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and John A.H. Wass ESSENTIALS The posterior pituitary produces arginine vasopressin, which has a key role in fluid homeostasis, and oxytocin, which stimulates uterine contraction during birth and ejection of milk during lactation. Cranial diabetes insipidus is the passage of large volumes (>3 litres/24 h) of dilute urine (osmolality <300 mOsm/kg) due to vasopressin deficient synthesis and/or release. The most common cause is lesions of the neurohypophysis or the hypothalamic me- dian eminence damaging the magnocellular neurons. It is diag- nosed by a water deprivation test revealing urine osmolality less than 300 mOsml/kg with concurrent plasma osmolality more than 290 mOsml/kg after dehydration and with urine osmolality rising to more than 750 mOsml/kg after desmopressin. MRI of the neuro- hypophysis is required to delineate the cause. Mild polyuria can be managed simply by ensuring adequate fluid intake; treatment with the long-acting vasopressin analogue, desmopressin (desamino, D-8 arginine vasopressin; DDAVP), is used for more severe cases. The syndrome of inappropriate antidiuresis is diagnosed when there is hyponatraemia with hypotonic plasma (osmolality <270 mOsm/kg), inappropriate urine osmolality (>100 mOsm/kg) and urinary sodium more than 20 mmol/litre, together with (1) no evidence of volume overload or hypovolaemia, and (2) normal renal, adrenal, and thyroid function. Few patients satisfy these strict criteria, but many conditions (e.g. malignant diseases, chest diseases, central nervous system dis- orders, and drugs) have been implicated. Aside from treatment (when possible) of the underlying cause, management requires fluid restric- tion and (rarely) infusion of hypertonic saline. Blockade of renal vaso- pressin receptors (V2) would be another option. Anatomy of the posterior pituitary gland The posterior pituitary gland, lying dorsally and caudally to the anterior pituitary, is connected by the hollow pituitary stalk to the hypothalamus in the floor of the third ventricle and is sometimes referred to as the neurohypophysis as it acts as an extension of the nervous system.

 In contrast to the anterior pituitary which develops from ecto- derm, is highly cellular, and is connected to the hypothalamus via the circulatory system, the posterior pituitary is derived from fore- brain and consists of nerve fibres which extend directly from the axonal terminals of hypothalamic neurons. The posterior pituitary hormones are

synthesized in the hypothal- amic supraoptic nucleus (located just lateral to and above the optic chiasm) and the paraventricular nuclei (located on each side of the third ventricle). They then migrate along the axons of these neurons as neurosecretory granules in the supraoptic–hypophyseal tract to the posterior pituitary before release into the circulation via branches of the inferior hypophyseal artery. The sensory signals that affect release of vasopressin and oxytocin are accumulated from the afferent fibres of osmoreceptors close to the hypothalamic nuclei, the brainstem, and also from the vagus and glossopharyngeal nerves receiving input from the pharynx and baroreceptors of the heart and great vessels (Fig. 13.2.2.1). The hypothalamic nuclei receive their blood supply from deriva- tives of the circle of Willis: the suprahypophyseal, anterior commu- nicating, anterior cerebral, posterior communicating, and posterior cerebral arteries. The inferior and superior hypophyseal arteries, formed from branches of the internal carotid artery, supply the pos- terior pituitary. The venous supply of the system drains to the dural, cavernous, and inferior petrosal sinuses. Vasopressin and oxytocin: Structure and synthesis Vasopressin and oxytocin have molecular weights of 1087 Da and 1007 Da, respectively, and are both nonapeptides with a disulphide bridge between the cysteine residues at positions 1 and 6 (Fig. 13.2.2.2). Oxytocin differs from vasopressin by only two amino acids with isoleucine for phenylalanine at position 3 and leucine for arginine at position 8. The genes for both these hormones lie 8 kb apart on chromosome 20q13. They encode 145-amino acid pre- cursors comprising a signal peptide, the specific vasopressin, or oxy- tocin sequence, a hormone-specific peptide called a neurophysin, and a C-terminal peptide. The vasopressin precursor also has a glycoprotein at the C-terminus. The hormones are initially packaged in granules as a precursor complex of neurophysin and oxytocin or vasopressin. During transport of these neurosecretory granules to the posterior pituitary, endopeptidases cleave off the active hormone from the neurophysin and the final products are stored in the nerve termini in the gland. The synthesis of vasopressin and oxytocin occurs in separate neurons within the paraventricular and supraoptic nucleus which allows the individual release of hormones. On stimulus of the ap- propriate magnocellular cell body, an action potential propagates along the axon, causing an influx of calcium at the axon terminal and releasing the hormone’s neurosecretory granules into the peri- vascular space. Neurophysin is also released but has no further role after acting as a carrier protein in the neurons. The hormones are unbound in the circulation and their half-life is short, that of vasopressin being about 10 min. They are degraded by endothelial and circulating endopeptidases and aminopeptidases; vasopressin is mainly cleared in the liver and kidneys, while oxytocin is also cleared in the uterus. Oxytocin: Physiology and functions Oxytocin binds to a G protein-coupled cell surface receptor on target cells to mediate a variety of physiological effects, but princi- pally regulation of lactation, parturition, reproductive, and maternal behaviour. It is named after the Greek phrase meaning ‘rapid birth’. It has no known role in men but has been postulated to aid con- traction of the seminal vesicles. In women oxytocin receptors are ex- pressed predominantly in uterine and breast myometrial cells. Their numbers are increased by oestrogen and during pregnancy. The hor- mone causes uterine contraction when cervical dilatation triggers oxytocin release during parturition. It is also released in response Anterior pituitary Posterior pituitary Median eminence Third ventricle Floor of ventricle Optic chiasm Paraventricular nucleus Supraoptic nucleus Brainstem Fig. 13.2.2.1 Schematic representation of the neuronal pathways from the paraventricular and supraoptic nuclei. The nerves project to the posterior pituitary, the median eminence, the floor of the third ventricle, and the brainstem. Afferent fibres from the osmoreceptors and thirst centre are shown. This article was published in Clinical Endocrinology, Besser GM, Thorner MO (eds) pp. 5.1–5.14, © Mosby-Wolfe (2002). s s s s s s NH2 3. Phe 4. Gln 2.

Tyr 5. Cys 7. Pro 8. Arg 9. Gly Desmopressin (1-desamino-8-D-arginine casopressin DDAVP) Oxytocin Argininie vascopressin NH2 5. Cys 7. Pro 8. Leu 9. Gly 4. Glu 3. Ile 5. Cys 7. Pro 8. D-Arg 9. Gly

5. Asn
6. Asn
7. Phe
8. Cys
9. Tyr
10. Glu
11. Tyr
12. Asn
13. Cys
14. Cys Fig. 13.2.2.2 The structure of vasopressin, oxytocin, and desmopressin. Amino acid differences are highlighted in bold.

13.2.2 Disorders of the posterior pituitary gland 2279 to suckling when breast duct smooth muscle contraction leads to ejection of breast milk during breastfeeding. The importance of oxytocin in maintaining milk secretion is demonstrated in trans- genic mice with a knockout of oxytocin synthesis. These animals deliver their young normally, showing the involvement of several other hormones (prostaglandins, endothelins, adrenergic agonists, corticotropin-releasing hormone, glucocorticoids, and cytokines) in the initiation and completion of labour. They also produce their milk normally, demonstrating the role of prolactin. However, the mice are unable to release milk during suckling and the young die of dehydration. Administration of oxytocin to the knockout mothers restores milk secretion and the young survive. Vasopressin: Physiology and functions Vasopressin is also known as antidiuretic hormone (ADH) and these two names relate to the two physiological entities regulated by this hormone: pressure/volume and osmosis. However, there are sep- arate sensory inputs to these two systems and distinct receptors at the end-organs of response. There are three known vasopressin receptors: V1 receptors occur in vascular smooth muscle, V2 receptors are expressed in the col- lecting tubules of the kidney, and V3 receptors on anterior pituitary corticotrophs. The receptors are all seven-transmembrane-domain, G protein-coupled receptors; V1 and V3 signal by inositol phosphate pathways, while the V2 receptor activates adenylate cyclase with an increase in intracellular cAMP. The V2 receptor mediates the prin- cipal physiological effect of vasopressin, that of regulation of water reabsorption in the distal nephron. The presence of selective water channel proteins (aquaporins) in the wall of the distal nephron al- lows reabsorption of water from the lumen along an osmotic gra- dient with excretion of concentrated urine. Eight aquaporins have been cloned so far. The V2 receptor activation and subsequent re- lease of intracellular cAMP results in the insertion of aquaporin- 2 into the apical membrane of the collecting duct. The subsequent movement of water into the cell and renal interstitium accounts for the antidiuretic action of vasopressin. The function of the remaining vasopressin receptors is summarized in Table 13.2.2.1. Activation of the V1 receptor in vascular smooth muscle results in vasocon- striction and a rise in blood pressure with higher concentrations of vasopressin. The V3 receptor acts as one of the central regulators of secretion of ACTH in synergy with corticotropin-releasing hor- mone. In addition, V2 receptors stimulate the production of clotting factor VIII. Vasopressin release occurs in response to three key stimuli: (1) a rise in plasma osmolality, (2) a drop in blood pressure, and (3) a stressful event. These changes are

sensed by osmoreceptors in the hypothalamus and baroreceptors in the heart, aorta, and the great vessels. The principal physiological stimulus is a rise in plasma osmolality detected in the osmoreceptor cells. Figure 13.2.2.3 illus- trates the tight linear positive correlation between the plasma osmo- lality and release of vasopressin and thus, the exquisite sensitivity of this system which maintains plasma osmolality within the narrow range of 285 to 295 mosmol/kg. This correlation also exists between osmolality and thirst. A loss of extracellular water will stimulate vasopressin secretion to conserve water, accompanied by thirst, and a drive to drink. The regulation of thirst by osmolality is more im- portant physiologically than that induced by hypovolaemia. Most humans consume the bulk of their ingested water as a result of rela- tively unregulated fluid intake such as consumption of drinks with food or in tea, coffee, and soft drinks. This explains why in the syn- drome of inappropriate antidiuretic hormone described next, water intake must be consciously restricted to avoid overconsumption. Hypotension stimulates vasopressin release through the activation of baroreceptors in the carotid sinus and aortic arch and low-pressure receptors in the atria and pulmonary venous system. A significant drop in circulating volume (i.e. falls of 5–10% of arterial blood pres- sure), are required to increase vasopressin concentrations. However, in contrast to osmoregulated vasopressin secretion, a progressive decrease in blood pressure produces an exponential increase in plasma vasopressin. The subsequent water retention helps to restore blood volume. Vasopressin is also released under nonspecific stress. Although the precise role of vasopressin in the stress response is unknown, it is classified as a stress hormone as it is released, in re- sponse to, for example, neuroglycopenia, nausea, and emesis among other stimuli. There are also normal physiological states where the system is modified. In pregnancy, there is a resetting of the osmostat such that both increases and decreases in plasma vasopressin occur at an osmolality approximately 10 mosmol/kg less than the normal vaso- pressin concentration/plasma osmolality relationship. Furthermore, Table 13.2.2.1 Vasopressin receptor functions V1 V2 V3 Location Vascular smooth muscle Basolateral membrane of distal nephron Pituitary corticotroph Liver Platelets Central nervous system Function Smooth muscle contraction Increased production of aquaporin-2 and antidiuresis Enhanced ACTH release Stimulation of glycogenolysis Platelet adhesion Neurotransmitter Adapted from Ball SG, Baylis PH (2002). The neurohypophysis. In: Wass JAH, Shalet SM (eds) Oxford textbook of endocrinology and diabetes. Oxford University Press, Oxford.

 during pregnancy, there is degradation of the vasopressin by the pla- cental enzyme cysteine aminopeptidase; despite this, the hormone levels are often normal. Vasopressin concentrations increase with age, as does the response of vasopressin to osmotic stimulation. However, thirst recognition and thus fluid intake is reduced. These changes, along with a lessened ability to excrete a water load, pre- dispose older people to both hypernatraemia and hyponatraemia. Disorders of vasopressin secretion Diabetes insipidus Clinical manifestations and causes This is the passage of large volumes (>3 litres/24 h) of dilute urine (osmolality <300 mosmol/kg) and may be caused by: (1) deficient synthesis and/or release of vasopressin (cranial diabetes insipidus); this is the most common form of polyuric and polydipsic dis- order which occurs mainly due to lesions of the neurohypophysis or the hypothalamic median eminence (usually 80–90% of the magnocellular neurons of the hypothalamus need to be damaged before the manifestations of diabetes insipidus arise), (2) renal resistance to the actions of vasopressin (nephrogenic diabetes insipidus), and (3) excessive fluid intake (primary polydipsia) when the hypotonic polyuria is an appropriate physiological response. A further type of diabetes insipidus is the gestational one and relates to the increased metabolism of vasopressin by the

placental cysteine aminopeptidase. It usually develops in the second or third trimester of pregnancy and remits spontaneously 4 to 6 weeks after delivery. The clinical features of diabetes insipidus are polyuria, polydipsia, nocturia, and, in children, nocturnal enuresis and failure to thrive. The causes of cranial and nephrogenic diabetes insipidus are listed in Box 13.2.2.1. The most common causes of cranial diabetes insipidus are trauma (head injury, neurosurgery) and tumours. Removal of or damage to the posterior pituitary usually results in temporary diabetes insipidus lasting 6 weeks to 6 months as the proximal nerve endings grow out to capillaries in scar tissue formed and resume secretion. As hormone synthesis actually occurs higher up in the hypothal- amus, destruction here or at the level of the upper pituitary stalk or median eminence results in permanent diabetes insipidus. The most common solid tumour to produce diabetes insipidus is a craniopharyngioma. Suprasellar germinomas or pinealomas also commonly cause diabetes insipidus. Metastases to the pituitary 20 Plasma vasopressin (pmol/litre) 15 10 5 0 Lowest detectable level Normal detectable level Plasma osmolality (mosmol/kg) Theoretical threshold of vasopressin release 10 Thirst (cm) 8 4 2 0 Plasma osmolality (mosmol/kg) 6 280 300 320 280 300 320 Fig. 13.2.2.3 The relationship between plasma osmolality and plasma arginine vasopressin concentration, and between plasma osmolality and thirst. AVP concentrations and thirst sensation rise in a linear fashion in relation to plasma osmolality. This article was published in Clinical Endocrinology, Besser GM, Thorner MO (eds) pp. 5.1–5.14, © Mosby-Wolfe (2002). Box 13.2.2.1 Causes of cranial and nephrogenic diabetes insipidus Cranial diabetes insipidus Familial • Vasopressin-neurophysin gene mutations (autosomal dominant) • DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic at- rophy, deafness) (autosomal recessive) • X-linked recessive Acquired • Trauma (head injury, neurosurgery, cerebral hypoxia) • Tumours (e.g. craniopharyngioma, germinoma, pinealoma, metastases) • Inflammatory conditions (e.g. sarcoidosis, Langerhans cell histiocytosis, tuberculosis, lymphocytic hypophysitis, Guillain–Barré syndrome) • Infections (e.g. meningitis, encephalitis) • Autoimmune (antivasopressin neuron antibodies) • Vascular (aneurysm, arteriovenous malformations, infarction, Sheehan’s syndrome, sickle cell disease) • Drug/toxin-induced (e.g. ethanol, snake venom) • Idiopathic Nephrogenic diabetes insipidus Familial • X-linked recessive (V2-receptor defect) • Autosomal recessive (aquaporin-2 defect) • Autosomal dominant (aquaporin-2 defect) Acquired • Drugs (e.g. lithium, demeclocycline) • Metabolic (hypercalcaemia, hypokalaemia) • Chronic renal disease (polycystic kidneys, obstructive uropathy) • Osmotic diuresis (diabetes mellitus) • Infiltrative (e.g. amyloidosis, multiple myeloma, Sjogren’s disease)

 hypothalamic area are more likely to cause diabetes insipidus than a deficiency of anterior pituitary hormones because they lodge in the portal system of the hypothalamus. Lymphoma and infiltration with leukaemia are rare causes of diabetes insipidus. If the thirst centre is destroyed as part of the hypothalamic lesion (whether a tumour or any other cause), dangerous dehydration may ensue. Familial dia- betes insipidus is rare, accounting for approximately 5% of cranial diabetes insipidus, and may be caused by an autosomal dominant mutation in the vasopressin gene in the sequence encoding the precursor molecule or the signal peptide but not the peptide hor- mone itself. It is postulated that this causes abnormal folding of the precursor protein which then accumulates within the neurons and leads to cell death. As the pathology develops over time, diabetes insipidus becomes manifest when approximately 80% of the neurons have been destroyed. This is probably why symptoms are not present at birth but gradually develop between 1 and 6 years of age. Until recently there were two known causes of congenital nephro genic diabetes insipidus, an X-linked recessive mutation of the V2 receptor,

which accounts for 90% of cases, and an autosomal reces- sive mutation of the aquaporin-2 water channels. The two types can be discriminated by an infusion of desmopressin which leads to an increase in blood pressure, and in circulating von Willebrand factor and factor 8 in the autosomal recessive condition. These effects are expressed via V2 receptor signalling and, therefore, will not be seen in the X-linked form. Furthermore, an autosomal dominant muta- tion of the C-terminal intracellular tail of aquaporin-2 has been de- scribed. In all cases, in contrast to familial cranial diabetes insipidus, nephrogenic diabetes insipidus usually presents from birth with poly- uria and hypernatraemia. Without recognition the hypernatraemia, polyuria, vomiting, constipation, fever, irritability, and a failure to thrive may result in long-term cognitive impairment. More com- monly nephrogenic diabetes insipidus is due to acquired metabolic or pharmacological causes. The most common drugs leading to nephro- toxicity and to diabetes insipidus are lithium and demeclocycline. In primary polydipsia, there is inappropriate ingestion of ex- cess fluid. This leads to a slight decrease in plasma osmolality and suppressed vasopressin secretion which results in polyuria. As the kidney can excrete up to 18 litres of dilute urine per day, serum osmolality is usually maintained in the normal range. The volumes of urine passing through the collecting duct reduce inner medulla osmolality and the sustained reduction in vasopressin release leads to less aquaporins in the collecting duct cells. These abnormalities lead to an inability to concentrate urine maximally. This dysfunction returns to normal within days to weeks of decreased fluid ingestion. The syndrome may occur as a behavioural abnormality in patients with psychiatric disease. Diagnosis Diabetes insipidus can be diagnosed by simultaneously measuring serum and urine osmolarity in patients with polyuria (> 3 litres per 24 hours). In the presence of high serum osmolarity (>295 mosmol/litre), normally urine osmolarity should reach approximately 600 mosmol/ litre (urine osmolality/plasma osmolality should be ≥2). After the con- firmation of hypotonic polyuria, history and clinical presentation can provide useful diagnostic information. It should be noted however, that clinical data may be of limited value as patients with a preserved thirst mechanism may not differ biochemically to a significant de- gree. In complete absence of vasopressin, urine can reach a maximum dilution of 50 mosmol/kg and the deficiency will lead to passage of anywhere between 3 and 20 litres of urine in 24 h. With unrestricted access to water, normal circulating volume and sodium concentration are maintained by an intact thirst centre. Cranial diabetes insipidus can be masked by cortisol deficiency as glucocorticoids are necessary for renal excretion of a water load. Therefore, diabetes insipidus may only become manifest with the introduction of corticosteroids. Before the vasopressin axis is investigated, other aetiologies of polyuria such as diabetes mellitus, renal failure, hypokalaemia, and hypercalcaemia should be excluded. Following this, the most common investigation to discriminate normality from the various causes of diabetes insipidus is the water deprivation test (Box 13.2.2.2). This dynamic test assesses the ability to concentrate urine during con- trolled water deprivation and is then followed by an assessment of re- sponse to exogenous vasopressin to confirm renal sensitivity. Cranial diabetes insipidus can be diagnosed with paired urine osmolality Box 13.2.2.2 Water deprivation test Preparation The patient is allowed fluids overnight (if primary polydipsia is suspected, consider fluid deprivation overnight to avoid morning overhydration). A light breakfast is taken at 6.30 a.m.; no tea, coffee, or smoking. Deprivation of fluids for 8 hours (starting from 8:00 a.m.—check weight at the beginning of the test). Measure weight of patient and urine volume hourly during the test. Measure plasma and urine osmolalities every 2–3 hours. At 4:00 p.m. administer desmopressin 2 mcg IM and allow the patient to drink freely. If plasma osmolality >305 mOsm/kg or if 3% loss of body weight with plasma osmolality >305 mOsm/kg, proceed to desmopressin adminis- tration earlier. If the urine output has not decreased and/or urine

osmolality/plasma osmolality <2 but the plasma osmolality has not become concentrated to >295 mOsm/kg, continue water deprivation for a further hour and measure plasma and urine osmolalities –offer desmopressin after this. Continue measuring urine osmolality for the next 4 hours hourly (after the desmopressin administration) and measure hourly urine volumes. Stop test if >3% weight loss occurs. Plasma osmolality >295 mOsm/litre with inappropriately hypotonic urine (urine osmolality/plasma osmolality <2) during the fluid deprivation confirms diabetes insipidus (test is stopped). After administration of desmopressin, urine concentrates >800 mOsm/kg in cases of central diabetes insipidus and <300 mOsm/kg in nephrogenic diabetes insipidus. In partial diabetes insipidus or primary polydipsia, urine concentrates par- tially during the water deprivation (300–800 mOsm/kg) and further in- vestigations are needed (including prolonged water deprivation test or therapeutic trial of desmopressin).

SECTION 13 Endocrine disorders 2282 less than 300 mosmol/kg and plasma osmolality more than 290 mosmol/kg after dehydration; urine osmolality should rise more than 750 mosmol/kg after desmopressin. However, if the urine osmo- lality does not rise more than 300 mosmol/kg after dehydration and desmopressin, nephrogenic diabetes insipidus is confirmed. Patients with primary polydipsia should concentrate urine appropriately after dehydration, without a significant rise in plasma osmolality. There is no contraindication to the test providing the patient is fully hydrated. Interpretation also relies on normal thyroid and adrenal function; if function is impaired, the patient must be adequately treated before undergoing the test. In reality, further investigation is sometimes required, particularly when patients have partial forms of diabetes insipidus. Plasma vaso- pressin is measured directly in response to an infusion of 0.05 ml/kg per min of 5% hypertonic saline for 2 h. In cranial diabetes insipidus, there is no increased vasopressin, whereas in nephrogenic diabetes insipidus the vasopressin level is high with no increased urine osmo- lality. Alternatively, the diagnosis of diabetes insipidus can be made with a therapeutic trial of desmopressin with monitoring of plasma and urine osmolalities and plasma sodium. Patients with primary polydipsia develop progressive dilutional hyponatraemia, whereas those with nephrogenic diabetes insipidus remain unaffected. In cranial diabetes insipidus, there is an improvement in polyuria and polydipsia. Imaging of the neurohypophysis with MRI should also be undertaken to identify any possible cause of cranial diabetes insipidus. Treatment In cranial diabetes insipidus where polyuria is mild (<4 litres/24 h), patients with an intact thirst mechanism can be managed by advising an adequate fluid intake. With more severe symptoms, the treatment is the long-acting vasopressin analogue desmopressin (1-desamino-8-d arginine vasopressin), which acts predominantly on the V2 receptors in the kidney with almost no action at the V1 receptors in vascular smooth muscle. Desmopressin is given orally (100–1000 µg daily), intranasally (10–40 µg daily), or parenterally (0.1–2 µg daily). There is wide individual variation in bioavail- ability and, therefore, dose required for symptom control. Women with pre-existing cranial diabetes insipidus who become pregnant can be treated successfully with oral desmopressin which unlike the native hormone, is resistant to degradation by the cysteine aminopeptidase; the dose may be slightly higher than the one re- quired in the nongravid state. The main adverse effect desmopressin is dilutional hyponatraemia, making monitoring of serum sodium and osmolality essential. In nephrogenic diabetes insipidus, causative drugs should be withdrawn although their effects are not always reversible. High- dose desmopressin (up to 5 µg intramuscularly) can be effective in partial nephrogenic diabetes insipidus. Thiazide diuretics which re- duce urine output by increasing sodium excretion can be helpful. In addition, prostaglandin synthase inhibitors, such as indomethacin may be effective as prostaglandins locally inhibit the renal actions of vasopressin.

Diabetes insipidus with loss of thirst sensation (adipsic dia- betes insipidus) as a result of hypothalamic damage by tumours, infiltrative diseases, or neurosurgical interventions is a challenging condition managed by desmopressin and a prescribed regular fluid intake. These patients need to be monitored with daily weighing and fluid balance. In primary polydipsia, management is difficult, with reduced fluid intake being the only effective treatment; treatment of any underlying psychiatric condition is crucial. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) SIADH is a common cause of hyponatraemia and constitutes normovolaemic hyponatraemia as the increased water is dispersed though all compartments. The increased inappropriate vasopressin secretion leads to inappropriately concentrated urine, dilute plasma, and hyponatraemia with ongoing renal sodium excretion. The diag- nosis is considered when renal, adrenal, and thyroid function are normal; there is no evidence of volume overload or hypovolaemia and the biochemistry is consistent, that is, hyponatraemia and hypotonic plasma (osmolality <270 mosmol/kg), inappropriate urine osmolality (>100 mosmol/kg), and high urinary sodium (>20 mmol/litre). There are many causes (Box 13.2.2.3) and thus the Box 13.2.2.3 Causes of SIADH Malignant disease • Carcinoma (lung, duodenum, stomach, pancreas, bladder, ureter, prostate) • Thymoma • Lymphoma, leukaemia • Mesothelioma • Sarcoma • Carcinoid Chest disease • Infection (pneumonia, tuberculosis, empyema) • Pneumothorax • Asthma • Positive pressure ventilation • Cystic fibrosis Central nervous system disorders • Head injury • Infections (meningitis, encephalitis, abscess) • Tumour • Vascular disorders (haemorrhage, thrombosis) • Guillain–Barré syndrome • Acute intermittent porphyria • Psychosis • Hydrocephalus Drugs • Psychiatric drugs (phenothiazines, monoamine oxidase inhibitors, se- lective serotonin reuptake inhibitors) • Chemotherapy (vincristine, vinblastine, cisplatin) • Thiazides • Anticonvulsants (carbamazepine) • Clofibrate • Chlorpropamide • 3,4-Methylenedioxymethamphetamine (MDMA, ‘ecstasy’) • Lansoprazole Other • Hypothyroidism • Glucocorticoid deficiency • Idiopathic • Abdominal surgery

 diagnosis itself should prompt a hunt for underlying pathology. For further discussion see Chapter 21.2.1. Initially the condition is most often asymptomatic, as devel- opment of hyponatraemia is gradual. However, as sodium falls to 120 mmol/litre or less, it is associated with confusion, drowsiness, and seizures; rapid reduction in sodium or severe hyponatraemia can cause coma and death. Management of the condition is the same whatever the cause or type of SIADH. The underlying cause should be treated appropri- ately, and fluid restriction instituted to between 500 and 750 ml/24 h. This generally restores sodium levels and osmolality within a few days. Very rarely, hypertonic saline infusion may be required if the hyponatraemia is acute and symptomatic. This approach requires great caution because an overly rapid correction of hyponatraemia may cause brain damage, ultimately leading to the osmotic demye- lination syndrome. See Chapter 21.2.1 for further discussion. If the symptoms are not temporary and long-term fluid restric- tion is difficult for the patient, drugs such as demeclocycline that induce nephrogenic diabetes insipidus were used historically and can be effective, but this is no longer an appropriate approach. The most specific treatment for SIADH is to block the V2 receptor in the kidney. Vasopressin receptor antagonists, known as vaptans (e.g. Tolvaptan, a V2-receptor antagonist, and conivaptan, a combined V1/V2-receptor antagonist), can effectively correct hyponatraemia, but caution is required and patients need to be monitored closely in order to avoid rapid correction or overcorrection. Further studies comparing vaptans with other available treatments are needed to de- termine the place of these agents in the management algorithm, and also to assure regarding their safety. A rare but important differential diagnosis of SIADH is cerebral salt wasting. This is a rare complication of pituitary surgery or more commonly occurs after subarachnoid haemorrhage. It tends to occur 5 to 10 days following a neurological

event and is associated with hypovolaemia and hyponatraemia. It must be differentiated from SIADH as the treatments are quite different; fluid replacement in cere- bral salt wasting and fluid restriction in SIADH. The diagnosis of cere- bral salt wasting usually needs central venous pressure measurement as this demonstrates hypovolaemia compared with normovolaemia in SIADH. In cerebral salt wasting, the urinary sodium is often ex- tremely high and the plasma urate and haematocrit may be raised. FURTHER READING Bockenhauer D, Bichet DG (2015). Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol, 11, 576–88. Capatina C, et al. (2015). Diabetes insipidus after traumatic brain in- jury. J Clin Med, 13, 1448–62. Christ-Crain M, et al. (2019). Diabetes insipidus. Nat Rev Dis Primers, 5(1), 54. doi: 10.1038/s41572-019-0103-2. Ellison DH, Berl T (2007). The syndrome of inappropriate antidiuresis. N Engl J Med, 356, 2064–72. Endocrine Society (2016). Guidelines on management of hypopituit- arism. https://www.endocrine.org/news-room/press-release-archives/ 2016/endocrine-society-experts-issue-clinical-practice-guideline-on- hypopituitarism Fenske W, Allolio B (2012). Clinical review: current state and future perspectives in the diagnosis of diabetes insipidus: a clinical review. J Clin Endocrinol Metab, 97, 3426–37. Marlin BJ, et al. (2015). Oxytocin enables maternal behavior by balancing cortical inhibition. Nature, 520, 499–504. Peri A, Combe C (2012). Considerations regarding the management of hyponatraemia secondary to SIADH. Best Pract Res Clin Endocrinol Metab, 26, S16–S26. Peri A (2013). The use of vaptans in clinical endocrinology. J Clin Endocrinol Metab, 98, 1321–32.

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