NORMAL REGULATION OF ADRENAL GLUCOCORTICOID SECRETION
CHAPTER - II

ARGININE VASOPRESSIN AND ITS RELATED HORMONES

STRUCTURE OF ARGinine Vasopressin
2.1 Introduction

Arginine vasopressin (AVP), also known as vasopressin, argipressin or antidiuretic hormone (ADH), is a neurohypophysial hormone found in most mammals. Its two primary functions are to retain water in the body and to constrict blood vessels. Vasopressin regulates the body's retention of water by acting to increase water absorption in the collecting ducts of the kidney nephron. Vasopressin increases water permeability of the kidney's collecting duct by inducing translocation of aquaporin-CD water channels in the kidney nephron collecting duct plasma membrane.[107]

Vasopressin is a peptide hormone that controls the reabsorption of molecules in the tubules of the kidneys by affecting the tissue's permeability. It also increases peripheral vascular resistance, which in turn increases arterial blood pressure. It plays a key role in homeostasis, by the regulation of water, glucose, and salts in the blood. It is derived from a preprohormone precursor that is synthesized in the hypothalamus and stored in vesicles at the posterior pituitary.

Most of it is stored in the posterior pituitary to be released into the bloodstream; However, some AVP is also released directly into the brain, where it plays an important role in social behavior, sexual motivation and bonding.
CHEMICAL STRUCTURE OF ARGinine VASOPRESSIN
2.2 Physiology Function

One of the most important roles of AVP is to regulate the body's retention of water; it is released when the body is dehydrated and causes the kidneys to conserve water, thus concentrating the urine and reducing urine volume. At high concentrations, it also raises blood pressure by inducing moderate vasoconstriction.

In addition, it has a variety of neurological effects on the brain, having been found, for example, to 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\cite{93}. A very similar substance, Lysine Vasopressin (LVP) or lypressin, has the same function in pigs and is often used in human therapy.

2.2.1 Kidney

Vasopressin has two effects by which it contributes to increased urine osmolality (increased concentration) and decreased water excretion. These are:

1. Increasing the water permeability of distal tubule and collecting duct cells in the kidney, thus allowing water reabsorption and excretion of
more concentrated urine, i.e., antidiuresis. This occurs through insertion of water channels (Aquaporin-2) into the apical membrane of distal tubule and collecting duct epithelial cells. Aquaporin 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.

V2 receptors, which are G protein-coupled receptors on the basolateral plasma membrane of the epithelial cells, couple to the heterotrimeric G-protein Gs, which activates adenylyl cyclases III and VI to convert ATP into cAMP, plus 2 inorganic phosphates. The rise in cAMP then triggers the insertion of aquaporin-2 water channels by exocytosis of intracellular vesicles, recycling endosomes. 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. Cyclic-AMP activates protein Kinase A (PKA) by binding to its regulatory subunits and allowing them to detach from the catalytic subunits. Detachment exposes the catalytic site in the enzyme, allowing it to add phosphate groups to proteins (including the aquaporin-2 protein), which alters their functions.
2. Increasing permeability of the inner medullary portion of the collecting duct to urea by regulating the cell surface expression of urea transporters [125], 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.

2.2.2 Cardiovascular System

Vasopressin increases peripheral vascular resistance (vasoconstriction) and thus increases arterial blood pressure. This effect appears small in healthy individuals; however it becomes an important compensatory mechanism for restoring blood pressure in hypovolemic shock such as that which occurs during hemorrhage.

2.2.3 Central Nervous System

Vasopressin released within the brain has many actions:

- It has been implicated in memory formation, including delayed reflexes, image, short and long-term memory, though the mechanism remains unknown; these findings are controversial. However, the synthetic vasopressin analogue desmopressin has come to interest as a likely nootropic.
• Vasopressin is released into the brain in a circadian rhythm by neurons of the supraoptic nucleus.

• Vasopressin released from centrally projecting hypothalamic neurons is involved in aggression, blood pressure regulation and temperature regulation.

• It is likely that vasopressin acts in conjunction with corticotropin-releasing hormone to modulate the release of corticosteroids from the adrenal gland in response to stress, particularly during pregnancy and lactation in mammals.

• Selective AVPr1a blockade in the ventral pallidum has been shown to prevent partner preference in prairie voles, suggesting that these receptors in this ventral forebrain region are crucial for pair bonding\(^{[93]}\).

• Recent evidence suggests that vasopressin may have analgesic effects. The analgesia effects of vasopressin were found to be dependent on both stress and gender.

Evidence for this 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 promiscuous species in the distribution of AVP receptors, and sometimes in the distribution of vasopressin-containing axons, even when closely related species are compared\textsuperscript{[156]}.  

Moreover, studies involving either injecting AVP agonists into the brain or blocking the actions of AVP support the hypothesis that vasopressin is involved in aggression toward other males. There is also evidence that differences in the AVP receptor gene between individual members of a species might be predictive of differences in social behavior. One study has suggested that genetic variation in male humans affects pair-bonding behavior.  

The brain of males uses vasopressin as a reward for forming lasting bonds with a mate, and men with one or two of the genetic alleles are more likely to experience marital discord. The partners of the men with two of the alleles affecting vasopressin reception state disappointing levels of satisfaction, affection, and cohesion.  

Vasopressin receptors distributed along the reward circuit pathway, to be specific in the ventral pallidum, are activated when AVP is released during social interactions such as mating, in monogamous prairie voles.
The activation of the reward circuitry reinforces this behavior, leading to conditioned partner preference, and thereby initiates the formation of a pair bond\textsuperscript{[93]}.

2.3 Control

Vasopressin is secreted from the posterior pituitary gland in response to reductions in plasma volume, in response to increases in the plasma osmolality, and in response to \textit{Cholecystokinin (CCK)} secreted by the small intestine:

- Secretion \textit{in response to reduced plasma volume} is activated by pressure receptors in the veins, atria, and carotids.
- Secretion \textit{in response to increases in plasma osmotic pressure} is mediated by osmoreceptors in the hypothalamus.
- Secretion \textit{in response to increases in plasma CCK} is mediated by an unknown pathway.

The neurons that make AVP, in the hypothalamic \textit{Supraoptic Nuclei (SON)} and \textit{Paraventricular Nuclei(PVN)}, are themselves osmoreceptors, but they also receive synaptic input from other osmoreceptors located in regions adjacent to the anterior wall of the third
ventricle. These regions include the organum vasculosum of the lamina terminalis and the subfornical organ.

2.3.1 Many factors influence the secretion of vasopressin:

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

2.4 Secretion

The main stimulus for secretion of vasopressin is increased osmolality of plasma. Reduced volume of extracellular fluid also has this effect, but is a less sensitive mechanism.

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. However there are two other sources of AVP with important local effects:

- AVP is also synthesized by parvocellular neurosecretory neurons at the PVN, transported and released at the median eminence, which then 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 is also released into the brain by several different populations of smaller neurons.

2.5 Receptors

Below is a table summarizing some of the actions of AVP at its four receptors, differently expressed in different tissues and exerting different actions:
<table>
<thead>
<tr>
<th>Type</th>
<th>Second messenger system</th>
<th>Locations</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1A</td>
<td>Phosphatidylinositol/calcium</td>
<td>Liver, kidney, peripheral vasculature, brain</td>
<td>Vasoconstriction, gluconeogenesis, platelet aggregation, and release of factor VIII and von Willebrand factor; social recognition,(^{16}) circadian tau(^{148})</td>
</tr>
<tr>
<td>AVPR1B or AVPR3</td>
<td>Phosphatidylinositol/calcium</td>
<td>Pituitary gland, brain</td>
<td>Adrenocorticotropic hormone secretion in response to stress; social interpretation of olfactory cues(^{149})</td>
</tr>
<tr>
<td>AVPR2</td>
<td>Adenylate cyclase/cAMP</td>
<td>Basolateral membrane of the cells lining the collecting ducts of the kidneys (especially the cortical and outer medullary collecting ducts)</td>
<td>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(^{96})</td>
</tr>
<tr>
<td>VACM-1</td>
<td>Phosphatidylinositol/calcium</td>
<td>Vascular endothelium and renal collecting tubules</td>
<td>Increases cytosolic calcium and acts as an inverse agonist of cAMP accumulation</td>
</tr>
</tbody>
</table>
2.6 Role in Disease

Decreased AVP release or decreased renal sensitivity to AVP leads to diabetes insipidus, a condition featuring hypernatremia (increased blood sodium concentration), polyuria (excess urine production), and polydipsia (thirst).

High levels of AVP secretion, Syndrome of Inappropriate antidiuretic hormone, (SIADH) and resultant hyponatremia (low blood sodium levels) occurs in brain diseases and conditions of the lungs (small cell lung carcinoma). In the perioperative period, the effects of surgical stress and some commonly used medications (e.g., opiates, syntocinon, anti-emetics) lead to a similar state of excess vasopressin secretion. This may cause mild hyponatremia for several days.

Hyponatremia can be treated pharmaceutically through the use of vasopressin receptor antagonists. These include the approved drug Vaprisol and the phase III drug lixivaptan.

2.7 Pharmacology

Vasopressin Analogues

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) 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 infusion has also been used as a second line of management in septic shock patients not responding to high dose of inotropes (e.g., dopamine or norepinephrine).

2.8 The Role of Vasopressin Analogues in Cardiac arrest

Injection of vasopressors for the treatment of cardiac arrest was first suggested in the literature in 1896 when Austrian scientist Dr. R. Gottlieb described the vasopressor epinephrine as an "infusion of a solution of suprarenal extract that restore circulation when the blood pressure had been lowered to unrecordable levels by chloral hydrate." Modern interest in vasopressors as a treatment for cardiac arrest stem mostly from canine studies performed in the 1960s by anesthesiologists Dr. John W. Pearson and Dr. Joseph Stafford Redding in which they demonstrated improved outcomes with the use of adjunct intracardiac epinephrine injection during resuscitation attempts after induced cardiac arrest. Also contributing to the idea that vasopressors may be useful treatments in cardiac arrest are studies performed in the early to mid
1990's that found significantly higher levels of endogenous serum vasopressin in adults after successful resuscitation from out-of-hospital cardiac arrest compared to those who did not live.

Results of animal models have supported the use of either vasopressin or epinephrine in cardiac arrest resuscitation attempts, showing improved coronary perfusion pressure and overall improvement in short-term survival as well as neurological outcomes.

2.9 Related Hormones

2.9.1 Gonadotrophin - releasing hormone

Gonadotrophin-releasing hormone is released from nerve cells in the brain. It controls the production of luteinizing hormone and follicle stimulating hormone from the pituitary gland.

Alternative names for Gonadotrophin-Releasing Hormone: GnRH; gonadotropin-releasing hormone; luliberin; luteinizing-hormone-releasing hormone; LHRH.

Gonadotrophin-releasing hormone is produced and secreted by specialised nerve cells in the hypothalamus of the brain. It is released into tiny blood vessels that carry this hormone from the brain to the pituitary gland where it stimulates the production of two more hormones – follicle stimulating hormone and luteinizing hormone.
These hormones are released into the general circulation and act on the testes and ovaries to initiate and maintain their reproductive functions. Follicle stimulating hormone and luteinizing hormone control the level of hormones produced by the testes and ovaries (such as testosterone, oestradiol and progesterone) and are important in controlling the production of sperm in men and the maturation and release of an egg during each menstrual cycle in women.

2.9.2 Luteinizing Hormone

A luteinizing hormone test measures the amount of luteinizing hormone (LH) in a sample of blood or urine. LH is produced by the anterior pituitary gland.

- In women, LH helps regulate the menstrual cycle and egg production (ovulation). The level of LH in a woman's body varies with the phase of the menstrual cycle. It increases rapidly just before ovulation occurs, about midway through the cycle (day 14 of a 28-day cycle). This is called an LH surge. Luteinizing hormone and follicle-stimulating hormone levels rise and fall together during the monthly menstrual cycle.
- In men, LH stimulates the production of testosterone, which plays a role in sperm production.
2.9.3 Luteinizing Hormone (LH) Test

A luteinizing hormone (LH) test may be done to:

- help find the cause for a couple's inability to become pregnant (infertility). LH testing is commonly used to help evaluate:
  - A woman's egg supply (ovarian reserve).
  - A man's sperm count.
- help evaluate menstrual problems, such as irregular or absent menstrual periods (amenorrhea). This can help determine if the woman has gone through menopause.
- determine if a child is going through early puberty (also called precocious puberty). Puberty is early when it starts in girls younger than age 9 and in boys younger than age 10.
- determine why sexual features or organs are not developing when they should (delayed puberty).
- determine (usually with a urine sample) when a woman is ovulating. Home urine tests for ovulation are available.
- monitor a woman's response to medicines given to stimulate ovulation.

LH stimulates growth and development of the Leydig cells of the testis which produce testosterone. In females, LH promotes maturation of
the ovarian follicles and the secretion of oestrogen. It also stimulates the formation of the corpus luteum from the follicles after ovulation.

Testosterone is a steroid manufactured from cholesterol in the Leydig cells of the testis. It has a negative feedback effect on LH secretion from the anterior pituitary. It has important effects on protein anabolism and on growth, in addition to its well known role in the development and maintainance of male secondary sexual characteristics.

Testosterone concentrations are decreased for several days, while LH concentrations show variable changes. In female subjects, oestradiol concentrations decrease for up to 5 days postoperatively.

2.9.4 The Adrenocorticotropic Hormone (ACTH)

ACTH is a peptide of 39 amino acids. It is cut from a larger precursor Proopiomelanocortin (POMC).

ACTH acts on the cells of the adrenal cortex, stimulating them to produce

- glucocorticoids, like cortisol;
- mineralocorticoids, like aldosterone;
- androgens (male sex hormones, like testosterone).
• In the fetus, ACTH stimulates the adrenal cortex to synthesize a precursor of oestrogen called *Dehydroepiandrosterone Sulfate (DHEA-S)* which helps prepare the mother for giving birth.

Production of ACTH depends on the intermittent arrival of *Corticotropin-Releasing Hormone (CRH)* from the hypothalamus.

*Hyper*secretion of ACTH is a frequent cause of Cushing's disease.

The posterior lobe of the pituitary releases two hormones, both synthesized in the hypothalamus, into the circulation.

**2.9.5 Follicle-Stimulating Hormone (FSH)**

FSH, is secreted from the anterior pituitary. FSH is a heterodimeric glycoprotein consisting of

• The same alpha chain found in TSH (and LH)

• A beta chain of 118 amino acids, which gives it its unique properties.

Synthesis and release of FSH is triggered by the arrival from the hypothalamus of *Gonadotropin-Releasing Hormone (GnRH)*. The effect of FSH depends on one's sex.
FSH in females

In sexually-mature females, FSH (assisted by LH) acts on the follicle to stimulate it to release oestrogens.

FSH produced by recombinant DNA technology (Gonal-f®) is available to promote ovulation in women planning to undergo In Vitro Fertilization (IVF) and other forms of assisted reproductive technology.

FSH in males

In sexually-mature males, FSH acts on spermatogonia stimulating (with the aid of testosterone) the production of sperm.
THE HYPOTHALAMO–PITUITARY–ADRENAL (HPA) STRESS AXIS
REGULATION OF GONADOTROPIN-RELEASING HORMONE (GnRH), LUTEINIZING HORMONE (LH), AND FOLLICLE-STIMULATING HORMONE (FSH) SECRETION.