

Neuronal Control of Pituitary Function

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Authors' contributions

This work was carried out in collaboration among all authors. Author AUM designed the study. Author MON wrote the protocol and wrote the first draft of the manuscript. Authors MON and AOO managed the literature searches. Author SIG proofread the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The pituitary gland secretes a collection of hormones that jointly influence all cells and affect virtually all physiologic processes. The anterior pituitary (also called the adenohypophysis or pars anterior), is the glandular, anterior lobe that together with the posterior lobe (posterior pituitary, or the neurohypophysis) makes up the pituitary gland (hypophysis). The anterior pituitary is the central regulator of the endocrine system, coordinating signals from the hypothalamus centrally and endocrine organs peripherally. The posterior pituitary is not glandular as is the anterior pituitary, but is largely a collection of axonal projections from the hypothalamus that terminate behind the anterior pituitary, and serve as a site for the secretion of neurohypophysial hormones (oxytocin and vasopressin) directly into the blood. The Pituitary gland and the hypothalamus together act as master regulators of the entire endocrine system. Its function is controlled by Humoral, hormonal and neural stimuli. With humoral stimuli the endocrine glands secrete hormones directly according to the concentration of various ions and nutrients in the blood surrounding them. Neural stimuli are involved where hormones are released directly due to stimulation of the endocrine gland by nerves. This review is intended to highlight once again the neural control of pituitary function.

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1. INTRODUCTION

The pituitary gland is about 1/3 of an inch in diameter and weighing about 0.5 grams in humans [1]. It is a protrusion off the bottom of the hypothalamus and situated in a bony hollow (sella turcica), at the base of the brain just behind the bridge of the human nose. It is attached to the base of the brain by a thin stalk (the infundibulum). The sella turcica protects the pituitary gland and allows very little room for expansion. The pituitary controls the function of most other endocrine glands, including the thyroid, adrenals, the ovaries and testicles and is therefore sometimes called the master gland. In turn, the pituitary is controlled in large part by the hypothalamus. The hypothalamus, which controls the pituitary by sending messages, is situated immediately above the pituitary gland. Together with the hypothalamus - which belongs to a part of the brain known as the diencephalon - the pituitary gland controls the involuntary (vegetative) nervous system. This part of the nervous system manages

the balance of energy, heat and water in the body, which includes things like body temperature, heartbeat, urination, sleep, hunger and thirst. Without the pituitary, the body wouldn't reproduce, wouldn't grow properly and many other bodily functions wouldn't function. The hormones produced by the pituitary are not all produced continuously [2]. Most are released in bursts every 1 to 3 hours, with alternating periods of activity and inactivity. Some of the hormones, such as adrenocorticotrophic hormone (ACTH), growth hormone, and prolactin, follow a circadian rhythm: The levels rise and fall predictably during the day, usually peaking just before awakening and dropping to their lowest levels just before sleep [3]. The levels of other hormones vary according to other factors. For example, in women, the levels of luteinizing hormone and follicle-stimulating hormone, which control reproductive functions, vary during the menstrual cycle [4]. This gland secretes hormones from both the front area (anterior) and the back area (posterior) of the gland [5].

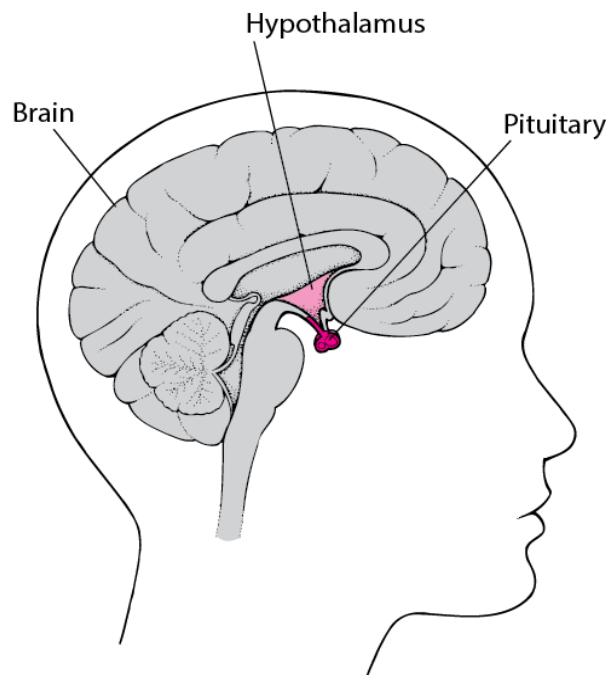


Fig. 1. Simplified diagram of the brain with location of the pituitary gland; MSD Manual March 2021

2. THE HYPOTHALAMUS-PITUITARY COMPLEX

The hypothalamus-pituitary complex serves to maintain homeostasis by monitoring and adjusting physiological processes through hormone secretion [6]. The pituitary gland and hypothalamus are closely connected both structurally and functionally. The hypothalamus is an important brain structure that has both nervous system and endocrine system function. It serves as a link between the two systems translating nervous system messages into endocrine hormones. The Hypothalamus serves as a communications centre for the pituitary gland, by sending messages or signals to the pituitary in the form of hormones which travel via the bloodstream and nerves down the pituitary stalk [6]. These signals, in turn, control the production and release of further hormones from the pituitary gland which signal other glands and organs in the body [7]. The hypothalamus influences the functions of temperature regulation, food intake, thirst and water intake, sleep and wake patterns, emotional behaviour and memory. The hypothalamus-pituitary complex is located in the diencephalon of the brain. The infundibulum which connects the hypothalamus and the pituitary gland contains vasculature and nerve axons. The

pituitary gland is divided into two distinct structures with different embryonic origins [7]. The posterior lobe houses the axon terminals of hypothalamic neurons. It stores and releases into the bloodstream two hypothalamic hormones: oxytocin and Antidiuretic Hormone (ADH). The anterior lobe is connected to the hypothalamus by vasculature in the infundibulum and produces and secretes six hormones. Their secretion is regulated, however, by releasing and inhibiting hormones from the hypothalamus. The six anterior pituitary hormones are: Growth Hormone (GH), Thyroid-Stimulating Hormone (TSH), Adrenocorticotropic Hormone (ACTH), Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and prolactin [1-3]. Hormone production and release are primarily controlled by negative feedback. In negative feedback systems, a stimulus elicits the release of a substance; once the substance reaches a certain level, it sends a signal that stops further release of the substance. In this way, the concentration of hormones in blood is maintained within a narrow range. For example, the anterior pituitary signals the thyroid to release thyroid hormones. Increasing levels of the released hormones in the blood then give feedback to the hypothalamus and anterior pituitary to inhibit further signaling to the thyroid gland [8].

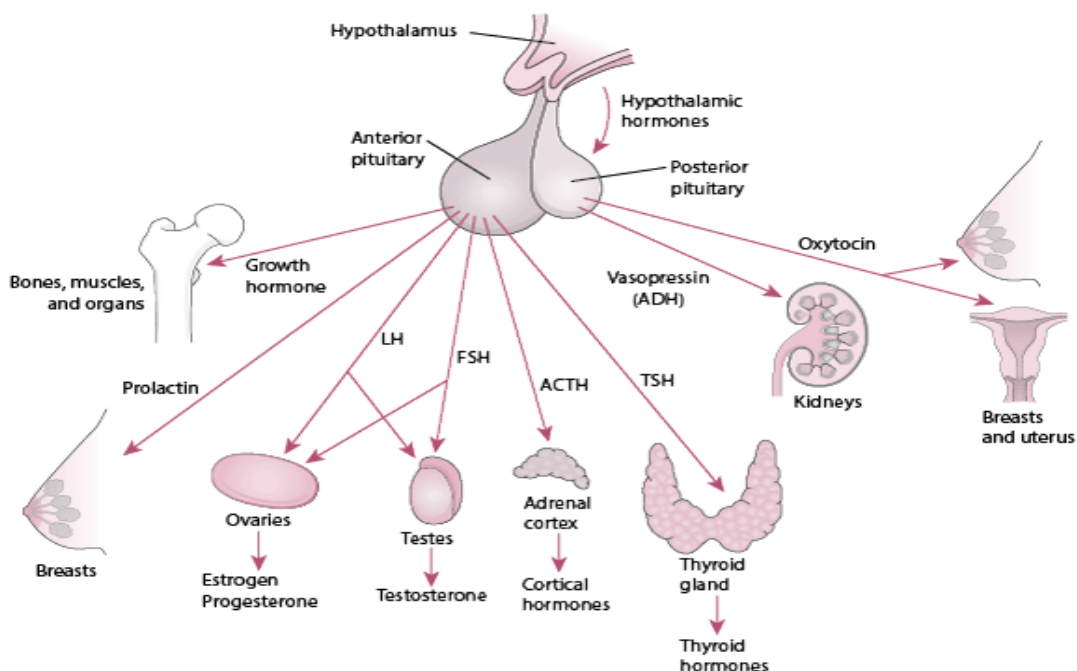


Fig. 2. Schematic Depiction of Pituitary hormonal Function; MSD Manual March 2021

2.1 Pituitary Function

The two different parts of the pituitary gland: the anterior and posterior lobes perform distinct functions. While the anterior lobe produces and releases hormones, the posterior lobe does not produce hormones-this is done by nerve cells in the hypothalamus-but it does release them into the circulation [9]. The hormones of the pituitary gland send signals to other endocrine glands to stimulate or inhibit their own hormone production [9].

2.2 Anterior Lobe

The anterior lobe of the pituitary gland is made up of several different types of cells that produce and release different types of hormones into the bloodstream and then travel through the blood vessels until they reach the various organs they have an effect on. Blood vessel connections between the hypothalamus and anterior pituitary allow hypothalamic hormones to control anterior pituitary hormone production and secretion.

The anterior lobe of the pituitary receives hypothalamic-releasing hormones from the hypothalamus that bind with receptors on endocrine cells in the anterior pituitary that regulate the release of adrenal hormones into the circulatory system. Hormones from the hypothalamus are rapidly degraded in the anterior pituitary, which prevents them from entering the circulatory system [9]. The anterior pituitary contains the pars distalis, and the pars tuberalis. The pars distalis is the distal part that comprises the majority of the anterior pituitary; it is where most pituitary hormone production occurs. The pars tuberalis on the other hand is the tubular part that forms a sheath that extends up from the pars distalis and wraps around the pituitary stalk [10]. This part of the pituitary gland is controlled by releasing factors from the hypothalamus. These factors reach the anterior pituitary via the hypophyseal portal system, venous channels allowing direct passage between the hypothalamus and the pituitary gland. The anterior gland secretes two types of hormones; trophic hormones and Direct-action hormones [9]. Trophic hormones stimulate a further endocrine gland and these include:

- i. The Follicle Stimulating Hormone (FSH) that regulates hormone production in the ovaries and testicles. This hormone is

involved with estrogen secretion and the growth of egg cells in women. It's also important for sperm cell production in men.

- ii. The Luteinizing Hormone (LH) which also has an effect on hormone production in the ovaries and testicles. This is involved in the production of estrogen in women and testosterone in men.
- iii. Adrenocorticotrophic Hormone (ACTH) which stimulates the adrenal glands to produce hormones such as adrenalin (epinephrine) and cortisol.
- iv. The Thyroid Stimulating Hormone (TSH) regulates hormone production in the thyroid gland. This hormone stimulates the thyroid gland to produce thyroid hormones, which regulate the body's energy balance, growth, and nervous system activity. The thyroid gland and the hormones it produces are crucial for metabolism. These are then controlled by negative feedback, whereby the product of the downstream endocrine gland limits the release of the original stimulating hormone.

Direct-action hormones on the other hand Act directly on non-endocrine tissues. There is no target gland, so release of these hormones is controlled by a balance of releasing and inhibitory factors from the hypothalamus. The group of hormones that have a direct effect includes growth hormone and prolactin [9-11].

Growth Hormone (GH) has an effect in many parts of the body – particularly the liver, bones, fat tissue and muscle tissue.

Growth hormone regulates growth and physical development in childhood and is important for maintaining a healthy body composition and well-being in adults. In adults, GH is important for maintaining muscle mass and bone mass. It also affects fat distribution in the body. It can stimulate growth in almost all of the tissues especially the primary targets of bones and muscles. GH is controlled by stimulatory somatocrinin (Growth Hormone Releasing Hormone) and inhibitory somatostatin. The other hormone that has a direct effect is Prolactin; which influences the mammary glands and ovaries. Prolactin helps women who are breastfeeding to produce milk. It also affects sex hormone levels from ovaries in women and from testes (testicles) in men, as well as fertility [12].

2.3 Posterior Lobe

The posterior pituitary comprises the posterior lobe of the pituitary gland and is part of the endocrine system. The posterior pituitary gland is largely a collection of axonal projections from the hypothalamus that terminate behind the anterior pituitary gland. The posterior pituitary consists mainly of neuronal projections (axons) extending from the supraoptic and paraventricular nuclei of the hypothalamus. These axons release peptide hormones into the capillaries of the hypophyseal circulation. These are then stored in neurosecretory vesicles (Herring bodies) before being secreted by the posterior pituitary into the systemic bloodstream. The posterior lobe of the pituitary gland develops as an extension of the hypothalamus. As such, it is not capable of producing its own hormones; instead, it stores hypothalamic hormones for later release into the systemic circulation [9-11]. The posterior pituitary extends from the neurons of the hypothalamus and is composed of two parts: The pars nervosa and the infundibular stalk. The pars nervosa, also called the neural lobe or posterior lobe, constitutes the majority of the posterior pituitary and is the storage site of oxytocin and vasopressin. The infundibular stalk, also known as the infundibulum or pituitary stalk, bridges the hypothalamic and hypophyseal systems. Also known as the neurohypophysis, the posterior pituitary gland releases Vasopressin and Oxytocin both of which act directly on non-endocrine tissue [9-11]. Vasopressin regulates the amount of water excreted by the kidneys and is therefore important in maintaining water balance in the body [2]. Vasopressin, the majority of which is released from the supraoptic nucleus in the hypothalamus prompts the kidneys to increase water absorption in the blood and is also called Anti-Diuretic Hormone (ADH). It thereby helps the body to conserve water and prevent dehydration. Oxytocin, most of which is released from the paraventricular nucleus in the hypothalamus causes the uterus to contract during childbirth and immediately after delivery to prevent excessive bleeding. Oxytocin also stimulates contractions of the milk ducts in the breast, which move milk to the nipple (the let-down) in lactating women. Oxytocin has some additional roles in both men and women [9]. The hormones of the posterior lobe of the pituitary gland are usually produced in the hypothalamus and stored in the posterior lobe until they're released [9-11].

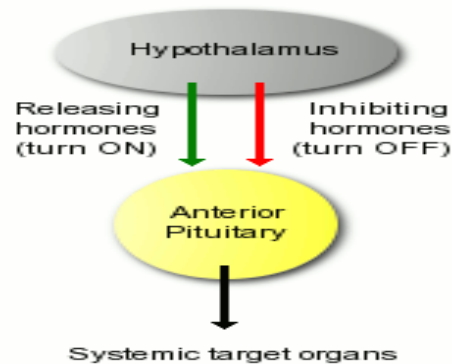


Fig. 3. Hypothalamus control of anterior pituitary function

<http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/index.html>

2.4 Pituitary Gland Dysfunction

The pituitary gland can malfunction in several ways, usually as a result of developing a noncancerous tumor (adenoma). The tumor may overproduce one or more pituitary hormones, or the tumor may press on the normal pituitary cells, causing underproduction of one or more pituitary hormones. The tumor may also cause enlargement of the pituitary gland, with or without disturbing hormone production. Pituitary tumors are usually noncancerous and apart from interfering with the release of hormones, they can also press against other areas of your brain, leading to vision problems or headaches. Sometimes there is overproduction of one hormone by a pituitary tumor and underproduction of another at the same time due to pressure. Sometimes excess cerebrospinal fluid can fill the space around the pituitary gland and compress it (resulting in empty sella syndrome). The pressure may cause the pituitary to overproduce or under produce hormones. Production of too little or too much of a pituitary hormone results in a wide variety of symptoms. Though Pituitary tumors are the most common pituitary disorder, they are not, in the great majority of cases, life-threatening. Pituitary tumors can disrupt the gland's normal ability to release hormones. There are two types of pituitary tumors—secretory and non-secretory. Secretory tumors secrete too much of a hormone, and non-secretory tumors don't secrete excess hormone. These hormonal imbalances can cause problems in many different areas of the body like growth or reproductive system function [10]. A secretory

tumor that is overproducing thyroid-stimulating hormone, for instance, will lead to hyperthyroidism. In hypopituitarism, the pituitary produces low levels of hormones. The insufficiency of pituitary hormone production causes a deficiency in the production of hormones in other glands. For example, a deficiency in thyroid-stimulating hormone (TSH) production can result in an under-active thyroid gland. Lack of thyroid hormone production slows down normal body functions. Symptoms that may arise include weight gain, weakness, constipation, and depression. Insufficient levels of adrenocorticotropic hormone (ACTH) production by the pituitary results in under-active adrenal glands. Adrenal gland hormones are important for maintaining vital body functions such as blood pressure control and water balance. This condition is also known as Addison's disease and can be fatal if not treated. In hyperpituitarism, the pituitary is overactive producing hormones in excess. An overproduction of growth hormone may result in acromegaly in adults. This condition results in excessive growth of bones and tissues in the hands, feet, and face. In children, overproduction of growth hormone may result in gigantism. Overproduction of ACTH causes the adrenal glands to produce too much cortisol, which results in problems related to metabolism regulation. Overproduction of the pituitary hormone TSH may result in hyperthyroidism, or the overproduction of thyroid hormones. An overactive thyroid produces symptoms such as nervousness, weight loss, irregular heartbeat, and fatigue [13].

Other disorders of the pituitary gland that can arise include:

1. **Acromegaly:** this condition, the pituitary gland produces too much growth hormone. This can lead to excessive growth, especially of the hands and feet. It's often associated with pituitary tumors.
2. **Diabetes insipidus.** This can be caused by a problem with the release of vasopressin. It's usually due to a head injury, surgery, or a tumor. As a result, people with this condition pass large amounts of heavily diluted urine. They may also feel like they need to drink a lot of water or other fluids.
3. **Cushing's disease.** The pituitary gland releases too much Adrenocorticotropic hormone in people with this condition. This can lead to easy bruising, high blood

pressure, weakness, and weight gain. It's often caused by a tumor near or in the pituitary gland.

4. **Hyperprolactinemia.** In this condition, the blood contains an unusually high amount of prolactin. This can lead to infertility and a decreased sex drive.
5. Another pituitary disorder is known as pituitary apoplexy. In some cases, pituitary function can be suddenly disrupted (due to bleeding or trauma), creating a life-threatening shortage of vital hormones. Depending on the injury, it can sometimes damage the pituitary gland and cause problems with memory, communication, or behavior [14,15].

2.5 Treatment for Pituitary Gland Dysfunction

Treatment for Pituitary Gland Dysfunction depends upon the cause of the anomaly. Hormone replacement is applied where there is hormone deficiency. Pituitary surgery is carried out if a tumour is discovered as the cause of the problems and radiotherapy is added where the tumour is found to be cancerous [16].

2.6 Control of Pituitary Function

Whilst the pituitary gland is known as the master endocrine gland, both of the lobes are under the control of the hypothalamus [9]. The anterior pituitary receives its signal from the parvocellular neurons and the posterior pituitary receives its signal from the magnocellular neurons. The hypothalamus produces releasing hormones and neurohypophysial hormones in specialized hypothalamic neurons which extend to the median eminence and posterior pituitary. The anterior lobe of the pituitary receives hypothalamic releasing hormones from the hypothalamus that bind with receptors on endocrine cells of the anterior pituitary that regulate the release of hormones into the circulatory system. The posterior pituitary develops as an extension of the hypothalamus and as such is not capable of producing its own hormones; instead it stores hypothalamic hormones for later release into the circulatory system. By detecting the levels of hormones produced by glands under the pituitary's control, the hypothalamus or the pituitary can determine how much stimulation the target glands need. There are three mechanisms by which the pituitary gland is stimulated to synthesize and release hormones and these are humoral stimuli, hormonal stimuli and neural stimuli [17].

2.7 Humoral Stimuli

The term “humoral” is derived from the term “humor,” which refers to bodily fluids such as blood. A humoral stimulus refers to the control of hormone release in response to changes in extracellular fluids such as blood or the ion concentration in the blood. For example, a rise in blood glucose levels triggers the pancreatic release of insulin. Insulin causes blood glucose levels to drop, which signals the pancreas to stop producing insulin in a negative feedback loop [18].

2.8 Hormonal Stimuli

Hormonal stimuli refer to the release of a hormone in response to another hormone. A number of endocrine glands release hormones when stimulated by hormones released by other endocrine glands. For instance, if the level of thyroid hormones in the body is high enough, the pituitary gland stops producing the hormone that stimulates the thyroid gland-Thyroid Stimulating Hormone (TSH). This works the other way round, too: If the level of thyroid hormones is too low, the pituitary gland and hypothalamus increase the production of thyroid-stimulating hormone. The thyroid gland then produces more thyroid hormones. The hypothalamus produces hormones that stimulate the anterior portion of the pituitary gland. The anterior pituitary in turn releases hormones that regulate hormone production by other endocrine glands. The anterior pituitary releases the thyroid-stimulating hormone, which then stimulates the thyroid gland to produce the hormones T_3 and T_4 . As blood concentrations of T_3 and T_4 rise, they inhibit both the pituitary and the hypothalamus in a negative feedback loop. Hormones from the hypothalamus are rapidly degraded in the anterior pituitary which prevents them from entering the circulatory system [19].

2.9 Neural Stimuli

A neural stimulus is a hormone that is released by the glands of the endocrine system. This is a non-voluntary process in which the nervous system stimulates the endocrine system to release neural stimuli. Neural stimulation of pituitary function refers to situations where hormones are released directly due to stimulation of the pituitary gland by nerves [20]. A neutral stimulus initially produces no specific response other than focusing attention. When used together with an unconditioned stimulus, the

neutral stimulus becomes a conditioned stimulus. With repeated presentations of both the neutral stimulus and the unconditioned stimulus, the neutral stimulus will elicit a response as well, known as a conditioned response. Once the neutral stimulus elicits a conditioned response, the neutral stimulus becomes known as a conditioned stimulus [20, 21]. The conditioned response is the same as the unconditioned response, but occurs in the presence of the conditioned stimulus rather than the unconditioned stimulus. In some cases, the nervous system directly stimulates endocrine glands to release hormones, which is referred to as neural stimuli. In a short-term stress response, the hormones epinephrine and norepinephrine are important for providing the bursts of energy required for the body to respond. Here, neuronal signalling from the sympathetic nervous system directly stimulates the adrenal medulla to release the hormones epinephrine and norepinephrine in response to stress. The cell bodies of the neurons of the posterior pituitary are located in the hypothalamus. ADH, also called vasopressin is a peptide hormone produced by cell bodies in the paraventricular and supraoptic nuclei of the hypothalamus. It is transported down axons into the posterior pituitary for storage, prior to release. ADH is released in response to reduction in plasma volume, a decrease in blood pressure (detected by baroreceptors in the left atrium, pulmonary vessels, aortic arch and carotid sinus), high levels of angiotensin 2, increased sympathetic activation or an increase in the osmolarity of the extracellular fluid (detected by osmoreceptors within the hypothalamus). If the osmolarity is high or the volume is low, ADH will be released. This acts on V2 receptors on the peritubular surface of the collecting ducts in the kidney. The permeability to water in the distal tubule and collecting duct is increased. More water therefore, moves out of the tubule and into the intracellular space. Urine volume decreases and urine concentration increases [17-21].

ADH also causes vasoconstriction of blood vessels as a secondary function. It binds to V1 receptors on vascular smooth muscle and acts via the IP3 signal transduction pathway. It increases the arterial pressure. Normal physiological concentrations do not cause vasoconstriction, if severe hypovolaemic shock is suffered, lots of ADH is released due to decreased plasma volume - the amount of ADH released is relative to the degree of

hypovolaemic. These very high levels help with a compensatory mechanism of increased vascular resistance. This increased vascular resistance increases arterial blood pressure. Stretch or volume receptors in the veins and atria can detect a decrease in volume of the blood. This causes nervous impulses to be sent to the hypothalamus, resulting in an increase in ADH production, conserving water at the kidneys. This mechanism is only triggered by a large loss of volume, but results in a large amount of ADH being produced [17].

Oxytocin, produced by cell bodies in the paraventricular and supraoptic nuclei of the hypothalamus is transported down axons into the posterior pituitary where they are stored prior to release. Release is controlled by neural activity in the nerve cells; neurosecretion. It acts on the smooth muscle of the mammary gland and uterus. Oxytocin stimulates milk let down via contraction of the mammary alveoli. Oxytocin release occurs via neural activity. The mammillae have a high density of sensory nerve fibres, and these detect suckling, or preparation for milking. Afferent sensory neurons enter the lumbar part of the spinal cord to the thalamus. They reach the cell bodies of neuroendocrine cells. Oxytocin is released from the nerve endings in the posterior pituitary gland and enters capillaries and the systemic circulation. Mammillary capillaries contract and the pressure within the alveoli increase. Resistance in the excretory ducts and mammilla canal is reduced, resulting in an increased milk outflow. Also during Stage 2 of parturition, the foetus engages the cervix. This initiates a neuroendocrine reflex, and is an example of a positive feedback mechanism, which occurs when stretch receptors in the cervix are stimulated. Sensory nerve endings in the cervix are stimulated causing afferent nerve impulses to be sent to the hypothalamus. Neuroendocrine cells of the paraventricular and supraoptic nuclei depolarise and oxytocin is secreted from the pars nervosa. Oxytocin enters the blood circulation and acts on the oxytocin receptors in the smooth muscle forming the wall of the uterus – the myometrium. Uterine contractions therefore, increase in strength and frequency [22-24]. For the neural control of the posterior pituitary gland, The magnocellular neurons receive afferent inputs from many hypothalamic, limbic and brainstem regions. Most of these inputs use either the excitatory neurotransmitter glutamate or the inhibitory transmitter GABA, and many derive from the regions adjacent to the magnocellular nuclei. The

rate of synthesis of both oxytocin and vasopressin varies proportionally with the abundance of mRNA for these peptides, and mRNA expression, in turn, closely matches the level of secretory demand [25].

3. CONCLUSION

The posterior pituitary (neurohypophysis) is a collection of hypothalamic axons that carry and release hormones that were made in the hypothalamus while the anterior pituitary (adenohypophysis) is an endocrine organ that receives releasing factors from the hypothalamus via blood vessels. Derived embryologically from a neural down growth, the anterior lobe is composed of axons that project from nerve cells in the hypothalamus and terminate on capillaries of the inferior hypophyseal artery. Neurohemal junctions are the fundamental functional modules of the major central neuroendocrine system, the median eminence. They are composed of nerve terminals and capillaries that are closely juxtaposed and thereby facilitate the release of chemical messengers from nerve terminals into the bloodstream. The neurohemal junctions in the median eminence and neurohypophysis facilitate the transport of neurohormones from the nerve terminals into the bloodstream. Most of the neurohormones that mediate the neural control of anterior pituitary hormone secretion are peptides that are synthesized in discrete hypothalamic nuclei. Hormone levels are primarily controlled through negative feedback, in which rising levels of a hormone inhibit its further release. Among The three mechanisms of pituitary hormone release, a neural stimulus is the most significant. Neural regulation of pituitary function can serve as a basis for understanding endocrine and reproduction dysfunction in a disease condition like epilepsy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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