The polyuric syndromes

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Introduction

Polyuric/hypertonic syndromes include those disorders where the kidney is unable to conserve water as it should and, therefore, the ratio of water to solute in body fluids is reduced. The three major classes of the polyuric syndromes are: solute or osmotic diuresis, central diabetes insipidus, and nephrogenic diabetes insipidus.

(i) Water homeostasis

Renal water handling includes at least three principal processes: water repletion, ADH release, and renal concentrating mechanisms.

The water repletion reaction

The cardinal element of understanding the water repletion reaction includes the following features. First, the system is deliberately redundant. For example, vasopressin release can be driven either by a 2% increase in extracellular fluid osmolality or by a rather larger—approximately 10%—decrease in circulating fluid volume. Second, water acquisition is driven not only by water conservation but also by thirst, the latter being mediated by angiotensin II formed intracerebrally. Finally, stimulation of the oropharyngeal reflex can modulate both vasopressin release and thirst. The negative feedback for the system involves yet another hormone, atrial natriuretic peptide, which suppresses both vasopressin release and angiotensin II release within the central nervous system.

ADH release

Arginine vasopressin is produced predominantly in the supraoptic and paraventricular nuclei of the hypothalamus. The AVP gene includes the exons which encode three peptide regions: one containing a signal peptide and vasopressin, one containing neurophysin II, and one containing glycoproteins. Posterior pituitary hormone biosynthesis thus involves synthesis of a 21 kDa pre-pro-hormone in magnocellular neurons; ribosomal transport, following glycosylation and membrane packaging, down the supraoptical hypothalamic tract as osmotically inactive neurosecretory granules; and storage in the posterior pituitary gland as a complex with neurophysins. The hormone itself is liberated quantally. There is, under normal circumstances, a linear increase in urine osmolality with increases in plasma vasopressin, generally reaching saturation at a plasma vasopressin in the range of 10 pg/ml [1,2].

Renal concentrating mechanisms

The key factors responsible for modulating urinary concentration and dilution, include proximal solute absorption and countercurrent multiplication. The proximal nephron is responsible for the isosmotic absorption of approximately two-thirds of glomerular filtrate. In solute diuresis, the volume of fluid delivered to the loop of Henle is increased dramatically. As a consequence, the ability of the loop to dissociate salt and water absorption is reduced.

The antidiuretic response system can be viewed as beginning with the single effect for countercurrent multiplication. Countercurrent multiplication is initiated by ADH-stimulated absorption of sodium chloride through apical Na/K/2Cl co-transporters in the medullary thick ascending limb. This results in the formation of a maximally dilute urine which is delivered to the early distal convoluted tubule. In the cortical collecting tubule, ADH activates the insertion of aquaporin-2 channels in apical membranes of cortical collecting tubules. These are permeable to water.
but not to urea, thus enriching urea concentration within collecting duct fluid. In the inner medullary collecting duct, urea enters thin ascending limbs (MTAL). Dilution of tubular fluid in thin ascending limbs occurs because NaCl exit occurs more rapidly than urea entry, so that fluid is diluted.

**The MTAL**

ADH increases the expression of Na,K,2Cl co-transport units in apical membranes; it alters the stoichiometry of the latter transporter from 2Na/2Cl to Na,K,2Cl; and it activates apical K channels. The rise in intracellular Cl⁻, in turn, activates basolateral Cl⁻ channels.

Two other factors downregulate the production of cAMP in MTAL cells. These include the calcium-sensing receptor (CaSR), a basolateral membrane molecule, which is activated by increases in extracellular fluid calcium. Activation of the calcium sensing receptor downregulates the activity of adenylate cyclase. Second, PGE₂ binding to basolateral membranes, by way of specific EP₃ receptors, also downregulates cAMP production.

**The collecting duct**

The apical membranes contain the ENaC Na channels and the aquaporin-2 water channels, cAMP prompts insertion of aquaporin-2 channels in apical membranes, and simultaneously activates apical Na⁺ channels.

**Impairment of urinary concentrating mechanisms**

ADH, by way of V₂ receptors, activates Gₛ, a guanine nucleotide-stimulated regulatory protein which enhances the activity of the catalytic subunit of adenylate cyclase. This effect is counterbalanced by PGE₂-mediated enhancement of Gₛ, a guanine nucleotide inhibitory subunit which downregulates the activity of the catalytic subunit of adenylate cyclase. Lithium, hypercalcaemia, hypokalaemia, and obstructive uropathy produce nephrogenic diabetes insipidus largely by impairing the activity of Gₛ.

In the modulation of urinary concentrating mechanisms, hypercalcaemia interferes both with NaCl absorption by the MTAL and with water absorption by the collecting duct, as do increases in prostaglandins. Increases in interstitial osmolality, above and beyond their effect on enhancing PGE₂, also impair directly the rate of salt absorption by the MTAL [3].

(ii) **The hypertonic/polyuric syndromes**

The hypertonic syndromes include those disorders where the ratio of water to solute in body fluids is reduced because: individuals do not have access to free water; and because the kidney is unable to conserve water as it should (polyuric syndromes). Fatality in these disorders is generally referable to cerebral shrinkage and/or circulatory collapse [4].

**Polyuric syndromes**

The three major classes of the polyuric syndromes are:

- *Solute or osmotic diuresis* occurs when the volume of fluid delivered to the loop of Henle is increased because of impaired proximal fluid absorption due to the presence of an unabsorbed solute.
- *Central diabetes insipidus* occurs because of a reduced availability of vasopressin. Reduced vasopressin production occurs when there is damage to the posterior pituitary gland. A form of polyuria related to this may occur in pregnancy, where increases in vasopressinase activity lead to an increase in the rate of vasopressin destruction [5]. Finally, in essential hypernatraemia, there is a reduction in osmoreceptor function, so that patients release vasopressin appropriately in response to volume reduction but not in response to an increase in osmolality.
- *Nephrogenic diabetes insipidus* occurs when the nephron becomes unresponsive to vasopressin.

**Central diabetes insipidus**

For permanent diabetes insipidus to occur, there must be a high section of the neurohypophyseal stalk with irreversible damage to the supraopticohypophyseal tract. In patients who have severe diabetes insipidus, the urine is invariably dilute, but increases significantly with vasopressin administration. In patients with partial diabetes insipidus, the urine may actually be partially concentrated after dehydration, but also rises approximately 30% after ADH therapy. Finally, in patients with nephrogenic diabetes insipidus, the urine is not only dilute but does not increase after vasopressin administration.

For the therapy of central diabetes insipidus, DDAVP is now available in three preparations: intravenous, as aerosol inhalant, and oral tablets. Because of the convenience of administration and because the pressor/antidiuretic ratio of DDAVP is much lower than that of aqueous vasopressin or lysine vasopressin snuff, DDAVP has become the drug of choice. The same statement may be made with respect to oral agents such as chlorpropamide or clofibrate, which potentiate vasopressin release in partial central diabetes insipidus. In general, the bioavailability of oral DDAVP is approximately 5% of intranasal DDAVP and about 0.2% of intravenous DDAVP [3].

**Primary polydipsia and central diabetes insipidus**

It is sometimes difficult to distinguish between individuals who have primary polydipsia and individuals who have central diabetes insipidus. Serum ADH levels, while available commercially, are not yet consistently reliable. Rather, it is easiest to rely on the fact that, in central diabetes insipidus, the serum sodium is invariably over 140 mEq/l, the polyuria is constant, and the 24 h urine volumes are less than 10 l.
Moreover, following water deprivation, there is no increase in urine osmolality until ADH is given.

**Essential hypernatraemia**

This disorder is one in which derangement of osmoreceptor function results in reduced ADH release and reduced thirst with increases in plasma osmolality. By way of contrast, with profound volume contraction, ADH release and thirst are both enhanced. In this disorder, chlorpropamide, which potentiates release of vasopressin, is a useful therapeutic approach.

**Nephrogenic diabetes insipidus**

Nephrogenic diabetes insipidus represents a disorder in which the kidney is unresponsive to vasopressin. The familial variety of nephrogenic diabetes insipidus includes two groups. The X-linked variety (90% of nephrogenic diabetes insipidus cases) is generally referable to a mutation in the V-2 ADH receptor, while the autosomal recessive variety, which is rare, is referable to a mutation in aquaporin-2. The latter group constitutes only 10% of individuals with nephrogenic diabetes insipidus. In both cases, the mutation, either in the V-receptor or in aquaporin-2, results in intracellular trapping either of the receptor or of the aquaporin.

Nephrogenic diabetes insipidus can also be acquired. Disorders such as lithium therapy, hypercalcaemia, hypocalcaemia, and ureteral obstruction all result in unresponsiveness to ADH because of downregulation of Gs. One may also see a polyuric nephrogenic diabetes insipidus-like syndrome in disorders where there is disruption of medullary architecture, for example, in sickle cell trait or sickle cell disease.

Dilution of tubular fluid in the thin ascending limb has been accounted for by assuming that the rate of NaCl diffusion out of thin ascending limbs exceeds the rate of urea transport into tubular fluid of thin ascending limbs. Recent experiments with CIC-K1 knockout mice (CIC-K1 is a Cl− channel mediating Cl− efflux in the thin ascending limb) have caused nephrogenic diabetes insipidus. As such, they provide further evidence for the antidiuretic response model [6].

Therapy for nephrogenic diabetes insipidus generally involves solute restriction. If patients have nephrogenic diabetes insipidus because of lithium toxicity, amiloride therapy, which blocks ENaC, thus preventing lithium entry into principal cells, is also helpful.

**Complications and treatment**

**Hypertonic encephalopathy**

Neurololgic symptoms develop when the serum sodium is 170 mmol/l, with coma and death occurring with serum sodium levels in excess of 200 mmol/l. In 1962, the inadvertent mixing of salt rather than sugar in the formula of newborn infants in a nursery in Binghamton, New York, generally known as the Binghamton disaster, had a fatality rate of over 50% because of hypertonic encephalopathy [4].

In acute hypernatraemia, brain solutes remain normal, and there is a profound reduction in brain water and shrinkage of cell volume. Within 24 h, cells accumulate NaCl and KCl, thus increasing brain solute concentration and minimizing brain shrinkage. By approximately 48 h, the accumulation of organic osmolytes increases intracellular brain solutes even further and restores brain volume to normal. These physiologic responses set stringent boundary conditions for the therapy of hypernatraemia.

**Treatment**

In acute hypernatraemia, osmotic equilibration between brain cells and body water occurs predominantly by water abstraction. Thus, one can reduce the serum sodium by approximately 10 mEq/l daily, which amounts to a reduction in plasma osmolality of about 20 mosm/kg H2O per day. The therapy of choice is normal saline, as the latter fluid is already osmotically dilute with respect to body water in hypernatraemic states. In chronic hypernatraemia, using one-half normal saline should be particularly prudent. Likewise, the rate at which the serum sodium is reduced should be at least half of the rate of correction of Na+ levels in acute hypernatraemia.

**Conclusions**

Disorders of renal water handling are manifested as polyuric syndromes. The three major classes of the polyuric syndromes are: solute or osmotic diuresis, central diabetes insipidus and nephrogenic diabetes insipidus. Complications and fatality in these disorders are a result of hypertonicity and are generally referable to cerebral shrinkage and/or circulatory collapse. Prognosis depends on treatment of hypernatraemia and on specific therapy of the aetiologic factors, wherever it is possible.

**References**