. In basic environments, dopamine is not protonated. In this free base form, it is less water-soluble and also more highly reactive. Because of the increased stability and water-solubility of the protonated form, dopamine is supplied for chemical or pharmaceutical use as dopamine hydrochloride—that is, the hydrochloride salt that is created when dopamine is combined with hydrochloric acid. In dry form, dopamine hydrochloride is a fine powder which is white to yellow in color.

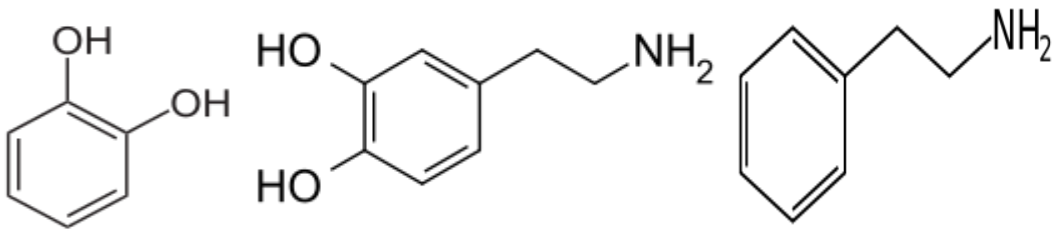

Figure-10: Catechol structure, Dopamine structure, Phenethylamine structure (Left to Right).

Biochemistry

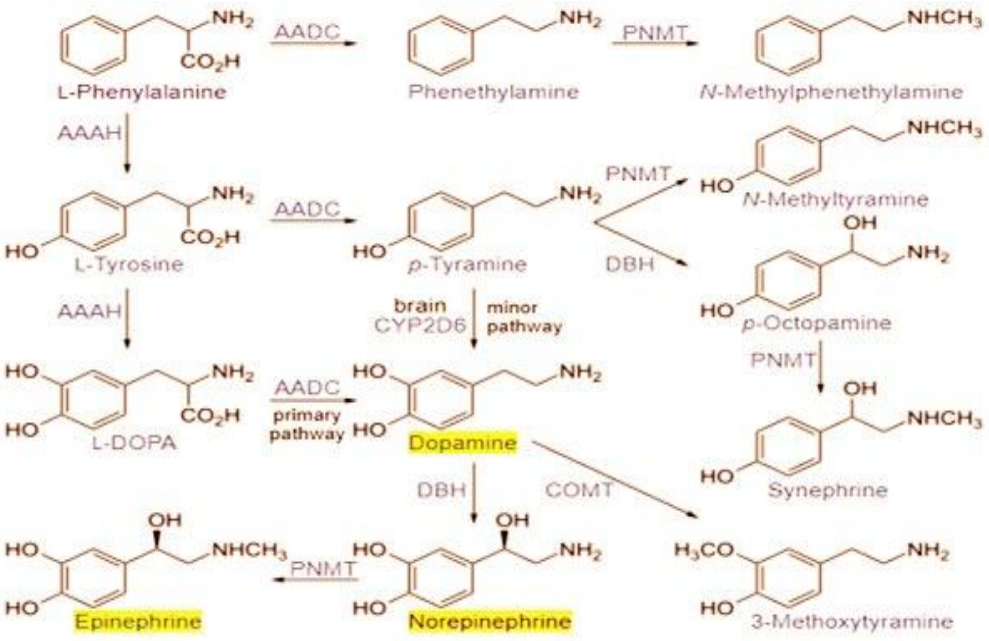

Figure-11: Biosynthetic pathways for catecholamines and trace amines in the human brain

Synthesis

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

Primary: L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine
Minor: L-Phenylalanine → L-Tyrosine → *p*-Tyramine → Dopamine
Minor: L-Phenylalanine → *m*-Tyrosine → *m*-Tyramine → Dopamine

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

L-Phenylalanine is converted into L-tyrosine by the enzyme phenylalanine hydroxylase, with molecular oxygen (O_2) and tetrahydrobiopterin as cofactors. L-Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase, with tetrahydrobiopterin, O_2, and iron (Fe^{2+}) as cofactors. L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (also known as DOPA decarboxylase), with pyridoxal phosphate as the cofactor.

Dopamine itself is used as precursor in the synthesis of the neurotransmitters norepinephrine and epinephrine. Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase, with O_2 and L-ascorbic acid as cofactors. Norepinephrine is converted into epinephrine by the enzyme phenylethanolamine *N*-methyltransferase with *S*-adenosyl-L-methionine as the cofactor.

Some of the cofactors also require their own synthesis. Deficiency in any required amino acid or cofactor can impair the synthesis of dopamine, norepinephrine, and epinephrine.

Degradation

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

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

In clinical research on schizophrenia, measurements of homovanillic acid in plasma have been used to estimate levels of dopamine activity in the brain. A difficulty in this approach however, is separating the high level of plasma homovanillic acid contributed by the metabolism of norepinephrine.

Although dopamine is normally broken down by an oxidoreductase enzyme, it is also susceptible to oxidation by direct reaction with oxygen, yielding quinones plus various free radicals as products. The rate of oxidation can be increased by the presence of ferric iron or other factors. Quinones and free radicals produced by autoxidation of dopamine can poison cells, and there is evidence that this mechanism may contribute to the cell loss that occurs in Parkinson's disease and other conditions.

Functions

Cellular effects

Table-1: Primary targets of dopamine in the human brain.

Family	Receptor	Gene	Type	Mechanism
D1-like	D_1	*DRD1*	G_s-coupled.	Increase intracellular levels of cAMP by activating adenylate cyclase.
	D_5	*DRD5*		
D2-like	D_2	*DRD2*	G_i-coupled.	Decrease intracellular levels of cAMP by inhibiting adenylate cyclase.
	D_3	*DRD3*		
	D_4	*DRD4*		
TAAR	TAAR1	*TAAR1*	G_s-coupled. G_q-coupled.	Increase intracellular levels of cAMP and intracellular calcium concentration.

Dopamine exerts its effects by binding to and activating cell surface receptors. In humans, dopamine has a high binding affinity at dopamine receptors and human trace amine-associated receptor 1 (hTAAR1). In mammals, five subtypes of dopamine receptors have been identified, labeled from D1 to D5. All of them function as metabotropic, G protein-coupled receptors, meaning that they exert their effects via a complex second messenger system. These receptors can be divided into two families, known as D1-like and D2-like. For receptors located on neurons in the nervous system, the ultimate effect of D1-like activation (D1 and D5) can be excitation (via opening of sodium channels) or inhibition (via opening of potassium channels); the ultimate effect of D2-like activation (D2, D3, and D4) is usually inhibition of the target neuron. Consequently, it is incorrect to describe dopamine itself as either excitatory or inhibitory: its effect on a target neuron depends on which types of receptors are present on the membrane of that neuron and on the internal responses of that neuron to the second messenger cAMP. D1 receptors are the most numerous dopamine receptors in the human nervous system; D2 receptors are next; D3, D4, and D5 receptors are present at significantly lower levels.

Storage, release, and reuptake

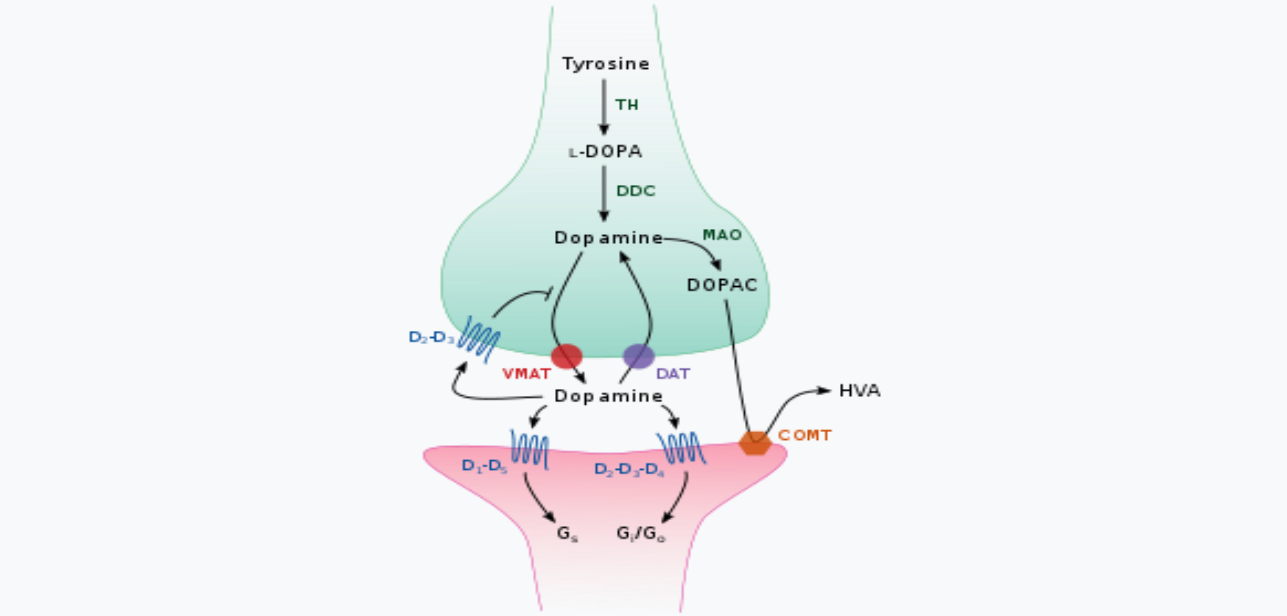

Figure-12: Dopamine processing in a synapse. After release dopamine can either be taken up again by the presynaptic terminal, or broken down by enzymes.

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

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

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

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

Nervous system

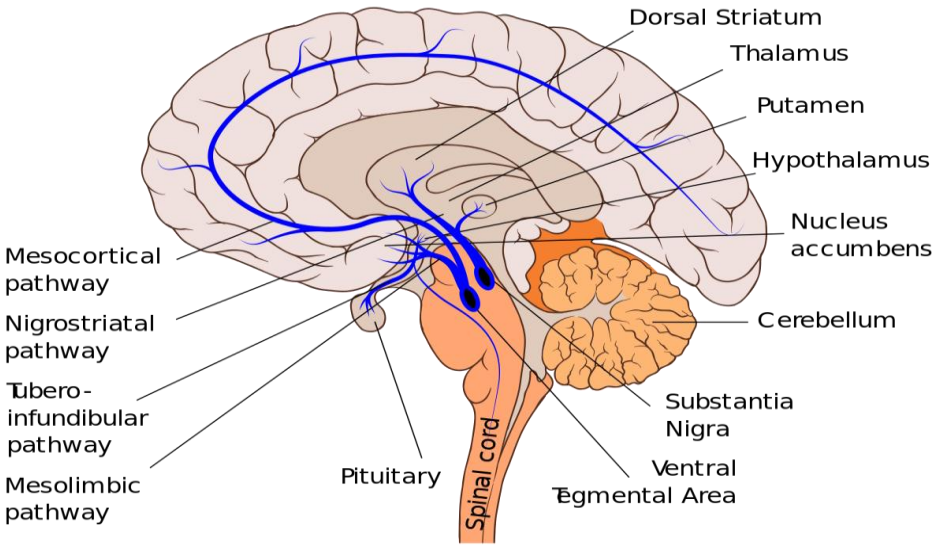

Figure-13: Major dopamine pathways. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex. The motor functions of dopamine are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the dorsal striatum.

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

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

The substantia nigra is a small midbrain area that forms a component of the basal ganglia. This has two parts—an input area called the pars compacta and an output area the pars reticulata. The dopaminergic neurons are found mainly in the pars compacta (cell group A8) and nearby (group A9). In humans, the projection of dopaminergic neurons from the substantia nigra pars compacta to the dorsal striatum, termed the *nigrostriatal pathway*, plays a significant role in the control of motor function and in learning new motor skills. These neurons are especially vulnerable to damage, and when a large number of them die, the result is a parkinsonian syndrome.

The ventral tegmental area (VTA) is another midbrain area. The most prominent group of VTA dopaminergic neurons projects to the prefrontal cortex via the mesocortical pathway and another smaller group projects to the nucleus accumbens via the mesolimbic pathway. Together, these two pathways are collectively termed the *mesocorticolimbic projection*. The VTA also sends dopaminergic projections to the amygdala, cingulate gyrus, hippocampus, and olfactory bulb. Mesocorticolimbic neurons play a central role in reward and other aspects of motivation. Accumulating literature shows that dopamine also plays a crucial role in aversive learning through its effects on a number of brain regions.

The posterior hypothalamus has dopamine neurons that project to the spinal cord, but their function is not well established. There is some evidence that pathology in this area plays a role in restless legs syndrome, a condition in which people have difficulty sleeping due to

an overwhelming compulsion to constantly move parts of the body, especially the legs.

The arcuate nucleus and the periventricular nucleus of the hypothalamus have dopamine neurons that form an important projection—the *tuberoinfundibular pathway* which goes to the pituitary gland, where it influences the secretion of the hormone prolactin. Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus is secreted into the hypophyseal portal system of the median eminence, which supplies the pituitary gland. The prolactin cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. In the context of regulating prolactin secretion, dopamine is occasionally called prolactin-inhibiting factor, prolactin-inhibiting hormone, or prolactostatin.

The zona incerta, grouped between the arcuate and periventricular nuclei, projects to several areas of the hypothalamus, and participates in the control of gonadotropin-releasing hormone, which is necessary to activate the development of the male and female reproductive systems, following puberty.

An additional group of dopamine-secreting neurons is found in the retina of the eye. These neurons are amacrine cells, meaning that they have no axons. They release dopamine into the extracellular medium, and are specifically active during daylight hours, becoming silent at night. This retinal dopamine acts to enhance the activity of cone cells in the retina while suppressing rod cells—the result is to increase sensitivity to color and contrast during bright light conditions, at the cost of reduced sensitivity when the light is dim.

Basal ganglia

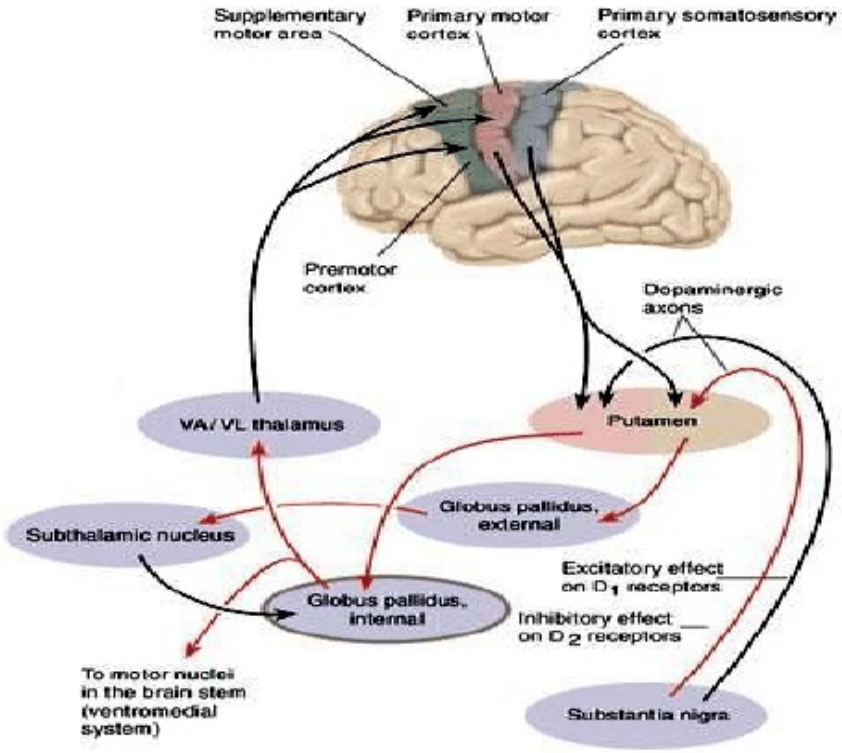

Figure-14: Main circuits of the basal ganglia. The dopaminergic pathway from the substantia nigra pars compacta to the striatum.

The largest and most important sources of dopamine in the vertebrate brain are the substantia nigra and ventral tegmental area. These structures are closely related to each other and functionally similar in many respects. Both are components of the mid brain. The largest component of the basal ganglia is the striatum. The substantia nigra sends a dopaminergic projection to the dorsal striatum, while the ventral tegmental area sends a similar type of dopaminergic projection to the ventral striatum.

Progress in understanding the functions of the basal ganglia has been slow. The most popular hypotheses, broadly stated, propose that the basal ganglia play a central role in action selection. The action selection theory in its simplest form proposes that when a person or animal is in a situation where several behaviors are possible, activity in the basal ganglia determines which of them is executed, by releasing that response from inhibition while continuing to inhibit other motor systems that if activated would generate competing behaviors. Thus the basal ganglia, in this concept, are

responsible for initiating behaviors, but not for determining the details of how they are carried out. In other words, they essentially form a decision-making system.

The basal ganglia can be divided into several sectors, and each is involved in controlling particular types of actions. The ventral sector of the basal ganglia (containing the ventral striatum and ventral tegmental area) operates at the highest level of the hierarchy, selecting actions at the whole-organism level. The dorsal sectors (containing the dorsal striatum and substantia nigra) operate at lower levels, selecting the specific muscles and movements that are used to implement a given behavior pattern.

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

The second important effect of dopamine is as a "teaching" signal. When an action is followed by an increase in dopamine activity, the basal ganglia circuit is altered in a way that makes the same response easier to evoke when similar situations arise in the future. This is a form of operant conditioning, in which dopamine plays the role of a reward signal.

Reward

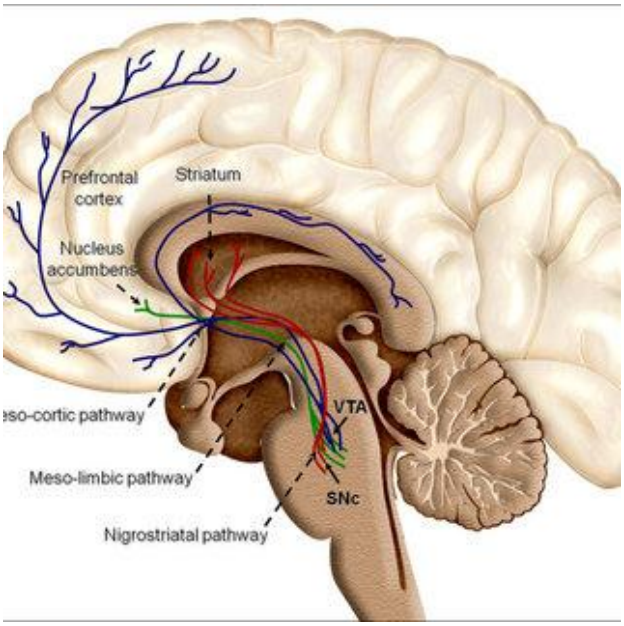

Figure-15: Illustration of dopaminergic reward structures.

In the language used to discuss the reward system, *reward* is the attractive and motivational property of a stimulus that induces appetitive behaviour (also known as approach behavior) and consummatory behavior. A rewarding stimulus is one that can induce the organism to approach it and choose to consume it. Pleasure, learning (e.g., classical and operant conditioning), and approach behavior are the three main functions of reward. As an aspect of reward, *pleasure* provides a definition of reward; however, while all pleasurable stimuli are rewarding, not all rewarding stimuli are pleasurable (e.g., extrinsic rewards like money). The motivational or desirable aspect of rewarding stimuli is reflected by the approach behavior that they induce, whereas the pleasure from intrinsic rewards results from consuming them after acquiring them. A neuropsychological model which distinguishes these two components of an intrinsically rewarding stimulus is the incentive salience model, where "wanting" or desire (less commonly, "seeking") corresponds to appetitive or approach behavior while "liking" or pleasure corresponds to consummatory behavior. In human drug addicts, "wanting" becomes dissociated with "liking" as the desire to use an addictive drug increase, while the pleasure obtained from consuming it decreases due to drug tolerance.

Within the brain, dopamine functions partly as a global reward signal. An initial dopamine response to a rewarding stimulus encodes information about

the salience, value, and context of a reward. In the context of reward-related learning, dopamine also functions as a *reward prediction error* signal, that is, the degree to which the value of a reward is unexpected. According to this hypothesis proposed by Montague, Dayan, and Sejnowski, rewards that are expected do not produce a second phasic dopamine response in certain dopaminergic cells, but rewards that are unexpected, or greater than expected, produce a short-lasting increase in synaptic dopamine, whereas the omission of an expected reward actually causes dopamine release to drop below its background level. The "prediction error" hypothesis has drawn particular interest from computational neuroscientists, because an influential computational-learning method known as temporal difference learning makes heavy use of a signal that encodes prediction error. This confluence of theory and data has led to a fertile interaction between neuroscientists and computer scientists interested in machine learning.

Evidence from microelectrode recordings from the brains of animals shows that dopamine neurons in the ventral tegmental area (VTA) and substantia nigra are strongly activated by a wide variety of rewarding events. These reward-responsive dopamine neurons in the VTA and substantia nigra are crucial for reward-related cognition and serve as the central component of the reward system. The function of dopamine varies in each axonal projection from the VTA and substantia nigra; for example, the VTA–nucleus accumbens shell projection assigns incentive salience ("want") to rewarding stimuli and its associated cues, the VTA–prefrontal cortex projection updates the value of different goals in accordance with their incentive salience, the VTA–amygdala and VTA–hippocampus projections mediate the consolidation of reward-related memories, and both the VTA–nucleus accumbens core and substantia nigra–dorsal striatum pathways are involved in learning motor responses that facilitate the acquisition of rewarding stimuli. Some activity within the VTA dopaminergic projections appears to be associated with reward prediction as well.

Pleasure

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

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

Outside the nervous system

Dopamine does not cross the blood–brain barrier, so its synthesis and functions in peripheral areas are to a large degree independent of its synthesis and functions in the brain. A substantial amount of dopamine circulates in the bloodstream, but its functions there are not entirely clear. Dopamine is found in blood plasma at levels comparable to those of epinephrine, but in humans, over 95% of the dopamine in the plasma is in the form of dopamine sulfate, a conjugate produced by the enzyme sulfotransferase 1A3/1A4 acting on free dopamine. The bulk of this dopamine sulfate is produced in the mesentery that surrounds parts of the digestive system. The production of dopamine sulfate is thought to be a mechanism for detoxifying dopamine that is ingested as food or produced by the digestive process—levels in the plasma typically rise more than fifty-fold after a meal. Dopamine sulfate has no known biological functions and is excreted in urine.

The relatively small quantity of unconjugated dopamine in the bloodstream may be produced by the sympathetic nervous system, the digestive system, or possibly other

organs. It may act on dopamine receptors in peripheral tissues, or be metabolized, or be converted to norepinephrine by the enzyme dopamine beta hydroxylase, which is released into the bloodstream by the adrenal medulla. Some dopamine receptors are located in the walls of arteries, where they act as a vasodilator and an inhibitor of norepinephrine release. These responses might be activated by dopamine released from the carotid body under conditions of low oxygen, but whether arterial dopamine receptors perform other biologically useful functions is not known.

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

Immune system

In the immune system dopamine acts upon receptors present on immune cells, especially lymphocytes. Dopamine can also affect immune cells in the spleen, bone marrow, and circulatory system. In addition, dopamine can be synthesized and released by immune cells themselves. The main effect of dopamine on lymphocytes is to reduce their activation level. The functional significance of this system is unclear, but it affords a possible route for interactions between the nervous system and immune system, and may be relevant to some autoimmune disorders.

Kidneys

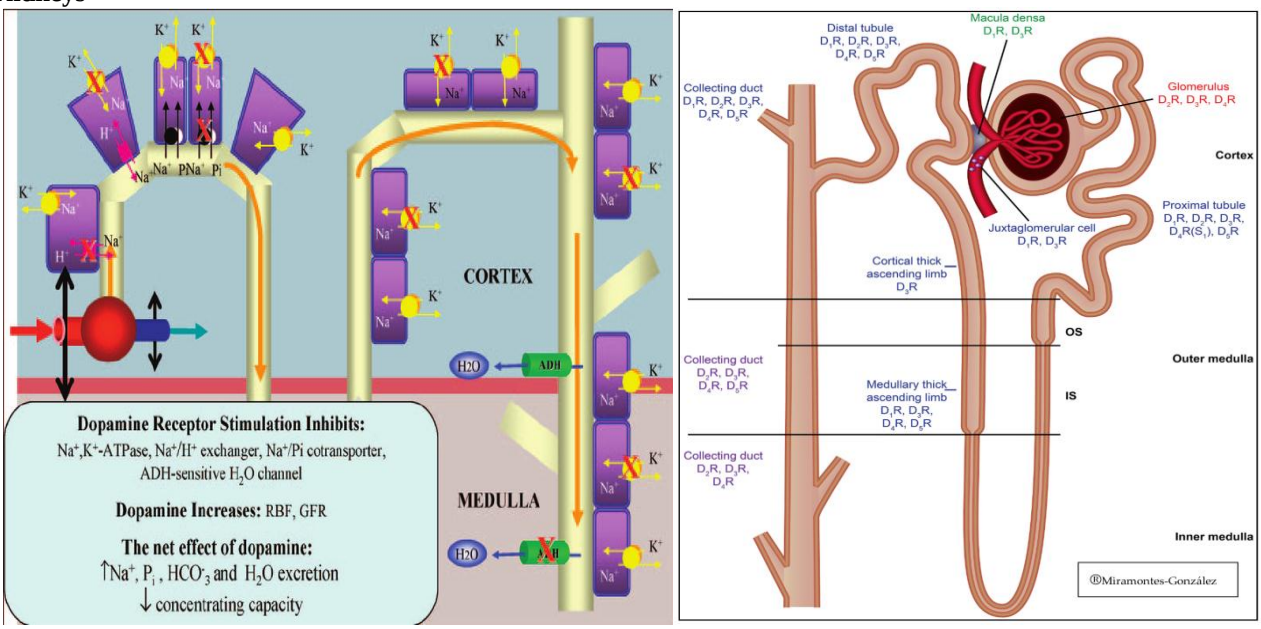

Figure-16: Effects of Dopamine In kidney.

The renal dopaminergic system is located in the cells of the nephron in the kidney, where all subtypes of dopamine receptors are present. Dopamine is also synthesized there, by tubule cells, and discharged into the tubular fluid. Its actions include increasing the blood supply to the kidneys, increasing the glomerular filtration rate, and increasing the excretion of sodium in the urine. Hence, defects in renal dopamine function can lead to reduced sodium excretion and consequently result in the development of high blood pressure. There is strong evidence that faults in the production of dopamine or in the receptors can result in a number of pathologies including oxidative stress, edema, and either genetic or essential hypertension. Oxidative stress can itself cause hypertension. Defects in the system can also be caused by genetic factors or high blood pressure.

Pancreas

In the pancreas the role of dopamine is somewhat complex. The pancreas consists of two parts, an exocrine and an endocrine component. The exocrine part synthesizes and secretes digestive enzymes and other substances, including dopamine, into the small intestine. The function of this secreted dopamine after it enters the small intestine is not clearly established—the possibilities include protecting the intestinal mucosa from damage and reducing gastrointestinal motility (the rate at which content moves through the digestive system).

The pancreatic islets make up the endocrine part of the pancreas, and synthesize and secrete hormones including insulin into the bloodstream. There is evidence that the beta cells in the islets that synthesize insulin contain dopamine receptors, and that dopamine acts to reduce the amount of insulin they release. The source of their dopamine input is not clearly established—it may come from dopamine that circulates in the bloodstream and derives from the sympathetic nervous system, or it

may be synthesized locally by other types of pancreatic cells.

Medical uses

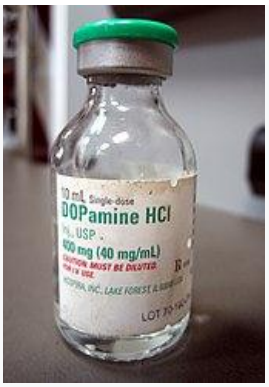

Figure-17: Dopamine HCl preparation, single dose vial for intravenous administration.

Dopamine as a manufactured medication is sold under the trade names Intropin, Dopastat, and Revimine, among others. It is on the World Health Organization's List of Essential Medicines. It is most commonly used as a stimulant drug in the treatment of severe low blood pressure, slow heart rate, and cardiac arrest. It is especially important in treating these in newborn infants. It is given intravenously. Since the half-life of dopamine in plasma is very short—approximately one minute in adults, two minutes in newborn infants and up to five minutes in preterm infants—it is usually given in a continuous intravenous drip rather than a single injection.

Its effects, depending on dosage, include an increase in sodium excretion by the kidneys, an increase in urine output, an increase in heart rate, and an increase in blood pressure. At low doses it acts through the sympathetic nervous system to increase heart muscle contraction force and heart rate, thereby increasing cardiac output and blood pressure. Higher doses also cause vasoconstriction that further increases blood pressure. Older literature also describes very low doses thought to improve kidney function without other consequences, but recent reviews have concluded that doses at such low levels are not effective and may sometimes be harmful. While some effects result from stimulation of dopamine receptors, the prominent cardiovascular effects result from dopamine acting at α_1, β_1, and β_2 adrenergic receptors.

Side effects of dopamine include negative effects on kidney function and irregular heartbeats. The LD_{50}, or lethal dose which is expected to prove fatal in 50% of the population, has been found to be: 59 mg/kg (mouse; administered intravenously); 95 mg/kg (mouse; administered intraperitoneally); 163 mg/kg (rat; administered intraperitoneally); 79 mg/kg (dog; administered intravenously).

A fluorinated form of L-DOPA known as fluorodopa is available for use in positron emission tomography to assess the function of the nigrostriatal pathway.

Disease, disorders, and pharmacology

The dopamine system plays a central role in several significant medical conditions, including Parkinson's disease, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, bipolar disorder, and addiction. Aside from dopamine itself, there are many other important drugs that act on dopamine systems in various parts of the brain or body. Some are used for medical or recreational purposes, but neurochemists have also developed a variety of research drugs, some of which bind with high affinity to specific types of dopamine receptors and either agonize or antagonize their effects, and many that affect other aspects of dopamine physiology, including dopamine transporter inhibitors, VMAT inhibitors, and enzyme inhibitors.

Aging brain

A number of studies have reported an age-related decline in dopamine synthesis and dopamine receptor density (i.e., the number of receptors) in the brain. This decline has been shown to occur in the striatum and extrastriatal regions. Decreases in the D_1, D_2, and D_3 receptors are well documented. The reduction of dopamine with aging is thought to be responsible for many neurological symptoms that increase in frequency with age, such as decreased arm swing and increased rigidity. Changes in dopamine levels may also cause age-related changes in cognitive flexibility.

Other neurotransmitters, such as serotonin and glutamate also show a decline in output with aging.

Multiple sclerosis

Studies reported that dopamine imbalance influences the fatigue in multiple sclerosis. In patients with multiple sclerosis, dopamine inhibits production of IL-17 and IFN-γ by peripheral blood mononuclear cells.

Parkinson's disease

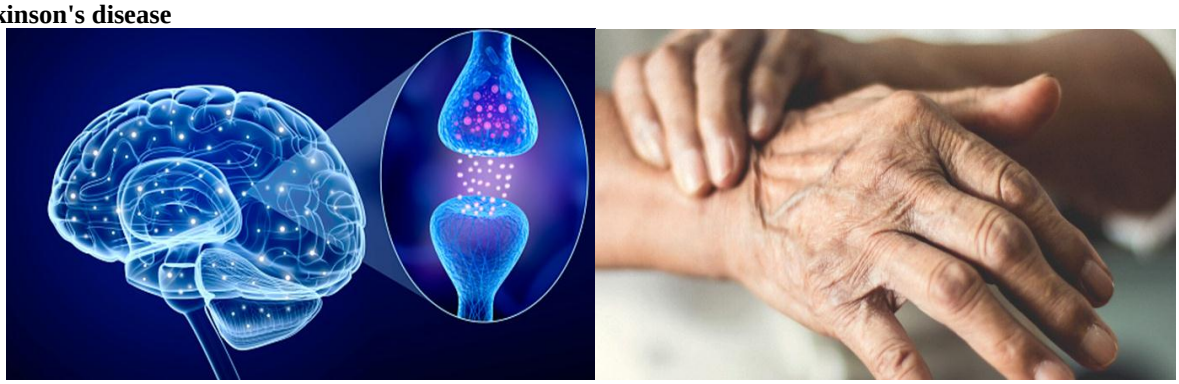

Figure-18: Nerve state in Parkinson's disease and symptoms.

Parkinson's disease is an age-related disorder characterized by movement disorders such as stiffness of the body, slowing of movement, and trembling of limbs when they are not in use. In advanced stages it progresses to dementia and eventually death. The main symptoms are caused by the loss of dopamine-secreting cells in the substantia nigra. These dopamine cells are especially vulnerable to damage, and a variety of insults, including encephalitis (as depicted in the book and movie "Awakenings"), repeated sports-related concussions, and some forms of chemical poisoning such as MPTP, can lead to substantial cell loss, producing a parkinsonian syndrome that is similar in its main features to Parkinson's disease. Most cases of Parkinson's disease, however, are idiopathic, meaning that the cause of cell death cannot be identified.

The most widely used treatment for Parkinsonism is administration of L-DOPA, the metabolic precursor for dopamine. L-DOPA is converted to dopamine in the brain and various parts of the body by the enzyme DOPA decarboxylase. L-DOPA is used rather than dopamine itself because, unlike dopamine, it is cap*a*ble of crossing the blood-brain barrier. It is often co-administered with an enzyme inhibitor of peripheral decarboxylation such as carbidopa or benserazide, to reduce the amount converted to dopamine in the periphery and thereby increase the amount of L-DOPA that enters the brain. When L-DOPA is administered regularly over a long time period, a variety of unpleasant side effects such as dyskinesia often begin to appear; even so, it is considered the best available long-term treatment option for most cases of Parkinson's disease.

L-DOPA treatment cannot restore the dopamine cells that have been lost, but it causes the remaining cells to produce more dopamine, thereby compensating for the loss to at least some degree. In advanced stages the treatment begins to fail because the cell loss is so severe that the remaining ones cannot produce enough dopamine regardless of L-DOPA levels. Other drugs that enhance dopamine function, such as bromocriptine and pergolide, are also sometimes used to treat Parkinsonism, but in most cases L-DOPA appears to give the best trade-off between positive effects and negative side-effects.

Dopaminergic medications that are used to treat Parkinson's disease are sometimes associated with the development of a dopamine dysregulation syndrome, which involves the overuse of dopaminergic medication and medication-induced compulsive engagement in natural rewards like gambling and sexual activity. The latter behaviors are similar to those observed in individuals with a behavioral addiction.

Drug addiction and psychostimulants

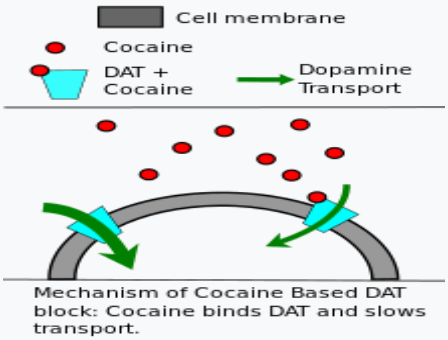

Figure-19: Cocaine increases dopamine levels by blocking dopamine transporters (DAT), which transport dopamine back into a synaptic terminal after it has been emitted.

Cocaine, substituted amphetamines (including methamphetamine), Adderall, methylphenidate (marketed as Ritalin or Concerta), and other psychostimulants exert their effects primarily or partly by increasing dopamine levels in the brain by a variety of mechanisms. Cocaine and methylphenidate are dopamine transporter blockers or reuptake inhibitors; they non-competitively inhibit dopamine reuptake, resulting in increased dopamine concentrations in the synaptic cleft. Like cocaine, substituted amphetamines and amphetamine also increase the concentration of dopamine in the synaptic cleft, but by different mechanisms.

The effects of psychostimulants include increases in heart rate, body temperature, and sweating; improvements in alertness, attention, and endurance; increases in pleasure produced by rewarding events; but at higher doses agitation, anxiety, or even loss of contact with reality. Drugs in this group can have a high addiction potential, due to their activating effects on the dopamine-mediated reward system in the brain. However some can also be useful, at lower doses, for treating attention deficit hyperactivity disorder (ADHD) and narcolepsy. An important differentiating factor is the onset and duration of action. Cocaine can take effect in seconds if it is injected or inhaled in free base form; the effects last from 5 to 90 minutes. This rapid and brief action makes its effects easily perceived and consequently gives it high addiction potential. Methylphenidate taken in pill form, in contrast, can take two hours to reach peak levels in the bloodstream, and depending on formulation the effects can last for up to 12 hours. These longer acting formulations have the benefit of reducing the potential for abuse, and improving adherence for treatment by using more convenient dosage regimens.

Figure-20: Methamphetamine hydrochloride also known as crystal meth.

A variety of addictive drugs produce an increase in reward-related dopamine activity. Stimulants such as nicotine, cocaine and methamphetamine promote increased levels of dopamine which appear to be the primary factor in causing addiction. For other addictive drugs such as the opioid heroin, the increased levels of dopamine in the reward system may play only a minor role in addiction. When people addicted to stimulants go through withdrawal, they do not experience the physical suffering associated with alcohol withdrawal or withdrawal from opiates; instead they experience craving, an intense desire for the drug characterized by irritability, restlessness, and other arousal symptoms, brought about by psychological dependence.

The dopamine system plays a crucial role in several aspects of addiction. At the earliest stage, genetic differences that alter the expression of dopamine receptors in the brain can predict whether a person will find stimulants appealing or aversive. Consumption of stimulants produces increases in brain dopamine levels that last from minutes to hours. Finally, the chronic elevation in dopamine that comes with repetitive high-dose stimulant consumption triggers a wide-ranging set of structural changes in the brain that are responsible for the behavioral abnormalities which characterize an addiction. Treatment of stimulant addiction is very difficult, because even if consumption ceases, the craving that comes with psychological withdrawal does not. Even when the craving seems to be extinct, it may re-emerge when faced with stimuli that are associated with the drug, such as friends, locations and situations. Association networks in the brain are greatly interlinked.

Psychosis and antipsychotic drugs

Psychiatrists in the early 1950s discovered that a class of drugs known as typical antipsychotics (also known as major tranquilizers), were often effective at reducing the psychotic symptoms of schizophrenia. The introduction of the first widely used antipsychotic, chlorpromazine (Thorazine), in the 1950s, led to the release of many patients with schizophrenia from institutions in the years that followed. By the 1970s researchers understood that these typical antipsychotics worked as antagonists on the D2 receptors. This

realization led to the so-called dopamine hypothesis of schizophrenia, which postulates that schizophrenia is largely caused by hyperactivity of brain dopamine systems. The dopamine hypothesis drew additional support from the observation that psychotic symptoms were often intensified by dopamine-enhancing stimulants such as methamphetamine, and that these drugs could also produce psychosis in healthy people if taken in large enough doses. In the following decades other atypical antipsychotics that had fewer serious side effects were developed. Many of these newer drugs do not act directly on dopamine receptors, but instead produce alterations in dopamine activity indirectly. These drugs were also used to treat other psychoses. Antipsychotic drugs have a broadly suppressive effect on most types of active behavior, and particularly reduce the delusional and agitated behavior characteristic of overt psychosis.

Later observations, however, have caused the dopamine hypothesis to lose popularity, at least in its simple original form. For one thing, patients with schizophrenia do not typically show measurably increased levels of brain dopamine activity. Even so, many psychiatrists and neuroscientists continue to believe that schizophrenia involves some sort of dopamine system dysfunction. As the "dopamine hypothesis" has evolved over time, however, the sorts of dysfunctions it postulates have tended to become increasingly subtle and complex.

Psycho pharmacologist Stephen M. Stahl suggested in a review of 2018 that in many cases of psychosis, including schizophrenia, three interconnected networks based on dopamine, serotonin, and glutamate – each on its own or in various combinations – contributed to an overexcitation of dopamine D2 receptors in the ventral striatum.

Attention deficit hyperactivity disorder

Altered dopamine neurotransmission is implicated in attention deficit hyperactivity disorder (ADHD), a condition associated with impaired cognitive control, in turn leading to problems with regulating attention (attentional control), inhibiting behaviors (inhibitory control), and forgetting things or missing details (working memory), among other problems. There are genetic links between dopamine receptors, the dopamine transporter, and ADHD, in addition to links to other neurotransmitter receptors and transporters. The most important relationship between dopamine and ADHD involves the drugs that are used to treat ADHD. Some of the most effective therapeutic agents for ADHD are psychostimulants such as methylphenidate (Ritalin, Concerta) and amphetamine (Evekeo, Adderall, Dexedrine), drugs that increase both dopamine and norepinephrine levels in the brain. The clinical effects of these psychostimulants in treating ADHD are mediated through the indirect activation of dopamine and norepinephrine receptors, specifically dopamine receptor D_1 and adrenoceptor α_2, in the prefrontal cortex.

Pain

Dopamine plays a role in pain processing in multiple levels of the central nervous system including the spinal cord, periaqueductal gray, thalamus, basal ganglia, and cingulate cortex. Decreased levels of dopamine have been associated with painful symptoms that frequently occur in Parkinson's disease.

Nausea

Nausea and vomiting are largely determined by activity in the area postrema in the medulla of the brainstem, in a region known as the chemoreceptor trigger zone. This area contains a large population of type D2 dopamine receptors. consequently, drugs that activate D2 receptors have a high potential to cause nausea. This group includes some medications that are administered for Parkinson's disease, as well as other dopamine agonists such as apomorphine. In some cases, D2-receptor antagonists such as metoclopramide are useful as anti-nausea drugs.

Comparative biology and evolution

Microorganisms

There are no reports of dopamine in archaea, but it has been detected in some types of bacteria and in the protozoan called *Tetrahymena*. Perhaps more importantly, there are types of bacteria that contain homologs of all the enzymes that animals use to synthesize dopamine. It has been proposed that animals derived their dopamine-synthesizing machinery from bacteria, via horizontal gene transfer that may have occurred relatively late in evolutionary time, perhaps as a result of the symbiotic incorporation of bacteria into eukaryotic cells that gave rise to mitochondria.

Animals

Dopamine is used as a neurotransmitter in most multicellular animals. In sponges there is only a single report of the presence of dopamine, with no indication of its function; however, dopamine has been reported in the nervous systems of many other radially symmetric species, including the cnidarian jellyfish, hydra and some corals. This dates the emergence of dopamine as a neurotransmitter back to the earliest appearance of the nervous system, over 500 million years ago in the Cambrian Period. Dopamine functions as a neurotransmitter in vertebrates, echinoderms, arthropods, molluscs, and several types of worm.

In every type of animal that has been examined, dopamine has been seen to modify motor behavior. In the model organism, nematode *Caenorhabditis elegans*, it reduces locomotion and increases food-exploratory movements; in flatworms it produces "screw-like" movements; in leeches it inhibits swimming and promotes crawling. Across a wide range of vertebrates, dopamine has an "activating" effect on behavior-switching and response selection, comparable to its effect in mammals.

Dopamine has also consistently been shown to play a role in reward learning, in all animal groups. As in all vertebrates – invertebrates such as roundworms, flatworms, molluscs and common fruit flies can all be trained to repeat an action if it is consistently followed by an increase in dopamine levels. In fruit flies, distinct elements for reward learning suggest a modular structure to the insect reward processing system that broadly parallels that in the mammalian one. For example, dopamine regulates short- and long-term learning in monkeys; in fruit flies, different groups of dopamine neurons mediate reward signals for short- and long-term memories.

It had long been believed that arthropods were an exception to this with dopamine being seen as having an adverse effect. Reward was seen to be mediated instead by octopamine, a neurotransmitter closely related to norepinephrine. More recent studies, however, have shown that dopamine does play a part in reward learning in fruit flies. It has also been found that the rewarding effect of octopamine is due to its activating a set of dopaminergic neurons not previously accessed in the research.

Plants

Figure-21: Dopamine can be found in the peel and fruit pulp of bananas.

Many plants, including a variety of food plants, synthesize dopamine to varying degrees.The highest concentrations have been observed in bananas—the fruit pulp of red and yellow bananas contains dopamine at levels of 40 to 50 parts per million by weight. Potatoes, avocados, broccoli, and Brussels sprouts may also contain dopamine at levels of 1 part per million or more; oranges, tomatoes, spinach, beans, and other plants contain measurable concentrations less than 1 part per million. The dopamine in plants is synthesized from the amino acid tyrosine, by biochemical mechanisms similar to those that animals use. It can be metabolized in a variety of ways, producing melanin and a variety of alkaloids as byproducts. The functions of plant catecholamines have not been clearly established, but there is evidence that they play a role in the response to stressors such as bacterial infection, act as growth-promoting factors in some situations, and modify the way that sugars are metabolized. The receptors that mediate these actions have not yet been identified, nor have the intracellular mechanisms that they activate.

Dopamine consumed in food cannot act on the brain, because it cannot cross the blood–brain barrier. However there are also a variety of plants that contain L-DOPA, the metabolic precursor of dopamine. The highest concentrations are found in the leaves and bean pods of plants of the genus *Mucuna*, especially in *Mucuna pruriens* (velvet beans), which have been used as a source for L-DOPA as a drug. Another plant containing substantial amounts of L-DOPA is *Vicia faba*, the plant that produces fava beans (also known as "broad beans"). The level of L-DOPA in the beans, however, is much lower than in the pod shells and other parts of the plant. The seeds of *Cassia* and *Bauhinia* trees also contain substantial amounts of L-DOPA.

In a species of marine green algae *Ulvaria obscura*, a major component of some algal blooms, dopamine is present in very high concentrations, estimated at 4.4% of dry weight. There is evidence that this dopamine functions as an anti-herbivore defense, reducing consumption by snails and isopods.

As a precursor for melanin

Melanins are a family of dark-pigmented substances found in a wide range of organisms. Chemically they are closely related to dopamine, and there is a type of

melanin, known as **dopamine-melanin**, that can be synthesized by oxidation of dopamine via the enzyme tyrosinase. The melanin that darkens human skin is not of this type: it is synthesized by a pathway that uses L-DOPA as a precursor but not dopamine. However, there is substantial evidence that the neuromelanin that gives a dark color to the brain's substantia nigra is at least in part dopamine-melanin.

Dopamine-derived melanin probably appears in at least some other biological systems as well. Some of the dopamine in plants is likely to be used as a precursor for dopamine-melanin. The complex patterns that appear on butterfly wings, as well as black-and-white stripes on the bodies of insect larvae, are also thought to be caused by spatially structured accumulations of dopamine-melanin.

Neurotensin

Neurotensin is a 13 amino acid neuropeptide that is implicated in the regulation of luteinizing hormone and prolactin release and has significant interaction with the dopaminergic system. Neurotensin was first isolated from extracts of bovine hypothalamus based on its ability to cause a visible vasodilation in the exposed cutaneous regions of anesthetized rats.

Neurotensin is distributed throughout the central nervous system, with highest levels in the hypothalamus, amygdala and nucleus accumbens. It induces a variety of effects, including analgesia, hypothermia and increased locomotor activity. It is also involved in regulation of dopamine pathways. In the periphery, neurotensin is found in enteroendocrine cells of the small intestine, where it leads to secretion and smooth muscle contraction.

Sequence and biosynthesis

Neurotensin shares significant sequence similarity in its 6 C-terminal amino acids with several other neuropeptides, including neuromedin N (which is derived from the same precursor). This C-terminal region is responsible for the full biological activity, the N-terminal portion having a modulatory role. The neurotensin/neuromedin N precursor can also be processed to produce large 125–138 amino acid peptides with the neurotensin or neuromedin N sequence at their C terminus. These large peptides appear to be less potent than their smaller counterparts, but are also less sensitive to degradation and may represent endogenous, long-lasting activators in a number of pathophysiological situations.

The sequence of bovine neurotensin was determined to be pyroGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH. Neurotensin is synthesized as part of a 169 or 170 amino acid precursor protein that also contains the related neuropeptide neuromedin N. The peptide coding domains are located in tandem near the carboxyl terminal end of the precursor and are bounded and separated by paired basic amino acid (lysine-arginine) processing sites.

Clinical significance

Neurotensin is a potent mitogen for colorectal cancer.

Neurotensin has been implicated in the modulation of dopamine signaling, and produces a spectrum of pharmacological effects resembling those of antipsychotic drugs; leading to the suggestion that neurotensin may be an endogenous neuroleptic. Neurotensin-deficient mice display defects in responses to several antipsychotic drugs consistent with the idea that neurotensin signaling is a key component underlying at least some antipsychotic drug actions. These mice exhibit modest defects in prepulse inhibition (PPI) of the startle reflex, a model that has been widely used to investigate antipsychotic drug action in animals. Antipsychotic drug administration augments PPI under certain conditions. Comparisons between normal and neurotensin-deficient mice revealed striking differences in the ability of different antipsychotic drugs to augment PPI. While the atypical antipsychotic drug clozapine augmented PPI normally in neurotensin-deficient mice, the conventional antipsychotic haloperidol and the newer atypical antipsychotic quetiapine were ineffective in these mice, in contrast to normal mice where these drugs significantly augmented PPI. These results suggest that certain antipsychotic drugs require neurotensin for at least some of their effects. Neurotensin-deficient mice also display defects in striatal activation following haloperidol, but not clozapine administration in comparison to normal wild type mice, indicating that striatal neurotensin is required for the full spectrum of neuronal responses to a subset of antipsychotic drugs.

Neurotensin is an endogenous neuropeptide involved in thermoregulation that can induce hypothermia and neuroprotection in experimental models of cerebral ischemia.

Gene expression

Neurotensin gene expression has been shown to be modulated by estrogen in both human SK-N-SH neuroblastoma cell cultures as well as in mice through interactions with cyclic AMP (cAMP) signaling. Specifically, estrogen increased cAMP activity and cAMP response element-binding protein phosphorylation in neuroblastoma cells prior to the induction of neurotensin gene transcription. Additionally, neurotensin gene transcription was blocked in knock-out mice lacking the RIIβ subunit of the protein kinase A holoenzyme.

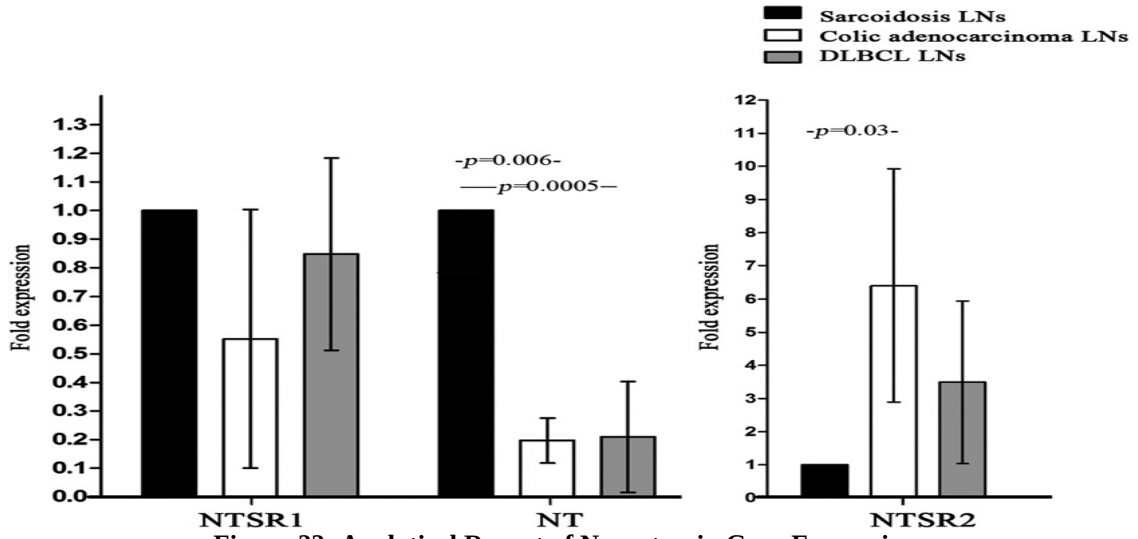

Figure-22: Analytical Report of Neurotensin Gene Expression.

These findings may indicate mechanisms of cross-talk signaling in brain hormone activity and expression of hormone-related genes. Other sex hormone-related changes in neurotensin expression have been associated with activity in the preoptic area. In female rats, neurotensin expression was shown to be at its highest in the medial preoptic area (mPOA) during the proestrus phase of the estrous cycle.

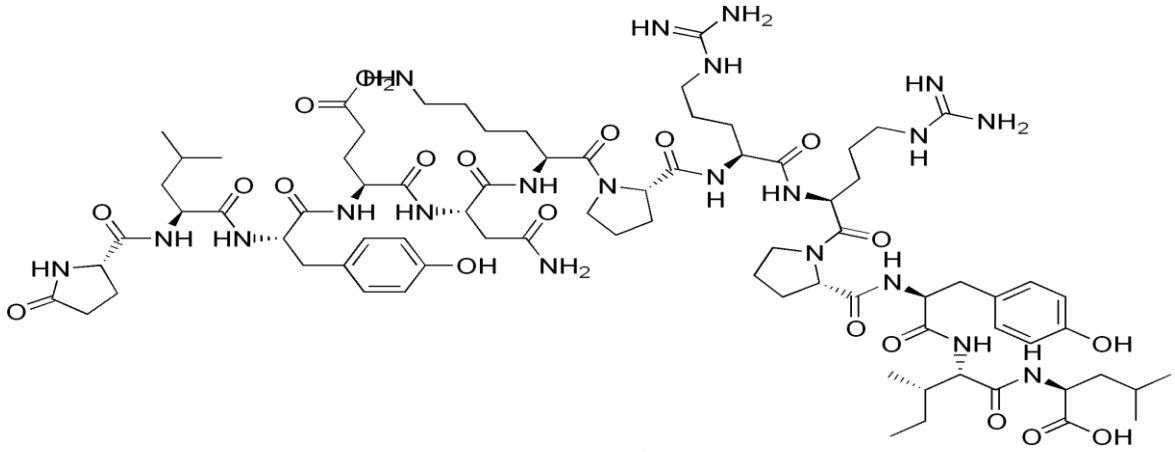

Figure-23: Neurotensin Structure.

Altered expression of neurotensin genes as well as neurotensin receptor genes have been exhibited in postpartum female mice. While neurotensin receptor 1 (Ntsr1) mRNA in the paraventricular nucleus of the hypothalamus (PVN) was lowered, neurotensin, but not neurotensin mRNA, was shown to be higher in the PVN. Neurotensin mRNA as well as the peptide itself were also expressed higher in the medial preoptic area (mPOA). These expression patterns were not shown in the virgin female control group, and align with other research implicating neurotensin gene expression variation in the regulation of maternal behaviors.

Other patterns of neurotensin expression related to the medial preoptic area show relation to the modulation of social reward. Analysis of neurotensin gene-labelled neurons revealed that neurotensin-containing neuronal projections from the mPOA to the ventral tegmental area (VTA) in mice were associated with the encoding of odor cues as well as social attraction, further implicating neurotensin in hormonal as well as reward signaling.

Neurotensin has also been implicated in learning processes. A study examining song development in male zebra finches showed variations in neurotensin and neurotensin receptor gene expression across different stages of song development. The early stage of transition between sensory and sensorimotor periods was marked by decreases in both neurotensin and neurotensin receptor mRNA expression, which may indicate a role of neurotensin in initiating sensorimotor learning. During the sensorimotor subsong stage, neurotensin gene expression and neurotensin receptor 1 (Ntsr1) gene expression exhibited complementary expression patterns in song-related brain regions, which may indicate changes in neuronal responses to neurotensin across development.[3]

Neurotensin also plays a role in peripheral tissues outside of the nervous system, mainly in the gastrointestinal tract, and has been implicated in cancer development. DNA promoter methylation has been shown to be a major regulator in the expression of neurotensin receptor 1 and 2 genes in colorectal cancer cells. Additionally, knock-down of the NTSR1 gene as well as treatment with a NTSR1 antagonist inhibited colorectal cancer cell proliferation and migration. Leiomyomas or fibroid tumors in uterine tissue have also been associated with higher expression of neurotensin and NTSR1.

Neurohypophysial hormones

Neurohypophysial hormones are synthesized in the magnocellular secretory neurons of the hypothalamus. They are then transported along neuronal axons within the infundibular stalk to their axon terminals forming the pars nervosa of the posterior pituitary, where they are stored and released into the systemic circulation. The synthesis, control, and release of those hormones is co-regulated by hormonal, local and synaptic signals. Neurohypophysial hormones include:

Oxytocin

Oxytocin (**Oxt** or **OT**) is a peptide hormone and neuropeptide normally produced in the hypothalamus and released by the posterior pituitary. It plays a role in social bonding, reproduction, childbirth, and the period after childbirth. Oxytocin is released into the bloodstream as a hormone in response to sexual activity and during labour. It is also available in pharmaceutical form. In either form, Oxytocin stimulates uterine contractions to speed up the process of childbirth. In its natural form, it also plays a role in bonding with the baby and milk production. Production and secretion of Oxytocin is controlled by a positive feedback mechanism, where its initial release stimulates production and release of further Oxytocin. For example, when Oxytocin is released during a contraction of the uterus at the start of childbirth, this stimulates production and release of more Oxytocin and an increase in the intensity and frequency of contractions. This process compounds in intensity and frequency and continues until the triggering activity ceases. A similar process takes place during lactation and during sexual activity.

Oxytocin is derived by enzymatic splitting from the peptide precursor encoded by the human OXT gene. The deduced structure of the active nonapeptide is:

Cys – Tyr – Ile – Gln – Asn – Cys – Pro – Leu – Gly – NH_2, or CYIQNCPLG-NH_2.

Etymology

The term "Oxytocin" derives from the Greek "ὠκυτόκος" (*ōkutókos*), based on ὀξύς (oxús), meaning "sharp" or "swift", and τόκος (tókos), meaning "childbirth". The adjective form is "oxytocic", which refers to medicines which stimulate uterine contractions, to speed up the process of childbirth.

Biochemistry

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

Biosynthesis

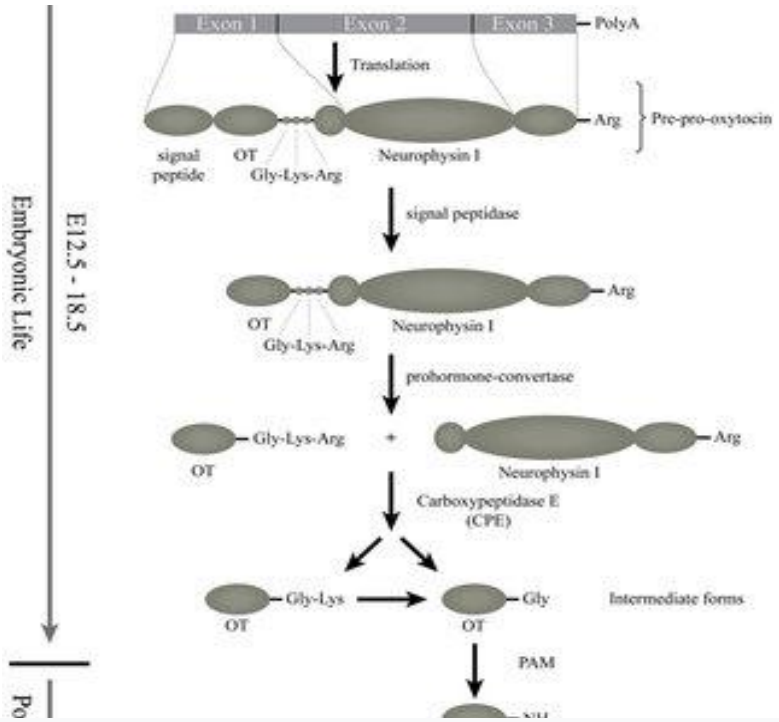

Figure-24: The biosynthesis of the different forms of OT.

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

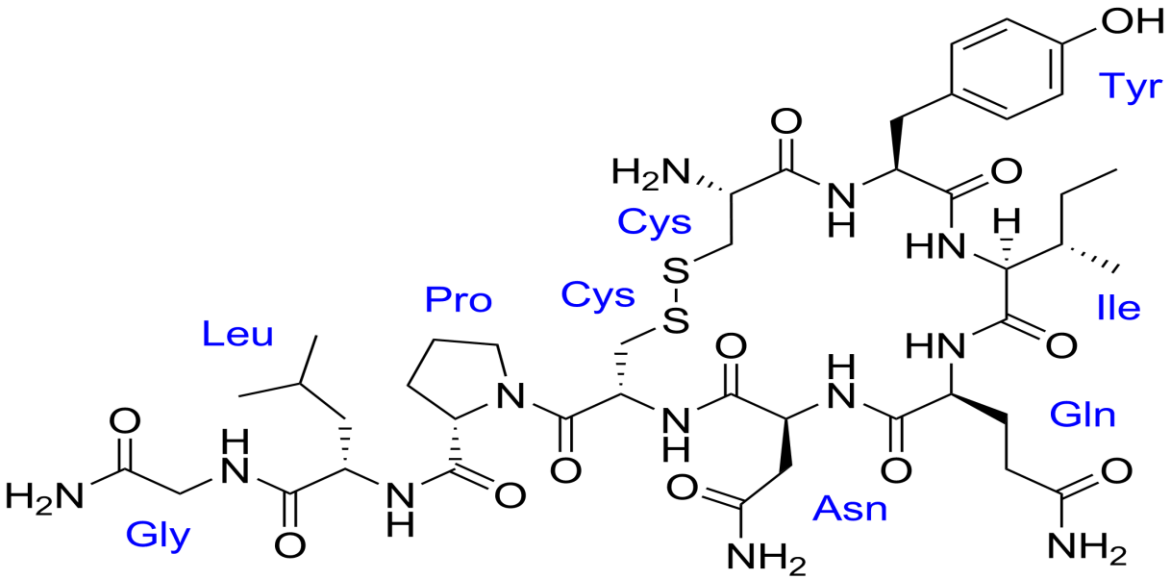

Figure-25: Oxytocin Structure.

The activity of the PAM enzyme system is dependent upon vitamin C (ascorbate), which is a necessary vitamin cofactor. By chance, sodium ascorbate by itself was found to stimulate the production of Oxytocin from ovarian tissue over a range of concentrations in a dose-dependent manner. Many of the same tissues (*e.g.* ovaries, testes, eyes, adrenals, placenta, thymus, and pancreas) where PAM (and oxytocin by default) is found are also known to store higher concentrations of vitamin C.

Oxytocin is known to be metabolized by the oxytocinase, leucyl/cystinyl aminopeptidase. Other oxytocinases are also known to exist. Amastatin, bestatin (ubenimex), leupeptin, and puromycin have been found to inhibit the enzymatic degradation of oxytocin, though they also inhibit the degradation of various other peptides, such as vasopressin, met-enkephalin, and dynorphin A.

Neural sources

In the hypothalamus, Oxytocin is made in magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei, and is stored in Herring bodies at the axon terminals in the posterior pituitary. It is then released into the blood from the posterior lobe (neurohypophysis) of the pituitary gland. These axons (likely, but dendrites have not been ruled out) have collaterals that innervate neurons in the nucleus accumbens, a brain structure where oxytocin receptors are expressed. The endocrine effects of hormonal oxytocin and the cognitive or behavioral effects of oxytocin neuropeptides are thought to be coordinated through its common release through these collaterals. Oxytocin is also produced by some neurons in the paraventricular nucleus that project to other parts of the brain and to the spinal cord. Depending on the species, oxytocin receptor-expressing cells are located in other areas, including the amygdala and bed nucleus of the stria terminalis.

In the pituitary gland, oxytocin is packaged in large, dense-core vesicles, where it is bound to neurophysin I as shown in the inset of the figure; neurophysin is a large peptide fragment of the larger precursor protein molecule from which oxytocin is derived by enzymatic cleavage.

Secretion of oxytocin from the neurosecretory nerve endings is regulated by the electrical activity of the oxytocin cells in the hypothalamus. These cells generate action potentials that propagate down axons to the nerve endings in the pituitary; the endings contain large numbers of oxytocin-containing vesicles, which are released by exocytosis when the nerve terminals are depolarised.

Non-neural sources

Endogenous oxytocin concentrations in the brain have been found to be as much as 1000-fold higher than peripheral levels.

Outside the brain, Oxytocin-containing cells have been identified in several diverse tissues, including in females in the corpus luteum and the placenta; in males in the testicles' interstitial cells of Leydig; and in both sexes in the retina, the adrenal medulla, the thymus and the

pancreas. The finding of significant amounts of this classically "neurohypophysial" hormone outside the central nervous system raises many questions regarding its possible importance in these diverse tissues.

Male

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

Female

Oxytocin is synthesized by corpora lutea of several species, including ruminants and primates. Along with estrogen, it is involved in inducing the endometrial synthesis of prostaglandin $F_{2\alpha}$ to cause regression of the corpus luteum.

Evolution

Virtually all vertebrates have an Oxytocin-like nonapeptide hormone that supports reproductive functions and a vasopressin-like nonapeptide hormone involved in water regulation. The two genes are usually located close to each other (less than 15,000 bases apart) on the same chromosome, and are transcribed in opposite directions (however, in fugu, the homologs are further apart and transcribed in the same direction).

The two genes are believed to result from a gene duplication event; the ancestral gene is estimated to be about 500 million years old and is found in cyclostomata (modern members of the Agnatha).

Biological function

Oxytocin has peripheral (hormonal) actions, and also has actions in the brain. Its actions are mediated by specific Oxytocin receptors. The Oxytocin receptor is a G-protein-coupled receptor, OT-R, which requires magnesium and cholesterol and is expressed in myometrial cells. It belongs to the rhodopsin-type (class I) group of G-protein-coupled receptors.

Studies have looked at oxytocin's role in various behaviors, including orgasm, social recognition, pair bonding, anxiety, in-group bias, situational lack of honesty, autism, and maternal behaviors. Oxytocin is believed to have a significant role in social learning. There are indicators that Oxytocin may help to decrease noise in the brain's auditory system, increase perception of social cues and support more targeted social behavior. It may also enhance reward responses. However, its effects may be influenced by context, such as the presence of familiar or unfamiliar individuals.

Physiological

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

- Milk ejection reflex/Letdown reflex: in lactating (breastfeeding) mothers, Oxytocin acts at the mammary glands, causing milk to be 'let down' into lactiferous ducts, from where it can be excreted via the nipple. Suckling by the infant at the nipple is relayed by spinal nerves to the hypothalamus. The stimulation causes neurons that make Oxytocin to fire action potentials in intermittent bursts; these bursts result in the secretion of pulses of Oxytocin from the neurosecretory nerve terminals of the pituitary gland.
- Uterine contraction: important for cervical dilation before birth, Oxytocin causes contractions during the second and third stages of labor. Oxytocin release during breastfeeding causes mild but often painful contractions during the first few weeks of lactation. This also serves to assist the uterus in clotting the placental attachment point postpartum. However, in knockout mice lacking the Oxytocin receptor, reproductive behavior and parturition are normal.
- In male rats, Oxytocin may induce erections. A burst of Oxytocin is released during ejaculation in several species, including human males; its suggested function is to stimulate contractions of the reproductive tract, aiding sperm release.
- Human sexual response: Oxytocin levels in plasma rise during sexual stimulation and orgasm. At least two uncontrolled studies have found increases in plasma Oxytocin at orgasm – in both men and women. Plasma Oxytocin levels are increased around the time of self-stimulated orgasm and are still higher than baseline when measured five minutes after self arousal. The authors of one of these studies speculated that oxytocin's effects on muscle contractibility may facilitate sperm and egg transport.

In a study measuring Oxytocin serum levels in women before and after sexual stimulation, the author suggests it serves an important role in sexual arousal. This study found genital tract stimulation resulted in increased Oxytocin immediately after orgasm. Another study reported increases of Oxytocin during sexual arousal could be in response to nipple/areola, genital, and/or genital tract stimulation as confirmed in other mammals. Murphy et al. (1987), studying men, found that plasma Oxytocin levels remain unchanged during sexual arousal, but that levels increase sharply after ejaculation, returning to baseline levels within 30

minutes. In contrast, vasopressin was increased during arousal but returned to baseline at the time of ejaculation. The study concludes that (in males) vasopressin is secreted during arousal, while Oxytocin is only secreted after ejaculation. A more recent study of men found an increase in plasma Oxytocin immediately after orgasm, but only in a portion of their sample that did not reach statistical significance. The authors noted these changes "may simply reflect contractile properties on reproductive tissue".

- Due to its similarity to vasopressin, it can reduce the excretion of urine slightly, and so it can be classified as an antidiuretic. In several species, Oxytocin can stimulate sodium excretion from the kidneys (natriuresis), and, in humans, high doses can result in low sodium levels (hyponatremia).
- Cardiac effects: Oxytocin and Oxytocin receptors are also found in the heart in some rodents, and the hormone may play a role in the embryonal development of the heart by promoting cardiomyocyte differentiation. However, the absence of either Oxytocin or its receptor in knockout mice has not been reported to produce cardiac insufficiencies.
- Modulation of hypothalamic-pituitary-adrenal axis activity: Oxytocin, under certain circumstances, indirectly inhibits release of adrenocorticotropic hormone and cortisol and, in those situations, may be considered an antagonist of vasopressin.
- Preparing fetal neurons for delivery (in rats): crossing the placenta, maternal Oxytocin reaches the fetal brain and induces a switch in the action of neurotransmitter GABA from excitatory to inhibitory on fetal cortical neurons. This silences the fetal brain for the period of delivery and reduces its vulnerability to hypoxic damage.
- Feeding: a 2012 paper suggested that oxytocin neurons in the para-ventricular hypothalamus in the brain may play a key role in suppressing appetite under normal conditions and that other hypothalamic neurons may trigger eating via inhibition of these oxytocin neurons. This population of oxytocin neurons is absent in Prader-Willi syndrome, a genetic disorder that leads to uncontrollable feeding and obesity, and may play a key role in its Pathophysiology. Research on the oxytocin-related neuropeptide asterotocin in starfish also showed that in echinoderms, the chemical induces muscle relaxation, and in starfish specifically caused the organisms to evert their stomach and react as though feeding on prey, even when none were present.

Psychological

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

Bonding

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

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

- Human in-group bonding: Oxytocin can increase positive attitudes, such as bonding, toward individuals with similar characteristics, who then become classified as "in-group" members, whereas individuals who are dissimilar become classified as "out-group" members. Race can be used as an example of in-group and out-group tendencies because society often categorizes individuals into groups based on race (Caucasian, African American, Latino, etc.). One study that examined race and empathy found that participants receiving nasally administered Oxytocin had stronger reactions to pictures of in-group members making pained faces than to pictures of out-group members with the same expression. Moreover, individuals of one race may be more inclined to help individuals of the same race than individuals of another race when they are experiencing pain. Oxytocin has also been implicated in lying when lying would prove beneficial to other in-group members. In a study where such a relationship was examined, it was found that when individuals were administered oxytocin, rates of dishonesty in the participants' responses increased for their in-group members when a beneficial outcome for their group was expected. Both of these examples show the tendency of individuals to act in ways that benefit those considered to be members of their social group, or in-group.

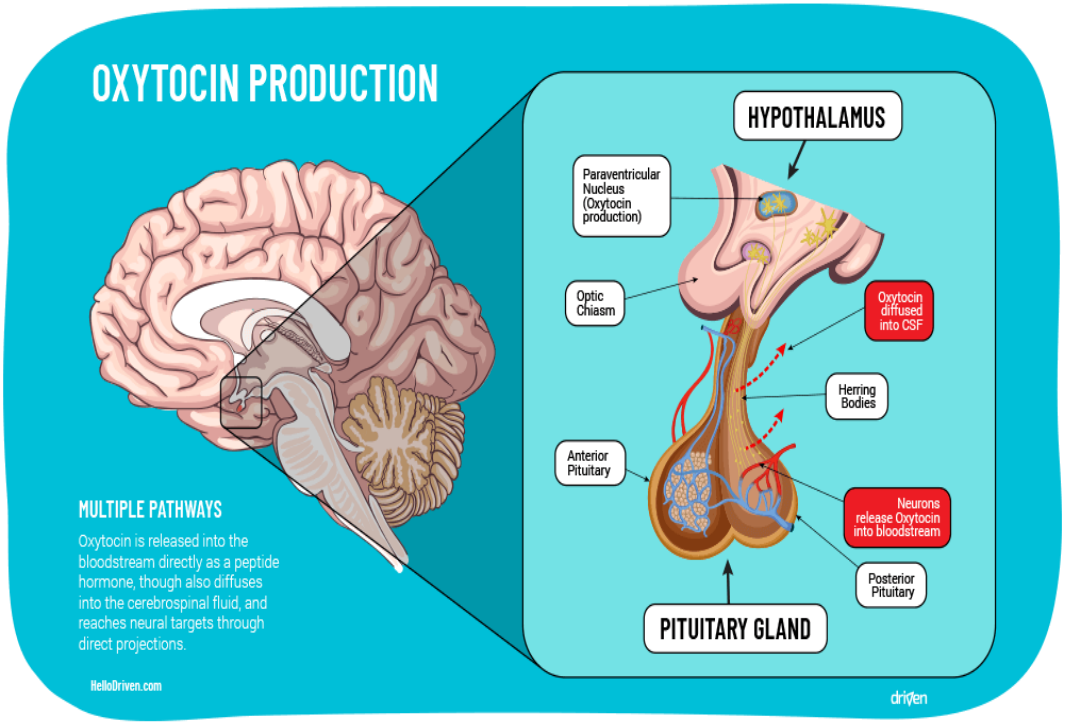

Figure-26: Oxytocin's work in Brain.

Oxytocin is not only correlated with the preferences of individuals to associate with members of their own group, but it is also evident during conflicts between members of different groups. During conflict, individuals receiving nasally administered oxytocin demonstrate more frequent defense-motivated responses toward in-group members than out-group members. Further, oxytocin was correlated with participant desire to protect vulnerable in-group members, despite that individual's attachment to the conflict. Similarly, it has been demonstrated that when oxytocin is administered, individuals alter their subjective preferences in order to align with in-group ideals over out-group ideals. These studies demonstrate that oxytocin is associated with intergroup dynamics. Further, oxytocin influences the responses of individuals in a particular group to those of another group. The in-group bias is evident in smaller groups; however, it can also be extended to groups as large as one's entire country leading toward a tendency of strong national zeal. A study done in the Netherlands showed that Oxytocin increased the in-group favoritism of their nation while decreasing acceptance of members of other ethnicities and foreigners. People also show more affection for their country's flag while remaining indifferent to other cultural objects when exposed to oxytocin. It has thus been hypothesized that this hormone may be a factor in xenophobic tendencies secondary to this effect. Thus, oxytocin appears to affect individuals at an international level where the in-group becomes a specific "home" country and the out-group grows to include all other countries.

Drugs

- **Drug interaction:** According to several studies in animals, oxytocin inhibits the development of tolerance to various addictive drugs (opiates, cocaine, alcohol), and reduces withdrawal symptoms. MDMA (ecstasy) may increase feelings of love, empathy, and connection to others by stimulating oxytocin activity primarily via activation of serotonin 5-HT1A receptors, if initial studies in animals apply to humans. The anxiolytic drug buspirone may produce some of its effects via 5-HT1A receptor-induced oxytocin stimulation as well.
- **Addiction vulnerability:** Concentrations of endogenous oxytocin can impact the effects of various drugs and one's susceptibility to substance use disorders, with higher concentrations associated with lower susceptibility. The status of the endogenous oxytocin system can enhance or reduce susceptibility to addiction through its bidirectional interaction with numerous systems, including the dopamine system, the hypothalamic–pituitary–adrenal axis and the immune system. Individual differences in the endogenous oxytocin system based on genetic predisposition, gender and environmental influences, may therefore affect addiction vulnerability. Oxytocin may be related to the place conditioning behaviors observed in habitual drug abusers.

Fear and anxiety

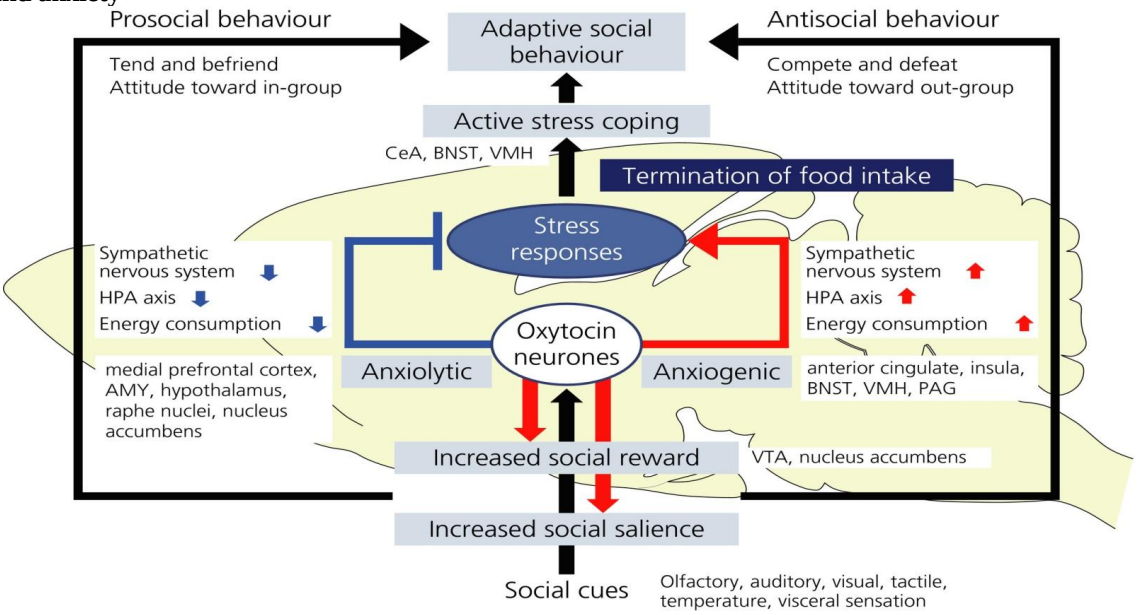

Figure-27: Stress control role of Oxytocin.

Oxytocin is typically remembered for the effect it has on prosocial behaviors, such as its role in facilitating trust and attachment between individuals. However, oxytocin has a more complex role than solely enhancing prosocial behaviors. There is consensus that oxytocin modulates fear and anxiety; that is, it does not directly elicit fear or anxiety. Two dominant theories explain the role of oxytocin in fear and anxiety. One theory states that oxytocin increases approach/avoidance to certain social stimuli and the second theory states that oxytocin increases the salience of certain social stimuli, causing the animal or human to pay closer attention to socially relevant stimuli.

Nasally administered oxytocin has been reported to reduce fear, possibly by inhibiting the amygdala (which is thought to be responsible for fear responses). Indeed, studies in rodents have shown oxytocin can efficiently inhibit fear responses by activating an inhibitory circuit within the amygdala. Some researchers have argued oxytocin has a general enhancing effect on all social emotions, since intranasal administration of oxytocin also increases envy and *Schadenfreude*. Individuals who receive an intranasal dose of oxytocin identify facial expressions of disgust more quickly than individuals who do not receive oxytocin. Facial expressions of disgust are evolutionarily linked to the idea of contagion. Thus, oxytocin increases the salience of cues that imply contamination, which leads to a faster response because these cues are especially relevant for survival. In another study, after administration of oxytocin, individuals displayed an enhanced ability to recognize expressions of fear compared to the individuals who received the placebo. Oxytocin modulates fear responses by enhancing the maintenance of social memories. Rats that are genetically modified to have a surplus of oxytocin receptors display a greater fear response to a previously conditioned stressor. Oxytocin enhances the aversive social memory, leading the rat to display a greater fear response when the aversive stimulus is encountered again.

Mood and depression

Oxytocin produces antidepressant-like effects in animal models of depression, and a deficit of it may be involved in the Pathophysiology of depression in humans. The antidepressant-like effects of oxytocin are not blocked by a selective antagonist of the oxytocin receptor, suggesting that these effects are not mediated by the oxytocin receptor. In accordance, unlike oxytocin, the selective non-peptide oxytocin receptor agonist WAY-267,464 does not produce antidepressant-like effects, at least in the tail suspension test. In contrast to WAY-267,464, carbetocin, a close analogue of oxytocin and peptide oxytocin receptor agonist, notably does produce antidepressant-like effects in animals. As such, the antidepressant-like effects of oxytocin may be mediated by modulation of a different target, perhaps the vasopressin V_{1A} receptor where oxytocin is known to weakly bind as an agonist.

Oxytocin mediates the antidepressant-like effects of sexual activity. A drug for sexual dysfunction, sildenafil enhances electrically evoked oxytocin release from the pituitary gland. In accordance, it may have promise as an antidepressant.

Sex differences

It has been shown that oxytocin differentially affects males and females. Females who are administered oxytocin are overall faster in responding to socially relevant stimuli than males who received oxytocin. Additionally, after the administration of oxytocin, females show increased amygdala activity in response to threatening scenes; however, males do not show increased amygdala activation. This phenomenon can be

explained by looking at the role of gonadal hormones, specifically estrogen, which modulate the enhanced threat processing seen in females. Estrogen has been shown to stimulate the release of oxytocin from the hypothalamus and promote receptor binding in the amygdala.

It has also been shown that testosterone directly suppresses oxytocin in mice. This has been hypothesized to have evolutionary significance. With oxytocin suppressed, activities such as hunting and attacking invaders would be less mentally difficult as oxytocin is strongly associated with empathy.

Social

- Affecting generosity by increasing empathy during perspective taking: In a neuroeconomics experiment, intranasal oxytocin increased generosity in the Ultimatum Game by 80%, but had no effect in the Dictator Game that measures altruism. Perspective-taking is not required in the Dictator Game, but the researchers in this experiment explicitly induced perspective-taking in the Ultimatum Game by not identifying to participants into which role they would be placed. Serious methodological questions have arisen, however, with regard to the role of oxytocin in trust and generosity. Empathy in healthy males has been shown to be increased after intranasal oxytocin This is most likely due to the effect of oxytocin in enhancing eye gaze. There is some discussion about which aspect of empathy oxytocin might alter – for example, cognitive vs. emotional empathy. While studying wild chimpanzees, it was noted that after a chimpanzee shared food with a non-kin related chimpanzee, the subjects' levels of oxytocin increased, as measured through their urine. In comparison to other cooperative activities between chimpanzees that were monitored including grooming, food sharing generated higher levels of oxytocin. This comparatively higher level of oxytocin after food sharing parallels the increased level of oxytocin in nursing mothers, sharing nutrients with their kin.
- Trust is increased by oxytocin. Disclosure of emotional events is a sign of trust in humans. When recounting a negative event, humans who receive intranasal oxytocin share more emotional details and stories with more emotional significance. Humans also find faces more trustworthy after receiving intranasal oxytocin. In a study, participants who received intranasal oxytocin viewed photographs of human faces with neutral expressions and found them to be more trustworthy than those who did not receive oxytocin. This may be because oxytocin reduces the fear of social betrayal in humans. Even after experiencing social alienation by being excluded from a conversation, humans who received oxytocin scored higher in trust on the Revised NEO Personality Inventory. Moreover, in a risky investment game, experimental subjects given nasally administered oxytocin displayed "the highest level of trust" twice as often as the control group. Subjects who were told they were interacting with a computer showed no such reaction, leading to the conclusion that oxytocin was not merely affecting risk aversion. When there is a reason to be distrustful, such as experiencing betrayal, differing reactions are associated with oxytocin receptor gene (OXTR) differences. Those with the CT haplotype experience a stronger reaction, in the form of anger, to betrayal.
- Romantic attachment: In some studies, high levels of plasma oxytocin have been correlated with romantic attachment. For example, if a couple is separated for a long period of time, anxiety can increase due to the lack of physical affection. Oxytocin may aid romantically attached couples by decreasing their feelings of anxiety when they are separated.
- Group-serving dishonesty/deception: In a carefully controlled study exploring the biological roots of immoral behavior, oxytocin was shown to promote dishonesty when the outcome favored the group to which an individual belonged instead of just the individual.
- Oxytocin affects social distance between adult males and females, and may be responsible at least in part for romantic attraction and subsequent monogamous pair bonding. An oxytocin nasal spray caused men in a monogamous relationship, but not single men, to increase the distance between themselves and an attractive woman during a first encounter by 10 to 15 centimeters. The researchers suggested that oxytocin may help promote fidelity within monogamous relationships. For this reason, it is sometimes referred to as the "bonding hormone". There is some evidence that oxytocin promotes ethnocentric behavior, incorporating the trust and empathy of in-groups with their suspicion and rejection of outsiders. Furthermore, genetic differences in the oxytocin receptor gene (OXTR) have been associated with maladaptive social traits such as aggressive behavior.[4]
- Social behavior and wound healing: Oxytocin is also thought to modulate inflammation by decreasing certain cytokines. Thus, the increased release in oxytocin following positive social interactions has the potential to improve wound healing. A study by Marazziti and colleagues used heterosexual couples to investigate this possibility. They found increases in plasma oxytocin following a social interaction were correlated with faster wound healing. They hypothesized this was due to oxytocin reducing inflammation, thus allowing the wound to heal more quickly. This study provides preliminary evidence that positive social interactions may directly influence aspects of health. According to a study published in 2014, silencing of oxytocin receptor interneurons in the medial prefrontal cortex (mPFC)

of female mice resulted in loss of social interest in male mice during the sexually receptive phase of the estrous cycle. Oxytocin evokes feelings of contentment, reductions in anxiety, and feelings of calmness and security when in the company of the mate. This suggests oxytocin may be important for the inhibition of the brain regions associated with behavioral control, fear, and anxiety, thus allowing orgasm to occur. Research has also demonstrated that oxytocin can decrease anxiety and protect against stress, particularly in combination with social support. It is found, that endocannabinoid signaling mediates oxytocin-driven social reward. According to a study published in 2008, its results pointed to how a lack of oxytocin in mice saw a abnormalities in emotional behavior. Another study in conducted in 2014, saw similar results with a variation in the oxytocin receptor is connected with dopamine transporter and how levels of oxytocin are dependent on the levels of dopamine transporter levels. One study explored the effects of low levels of oxytocin and the other on possible explanation of what affects oxytocin receptors. As a lack of social skills and proper emotional behavior are common signs of Autism, low levels of oxytocin could become a new sign for individuals that fall into the Autism Spectrum.

Chemistry

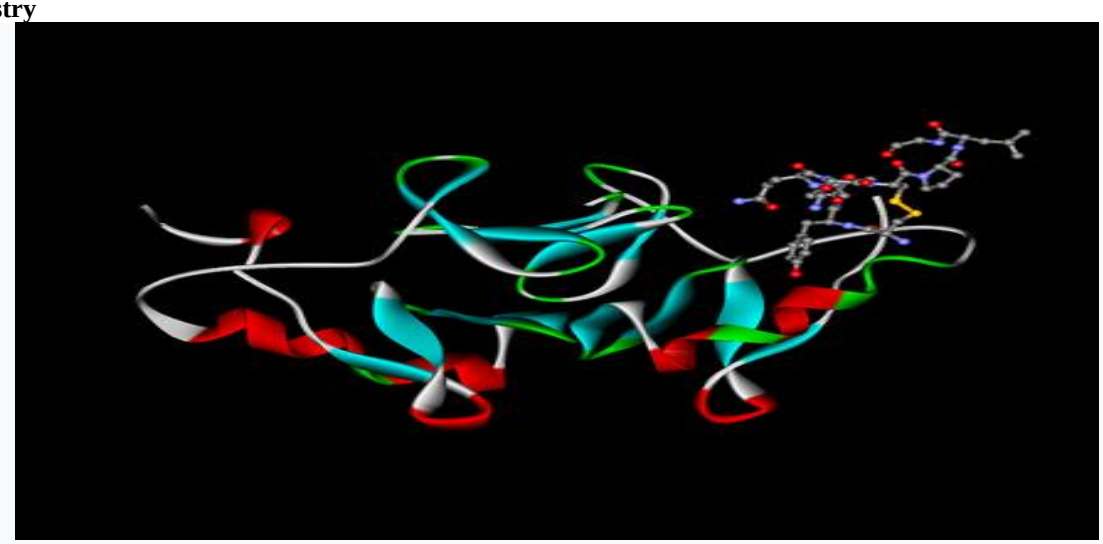

Figure-28: Oxytocin (ball-and-stick) bound to its carrier protein neurophysin (ribbons).

Oxytocin is a peptide of nine amino acids (a nonapeptide) in the sequence cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-amide **(Cys – Tyr – Ile – Gln – Asn – Cys – Pro – Leu – Gly – NH_2**, or CYIQNCPLG-NH_2); its *C*-terminus has been converted to a primary amide and a disulfide bridge joins the cysteine moieties. Oxytocin has a molecular mass of 1007 Da, and one international unit (IU) of oxytocin is the equivalent of 1.68 μg of pure peptide.

While the structure of oxytocin is highly conserved in placental mammals, a novel structure of oxytocin was reported in 2011 in marmosets, tamarins, and other new world primates. Genomic sequencing of the gene for oxytocin revealed a single in-frame mutation (thymine for cytosine) which results in a single amino acid substitution at the 8-position (proline for leucine). Since this original Lee *et al.* paper, two other laboratories have confirmed Pro8-OT and documented additional oxytocin structural variants in this primate taxon. Vargas-Pinilla *et al.* sequenced the coding regions of the OXT gene in other genera in new world primates and identified the following variants in addition to Leu8- and Pro8-OT: Ala8-OT, Thr8-OT, and Val3/Pro8-OT. Ren *et al.* identified a variant further, Phe2-OT in howler monkeys.

The biologically active form of oxytocin, commonly measured by RIA and/or HPLC techniques, is the oxidized octapeptide oxytocin disulfide, but oxytocin also exists as a reduced straight-chain (non-cyclic) dithiol nonapeptide called oxytoceine. It has been theorized that oxytoceine may act as a free radical scavenger, as donating an electron to a free radical allows oxytoceine to be re-oxidized to oxytocin via the dehydroascorbate / ascorbate redox couple.

Recent advances in analytical instrumental techniques highlighted the importance of liquid chromatography (LC) coupled with mass spectrometry (MS) for measuring oxytocin levels in various samples derived from biological sources. Most of these studies optimized the oxytocin quantification in electrospray ionization (ESI) positive mode, using $[M+H]^+$ as the parent ion at mass-to-charge ratio (*m/z*) 1007.4 and the fragment ions as diagnostic peaks at *m/z* 991.0, *m/z* 723.2 and *m/z* 504.2. These important ion selections paved the way for the development of current methods of oxytocin quantification using MS instrumentation.

The structure of oxytocin is very similar to that of vasopressin. Both are nonapeptides with a single disulfide bridge, differing only by two substitutions in the amino acid sequence (differences from oxytocin bolded for clarity):**Cys – Tyr – Phe – Gln – Asn – Cys – Pro – Arg – Gly – NH_2**. Oxytocin and vasopressin were isolated and their total synthesis reported in 1954, work for which Vincent du Vigneaud was awarded the 1955 Nobel Prize in Chemistry with the citation: "for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone."

Oxytocin and vasopressin are the only known hormones released by the human posterior pituitary gland to act at a distance. However, oxytocin neurons make other peptides, including corticotropin-releasing hormone and dynorphin, for example that act locally. The magnocellular neurosecretory cells that make oxytocin are adjacent to magnocellular neurosecretory cells that make vasopressin. These are large neuroendocrine neurons which are excitable and can generate action potentials.

Vasopressin

Vasopressin, also called **antidiuretic hormone** (**ADH**), **arginine vasopressin** (**AVP**) or **argipressin**, is a hormone synthesized from the *AVP* gene as a peptide prohormone in neurons in the hypothalamus, and is converted to AVP. It then travels down the axon terminating in the posterior pituitary, and is released from vesicles into the circulation in response to extracellular fluid hypertonicity (hyperosmolality). AVP has two primary functions. First, it increases the amount of solute-free water reabsorbed back into the circulation from the filtrate in the kidney tubules of the nephrons. Second, AVP constricts arterioles, which increases peripheral vascular resistance and raises arterial blood pressure.

A third function is possible. Some AVP may be released directly into the brain from the hypothalamus, and may play an important role in social behavior, sexual motivation and pair bonding, and maternal responses to stress.

Vasopressin induces differentiation of stem cells into cardiomyocytes and promotes heart muscle homeostasis. It has a very short half-life, between 16 and 24 minutes.

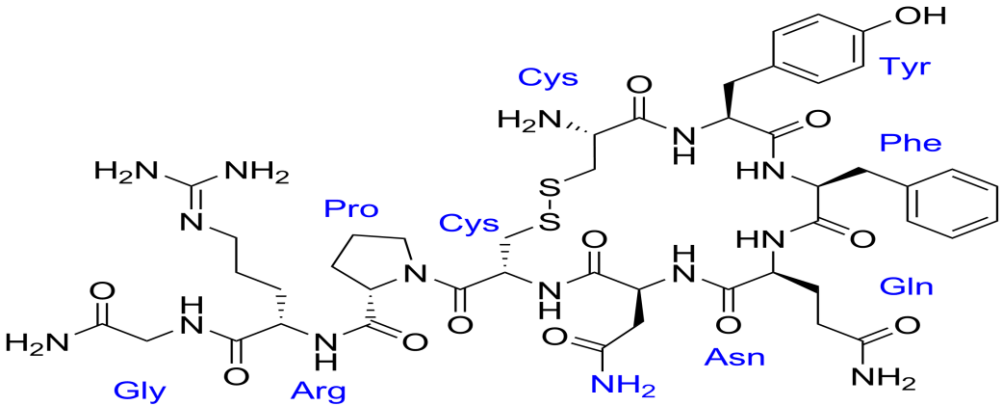

Figure-29: Vasopressin Structure.

Physiology

Function

Vasopressin regulates the tonicity of body fluids. It is released from the posterior pituitary in response to hypertonicity and causes the kidneys to reabsorb solute-free water and return it to the circulation from the tubules of the nephron, thus returning the tonicity of the body fluids toward normal. An incidental consequence of this renal reabsorption of water is concentrated urine and reduced urine volume. AVP released in high concentrations may also raise blood pressure by inducing moderate vasoconstriction.

AVP also may have a variety of neurological effects on the brain. It may influence pair-bonding in voles. The high-density distributions of vasopressin receptor AVPr1a in prairie vole ventral forebrain regions have been shown to facilitate and coordinate reward circuits during partner preference formation, critical for pair bond formation.

A very similar substance, *lysine vasopressin* (**LVP**) or **lypressin** has the same function in pigs and its synthetic version was used in human AVP deficiency, although it has been largely replaced by desmopressin.

Kidney

Vasopressin has three main effects which are:

1. Increasing the water permeability of distal and cortical collecting tubules (DCT & CCT), as well as outer and inner medullary collecting duct (OMCD & IMCD) in the kidney, thus allowing water reabsorption and excretion of more concentrated urine, i.e., antidiuresis. This occurs through increased transcription and insertion of water channels (Aquaporin-2) into the apical membrane of collecting tubule and collecting duct epithelial

cells. Aquaporins allow water to move down their osmotic gradient and out of the nephron, increasing the amount of water re-absorbed from the filtrate (forming urine) back into the bloodstream. This effect is mediated by V2 receptors. Vasopressin also increases the concentration of calcium in the collecting duct cells, by episodic release from intracellular stores. Vasopressin, acting through cAMP, also increases transcription of the aquaporin-2 gene, thus increasing the total number of aquaporin-2 molecules in collecting duct cells.

2. Increasing permeability of the inner medullary portion of the collecting duct to urea by regulating the cell surface expression of urea transporters, which facilitates its reabsorption into the medullary interstitium as it travels down the concentration gradient created by removing water from the connecting tubule, cortical collecting duct, and outer medullary collecting duct.
3. Acute increase of sodium absorption across the ascending loop of Henle. This adds to the countercurrent multiplication which aids in proper water reabsorption later in the distal tubule and collecting duct.

Central nervous system

Vasopressin released within the brain may have several actions:

- Vasopressin is released into the brain in a circadian rhythm by neurons of the suprachiasmatic nucleus.
- Vasopressin released from posterior pituitary is associated with nausea.
- Recent evidence suggests that vasopressin may have analgesic effects. The analgesia effects of vasopressin were found to be dependent on both stress and sex.

Regulation

Gene regulation

Vasopressin is regulated by *AVP* gene expression which is managed by major clock controlled genes. In this circadian circuit known as the transcription-translation feedback loop (TTFL), Per2 protein accumulates and is phosphorylated by CK1E. Per2 subsequently inhibits the transcription factors Clock and BMAL1 in order to reduce Per2 protein levels in the cell. At the same time, Per2 also inhibits the transcription factors for the *AVP* gene in order to regulate its expression, the expression of vasopressin, and other *AVP* gene products.

Many factors influence the secretion of vasopressin:

- Ethanol (alcohol) reduces the calcium-dependent secretion of AVP by blocking voltage-gated calcium channels in neurohypophysial nerve terminals in rats.
- Angiotensin II stimulates AVP secretion, in keeping with its general pressor and pro-volumic effects on the body.
- Atrial natriuretic peptide inhibits AVP secretion, in part by inhibiting Angiotensin II-induced stimulation of AVP secretion.
- Cortisol inhibits secretion of antidiuretic hormone.

Production and secretion

The physiologic stimulus for secretion of vasopressin is increased osmolality of the plasma, monitored by the hypothalamus. A decreased arterial blood volume, (such as can occur in cirrhosis, nephrosis and heart failure), stimulates secretion, even in the face of decreased osmolality of the plasma: it supersedes osmolality, but with a milder effect. In other words, vasopressin is secreted in spite of the presence of hypoosmolality (hyponatremia) when the arterial blood volume is low.

The AVP that is measured in peripheral blood is almost all derived from secretion from the posterior pituitary gland (except in cases of AVP-secreting tumours). Vasopressin is produced by magnocellular neurosecretory neurons in the paraventricular nucleus of hypothalamus (PVN) and supraoptic nucleus (SON). It then travels down the axon through the infundibulum within neurosecretory granules that are found within Herring bodies, localized swellings of the axons and nerve terminals. These carry the peptide directly to the posterior pituitary gland, where it is stored until released into the blood.

There are other sources of AVP, beyond the hypothalamic magnocellular neurons. For example, AVP is also synthesized by parvocellular neurosecretory neurons of the PVN, transported and released at the median eminence, from which it travels through the hypophyseal portal system to the anterior pituitary, where it stimulates corticotropic cells synergistically with CRH to produce ACTH (by itself it is a weak secretagogue).

Vasopressin during surgery and anaesthesia

Vasopressin concentration is used to measure surgical stress for evaluation of surgical techniques. Plasma vasopressin concentration is elevated by noxious stimuli, predominantly during abdominal surgery, especially at gut manipulation and traction of viscera.

Receptors

Types of AVP receptors and their actions

Type	Second messenger system	Locations	Actions	Agonists	Antagonists
AVPR1A	Phosphatidylinositol /calcium	Liver, kidney, peripheral vasculature, brain	Vasoconstriction, gluconeogenesis, platelet aggregation, and release of factor VIII and von Willebrand factor; social recognition, circadian tau	Felypressin	
AVPR1B or AVPR3	Phosphatidylinositol /calcium	Pituitary gland, brain	Adrenocorticotropic hormone secretion in response to stress; social interpretation of olfactory cues		
AVPR2	Adenylate cyclase/cAMP	Basolateral membrane of the cells lining the collecting ducts of the kidneys (especially the cortical and outer medullary collecting ducts)	Insertion of aquaporin-2 (AQP2) channels (water channels). This allows water to be reabsorbed down an osmotic gradient, and so the urine is more concentrated. Release of von Willebrand factor and surface expression of P-selectin through exocytosis of Weibel-Palade bodies from endothelial cells	AVP, desmopressin	"-vaptan" diuretics, i.e. tolvaptan

Structure and relation to oxytocin

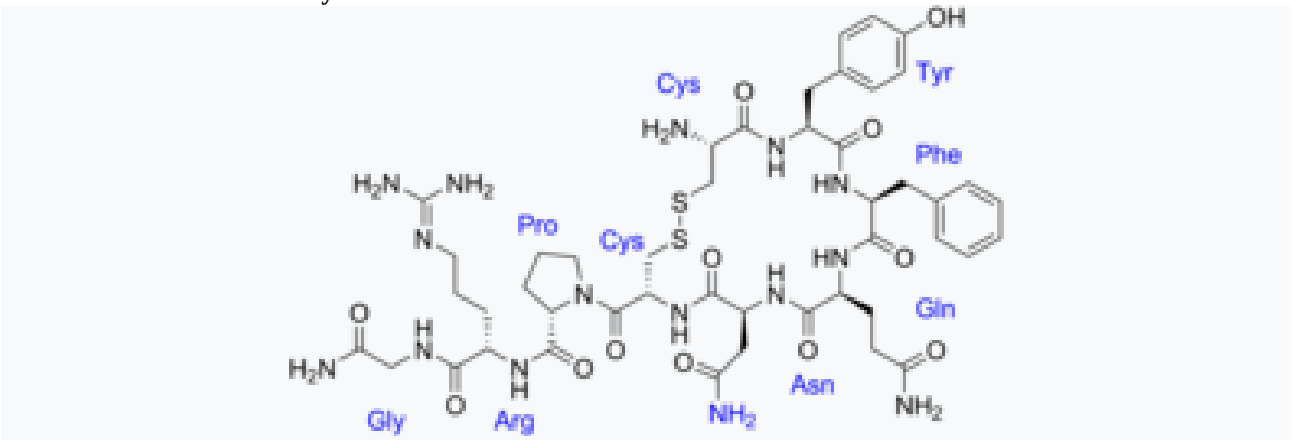

Figure-30: Chemical structure of the arginine vasopressin (argipressin) with an arginine at the 8th amino acid position. Lysine vasopressin differs only in having a lysine in this position.

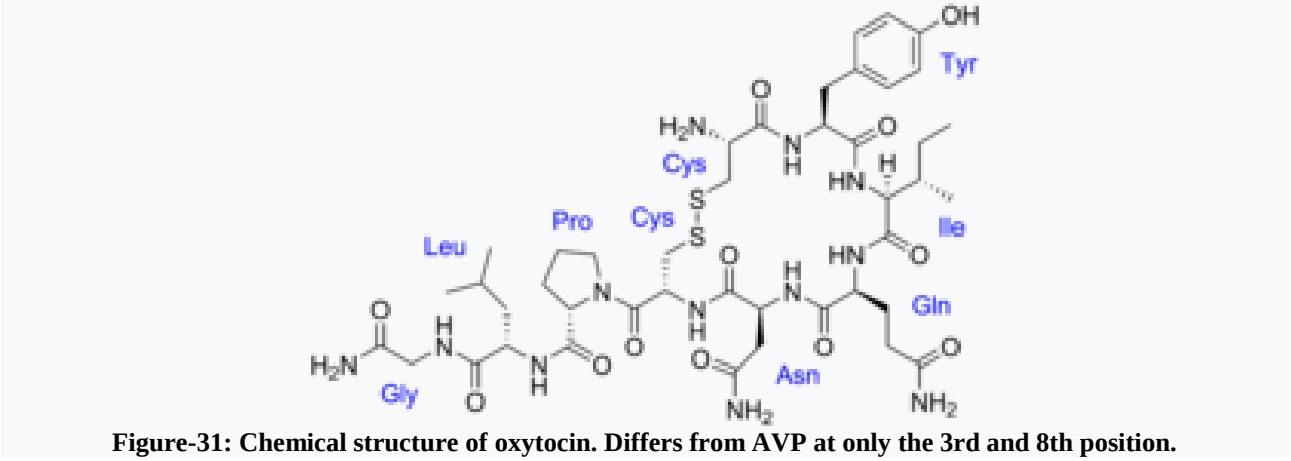

Figure-31: Chemical structure of oxytocin. Differs from AVP at only the 3rd and 8th position.

The vasopressins are peptides consisting of nine amino acids (nonapeptides). The amino acid sequence of arginine vasopressin (argipressin) is **Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2,** with the cysteine residues forming a disulfide bond and the *C*-terminus of the sequence converted to a primary amide. Lysine vasopressin (lypressin) has a lysine in place of the arginine as the eighth amino acid, and is found in pigs and some related animals, whereas arginine vasopressin is found in humans.

The structure of oxytocin is very similar to that of the vasopressins: It is also a nonapeptide with a disulfide bridge and its amino acid sequence differs at only two

positions. The two genes are located on the same chromosome separated by a relatively small distance of less than 15,000 bases in most species. The magnocellular neurons that secrete vasopressin are adjacent to magnocellular neurons that secrete oxytocin, and are similar in many respects. The similarity of the two peptides can cause some cross-reactions: oxytocin has a slight antidiuretic function, and high levels of AVP can cause uterine contractions.

Comparison of vasopressin and oxytocin neuropeptide families

Vertebrate Vasopressin Family		
Cys-Tyr-**Phe**-Gln-Asn-Cys-Pro-**Arg**-Gly-NH_2	Argipressin (AVP, ADH)	Most mammals
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2	Lypressin (LVP)	Pigs, hippos, warthogs, some marsupials
Cys-Phe-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2	Phenypressin	Some marsupials
Cys-Tyr-**Ile**-Gln-Asn-Cys-Pro-**Arg**-Gly-NH_2	Vasotocin†	Non-mammals
Vertebrate Oxytocin Family		
Cys-Tyr-**Ile**-Gln-Asn-Cys-Pro-**Leu**-Gly-NH_2	Oxytocin (OXT)	Most mammals, ratfish
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Pro-Gly-NH_2	Prol-Oxytocin	Some New World monkeys, northern tree shrews
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Ile-Gly-NH_2	Mesotocin	Most marsupials, all birds, reptiles, amphibians, lungfishes, coelacanths
Cys-Tyr-Ile-Gln-Ser-Cys-Pro-Ile-Gly-NH_2	Seritocin	Frogs
Cys-Tyr-Ile-Ser-Asn-Cys-Pro-Ile-Gly-NH_2	Isotocin	Bony fishes
Cys-Tyr-Ile-Ser-Asn-Cys-Pro-Gln-Gly-NH_2	Glumitocin	skates
Cys-Tyr-Ile-Asn/Gln-Asn-Cys-Pro-Leu/Val-Gly-NH_2	Various tocins	Sharks
Invertebrate VP/OT Superfamily		
Cys-Leu-Ile-Thr-Asn-Cys-Pro-Arg-Gly-NH_2	Inotocin	Locust
Cys-Phe-Val-Arg-Asn-Cys-Pro-Thr-Gly-NH_2	Annetocin	Earthworm
Cys-Phe-Ile-Arg-Asn-Cys-Pro-Lys-Gly-NH_2	Lys-Connopressin	Geography & imperial cone snail, pond snail, sea hare, leech
Cys-Ile-Ile-Arg-Asn-Cys-Pro-Arg-Gly-NH_2	Arg-Connopressin	Striped cone snail
Cys-Tyr-Phe-Arg-Asn-Cys-Pro-Ile-Gly-NH_2	Cephalotocin	Octopus
Cys-Phe-Trp-Thr-Ser-Cys-Pro-Ile-Gly-NH_2	Octopressin	Octopus
†Vasotocin is the evolutionary progenitor of all the vertebrate neurohypophysial hormones.		

Medical use

Vasopressin is used to manage anti-diuretic hormone deficiency. Vasopressin is used to treat diabetes insipidus related to low levels of antidiuretic hormone. It is available as Pressyn.

Vasopressin has off-label uses and is used in the treatment of vasodilatory shock, gastrointestinal bleeding, ventricular tachycardia and ventricular fibrillation.

Vasopressin agonists are used therapeutically in various conditions, and its long-acting synthetic analogue desmopressin is used in conditions featuring low vasopressin secretion, as well as for control of bleeding (in some forms of von Willebrand disease and in mild haemophilia A) and in extreme cases of bedwetting by children. Terlipressin and related analogues are used as vasoconstrictors in certain conditions. Use of vasopressin analogues for esophageal varices commenced in 1970.

Vasopressin infusions are also used as second line therapy for septic shock patients not responding to fluid resuscitation or infusions of catecholamines (e.g., dopamine or norepinephrine) to increase the blood pressure while sparing the use of catecholamines. These argipressins have much shorter elimination half-life (around 20 minutes) comparing to synthetic non-arginine vasopresines with much longer elimination half-life of many hours. Further, argipressins act on V1a, V1b, and V2 receptors which consequently lead to higher eGFR and lower vascular resistance in the lungs. A number of injectable arginine vasopressins are currently in clinical use in the United States and in Europe.

Pharmacokinetics

Vasopressin is administered through an intravenous device, intramuscular injection or a subcutaneous injection. The duration of action depends on the mode of administration and ranges from thirty minutes to two hours. It has a half life of ten to twenty minutes. It is widely distributed throughout the body and remains in the extracellular fluid. It is degraded by the liver and excreted through the kidneys. Arginine vasopressins for use in septic shock are intended for intravenous use only.

Side effects

The most common side effects during treatment with vasopressin are dizziness, angina, chest pain, abdominal cramps, heartburn, nausea, vomiting, trembling, fever, water intoxication, pounding sensation in the head, diarrhoea, sweating, paleness, and flatulence. The most severe adverse reactions are myocardial infarction and hypersensitivity.

Contraindications

The use of lysine vasopressin is contraindicated in the presence of hypersensitivity to beef or pork proteins, increased BUN and chronic kidney failure. It is recommended that it be cautiously used in instances of perioperative polyuria, sensitivity to the drug, asthma, seizures, heart failure, a comatose state, migraine headaches, and cardiovascular disease.

Interactions

- Alcohol - may lower the antidiuretic effect
- Carbamazepine, chloropropamide, clofibrate, tricyclic antidepressants and fludrocortisone may raise the diuretic effect
- Lithium, demeclocycline, heparin or norepinephrine may lower the antidiuretic effect
- Vasopressor effect may be higher with the concurrent use of ganglionic blocking medications

Role in disease

There may be a connection between arginine vasopressin and autism.

Deficiency

Decreased AVP release (neurogenic — i.e. due to alcohol intoxication or tumour) or decreased renal sensitivity to AVP (nephrogenic, i.e. by mutation of V2 receptor or AQP) leads to diabetes insipidus, a condition featuring hypernatremia (increased blood sodium concentration), polyuria (excess urine production), and polydipsia (thirst).

Excess

Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) in turn can be caused by a number of problems. Some forms of cancer can cause SIADH, particularly small cell lung carcinoma but also a number of other tumors. A variety of diseases affecting the brain or the lung (infections, bleeding) can be the driver behind SIADH. A number of drugs have been associated with SIADH, such as certain antidepressants (serotonin reuptake inhibitors and tricyclic antidepressants), the anticonvulsant carbamazepine, oxytocin (used to induce and stimulate labor), and the chemotherapy drug vincristine. It has also been associated with fluoroquinolones (including ciprofloxacin and moxifloxacin). Finally, it can occur without a clear explanation. Hyponatremia can be treated pharmaceutically through the use of vasopressin receptor antagonists.

Animal studies

Evidence for an effect of AVP on monogamy vs polygamy comes from experimental studies in several species, which indicate that the precise distribution of vasopressin and vasopressin receptors in the brain is associated with species-typical patterns of social behavior. In particular, there are consistent differences between monogamous species and polygamous species in the distribution of AVP receptors, and sometimes in the distribution of vasopressin-containing axons, even when closely related species are compared.

Human studies

Vasopressin has shown no tropic effects on pain perception and cognitive function. Vasopressin also plays a role in autism, major depressive disorder, bipolar disorder, and schizophrenia.

This is through this pathway that the vast majority of oxytocin and vasopressin hormones reach the systemic circulation.

Adrenomedullary hormones

Adrenomedullary hormones are catecholamines secreted from the adrenal medulla by chromaffin cells, neurosecretory cells connected to the central nervous system. The synthesis, storage (in chromaffin cells) and release of catecholamines is co-regulated by synaptic input from their respective pre-synaptic sympathetic neurons, as well as hormonal and local inputs. The adrenomedullary hormones are:

Adrenaline

Adrenaline, also known as **epinephrine**, is a hormone and medication which is involved in regulating visceral functions (e.g., respiration). Adrenaline is normally produced both by the adrenal glands and by a small number of neurons in the medulla oblongata. It plays an important role in the fight-or-flight response by increasing blood flow to muscles, output of the heart by acting on the SA node, pupil dilation response and blood sugar level. It does this by binding to alpha and beta receptors. It is found in many animals and some single-celled organisms. Polish physiologist Napoleon Cybulski first isolated adrenaline in 1895.

Medical uses

As a medication, it is used to treat a number of conditions including allergic reaction anaphylaxis, cardiac arrest, and superficial bleeding. Inhaled adrenaline may be used to improve the symptoms of croup. It may also be used for asthma when other treatments are not effective. It is given intravenously, by injection into a muscle, by inhalation, or by injection just under the skin. Common side effects include shakiness, anxiety, and sweating. A fast heart rate and high blood pressure may occur. Occasionally it may result in an abnormal heart rhythm. While the safety of its use during pregnancy and breastfeeding is unclear, the benefits to the mother must be taken into account.

A case has been made for the use of adrenaline infusion in place of the widely accepted treatment of inotropes for preterm infants with clinical cardiovascular compromise. Although there is sufficient data which strongly recommends adrenaline infusions as a viable treatment, more trials are needed in order to conclusively determine that these infusions will successfully reduce morbidity and mortality rates among preterm, cardiovascularly compromised infants.

Physiological effects

The adrenal medulla is a minor contributor to total circulating catecholamines (L-DOPA is at a higher concentration in the plasma), though it contributes over 90% of circulating adrenaline. Little adrenaline is found in other tissues, mostly in scattered chromaffin cells, and in a small number of neurons which use adrenaline as a neurotransmitter.

Following adrenalectomy, adrenaline disappears below the detection limit in the blood stream.

Pharmacological doses of adrenaline stimulate α_1, α_2, β_1, β_2, and β_3 adrenoceptors of the sympathetic nervous system. Sympathetic nerve receptors are classified as adrenergic, based on their responsiveness to adrenaline the term "adrenergic" is often misinterpreted in that the main sympathetic neurotransmitter is noradrenaline, rather than adrenaline, as discovered by Ulf von Euler in 1946. Adrenaline does have a β_2 adrenoceptor-mediated effect on metabolism and the airway, there being no direct neural connection from the sympathetic ganglia to the airway.

The concept of the adrenal medulla and the sympathetic nervous system being involved in the flight and fright response was originally proposed by Walter Bradford Cannon. But the adrenal medulla, in contrast to the adrenal cortex, is not required for survival. In adrenalectomized patients hemodynamic and metabolic responses to stimuli such as hypoglycemia and exercise remain normal.

Exercise

One physiological stimulus to adrenaline secretion is exercise. This was first demonstrated by measuring the dilation of a (denervated) pupil of a cat on a treadmill, later confirmed using a biological assay on urine samples. Biochemical methods for measuring catecholamines in plasma were published from 1950 onwards. Although much valuable work has been published using fluorimetric assays to measure total catecholamine concentrations, the method is too non-specific and insensitive to accurately determine the very small quantities of adrenaline in plasma. The development of extraction methods and enzyme-isotope derivate radio-enzymatic assays (REA) transformed the analysis down to a sensitivity of 1 pg for adrenaline. Early REA plasma assays indicated that adrenaline and total catecholamines rise late in exercise, mostly when anaerobic metabolism commences.

During exercise, the adrenaline blood concentration rises partially from the increased secretion of the adrenal medulla and partly from the decreased metabolism of adrenaline due to reduced blood flow to the liver. Infusion of adrenaline to reproduce exercise circulating concentrations of adrenaline in subjects at rest has little hemodynamic effect, other than a small β_2-mediated fall in diastolic blood pressure. Infusion of adrenaline well within the physiological range suppresses human airway hyper-reactivity sufficiently to antagonize the constrictor effects of inhaled histamine.

A link between the sympathetic nervous system and the lungs was shown in 1887 when Grossman showed that stimulation of cardiac accelerator nerves reversed muscarine-induced airway constriction. In experiments in the dog, where the sympathetic chain was cut at the

level of the diaphragm, Jackson showed that there was no direct sympathetic innervation to the lung, but that bronchoconstriction was reversed by release of adrenaline from the adrenal medulla. An increased incidence of asthma has not been reported for adrenalectomized patients; those with a predisposition to asthma will have some protection from airway hyper-reactivity from their corticosteroid replacement therapy. Exercise induces progressive airway dilation in normal subjects that correlates with work load and is not prevented by beta blockade. The progressive dilation of the airway with increasing exercise is mediated by a progressive reduction in resting vagal tone. Beta blockade with propranolol causes a rebound in airway resistance after exercise in normal subjects over the same time course as the bronchoconstriction seen with exercise induced asthma. The reduction in airway resistance during exercise reduces the work of breathing.[5]

Emotional response

Every emotional response has a behavioral component, an autonomic component, and a hormonal component. The hormonal component includes the release of adrenaline; an adrenomedullary response that occurs in response to stress and that is controlled by the sympathetic nervous system. The major emotion studied in relation to adrenaline is fear. In an experiment, subjects who were injected with adrenaline expressed more negative and fewer positive facial expressions to fear films compared to a control group. These subjects also reported a more intense fear from the films and greater mean intensity of negative memories than control subjects. The findings from this study demonstrate that there are learned associations between negative feelings and levels of adrenaline. Overall, the greater amount of adrenaline is positively correlated with an aroused state of negative feelings. These findings can be an effect in part that adrenaline elicits physiological sympathetic responses including an increased heart rate and knee shaking, which can be attributed to the feeling of fear regardless of the actual level of fear elicited from the video. Although studies have found a definite relation between adrenaline and fear, other emotions have not had such results. In the same study, subjects did not express a greater amusement to an amusement film nor greater anger to an anger film. Similar findings were also supported in a study that involved rodent subjects that either were able or unable to produce adrenaline. Findings support the idea that adrenaline does have a role in facilitating the encoding of emotionally arousing events, contributing to higher levels of arousal due to fear.

Memory

It has been found that adrenergic hormones, such as adrenaline, can produce retrograde enhancement of long-term memory in humans. The release of adrenaline due to emotionally stressful events, which is endogenous adrenaline, can modulate memory consolidation of the events, ensuring memory strength that is proportional to memory importance. Post-learning adrenaline activity also interacts with the degree of arousal associated with the initial coding. There is evidence that suggests adrenaline does have a role in long-term stress adaptation and emotional memory encoding specifically. Adrenaline may also play a role in elevating arousal and fear memory under particular pathological conditions including post-traumatic stress disorder. Overall, "Extensive evidence indicates that epinephrine (EPI) modulates memory consolidation for emotionally arousing tasks in animals and human subjects." Studies have also found that recognition memory involving adrenaline depends on a mechanism that depends on β adrenoceptors. Adrenaline does not readily cross the blood–brain barrier, so its effects on memory consolidation are at least partly initiated by β adrenoceptors in the periphery. Studies have found that sotalol, a β adrenoceptor antagonist that also does not readily enter the brain, blocks the enhancing effects of peripherally administered adrenaline on memory. These findings suggest that β adrenoceptors are necessary for adrenaline to have an effect on memory consolidation.

Pathology

Increased adrenaline secretion is observed in pheochromocytoma, hypoglycemia, myocardial infarction and to a lesser degree in essential tremor (also known as benign, familial or idiopathic tremor). A general increase in sympathetic neural activity is usually accompanied by increased adrenaline secretion, but there is selectivity during hypoxia and hypoglycaemia, when the ratio of adrenaline to noradrenaline is considerably increased. Therefore, there must be some autonomy of the adrenal medulla from the rest of the sympathetic system.

Myocardial infarction is associated with high levels of circulating adrenaline and noradrenaline, particularly in cardiogenic shock.

Benign familial tremor (BFT) is responsive to peripheral β adrenergic blockers and β_2-stimulation is known to cause tremor. Patients with BFT were found to have increased plasma adrenaline, but not noradrenaline.

Low, or absent, concentrations of adrenaline can be seen in autonomic neuropathy or following adrenalectomy. Failure of the adrenal cortex, as with Addison's disease, can suppress adrenaline secretion as the activity of the synthesing enzyme, phenylethanolamine-*N*-methyltransferase, depends on the high concentration of cortisol that drains from the cortex to the medulla.

Terminology

In 1901, Jōkichi Takamine patented a purified extract from the adrenal glands which was trademarked by Parke, Davis & Co in the US. The British Approved Name and European Pharmacopoeia term for this drug is hence *adrenaline*.

However, the pharmacologist John Abel had already prepared an extract from adrenal glands as early as 1897, and coined the name *epinephrine* to describe it (from the Greek *epi* and *nephros*, "on top of the kidneys"). In the belief that Abel's extract was the same as Takamine's (a belief since disputed), epinephrine became the generic name in the US, and remains the pharmaceutical's United States Adopted Name and International Nonproprietary Name (though the name adrenaline is frequently used).

The terminology is now one of the few differences between the INN and BAN systems of names. Although European health professionals and scientists preferentially use the term *adrenaline*, the converse is true among American health professionals and scientists. Nevertheless, even among the latter, receptors for this substance are called *adrenergic receptors* or *adrenoceptors*, and pharmaceuticals that mimic its effects are often called *adrenergics*. The history of adrenaline and epinephrine is reviewed by Rao.

Mechanism of action

Physiologic responses to adrenaline by organ	
Organ	**Effects**
Heart	Increases heart rate; contractility; conduction across AV node
Lungs	Increases respiratory rate; bronchodilation
Liver	Stimulates glycogenolysis
Muscle	Stimulates glycogenolysis and glycolysis
Brain	
Systemic	Vasoconstriction and vasodilation
	Triggers lipolysis
	Muscle contraction

As a hormone, adrenaline acts on nearly all body tissues by binding to adrenergic receptors. Its effects on various tissues depend of the type of tissue and expression of specific forms of adrenergic receptors. For example, a high level of adrenaline causes smooth muscle relaxation in the airways but causes contraction of the smooth muscle that lines most arterioles.

Adrenaline is a no selective agonist of all adrenergic receptors, including the major subtypes α_1, α_2, β_1, β_2, and β_3. Adrenaline's binding to these receptors triggers a number of metabolic changes. Binding to α-adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle, and stimulates glycolysis and inhibits insulin-Mediated glycogenesis in muscle. β adrenergic receptor binding triggers glucagon secretion in the pancreas, increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together, these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body.

Adrenaline causes liver cells to release glucose into the blood, acting through both alpha and beta adrenergic receptors to stimulate glycogenolysis. Adrenaline binds to β_2 receptors on liver cells, which changes conformation and helps G_s, a heterotrimeric G protein, exchange GDP to GTP. This trimeric G protein dissociates to G_s alpha and G_s beta/gamma subunits. G_s alpha stimulates adenylyl cyclase, thus converting adenosine triphosphate into cyclic adenosine monophosphate (AMP). Cyclic AMP activates protein kinase A. Protein kinase A phosphorylates and partially activates phosphorylase kinase. Adrenaline also binds to α_1 adrenergic receptors, causing an increase in inositol trisphosphate, inducing calcium ions to enter the cytoplasm. Calcium ions bind to calmodulin, which leads to further activation of phosphorylase kinase. Phosphorylase kinase phosphorylates glycogen phosphorylase, which then breaks down glycogen leading to the production of glucose.

Adrenaline also has significant effects on the cardiovascular system. It increases peripheral resistance via α_1 receptor-dependent vasoconstriction and increases cardiac output by binding to β_1 receptors. The goal of reducing peripheral circulation is to increase coronary and cerebral perfusion pressures and therefore increase oxygen exchange at the cellular level. While adrenaline does increase aortic, cerebral, and carotid circulation pressure, it lowers carotid blood flow and end-tidal CO_2 or E_TCO_2 levels. It appears that adrenaline may be improving macrocirculation at the expense of the capillary beds where actual perfusion is taking place.

Measurement in biological fluids

Adrenaline may be quantified in blood, plasma or serum as a diagnostic aid, to monitor therapeutic administration, or to identify the causative agent in a potential poisoning victim. Endogenous plasma adrenaline concentrations in resting adults are normally less than 10 ng/L, but may increase by 10-fold during exercise and by 50-fold or more during times of stress. Pheochromocytoma patients often have plasma adrenaline levels of 1000–10,000 ng/L. Parenteral administration of adrenaline to

acute-care cardiac patients can produce plasma concentrations of 10,000 to 100,000 ng/L.

Biosynthesis and regulation

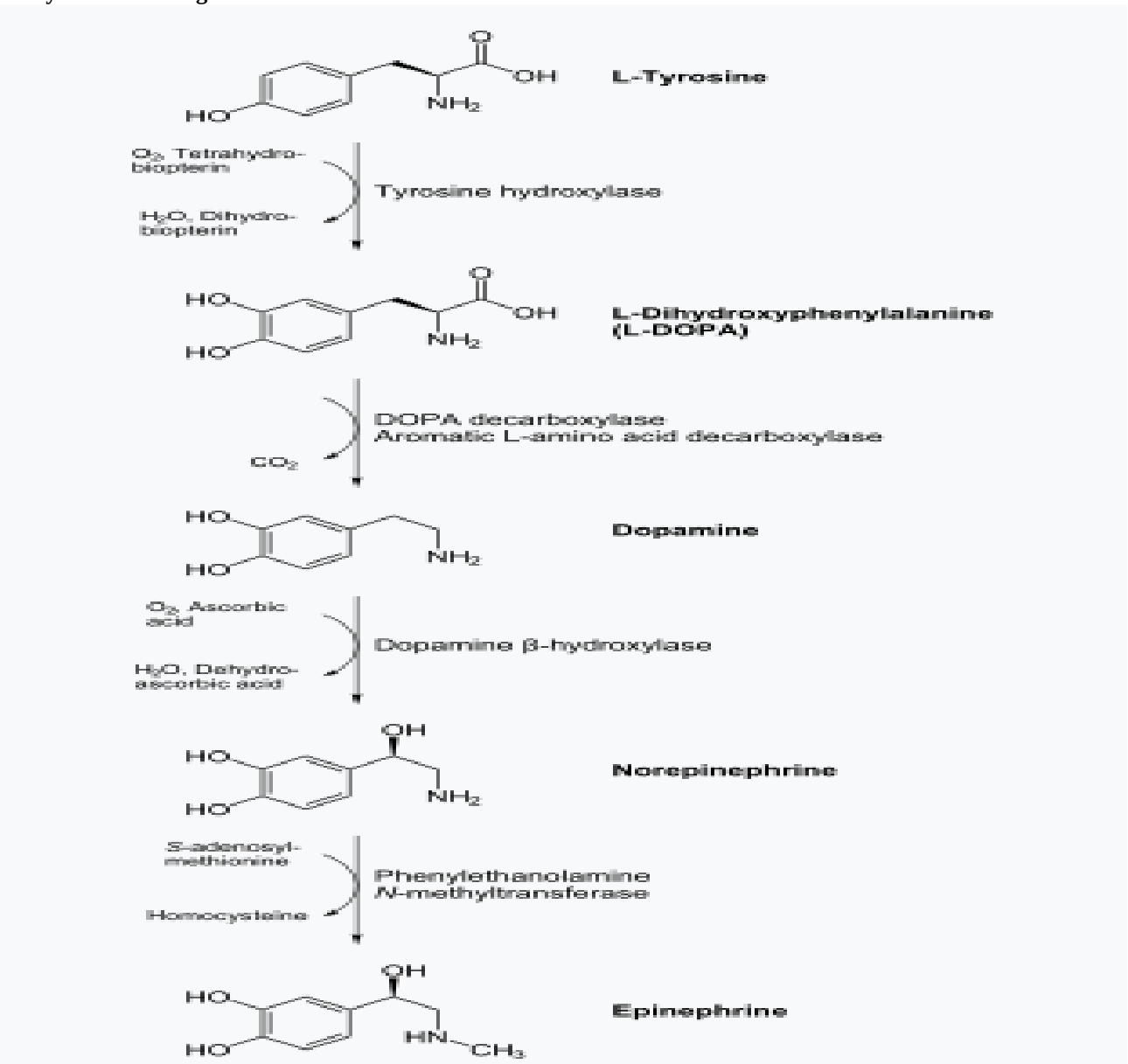

Figure-32: The biosynthesis of adrenaline involves a series of enzymatic reactions.

In chemical terms, adrenaline is one of a group of monoamines called the catecholamines. Adrenaline is synthesized in the chromaffin cells of the adrenal medulla of the adrenal gland and a small number of neurons in the medulla oblongata in the brain through a metabolic pathway that converts the amino acids phenylalanine and tyrosine into a series of metabolic intermediates and, ultimately, adrenaline. Tyrosine is first oxidized to L-DOPA by tyrosine hydroxylase, this is the rate-limiting step. Then it is subsequently decarboxylated to give dopamine by DOPA decarboxylase (aromatic L-amino acid decarboxylase). Dopamine is then converted to noradrenaline by dopamine beta-hydroxylase which utilizes ascorbic acid (vitamin C) and copper. The final step in adrenaline biosynthesis is the methylation of the primary amine of noradrenaline. This reaction is catalyzed by the enzyme phenylethanolamine *N*-methyltransferase (PNMT) which utilizes *S*-adenosyl methionine (SAMe) as the methyl donor. While PNMT is found primarily in the cytosol of the endocrine cells of the adrenal medulla (also known as chromaffin cells), it has been detected at low levels in both the heart and brain.

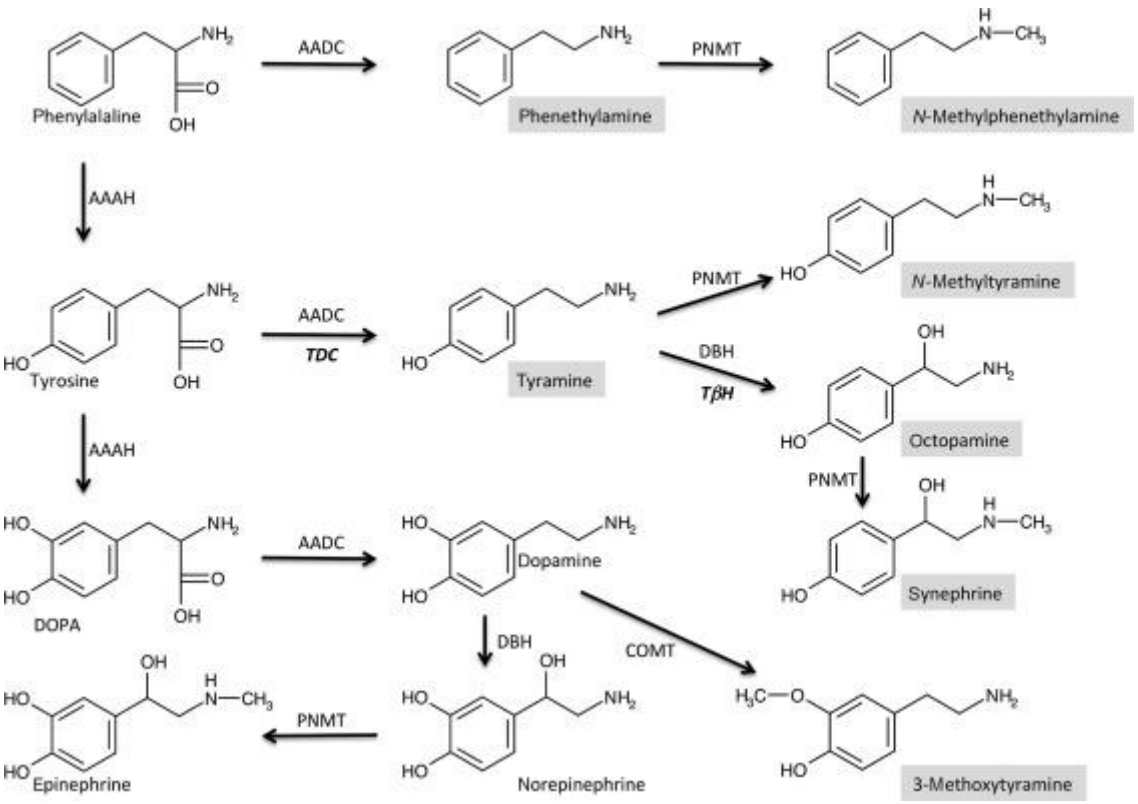

Figure-33: Biosynthetic pathways for catecholamines and trace amines in the human brain.

Regulation

The major physiologic triggers of adrenaline release center upon stresses, such as physical threat, excitement, noise, bright lights, and high or low ambient temperature. All of these stimuli are processed in the central nervous system.

Adrenocorticotropic hormone (ACTH) and the sympathetic nervous system stimulate the synthesis of adrenaline precursors by enhancing the activity of tyrosine hydroxylase and dopamine β-hydroxylase, two key enzymes involved in catecholamine synthesis. ACTH also stimulates the adrenal cortex to release cortisol, which increases the expression of PNMT in chromaffin cells, enhancing adrenaline synthesis. This is most often done in response to stress. The sympathetic nervous system, acting via splanchnic nerves to the adrenal medulla, stimulates the release of adrenaline. Acetylcholine released by preganglionic sympathetic fibers of these nerves acts on nicotinic acetylcholine receptors, causing cell depolarization and an influx of calcium through voltage-gated calcium channels. Calcium triggers the exocytosis of chromaffin granules and, thus, the release of adrenaline (and noradrenaline) into the bloodstream. For noradrenaline to be acted upon by PNMT in the cytosol, it must first be shipped out of granules of the chromaffin cells. This may occur via the catecholamine-H^+ exchanger VMAT1. VMAT1 is also responsible for transporting newly synthesized adrenaline from the cytosol back into chromaffin granules in preparation for release.

Unlike many other hormones adrenaline (as with other catecholamines) does not exert negative feedback to down-regulate its own synthesis. Abnormally elevated levels of adrenaline can occur in a variety of conditions, such as surreptitious adrenaline administration, pheochromocytoma, and other tumors of the sympathetic ganglia.

Its action is terminated with reuptake into nerve terminal endings, some minute dilution, and metabolism by monoamine oxidase and catechol-*O*-methyl transferase.

Society and culture

Adrenaline junkie

An *adrenaline junkie* is somebody who engages in sensation-seeking behavior through "the pursuit of novel and intense experiences without regard for physical, social, legal or financial risk". Such activities include extreme and risky sports, substance abuse, unsafe sex, and crime. The term relates to the increase in circulating levels of adrenaline during physiological stress. Such an increase in the circulating concentration of adrenaline is secondary to activation of the sympathetic nerves innervating the adrenal medulla, as it is rapid and not present in animals where the adrenal gland has been removed. Although such stress triggers adrenaline release, it also activates many other responses within the central nervous system reward system which drives behavioral responses, so while the circulating adrenaline concentration is present, it may not drive behavior. Nevertheless, adrenaline infusion alone does increase

alertness and has roles in the brain including the augmentation of memory consolidation.

Norepinephrine

Norepinephrine (**NE**), also called **noradrenaline** (**NA**) or **noradrenalin**, is an organic chemical in the catecholamine family that functions in the brain and body as both a hormone and neurotransmitter. The name "noradrenaline," derived from Latin roots meaning "at/alongside the kidneys," is more commonly used in the United Kingdom; in the United States, "norepinephrine," derived from Greek roots having that same meaning, is usually preferred. "Norepinephrine" is also the international non-proprietary name given to the drug. Regardless of which name is used for the substance itself, parts of the body that produce or are affected by it are referred to as **noradrenergic**.

The general function of norepinephrine is to mobilize the brain and body for action. Norepinephrine release is lowest during sleep, rises during wakefulness, and reaches much higher levels during situations of stress or danger, in the so-called fight-or-flight response. In the brain, norepinephrine increases arousal and alertness, promotes vigilance, enhances formation and retrieval of memory, and focuses attention; it also increases restlessness and anxiety. In the rest of the body, norepinephrine increases heart rate and blood pressure, triggers the release of glucose from energy stores, increases blood flow to skeletal muscle, reduces blood flow to the gastrointestinal system, and inhibits voiding of the bladder and gastrointestinal motility.

In the brain, noradrenaline is produced in nuclei that are small yet exert powerful effects on other brain areas. The most important of these nuclei is the locus coeruleus, located in the pons. Outside the brain, norepinephrine is used as a neurotransmitter by sympathetic ganglia located near the spinal cord or in the abdomen, as well as Merkel cells located in the skin. It is also released directly into the bloodstream by the adrenal glands. Regardless of how and where it is released, norepinephrine acts on target cells by binding to and activating adrenergic receptors located on the cell surface.

A variety of medically important drugs work by altering the actions of noradrenaline systems. Noradrenaline itself is widely used as an injectable drug for the treatment of critically low blood pressure. Beta blockers, which counter some of the effects of noradrenaline by blocking their receptors, are frequently used to treat glaucoma, migraine, and a range of cardiovascular problems. Alpha blockers, which counter a different set of noradrenaline effects, are used to treat several cardiovascular and psychiatric conditions. Alpha-2 agonists often have a sedating effect and are commonly used as anesthesia-enhancers in surgery, as well as in treatment of drug or alcohol dependence. Many important psychiatric drugs exert strong effects on noradrenaline systems in the brain, resulting in side-effects that may be helpful or harmful.[6]

Structure

Norepinephrine is a catecholamine and a phenethylamine. Its structure differs from that of epinephrine only in that epinephrine has a methyl group attached to its nitrogen, whereas the methyl group is replaced by a hydrogen atom in norepinephrine. The prefix *nor-* is derived as an abbreviation of the word "normal", used to indicate a demethylated compound.

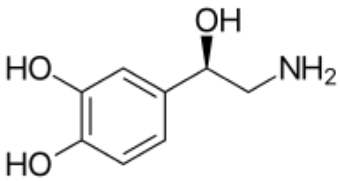

Figure-34: Norepinephrine structure.

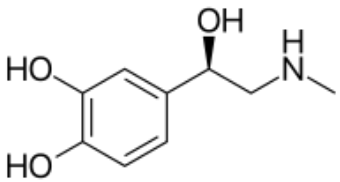

Figure-35: Epinephrine structure.

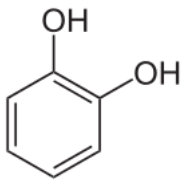

Figure-36: Catechol structure.

Biochemical mechanisms

Biosynthesis

Norepinephrine is synthesized from the amino acid tyrosine by a series of enzymatic steps in the adrenal medulla and postganglionic neurons of the sympathetic nervous system. While the conversion of tyrosine to dopamine occurs predominantly in the cytoplasm, the conversion of dopamine to norepinephrine by dopamine β-monooxygenase occurs predominantly inside neurotransmitter vesicles. The metabolic pathway is:

Phenylalanine → Tyrosine → L-DOPA → Dopamine → Norepinephrine

Thus the direct precursor of norepinephrine is dopamine, which is synthesized indirectly from the essential amino acid phenylalanine or the non-essential amino acid tyrosine. These amino acids are found in nearly every protein and, as such, are provided by ingestion of protein-containing food, with tyrosine being the most common.

Phenylalanine is converted into tyrosine by the enzyme phenylalanine hydroxylase, with molecular oxygen (O_2) and tetrahydrobiopterin as cofactors. Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase, with tetrahydrobiopterin, O_2, and probably ferrous iron (Fe^{2+}) as cofactors. Conversion of tyrosine to L-DOPA is inhibited by Metyrosine, a tyrosine analog. L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (also known as DOPA decarboxylase), with pyridoxal phosphate as a cofactor. Dopamine is then converted into norepinephrine by the enzyme dopamine β-monooxygenase (formerly known as *dopamine β-hydroxylase*), with O_2 and ascorbic acid as cofactors.

Norepinephrine itself can further be converted into epinephrine by the enzyme phenylethanolamine *N*-methyltransferase with *S*-adenosyl-L-methionine as cofactor.

Degradation

In mammals, norepinephrine is rapidly degraded to various metabolites. The initial step in the breakdown can be catalyzed by either of the enzymes monoamine oxidase (mainly monoamine oxidase A) or COMT. From there the breakdown can proceed by a variety of pathways. The principal end products are either Vanillylmandelic acid or a conjugated form of MHPG, both of which are thought to be biologically inactive and are excreted in the urine.

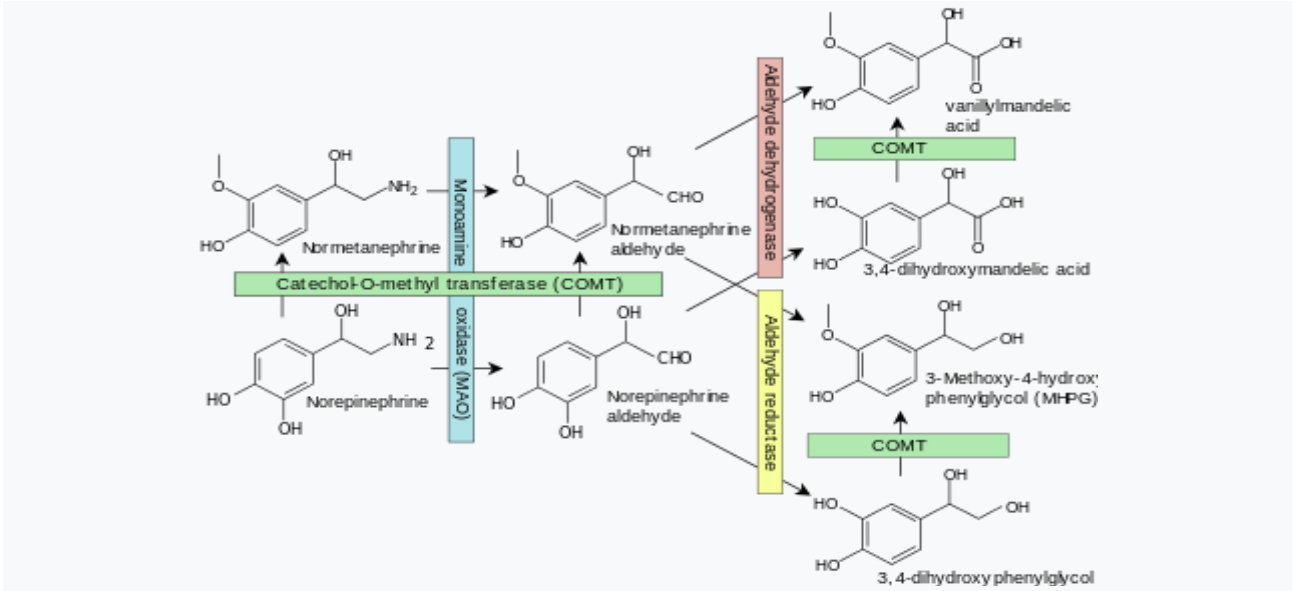

Figure-37: Norepinephrine degradation. Metabolizing enzymes are shown in boxes.

Functions

Cellular effects

Adrenergic receptors in the mammal brain and body			
Family	**Receptor**	**Type**	**Mechanism**
Alpha	α_1	G_q-coupled.	Increase IP_3 and calcium by activating phospholipase C.
	α_2	G_i/G_o-coupled.	Decrease cAMP by inhibiting adenylate cyclase.
Beta	β_1	G_s-coupled.	Increase cAMP by activating adenylate cyclase.
	β_2, β_3		

Like many other biologically active substances, norepinephrine exerts its effects by binding to and activating receptors located on the surface of cells. Two broad families of norepinephrine receptors have been identified, known as alpha and beta adrenergic receptors. Alpha receptors are divided into subtypes α_1 and α_2; beta receptors into subtypes β_1, β_2, and β_3. All of these function as G protein-coupled receptors, meaning that they exert their effects via a complex second messenger system. Alpha-2 receptors usually have inhibitory effects, but many are located pre-synaptically (i.e., on the surface of the cells that release norepinephrine), so the net effect of alpha-2 activation is often a decrease in the amount of norepinephrine released. Alpha-1 receptors and all three types of beta receptors usually have excitatory effects.

Storage, release, and reuptake

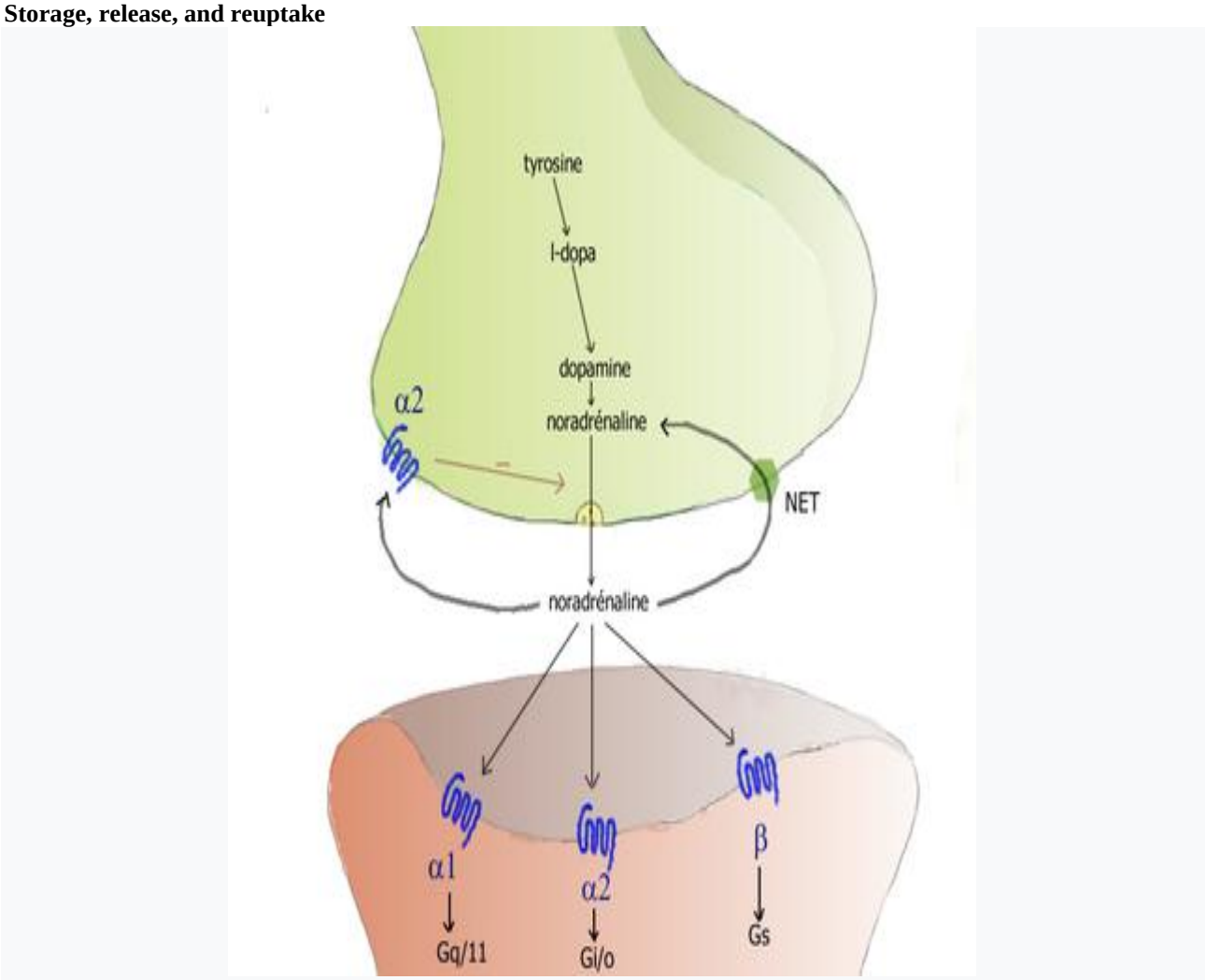

Figure-38: Norepinephrine (labeled "noradrenaline" in this drawing) processing in a synapse. After release norepinephrine can either be taken up again by the presynaptic terminal, or broken down by enzymes.

Inside the brain norepinephrine functions as a neurotransmitter, and is controlled by a set of mechanisms common to all monoamine neurotransmitters. After synthesis, norepinephrine is transported from the cytosol into synaptic vesicles by the vesicular monoamine transporter (VMAT). VMAT can be inhibited by Reserpine causing a decrease in neurotransmitter stores. Norepinephrine is stored in these vesicles until it is ejected into the synaptic cleft, typically after an action potential causes the vesicles to release their contents directly into the synaptic cleft through a process called exocytosis.

Once in the synapse, norepinephrine binds to and activates receptors. After an action potential, the norepinephrine molecules quickly become unbound from their receptors. They are then absorbed back into the presynaptic cell, via reuptake mediated primarily by the norepinephrine transporter (NET). Once back in the cytosol, norepinephrine can either be broken down by monoamine oxidase or repackaged into vesicles by VMAT, making it available for future release.

Sympathetic nervous system

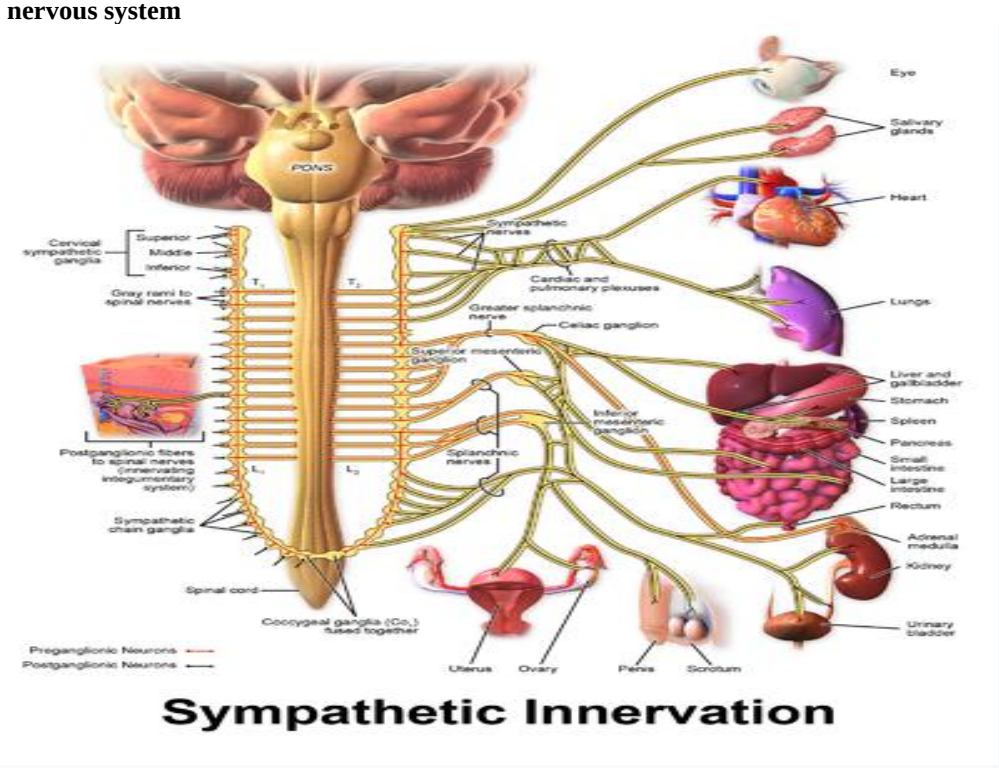

Figure-39: Schema of the sympathetic nervous system, showing the sympathetic ganglia and the parts of the body to which they connect.

Norepinephrine is the main neurotransmitter used by the sympathetic nervous system, which consists of about two dozen sympathetic chain ganglia located next to the spinal cord, plus a set of prevertebral ganglia located in the chest and abdomen. These sympathetic ganglia are connected to numerous organs, including the eyes, salivary glands, heart, lungs, liver, gallbladder, stomach, intestines, kidneys, urinary bladder, reproductive organs, muscles, skin, and adrenal glands. Sympathetic activation of the adrenal glands causes the part called the adrenal medulla to release norepinephrine (as well as epinephrine) into the bloodstream, from which, functioning as a hormone, it gains further access to a wide variety of tissues.

Broadly speaking, the effect of norepinephrine on each target organ is to modify its state in a way that makes it more conducive to active body movement, often at a cost of increased energy use and increased wear and tear. This can be contrasted with the acetylcholine-mediated effects of the parasympathetic nervous system, which modifies most of the same organs into a state more conducive to rest, recovery, and digestion of food, and usually less costly in terms of energy expenditure.

The sympathetic effects of norepinephrine include

- In the eyes, an increase in production of tears, making the eyes more moist, and pupil dilation through contraction of the iris dilator.
- In the heart, an increase in the amount of blood pumped.
- In brown adipose tissue, an increase in calories burned to generate body heat (thermogenesis).
- Multiple effects on the immune system. The sympathetic nervous system is the primary path of interaction between the immune system and the brain, and several components receive sympathetic inputs, including the thymus, spleen, and lymph nodes. However the effects are complex, with some immune processes activated while others are inhibited.
- In the arteries, constriction of blood vessels, causing an increase in blood pressure.
- In the kidneys, release of renin and retention of sodium in the bloodstream.
- In the liver, an increase in production of glucose, either by glycogenolysis after a meal or by gluconeogenesis when food has not recently been consumed. Glucose is the body's main energy source in most conditions.
- In the pancreas, increased release of glucagon, a hormone whose main effect is to increase the production of glucose by the liver.
- In skeletal muscles, an increase in glucose uptake.
- In adipose tissue (i.e., fat cells), an increase in lipolysis, that is, conversion of fat to substances that can be used directly as energy sources by muscles and other tissues.
- In the stomach and intestines, a reduction in digestive activity. This results from a generally inhibitory effect of norepinephrine on the enteric nervous system, causing decreases in gastrointestinal

mobility, blood flow, and secretion of digestive substances.

Noradrenaline and ATP are sympathetic co-transmitters. It is found that the endocannabinoid anandamide and the cannabinoid WIN 55,212-2 can modify the overall response to sympathetic nerve stimulation, which indicates that prejunctional CB1 receptors mediate the sympatho-inhibitory action. Thus cannabinoids can inhibit both the noradrenergic and purinergic components of sympathetic neurotransmission.

Central nervous system

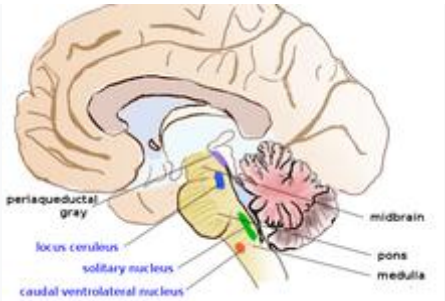

Figure-40: Brain areas containing noradrenergic neurons.

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

Noradrenergic neurons (i.e., neurons whose primary neurotransmitter is norepinephrine) are comparatively few in number, and their cell bodies are confined to a few relatively small brain areas, but they send projections to many other brain areas and exert powerful effects on their targets. These noradrenergic cell groups were first mapped in 1964 by Annica Dahlström and Kjell Fuxe, who assigned them labels starting with the letter "A" (for "aminergic").In their scheme, areas A1 through A7 contain the neurotransmitter norepinephrine (A8 through A14 contain dopamine). Noradrenergic cell group A1 is located in the caudal ventrolateral part of the medulla, and plays a role in the control of body fluid metabolism. Noradrenergic cell group A2 is located in a brainstem area called the solitary nucleus; these cells have been implicated in a variety of responses, including control of food intake and responses to stress. Cell groups A5 and A7 project mainly to the spinal cord.[7]

The most important source of norepinephrine in the brain is the locus coeruleus, which contains noradrenergic cell group A6 and adjoins cell group A4. The locus coeruleus is quite small in absolute terms—in primates it is estimated to contain around 15,000 neurons, less than one-millionth of the neurons in the brain—but it sends projections to every major part of the brain and also to the spinal cord.

The level of activity in the locus coeruleus correlates broadly with vigilance and speed of reaction. LC activity is low during sleep and drops to virtually nothing during the REM (dreaming) state. It runs at a baseline level during wakefulness, but increases temporarily when a person is presented with any sort of stimulus that draws attention. Unpleasant stimuli such as pain, difficulty breathing, bladder distension, heat or cold generate larger increases. Extremely unpleasant states such as intense fear or intense pain are associated with very high levels of LC activity.

Norepinephrine released by the locus coeruleus affects brain function in a number of ways. It enhances processing of sensory inputs, enhances attention, enhances formation and retrieval of both long term and working memory, and enhances the ability of the brain to respond to inputs by changing the activity pattern in the prefrontal cortex and other areas. The control of arousal level is strong enough that drug-induced suppression of the LC has a powerful sedating effect.

There is great similarity between situations that activate the locus coeruleus in the brain and situations that activate the sympathetic nervous system in the periphery: the LC essentially mobilizes the brain for action while the sympathetic system mobilizes the body. It has been argued that this similarity arises because both are to a large degree controlled by the same brain structures, particularly a part of the brainstem called the nucleus gigantocellularis.

Skin

Norepinephrine is also produced by Merkel cells which are part of the somatosensory system. It activates the afferent sensory neuron.

Pharmacology

A large number of important drugs exert their effects by interacting with norepinephrine systems in the brain or body. Their uses include treatment of cardiovascular problems, shock, and a variety of psychiatric conditions. These drugs are divided into: sympathomimetic drugs which mimic or enhance at least some of the effects of norepinephrine released by the sympathetic nervous system; sympatholytic drugs, in contrast, block at least some of the effects. Both of these are large

groups with diverse uses, depending on exactly which effects are enhanced or blocked.

Norepinephrine itself is classified as a sympathomimetic drug: its effects when given by intravenous injection of increasing heart rate and force and constricting blood vessels make it very useful for treating medical emergencies that involve critically low blood pressure. Surviving Sepsis Campaign recommended norepinephrine as first line agent in treating septic shock which is unresponsive to fluid resuscitation, supplemented by vasopressin and epinephrine. Dopamine usage is restricted only to highly selected patients.

Beta blockers

These are sympatholytic drugs that block the effects of beta adrenergic receptors while having little or no effect on alpha receptors. They are sometimes used to treat high blood pressure, atrial fibrillation and congestive heart failure, but recent reviews have concluded that other types of drugs are usually superior for those purposes. Beta blockers may be a viable choice for other cardiovascular conditions, though, including angina and Marfan syndrome. They are also widely used to treat glaucoma, most commonly in the form of eye drops. Because of their effects in reducing anxiety symptoms and tremor, they have sometimes been used by entertainers, public speakers and athletes to reduce performance anxiety, although they are not medically approved for that purpose and are banned by the International Olympic Committee.

However, the usefulness of beta blockers is limited by a range of serious side effects, including slowing of heart rate, a drop in blood pressure, asthma, and reactive hypoglycemia. The negative effects can be particularly severe in people who suffer from diabetes.

Alpha blockers

These are sympatholytic drugs that block the effects of adrenergic alpha receptors while having little or no effect on beta receptors. Drugs belonging to this group can have very different effects, however, depending on whether they primarily block alpha-1 receptors, alpha-2 receptors, or both. Alpha-2 receptors, as described elsewhere in this article, are frequently located on norepinephrine-releasing neurons themselves and have inhibitory effects on them; consequently, blockage of alpha-2 receptors usually results in an increase in norepinephrine release. Alpha-1 receptors are usually located on target cells and have excitatory effects on them; consequently, blockage of alpha-1 receptors usually results in blocking some of the effects of norepinephrine. Drugs such as phentolamine that act on both types of receptors can produce a complex combination of both effects. In most cases when the term "alpha blocker" is used without qualification, it refers to a selective alpha-1 antagonist.

Selective alpha-1 blockers have a variety of uses. Since one of their effects is to inhibit the contraction of the smooth muscle in the prostate, they are often used to treat symptoms of benign prostatic hyperplasia. Alpha-blockers also likely help people pass their kidney stones. Their effects on the central nervous system make them useful for treating generalized anxiety disorder, panic disorder, and posttraumatic stress disorder. They may, however, have significant side-effects, including a drop in blood pressure.

Some antidepressants function partly as selective alpha-2 blockers, but the best-known drug in that class is yohimbine, which is extracted from the bark of the African yohimbe tree. Yohimbine acts as a male potency enhancer, but its usefulness for that purpose is limited by serious side-effects including anxiety and insomnia. Overdoses can cause a dangerous increase in blood pressure. Yohimbine is banned in many countries, but in the United States, because it is extracted from a plant rather than chemically synthesized, it is sold over the counter as a nutritional supplement.

Alpha-2 agonists

These are sympathomimetic drugs that activate alpha-2 receptors or enhance their effects. Because alpha-2 receptors are inhibitory and many are located presynaptically on norepinephrine-releasing cells, the net effect of these drugs is usually to reduce the amount of norepinephrine released. Drugs in this group that are capable of entering the brain often have strong sedating effects, due to their inhibitory effects on the locus coeruleus. Clonidine, for example, is used for the treatment of anxiety disorders and insomnia, and also as a sedative premedication for patients about to undergo surgery. Xylazine, another drug in this group, is also a powerful sedative and is often used in combination with ketamine as a general anaesthetic for veterinary surgery—in the United States it has not been approved for use in humans.[8]

Stimulants and antidepressants

These are drugs whose primary effects are thought to be mediated by different neurotransmitter systems (dopamine for stimulants, serotonin for antidepressants), but many also increase levels of norepinephrine in the brain. Amphetamine, for example, is a stimulant that increases release of norepinephrine as well as dopamine. Monoamine oxidase inhibitors are antidepressants that inhibit the metabolic degradation of norepinephrine as well as serotonin and dopamine. In some cases it is difficult to distinguish the norepinephrine-mediated effects from the effects related to other neurotransmitters.

Diseases and disorders

A number of important medical problems involve dysfunction of the norepinephrine system in the brain or body.

Sympathetic hyperactivation

Hyperactivation of the sympathetic nervous system is not a recognized condition in itself, but it is a component of a number of conditions, as well as a possible consequence of taking sympathomimetic drugs. It causes a distinctive set of symptoms including aches and pains, rapid heartbeat, elevated blood pressure, sweating, palpitations, anxiety, headache, paleness, and a drop in blood glucose. If sympathetic activity is elevated for an extended time, it can cause weight loss and other stress-related body changes.

The list of conditions that can cause sympathetic hyperactivation includes severe brain injury, spinal cord damage, heart failure, high blood pressure, kidney disease, and various types of stress.

Pheochromocytoma

A pheochromocytoma is a rarely occurring tumor of the adrenal medulla, caused either by genetic factors or certain types of cancer. The consequence is a massive increase in the amount of norepinephrine and epinephrine released into the bloodstream. The most obvious symptoms are those of sympathetic hyperactivation, including particularly a rise in blood pressure that can reach fatal levels. The most effective treatment is surgical removal of the tumor.

Stress

Stress, to a physiologist, means any situation that threatens the continued stability of the body and its functions. Stress affects a wide variety of body systems: the two most consistently activated are the hypothalamic-pituitary-adrenal axis and the norepinephrine system, including both the sympathetic nervous system and the locus coeruleus-centered system in the brain. Stressors of many types evoke increases in noradrenergic activity, which mobilizes the brain and body to meet the threat. Chronic stress, if continued for a long time, can damage many parts of the body. A significant part of the damage is due to the effects of sustained norepinephrine release, because of norepinephrine's general function of directing resources away from maintenance, regeneration, and reproduction, and toward systems that are required for active movement. The consequences can include slowing of growth (in children), sleeplessness, loss of libido, gastrointestinal problems, impaired disease resistance, slower rates of injury healing, depression, and increased vulnerability to addiction.

ADHD

Attention deficit hyperactivity disorder is a psychiatric condition involving problems with attention, hyperactivity, and impulsiveness. It is most commonly treated using stimulant drugs such as methylphenidate (Ritalin), whose primary effect is to increase dopamine levels in the brain, but drugs in this group also generally increase brain levels of norepinephrine, and it has been difficult to determine whether these actions are involved in their clinical value. There is also substantial evidence that many people with ADHD show biomarkers involving altered norepinephrine processing. Several drugs whose primary effects are on norepinephrine, including guanfacine, clonidine, and atomoxetine, have been tried as treatments for ADHD, and found to have effects comparable to those of stimulants.

Autonomic failure

Several conditions, including Parkinson's disease, diabetes and so-called pure autonomic failure, can cause a loss of norepinephrine-secreting neurons in the sympathetic nervous system. The symptoms are widespread, the most serious being a reduction in heart rate and an extreme drop in resting blood pressure, making it impossible for severely affected people to stand for more than a few seconds without fainting. Treatment can involve dietary changes or drugs.

Comparative biology and evolution

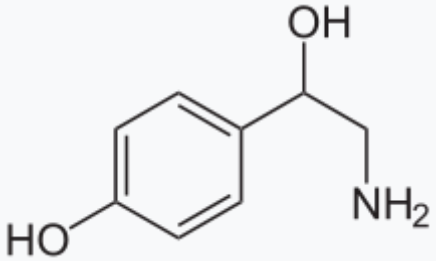

Figure-41: Chemical structure of octopamine, which serves as the homologue of norepinephrine in many invertebrate species.

Norepinephrine has been reported to exist in a wide variety of animal species, including protozoa placozoa and cnidaria (jellyfish and related species), but not in ctenophores (comb jellies), whose nervous systems differ greatly from those of other animals. It is generally present in deuterostomes (vertebrates, etc.), but in protostomes (arthropods, molluscs, flatworms, nematodes, annelids, etc.) it is replaced by octopamine, a closely related chemical with a closely related synthesis pathway. In insects, octopamine has alerting and activating functions that correspond (at least roughly) with the functions of norepinephrine in vertebrates. It has been argued that octopamine evolved to replace norepinephrine rather than *vice versa*; however, the nervous system of amphioxus (a primitive chordate) has been reported to contain octopamine but not

norepinephrine, which presents difficulties for that hypothesis.[9]

Enteric neurohormone

Enterochromaffin cells in the epithelia lining the lumen of the digestive tract secrete serotonin, while enterochromaffin-like cells at the stomach glands secrete histamine. Their synthesis, storage, and release of hormones is co-regulated by hormonal, local and nervous inputs.

CONCLUSION

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

Here, we consider briefly the implications of high parameter correlations by evaluating episodic neurohormone release for two typical luteinizing hormone (LH) time series, in which both basal and pulsatile hormone release are assumed to coexist and the hormone half-life is unknown. We show by systematic parameter grid searches consisting of approximately 1250 combinations of half-life and basal secretion rates that any given estimated value of the basal secretion rate is associated with a substantial range of plausible LH half-lives, and vice versa. Moreover, by estimating statistical confidence intervals for the parameter values rigorously, compared to a conventional asymptotic standard error estimation method, we show that asymptotic standard errors are inappropriate descriptors of the asymmetric and multidimensional confidence interval contours generated by this nonlinear-estimation problem.

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