NORMAL AND ABNORMAL PHYSIOLOGY OF THE HYPOTHALAMUS-POSTERIOR PITUITARY (INCLUDING DI AND SIADH)

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The hypothalamus and posterior pituitary form a complex neurohumoral system. This chapter will concentrate on the physiology and pathophysiology of two hormones made by the hypothalamus and posterior pituitary, vasopressin (VP) and oxytocin (OT), which have key roles in body fluid homeostasis and reproductive function. We will outline the anatomical, cellular and molecular basis of their regulation and function, together with the clinical problems associated with defects in production and action.

PART 1. ANATOMY, CELL BIOLOGY AND PHYSIOLOGY OF THE HYPOTHALAMO-POSTERIOR PITUITARY AXIS

1. The anatomy of the Neurohypophysis

In contrast to the anterior pituitary gland, the posterior pituitary is derived from the forebrain during development and is composed predominantly of neural tissue. The posterior pituitary lies below the hypothalamus, with which it forms a structural and functional unit: the neurohypophysis. The neurohypophysis consists of three parts: the supraoptic and paraventricular nuclei of the hypothalamus (containing the cell bodies of the magnocellular, neurosecretory neurons that synthesize and secrete VP and OT); the supraoptico-hypophyseal tract (which includes the axons of these neurons; and the posterior pituitary (where the axons terminate on capillaries of the inferior hypophyseal artery).

The supraoptic nucleus (SON) is situated along the proximal part of the optic tract. It consists of the cell bodies of discrete vasopressinergic and oxytotic magnocellular neurons projecting to the posterior pituitary along the supraoptico-hypophyseal tract. The paraventricular nucleus (PVN) also contains discrete vasopressinergic and oxytotic magnocellular neurons projecting to the posterior pituitary along the supraoptico-hypophyseal tract. The PVN contains additional, smaller parvicellular neurons projecting to the median eminence and additional extra-hypothalamic areas including forebrain, brain stem, and spinal cord. Some of these parvicellular neurons are vasopressinergic. A group of those projecting via the median eminence co-secrete VP and corticotrophin releasing hormone (CRH), and terminate in the hypophyseal-portal bed of the anterior pituitary. These neurons have a role in the regulation of adrenocorticotrophin (ACTH) release.

A schematic overview of the anatomy of the neurohypophysis, together with the its major connections, is shown in Figure 1.

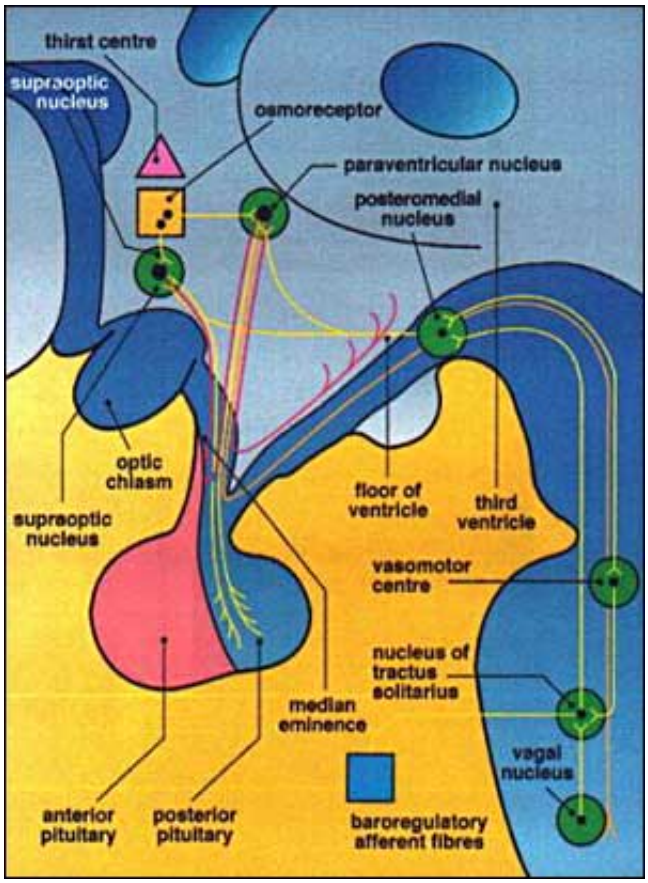

Figure 1.Schematic representation of the anatomy of the neurohypophysis, and it’s major afferent and efferent connections.

The posterior pituitary receives an arterial blood supply from the inferior hypophyseal artery and the artery of the trabecula (a branch of the superior hypohyseal artery), derivatives of the

internal carotid artery and its branches. The SON and PVN receive an arterial supply from the suprahypophyseal, anterior communicating, anterior cerebral, posterior communicating and posterior cerebral arteries, all derived from the circle of Willis. Venous drainage of the neurohyphysis is via the dural, cavernous and inferior petrosal sinuses.

2. Molecular-cell biology of Vasopressin and Oxytocin

VP is a 9 amino acid peptide with a disulphide bridge between the cysteine residues at positions 1 and 6 (Figure 2). Most mammals have the amino-acid arginine at position 8, though in the Pig family arginine is substituted by lysine. The structure of OT differs from that of VP by only 2 amino acids: isoleucine for phenylalanine at position 3; and leucine for arginine at position 8. Non-mammalian species have a variety of peptides very similar to VP and OT, suggesting they derive from a common ancestral gene.

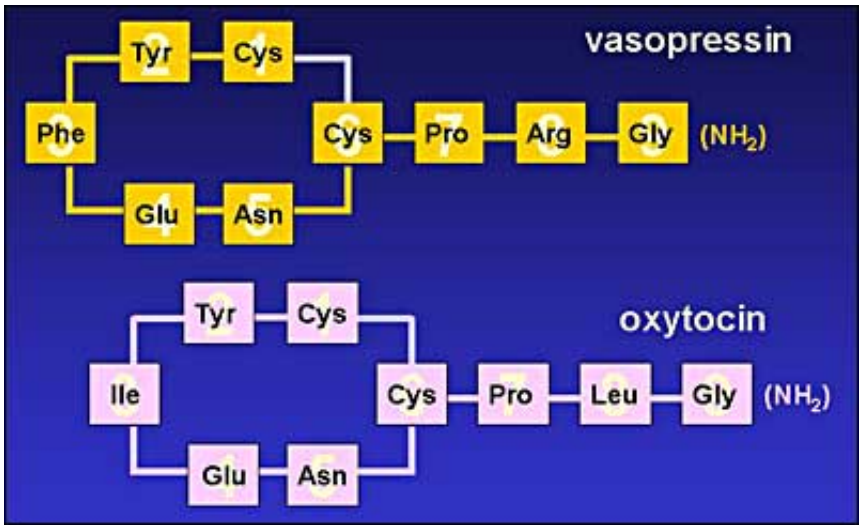

Figure 2.The structural and chemical characteristics of Vasopressin and Oxytocin. The cyclical peptides differ in only 2 amino acid positions. Both contain disulphide bridges between Cysteine residues at positions 1 and 6.

2.1. The Vasopressin-Neurophysin and Oxytocin-Neurophysin genes

The genes encoding VP and OT are in tandem array on chromosome 20 in Man, separated by 8 Kb of DNA. Each has 3 exons, and encodes a polypeptide precursor with a modular structure: an amino-terminal signal peptide; the VP or OT peptide; a hormone-specific mid-molecule peptide termed a neurophysin (NPI and NPII for OT and VP respectively); and a carboxyl-terminal peptide known as co-peptin (Figure 3). There is considerable homology between the NP sequences of the VP-NP and OT-NP genes, positions 10-74 of the NP sequences being highly conserved at the amino acid level.

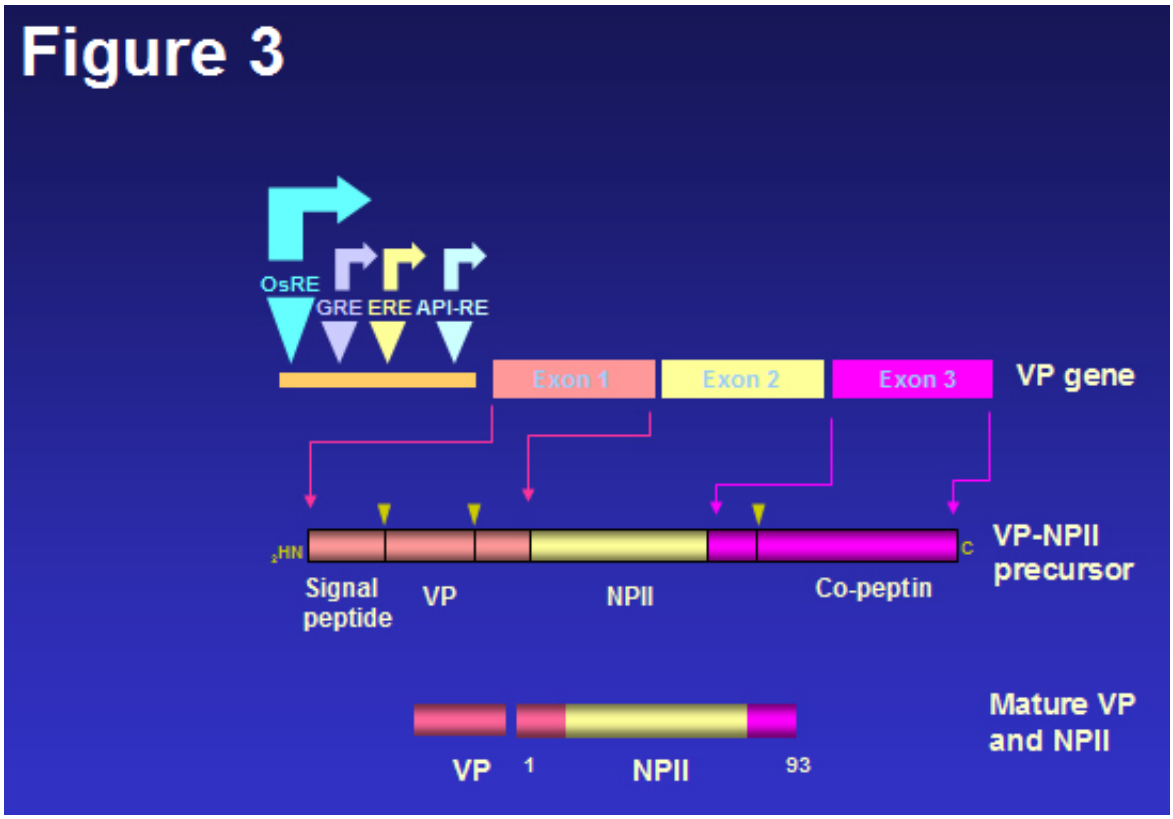

Figure 3.Structural organization of the Vasopressin-neurophysin II gene, and processing of its product. The VP-NPII gene has 3 exons. Translation of the mRNA yields a larger preprohormone precursor, subsequently modified through substantial post-translational modification. The OT gene has a similar structure, and its product undergoes similar processing and post-translational modification. VP: Vasopressin; NPII: Neurophysin II.

Hypothalamic-specific expression of the VP gene is conferred through selective repressor elements within the structural gene and its 5′ flanking sequence. Regulatory control of VP gene expression is mediated through positive and negative elements in the proximal promoter. Several transcription factors bind to these elements. AP1, AP2 and CREB stimulate VP gene expression. The glucocorticoid receptor (GR) represses expression (1, 2). The human, rat and mouse OT promoters contain half oestrogen-response elements, and IL-6 response elements. To date, the functional significance of these remains unclear (3).

VP gene expression can also be regulated at a post-transcriptional level. The length of the poly (A) tail of VP mRNA increases in response to water deprivation, influencing mRNA stability (4). VP mRNA also contains a dendritic localization sequence (DLS). Interaction of the DLS with a multifunctional poly(A) binding protein (PABP) may play key role in RNA stabilization, initiation of translation and translational silencing (5).

2.2. Synthesis, release, and metabolism of Vasopressin and Oxytocin

Synthesis of the VP and OT precursors occurs in the cell bodies of discrete vasopressinergic and oxytotic magnocellular neurosecretory neurons within the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. Generation of the mature hormone entails post-translational modification of the large primary precursor (Figure 4). Following ribosomal translation of the respective mRNA, the carboxyl terminal domain of the precursor is glycosylated, and the product packaged in vesicles of the regulated secretory pathway. These migrate along the axons of the magnocellular neurons, during which the precursor is cleaved by basic endopeptidases into the mature hormone and the associated NP. These are stored in secretory granules within the terminals of the magnocellular neurons in the posterior pituitary. Increased firing frequency of vasopressinergic and oxytotic neurons opens voltage-gated Ca2+ channels in these nerve terminals. This, in turn, leads to transient Ca2+ influx, fusion of the neurosecretory granules with the nerve terminal membrane, and release of the hormone and its NP into the systemic circulation in equimolar quantities. NPs act as carrier proteins for VP and OT during axonal migration, and appear to serve no other function.

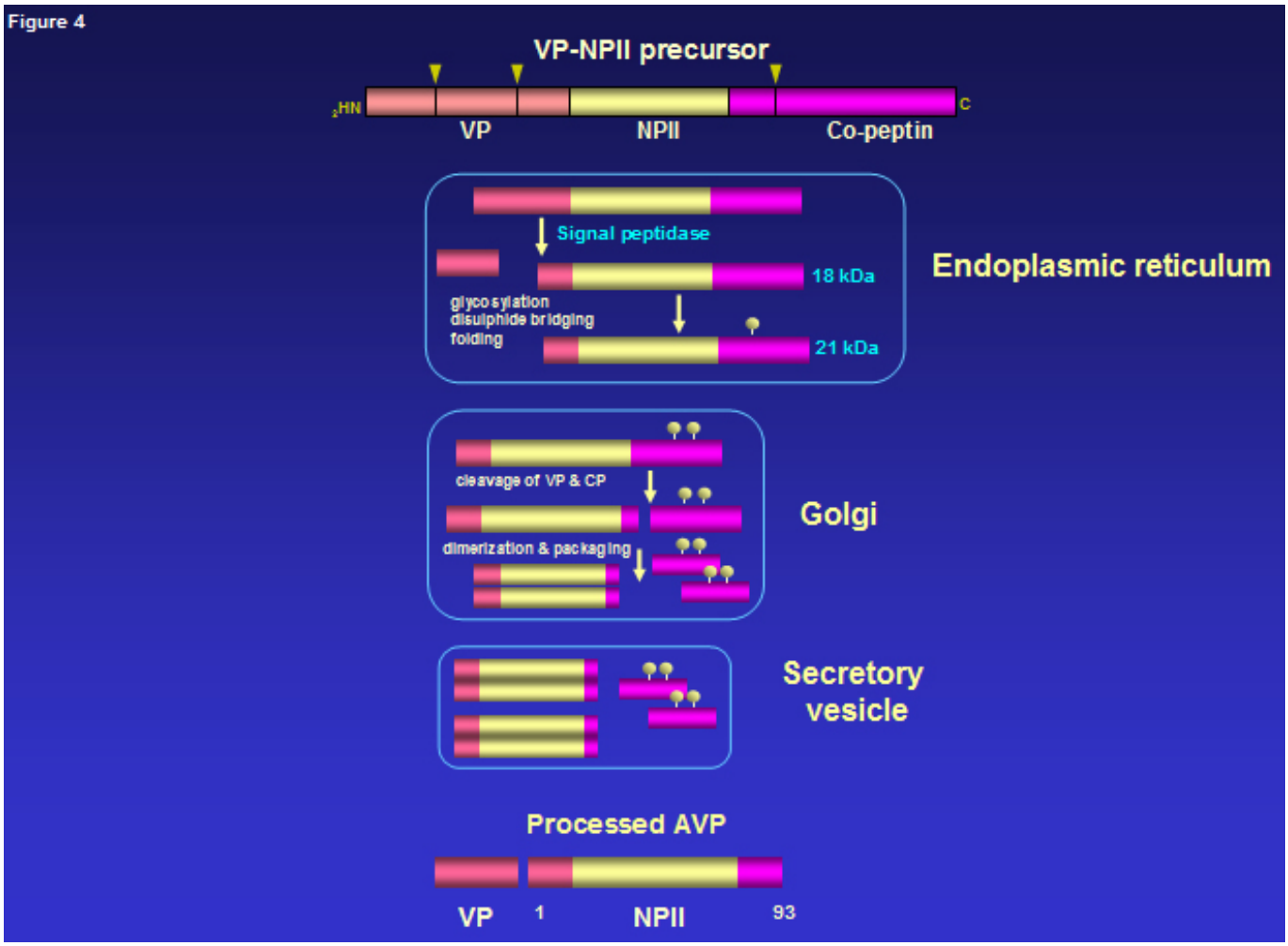

Figure 4.Schematic overview of the post-translational processing of the Vasopressin-neurophysin II gene product. Sequential modification of the VP-NPII preprohormone in endoplasmic reticulum and golgi lead to trafficking through the regulated secretory pathway and ultimately release from neurosecretory vesicles in the posterior pituitary. A small amount of partially processed precursor is released through the constitutive secretory pathway. OT is

processed in a similar manner.

VP and OT circulate unbound to plasma proteins, though VP does bind to specific receptors on platelets. VP concentrations in platelet-rich plasma are 5-fold higher than in platelet-depleted plasma (6). VP and OT have short circulating half-lives of 5-15 minutes. Several endothelial and circulating endo- and amino-peptidases degrade the peptides. A specific placental cysteine amino-peptidase degrades VP and OT rapidly during pregnancy and the peri-partum period.

3. The physiology of Vasopressin

VP is a key component in the regulation of fluid and electrolyte balance, through direct effects on renal water handling. However, the physiology of VP has a wider context, encompassing roles in the integrated response to changes in cardiovascular status.

3.1. Vasopressin receptors

There are three distinct VP receptor (V-R) subtypes (Table 1). All have seven transmembrane spanning domains, and all are G protein coupled. They are encoded by different genes and differ in tissue distribution, down-stream signal transduction and function. The human V2-R gene maps to Xq28. Interestingly, the V2-R is up regulated by its ligand (7).

Table 1. Vasopressin receptor subtypes

	Vasopressin receptor		
	V1a	**V1b**	**V2**
Expression	• Vascular smooth muscle • Liver • Platelets • CNS	Pituitary corticotroph	Basolateral membrane of distal nephron
Amino acid structure	418 amino acids (human)	424 amino acids (human)	370 amino acids (human)
Second messenger system	Gq/11mediated phospholipase C activation: Ca2+, inositol triphosphate & diacyl glycerol mobilization	As V1a	G□□s mediated adenylate cyclase activation: cAMP production & protein kinase A stimulation
Physiological effects	• Smooth muscle	Enhanced ACTH release	Increased production & action of

	contraction • Stimulation of glycogenolysis. • Enhanced platelet adhesion • Neurotransmitter & neuromodulatory function		aquaporin-2

3.2. Vasopressin and renal water handling

Although VP has multiple actions, its principle physiological effect is in the regulation of water resorption in the distal nephron, the structure and transport processes of which allow the kidney to both concentrate and dilute urine in response to the prevailing circulating VP concentration. Active transport of solute out of the thick ascending loop of Henle generates an osmolar gradient in the renal interstitium, which increases from renal cortex to inner medulla, a gradient through which distal parts of the nephron pass en route to the collecting system. VP stimulates the expression of a specific water channel protein (aquaporin) on the luminal surface of the interstitial cells lining the collecting duct. The presence of aquaporin (AQP) in the wall of the distal nephron allows resorption of water from the duct lumen along an osmotic gradient, and excretion of concentrated urine.

To date, 13 different mammalian AQPs have been identified, seven of which (AQP1-4, AQP6-8) are found in the kidney (8). AQPs act as passive pores for small substrates and are divided into 2 families: the water only channels; and the aquaglyceroporins that can conduct other small molecules such as glycerol and urea. Most favor substrates that are neutral. However, this is not always the case. For example, AQP6 is a gated ion channel. AQPs are involved in a variety of cell processes: small molecule permeation; gas conduction and cell-cell interaction. As with other membrane channels, specific structural arrangements within the primary, secondary and tertiary structure convey the three functional characteristics of permeation, selectivity and gating. The structure of AQPs involves 2 tandem repeats, each formed from 3 transmembrane domains, together with 2 highly conserved loops containing the signature motif asparagine-proline-alanine (NPA). All AQPs form homotetramers in the membrane, providing 4 functionally independent pores with an additional central pore formed between the 4 monomers. Water can pass through all the 4 independent channels of water-permeable AQPs. There are data to suggest that the central pore may act as independent channel in some AQPs (9, 10).

AQP1 is constitutively expressed in the apical and basolateral membranes of the proximal tubule and descending loop of Henle, where it facilitates isotonic fluid movement. Loss of function mutations of AQP1 in man lead to defective renal water conservation (11).

AQP2 is expressed on the luminal surface of collecting duct cells and is the water channel responsible for VP-dependant water transport from the lumen of the nephron into the collecting

duct cells. V2-R activation in collecting duct cells increases AQP2 gene expression and accelerates trafficking of presynthesised AQP2 protein to the luminal membrane, where AQP2 monomers are assembled into functional homo-tetrameric water channels.

Maximum diuresis occurs at plasma VP concentrations of 0.5 pmol/L or less. As VP levels rise, there is a sigmoid relationship between plasma VP concentration and urine osmolality, with maximum urine concentration achieved at plasma VP concentrations of 3-4 pmol/L (Figure 5). Following persistent VP secretion, anti-diuresis may diminish. Down-regulation of both V2-R function and AQP2 expression may be responsible for this escape phenomenon (12).

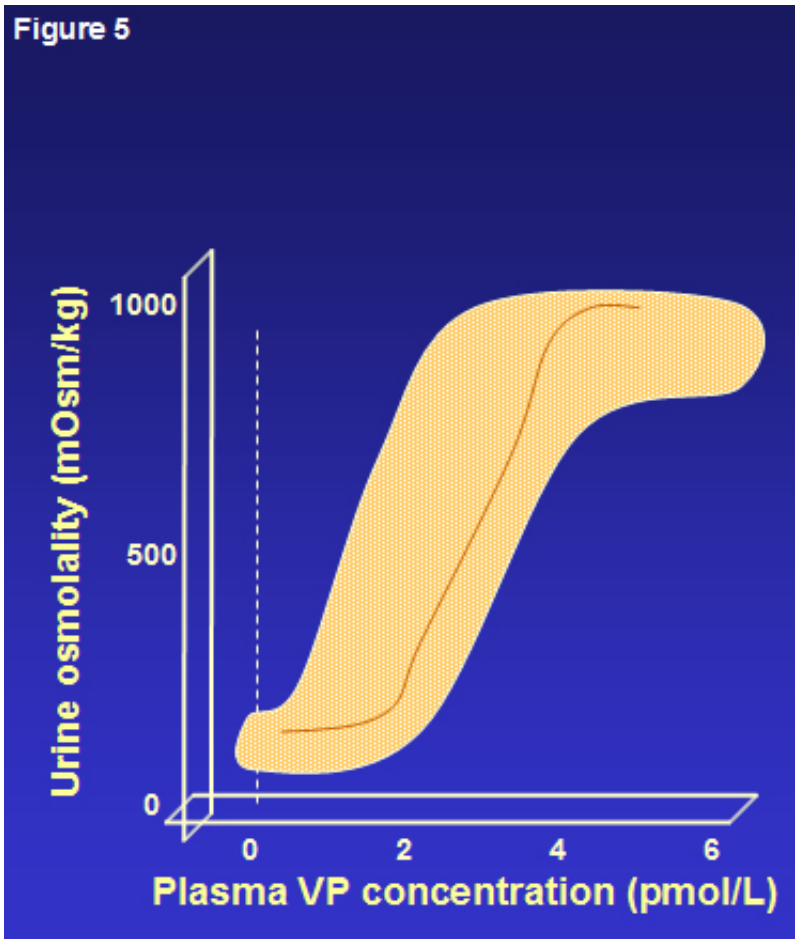

Figure 5.

VP has additional effects at other sites in the nephron: decreasing medullary blood flow; stimulating active urea transport in the distal collecting duct; and stimulating active sodium transport into the renal interstitium. These contribute to the generation and maintenance of a hypertonic medullary interstitium, and augment VP-dependent water resorption.

3.3. Regulation of Vasopressin release

3.3.1. Osmoregulation of Vasopressin

Plasma osmolality is the most important determinant of VP secretion. The osmoregulatory systems for thirst and VP secretion, and in turn the actions of VP on renal water excretion, maintain plasma osmolality within narrow limits: 284 to 295 mOsmol/kg. The relationship between plasma osmolality and plasma VP concentration has 3 characteristics.

- The osmotic threshold or ‘set point’ for VP release.
- The shape of the line describing changes in plasma VP concentration with changing plasma osmolality
- The sensitivity of the osmoregulatory mechanism coupling plasma osmolality and VP release.

Increases in plasma osmolality increase plasma VP concentrations in a linear manner (Figure 6). The abscissal intercept of this line indicates the mean ‘osmotic threshold’ for VP release (284 mOsmol/kg): the mean plasma osmolality above which plasma VP increases in response to increases in plasma osmolality. There is no level of plasma osmolality below which VP release is truly completely suppressed. However, the concept of an osmolar threshold remains a practical tool with which to characterize the physiology of osmoregulation. VP levels increase from a basal rate through activation of stimulatory osmoreceptor afferents, and decrease to minimal values when this drive is removed and synergistic inhibitory afferents are activated. The slope of the line relating plasma osmolality to plasma VP concentration reflects the sensitivity of osmoregulated VP release. There are considerable inter-individual variations in both the threshold and sensitivity of VP release. However, they are remarkably reproducible within an individual over time (13).

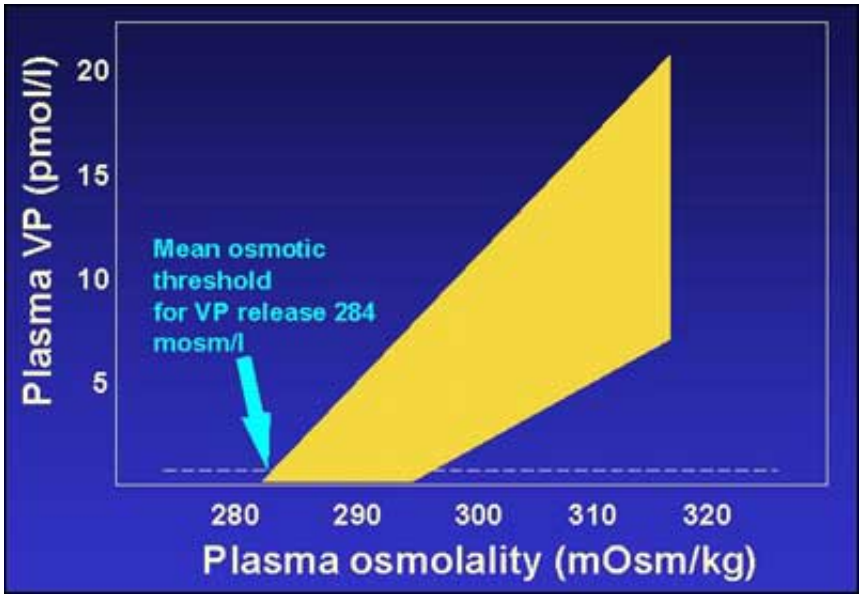

Figure 6.The relationship of plasma VP concentration to changes in plasma osmolality during controlled hypertonic stimulation. VP concentration determined during progressive hypertonicity induced by infusion of 855 mmol/l saline in a group of healthy adults. Increases in plasma osmolality increase plasma VP concentrations in a linear manner, defined by the function,

plasma VP = 0.43 (plasma osmolality – 284), r = +0.96. The abscissal intercept of this regression line indicates the mean ‘osmotic threshold’ for VP release: the mean plasma osmolality above which plasma VP starts to increase. The shaded area represents the range of normal response. LD represents the limit of detection of the assay, 0.3 pmol/l.

There are situations where the normal relationship between plasma osmolality and VP concentration breaks down.

- Rapid changes of plasma osmolality: rapid increases in plasma osmolality result in exaggerated VP release.
- During the act of drinking: drinking rapidly suppresses VP release, through afferent pathways originating in the oropharynx.
- Pregnancy: the osmotic threshold for VP release is lowered in pregnancy.
- Aging: plasma VP concentrations increase with age, together with enhanced VP responses to osmotic stimulation.

Age-related changes in VP production can be accompanied by blunting of thirst appreciation, reduced fluid intake, decreased ability to excrete a free water load, and reduced renal concentrating capacity. These changes predispose the elderly to both hyper- and hyponatraemia.

3.3.2. Baroregulation of Vasopressin

Reductions in circulating volume stimulate VP release through activation of mechanoreceptors in the cardiac atria and central veins. Hypotension stimulates VP release independently through aortic arch and carotid sinus afferents. Falls in arterial blood pressure of 5 to 10 per cent are necessary to increase circulating VP concentrations in man. Progressive reduction in blood pressure produces an exponential increase in plasma VP, in contrast to the linear increases of osmoregulated VP release. Baroregulated VP responses can be modified by other neurohumoral influences triggered as part of the coordinated neurohumoral response to changes in circulating volume and blood pressure. Atrial natriuretic peptide (ANP) inhibits, while norepinephrine augments baroregulated VP release.

3.3.3. Additional mechanisms regulating Vasopressin release

A number of other stimuli influence VP release independent of osmotic and haemodynamic status.

- Nausea and emesis.
- Manipulation of abdominal contents.

Both may contribute to high plasma VP values observed after surgery. VP production is also increased by systemic immune-response mediators and inflammatory triggers, including

histamine and bacterial lipopolysaccharide (14).

3.3.4. Neurophysiology of VP release

As befits its major function and physiological role, VP production by the neurohypophysis is influenced by sensory signals chiefly reflecting osmotic status and blood pressure/circulating volume. The relationships of the SON and PVN with the autonomic afferents and central nervous system nuclei responsible for osmo- and baroregulation are key to the physiological regulation of VP.

Functional osmoreceptors are situated in anterior circumventricular structures: the subfornicular organ (SFO), and the organum vasculosum of the lamina terminalis (OVLT). Local fenestrations in the blood brain barrier at these sites allow neural tissue direct contact with the circulation. Subsequent sensory input to the SON and PVN is via glutaminergic afferents. Artial natriuretic peptide may act to inhibit this pathway (15).

VP neurons themselves may also have independent osmoreceptor properties. V-Rs are present on vasopressinergic neurons of both the PVN and SON, highlighting the potential for autocontrol of VP release through the action of magnocellular neurites (16, 17).

Baroregulatory influences on neurohypophyseal VP release derive from aortic arch, carotid sinus, cardiac atrial, and great vein afferents via cranial nerves IX and X. Ascending pojections are via the nucleus tractus solitarius (NTS) in the brain stem. From the NTS, further afferents project to the SON and PVN, which also receive additional adrenergic afferents from other brain stem nuclei involved in cardiovascular control, such as the locus coeruleus. These nucleiii may therefore act to integrate a number of afferent inputs that reflect volume status. Ascending baroregulatory pathways must affect some

tonic inhibition of VP release, as interruption increases plasma VP levels (18, 19).

4. Additional Effects of Vasopressin

4.1. Cardiovascular Effects

VP is a potent pressor agent; its effects mediated through a specific receptor (V1-R) expressed by vascular smooth muscle cells. Though systemic effects on arterial blood pressure are only apparent at high concentrations, VP is important in maintaining blood pressure in mild volume depletion. The most striking vascular effects of VP are in the regulation of regional blood flow. The sensitivity of vascular smooth muscle to the pressor effects of VP varies according to the vascular bed. Vasoconstriction of splanchnic, hepatic and renal vessels occur at VP concentrations close to the physiological range. Furthermore, there are differential pressor responses within a given vascular bed. Selective effects on intrarenal vessels lead to redistribution of renal blood flow from medulla to cortex. Baroregulated VP release thus constitutes one of the key physiological mediators of an integrated haemodynamic response to volume depletion.

4.2. Effects on the Pituitary

VP is an ACTH secretagogue, acting through pituitary corticotroph-specific V1b-Rs. Though the effect is weak in isolation, VP and CRF act synergistically. VP and CRF co-localize in neurohypophyseal parvicellular neurons projecting to the median eminence and the neurohypophyseal portal blood supply of the anterior pituitary. Levels of both VP and CRF in these neurons are inversely related to glucocorticoid levels, consistent with a role in feedback regulation.

4.3. CNS effects of Vasopressin

Vasopressinergic fibres and V-Rs are present in CNS neural networks anatomically and functionally independent of the neurohypophysis, including the cerebral cortex and limbic system. . The relevance of central vasopressinergic systems to the neurohypophyseal-systemic VP axis is unclear. In rodents, central vasopressinergic systems have key roles in mediating complex social behavior. There are similar emerging data in man, with studies linking *V1a-R* gene sequence variation with autistic spectrum disorder, social phobia and interpersonal behaviour patterns (20, 21, 22).

5. Thirst

Thirst and drinking are key processes in the maintenance of fluid and electrolyte balance. Thirst perception and the regulation of water ingestion involve complex, integrated neural and neurohumoral pathways. The osmoreceptors regulating thirst are situated in the circumventricular AV3V region of the hypothalamus, distinct from those mediating VP release (23). Projections to higher centers remain largely unmapped. There is a linear relationship between thirst and plasma osmolalities in the physiological range (Figure 7). The mean osmotic threshold for thirst perception is 281 mOsm/kg, similar to that for VP release. Thirst occurs when plasma osmolality rises above this threshold. As with osmoregulated VP release, the characteristics of osmoregulated thirst remain consistent within an individual on repeated testing, despite wide inter-individual variation (13).

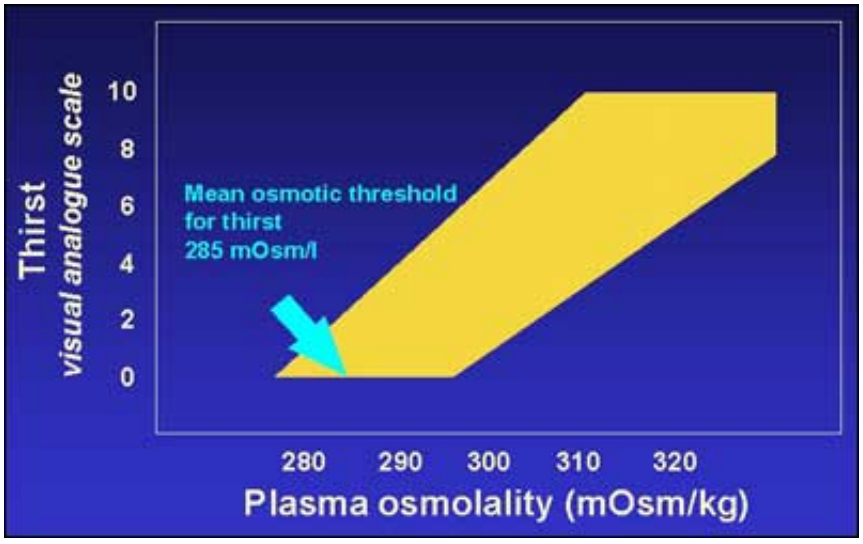

Figure 7.The relationship of thirst to plasma osmolality during controlled hypertonic stimulation. Data obtained from analysis of thirst (by visual analogue scale) during progressive hypertonicity induced by infusion of 855 mmol/l saline in a group of healthy adults. There is a linear relationship between thirst and plasma osmolalities in the physiological range, defined by the function: thirst = 0.39 (plasma osmolality – 285), r = +0.95. The shaded area represents the range of normal response.

As with VP release, there are also specific physiological situations in which the relationship between plasma osmolality and thirst breaks down.

- The act of drinking: reduces osmotically stimulated thirst.
- Extracellular volume depletion: this stimulates thirst through volume-sensitive cardiac afferents and the generation of circulating and intracerebral Angiotensin II, a powerful dipsogen.
- Pregnancy, the luteal phase of the menstrual cycle and super ovulation syndrome: these states reduce the osmolar threshold for thirst.
- Aging: both thirst appreciation and fluid intake can be blunted in the elderly

6. The Integrated Physiology of Vasopressin and Thirst in Water Homeostasis

As the major circulating cation, sodium concentration is rigorously maintained within the range of 135-144 mmols/l. Fluid volumes within the circulating, interstitial and intracellular compartments are also critical physiological parameters. The regulation of fluid and electrolyte balance is intimately linked with that of circulating volume; common systems are involved in both processes. The inter-relationships of sodium and water excretion with circulating volume regulation are key to appreciating the position of VP in the physiology of fluid homeostasis.

At plasma osmolalities of 285-295 mOsm/kg, osmolar balance can be maintained by VP-dependent regulation of renal water loss: a rise in plasma osmolality within this range producing a progressive increase in plasma VP and a resultant antidiuresis. Though further increases in plasma osmolality stimulate further VP release, this does reduce renal water excretion further: correction of plasma osmolality back to the range over which VP can maintain osmolar balance requires thirst-stimulated drinking. As the osmolar threshold for thirst is similar to that for VP release, the maintenance of water balance through a combination of VP release and thirst is a seamless, coordinated process.

If excessive fluid volumes are consumed, greater than those demanded by thirst, plasma VP levels are suppressed to < 0.3 pmol/l, resulting in maximum diuresis. Ingestion of water in excess of this causes a reduction of plasma osmolality into the sub-normal range, and hyponatraemia.

VP release is also regulated by other, non-osmotic stimuli (e.g. baroregulated VP release). This multi-component regulation has a hierarchy. Moderate hypovolaemia shifts the relationship of plasma osmolality and plasma VP concentration to the left; osmoregulation being maintained around a lower osmolar set point. As the degree of hypovolaemia progresses, baroregulated VP release overrides the osmolar set point. Antidiuresis is maintained, despite potential hyponatraemia, as circulating volume and blood pressure are supported through reduced urine losses and direct pressor effects. Coincident activation of the systemic and intra-cerebral Renin-Angiotensin systems stimulates drinking and augments VP release, in addition to producing independent pressor and anti-natriuretic effects. The physiological and pathophysiological responses to hypovolaemia thus involve an integrated neurohumoral cascade, of which VP is a key component.

7. The Physiology of Oxytocin

OT binds to specific G-protein coupled cell surface receptors (OT-Rs) on target cells to mediate a variety of physiological effects, largely concerned with reproductive function. The classical physiological roles of OT are the regulation of lactation, parturition and reproductive behavior. Data from transgenic animals with targeted disruption of the oxytocin gene (and thus lacking OT) have forced a review of this dogma (24).

7.1. Oxytocin and lactation

In the rat, stimulation of vagal sensory afferents in the nipple by the act of suckling triggers reflex synchronized firing of oxytotic magnocellular neurons in the neurohypophysis, and corresponding pulsatile OT release. OT acts on OT-Rs on smooth muscle cells lining the milk ducts of the breast, initiating milk ejection. OT is essential for completion of this milk ejection reflex in rodent. Mice lacking OT fail to transfer milk to their suckling young. This deficit is corrected by injection of OT. In contrast, women lacking posterior pituitary function can breast-feed normally, illustrating that OT is not necessary for lactation in man. Pituitary lactotrophs express OT-R mRNA, and OT released into the hypophyseal portal blood supply from the median eminence can stimulate prolactin release. However, the role of OT in the physiology of prolactin release remains unclear (3).

7.2. Oxytocin and parturition

OT is a uterotonic agent. In many mammals, there is both an increase in OT secretion and an increase in uterine responsiveness to OT during parturition (3). These data suggest a key role for the hormone in the initiation and progression of labour. Falling progesterone concentrations toward the end of pregnancy lead to up-regulation of uterine myometrial OT-Rs, enhanced contractility, and increased sensitivity to circulating OT. Stretching of the ‘birth canal’ during parturition leads to the stimulation of specific autonomic afferents, reflex firing of oxytotic neurons and OT release. A positive feedback loop is formed, OT stimulating uterine contraction further and enhancing the production of additional local uterotonic mediators such as prostaglandins. The difficulties of analyzing pulsatile release, and the short circulating half-life of the hormone (due to placental cysteine aminopeptidase), have made it difficult to demonstrate

increased circulating OT levels in women during labour. Mice lacking OT have normal parturition. Moreover, women with absent posterior pituitary function can have a normal labour. However, the importance of OT in the birth process is highlighted by the effectiveness of OT antagonists in the management of pre-term labour (25).

Recent data have highlighted an additional role of OT in parturition. Maternal OT produces a switch to inhibitory GABAergic signaling in the fetal CNS. This, in turn, increases fetal neuronal resistance to damage that may occur during delivery. OT therefore mediates direct adaptive mother-fetal signaling during parturition (26).

7.3. Oxytocin and behavior

OT-R expression is widespread in the CNS of many species. As with VP, OT has been implicated in the regulation of complex reproductive and social behaviours (27).

There is clear evidence that OT has important influences on reproductive behavior in rat; facilitating both lordosis and the development of maternal behavior patterns (3). However, mice lacking OT exhibit normal sexual and maternal behavior, suggesting behavioral effects may be species-specific. Central oxytotic transmission reduces anxiety behavior and hypothalamo-pituitary-adrenal stress responses in female rats (28). However, there are data indicating that central oxytotic function may be required for normal adrenocorticotropin responses to stress. It may be that OT has a complex role in the stress response, with context-dependent differential effects (29).

OT release from dendrites and nerve terminals of hypothalamic magnocellular neurons can be regulated differentially by other neuropeptides. This highlights both differential function and the potential for magnocellular OT to contribute to central oxytotic neurotransmission (30).

7.4. Integrated physiology of Oxytocin

The human and mouse data highlighting normal reproductive function in the absence of OT question the physiological role of the hormone. However, there are some important qualifications. The mouse gravid uterus does not express OT-Rs, in contrast to human and rat. It is not surprising therefore that parturition is normal in the OT null-mouse. In contrast to rat, maternal behavior evolves gradually in mouse, and is not acquired rapidly in the post-partum period. Mouse may therefore not be a good model for the uterine and behavioral effects of OT. Secondly, there may be variable, species-specific redundancy in some of the physiological pathways in which OT is involved. The modeling of OT’s role in normal (human) physiology using responses found in its absence (in certain rodents) should be made with caution.

PART 2. CLINICAL PROBLEMS SECONDARY TO DEFECTS IN THE HYPOTHALAMO-POSTERIOR PITUITARY AXIS

Defects in the production or action of VP manifest as clinical problems in maintaining plasma

sodium concentration and fluid balance, reflecting the key role of the hormone in these processes.

A further group of related clinical conditions reflect primary defects in thirst. In some cases, the two may coincide, reflecting the close anatomical and functional relationship of both processes.

There are no recognized clinical consequences resulting from defects in OT production or action.

1. Diabetes Insipidus

1.1. Classification

Diabetes insipidus (DI) is characterized by production of dilute urine in excess of 3l/24 hours (>40 ml/kg/24 hours in adults, >100 ml/kg/24 hours in infants). DI arises through one of three mechanisms (Table 2).

- Deficiency of VP: hypothalamic diabetes insipidus (HDI).
- Renal resistance to the antidiuretic action of VP: nephrogenic diabetes insipidus (NDI).
- Inappropriate, excessive water drinking: dipsogenic diabetes insipidus (DDI).

Table 2. Classification of Diabetes Insipidus		
A. Hypothalamic diabetes insipidus		
Primary	Genetic	• DIDMOAD (Wolfram) syndrome • Autosomal dominant • Autosomal recessive
	Developmental syndromes	*Septo-optic dysplasia*
	Idiopathic	
Secondary/acquired	Trauma	• Head injury • Post surgery (transcranial, transphenoidal)
	Tumour	• *Craniopharyngiom* • *Germ cell tumours* • *Metastases* • *Pituitary macroadenoma*
	Inflammatory	• Granulonulomas • Sarcoidosis, • Histiocytosis • Infection • Infundibulo-neurohypophysitis • Guillaine-Barre

		Syndrome • Autoimmune (anti-VP neuron antibodies)
	Vascular	• Aneurysm • Infarction • Sheehan's syndrome • Sickle cell disease
	Pregnancy (associated with vasopressinase)	
B. Nephrogenic diabetes insipidus		
Primary Secondary	Genetic	• *X-linked recessive (V2-R defect)* • *Autosomal recessive (AQP2 defect)* • *Autosomal dominant (AQP2 defect)*
	Idiopathic	
	Chronic renal disease	• Polycystic kidneys • Obstructive uropathy
	Metabolic disease	• Hypercalcaemia • Hypokalaemia
	Drug induced	• Lithium • Demeclocycline
	Osmotic diuretics	• Glucose • Mannitol
	Systemic disorders	• Amyloidosis • Myelomatosis
	Pregnancy	
C. Dipsogenic diabetes insipidus		
	Compulsive water drinking	
	Associated with affective disorders	
	Drug induced?	
	Structural/organic hypothalamic disease	• Sarcoid • Tumours involving hypothalamus • Head injury • Tuberculous meningitis

1.2. Hypothalamic Diabetes Insipidus (HDI)

HDI (also known as neurogenic, central, or cranial DI) is the result of partial or complete lack of osmoregulated VP secretion. Plasma VP concentrations are inappropriately low with respect to prevailing plasma osmolalities. Presentation with HDI implies destruction or loss of function of more than 80% of vasopressinergic magnocellular neurons. It is rare (estimated prevalence of 1: 25000), with an equal gender distribution. Though persistent polyuria can lead to dehydration,

most patients can maintain water balance through appropriate polydipsia if given free access to water.

1.2.1. Aetiology

Most cases of HDI are acquired. Trauma (head injury or surgery) can produce HDI through damage to the hypothalamus, pituitary stalk, or posterior pituitary. Pituitary stalk trauma may lead to a triphasic disturbance in water balance, an immediate polyuric phase followed within days by a more prolonged period (up to several weeks) of antidiuresis suggestive of VP excess. This second phase can be followed by reversion to HDI, or recovery. This characteristic 'triple response' reflects initial axonal damage; the subsequent unregulated release of large amounts of pre-synthesized VP; and either recovery or development of permanent HDI (as determined by the magnitude of initial damage to vasopressinergic neurons). The initial polyuric phase is associated with the presence of circulating inhibitors of VP action, which may be partly processed VP precursors (31). All phases of the response are not apparent in all cases.

Acute HDI has been noted to occur in some 22% of non-selected patients presenting with traumatic brain injury (TBI). The condition persisted in approximately 7% of the total TBI cohort on long term follow up (32).

Hypothalamic tumours or pituitary metastases (e.g. breast or bronchus) can present with HDI. However, primary pituitary tumours rarely cause HDI. In childhood, craniopharyngioma and germinoma/teratoma are a relatively common cause (33) (Figure 8). HDI can present in pregnancy: placental vasopressinase activity decompensating previously antidiuretic capacity through increased VP degradation. Polyuria and polydipsia often revert to normal after delivery. Permanent HDI may develop if the natural history of the defect is progressive.

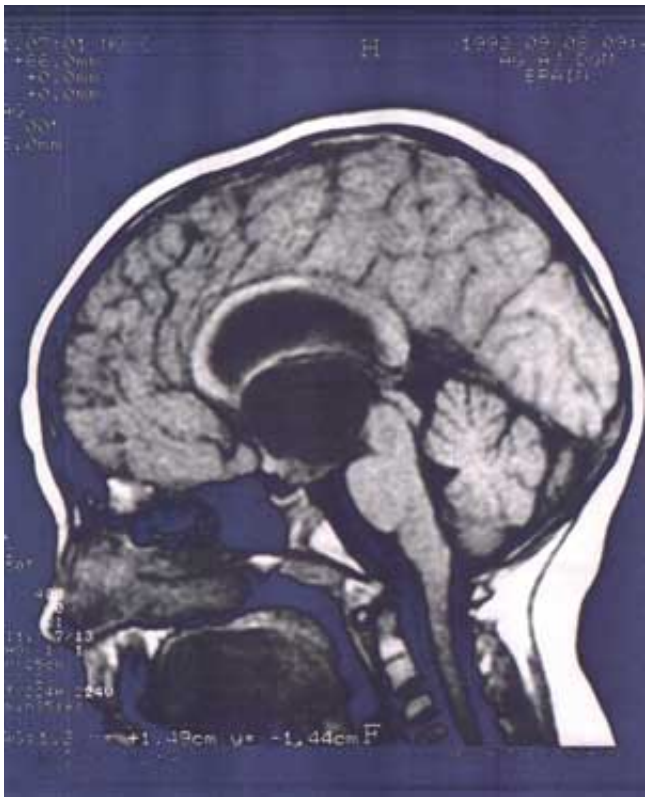

Figure 8.Sagital MRI of suprasellar cystic craniopharyngioma in a child presenting with hypothalamic diabetes insipidus. The child presented with a 2-month history of polyuria and polydipsia. Treatment was with cyst decompression and sub-total surgical excision.

Familial forms account for 5% of HDI. The Wolfram (WS) or DIDMOAD syndrome is a rare autosomal recessive, progressive neuro-degenerative disorder characterized by the association of HDI with *d* iabetes *m* ellitus, *o* ptic *a* trophy and bilateral sensorineural *d* eafness. The natural history is one of sequential development of the features, but this can be distorted by factors influencing presentation. Diabetes mellitus and optic atrophy are often the first manifestation, generally presenting the first or second decade. HDI and deafness follow in the second or third decade. Additional features may then follow: renal outflow tract dilatation is common. Gonadal atrophy and progressive ataxia with brain stem dysfunction can occur. WS is caused by loss of function mutations in the *WFSI* gene. Found on Ch.4p16, this gene encodes an 890 amino-acid glycoprotein (Wolframin). At the cellular level, wolframin is expression restricted to the endoplasmic reticulum. Interestingly, non-inactivating mutations in the same gene are associated with non-syndromic autosomal dominant sensorineural hearing loss, suggesting the possibility of a spectrum disorder. An additional locus for WS has been identified at Ch.4q22-24, indicating the syndrome may be genetically heterogeneous (34, 35, 36).

Autosomal dominant familial HDI is caused by loss of function mutations in exons 1 and 2 of the VP gene (Figure 9). It typically presents in childhood, though the age of presentation varies considerably, reflecting variation in the progressive loss of VP secretion. Growth retardation

may be an early sign (37). Mutant VP precursors accumulate in the endoplasmic reticulum of vasopressinergic neurons, to which they are neurotoxic; the basis of both the progressive loss of VP release, and the dominant inheritance (38, 39). Spontaneous remission of symptoms has been reported in middle age. The mechanism of this phenomenon is unclear. As VP secretion does not recover, both increased renal sensitivity to residual VP secretion and VP-independent AQP2 expression have been proposed.

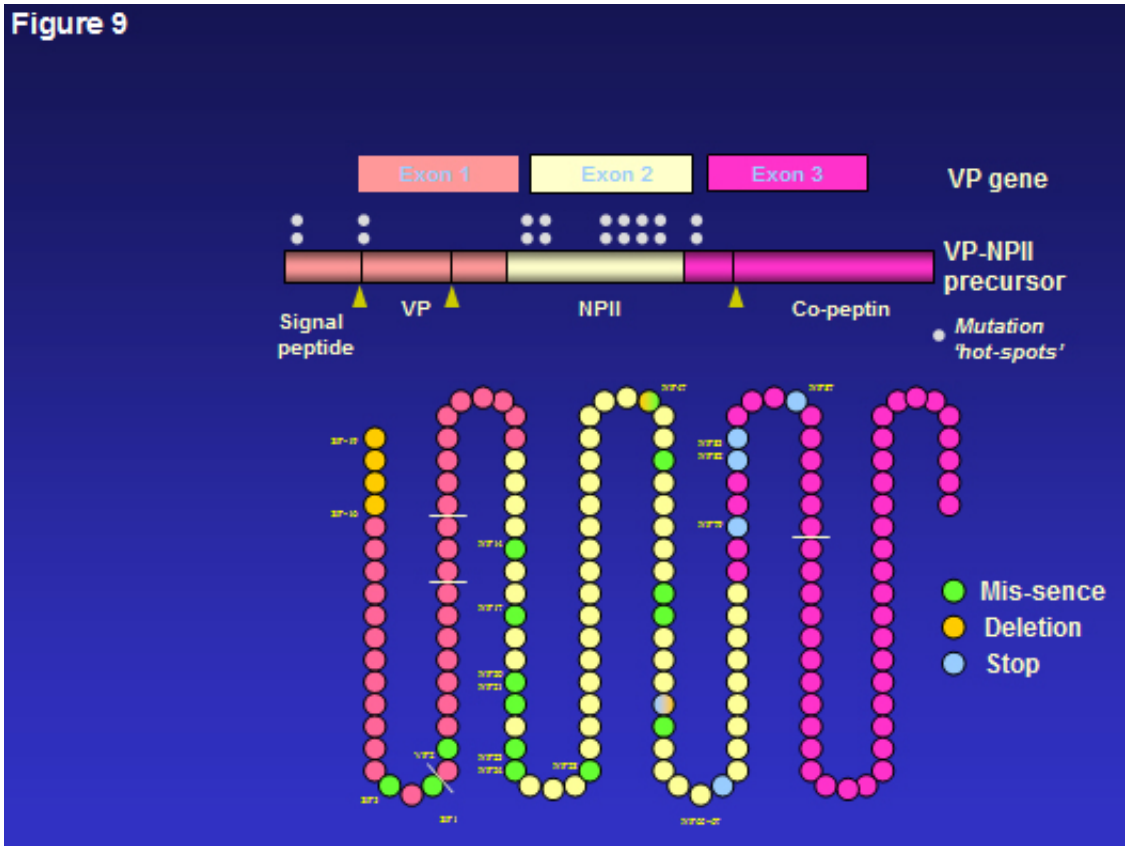

Figure 9.Schematic diagram of the Vasopressin-neurophysin II gene and its product, showing the location and type of mutations identified in autosomal dominant familial hypothalamic diabetes insipidus. Though mutations have been described in all three exons, and involve all parts of the VP-NPII precursor except the co-peptin moiety, the majority occur in exons 1or 2.

1.2.2. *Investigation*

Investigation has the following aims.

- To confirm DI
- To classify the DI: HDI, NDI or DDI
- To establish the aetiology of the specific form of DI

After establishing polyuria (and thus DI), and excluding hyperglycaemia, hypokalaemia,

hypercalcaemia and significant renal insufficiency, attention should be focused on the VP axis.

Direct measurement of plasma VP in response to osmotic stimulation differentiates HDI from other causes of polyuria. However, access to reliable VP assays has been limited. An indirect test using a surrogate endpoint of VP release has thus been developed, assessing the capacity to concentrate urine during the osmotic stress of controlled water deprivation (the water deprivation test). Renal sensitivity to exogenous VP can be determined as part of the test (Table 3). Diagnostic interpretation is as follows.

- HDI: urine osmolality less than 300mOsm/kg accompanied by plasma osmolality greater than 290 mOsm/kg after dehydration; urine osmolality should rise above 750 mOsm/kg after desmopressin (DDAVP).
- NDI: failure to increase urine osmolality above 300 mOsm/kg after dehydration, with no response to DDAVP.
- DDI: appropriate urine concentration during dehydration, without significant rise in plasma osmolality.

Table 3. Protocol for water deprivation/desmopressin test

Preparation	• Free access to fluid overnight prior to test • Avoid caffeine and smoking 0750h weigh patient
Dehydration phase	• 0800 plasma and urine osmolality, and urine volume • Restrict fluids for 8hrs • Weigh patient at 2 hourly intervals • Plasma and urine osmolality, and urine volume measurements 2 hourly • Stop test if weight loss exceeds 5% of starting weight, or thirst is intolerable • Supervise patient closely to avoid non-disclosed drinking
DDAVP phase	• Inject intramuscularly 1mcg desmopressin • Allow patient to eat and drink up to 1.5-2.0 times the volume of urine passed during dehydration phase • Plasma and urine osmolality, and urine volume measurements hourly to 2000hrs • Plasma sodium and osmolality 0900h next day

In practice, the test often gives indeterminate results. This is for a number of reasons.

- Incomplete defects or mild forms of DI: many presentations are incomplete or mild.

Water deprivation testing in such cases can give results that appear normal.

- Secondary partial NDI: dissipation of the intra-renal medullary concentration gradient due to prolonged polyuria (independent of aetiology) can produce partial NDI. This can make interpretation of the water deprivation test difficult.

Differentiation of HDI from other forms of DI can be made by direct measurement of plasma VP during the controlled osmotic stress of a hypertonic 5% – sodium chloride infusion (40). Patients with HDI have undetectable VP levels during the progressive hyperosmolar stress, or values falling to the right of the normogram relating plasma VP to plasma osmolality (Figure 10). In NDI, plasma VP is inappropriately high for the prevailing osmolality, consistent with VP resistance. In DDI, the relationship of plasma VP to plasma osmolality is normal. Parallel assessment of the thirst response to hyperosmolar stress may show inappropriate thirst perception in this situation. Hypertonic stress testing is not interpretable if it produces significant nausea, as this acts as a powerful non-osmotic stimulus of VP release.

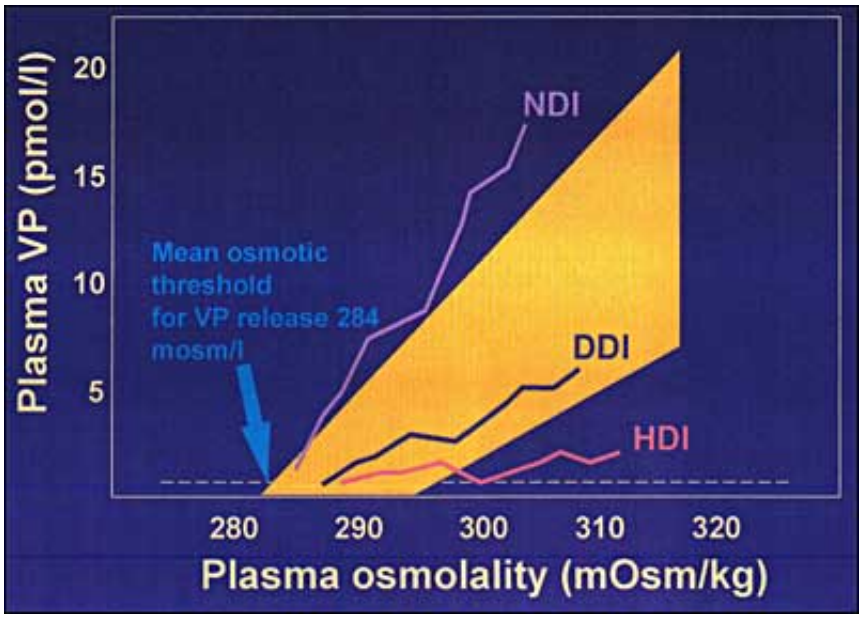

Figure 10.The relationship of plasma VP concentration to changes in plasma osmolality during controlled hypertonic stimulation in diabetes insipidus. Measurement of plasma VP during controlled hypertonic stress testing can effectively differentiate between HDI, NDI and DDI.

The concentration of VP in urine is higher than in plasma and consequently VP is detectable by a wider range of available assays. Measurement of urinary VP concentrations during osmotic stress has been proposed as an alternative diagnostic test for of HDI. The relative utility of this approach over hypertonic stress testing with measurement of plasma VP remains to be defined (41).

In situations where a water deprivation test has proved non-diagnostic, a controlled therapeutic

trial of DDAVP is a pragmatic alternative to VP measurements during hypertonic stress: 10-20mcg of intra-nasal DDAVP per day for 2-4 weeks, with monitoring of plasma sodium every 2-3 days. Patients with DDI exhibit progressive dilutional hyponatraemia, whereas those with NDI remain unaffected. Patients with HDI experience improvement in polyuria and polydipsia, but remain normonatraemic. In kindreds with familial autosomal dominant HDI, sequencing of the *VP* gene can help to establish the diagnosis in at-risk individuals where the water deprivation test is equivocal (42).

In HDI, imaging of the hypothalamus, pituitary and surrounding structures with MRI is essential to exclude mass lesions. If no mass lesion is identified, imaging should be repeated after 12-24 months so that slow growing germ cell tumours are not missed. Idiopathic and familial HDI are associated with loss of the normal hyperintense signal of the posterior pituitary on T1-weighted images (Figure 11). Signal intensity is correlated strongly with VP content of the gland (43). In the absence of appropriate history and diagnostic testing, the loss of a posterior pituitary bright spot does not make the diagnosis of HDI. Conversely, presence of an appropriate bright spot does not preclude the diagnosis of HDI.

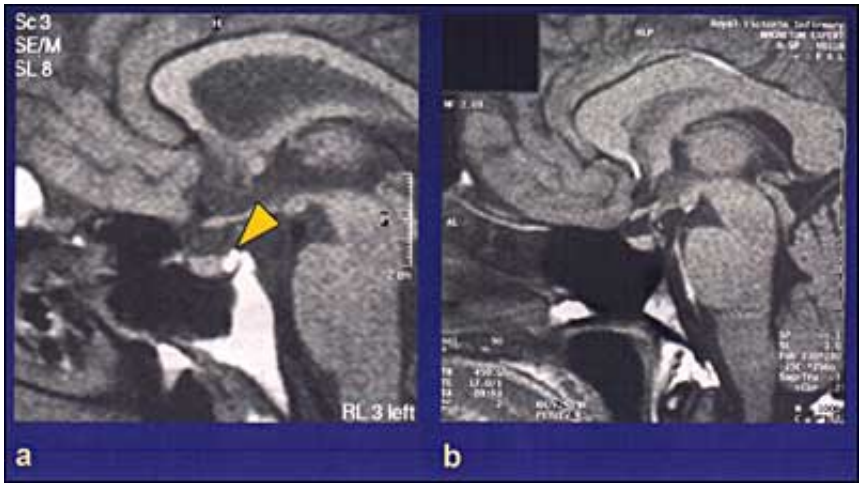

Figure 11.Loss of the posterior pituitary ‘bright spot’ on T1 weighted MRI in hypothalamic diabetes insipidus. The normal posterior pituitary can be demonstrated as a ‘bright spot’ within the sella turcica on T1-weighted MRI (a). This increased signal intensity can be lost in HDI (b). An ectopic posterior pituitary ‘bright-spot’ can be seen some cases of childhood onset hypopituitarism, implying failure to complete normal developmental migration. Function can be normal despite the aberrant position

Evidence of organ-specific autoimmune disease is common in patients with isolated HDI. Circulating antibodies to VP secreting neurons can be found in 30% of patients classified previously as having idiopathic HDI. Presence is particularly associated with pituitary stalk thickening on MRI. However, specificity of the test is low. Anti-VP neurone antibodies can be found at low prevalence in patients with HDI secondary to Histiocytosis X and following pituitary surgery. Nevertheless, they may help in establishing a diagnosis of autoimmune HDI in some

patients (44).

1.2.3. Treatment

The treatment of choice for those with significant symptoms is the synthetic, long-acting VP analogue DDAVP: intranasal spray (5-100 mcg daily); parenteral injection (0.1-2.0 mcg daily); or oral (100-1000 mcg daily), in divided doses. There is wide individual variation in the dose required to control symptoms. Dilutional hyponatraemia is the most serious potential adverse effect. This can be avoided by omitting treatment on a regular basis (perhaps weekly), to allow a short period of breakthrough polyuria and thirst. It is common for patients using oral DDAVP to experience intermittent breakthrough symptoms.

2. Nephrogenic Diabetes Insipidus (NDI)

NDI is due to renal resistance to the antidiuretic effects of VP. Primary familial forms are rare. X-linked recessive familial NDI is caused by inherited loss of function mutations of the V2-R. Over seventy different mutations have been described, affecting all aspects of receptor function: expression; ligand binding; and G-protein coupling. Most lead to complete loss of function, though a few are associated with a mild phenotype (45).

10% of kindreds with familial NDI have an autosomal recessive form, with normal V2-R function. Affected individuals harbour loss of function mutations of the AQP2 gene. Most mutations occur in the region coding for the transmembrane domain of the protein. Additional rare kindreds have been described harbouring a mutation in the portion of the gene encoding the carboxyl-terminal intracellular tail of AQP2. The NDI of these kindreds is inherited as an autosomal dominant trait, mutant protein sequestering the product of the wild type AQP2 allele within mixed tetramers in a dominant-negative manner (46).

More commonly, NDI is due to a variety of acquired metabolic or drug effects (Table 2). The final common pathway producing NDI in many of these cases is down-regulation of AQP2 expression. NDI secondary to lithium toxicity can persist after drug withdrawal, and can be irreversible.

Secondary/acquired cases of NDI are managed by removing the underlying cause, and ensuring adequate hydration. Additional measures can be used for persistent, severe symptoms. These rarely reduce urine volumes by more than 50%. High dose DDAVP (4 mcg im. bd) can produce a response in partial NDI, especially if the lesion is acquired. Additional treatment options, which can be used alone or in combination, include the following.

- Thiazide diuretics: hydrochlorothiazide 25 mg/24 hours.
- Non-steroidal anti-inflammatory drugs: ibuprofen 200 mg/24 hours.
- Low salt diets.

All probably work through reducing glomerular filtration rate, and reducing diluting capacity of the distal nephron.

3. Dipsogenic Diabetes Insipidus (DDI)

DDI is a polyuric syndrome secondary to excess fluid intake. Though structural abnormalities may be the cause, it is generally a manifestation of primary hyperdipsia, psychiatric disease, or secondary to drug effects. It can be associated with several abnormalities of thirst perception.

- A low osmotic threshold for thirst.
- An exaggerated thirst response to osmotic challenge
- An inability to suppress thirst at low osmolalities

The structural and/or functional bases for these abnormalities have not been identified. The association of DDI with affective disorders is well recognized. Up to 20% of patients with chronic schizophrenia have polydipsia. Although this may reflect the primary thought disorder, abnormalities in osmoregulated VP release and thirst have been described (13). Whether these reflect long term effects of drug therapy, or primary defects in central processing, are unclear.

Though difficult, the treatment of DDI should address the underlying disorder. Switching to Clozapine may reduce polydipsia in those patients with refractory schizophrenia and a history of hyponatraemia on other dopamine antagonists. Individuals with persistent DDI are at risk of hyponatraemia if treated with DDAVP. Reduced fluid intake is the only rational treatment.

4. Syndrome of inappropriate antidiuresis

4.1. Hyponatraemia

Hyponatraemia (a plasma sodium concentration less than 130 mmols/l) is a common source of morbidity and increased mortality in clinical practice, occurring in 15% of hospitalized patients (47, 48). Hyponatraemia is not invariably associated with a low serum osmolality; high concentrations of other circulating osmolytes (e.g. glucose) can lead to fall in plasma sodium that is appropriate to maintain normal osmolar status. A reduced plasma aqueous phase secondary to dyslipidaemia can result in hyponatraemia but normal plasma osmolality, but this problem is seen rarely with modern biochemical analysers (Table 4). In many clinical situations, hyponatraemia is multifactorial.

Table 4. Causes of hyponatraemia

Pseudohyponatraemia	**Reduced renal free water clearance**	
Hyperglycemia Hyperlipidaemia Non-physiological osmolyte	Hypovolaemia Cardiac failure Nephrotic syndrome Hypothyroidism Hypoadrenalism SIAD	• Drugs • Renal failure • Portal hypertension & ascites • Hypoalbuminaemia • Sepsis & vascular leak

Sodium depletion		Nephrogenic syndrome of antidiuresis	syndromes • Fluid sequestration
Renal loss	• Diuretics • Salt wasting nephropathy • Hypoadrenalism • Central salt wasting		
Extra-renal loss	• Gut loss		
Excess water intake			
Dipsogenic DI Sodium-free, hyposomolar irrigant solutions Dilute infant feeding formula Exercise-associated hyponatraemia			

Given the physiological effects of VP on reducing renal water excretion, it is a clear and favoured candidate as a mediator in any pathophysiological situation of which hyponatraemia is a feature. Importantly however, even when VP plays a role in the development of hyponatraemia, VP production may not be inappropriate. Hyponatraemia may reflect an appropriate physiological response to volume depletion. To maintain circulating volume in hypovolaemia, baroregulated VP release may proceed despite plasma osmolalities below the osmotic threshold for VP release. This can result in hyponatraemia, which can become chronic. Though clinical assessment can identify the extracellular volume status of some patients, problems can arise in recognizing mild forms of hypovolaemia. This is important for planning intervention. Hyponatraemia due to the central salt wasting is important to differentiate from that of VP excess. They can both occur following brain injury (trauma or neurosurgery). However, central salt wasting is a hypovolaemic condition, requiring fluid resuscitation rather than restriction. Careful clinical assessment, calculation of urine sodium excretion, and adjunctive invasive monitoring may be required to differentiate the conditions.

4.2. Pathophysiology of SIAD

An individual with hypoosmolar plasma, a normal circulating volume, and a plasma VP concentration high for the prevailing osmolality, has a syndrome of inappropriate antidiuresis (SIAD. Four patterns of abnormal VP secretion have been identified (49). Absolute plasma VP concentrations may not be strikingly high and in fact VP measurement is not helpful in establishing the diagnosis. The key finding is that that they are inappropriate for the prevailing plasma osmolality (Table 5).

Table 5. Classification of SIAD		
	Characteristics	Prevalence
SIAD Type A	• Wide fluctuations in plasma VP concentration independent of plasma osmolality	35%

SIAD Type B	• Osmotic threshold for VP release subnormal • Osmoregulation around subnormal osmolar set point	30%
SIAD Type C	• Failure to suppress VP release at low plasma osmolality • Normal response to osmotic stimulation	
SIAD Type D	• Normal osmoregulated VP release • Unable to excrete water load.	<10%

4.3. Aetiology of SIAD

Many conditions have been reported to cause SIAD, though the mechanism(s) of inappropriate VP release are not clear in many cases (Table 6). SIAD is a non-metastatic manifestation of small cell lung cancer and other malignancies. Some tumours express VP ectopically. However, excessive posterior pituitary VP secretion also occurs in association with malignancy. The normal osmoregulated VP release found in the Type D syndrome suggests an increase in renal sensitivity to VP, or the action of an additional antidiuretic factor.

Table 6. Causes of SIAD	
Neoplastic disease	**Chest disorders**
Carcinoma (bronchus, duodenum, pancreas, bladder, ureter, prostate) Thymoma Mesothelioma Lymphoma, leukemia Ewing's sarcoma Carcinoid Bronchial adenoma	Pneumonia Tuberculosis Empyema Cystic fibrosis Pneumothorax Aspergillosis
Neurological disorders	**Drugs**
Head injury, neurosurgery Brain abscess or tumour Meningitis, encephalitis Guillain-Barré syndrome Cerebral hemorrhage Cavernous sinus thrombosis Hydrocephalus Cerebellar and cerebral atrophy Shy-Drager syndrome Peripheral neuropathy Seizures Sub-dural hematoma Alcohol withdrawal	Sulphonylureas Opiates Alkylating agents & Vinca alkaloids Thiazides & Loop diuretics Dopamine antagonists Tricyclic antidepressants MAOIs SSRIs 3,4-MDMA ("Ecstasy") Anti-convulsants
Miscellaneous	
Idiopathic Psychosis Porphyria Abdominal surgery	

SIAD is a common mechanism of drug-induced hyponatraemia, and can reflect direct stimulation of VP release from the hypothalamus; indirect action on the hypothalamus; or aberrant resetting of the hypothalamic osmostat (50). The prevalence of hyponatraemia in patients taking high dose dopamine antagonists is greater than 25%, and is not restricted to one class of these drugs. Hyponatraemia secondary to antidepressants is well recognized, occurring

with most SSRIs, and the related drug Venlafaxine. It can arise in the first few weeks of treatment. Those patients on concurrent diuretic therapy are particularly at risk; indicating hypovolaemia contributes to the hyponatraemia in many cases. Anticonvulsants are another common cause of SIAD and hyponatraemia. The frequency in patients treated with carbamazepine (CBZ) ranges from 4.8 to 40%. Increased sensitivity of central osmoreceptors and increased renal responses to VP have both been described with CBZ.

Table 7. Mechanisms of drug induced hyponatraemia			
Reduction in free water clearance		**Sodium depletion**	
SIAD	Dopamine antagonists Tricyclic antidepressants MAOIs SSRIs Venlafaxine Opiates Carbamazepine Oxcarbazipine Sodium valproate 3,4-MDMA ('ecstasy') Clofibrate Cyclophosphamide Sulphonylureas	Diuretics	Spironolactone Thiazides Loop diuretics
VP-like activity	DDAVP Oxytocin	ACE inhibitors Angiotensin II receptor antagonists	
Potentiation of VP action	NSAIDS Carbamazepine Sulphonylureas Cyclophosphamide	Direct renal toxicity	Cyclophosphamide Ifosfamide Cisplatin Carboplatin Vincristine Vinblastine

4.4. Clinical features and diagnosis of SIAD

The major features in the diagnosis of SIAD are given in (Table 8). The most frequent difficulty in clinical practice is in distinguishing SIAD from chronic, mild hypovolaemia. Urine osmolality tends to be higher than plasma osmolality in both groups. Similarly, plasma VP concentrations will be detectable or elevated in both. Neither is therefore diagnostic of SIAD. Though emphasis is often placed on precise cut-off figures for urine *vs* . plasma osmolality, in essence the diagnosis hinges on the excretion of urine that is simply not maximally dilute in the context of a dilute plasma (ie. urine concentration greater than 100mOsm/Kg). Measurement of urinary sodium concentration is important. Renal sodium excretion should be above 20mol/L to make a diagnosis of SIAD. Below this value, volume depletion needs to be considered more likely. SIAD is often associated with urine sodium concentrations of 60 mmol/L or more. In fact, the hyponatraemia of chronic SIAD is not simply the result haemodilution through reduced water excretion. Rather, as SIAD is a volume expanded state, there is evidence of mild sodium loss as other homeostatic regulators of volume homeostasis attempt to minimize volume expansion (51).

Table 8. Diagnostic criteria for SIAD

Hyponatraemia with appropriately low plasma osmolality Urine osmolality > 100mOsm/Kg Renal sodium excretion >20 mmol/L Absence of hypotension, hypovolaemia and oedema-forming states Normal renal and adrenal function

Measurement of urinary AQP2 excretion may be useful in the differentiation of SIAD from other causes of hyponatraemia (52). However, while there is a positive correlation between plasma VP concentration and urinary excretion of AQP2, urinary AQP2 cannot differentiate clearly between hyponatraemic states associated with significant VP production. SIAD and chronic hypovolaemia may generate similar plasma VP concentrations and similar urine AQP2 levels. These two conditions are the most common differential diagnoses which we have difficulty in resolving. In addition, there may be situations in which VP levels, urinary AQP2 excretion and renal concentrating ability are dissociated (e.g. following glucocorticoid replacement in hypopituitarism, central volume expansion, the newborn, the elderly). The clinical utility of the test may therefore be limited and it's precise role remains to be clarified (53, 54).

Inappropriate VP production leading to hyponatraemia can be confirmed indirectly by assessing excretion of a standard water load over a fixed time: the water load test (Table 9). Concurrent plasma VP measurement may add value, but is not required for interpretation. Normal subjects excrete 78-82% of the ingested water load in the 4h observation period. This may be reduced to 30-40% of the ingested load in the presence of constitutive VP production. The test is not often required to establish a diagnosis but it can be useful in the management of chronic or recurrent hyponatraemia (55, 56). .

Table 9. Protocol for water load test	
Preparation	• Free access to fluid overnight prior to test • Avoid caffeine and smoking • 0730h weigh patient • Cannulate patient • Rest patient 30 minutes
Water load phase	• 0800 plasma and urine osmolality, plasma VP • Patient to drink 20mL/kg water over 15 minutes • Measure hourly urine output for 4 hours • Measure urine osmolality, plasma osmolality and plasma VP hourly

	for 4 hours

Recovery phase	• Plasma sodium 2 hours after test completed • Plasma sodium and osmolality 0900h next day

4.5 Exercise associated hyponatraemia

Extreme endurance exercise is a profound physiological stressor. While the magnitude of the physiological stress is likely to reflect a number of factors, duration of the event and the effort of entailed are likely to be major contributors. Non-osmoregulated VP release is a feature of extreme endurance exercise: a reflection of the stressed state. When combined with reduced renal blood flow, another feature of extreme endurance exercise, this can lead to a marked antidiuretic state. If endurance athletes maintain a fluid intake in excess of water loss, hyponatraemia will ensue. This can be further complicated if there is aggressive fluid resuscitation in the event of collapse. There is a positive correlation between the odds ratio for developing hyponatraemia during extreme endurance exercise and the length of time taken to complete the event. Athletes developing hyponatraemia also demonstrate weight gain over the course of the event, clearly implicating water intake in excess of water loss. Athletes should be advised to follow their thirst as they run and to avoid simply taking on fluid. Health professionals attending endurance events need to be aware of the problem of exercise associated hyponatraemia. In addition, they should avoid attempting resuscitation with large volumes of hypotonic fluid in the absence of appropriate indications and without biochemical monitoring (57, 58).

4.6 Nephrogenic syndrome of Inappropriate antidiuresis

The action of VP on renal water excretion is mediated by the G-protein-coupled V2-R and loss of function mutations of the V2-R are the cause of X-linked nephrogenic diabetes insipidus. Recent studies have identified rare individuals with the reciprocal problem (Figure 12). They harbour constitutively activating mutations in the V2-R that lead to VP-independent, but V2-R mediated, antidiuresis associated with persistent hyponatraemia. This nephrogenic syndome of inappropriate antidiuresis (NSIAD) can have a variable phenotype. NSIAD was initially described in male infants with persistent hyponatraemia (59). However, subsequent studies have found the condition is not limited to males and may manifest in adulthood (60). Given the V2-R is carried on the X-chromosome, this would be in keeping with the condition being X-linked but, as the underlying mutation is activating, expression is possible in heterozygous females. The true prevalence of NSIAD is not known. However, as some 10% of patients with SIAD have undetectable VP, it seems likely that at least some of these cases may be due to activating mutations of the V2-R.

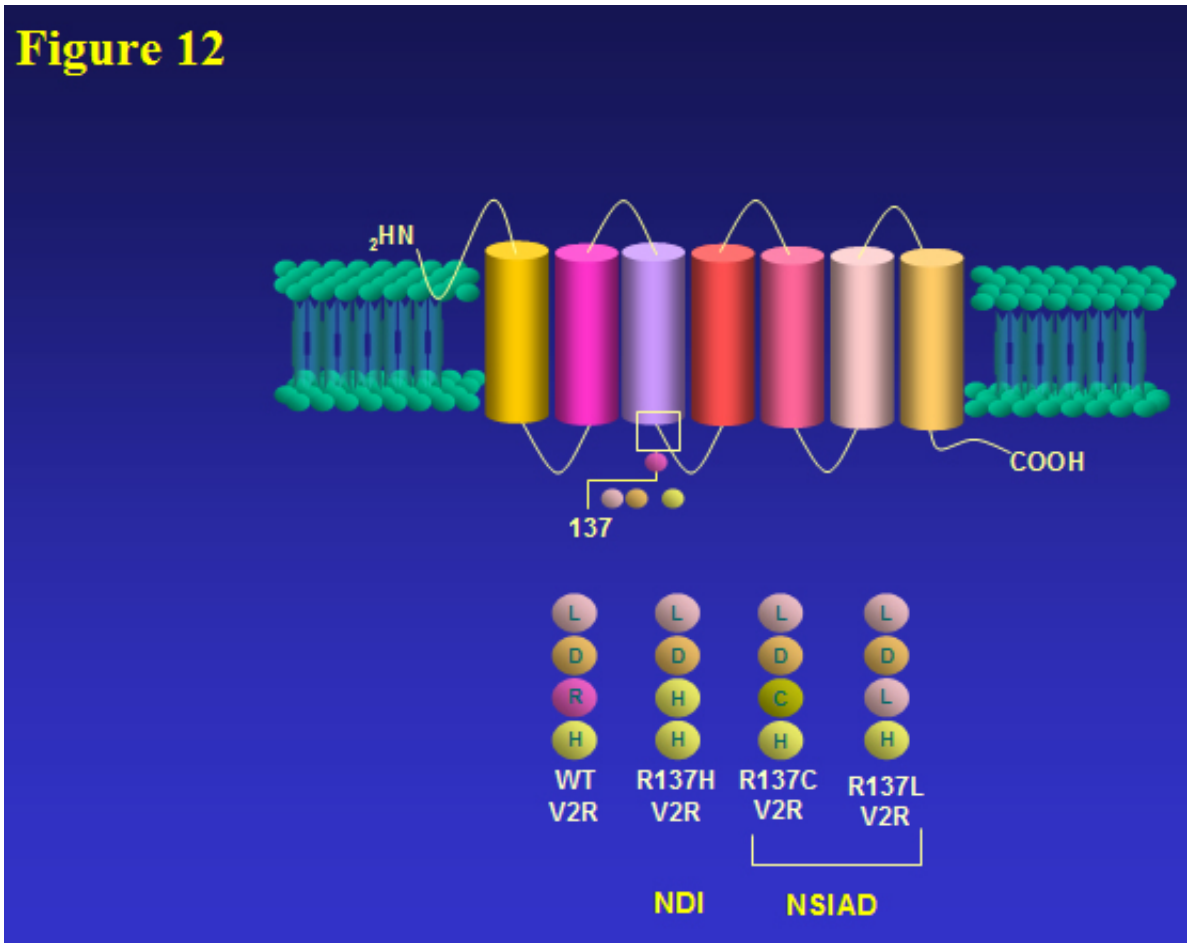

Figure 12.The V2-R is a 7 transmembrane spanning domain G-protein coupled receptor. Codon 137 of theV2-Rgene encodes an amino acid located at the cytoplasmic boundary of the third transmembrane spanning domain. Mutations of theV2-Rgene affecting codon 137 cause both NDI and NSIAD. Codon 137 of the wild type V2-R encodes the amino acid Arginine (R). In X-linked NDI, the V2-R gene is mutated such that codon 137 encodes the amino acid Histidine (H). This renders the receptor inactive and unable to couple ligand binding with G-protein activation. Mutations in theV2-Rgene found in NSIAD also affect codon 137; changing the amino acid of the receptor to either Cysteine (C) or Leucine (L).

4.7 Central salt wasting

This acquired primary natriuresis is a rare cause of hyponatraemia with hypovolaemia. The underlying mechanism(s) remain unclear, but may involve increased release of natriuretic peptides and/or reduced sympathetic drive. CSW is seen in a variety of neurosurgical situations. Diagnosis hinges on the natural history of the process: the development of hyponatraemia being preceded by natriuresis and diuresis with ensuing clinical and biochemical features of hypovolaemia. In contrast to SIAD therefore, urea and creatinine are elevated and there may be postural hypotension. The simple observation of weight loss over the period in question can be

helpful. CSW is a particular concern for the neurosurgical patient in whom autoregulation of cerebral blood flow is disturbed and in whom small reductions in circulating volume can reduce cerebral perfusion. Syndrome of inappropriate antidiuresis (SIAD) can occur in the same group of patients. Both conditions are associated with urine sodium concentrations greater than 40mmols/L. However, the natriuresis of CSW is much more profound than that of SIAD. Importantly, it precedes the development of hyponatraemia. The management of CSW is volume replacement with 0.9% saline. The rate of replacement needs to reflect preceding and on-going sodium loss together with the requirement for circulating volume support (61).

4.8. Management of hyponatraemia secondary to SIAD

The morbidity and mortality of hyponatraemia secondary to SIAD are the result of disturbance in central nervous system (CNS) function: the combined impact of cerebral oedema and direct neuronal dysfunction (Table 9). Values of serum sodium around 100 mmol/L are life threatening. However, patients commonly have mild symptoms or are asymptomatic, especially if hyponatraemia is less severe and develops slowly. This reflects CNS adaptation: brain oedema being limited by efflux of organic solutes. However, this adaptation can complicate the management of hyponatraemia. Rapid correction plasma sodium following the gradual development of hyponatraemia (which has resulted in a degree of CNS adaptation) can lead to significant changes in brain volume as the osmolar gradient across the blood-brain barrier alters. This can trigger CNS demyelination. This is a rare but serious complication of hyponatraemia and its treatment. It can develop within 1-4 days of rapid (>12 mmols per 24 hours) correction of plasma sodium, irrespective of the method employed to achieve it. It can even occur when sodium levels are corrected slowly. Other factors (hepatic failure, potassium depletion, malnutrition) may play a role in susceptibility. Neurological manifestations include quadriplegia, opthalmoplegia, pseudo-bulbar palsy and coma.

Table 9. Clinical features of hyponatraemia secondary to SIAD

- Headache
- Nausea
- Vomiting
- Muscle cramps
- Lethargy
- Disorientation
- Seizure
- Coma
- Brain-stem herniation
- Death

Chronic asymptomatic hyponatraemia, with plasma sodium concentrations greater than 125 mmol/L may not require specific treatment. More severe degrees of hyponatraemia, particularly if symptomatic, require some form of intervention. While previously there has been little consensus on optimal treatment (47), this may now be changing. Where identifiable, correction of the underlying cause(s) is appropriate. This begins with identifying SIAD correctly as the cause of hyponatraemia: most commonly, this involves excluding mild or moderate hypovolaemia Withdrawal of drugs contributing to SIAD is important where possible. Such

approaches may prevent worsening hyponatraemia and allow the bodies own physiology to address the deficit in plasma sodium. Any additional intervention, if required, should adhere to two key principles.

- Correction should not risk morbidity and mortality (such as that from osmotic demyelination) in excess of that associated with the initial degree of hyponatraemia.
- Correction should be at sufficient pace to reverse life-threatening features of hyponatraemia as quickly as is feasible and safe.

It is thus key to identify the degree of symptoms attributable to hyponatraemia; consider the time over which hyponatraemia has developed; focus on the clinical endpoint of intervention; and identify the target plasma sodium to be achieved.

4.8.1. Initial intervention in hyponatraemia associated with SIAD

Fluid restriction of 0.5–1L/day is a reasonable initial intervention when the clinical condition is not critical. The aim should be to have plasma sodium increase at a rate not exceeding 8-10 mmols/L per 24 hours. Plasma sodium therefore needs to be measured regularly. All fluids need to be included in the restriction. As SIAD is associated with a degree of natriuresis, sodium intake should be maintained. Fluid restriction may need to be maintained for several days before sodium levels rise and it is important that a negative fluid balance is confirmed during this period. Prolonged fluid restriction can be distressing. The higher the baseline urine osmolality, the less likely fluid restriction is to be effective.

Hyponatraemia due to SIAD can sometimes be associated with symptoms that are life threatening. This may reflect the degree of hyponatraemia; a rapid fall in plasma sodium; or a combination of both. In this situation, a more aggressive intervention may be required with hypertonic 3% sodium chloride. However, it is key that the aim of such an approach is clear.

- Reversal of life-threatening manifestations of hyponatraemia.

- Moderation of other non-life threatening manifestations of hyponatraemia.

Critically, important clinical end-points may be achieved through only a relatively small rise in sodium of 2-4 mmols/L over 2-4 hours. Normalisation of plasma sodium is not the therapeutic target. Plasma sodium concentration should rise no more than 1-2 mmol/L per hour, with a total increment of no more than 8-10 mmol/L per 24 hours. One method of calculating the volume of administered fluid required over a given period is as follows (47).

- Volume required = (Change in plasma [Na+] required over target period) / (Change in plasma [Na+] produced by 1l of replacement fluid) The change in plasma sodium concentration brought about by 1l of fluid replacement is calculated according to the following equation.
- Change in serum [Na+] = ([Na+] concn. of replacement fluid – plasma [Na+]) / (Estimated total body water (in litres) + 1)
- Total body water is calculated as a fraction of total body weight (Table 10).

Table 10. Total body water (in litres) as a fraction of body weight (kg)	
Children Non-elderly men Non-elderly women Elderly men Elderly women	0.6 0.6 0.5 0.5 0.45

If such an approach is used, it is imperative that the fluid regimen is reassessed at regular intervals, guided by careful clinical assessment and laboratory monitoring.

The utility of fixed replacement models in day to day practice can be limited. There are inherent inaccuracies in many models of used to calculate electrolyte deficits. Importantly though, the basis of this approach is limited if partial correction to clinical end-points is accepted and asymmetric increases in plasma sodium in the first 1–4 hours of intervention are employed. An alternative approach, through the careful monitoring of the impact on clinical and biochemical endpoints of 100 ml boluses of 3% sodium chloride, can be used. Hypertonic fluid should be stopped when the defined clinical target or a sodium concentration of 125 mmol/L is reached, whichever is first. These parameters serve to reduce the neurological morbidity of hyponatraemia while minimising the risk of precipitating osmotic demyelination (62).

4.8.2. Approaches to recurrent or persisting hyponatraemia associated with SIAD

Hyponatraemia may persist or recur after initial intervention. In such circumstances it is important that the underlying diagnosis is reviewed and the basis for intervention reconsidered. Drug withdrawal may not be possible or only partly successful in correcting plasma sodium. Fluid restriction may be only partly effective or may prove non-sustainable. Clinicians may thus have to balance the merits of incremental intervention with those of tolerating mild, persisting hyponatraemia.

Demeclocycline is effective in management of hyponatraemia of SIAD. It produces a form of NDI and so increases renal water loss even in the presence of VP. Treatment is 600–1200 mg/day in divided doses. There is a lag time of some 3–4 days in onset of action. Treatment should be stopped if significant renal impairment develops. Lithium has similar effects to demeclocycline, though the effects are less consistent and are associated with more adverse effects.

Urea at doses of 30 g/day by mouth can be used to treat persisting hyponatraemia of SIAD. Urea improves increases renal free water excretion and decreases urinary sodium excretion. Even if only partially effective, it may allow reduction in water restriction and improve quality of life.

The non-peptide V2-R antagonists (Vaptans) are a rational approach to the management of hyponatraemia mediated through the action of VP. They increase renal water excretion without a significant impact on renal electrolyte loss. This property of aquaresis is key to their potential role in this area. V2-R antagonists are classified as either selective (V2-R specific) or non-selective (V2- and V1a antagonism). Both are effective in the treatment of hyponatraemia associated with normal or increased plasma volume. They can impact on plasma sodium within 4-6 hours and appear to be well tolerated (63). The place of V-R antagonists in the management of hyponatraemia due to SIAD is currently under development and needs to

balance time course of action; short and long term tolerance; and long term efficacy in specific clinical contexts (64).

5. Adipsic and hypodipsic syndromes

Adipsic and hypodipsic disorders are characterized by inadequate spontaneous fluid intake due to defects in osmoregulated thirst. Patients deny thirst and not drink, despite dehydration and hypovolaemia. If the defect is mild, the resultant hypernatraemia is often well tolerated. Severe disorders can lead to somnolence, seizures and coma. Because of the close anatomical relationship of the osmoregulatory centers for thirst and VP release, adipsic syndromes are often associated with defects in osmoregulated VP release and HDI.

5.1. Classification and etiology

Four patterns of adipsic/hypodipsic syndrome are recognized (Table 11, Figure 13). Causes are outlined in Table 12. Patients with the Type A syndrome osmoregulate around a supra-normal osmolar set point and are protected from extreme hypernatraemia, as are those with the Type B syndrome. In Type C adipsia, osmoregulated thirst and VP release are absent. Patients present with adipsic HDI. Precipitants include rupture and repair of anterior communicating artery (ACA) aneurysm, as the osmoreceptors mediating both thirst and VP release receive a blood supply from perforating branches of the anterior cerebral artery and ACA. Some patients with the Type C syndrome have constitutive low level VP release, and are at risk of dilutional hyponatraemia (13).

Table 11. Classification of adipsic and hypodipsic syndromes

Adipsia/hypodisia Syndrome	**Osmoregulated Thirst**	**Osmoregulated VP release**
Type A (essential hypernatraemia)	*Osmotic threshold increased Normal sensitivity*	*Osmotic threshold increased Normal sensitivity Normal non-osmotic stimulation*
Type B	*Normal osmotic threshold Reduced sensitivity*	*Normal osmotic threshold Reduced sensitivity Normal non-osmotic stimulation*
Type C	*No response to osmotic stimulation*	*Persistent low level VP release No response to osmotic stimulation Normal non-osmotic stimulation*
Type D	*No response to osmotic stimulation*	*Normal*

Table 12. Causes of adipsic and hypodipsic syndromes

Neoplastic (50%)	
Primary	*Craniopharyngioma Pinealoma Meningioma*
Secondary	*Pituitary tumour Bronchial carcinoma Breast carcinoma*
Granulomatous (20%) *Histiocytosis Sarcoidosis*	

Miscellaneous (15%) *Hydrocephalus Ventricular cyst Trauma Toluene poisoning*
Vascular (15%) *Internal carotid artery ligation Anterior communicating artery aneurysm Intrahypothalamic haemorrhage*

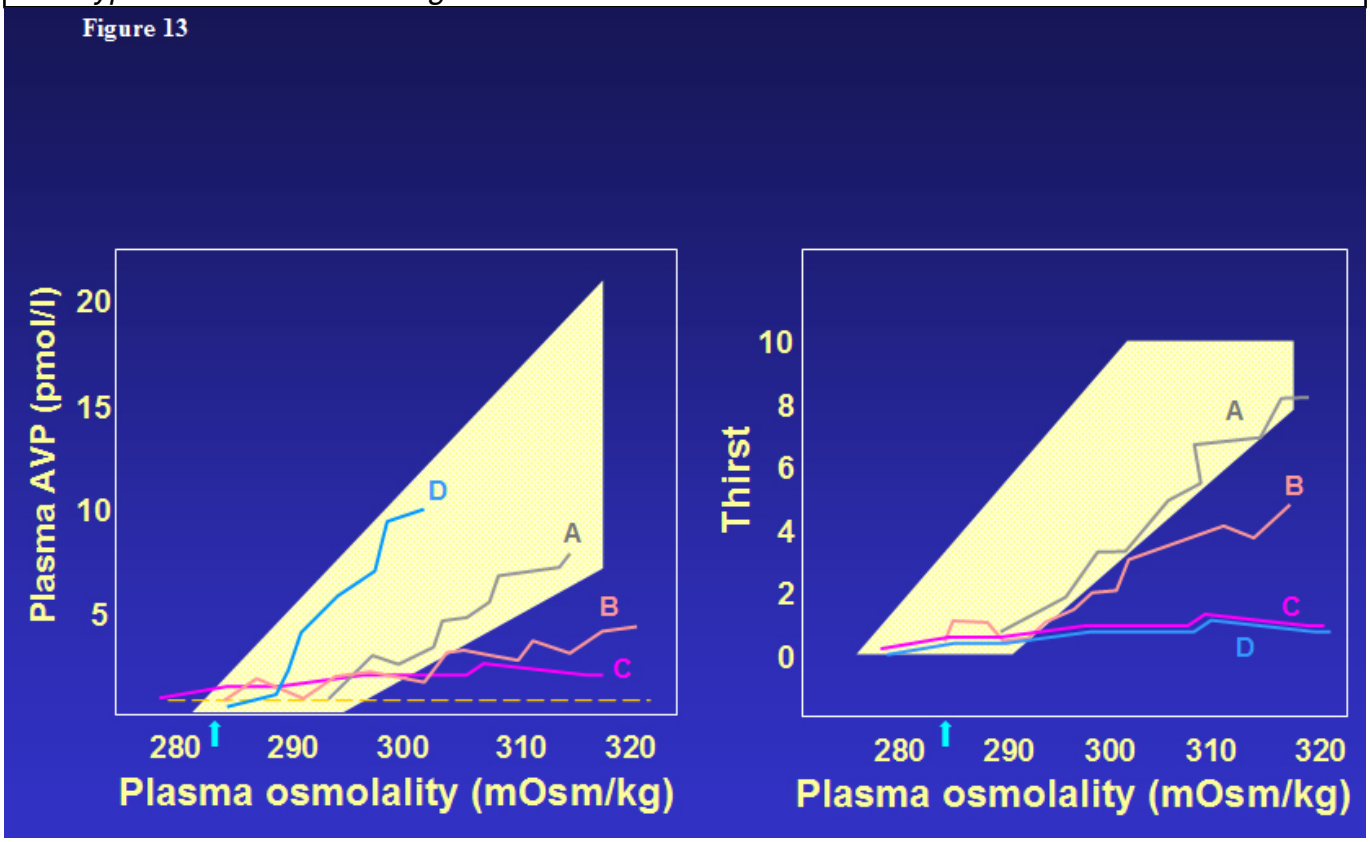

Figure 13.Patterns of plasma VP and thirst responses to hypertonic stress in patients with Adipsic syndromes. Normal range responses to osmolar stimulation are shown by the shaded areas. The 4 types of adipsic syndrome are demonstrated. Patients with the Type A syndrome osmoregulate around a higher osmolar set point, while those with the Type B syndrome mount VP and thirst responses but with reduced sensitivity. Patients with the Type C syndrome have much reduced or absent VP and thirst responses to osmolar stimulation. Those with the Type D syndrome demonstrate normal VP responses to osmolar stimulation but much reduced thirst responses.

5.2. Management

As those with Type A and Type B adipsia are protected from extreme hypernatraemia, treatment is to recommend an obligate fluid intake of about 2L/24 hours with appropriate adjustment for climate and season. If fluid balance cannot be maintained during intercurrent illness, hospital in-patient management may be required. The adipsic HDI of the Type C syndrome can be difficult to manage. The structural and vascular problems producing the syndrome often lead to associated defects in short term memory and task organization, complicating long-term management. A pragmatic approach is to effectively dictate an

acceptable urine output (1-2L/24 hours) with regular DDAVP (producing a fixed obligate antidiuresis). Together with an estimation of standard insensible fluid loss (approximately 0.4L), this can be set to create a fixed net fluid loss of some 2Ls. In turn, this can be balanced by a daily fluid intake that varies in response to depending on day to day fluctuations from a target weight at which the patient is euvolaemic and normonatraemic.

- Daily fluid intake = 2L + (daily weight in Kg- target weight in Kg).

Plasma sodium should be checked weekly, to avoid the creeping development of hyper- and hyponatraemia as dry weight changes. This approach can result in stable fluid balance and successful independent living (65).

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