

CHAPTER 1

INTRODUCTION TO VASOPRESSIN

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1. Brief Historical Perspective

We now know quite a lot about vasopressin. For instance, we have known for some time that it is a nonapeptide molecule associated chiefly with the hypothalamus and posterior lobe of the pituitary gland (the neurohypophysial system), and that it has a variety of physiological actions linked to specific receptors and intracellular second messenger systems. We know something about clinical conditions arising from an absence, or an excess, of its renal actions, and to a lesser extent its potential pathological role in other clinical conditions. We also know lots of other interesting facts about this molecule which may, or may not, be of physiological and clinical relevance. But how did we get here?

It is fascinating to see how the current perception of vasopressin is based on a number of different developing strands (e.g. hormone synthesis, structure, actions, receptors, clinical disease) which ultimately come together to give us the more complete canvas we see today. In particular, vasopressin research has played an important part in our present understanding of the process of neuromolecular synthesis and secretion, at least partly because the neurohypophysial neurones, the main physiological source of the hormone, are larger than the average nerve cell (magnocellular) and are therefore more readily manipulated.

Below, I have attempted to portray these various research strands from a chronological viewpoint as well as from the more logical, perhaps classical, progression of system components such as anatomical structure, synthesis, storage, release, etc. This brief and necessarily incomplete historical perspective covers the essential developments in vasopressin research up to the early 1980s, after which further details will be found in subsequent relevant chapters. While we think we know a lot about vasopressin today, the more we learn, the more we find we don't understand. This is particularly relevant with respect to the rapid advances being made following genetic and proteomic manipulations which will require yet more physiological studies to appreciate their significance.

As an endocrinologist, I shall refer generally to the hormone as vasopressin (VP) since this was the name originally given to the active principle derived from posterior pituitary extracts. However, the molecule is still sometimes given the name antidiuretic hormone (ADH), mainly by renal physiologists, in honour of its main recognised physiological, and clinically relevant, action.

2. General Development, Anatomy and Structure of the Neurohypophysial System

The pituitary gland, or hypophysis, is a small gland attached to the base of the brain. It was first described by Galen (129–216AD), who proposed that it drained phlegm from the brain to the nasopharynx. The embryological origin of the pituitary was described much later by Rathke in 1838, who described its development as a consequence of the fusion of an upward growth of the primitive buccal cavity (subsequently known as Rathke's pouch) with a downward growth from the brain, specifically from the hypothalamus. The internal structure of the gland conforms to its embryological origin: the anterior lobe (the adenohypophysis), which develops from Rathke's pouch, is comprised of typical secretory cells, while the posterior lobe (the neurohypophysis) consists mainly of nerve

fibres descending from the hypothalamus. In most vertebrates there is also an intermediate zone between the anterior and posterior lobes called the pars intermedia, which was first described by Peremeschko in 1867. In adult humans this lobe is almost non-existent, except in women during pregnancy.

The first anatomical studies demonstrating nerve fibres in the posterior, or neural, lobe of the pituitary gland were described by Ecker in 1853, and later by others such as Ramon y Cajal, who in 1894 identified a nucleus of nerve cell bodies situated behind the optic chiasma. This supraoptic nucleus, together with the paraventricular nucleus which lies around the third ventricle, provide the hypothalamic neurones whose axons traverse the basal part of the hypothalamic median eminence to enter the posterior lobe of the pituitary. These supraoptic and paraventricular neurones, as nerve bundles, are called the hypothalamo-neurohypophysial nerve tracts. They are initially myelinated but lose their myelin sheaves as soon as they enter the median eminence.

An interesting feature of the neurohypophysial axons is that they are larger than normal nerve axons and are thus referred to as magnocellular neurones. Another interesting feature is the presence of dilations, or swellings, along the nerve axons and at the nerve terminals, called Herring bodies. Herring was the first person to describe colloid droplets in the neural lobe in 1908. Other cell types are present within the neural lobe: glial cells, and cells called pituicytes (astrocytes) which are often seen closely associated with the nerve axons. Developmentally, magnocellular vasopressinergic neurones originate from cell precursors lining the third ventricle, which migrate first to the supraoptic region of the developing hypothalamus and then to the paraventricular, and other areas such as the suprachiasmatic nuclei.

Another vasopressinergic pathway which influences the pituitary gland consists of normal, smaller (parvocellular) neurones originating in the hypothalamic paraventricular nucleus and terminating in the median eminence region at the base of the hypothalamus. Vasopressin released

by these neurones enters the primary capillary network in the median eminence and is transported to its target cells in the anterior pituitary (corticotroph cells) by the specialised portal system which links it to a second capillary plexus distributed throughout the anterior pituitary. Other vasopressinergic fibres originating mainly in the paraventricular, but also from the supraoptic, nuclei have axons terminating in various other parts of the brain (Fig. 1).

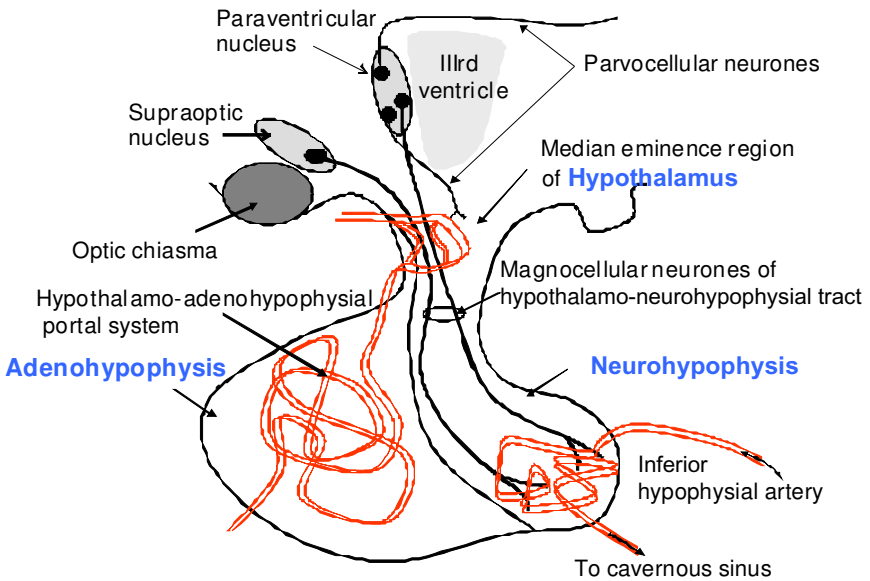


Figure 1. Cross-section of the hypothalamo-pituitary axis identifying the magnocellular neurones of the neurohypophysis and the blood supply from the inferior hypophysial artery. Also shown are the paraventricular parvocellular neurones which either terminate on the walls of the primary capillary plexus in the median eminence or terminate on other distant parts of the brain.

3. Synthesis, Storage and Release of Neurohypophysial Hormones

Vasopressin is detected as early as the tenth week of development in the human, following the extension of axons into the posterior lobe of the pituitary. Bargmann and Scharrer in 1951 were the first to hypothesise that the synthesis of the neurohypophysial hormones occurs in the neurone cell bodies located in the hypothalamic nuclei. The molecules then pass down the nerve axons to be stored and released from the terminals in the posterior pituitary. Evidence leading to the acceptance of this hypothesis was provided by the studies of Sachs and colleagues, who further proposed that vasopressin was initially synthesised in the neurones as an inactive precursor molecule and that the biologically active molecule appears during the formation and migration of granules within the cytoplasm (Sachs and Takabataki, 1964; Sachs *et al.*, 1969). The granules accumulate in the nerve terminals and in the Herring bodies. The structure of oxytocin was elucidated by du Vigneaud and colleagues (1953a) and independently by Tuppy (1953), who identified eight amino acids (nine when the cystine is replaced by two sulphide bond-linked cysteines after oxidation) made up into a ring of six amino acids and a short side branch of three amino acids. A remarkably similar structure was identified for vasopressin. This molecule is found in most mammals (including man), and consists of the same amino acids, except for the replacement of the leucine in the side branch of oxytocin by arginine, and isoleucine in the ring by phenylalanine (du Vigneaud *et al.*, 1953b; Acher and Chauvet, 1953). Du Vigneaud's team (du Vigneaud *et al.*, 1957) went on to identify the slightly modified vasopressin molecule in members of the Suina (e.g. pig) family, in which the arginine is replaced by lysine, hence reference to arginine vasopressin (AVP) or lysine vasopressin (LVP) (see Fig. 2).

We now know that the oxytocin and vasopressin molecules, like other polypeptide hormones, are post-translational products processed from larger prohormones which are enzymatically cleaved into the component

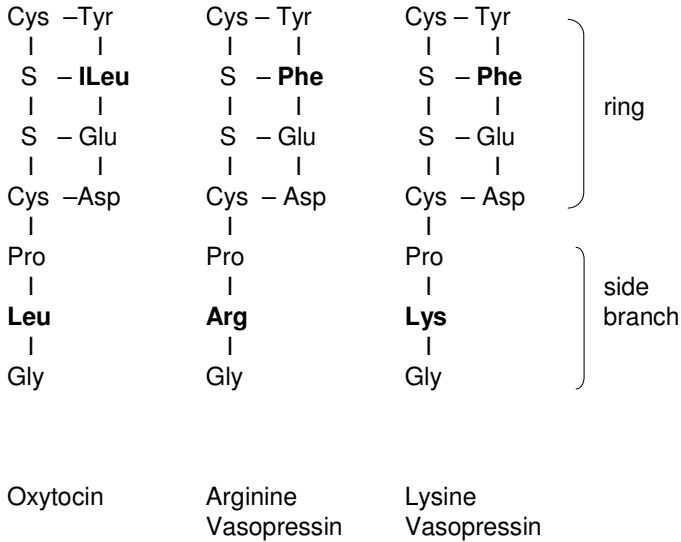


Figure 2. The amino acid sequences of oxytocin and the two mammalian forms of vasopressin.

hormones and their related proteins, the neurophysins (MW approximately 10,000) (Gainer *et al.*, 1977a, 1977b). Neurophysin I is the protein derived from the oxytocin precursor, while neurophysin II is a glycoprotein associated with vasopressin (Russell *et al.*, 1980). This processing occurs within the neurosecretory granules formed in the Golgi complex of the neurone cell bodies, with the relevant proteolytic enzymes identified within them (Gainer, 1983). An additional cleavage product from the provasopressin molecule is a glycopeptide of unclear function. All cleavage products are released into the general circulation (see Chapter 3).

In addition to the axonal transport of vasopressin and its associated molecules within granules, it is possible that some of these molecules are

released from the granules and are transported directly down the axons. The neurohypophysial hormones are released from the storage granules to the exterior by the process of exocytosis, as originally proposed by Douglas and Poissner (1964). The process is the result of stimulus-secretion coupling, in which the stimulus activates the neurone and, as in other nerves, the action potential travels down the axon and depolarizes the terminal membrane, which leads to an influx of calcium ions. This is necessary for the subsequent fusion of the granule membrane with the neuronal cell membrane following Ca^{++} -calmodulin-dependent activation of a neuronal ATPase. Consequently, the granule contents are released into the blood vessels which lie in close proximity to the nerve terminals (Douglas, 1973).

More recently, it has become clear that vasopressin is also synthesized in other tissues, including the sympathetic ganglia (Hanley *et al.*, 1984), the adrenals (Nussey *et al.*, 1984; Guillon *et al.*, 1998), the ovaries (Fuller *et al.*, 1985; Stones *et al.*, 1996), the testis (Kasson *et al.*, 1985; Fillion *et al.*, 1993), the heart (Hupf *et al.*, 1999; Watanabe *et al.*, 2005) and even the thymus (Jessop *et al.*, 1995). Certainly there is plenty of evidence for the presence of vasopressin receptors (R) in all of these, and other, tissues, for example V1R in sympathetic ganglia (Kiralý *et al.*, 1986), V1aR and V1bR in adrenal medulla (Grazzini *et al.*, 1996; Guillon *et al.*, 1998), V1R in heart-derived myocytes (Reilly *et al.*, 1998; Brostrom *et al.*, 2000), V1aR, V1bR and V2R in the gastrointestinal tract (Monstein *et al.*, 2008) and V1R in the liver (Gopalakrishnan *et al.*, 1986). These findings certainly imply that vasopressin is a potential local autocrine regulator, if nothing else, in many tissue systems.

4. Vasopressin Assays

Fractionation and purification of posterior pituitary extracts was achieved initially using the extraction method described by Kamm *et al.* in 1928 which involved heating of the extract in 0.25% acetic acid. Identification of the two hormones oxytocin and vasopressin was made possible by the development of bioassays for oxytocic activity (e.g. rat uterine muscle

contraction, milk ejection in the anaesthetized lactating rat) and vasoconstrictor or antidiuretic activities for vasopressin. The development of sensitive and specific assays has been an extremely important factor in the vast expansion of our knowledge of endocrinology over the last 50 years. Initially these assays were based on the biological responses of sensitive tissues or animal preparations, called bioassays.

It has long been appreciated that the measurement of vasopressin concentrations in biological fluids by means of dose-related vasoconstriction of arterial strips or increases in arterial blood pressure in an animal model is of limited practical value, as it is generally insensitive within the normal physiological range. One example is an assay using the proximal part of the guinea pig colon developed by Botting in 1965 which was reportedly quite sensitive (to as low as 1 microunit/ml), although published data indicate 100 microunits/ml as being the lowest effective concentration shown. In general, the more sensitive bioassays for vasopressin were developed using the antidiuretic action of the hormone as the dose-dependent measurable variable. This included the movement of water across amphibian skin or bladder, which is stimulated by vasopressin (Heller, 1941).

Since sodium transport across frog or toad skin is also stimulated by vasopressin, this too was measured using strips of skin (Morel *et al.*, 1958), as determined by short-circuit current changes induced with different doses of hormone. However, the mainstay in vasopressin bioassays became the ethanol-anaesthetised water-loaded rat, with the hormone administered intravenously, as first described by Jeffers *et al.* in 1942. The use of ethanol as the anaesthetic was particularly advantageous because this drug also inhibits the endogenous release of vasopressin. The maintenance of the rat in a state of hydration also inhibited endogenous hormone release, making the preparation more sensitive for longer (Dicker, 1953). The first vasopressin radioimmunoassay was developed in the early 1970s (Robertson *et al.*, 1970). Problems in getting specific sensitive antibodies for vasopressin delayed the widespread use of this technique for many years.

5. Physiological Actions

In 1895, Oliver and Schaffer administered a crude posterior pituitary extract to a dog which produced an increase in arterial blood pressure. They consequently named the active ingredient vasopressin. It took many years before the main physiological action, the antidiuretic effect, of vasopressin was described, following the important studies of Starling and Verney (1925), Pickford (1936) and other researchers. Vasopressin was then 'adopted' by renal physiologists for a while and it became commonly known as the Antidiuretic Hormone (ADH).

The micropuncture studies of Gottschalk and Mylle (1959) and others indicated that vasopressin must increase the permeability to water in the distal tubule of the renal nephron. Perfusion of rabbit collecting tubules with the hormone resulted in a threefold increase in water permeability (Grantham and Burg, 1966). Berliner and Bennett (1967) concluded that all the known effects of ADH at physiological concentrations could be explained by modifications of permeability to water that the hormone induces in the most distal parts of the nephron. While other renal sites and actions have now been identified (see Chapter 6), it is accepted that the collecting duct remains the principal region of the nephron where the antidiuretic effect of vasopressin is exerted.

But does vasopressin actually have any physiological effect on the cardiovascular system, and what about actions associated with the other vasopressinergic nerve pathways that have been described? Early work investigating the effect of vasopressin on isolated arterial strips indicated species, vessel and dose-specific effects (Dodd and Daniel, 1960). The intra-arterial infusion of vasopressin extracts (Pitressin) into the isolated hind limb of a dog produced quite pronounced vasoconstriction (Diana and Masden, 1965), while Rocha e Silva and Rosenberg (1969) showed that infusion of vasopressin in dogs at doses producing plasma concentrations comparable with those attained after haemorrhage are pressor, providing that the baroreceptor reflex is abolished. Altura (1973) compared the constrictor effects of various known vasoactive substances on the diameters of mesenteric arteriolar cross-sections and showed that

vasopressin was more potent than any other known endogenous pressor agent, including angiotensin II. This, and later, work gradually re-established the neurohypophysial hormone as a pressor substance, and vasopressin is now its current generally accepted name (see Chapter 7). In the last 25 years, other actions of vasopressin have been described including its action as an adenohypophysial hormone (corticotrophin) releasing factor (see Chapter 9), the stimulation of factor VIII and von Willbrandt factor synthesis (see Chapter 7). In addition, there is now much interest in the central actions of this neuropeptide (see Chapter 10).

Interestingly, as indicated in Chapter 9, vasopressin can be considered a stress hormone, i.e. one that is released in response to various stressors. As such, and like most, if not all, other stress hormones, vasopressin promotes an increase in blood glucose concentration by stimulating hepatic glycogenolysis (Hems *et al.*, 1975; Hems *et al.*, 1978) predominantly in the perivenous zone (Schmeisch *et al.*, 2005). Vasopressin also stimulates tricarboxylic acid cycle activity (Patel, 1986).

Currently, it is increasingly appreciated that vasopressin has a number of disparate effects on the body, both peripheral and central, as indicated in Fig. 3.

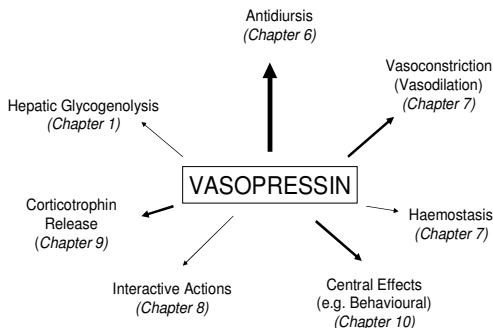


Figure 3. The principal known effects of vasopressin and the chapters which consider them in more detail.

6. Receptors and Mechanisms of Action

Three different receptors have now been identified for vasopressin and these are V1a, V1b and V2 receptors. The V1a receptor is found in many parts of the body, including the vasculature, heart, liver, kidneys, brain and platelets. The closely related V1b receptor is mainly specific to corticotroph cells in the anterior pituitary, while the V2 receptors are mainly located on the principal cells of the renal distal nephrons but also probably on endothelial cells. These receptor types are considered further in Chapters 4 and 5.

The ubiquitous second messenger system involving the action of the enzyme adenylyl cyclase on adenosine triphosphate (ATP) with the resultant formation of cyclic adenosine monophosphate (cAMP) was first described for the catecholamine adrenaline by Sutherland and Rall in 1958. Later, Orloff and Handler (1964) proposed cAMP as the second messenger through which vasopressin exerted its antidiuretic effect. More details of the intracellular mechanisms stimulated by the arrival of vasopressin at the cell membrane have been provided over the last 30 years, following the rapid expansion of molecular and cellular biology. Of particular importance has been the determination of the vasopressin receptors and their relationships with the intracellular second messenger systems, of which the generation of cAMP is one and inositol triphosphate is another (see Chapter 4).

7. Circulation and Metabolism

In the blood, vasopressin is not believed to be associated with erythrocytes, as early reports indicated that it can be accounted for entirely in the plasma fraction, as determined by bioassay (Heller and Zaidi, 1957). However, data for its circulation as a protein-bound molecule were conflicting. Lauson (1967) concluded in a review that it was likely that most, if not all, of the vasopressin in blood circulates as the free unbound molecule. It is also accepted that since the necessary pH for vasopressin-neurophysin binding is far lower than the plasma pH,

this co-released protein cannot play any part in the transportation of the hormone in the blood. Estimates of the half-life for vasopressin (8-arginine vasopressin) based on the loss of biological activity in blood range from 0.9 min in rat (Ginsburg, 1957) to 5.9 min in dog (Share, 1962) and 4.9 min in humans (Silver *et al.*, 1961).

More recently there have also been a number of reports indicating that the plasma vasopressin concentration actually represents only a small proportion of the total hormone content of the blood, with the major component located within the circulating platelets. One study showed that in rats, approximately 30% of circulating vasopressin was found in platelets (Lee-Kwon *et al.*, 1984), while other studies have suggested values ranging from approximately 50% in dogs (Share *et al.*, 1985) and in humans (Bichet *et al.*, 1987) to 90% in humans (Chesney *et al.*, 1985; Nussey *et al.*, 1986).

Clearance of vasopressin from the blood is associated mainly with renal and hepatic activities, as determined by studies in the whole animal or in isolated perfused organs. Interestingly, renal clearance estimates for vasopressin of between 50% (Ginsburg and Heller, 1953; Dicker, 1954) and 70% (Crawford and Pinkham, 1954) were determined from studies using nephrectomised rats. Some vasopressin appears unchanged in the urine, indicating that a considerable inactivation of the neurohypophysial hormone takes place in the kidneys. Values for the renal excretion of vasopressin vary (see Lauson, 1967). In one study, excreted vasopressin, expressed as a percentage of the dose of pitressin tannate in oil administered, varied from <1 to 5% (Laycock and Williams, 1973).

Clearance by the liver is also quite well established, following splanchnic vascular ligation studies (Ginsburg and Heller, 1953), and this accounts for most of the remaining removal of vasopressin from the blood. However, it is worth noting that some circulating vasopressin could be inactivated by a plasma vasopressinase, as suggested by Werle (1960), which might be an enzyme such as fibrinolysin. Furthermore, in pregnancy the increase in circulating oxytocinase correlates not only

with the removal of oxytocin but also vasopressin from the blood (Croxatto, *et al.*, 1953). For more information, see Chapter 3.

8. Control of Release of Vasopressin

Studies by Verney (1947), O'Connor (1950) and other researchers were instrumental in identifying not only vasopressin's renal water reabsorption effect but also how this is linked to its release when the plasma osmolality increases, as first suggested by Chambers *et al.*, (1945). Initially the 'osmoreceptors' were located in the anterior hypothalamus (Jewell and Verney, 1957). Vasopressin is released by changes in plasma osmolality, but only by those solutes which remain in the extracellular fluid. Molecules which readily cross cell membranes such as urea have no effect. While it is now clear that the supraoptic (and presumably paraventricular) neuronal cell bodies are directly sensitive to changes in sodium ions in the extracellular medium (Leng *et al.*, 1981), it is generally accepted that the true osmoreceptors themselves lie outside the restrictive blood brain barrier. Indeed, various circumventricular organs such as the subfornical organ and the organum vasculosum of the lamina terminalis have been shown to mediate the changes in plasma osmolality with the release of neurohypophysial vasopressin (Thresher *et al.*, 1982).

Other influences on vasopressin secretion, particularly those associated with known neurotransmitters such as acetylcholine (Pickford, 1939) and catecholamines (O'Connor & Verney, 1945) have also been identified. These early studies were indicative of possible influences on the neurohypophysis, either via central nerve pathways or via the circulation. Central pathways were also implicated by studies of the effect of various stresses on water balance and vasopressin release (O'Connor and Verney, 1942). While conclusions drawn from early studies on the effect of blood loss on vasopressin release were variable, it became increasingly apparent that haemorrhage was a powerful stimulus (Ginsburg and Brown, 1956) and that the fall in blood pressure was the likely stimulus. Baroreceptor involvement was implicated in the release of vasopressin

(and its consequent effect on arterial blood pressure) in various studies (Cowley *et al.*, 1974; Bisset and Chowdrey, 1984). See Chapter 11 for further information about mechanisms of control of neurohypophysial vasopressin secretion.

9. Clinical Aspects of Vasopressin

If vasopressin cannot exert its principal physiological action on the renal collecting ducts, then the final concentrating ability of the kidney is lost. The large volumes of dilute urine excreted in consequence gives rise to the condition of diabetes insipidus (the excretion of a large volume of tasteless, or insipid, urine). The absence or lack of circulating vasopressin because of a malfunctioning hypothalamo-neurohypophysial system results in the condition of central (hypothalamic), or cranial, diabetes insipidus. This form of the disease can nowadays be readily treated with a vasopressin agonist acting on V2 receptors. The other form of this disease, characterised by the presence of circulating vasopressin, but lacking collecting duct responsiveness to the hormone (target tissue insensitivity) is known as nephrogenic diabetes insipidus. This can only be partially treated at present. There is currently much interest in the use of vasopressin receptor antagonists in conditions such as hyponatraemia and congestive heart failure. The vasoconstrictor effect of vasopressin is also useful in the treatment of bleeding disorders such as oesophageal varices. Another clinical use of vasopressin is related to its effect on the synthesis of factor VIII and the von Willbrandt factor. These clinical aspects of vasopressin are discussed more fully elsewhere (Chapter 12).

10. Conclusion

We have known of the existence of the neurohypophysial peptide vasopressin for many years and we have appreciated the clinical consequences of its absence resulting from the loss of its principal physiological action in the renal collecting duct. However, we have learnt that this hormone has other peripheral effects, particularly its

ability to vasoconstrict arteriolar smooth muscle, as a releasing hormone for the adenohipophysial hormone corticotrophin, and we are beginning to appreciate some of its central effects such as on different adaptive behaviours. Vasopressin and the neurohypophysial system have also been instrumental in our current understanding of neuropeptide secretion, storage and release. Future research will undoubtedly provide us with much more information about this interesting peptide and its involvement in physiological processes, and its likely clinical consequences.

Bibliography

- Acher R., Chauvet J. (1953). La structure de la vasopressine du boeuf. *Biochem Biophys Acta* 12: 487–488
- Altura B.M. (1973). Selective microvascular constrictor actions of some neurohypophysial peptides. *Eur J Pharmacol* 24: 49–60
- Bargmann W., Scharrer E. (1951). The site of origin of the hormones of the posterior pituitary. *Am Sci* 39: 255–259
- Berliner R.W., Bennett C.M. (1967). Concentration of urine in the mammalian kidney. *Am J Med* 42: 777–789
- Bichet D.G., Arthus M-F., Barjon J.N., Lonergan M., Kortas C. (1987). Human platelet fraction arginine vasopressin. Potential physiological role. *J Clin Invest* 79: 881–887
- Bisset G.W., Chowdrey H.S. (1984). A cholinergic link in the reflex release of vasopressin by hypotension in the rat. *J Physiol* 354: 523–545
- Botting J.H. (1965). An isolated preparation with a selective sensitivity to vasopressin. *Br J Pharmacol Chemother* 24: 156–62
- Brostrom M.A., Reilly B.A., Wilson F.J., Brostrom C.O. (2000). Vasopressin-induced hypertrophy in H9c2 heart-derived myocytes. *Int J Biochem Cell Biol* 32: 993–1006
- Chambers G.H., Melville E.V., Hare R.S., Hare K. (1945). Regulation of the release of pituitrin by changes in the osmotic pressure of the plasma. *Am J Physiol* 144: 311–320
- Chesney CM., Crofton J.T., Pifer D.D., Brooks D.P., Huch K.M., Share L. (1985). Subcellular localization of vasopressin-like material in platelets. *J Lab Clin Med* 106: 314–318
- Cowley A.W., Monos E., Guyton A.C. (1974). Interaction of vasopressin and the baroreceptor reflex system in the regulation of arterial blood pressure in the dog. *Circ Res* 34: 505–514
- Croxatto H., Vera C., Barnafi L. (1953). Inactivation of antidiuretic hormone by blood serum of the pregnant woman. *Proc Soc Exp Biol* 83: 784–786
- Crawford J.D., Pinkham B. (1954). The removal of circulating antidiuretic hormone by the kidney. *Endocrinol* 55: 699–700
- Diana J.N., Masden R.R. (1965). Effect of vasopressin infusion and sciatic nerve stimulation in isolated dog hindlimb. *Am J Physiol* 209: 390–396
- Dicker S.E. (1953). A method for the assay of very small amounts of antidiuretic activity with a note on the antidiuretic titre of rat's blood. *J Physiol* 122: 149–157
- Dodd W.A., Daniel E.E. (1960). Electrolytes and arterial muscle contractility. *Circ Res* 8: 451–463

- Douglas W.W. (1963). A possible method of neurosecretion. Release of vasopressin by depolarization and its dependence on calcium. *Nature* 197: 81–82
- Douglas W.W. (1973). How do neurones secrete peptides? Exocytosis and its consequences including synaptic vesicle formation in the hypothalamo-neurohypophysial system. *Prog Brain Res* 39: 21–39
- Douglas W.W., Poissner A.M. (1964). Stimulus-secretion coupling in a neurosecretory organ. The role of calcium in the release of vasopressin from the neurohypophysis. *J Physiol* 172: 1–18
- Fillion C., Malassine A., Tahri-Joutei A., Allevard A.M., Bedin M., Gharib C., Hugues J.N., Pointis G. (1993). Immunoreactive arginine vasopressin in the testis: immunocytochemical localization and testicular content in normal and experimental cryptorchid mouse. *Biol Reprod* 48: 786–792
- Fuller P.J., Clements J.A., Tregear G.W., Nicolaidis I., Whitfield P.L., Funder J.W. (1985). Vasopressin-neurophysin II gene expression in the ovary: studies in Sprague-Dawley, Long-Evans and Brattleboro rats. *J Endocrinol* 105: 317–321
- Gainer H. (1983). Precursors of vasopressin and oxytocin. In *The Neurohypophysis: structure, function and control*. *Pro In Brain Res* 60: 205–215
- Gainer H., Sarne Y., Brownstein J.J. (1977a). Neurophysin in biosynthesis: conversion of a putative precursor during axonal transport. *Science* 195: 1354–1356
- Gainer H., Sarne Y., Brownstein J.J. (1977b). Biosynthesis and axonal transport of rat neurohypophysial proteins and peptides. *J Cell Biol* 73: 366–381
- Ginsburg M. (1957). The clearance of vasopressin from the splanchnic vascular area and the kidneys. *J Endocrinol* 16: 217–226
- Ginsburg M., Brown L.M. (1956). Effect of anaesthetics and haemorrhage on the release of neurohypophysial antidiuretic hormone. *Br J Pharmacol* 14: 327–333
- Ginsburg M. & Heller, H. (1953). The clearance of injected vasopressin from the circulation and its fate in the body. *J Endocrinol* 9: 283–291
- Gopalakrishnan V., Triggle C.R., Sulakhe P.V., McNeill J.R. (1986). Characterization of a specific high affinity [3H] arginine 8 vasopressin-binding site on liver microsomes from different strains of rat and the role of magnesium. *Endocrinol* 118: 990–997
- Gottschalk C.W., Mylle M. (1959). Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the countercurrent hypothesis. *Am J Physiol* 194: 927–936
- Grantham J.J., Burg M.B. (1966). Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. *Am J Physiol* 211: 255–259
- Grazzini E., Boccara G., Joubert D., Trueba M., Durroux T., Guillon G., Gallo-Payet N., Chouinard L., Payet M.D., Serradeil-LeGal C. (1998). Vasopressin regulates adrenal functions by acting through different vasopressin receptor subtypes. *Adv Exp Med Biol* 449: 325–334
- Grazzini E., Lodboerer A.M., Perez-Martin A., Joubert D., Guillon G. (1996). Molecular and functional characterization of V1b vasopressin receptor in rat adrenal medulla. *Endocrinol* 137: 3906–3914
- Guillon G., Grazzini E., Andrez M., Breton C., Trueba M., Serradeil-LeGal C., Boccara G., Derick S., Chouinard L., Gallo-Payet N. (1998). Vasopressin: a potent

- autocrine/paracrine regulator of mammal adrenal functions. *Endocr Res* 24: 703–710
- Hanley M.R., Benton H.P., Lightman S.L., Todd K., Bone E.A., Fretten P., Palmer S., Kirk C.J. & Michell R.H. (1984). A vasopressin-like peptide in the mammalian sympathetic nervous system. *Nature* 309: 358–361
- Heller H. (1941). Differentiation of an (amphibian) water balance principle from the antidiuretic principle of the pituitary gland. *J Physiol* 100: 125–141
- Heller H., Zaidi S.M. (1957). The metabolism of exogenous and endogenous antidiuretic hormone in the kidney and liver *in vivo*. *Br J Pharmacol Chemother* 12: 284–292
- Hemms D.A., Whitton P.D., Ma G.Y. (1975). Metabolic actions of vasopressin, glucagon and adrenalin in the intact rat. *Biochim Biophys Acta* 411: 155–164
- Hemms D.A., Rodrigues L.M., Whitton P.D. (1978). Rapid stimulation by vasopressin, oxytocin and angiotensin II of glycogen degradation in hepatocyte suspensions. *Biochem J* 172: 311–317
- Herring P.T. (1908). A contribution to the comparative physiology of the pituitary body. *Quart J Exp Biol* 1: 261–280
- Hupf H., Grimm D., Riegger G.A.J., Schunkert H. (1999). Evidence for a vasopressin system in the rat heart. *Circ Res* 84: 365–370
- Jeffers W.A., Livezey M.M., Austin J.H. (1942). Method for demonstrating the antidiuretic action of minute amounts of pitressin: statistical analysis of results. *Proc Soc Exp Biol* 50: 184–188
- Jessop D.S., Murphy D., Larsen P.J. (1995). Thymic vasopressin (AVP) transgene expression in rats: a model for the study of thymic AVP hyper-expression in T cell differentiation. *J Neuroimmunol* 62: 85–90
- Jewell P.A., Verney E.B. (1957). An experimental attempt to determine the site of the neurohypophysial osmoreceptors in the dog. *Phil Trans B* 240: 197–324
- Kamm O. (1928). The dialysis of pituitary extracts. *Science* 67: 199–200
- Kasson B.G., Meidan R., Hsueh A.J. (1985). Identification and characterization of arginine vasopressin-like substances in the rat testis. *J Biol Chem* 260: 5302–5307
- Kiraly M., Audigier S, Tribollet E., Barbaris C., Dolivo M., Dreifuss J.J. (1986). Biochemical and electrophysiological evidence of functional vasopressin receptors in the rat superior cervical ganglion. *Proc Natl Acad Sci* 83: 5335–5339
- Lauson H.D. (1967). Metabolism of antidiuretic hormones. *Am J Med* 42: 713–744
- Laycock J.F., Williams P.G. (1973). The effect of vasopressin (Pitressin) administration on sodium, potassium and urea excretion in rats with and without diabetes insipidus (DI) with a note on the excretion of vasopressin in the DI rat. *J Endocrinol* 56: 111–120
- Lee-Kwon W.J., Share L., Crofton J.T., Brooks D.P. (1984). Effect of angiotensin II on vasopressin in plasma and platelets in SH and WKY rats. *Clin Exp Hypertens A* 6: 1653–1672
- Leng G., Mason W.T., Dyer R.G. (1981). The supraoptic nucleus as an osmoreceptor. *Neuroendocrinol* 34: 7–82
- Monstein H.J., Truesdsson M., Ryberg A., Ohlsson B. (2008). Vasopressin receptor mRNA expression in the human gastrointestinal tract. *Eur Surg Res* 40: 34–40

- Morel F., Maetz J., Lucerain C. (1958). The action of two neurohypophysial peptides on the active transport of sodium and the net flux of water across the skin of various species of anuran frogs and toads. *Biochim Biophys Acta* 28: 619–626
- Nussey S.S., Ang V.T., Bevan D.H., Jenkins J.S. (1986). Human platelet arginine vasopressin. *Clin Endocrinol* 24: 427–433
- Nussey S.S., Ang V.T., Jenkins J.S., Chowdrey H.S., Bisset G.W. (1984). Brattleboro rat adrenal contains vasopressin. *Nature* 310: 64–66
- O’Conner W.J. (1950). The role of the neurohypophysis of the dog in determining urinary changes and the antidiuretic activity of urine following administration of sodium chloride. *Quart J exp Physiol* 36: 21–48
- O’Conner W.J. Verney E.B. (1942). The effect of removal of the posterior lobe of the pituitary on the inhibition of water diuresis by emotional stress. *Quart J Exp Physiol* 31: 393–408
- O’Conner W.J., Verney E.B. (1945). The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. *Quart J Exp Physiol* 33: 77–90
- Oliver G., Schafer E.A. (1895). On the physiological action of extracts of pituitary body and certain other glandular organs: preliminary communication. *J Physiol* 18: 277–279
- Orloff J., Handler J.S. (1964). The cellular action of antidiuretic hormone. *Am J Physiol* 36: 686–697
- Patel T.B. (1986). Hormonal regulation of the tricarboxylic acid cycle in the isolated perfused rat liver. *Eur J Biochem* 159: 15–22
- Pickford M. (1936). Inhibition of water diuresis by pituitary (post lobe) extract and its relation to the water load of the body. *J Physiol* 87: 291–297
- Pickford M. (1939). The inhibitory effect of acetylcholine on diuresis in the dog and its pituitary transmission. *J Physiol* 95: 226–238
- Ramon y Cajal J. (1894). Algunas contribuciones al conocimiento del sistema ganglionar del cerebro. III Hipofisis. *Ann Soc Exp Hist Nat* 2
- Reilly B.A., Brostrom M.A. Brostrom C.O. (1998). Regulation of protein synthesis in ventricular myocytes by vasopressin. The role of sarcoplasmic/endoplasmic reticulum Ca²⁺ stores. *J Biol Chem* 273: 3747–3755
- Robertson G.L., Klein L.A., Roth J., Gordon P. (1970). Immunoassay of plasma vasopressin in man. *Proc Nat Acad Sci* 66: 12988–1305
- Rocha e Silva M. Jr., Rosenberg M. (1969). The release of vasopressin in response to haemorrhage and its role in the mechanism of blood pressure regulation. *J Physiol* 202: 535–557
- Russell J.T., Brownstein M.J., Gainer H. (1980). Biosynthesis of vasopressin, oxytocin and neurophysins: isolation and characterization of two common precursors (prepressophysin and prooxyphysin). *Endocrinol* 107: 1880–1891
- Sachs H., Fawcett P., Takabatake Y., Portanova R. (1969). Biosynthesis and release of vasopressin and neurophysin. *Recent Prog Horm Res* 25: 447–491
- Sachs H., Takabatake Y. (1964). Evidence for a precursor in vasopressin biosynthesis. *Endocrinology* 75: 943–948

- Share L. (1962). Vascular volume and blood level of antidiuretic hormone. *Am J Physiol* 202: 791–794
- Share L., Crofton J.T., Brooks D.P., Chesney C.M. (1985). Platelet and plasma vasopressin in dogs during hydration and vasopressin infusion. *Am J Physiol* 249: R313–R316
- Silver L., Schwartz I.E., Fong C.T.O., Debons A.F., Dahl L.K. (1961). Disappearance of plasma radioactivity after injection of H³ or I¹³¹ labelled arginine vasopressin. *J Appl Physiol* 16: 1097–1099
- Schmeisch A.P., de Olivera D.S., Ide I.T., Suzuki-Kemmelmeier F., Bracht A. (2005). Zonation of the metabolic action of vasopressin in the bivascularly perfused rat liver. *Regul Pept* 129: 233–243
- Starling E.H., Verney E.B. (1925). The secretion of urine as studied on the isolated kidney. *Proc Roy Soc Med B* 97: 321–363
- Stones R.W., Vials A., Milner P., Beard R.W., Burnstock G. (1996). Release of vasoactive agents from the isolated perfused human ovary. *Eur J Obstet Gynecol Reprod Biol* 67: 191–196
- Sutherland E.W., Rall T.W. (1958) Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles. *J Biol Chem* 232: 1077–1091
- Thrasher T.N., Keil L.C., Ramsey D.J. (1982). Lesions of the organum vasculosum of the lamina terminalis (OVLT) attenuate osmotically induced drinking and vasopressin secretion in the dog. *Endocrinol* 110: 1837–1839
- Tuppy H. (1953). The amino acid sequence in oxytocin. *Biochim Biophys Acta* 11: 449–450
- Verney E.B. (1947) The antidiuretic hormone and the factors which determine its release. *Proc Roy Soc Med B* 135: 25–106
- du Vigneaud V., Ressler C., Tripett S. (1953a). The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. *J Biol Chem* 205: 949–957
- du Vigneaud V., Lawler H.C., Popenoe E.A. (1953b). Enzymic cleavage of glycinamide from vasopressin and a proposed structure for this pressor-antidiuretic hormone of the posterior pituitary. *J Am Chem Soc* 75: 4880–4881
- du Vigneaud V., Bartlett M.F., Joell A. (1957). The synthesis of lysine vasopressin. *J Am Chem Soc* 79: 5572–5575
- Watanabe I., Tani S., Nagao K., Anazawa T., Kawamata H., Ohguchi S., Kanmatsuse K., Kushiro T. (2005). Regulation of arginine vasopressin in the human heart. *Circ J* 69: 1401–1404
- Werle E. (1960). Comment in discussion in: Polypeptides which affect smooth muscle and blood vessels. Ed. M.Schachter, 89–90