

CHAPTER 2 THE NEUROHYPOPHYSIS: ENDOCRINOLOGY OF VASOPRESSIN AND OXYTOCIN

Professor SG Ball PhD, FRCP

Honorary Professor of Medicine and Endocrinology, Central Manchester University Hospitals Foundation Trust and Manchester Academic Health Science Centre, Manchester, UK.

Revised 22 April 2017

ABSTRACT

The neurohypophysis is the structural foundation of a neuro-humoral system coordinating fluid balance and reproductive function through the action of two peptide hormones: vasopressin and oxytocin. Vasopressin is the principle endocrine regulator of renal water excretion, facilitating adaptive physiological responses to maintain plasma volume and plasma osmolality. Oxytocin is important in parturition and lactation. Data support a wider role for both peptides in the neuro-regulation of complex behaviour. Clinically, deficits in the production or action of vasopressin manifest as diabetes insipidus. An understanding of the physiology and pathophysiology of vasopressin is also critical in approaching the diagnosis and management of hyponatraemia, the most common electrolyte disturbance in clinical practice. The chapter explores the anatomy, physiology and pathophysiology of the neurohypophysis, vasopressin and oxytocin: highlighting developments in the neural basis of osmo-sensing; the mechanism of action of vasopressin and oxytocin; together with a description of the cell and molecular biology underpinning some of the disease processes in which both the structure and functions of the two hormones are involved. For complete coverage of this and related areas of endocrinology, please visit www.endotext.org.

The neurohypophysis consists of three parts: the supraoptic and paraventricular nuclei of the hypothalamus; the supraoptico-hypophyseal tract; and the posterior pituitary. The neurohypophysis is one component of a complex neurohumoral system coordinating physiological responses to changes in both the internal and external environment. This chapter will concentrate on the physiology and pathophysiology of two hormones made by the hypothalamus and posterior pituitary, vasopressin (VP) and oxytocin (OT). These hormones have key roles in water balance and reproductive function.

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

1. THE ANATOMY OF THE NEUROHYPOPHYSIS

The posterior pituitary is derived from the forebrain during development and is composed predominantly of neural tissue. It lies below the hypothalamus, with which it forms a structural and functional unit: the neurohypophysis.

The supraoptic nucleus (SON) is situated along the proximal part of the optic tract. It consists of the cell bodies of discrete vasopressinergic and oxytocic magnocellular neurons projecting to the posterior pituitary along the supraoptico-hypophyseal tract. The paraventricular nucleus (PVN) also contains

discrete vasopressinergic and oxytocic magnocellular neurons, also projecting to the posterior pituitary along the supraoptico-hypophyseal tract. The PVN contains additional, smaller parvocellular neurons that project to the median eminence and additional extra-hypothalamic areas including forebrain, brain stem, and spinal cord. Some of these parvocellular 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 and other vasopressinergic parvocellular neurons terminating in the hypophyseal-portal bed have a role in the regulation of adrenocorticotrophin (ACTH) release from the anterior pituitary gland, acting synergistically with CRH produced by other hypothalamic neurons.

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

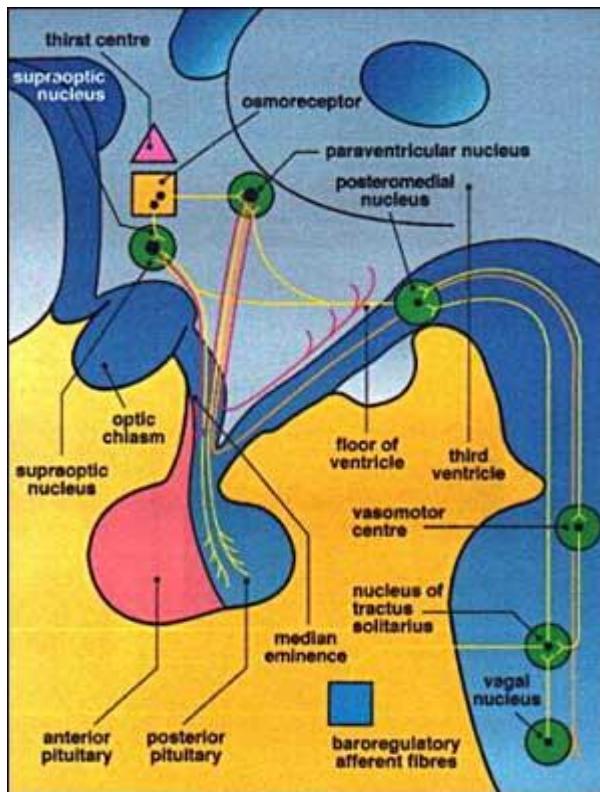


Figure 1. Schematic representation of the anatomy of the neurohypophysis, and its major afferent and efferent connections.

The posterior pituitary receives an arterial blood supply from the inferior hypophyseal artery and the artery of the trabecula (a branch of the superior hypophyseal artery), derivatives of the internal carotid artery and its branches. The SON and PVN receive an arterial supply from the supra-hypophyseal, anterior communicating, anterior cerebral, posterior communicating and posterior cerebral arteries, all derived from the circle of Willis. Venous drainage of the neurohypophysis 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.

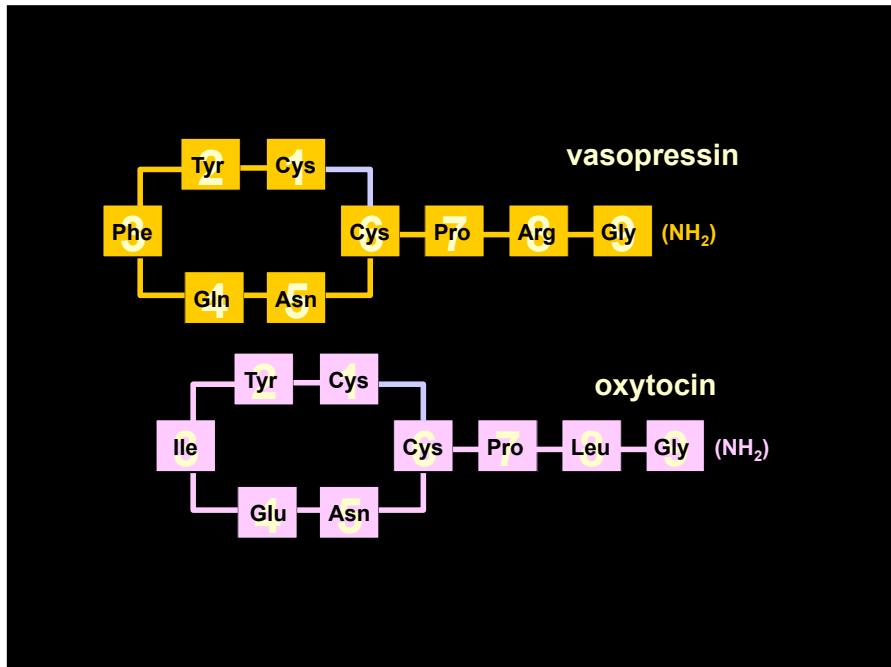


Figure 2. The structural and chemical characteristics of Vasopressin and Oxytocin. The cyclical peptides differ in only 2 amino acid positions. Both contain disulphide bridges between Cysteine residues at positions 1 and 6

2.1. The Vasopressin-Neurophysin and Oxytocin-Neurophysin genes

The genes encoding VP and OT are in a head to head tandem array on chromosome 20p13 in Man, separated by 12 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.

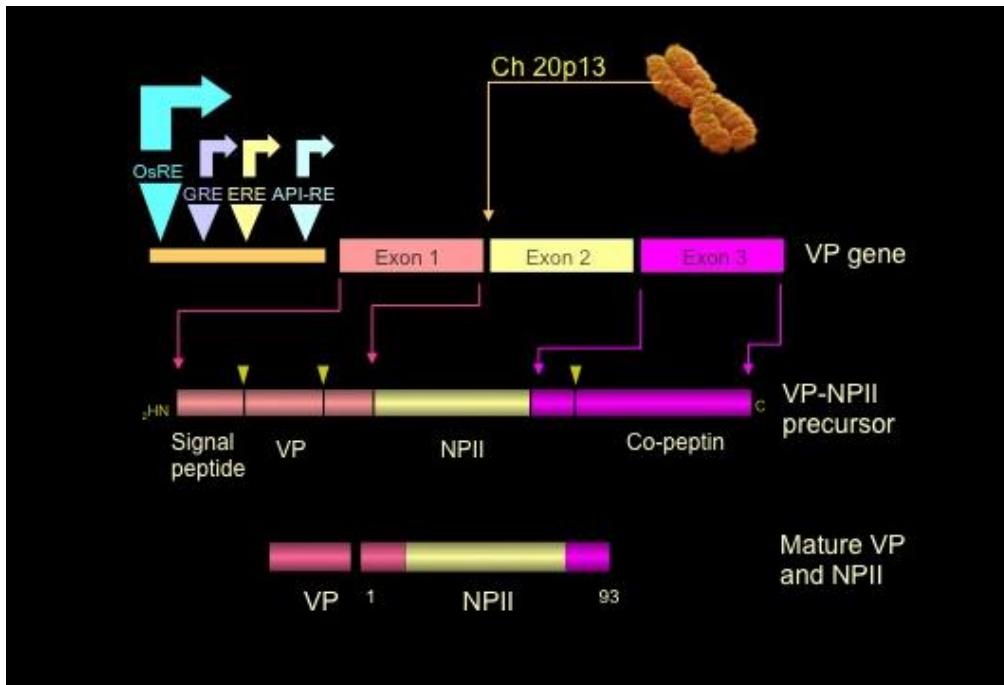


Figure 3. Structural organization of the Vasopressin-neurophysin II gene, and processing of its product. The VP-NPII gene has 3 exons. Translation of the mRNA yields a larger preprohormone precursor, subsequently modified through substantial post-translational modification. The OT gene has a similar structure, and its product undergoes similar processing and post-translational modification. VP: Vasopressin. NPII: Neurophysin II. OsRE: osmo-sensitive response element. GRE: glucocorticoid response element. ERE: oestrogen response element. AP1-RE: AP1 response element.

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 (3). The inter-genic region between the *VP* and *OT* genes contains regulatory elements responsible for selective expression. The region -288 to -116 5' upstream of the *VP* gene promoter confers cell-type (magnocellular neuron) specific expression of the *VP* gene (4).

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 oxytocic 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 oxytocic neurons opens voltage-gated Ca^{2+} channels in these nerve terminals. This, in turn, leads to transient Ca^{2+} 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.

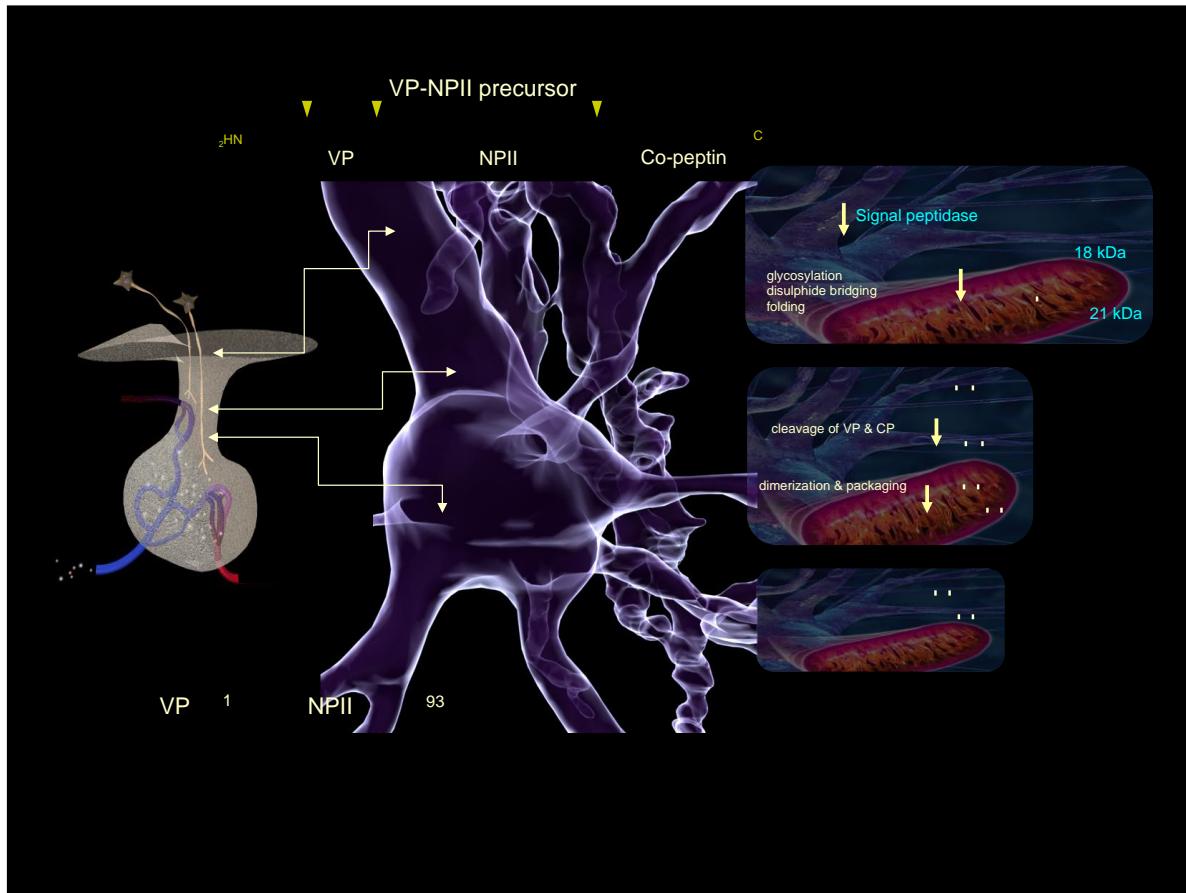


Figure 4. Schematic overview of the post-translational processing of the VP-NP II gene product. Sequential modification of 164 amino-acid VP-NPII preprohormone in endoplasmic reticulum and golgi lead to trafficking through the regulated secretory pathway and ultimately release from neurosecretory vesicles in the posterior pituitary. VP-NPII precursor is complexed as tetramers or high oligomers during processing. 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	<ul style="list-style-type: none"> •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: Ca^{2+} , inositol triphosphate & diacyl glycerol mobilization	As V1a	G α s mediated adenylate cyclase activation: cAMP production & protein kinase A stimulation
Physiological effects	<ul style="list-style-type: none"> •Smooth muscle contraction •Stimulation of glycogenolysis. •Enhanced platelet adhesion •Neurotransmitter & neuromodulatory function 	Enhanced ACTH release	Increased synthesis & assembly of 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 AQPs have been identified in Man, seven of which (AQP1-4, AQP6-8) are found in the kidney. 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 are substrates 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 AQP_s 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 AQP_s 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 AQP_s. There are data to suggest that the central pore may act as independent channel in some AQP_s (8, 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 produces a biphasic increase in expression of AQP2. Ligand-receptor binding triggers an intracellular phosphorylation cascade ultimately resulting in phosphorylation of the nuclear transcription factor CREB and expression of c-Fos. In turn, these transcription factors stimulate AQP2 gene expression through CRE and AP-1 elements in the AQP2 gene promoter. In addition, VP stimulates an immediate increase in AQP2 expression by accelerating trafficking and assembly of pre-synthesized protein 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..

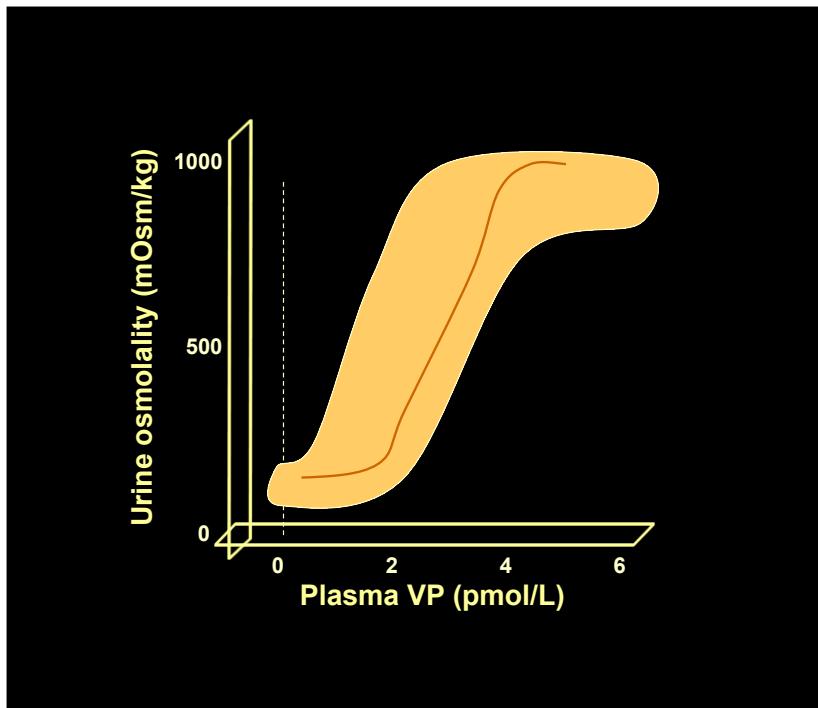


Figure 5. The relationship of plasma VP concentration to urine osmolality. Shaded area represents range of normal; single line indicates representative individual.

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. VP up-regulates the bumetanide-sensitive sodium-potassium-chloride cotransporter (SLC12A1) in the thick ascending loop of Henle through both a rapid acceleration of post-translational processing/trafficking and an increase in SLC12A1 gene expression. Together, these contribute to the generation and maintenance of a hypertonic medullary interstitium, and augment VP-dependent water resorption (12).

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).

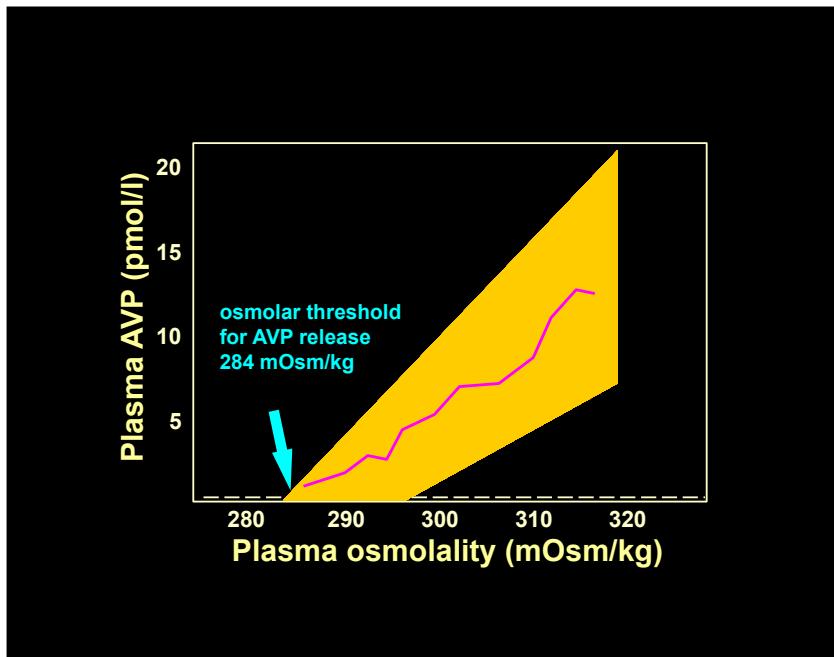


Figure 6. The relationship of plasma VP concentration to changes in plasma osmolality during controlled hypertonic stimulation. VP concentration determined during progressive hypertonicity induced by infusion of 855 mmol/l saline in a group of healthy adults. Increases in plasma osmolality increase plasma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

As befits its major function and physiological role, VP production by the neurohypophysis is influenced by sensory signals 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. Moreover, these neurons integrate osmolar status with additional endocrine signals reflecting circulating volume status through the action of angiotensin II (A-II), relaxin, and atrial natriuretic peptide (ANP). A-II and relaxin excite both OT and VP magnocellular neurons. In contrast, ANP inhibits VP neuron activity. VP neurons themselves have independent osmo-sensing properties and V-Rs are present on vasopressinergic neurons of both the PVN and SON, highlighting the potential for auto-control of VP release through direct osmoregulation and short loop feedback (14).

VP magnocellular neurons in the SON and PVN co-express the peptide Apelin and its G-protein coupled receptor. A 'yin and yang' relationship has been proposed between VP and this 36 amino-acid peptide (and indeed it's shorter active derivatives Apelin-17 and Apelin-13). Intra-cerebroventricular injection of Apelin-17 inhibits the phasic firing of VP magnocellular neurons, reducing VP release and stimulating aquaresis. Hypertonic stress and water loading have reciprocal effects on plasma VP and Apelin concentrations. Apelin receptors are also co-expressed in VP target cells in the renal collecting duct. VP and Apelin are thus regulated in opposite directions to maintain volume and osmolar homeostasis (15-18).

Changes in the osmotic environment of osmo-sensitive neurons in the OVLT, SFO and vasopressinergic neurons of the SON and PVN result in altered cell volume. These physical changes alter the activity of the stretch-sensitive cationic channel TRPV1, expressed on the cell surface of these neurons. TRPV1 thus acts as the transduction mechanism linking changes in osmolality to altered membrane potential and firing frequency. Osmoregulatory function is not lost in *Trpv1^{-/-}* mice, indicating additional osmo-sensing pathways must be in operation (19).

A related, but distinct osmo-sensory input feeds additional data on peripheral osmolar status to the neurohypophysis. Hepatic portal blood vessels contain sensory neurons responsive to changes in the osmolality of peripheral blood. In contrast to central mechanisms, the key transducing element of the peripheral process is the stretch-sensitive ion channel, TRPV4. Plasma osmolality is frequently elevated in patients after liver transplant in which the donor organ is denervated, demonstrating the function of this peripheral pathway (20).

Osmosensitivity of VP release is influenced by circadian rhythms. VP release increases during sleep. This effect is mediated by clock neurons projecting from the suprachiasmatic nucleus, increasing the activity of osmosensory afferent input to the SON (21).

3.3.2. Baroregulation of Vasopressin

Reductions in circulating volume stimulate VP release. 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.

Baroregulatory influences on neurohypophyseal VP release derive from aortic arch, carotid sinus, cardiac atrial, and great vein stretch-sensitive afferents via cranial nerves IX and X. Ascending projections 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 nuclei 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 (22, 23).

Osmoregulated VP responses can be modified by factors triggered as part of the coordinated neurohumoral response to changes in circulating volume and blood pressure. A-II amplifies the proportional relationship between osmolality and action potential firing in the SON. The peptide produces this effect through polymerisation of intracellular actin filaments, resulting in altered cell shape, a mechanism that is synergistic with that mediating responses to changes in extracellular osmolality. A-II thus enhances osmosensitivity. This mechanism underpins the changes in osmo-regulated VP release in hypo- and hypervolaemia : the osmotic threshold and sensitivity of VP release is lowered by hypovolaemia ; while the converse is found in hypervolaemia and hypertension (15).

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.

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 parvocellular 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. Effects of VP on regulation of bone mass

VP inhibits osteoblast formation, an effect that is opposed by oxytocin, which stimulates osteoblast formation. Mice rendered deficient in VPr1a (*Avpr1a^{-/-}*) have a high bone mass while both haploinsufficiency for oxytocin and deletion of the oxytocin receptor (*Oxr^{-/-}*) result in osteopenia. The role of both hormones in the regulation of skeletal physiology remains to be explored further (24).

4.4. Behavioral 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. An increasing amount of data highlight the role of central vasopressinergic systems in mediating complex social behavior. Data in Man link *V1a-R* gene sequence variation with a range of normal and abnormal behaviour patterns, including gender dimorphic behaviour. Dysregulation of central VP action may be a distal end point in complex conditions characterised by altered social and emotional behaviour (25, 26).

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. As with those mediating VP release, the osmoreceptors regulating thirst are situated in the OVLT, effectively outside the blood-brain barrier and distinct from those mediating VP release. Neural activity in and around the OVLT remains active in hyperosmolar states following immediate satiety of thirst, indicating that other centres must be involved in thirst perception. The anterior cingulate cortex and insular cortex receive input from osmo-sensitive afferents and have been implicated as key higher centres in thirst pathways (16).

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.

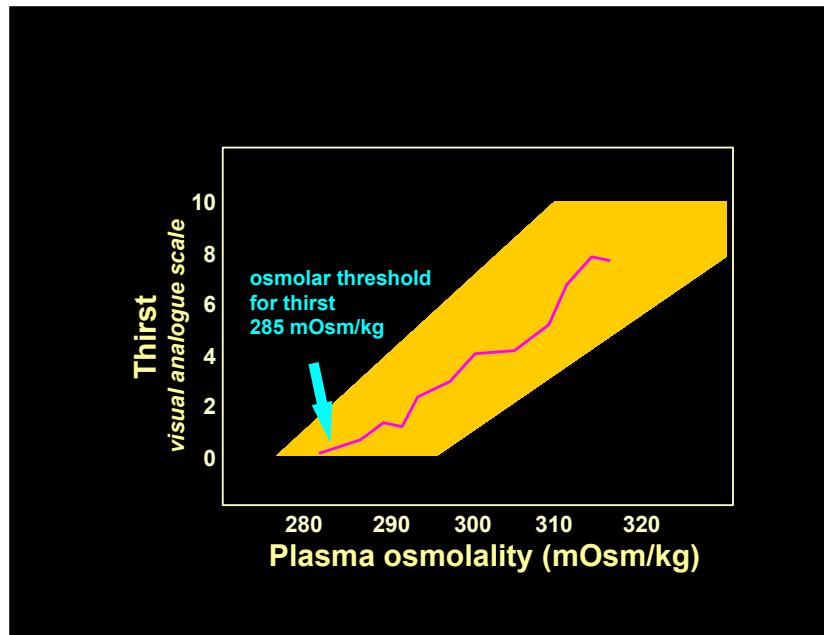


Figure 7. The relationship of thirst to plasma osmolality during controlled hypertonic stimulation. Data obtained from analysis of thirst (by visual analogue scale) during progressive hypertonicity induced by infusion of 855 mmol/l saline in a group of healthy adults. There is a linear relationship between 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 intra-cerebral A-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

The act of drinking reduces thirst perception before any change in plasma osmolality. This effect is produced through three mechanisms: oropharyngeal sensory afferents; gastro-intestinal stretch-sensitive afferents; and peripheral osmoreceptors in the hepatic portal vein. Recent data have highlighted how thirst-promoting neurons in the SFO integrate sensory inputs from the oropharynx (drinking and food composition) with central osmolar status to influence thirst perception. This complex mechanism effectively explains anticipatory changes in water consumption that precede changes in plasma osmolality (27).

As with VP release, hypovolaemia resets the relationship between plasma osmolality and thirst. A-II is one of the key mediators of this physiological response. Peripheral A-II generation can act on central osmoreceptors, to increase both thirst and VP release. An independent, intra-cerebral A-II system is activated in parallel. A-II is a powerful central dipsogen.

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. The regulation of fluid and electrolyte balance is intimately linked with that of circulating volume: VP occupies a central role.

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 not 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 conventional osmolar set point. Antidiuresis is maintained, despite hyponatraemia, as circulating volume and blood pressure are supported through reduced urine water losses and direct pressor effects of VP. Coincident activation of the systemic and intra-cerebral Renin-Angiotensin systems stimulates drinking and forms the basis of this shift in the VP axis, 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 (28).

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.

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 (29).

The role of OT in parturition is not limited to maternal responses. 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 in line with a wider-ranging role in maternal-fetal physiology (30).

7.3. Oxytocin and behavior

OT-R expression is widespread in the CNS of many species and OT has widespread roles as a neurotransmitter, including neural networks that mediate a range of complex behaviors. In some cases, these overlap those involving VP (25, 26).

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 or the potential for considerable redundancy in neural pathways. Central oxytotic transmission reduces anxiety behavior and hypothalamo-pituitary-adrenal stress responses in female rats.. It may be that OT has a complex role in the stress response, with context-dependent differential effects.

Central OT pathways have been implicated in social recognition, affiliative behavior and social bonding. This clustering has raised interest in the role of OT and OT-pathways in the development of autistic spectrum disorder (ASD). A number of association studies have demonstrated linkage between ASD and OT-R polymorphisms. However, to date the effect size is inconsistent. Recent data have highlighted associations with the single nucleotide polymorphisms (SNPs) rs7632287, rs237887, rs2268491 and rs2254298 (31-33).

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.

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	<ul style="list-style-type: none">• <i>Wolfram syndrome</i>• <i>Autosomal dominant</i>• <i>Autosomal recessive</i>
	Developmental syndromes	<i>Septo-optic dysplasia</i>
	Idiopathic	
Secondary/acquired	Trauma	<ul style="list-style-type: none">• <i>Head injury</i>• <i>Post surgery (transcranial, transphenoidal)</i>
	Tumour	<ul style="list-style-type: none">• <i>Craniopharyngioma</i>• <i>Germ cell tumours</i>• <i>Metastases</i>• <i>Pituitary macroadenoma</i>
	Inflammatory	<ul style="list-style-type: none">• <i>Granulomatoses</i> (<i>Sarcoidosis, Histiocytosis</i>)• <i>Infection</i>• <i>Infundibulo-neurohypophysitis</i>• <i>Guillaine-Barre Syndrome</i>• <i>Autoimmune</i> (<i>anti-VP neuron antibodies</i>)
	Vascular	<ul style="list-style-type: none">• <i>Aneurysm</i>• <i>Infarction</i>• <i>Sheehan's syndrome</i>• <i>Sickle cell disease</i>
	Pregnancy (associated with increased vasopressinase expression)	
B. Nephrogenic diabetes insipidus		

Primary	Genetic	<ul style="list-style-type: none"> • <i>X-linked recessive (V2-R defect)</i> • <i>Autosomal recessive (AQP2 defect)</i> • <i>Autosomal dominant (AQP2 defect)</i>
Secondary		
	Idiopathic	
	Chronic renal disease	<ul style="list-style-type: none"> • <i>Polycystic kidneys</i> • <i>Obstructive uropathy</i>
	Metabolic disease	<ul style="list-style-type: none"> • <i>Hypercalcaemia</i> • <i>Hypokalaemia</i>
	Drug induced	<ul style="list-style-type: none"> • <i>Lithium</i> • <i>Demeclacycline</i>
	Osmotic diuretics	<ul style="list-style-type: none"> • <i>Glucose</i> • <i>Mannitol</i>
	Systemic disorders	<ul style="list-style-type: none"> • <i>Amyloidosis</i> • <i>Myelomatosis</i>
	Pregnancy	

C. Dipsogenic diabetes insipidus

	Compulsive water drinking	
	Associated with affective disorders	
	Drug induced?	
	Structural/organic hypothalamic disease	<ul style="list-style-type: none"> • <i>Sarcoidosis</i> • <i>Tumours involving hypothalamus</i> • <i>Head injury</i> • <i>Tuberculous meningitis</i>

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). 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 (34; Figure 8).

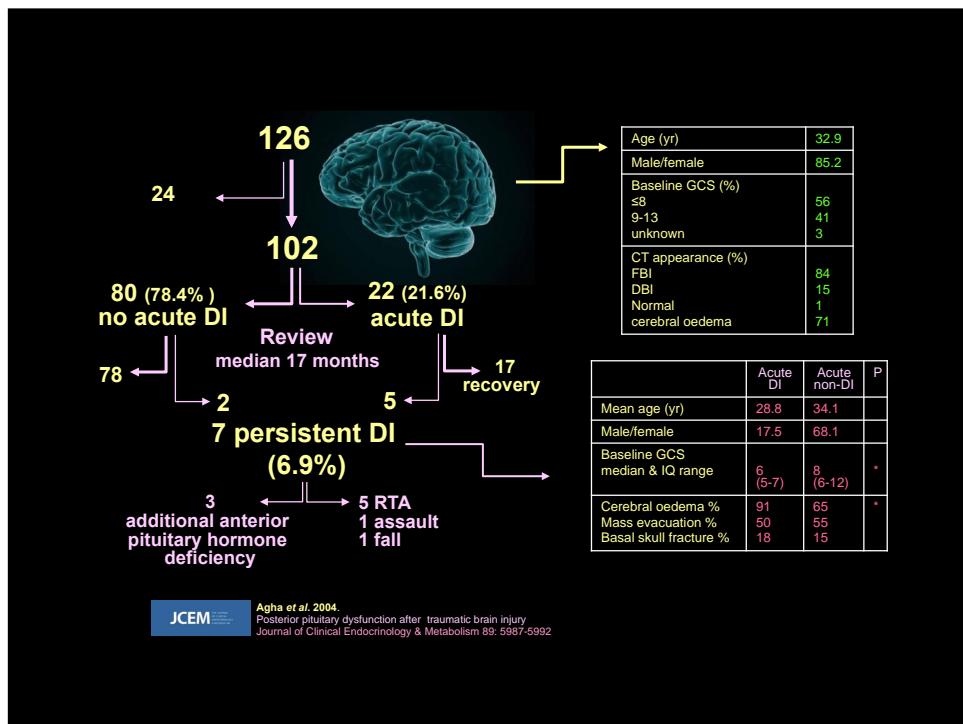


Figure 8. Development of DI following TBI. Data from Agha *et al.* 2004. Posterior pituitary dysfunction after traumatic brain injury. Journal of Clinical Endocrinology & Metabolism 89, 5987-5992. Boxes indicate demographics and details of patient cohort studied. 126 patients were recruited to the longitudinal study; of those, outcome data were available for review in 102. DBI: diffuse brain injury. FBI: focal brain injury. GCS: Glasgow coma scale. RTA: road traffic accident.

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 (35) (Figure 9). 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 9. Sagittal 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. Wolfram syndrome (WS) or DIDMOAD is a rare autosomal recessive, progressive neuro-degenerative disorder characterized by the association of HDI with diabetes mellitus, optic atrophy and bilateral sensorineural deafness. 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. Central nervous system manifestations include progressive ataxia, cognitive impairment and brain stem dysfunction. Diffuse leukoencephalopathy can be seen on MRI. Renal outflow tract dilatation is common and gonadal can occur.

Genetic linkage and positional cloning studies have identified two subtypes of WS. WS1 is caused by loss of function mutations in the *WFS1* gene found on Ch.4p16. This gene encodes an 890 amino-acid glycoprotein (wolframin). At the cellular level, wolframin expression is restricted to the endoplasmic reticulum (ER) where it regulates ER stress and calcium homeostasis. Loss of function of wolframin triggers neuronal apoptosis. 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. WS2 is characterised by optic atrophy and diabetes mellitus, with additional features of peptic ulcer disease and bleeding tendency not seen in WS1. WS2 is caused by loss of function mutations in *CISD2* gene, which codes for a protein expressed on both ER and the outer mitochondrial membrane. Mutations in *CISD2* disrupt calcium flux between ER and mitochondria, disrupting organelle function, leading to autophagy and cell death in a manner similar to that seen in several other neurodegenerative diseases (36, 37).

Autosomal dominant familial HDI is caused by loss of function mutations affecting 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. 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).

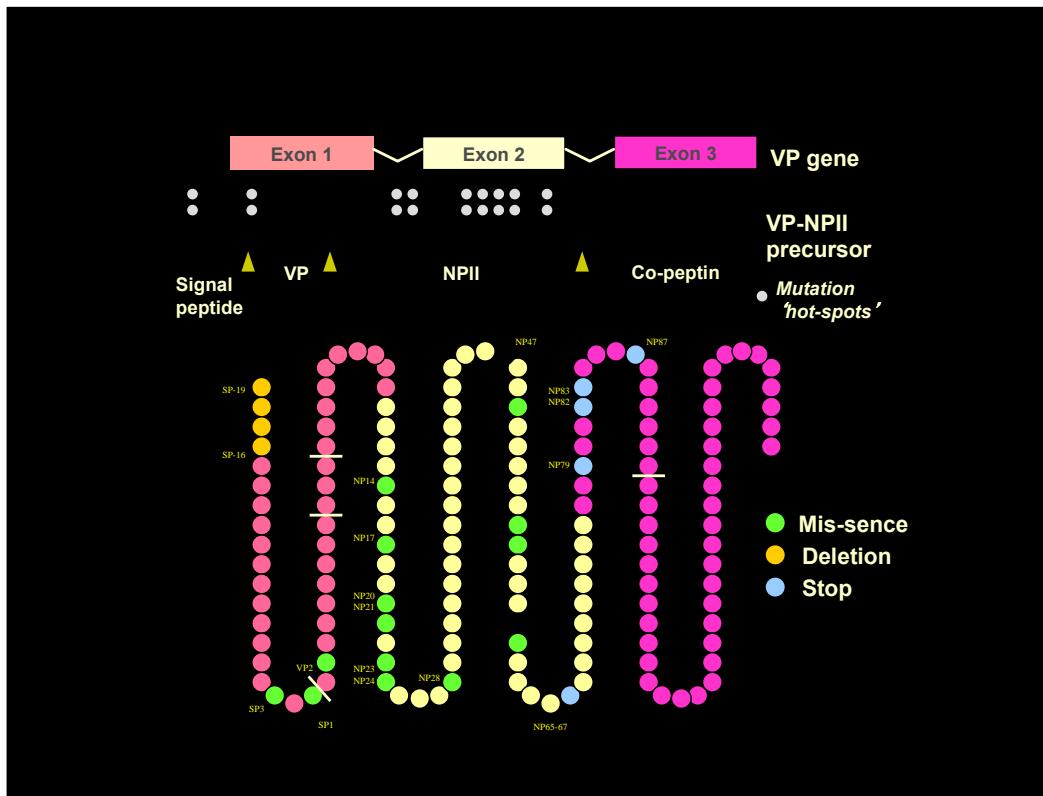


Figure 10. Schematic diagram of the Vasopressin-neurophysin II gene and its product, showing the location and type of mutations identified in autosomal dominant familial hypothalamic diabetes insipidus. Though mutations have been described in all three exons and involve all parts of the VP-NPII precursor except the co-peptin moiety, the majority occur in exons 1 or 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	<ul style="list-style-type: none"> • Free access to fluid overnight prior to test • Avoid caffeine and smoking 0750h weigh patient
Dehydration phase	<ul style="list-style-type: none"> • 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 • <u>Stop test if weight loss exceeds 5% of starting weight, or thirst is intolerable</u> • Supervise patient closely to avoid non-disclosed drinking
DDAVP phase	<ul style="list-style-type: none"> • 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. 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 11). 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

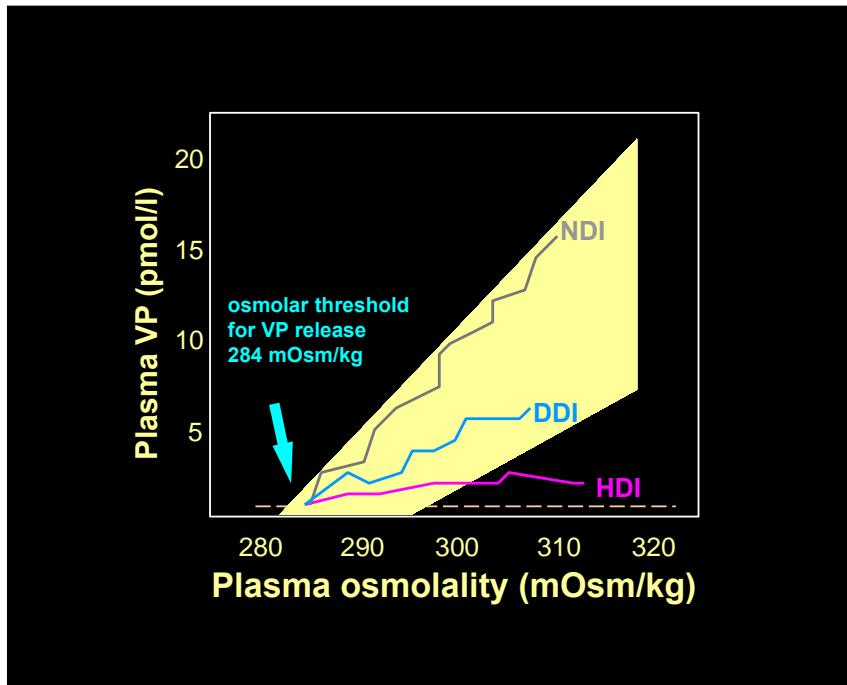


Figure 11. The relationship of plasma VP concentration to changes in plasma osmolality during controlled hypertonic stimulation in diabetes insipidus. Measurement of plasma VP during controlled hypertonic stress testing can effectively differentiate between HDI, NDI and DDI.

Co-peptin (the c-terminal portion of the VP-precursor) is secreted in equimolar amounts to VP and is more stable in plasma. This makes it attractive as a potential alternative analyte to VP during water deprivation or graded hyper-osmolar stimulation.. Several commercial assays for co-peptin are available and recent data confirm it's utility in defining the aetiology of polyuric and polydipsic states (39).

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 (40).

In establishing the underlying mechanisms of HDI once the diagnosis is confirmed, imaging of the hypothalamus, pituitary and surrounding structures with MRI is essential. 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 hyper-intense signal of the posterior pituitary on T1-weighted images (Figure 12). Signal intensity is correlated strongly with VP content of the gland (41). In the absence of appropriate history and diagnostic testing, the loss of a posterior pituitary bright spot does not make the diagnosis of HDI. Importantly, presence of an appropriate bright spot does not exclude the diagnosis of HDI.

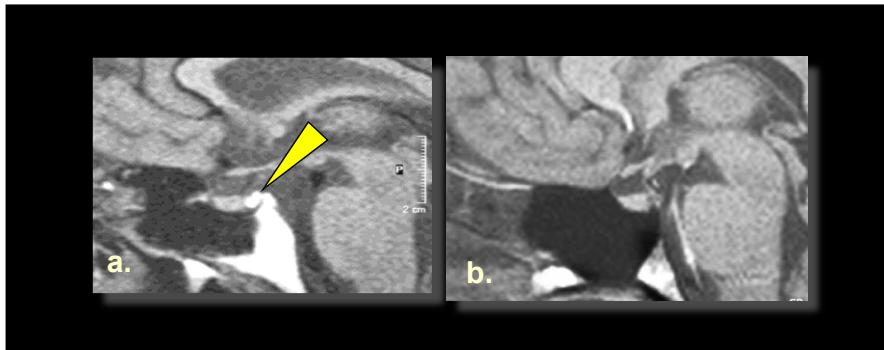


Figure 12. Loss of the posterior pituitary 'bright spot' on T1 weighted MRI in hypothalamic diabetes insipidus. The normal posterior pituitary can be demonstrated as a 'bright spot' within the sella turcica on T1-weighted MRI (a). This increased signal intensity can be lost in HDI (b). An ectopic posterior 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 anterior pituitary dysfunction should be looked for in HDI, though it is relatively uncommon in the adult population. Interestingly, evidence of organ-specific autoimmune disease is relatively common in adult patients with isolated HDI, consistent with an autoimmune basis for the condition (42).

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, and can be split into two types: a 'pure' type, associated with water loss alone; a second, more complex type associated with water loss together with a wider tubulopathy. 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.. 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.. Defects in thick ascending limb and distal tubular sodium-chloride transport underlie a range of inherited tubulopathies producing mixed ion and water loss, including inherited forms of Bartter syndrome (43, 44).

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 is characterized by dysregulated AQP2 expression and trafficking along the whole collecting duct as well as dysregulated expression of the amiloride-sensitive epithelial sodium channel (ENaC) in the cortical collecting duct. Lithium enters collecting duct cells through ENaC expressed on the apical cell membrane and leads to inhibition of glycogen synthase kinase type 3 \square (GSK-3 \square) signaling

pathways. NDI secondary to lithium toxicity can persist after drug withdrawal, and may be irreversible. (45).

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. There are data to support the use of amiloride in NDI caused by lithium. 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. The selective phosphodiesterase inhibitor Sildenafil enhances cyclic guanosine monophosphate-mediated apical membrane trafficking 5f AQP2 and has been shown to improve aquaresis in X-linked NDI through bypassing defective V2-R signaling (46).

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. 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 (serum sodium <135 mmol/l) is a clinical feature in some 15–20% of non-selected emergency admissions to hospital. It is associated with increased morbidity and mortality across a range of conditions. Moreover, data support the association of hyponatraemia correction with improvements in clinical outcome. However, the relationship of serum sodium and outcome is not straightforward. Co-morbidity and disease severity, rather than hyponatraemia per se, may make a significant contribution to adverse outcome in these patients. Further data are needed to clarify whether the relationship between sodium levels and outcome is causal or the association of two variables linked with disease severity (47–49).

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 artefactual hyponatraemia with normal plasma osmolality, even when using an ion-specific electrode. This is consequent to the use of a standard dilution step in most clinical biochemistry laboratories. This type of artefactual hyponatraemia is not seen when a direct potentiometric method is used, such as when using a blood-gas analyser. In many clinical situations, hyponatraemia is multifactorial (Table 4).

Table 4. Causes of hyponatraemia		
Pseudohyponatraemia		Reduced renal free water clearance
Hyperglycemia Hyperlipidaemia Non-physiological osmolyte Elevated paraprotein		Hypovolaemia Cardiac failure Nephrotic syndrome Hypothyroidism Hypoadrenalinism SIAD Nephrogenic syndrome of antidiuresis
Sodium depletion		•Drugs •Renal failure •Portal hypertension & ascites •Hypoalbuminaemia •Sepsis •Fluid sequestration
Renal loss	•Diuretics •Salt wasting nephropathy •Hypoadrenalinism •Central salt wasting	
Extra-renal loss	•Gut loss	
Excess water intake		
Dipsogenic DI Sodium-free, hyposmolar irrigant solutions Dilute infant feeding formula Exercise-associated hyponatraemia		

VP plays a key role in many pathophysiological situations 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 persistent. Though clinical assessment can identify the extracellular volume status of some patients, it is unreliable and has poor sensitivity and specificity (50).

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. Absolute plasma VP concentrations may not be strikingly high and in fact VP measurement is not helpful in establishing the diagnosis. The key feature is 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 Thiazide 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. 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. 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 Oxcarbamazepine 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. Excretion of urine that is not maximally dilute in the context of dilute plasma (i.e. urine concentration greater than 100mOsm/Kg) indicates the action of VP on renal water resorption. Importantly however, it does not define whether this action is appropriate (for instance in the context of hypovolaemia and baro-stimulated VP release) or inappropriate. Measurement of urinary sodium concentration is key in the differential diagnosis of SIAD from hypovolaemia. Renal sodium excretion should be above 30mol/L to make a diagnosis of SIAD. Below this value, volume depletion needs to be considered more likely and below 20 mmol/L, hypovolaemia is the likely cause of hyponatraemia. SIAD is often associated with urine sodium concentrations of 60 mmol/L or more. SIAD

is a volume-expanded state and there is evidence of mild sodium loss as other homeostatic regulators of volume homeostasis attempt to minimize volume expansion. The utility of urinary sodium concentration in defining the aetiology of hyponatraemia is limited by concurrent use of drugs that produce a natriuresis: diuretics, angiotensin converting enzyme inhibitors and angiotensin II antagonists. In this situation, a serum urate <4 mg/dl, or a fractional urate excretion >12% can help differentiate SIAD from mild hypovolaemia (51, 52).

Table 8. Diagnostic criteria for SIAD

Hyponatraemia
Urine Osm > 100 mOsm/kg
<ul style="list-style-type: none"> • sub-maximum concentration
Exclusion of hypovolaemia
<ul style="list-style-type: none"> •urine Na⁺ > 20-30 mmol/L •absence of hypotension •absence of oedema
Absence of
<ul style="list-style-type: none"> •adrenal failure •hypothyroidism

As with its use to support the diagnosis of CDI, measurement of co-peptin has been proposed as a further adjunct in the differential diagnosis for hyponatraemia: serum co-peptin levels being low in those situations in which effective circulating volumes are expanded (53).

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). 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 should not be required to establish a diagnosis in clinical practice and is largely a research-based tool.,(54).

Table 9. Protocol for water load test

Preparation	<ul style="list-style-type: none"> •Free access to fluid overnight prior to test •Avoid caffeine and smoking •0730h weigh patient •Cannulate patient •Rest patient 30 minutes
Water load phase	<ul style="list-style-type: none"> •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	<ul style="list-style-type: none"> •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 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 and electrolyte loss as the cause. Occasional runners should be advised to follow their thirst as they run and avoid rigid, time-based fluid intake. 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 (55).

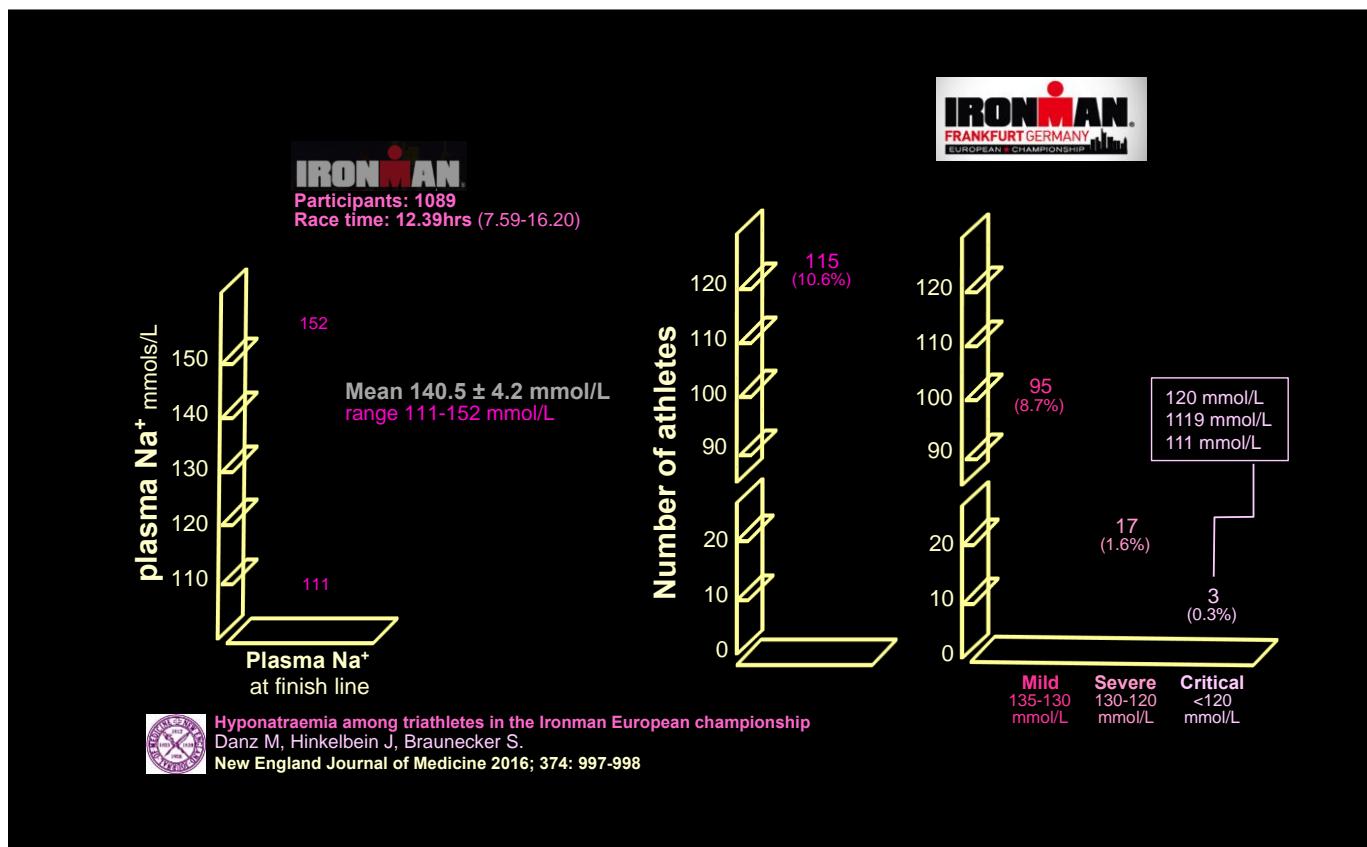


Figure 13. Exercise associated hyponatraemia in triathletes. 1089 triathletes were studied. The mean plasma sodium level at the finish was 140.5 ± 4.2 mmol/L (range 111-152). Among athletes completing the study events, 10.6% had documented hyponatraemia: 8.7% mild; 1.6% severe; and 0.3% critical (3 athletes in total with plasma sodium levels 120, 119, and 111 mmol/L respectively). Multivariate analysis showed a significant association between development of hyponatraemia and the following factors: female gender; longer times to complete a race. Critical hyponatraemia occurred in participants who finished in the 12th and 14th hours of the race (56).

4.6 Nephrogenic syndrome of inappropriate antidiuresis

The G-protein-coupled V2-R mediates the action of VP on renal water excretion. Rare kindreds have been found that harbour constitutively activating mutations in the V2-R that lead to VP-independent, V2-R mediated, antidiuresis associated with persistent hyponatraemia (Figure 14). This nephrogenic

syndrome of inappropriate antidiuresis (NSIAD) was initially described in male infants with persistent hyponatraemia in keeping with the haploinsufficiency associated with the *V2-R* gene being on the X chromosome. However, subsequent studies have found the condition is not limited to males, expression of the condition being clearly identified in heterozygous females. The true prevalence of NSIAD is not known. However, as some 10% of patients with SIAD have been described as having undetectable VP, it seems likely that at least some of these cases may be due to activating mutations of the *V2-R* (56, 57).

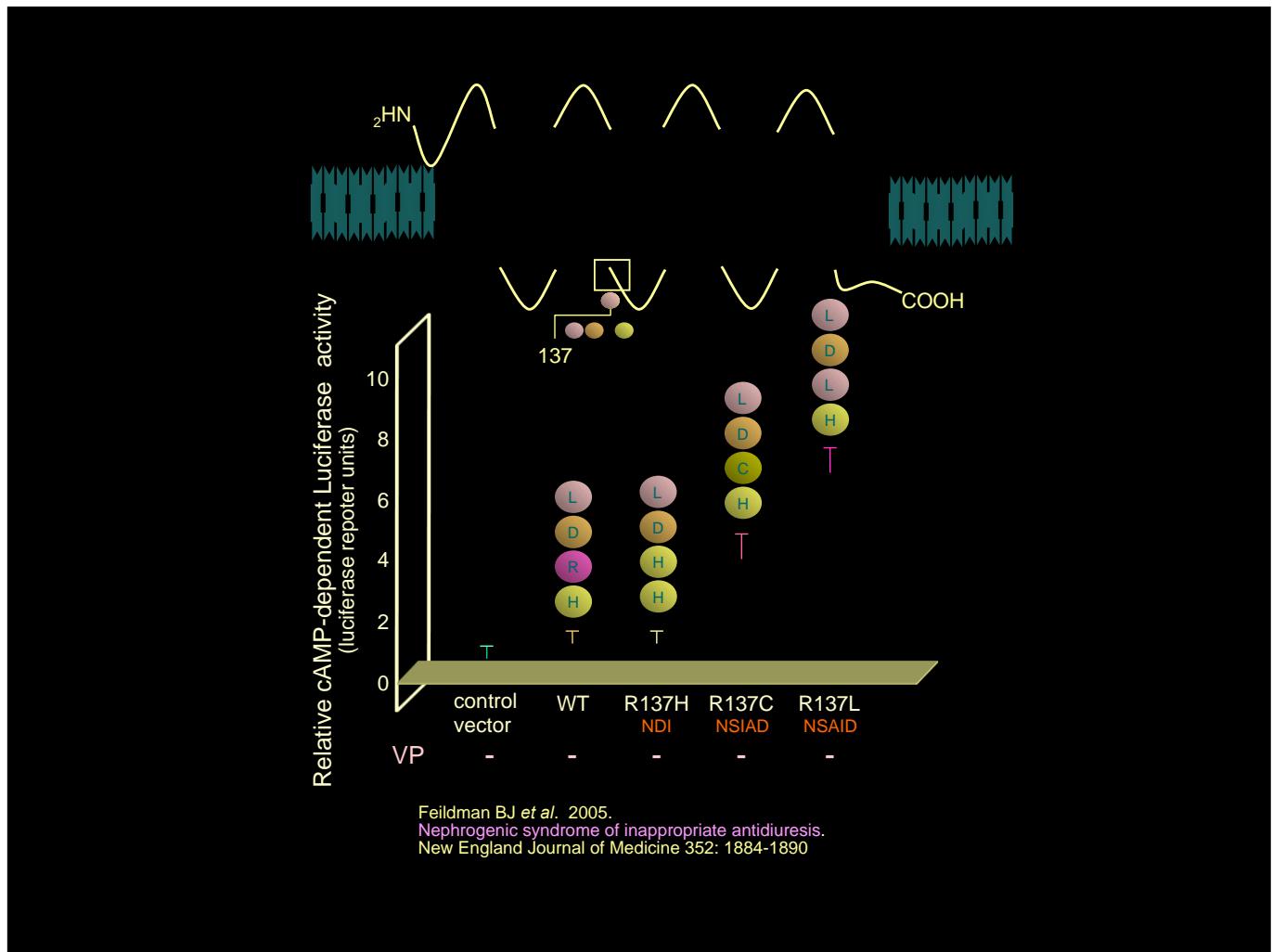


Figure 14. In vitro bioactivity of different *V2-R* constructs relative to wild type (WT) in a cAMP-dependent luciferase reporter system in the absence of VP. The R137H construct is the *V2-R* found in X-linked NDI. R137C and R137L are receptor variants found in NSIAD. Constructs differ only by the amino acid at position 137. R137C and R137L found in NSIAD demonstrate constitutive, VP-independent activity. R: arginine. H: histidine. C: cysteine. L: leucine.

4.7 Central salt wasting

This acquired, primary natriuretic state remains a subject of controversy. It has been characterised as a combination of hyponatraemia with hypovolaemia associated with neurological or (more often) neurosurgical pathologies. The underlying mechanism(s) remain unclear, but increased release of natriuretic peptides and/or reduced sympathetic drive have been proposed. The diagnosis of central salt wasting (CSW) hinges on the natural history: the development of hyponatraemia being preceded by natriuresis and diuresis with ensuing clinical and biochemical features of hypovolaemia. In contrast to SIAD, 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.

SIAD can occur in the same group of patients in whom CSW has been reported. Both CSW and SIAD are associated with urine sodium concentrations greater than 40mmols/L. However, the natriuresis of CSW is much more profound than that of SIAD and precedes the development of hyponatraemia. 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. The management of CSW is volume replacement with 0.9% saline; while the cause-directed approach to SIAD would often involve restriction of fluid. The clinical and practice context, together with the opposed cause-directed management approaches to CSW and SIAD can lead to significant tension. A cause-independent approach to the management of the neurosurgical patient with hyponatraemia is often the practical and pragmatic approach to take: balancing management of hyponatraemia with the need to avoid threatening cerebral perfusion and avoidable vasospasm (58). A prospective, single centre study of 100 patients developing hyponatraemia after subarachnoid haemorrhage failed to identify a case of CSW: hyponatraemia being attributable to SIAD, glucocorticoid deficiency or inappropriate fluid administration (Figure 15).

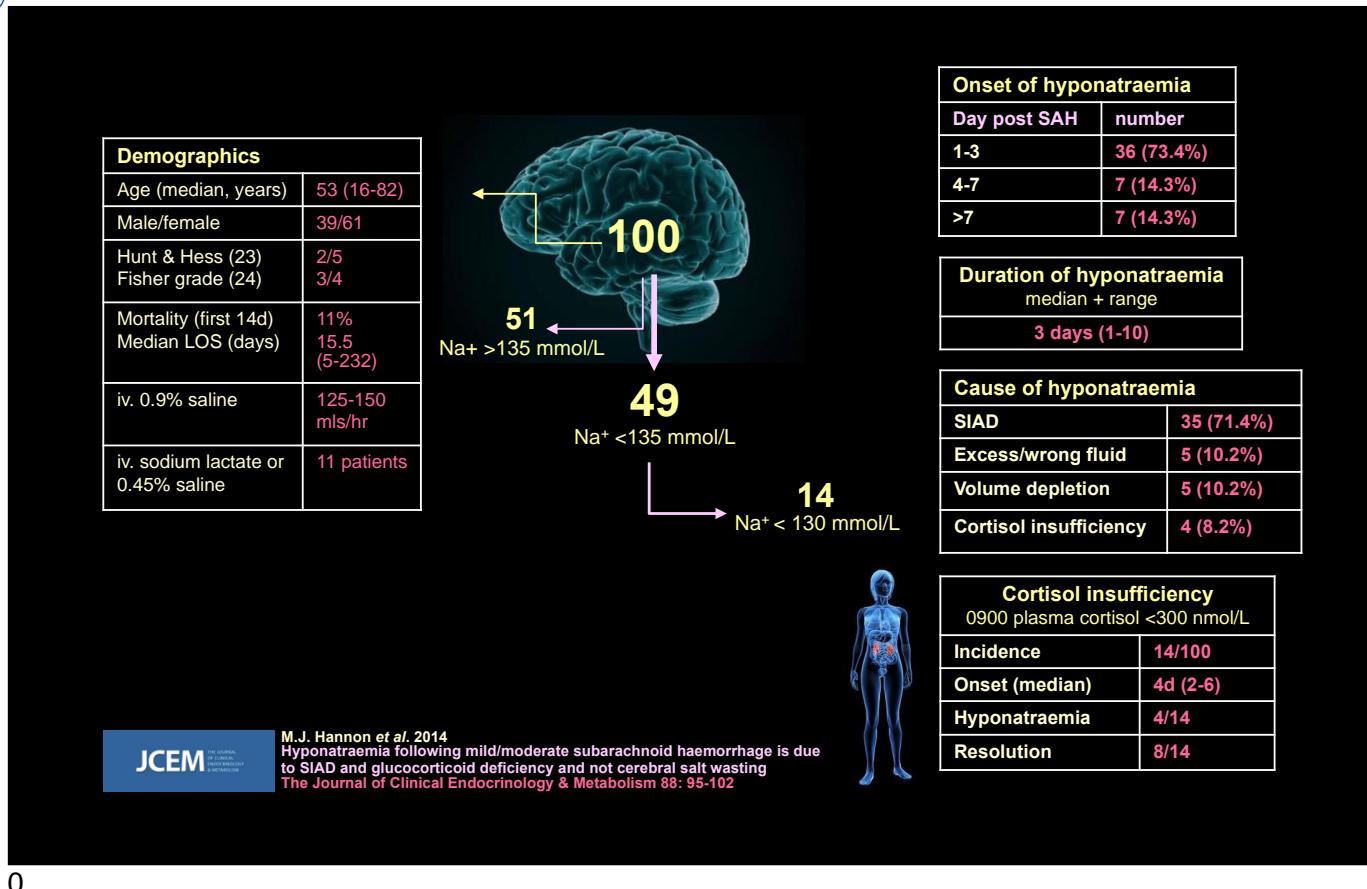


Figure 15. Hyponatraemia after subarachnoid haemorrhage. Prospective study of 100 patients. Demographics, outcomes and aetiology of hyponatraemia noted. SAH: subarachnoid haemorrhage (59).

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). While it is intuitive that the greater the derangement in serum sodium should be

associated with the most profound neurological disturbance, the relationship between serum sodium and neurological function is not simple. Patients with marked biochemical disturbance may have mild symptoms if hyponatraemia develops over a prolonged period.. This reflects CNS adaptation: brain oedema being limited by efflux of organic solutes. This adaptation can complicate the management of hyponatraemia. Rapid correction of serum 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 (osmotic demyelination syndrome, ODS). This is a rare but serious complication of hyponatraemia and its treatment. ODS develops within 1-4 days of rapid (>10-12 mmols per 24 hours) correction of serum 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, ophthalmoplegia, pseudo-bulbar palsy and coma.

Table 9. Clinical features of hyponatraemia secondary to SIAD

- | |
|---|
| <ul style="list-style-type: none"> • Headache • Nausea • Vomiting • Muscle cramps • Lethargy • Disorientation • Seizure • Coma • Brain-stem herniation |
|---|

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

Chronic asymptomatic hyponatraemia, with serum sodium concentrations greater than 130 mmol/L may not require specific treatment. More severe degrees of hyponatraemia, particularly if associated with symptoms, require some form of intervention..

4.8.1. Management of hyponatraemia associated with severe or moderately severe symptoms

Hyponatraemia associated with severe or moderately severe symptoms requires urgent management and as an emergency. Treatment is cause-independent. Treatment should be given priority over establishing the aetiology of hyponatraemia. The aim of treatment is to reduce immediate risk through increasing serum sodium to a level that decreases morbidity and mortality. Importantly, the rate of increase in serum sodium must be at a rate that does not result in harm through precipitating ODS (Figure 16). The immediate target should not be to normalise serum sodium. Once the patient is stable, investigations to establish the cause of hyponatraemia can begin, the outcome of which subsequently guiding cause-directed therapy (51, 60, 61).

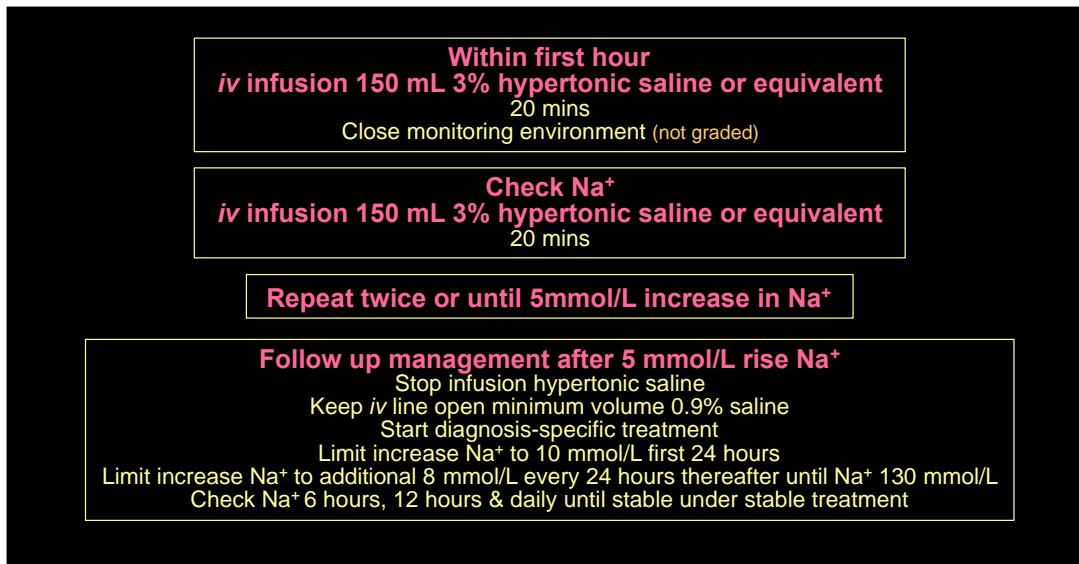


Figure 16. Immediate, cause-independent management of hyponatraemia associated with severe or moderately severe symptoms.

Previous strategies for the emergency management of hyponatraemia have stratified patients based on presumed duration of the electrolyte disturbance. Furthermore, some have advocated hypertonic fluid administration volume and rates based on calculated deficits in serum sodium using a standard formula (62). A more pragmatic and reliable approach to patient stratification is to base the decision on use of hypertonic fluid on patient symptoms and signs; while the determining hypertonic fluid prescription by calculated serum sodium deficit is associated with a significant risk of over-correction (63). Over-correction of hyponatraemia (increase in serum sodium above the recommended rate) should prompt review of the fluid regimen and consideration of active management with hypotonic fluid, with or without concurrent use of DDAVP (51, 64).

4.8.2. Management of SIAD associated with mild to moderate symptoms

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 normalise and it is important that a negative fluid balance is confirmed during this period. As cause-directed therapy progresses (e.g. treatment of underlying infection or removal of drug causing SIAD), fluid restriction may be relaxed.

4.8.3. Drug treatment in 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. Withdrawing the drug producing SIAD may not be possible, or may be only partly successful in correcting serum sodium. In other situations, fluid restriction may be only partly effective, be poorly tolerated or may prove non-sustainable. Clinicians may thus have to balance the merits of incremental intervention with those of tolerating mild, persisting hyponatraemia.

Demeclocycline has been used for many years 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. Photosensitive skin reactions are a significant additional adverse effect. There are very limited data to support long-term efficacy. Urea at doses of 30 g/day by mouth has been used to treat the hyponatraemia of persisting

SIAD. Urea increases renal free water excretion and decreases urinary sodium excretion. However, access to therapeutic preparations is limited and experience with its use is not widespread.

V2-R antagonists (Vaptans) are a rational approach to the management of hyponatraemia due to SIAD. They are aquretic, increasing renal water excretion without impacting on renal electrolyte loss. V2-R antagonists are classified as either selective (V2-R specific) or non-selective (V2- and V1a-R antagonism). Both increase serum sodium in patients with normal or increased plasma volume. They can impact on plasma sodium within 4-6 hours. While undoubtedly attractive, the place of V-R antagonists in the management of SIAD remains to be clarified. This reflects the absence of robust data on cost-utility together with the absence of data addressing key patient-orientated outcomes other than serum sodium (63-65).

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 10, Figure 17). 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.

Table 10. Classification of adipsic and hypodipsic syndromes

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

Table 11. Causes of adipsic and hypodipsic syndromes

Neoplastic (50%)	
Primary	<i>Craniopharyngioma</i> <i>Germ cell tumour</i> <i>Meningioma</i>
Secondary	<i>Pituitary tumour</i> <i>Bronchial carcinoma</i> <i>Breast carcinoma</i>
Granulomatous (20%)	
<i>Histiocytosis</i> <i>Sarcoidosis</i>	
Miscellaneous (15%)	
<i>Hydrocephalus</i> <i>Ventricular cyst</i> <i>Trauma</i> <i>Toluene poisoning</i>	
Vascular (15%)	
<i>Internal carotid artery ligation</i> <i>Anterior communicating artery aneurysm</i> <i>Intra-hypothalamic haemorrhage</i>	

	VP release	Thirst
Type A	osmolar threshold ↑ sensitivity ↔	osmolar threshold ↑ sensitivity ↔
Type B	osmolar threshold ↔ sensitivity ↓	osmolar threshold ↔ sensitivity ↓
Type C	osmolar threshold ↓ sensitivity • ↓	osmolar threshold • sensitivity •
Type D	osmolar threshold ↔ sensitivity ↔	osmolar threshold • sensitivity •

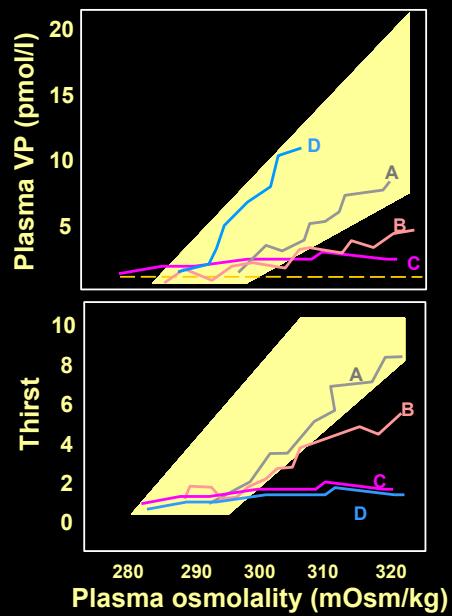


Figure 18. Patterns of plasma VP and thirst responses to hypertonic stress in patients with adipsic syndromes. Normal range responses to osmolar stimulation are shown by the shaded areas. The 4 types of adipsic syndrome are demonstrated. Patients with the Type A syndrome osmoregulate around a higher 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 euvoalaemic 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 (66).

References

1. Waller SJ, Ratty A, Burbach JPH, Murphy D 1998. Transgenic and transcriptional studies on neurosecretory cell gene expression. *Cellular & Molecular Neurobiology* 18, 149-171.
2. Iwasaki Y, Oiso Y, Saito H, Majzoub JA 1997. Positive and negative regulation of the rat vasopressin gene promoter. *Endocrinology* 138, 5266-5274.
3. Russell JA, Leng G 1998. Sex, parturition and motherhood without oxytocin? *Journal of Endocrinology* 157, 343-359.
4. Ponzio TA, Fields RL, Rashid OM, Salinas YD, Lubelski D, et al. 2012. Cell-type specific expression of the vasopressin gene analyzed by AAV mediated gene delivery of promoter deletion constructs into the rat SON in vivo. *PLoS ONE* 7, e48860
5. Mohr E, Kachele I, Mullin C et al. 2002. Rat vasopressin mRNA: a model system to characterize cis-acting elements and trans-acting factors in dendritic mRNA sorting. *Progress in Brain Research* 139, 211-24.
6. Bichet DG, Arthus M-F, Barjon JN, et al. 1987. Human platelet fraction arginine-vasopressin: Potential physiological role. *Journal of Clinical Investigation* 79, 881-887.
7. Laycock JF, Hanoune J 1998. From vasopressin receptor to water channel: intracellular traffic, constraint and by-pass. *Journal of Endocrinology* 159, 361-372.
8. King LS, Yasui M 2002. Aquaporins and disease: lessons from mice to humans. *Trends in Endocrinology and Metabolism* 13, 355-60.
9. Nielsen S, Kwon T-H, Frokiaer J, Agre P 2007. Regulation and dysregulation of aquaporins in water balance disorders. *Journal of Internal Medicine* 261, 53-64.
10. Verkman AS 2011. Aquaporins at a glance. *Journal of Cell Science* 124, 2107-2112.
11. King LS, Choi M, Fernandez PC, Cartron JP, Agre P 2001. Defective urinary-concentrating ability due to a complete deficiency of aquaporin-1. *New England Journal of Medicine* 345, 175-179.
12. Knepper MA, Kwon T-H, Nielsen S 2016. Molecular physiology of water balance. *New England Journal of Medicine* 372,, 1348-1358.
13. McKenna K, Thompson C 1998. Osmoregulation in clinical disorders of thirst and thirst appreciation. *Clinical Endocrinology* 49, 139-152.
14. Prager-Khoutorsky M, Bourque CW 2009. Osmosensation in vasopressin neurons: changing density to optimize function. *Trends in Neuroscience* 33, 76-83.
15. Roberts EM, Newson MJF, Pope GR et al. 2009. Abnormal fluid homeostasis in apelin receptor knockout mice. *Journal of Endocrinology* 202, 453-462.
16. Azizi M, Iturrioz X, Blanchard A et al. 2008. Reciprocal regulation of plasma apelin and vasopressin by osmotoc stimuli. *Journal of the American Society of Nephrology* 19, 1015-1024.
17. Liorens-Cortes C, Moos F 2012. Apelin and vasopressin: two work better than one. *Journal of Neuroendocrinology* 245, 1085-1086.

18. Blanchard A, Steichen O, De Mota N *et al.* 2013. An abnormal Apelin/Vasopressin balance may contribute to water retention in patients with the syndrome of inappropriate antidiuretic hormone (SIADH) and heart failure. *Journal of Clinical Endocrinology and Metabolism* 98, 2084-2089
19. Bourque CW 2008. Central mechanisms of osmosensation and systemic osmoregulation. *Nature reviews Neuroscience* 9, 519-531.
20. Lechner SG, Markworth S, Poole K *et al.* 2011. The molecular and cellular identity of peripheral osmoreceptors. *Neuron* 69, 332-344.
21. Trudel E, Bourque CW 2012. Circadian modulation of osmoregulated firing in rat supraoptic neurones. *Journal of Neuroendocrinology* 24, 577-586.
22. Cunningham JT, Bruno SB, Grindstaff RR *et al.* 2002. Cardiovascular regulation of supraoptic vasopressin neurons. *Progress in Brain Research* 139, 257-73.
23. Ishikawa S, Schrier RW 2003. Pathophysiological roles of arginine vasopressin and aquaporin-2 in impaired water excretion. *Clinical Endocrinology* 58, 1-17.
24. Sun L, Tamma R, Yuen T *et al.* 2016. Functions of vasopressin and oxytocin in bone mass regulation. *Proceedings of the National Academy of Science* 113, 164-169.
25. Aspé-Sánchez M, Moreno M, Rivera, MI *et al.* 2015. Oxytocin and vasopressin receptor gene polymorphisms: role in social and psychiatric traits. *Frontiers in Neuroscience* 9, 510.
26. Dumais KM, Veenema AH 2016. Vasopressin and oxytocin receptor systems in the brain: sex differences and sex-specific regulation of social behavior. *Frontiers in Neuroendocrinology* 40, 1-23.
27. Zimmerman CA, Lin Y-C, Leib DE *et al.* 2016. Thirst neurones anticipate the homeostatic consequences of eating and drinking. *Nature* 537, 680-684.
28. Nishimori K, Young LJ, Guo Q, Wang Z *et al.* 1996. Oxytocin is required for nursing but is not essential for parturition or reproductive behaviour. *Proceedings of the National Academy of Sciences of the USA* 93, 11699-11704.
29. Goodwin TM, Valenzuela GJ, Silver H, Creasy G 1996. Dose ranging study of the oxytocin antagonist atosiban in the treatment of preterm labor. Atosiban Study Group. *Obstetrics and Gynecology* 88, 331-336.
30. Tyzio R, Cossart R, Khalilov I *et al.* 2006. Maternal Oxytocin triggers a transient Inhibitory switch in GABA signaling in the fetal brain during delivery. *Science* 15, 1788-1792.
31. Hammock EAD, Young LJ 2006. Oxytocin, vasopressin and pair bonding: implications for autism. *Philosophical Transactions of the Royal Society of London Behavioral and Biological Science* 29, 2187–2198.
32. LoPara D, Waldman ID 2015. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Molecular Psychiatry* 20, 640-646.

33. Lefevre A, Sirigu A 2016. The two fold role of oxytocin in social developmental disorders: a cause and a remedy? *Neuroscience and Biobehavioral Reviews* 63, 168-176
34. Aghar A , Thornton E *et al.* 2004. Posterior pituitary dysfunction after traumatic brain injury. *Journal of Clinical Endocrinology and Metabolism* 89, 5987-5992.
35. Baylis PH, Cheetham T 1998. Diabetes Insipidus. *Archives of Disease in Childhood* 79, 84-89.
36. Rigoli L, Di Bella C 2012. Wolfram syndrome 1 and Wolfram syndrome 2. *Current opinion in Pediatrics* 24, 512-517.
37. Rouzier C, Moore D, Delorme C *et al.* 2017. A novel CISD2 mutation associated with a classical Wolfram síndrome phenotype alters Ca²⁺ homeostasis and ER-mitochondria interactions. *Human Molecular Genetics* doi: 10.1093/hmg/ddx060. [Epub ahead of print].
38. Rutishauser J, Spiess M, Kopp P 2016. Genetic forms of neurohypophyseal diabetes insipidus. *Best Practice in Clinical Endocrinology & Metabolism* 30, 249-262.
39. Christ-Crain M, Morganthaler MG, Fenske W 2016. Copeptin as a biomarker and a diagnostic tool in the evaluation of patients with polyuria–polydipsia and hyponatremia. *Best Practice & Research Clinical Endocrinology & Metabolism* 30, 235 – 247.
40. Chitturi S, Harris M, Thomsett MJ *et al.* 2008. Utility of AVP gene testing in familial neurohypophyseal diabetes insipidus. *Clinical Endocrinology* 69, 926-930.
41. Kurokawa H, Fujisawa I, Nakano Y *et al.* 1998. Posterior lobe of the pituitary gland; correlation between signal intensity on T1-weighted images and vasopressin concentration. *Radiology* 207, 79-83.
42. Hannon MJ, Orr C, Moran C *et al.* 2012. Anterior hypopituitarism is rare and autoimmune disease is common in adults with idiopathic central diabetes insipidus. *Clinical Endocrinology* 76, 725-728.
43. Bockenbauer D, Bichet DG 2017. Nephrogenic diabetes insipidus. *Current Opinion in Pediatrics* 29, 199-205.
44. Hannsjorg S, Weber S, Komhoff M 2017. Bartter's and Gitelman's syndrome. *Current Opinion in Pediatrics* 29, 179-186.
45. Grunfeld J-P, Rossler BC 2009. Lithium nephrotoxicity revisited. *Nature Reviews Nephrology* 5, 2709-276.
46. Assadi F, Ghane Sharbaf G 2015. Sildenafil for the treatment of congenital diabetes insipidus. *American Journal of Nephrology* 42, 65-69.
47. Waikar SS, Mount DB, Curhan GC 2009. Mortality after hospitalisation with mild, moderate and severe hyponatremia. *American Journal of Medicine* 122, 857-865.
48. Chawla A, Sterns RH, Nigwekar SU, Cappuccio JD 2011. Mortality and serum sodium: do patients die with or from hyponatraemia? *Clinical Journal of American Society of Nephrology* 6, 960-965.

49. Corona G, Giuliani C, Verbalis *et al.* 2015. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. PLOS ONE 10, e0124105. <https://doi.org/10.1371/journal.pone.0124105>.
50. Ball, SG, Iqbal Z 2016. Diagnosis and treatment of hyponatraemia. Best Practice & Research Clinical Endocrinology & Metabolism 30:161-173.
51. Spasovski G, Vanholder R, Allolio B *et al.* 2014. Clinical practice guideline on diagnosis and treatment of hyponatraemia. European Journal of Endocrinology 170, G1–G47.
52. Fenske W, Stork S, Koschker A-C, Blechschmidt K *et al.* 2008. Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. Journal of Clinical Endocrinology and Metabolism 93, 2991-2997.
53. Fenske W, Stork S, Blechschmidt A *et al.* 2009. Copeptin in the differential diagnosis of hyponatremia. Journal of Clinical Endocrinology and Metabolism 94, 123-129.
54. Ball SG 2007. Vasopressin and disorders of water balance: the physiology and pathophysiology of vasopressin. Annals of Clinical Biochemistry 44, 417-431.
55. Rosner MH 2009. Exercise associated hyponatremia. Seminars in Nephrology 29, 271-281.
56. Danz M, Hinkelbein J, Braunecker S 2016. Hyponatraemia among triathletes in the Ironman European championship. New England Journal of Medicine 374, 997-998.
56. Feldman BJ, Rosenthal SM, Vargas GA *et al.* 2005. Nephrogenic syndrome of inappropriate antidiuresis. New England Journal of Medicine 352, 1884-1890.
57. Decaux G, Vandergheynst F, Bouko Y *et al.* 2007. Nephrogenic syndrome of inappropriate antidiuresis in adults: high phenotypic variability in men and women from a large pedigree. Journal of American Society of Nephrology 18, 606-612.
58. Yee AH, Burns JD, Eelco FM, Wijdicks FM 2010. Cerebral salt wasting: pathophysiology, diagnosis and treatment. Neurosurgery Clinics of North America 221, 339-352.
59. Hannon MJ, Behan LA, Brien MMC *et al.* 2014. Hyponatraemia following mild/moderate subarachnoid haemorrhage is due to SIAD and glucocorticoid deficiency and not cerebral salt wasting. Journal of Clinical Endocrinology and Metabolism 99: 291-298.
60. Verbalis JG, Goldsmith SR, Greenberg A *et al.* 2014. Diagnosis, evaluation and treatment of hyponatraemia: expert panel recommendations. The American Journal of Medicine 126, S1-S42.
61. Ball S, Barth J, Levy M 2016. Emergency management of severe symptomatic hyponatraemia in adults. Endocrine Connections 5, G4-G6.
62. Adrogue HJ, Madias NE 2000. Hyponatraemia. New England Journal of Medicine 342, 1581-1589.
63. Mohmand HK, Issa D, Ahmad Z *et al.* 2007. Hypertonic saline for hyponatraemia: risk of inadvertent overcorrection. Clinical Journal American Society of Nephrology 2, 1110-1117.
64. Sterns RH, Hix JK, Silver S 2010. Treating profound hyponatremia: a strategy for controlled correction. American Journal of Kidney Diseases 56, 774-779.

63. Decaux G, Soupart A, Vassart G. 2008. Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet* 371, 1624–32.
64. Gross PA, Wagner A, Decaux G. Vaptans are not the mainstay of treatment in hyponatremia: perhaps not yet. *Kidney International* 2011; 80: 594-600.
65. Bhandari S, Peri A, Cranston I *et al.* 2017. A systematic review of known interventions for the treatment of chronic nonhypovolaemic hypotonic hyponatraemia and a meta-analysis of the vaptans. *Clinical Endocrinology* doi: 10.1111/cen.13315. [Epub ahead of print].
66. Ball SG, Vaidja B, Baylis PH 1997. Hypothalamic adipsic syndrome: diagnosis and management. *Clinical Endocrinology* 47, 405-409.