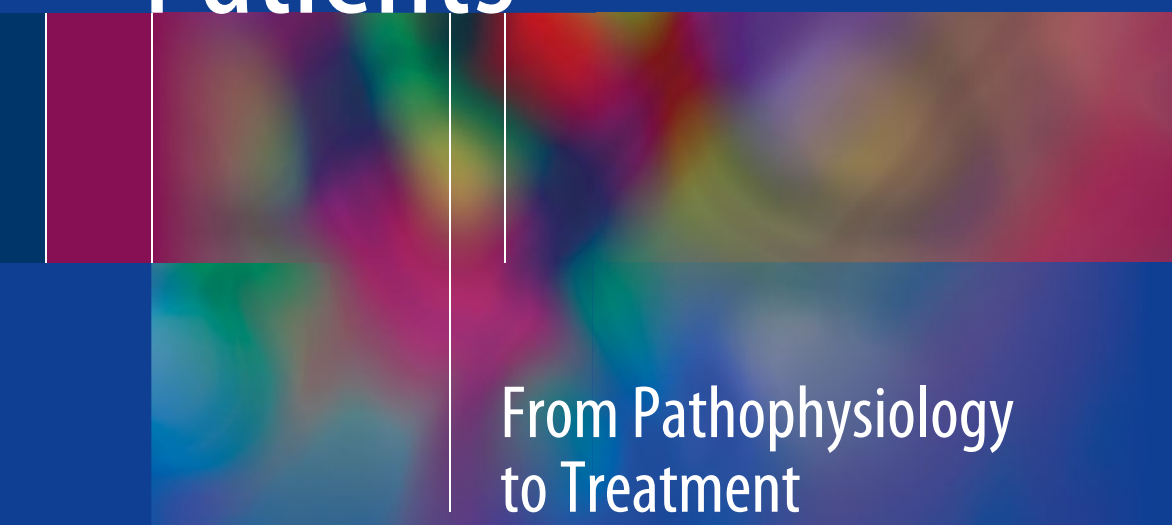
# Metabolic Disorders and Critically Ill Patients



## From Pathophysiology to Treatment

Carole Ichai
Hervé Quintard
Jean-Christophe Orban
*Editors*

Springer

# Metabolic Disorders and Critically Ill Patients

Carole Ichai • Hervé Quintard
Jean-Christophe Orban
Editors

# Metabolic Disorders and Critically Ill Patients

## From Pathophysiology to Treatment

Springer

*Editors*
Carole Ichai
Intensive Care Unit
Hôpital Pasteur 2
Centre Hospitalier Universitaire de Nice
Université Côte d'Azur
Nice
France

Hervé Quintard
Intensive Care Unit
Hôpital Pasteur 2
Centre Hospitalier Universitaire de Nice
Université Côte d'Azur
Nice
France

Jean-Christophe Orban
Intensive Care Unit
Hôpital Pasteur 2
Centre Hospitalier Universitaire de Nice
Université Côte d'Azur
Nice
France

Original French edition published by Springer-Verlag France, Paris, 2012,
ISBN 978-2-287-99026-7

ISBN 978-3-319-64008-2 ISBN 978-3-319-64010-5 (eBook)
https://doi.org/10.1007/978-3-319-64010-5

Library of Congress Control Number: 2017959327



Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Contents

# Part I

# Fluid and Electrolytes Disorders

# Water and Sodium Balance

1

Carole Ichai and Daniel G. Bichet

## 1.1 Introduction

Water is the major constituent of the body. It represents the unique solvant of various molecules (electrolytes) of our body. Although sodium is largely extracellular and potassium is intracellular, body fluids can be considered as being in a single "tub" containing sodium, potassium and water, because osmotic gradients are quickly abolished by water movements across cell membranes [1]. As such, the concentration of sodium in plasma water should equal the concentration of sodium plus potassium in total body water:

$$\left[\mathrm{Na}^{+}\right]\text{in plasma}\,\mathrm{H_2O} = 1.11 \times \left[\left(\mathrm{Na}^{+}\mathrm{e} + \mathrm{K}^{+}\mathrm{e}\right)\right] / \text{total boby}\,\mathrm{H_2O} - 25.6$$

This theoretical relationship was validated empirically by Edelman et al. [2] who used isotopes to measure exchangeable body cations and water. This equation has an intercept (−25.6); the regression line relating plasma sodium to the ratio of exchangeable ($Na^+ + K^+$) to total body water does not pass through zero because not all exchangeable sodium is free in solution. Exchangeable sodium is the major extracellular cation and sodium bound in polyanionic proteoglycans is also found in bone, cartilage and skin [1].

C. Ichai (✉)
Intensive Care Unit, Hôpital Pasteur 2, 30 Voie Romaine, 06001 Nice, Cédex 1, France

IRCAN (INSERM U1081, CNRS UMR 7284), University of Nice, Nice, France
e-mail: ichai@unice.fr

D.G. Bichet
Medicine and Molecular and Integrative Physiology, University of Montreal, Montréal, QC, Canada

Hôpital du Sacré-Cœur de Montréal, 5400 Boul Gouin O, Montréal, QC, Canada, H4J 1C5


C. Ichai et al. (eds.), *Metabolic Disorders and Critically Ill Patients*,
http://doi.org/10.1007/978-3-319-64010-5_1

Both water and sodium balances are physiologically strictly regulated by numerous hormonal, neuronal, and mechanical complex mechanisms in order to maintain intracellular and extracellular volumes constant.

## 1.2 Body Compartments and Water Shifts

### 1.2.1 Body Compartments and their Composition

Total body water (TBW) accounts for 50–70% of the total body weight in healthy adults. This proportion varies according to numerous parameters, such as age, sex and the lean mass/fat mass ratio (lean mass is very poor in water). TBW distributes for 2/3 in the intracellular volume (ICV), and the remaining 1/3 in the extracellular volume (ECV) [3–10].

The ICV is about 40% of total body weight. Potassium ($K^+$) is the most abundant intracellular cation (120 mmol/L), but large amount of proteins contribute also substantially to generate the oncotic pressure. The ECV is distributed into the plasma volume and the interstitial one. In normal physiological conditions, that is, in the absence of heart failure, cirrhosis and nephrotic syndrome, the plasma volume is equivalent to the "effective arterial blood volume" (EABV) which represents 1/4 to 1/3 of ECV, and 5% of the total body weight. In physiological situations, EABV is composed at 93% by water that contains various solutes. Some of them are ionized (anionic and cationic electrolytes) while others are not dissociated (blood urea nitrogen [BUN], glucose). Sodium ($Na^+$) is the most abundant plasma cation and, together with accompanying anions, are the major determinants of the osmotic force developed in the plasma. Non dissociated solutes (albumin, globulins and lipids) contribute for 7% of the plasma volume. The interstitial volume is 3/4 to 2/3 of the ECV, i.e. 15% of the total body weight. Contrary to the plasma volume which is anatomically limited by the capillary endothelium, the interstitial compartment is a less well defined space located around cells, lymph and conjunctive tissues. In terms of composition, the interstitial fluid is an ultrafiltrate of the plasma. Consequently, its composition is close compared to plasma, but due to its negligeable concentration in protein, sodium is quite lower and chloride higher in the interstitial compartment. For the same reasons, and because proteinates are impermeant solutes in the cells, the intracellular concentration in diffusible cations and in total ions is higher in cells: this is the Gibbs-Donnan equilibrium which creates an electrical difference in the membrane potential (Table 1.1).

### 1.2.2 Water and Electrolytes Shifts between the Body Compartments [3–10]

#### 1.2.2.1 Movements across Intracellular and Extracellular Fluids

Water moves freely across the semi-permeable cell membranes according to the osmotic gradient leading to a shift from the low to the high osmotic volume until reaching a transmembrane osmotic equilibrium (Fig. 1.1) [4, 11–15]. Therefore,

**Table 1.1** Main solutes and water composition of the body compartments

| | Extracellular volume | | Red blood cells | Intracellular volume |
|---|---|---|---|---|
| Solutes (mEq/L) | Blood plasma | Interstitial fluid | | |
| $Na^+$ | 142 | 137 | 19 | 10 |
| $K^+$ | 4 | 3 | 9.5 | 155 |
| $Mg^{++}$ | 2 | 2 | 5 | 10 |
| $Ca^{++}$ | 1 | 1 | – | – |
| $Cl^-$ | 105 | 111 | 10 | 10 |
| $HCO_3^-$ | 26 | 30 | 15 | 11 |
| $HPO_4^{2-}/H_2PO_4^-$ | 2 | 2.3 | 110 | 105 |
| $SO_4^{2-}$ | 1 | 1.2 | – | 2 |
| Blood urea nitrogen | 5 | 5 | – | – |
| Glucose | 5 | 5 | Variable | Variable |
| Organic acids$^-$ | 5 | 5 | – | – |
| Proteinates$^-$ | 17 | 0 | 320 | 74 |

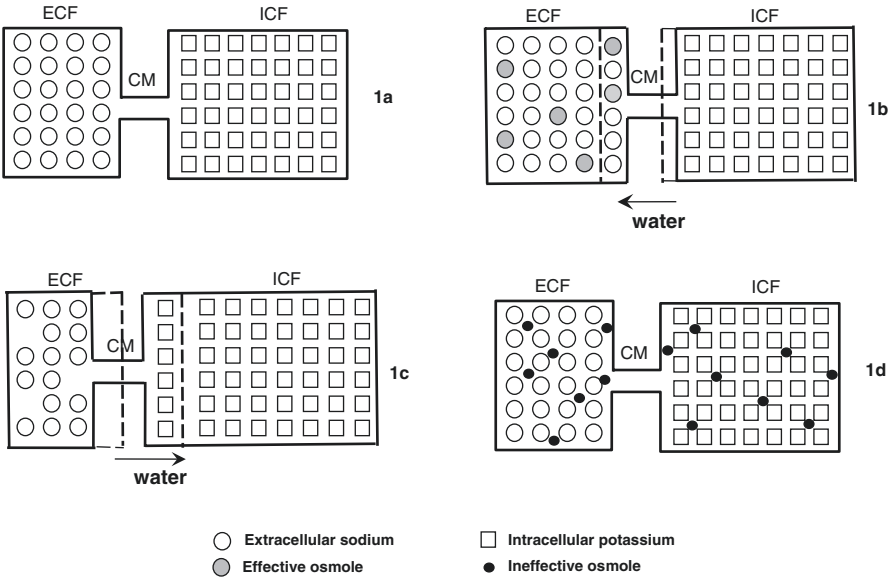



**Fig. 1.1** Water movements between the extracellular (ECV) and intracellular volume (ICV) through the cell membrane (CM). (**a**) Normal volume and distribution of water in the ECV and ICV. The osmotic forces produced by the extracellular effective osmoles (mainly sodium) and the intracellular ones (mainly potassium) are equal, so that there is no osmotic gradient and consequently no water shift across the cell membrane. ECV and ICV are isoosmotic and isotonic. (**b**) Decrease (dehydration) of ICV. The accumulation of effective solutes (sodium or glucose) in the ECF creates an transmembrane osmotic gradient which induces water to cross cell membrane from the ICV to the ECV until reaching the osmotic equilibrium between both compartments. (**c**) Increase (hyperhydration) of ICV. The loss of effective solutes (sodium or glucose) in the ECV creates a transmembrane osmotic gradient which induces water to cross cell membrane from the ECV to the ICV until reaching the osmotic equilibrium between both compartments. (**d**) Normal volume and distribution of water in the ECV and ICV. Ineffective solutes such as urea distributes equally between the ECV and ICV. Thus, osmotic forces developped by the extracellular effective and ineffective osmoles and the intracellular ones are equal, so that there is no osmotic gradient and consequently no water shift across the cell membrane. ECV and ICV are isotonic but hyperosmotic

cell volume (hydration) depends on the solute movements and concentrations between the intracellular and extracellular fluids. $Na^+$-$K^+$-ATPase expressed in all plasma membranes restricts $Na^+$ to the extracellular volume compartment while $K^+$ is maintained intracellularly. This active, ATP-dependent phenomenon, activates a two $Na^+$ efflux for a three $K^+$ influx and creates a transmembrane potential. Because $Na^+$ is the dominating cation in plasma, sodium concentration is the major determinant of plasma osmolality (Posm) and consequently of ICV. Other $Na^+$ cotransporters, symport (with glucose), antiport (with $Ca^{++}$ or $H^+$) are involved in various cell functions such as contractility, pH regulation, but not in the intracellular volume.

Not only $Na^+$, but many particles in the ICV and the ECV generate an osmotic force. However, their ability to induce an osmotic gradient and thus water shifts, depends on their capacity to distribute across the cell membrane [4, 11–15]. Diffusive or "ineffective" solutes such as urea and alcohols, which distribute equally in the ESV and the ICV are unable to promote any substantial osmotic gradient and do not modify cell volume. On contrary, non diffusive or "effective" extracellular solutes, i.e. $Na^+$ and its associated anions, are responsible for a transmembrane osmotic gradient leading to water efflux and cell shrinkage. The osmotic effect of glucose depends on the nature of tissues. Specific transporters (GLUT transporters), allow glucose to penetrate freely in non-insulin requiring tissues like blood cells, immune cells and brain cells. In this case, glucose behaves as an ineffective solute. By contrast glucose requires insulin to enter in the cells of insulin-dependent tissues (myocardium, skeletal muscle, adipose tissue) and is therefore here an effective osmoles that creating an osmotic gradient and ICV dehydration in case of hyperglycemia (insulin deficiency or resistance).

Total plasma osmolarity is defined as the concentration of all solutes (effective and ineffective) in a liter of plasma (mosm/L). Plasma osmolality is also the concentration of all solutes but in a kilogram of plasma water (mosm/kg). Both are very close in physiological situations and usually merged, because water plasma accounts for 93% of 1 l of plasma. Total plasma osmolality can be measured (mPosm [mosm/kg]) in the laboratory using the delta cryoscopic method (freezing point of the plasma) which provides a global value of all osmoles present in the plasma, regardless their normal or abnormal presence and their transmembrane diffusive properties. Posm can be easily calculated at bedside (cPosm [mosm/L]) considering the major electrolytes contained in plasma by the following formula: cPosm [mosm/L] = ([$Na^+ \times 2$] + glycemia + urea) (mmol/L) = 280–295 mosm/L. Because this calculation overrides abnormal (not usually measured) and minor plasma osmoles, mPosm is slightly higher than cPosm. The difference between these two parameters is known as the osmotic gap (OG = mPosm − cPosm), its value is around 10 mosm/L. Plasma tonicity (or effective osmolarity) refers to only major effective osmoles and is calculated using the following formula: P tonicity = [$Na^+ \times 2$) + glycemia] (mmol/L) = 270−285 mosm/L. P tonicity is therefore the best practical parameter for evaluating accurately the ICV [4, 10, 11].

For practical reasons, mPosm which is rarely obtained and cPOsm not calculated in most emergency situations since they are not accurate tools for determining ICV. Plasma tonicity, however, easily evaluates the intracellular hydration (Fig. 1.1). Plasma hypertonicity induces a water efflux from the cells to the ECV across the cell

**Table 1.2** Permeability properties of main plasma osmoles and their impact on osmolarities and intracellular volume

| Solutes | mPOsm (mOsm/kg) | cPOsm (mOsm/L) | P tonicity (mOsm/L) | Intracellular volume |
|---|---|---|---|---|
| *"Effective" osmoles* | | | | |
| Glucose, glycine-glycerol, Histidine-tryptophan-ketoglutarate, hyperosmolar radiocontrast media | Hyperosmolality | Hyperosmolarity | Hypertonicity | Decreased (dehydration) |
| *"Ineffective" osmoles* | | | | |
| Urea alcohol, ethylene glycol, Methanol[a] | Hyperosmolality<br>Hyperosmolality | Hyperosmolarity<br>Isoosmolarity | Isotonicity<br>Isotonicity | Normal<br>Normal |

*mPosm* measured total plasma osmolality, *cPosm* calculated plasma osmolarity
[a]solutes associated with an increased mPosm and osmotic gap

membrane and always indicates a decrease in ICV (Fig. 1.1b). On the opposite, an increased in ICV with cell oedema is secondary to a water influx in cells due to plasma hypotonicity (Fig. 1.1c). The increased plasma concentration of diffusible osmoles induces a comparable hyperosmolarity in both extracellular and intracellular compartments without any osmotic gradient nor water shift as plasma is isotonic (Fig. 1.1d). In this latter situation, mPosm and OG will be useful and guide the diagnosis indicating the presence in plasma of high concentration of abnormal osmoles such as ethylene-glycol, methanol, mannitol, glycine or alcohols (Table 1.2). The precise identification of the additional solute is based on the clinical history and the specific biological measurement not always available in smaller centers.

#### 1.2.2.2 Movements Across Interstitial and Plasma Fluids

Water shifts within the ECV between the interstitial and plasma compartment through the capillary endothelial cells. In physiological situations, this barrier is permeable to water and dissolved solutes, but totally impermeable to proteins which remain in the vascular bed. According to the Starling law, the direction of water movements between these two compartments is determined by the filtration pressure [4, 11–15]. This pressure depends on two opposite forces, the transmural hydrostatic and oncotic pressures: Filtration pressure = (Pc − Pi) - (πp − πi) (mmHg), Pc and Pi are respectively capillary and interstitial hydrostatic pressures, πp and πi are respectively plasma and interstitial oncotic pressures. Because protein remains in the plasma (πp = 10 mmHg), πi is negligeable. Hydrostatic pressures lead to extrude water, while oncotic ones to retain it. Thus, the direction of water flux is different among the localisation of capillary:

– on the arterial side, the high Pc is > Pi + πp and water shifts from the plasma to the interstitial space, allowing the distribution of oxygen, nutriments, hormones to the tissues

– on the venous side, the low Pc is < Pi + πp and the direction of water shift is inverted from the interstitial to the plasma volume allowing the elimination of various tissue wastes.

Interstitial oedema refers to an abnormal extracellular water distribution characterized by a sodium and water accumulation in the interstitial volume. These pathological situations can be the consequence of abnormal filtration pressure as frequently observed in severe hypoalbuminemia (cirrhosis, malnutrition) or abnormal increased vascular permeability related to endothelial cell dysfunction as observed in systemic inflammation or sepsis.

Plasma tonicity is the only accurate tool to assess the intracellular volume. Plasma hypertonicity always indicates an intracellular dehydration and hypernatremia is usually considered as the parameter allowing to assess intracellular volume. If natremia indicates always plasma hypertonicity, this is not the case for hyponatremia which can be associated with iso-, hypo- and hypertonicity (see chapter on dysnatremias). Total body sodium (quantity) which differs from natremia (plasma concentration) is the determinant of extracellular volume. A decreased in total body sodium indicates a low extracellular volume, with low effective arterial blood volume, i.e. hypovolemia.

## 1.3 Body Water Balance and Its Regulation

Preservation of cell volume is fundamental to maintain cell functions and avoid cell death. Variations in cell volume mainly result from changes in extracellular tonicity, but sometimes from modifications in intracellular osmoles concentration induced by metabolic derangements such as hypothermia or hypoxia/ischemia. Therefore, ECV tonicity must be maintained in a stable range thanks to a very narrow control of TBW volume. A close equilibrium between water intake and output allows such a strict regulation resulting in the control of body water homeostasis.

In a 70 kg-male adult, exogenous water is ingested orally and represents 1500–2500 mL/day, which is mostly reabsorbed (for about 90%) in the digestive tube. Daily water excretion is essentially performed by the kidney which produces a mean urine output of 1000–2000 mL/day (0.5–1 mL/kg/day). Water faecal losses are normally negligeable (50–100 ml/day) and insensible water losses (pulmonary and cutaneous) represent 500–1000 mL/day (Fig. 1.2) [4, 6, 11–13].

Body water homeostasis is controlled by three essential mechanisms: (1) the neurohormonal effect of vasopressin which regulates water urinary excretion and the renal sympathetic nerve activity [16], (2) the behavioral sensation of thirst which controls water intake and (3) the capacity of the kidneys to excrete diluted or concentrated urine. These three factors maintain plasma isotonicity despite wide daily variations in salt and water intake. Vasopressin and thirst are mainly triggered by osmotic and baro-volumic neurohormonal stimuli but many non osmotic- non baro/volumic stimuli have also been described [17].

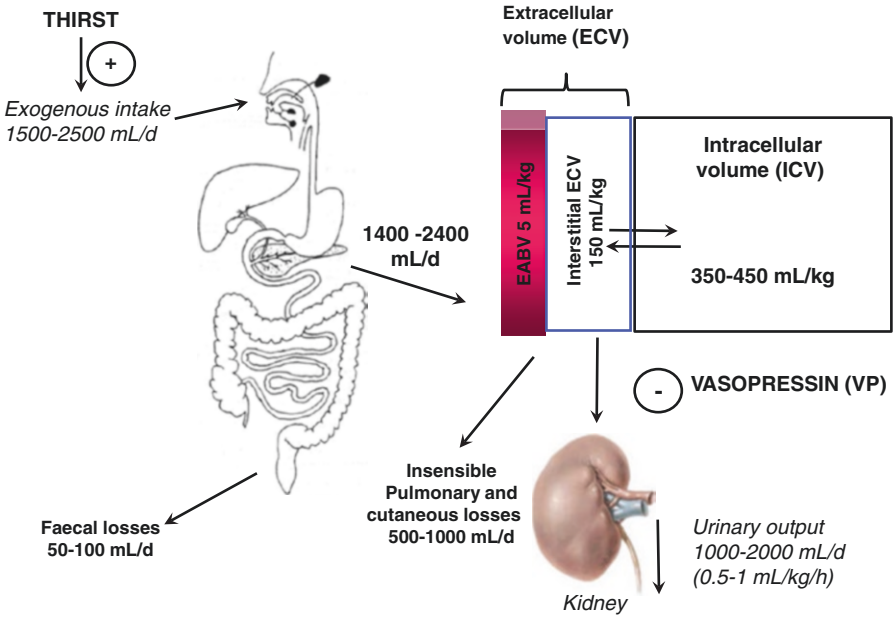



**Fig. 1.2** Water balance and its major regulating mechanisms in a 70 kg adult. Water intake coming essentially from the exogenous drinks is equilibrate by water output. By regulating urine output, kidney plays an essential role in total body water balance. After its ingestion, water is massively reabsorbed by the gastrointestinal system and is further distributed in body compartments. Water homeostasis is mainly maintained thanks to vasopressin which controls urine output, and thirst which controls water oral intake

## 1.3.1 Regulation of Vasopressin Release and Thirst

### 1.3.1.1 Osmotic Regulation

Vasopressin, a nonapeptide hormone, is synthetized by magnocellular neurons located in the supraoptic (SOV) and paraventricular nuclei (PVN) of the anterior hypothalamus. Vasopressin is then transported along axons to be stored and released in the posterior pituitary. Vasopressin is also released from dendrites in the PVN and alters the function of pre-autonomic neurons in the PVN [18]. Specialized osmoreceptor structures are located at the BBB interface in the lamina terminalis in the anterior and dorsal wall of the third ventricle. Among these circumventricular organs (CVOs), the subfornical (SFO) and the organum vasculosum of the lamina terminalis (OVLT) are strategically placed to sense plasma osmotic signals. Tonicity is perceived specifically by these neuronals groups. All cells of an organism are responding to dehydration or to hyperhydration by changing their volume but cells of the subfornical organ (SFO), organum vasculosum of the lamina terminalis (OVLT), median preoptic nucleus (MnPO) are "perfect" osmoreceptors, that is, their changes in volume are maintained as long as the osmotic stimulus persists [19] (Fig. 1.3a). Cell shrinking during dehydration is mechanically coupled to the activation of Transient Receptor Potential Vanilloid (TRPV) channels through a denseley

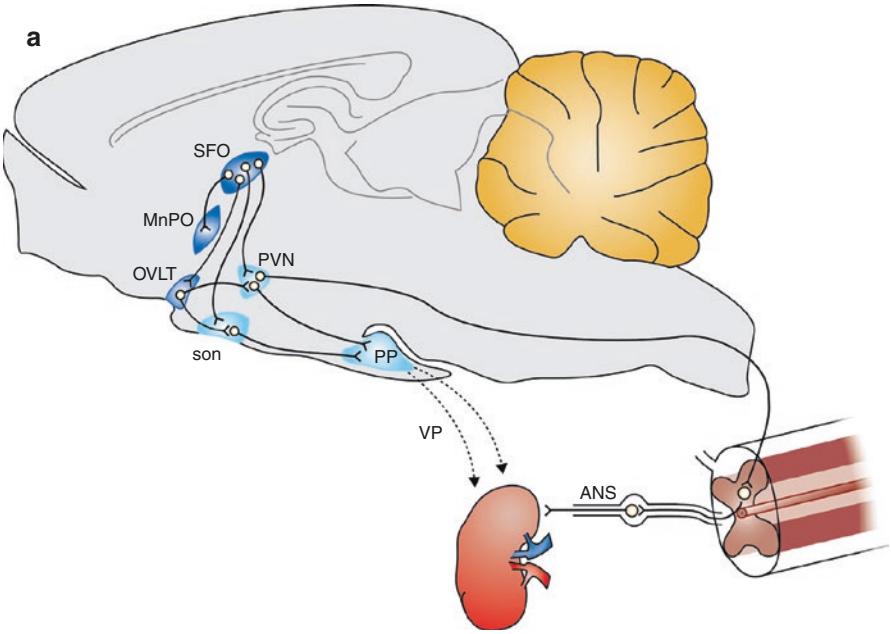



**Fig. 1.3** Major osmoregulatory areas and pathways, of the central nervous system involved in mamalian. (**a**) Schematic representation of the osmoregulatory pathway of the hypothalamus (sagittal section of midline of ventral brain around the third ventricle in mice). Neurons (*lightly filled circles*) in the lamina terminalis (OVLT), median preoptic nucleus (MnPO) and subfornical organ (SFO) - that are responsive to plasma hypertonicity send efferent axonal projections (*black lines*) to magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON). The axons of these magnocellular neurons form the hypothalamo-neurohypophyseal pathway that courses in the median eminence to reach the posterior pituitary, where neurosecretion of vasopressin and oxytocin occurs. Dendritic vasopressin release during dehydration will stimulate sympathetic preautonomic cells in the PVN and directly increased renal nerve stimulation, a central integrated response to restore tonicity and volume. Modified from Wilson Y et al. [67] with permission. (**b**) Cell autonomous osmoreception in vasopressin neurons. Changes in osmolality cause inversely proportional changes in some volume. Shrinkage activates transient receptor vanilloid-type (TRPV1) channels and the ensuing depolarization increases action potential firing rate and vasopressin (VP) release from axon terminals in the neurohypophysis. Increased VP levels in blood enhance water reabsorption by the kidney (antidiuresis) to restore extracellular fluid osmolality toward the set point. Hypotonic stimuli inhibit TRPV1. The resulting hyperpolarization and inhibition of firing reduces VP release and promotes diuresis. Modified from Prager-Khoutorsky M et al. [19] with permission. (c) Osmoregulatory circuits in the mammalian brain and the periphery. Neurons and pathways are color-coded to distinguish osmosensory, integrative and effector areas. Afferent pathways from the OVLT to ACC are responsible for thirst perception. Central preautonomic neurons in the PVN are responsible for the increased renal sympathetic activity mediated by perception of dehydration by magnocellular cells in closed proximity (see Fig. 1.3a). *ACC* anterior cingulate cortex, *AP* area postrema, *DRG* dorsal root ganglion, *IML*, intermediolateral nucleus, *INS* insula, *MnPO* median preoptic nucleus, *NTS* nucleus tractus solitarius, *OVLT* organum vasculosum laminae terminalis, *PAG* periaqueductal grey, *PBN* parabrachial nucleus, *PP* posterior pituitary, *PVN* paraventricular nucleus, *SFO* subfornical organ, *SN* sympathetic nerve, *SON* supraoptic nucleus, *SpN* splanchnic nerve, *THAL* thalamus, *VLM* ventrolateral medulla. Reproduced from Bourque CW [17] with permission

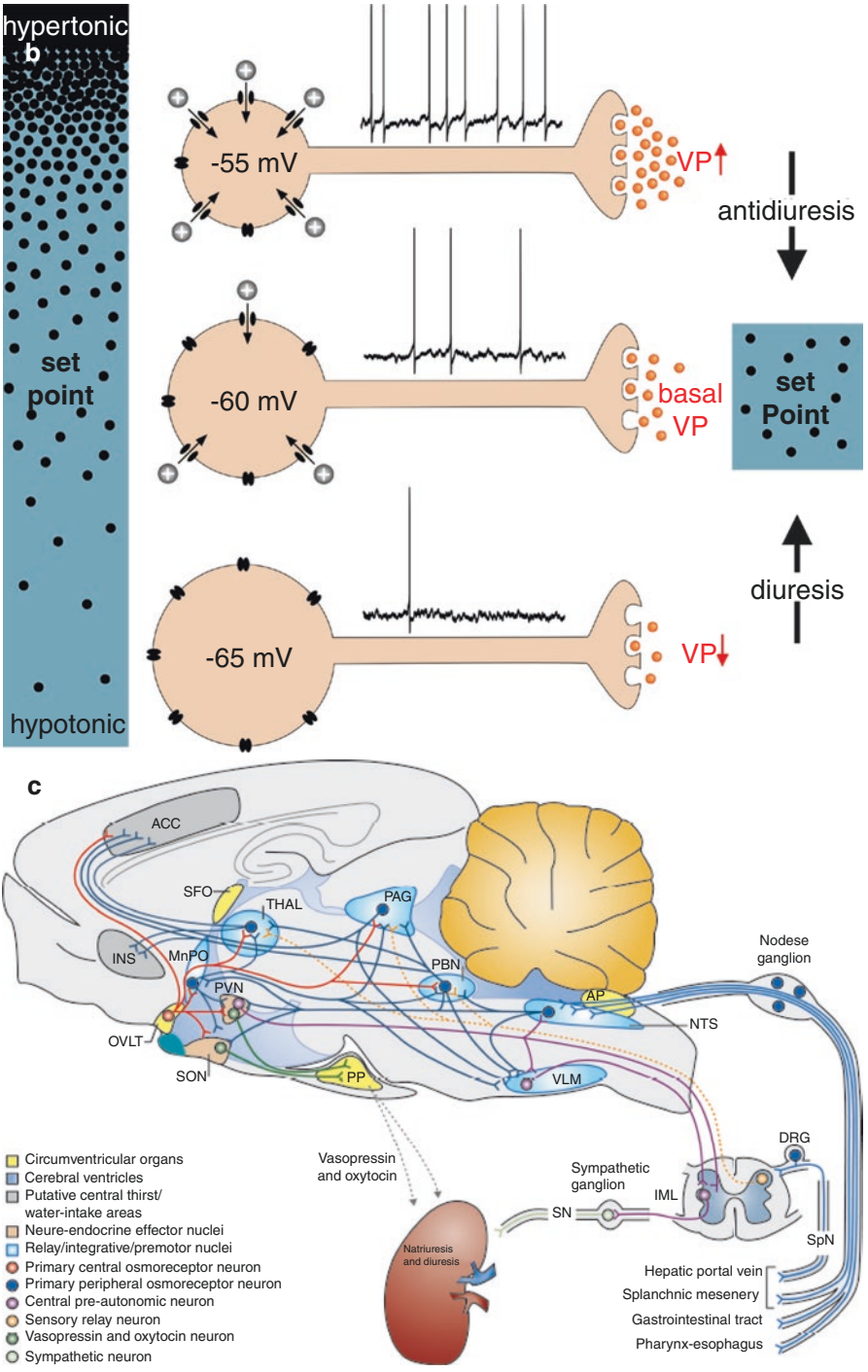



**Fig. 1.3** (continued)

interweaved microtubule networks present only in osmosensitive cells [19] including excitatory thirst neurons from the SFO [20]. These excitatory SFO neurons project to the magnocellular cells of the SON and PVN producing vasopressin and, as a consequence, these neurosecretory cells will be depolarized and vasopressin will be released both from axonal and dendrites terminals. Dendritic vasopressin release during dehydration will stimulate sympathetic pre-autonomic cells in the PVN and directly increased renal nerve stimulation, a central integrated response to restore tonicity and volume [16]. Vasopressin producing cells in SON and PVN also bear TRPV1 channels, they depolarize during dehydration and hyperpolarize during overhydration. The net result of depolarization will be vasopressin release (Fig. 1.3b).

Thirst cells of the anterior wall of the third ventricle also project to two concious areas, the anterior cingulate cortex and the insula delivering a concious assessment of the dehydration state and, probably, of the necessary water volume to quench thirst. This is a unique situation where tonicity is consciously perceived, analogous to the hunger perception. Also thirst promoting neurons transmit negative valence teaching signals that are actively avoided in experimental animals [22] (Fig. 1.3c).

The OVLT, SFO, MnPO and the pituitary gland do not have a blood brain barrier, that is their capillary endothelium is fenestrated and allows a full exposure to plasma osmotic and hormonal variations including angiotensin II. Excitatory thirst neurons of the SFO specifically expressed AT1 angiotensin receptors [21] most probably explaining the osmoregulatory gain observed with increased circulating plasma levels of angiotensin [23]. This osmoregulatory gain is clinically important since, for the same osmotic stimulus, more vasopressin will be released when plasma angiotensin II is elevated, a common situation seen with hypotension and decreased effective blood volume of heart failure and decompensated cirrhosis, where hyponatremia with high vasopressin levels are often observed.

Hepatic sensory neurons also function as osmoreceptors: they express TRPV4 channels and signal hypo-osmotic stimuli from portal blood via the thoracic dorsal root ganglia with connections to vasopressin producing cells. This explains why liver transplant patient's osmolality is significantly higher as compared to normal subjects, since, in these liver denervated transplant patients, there is no inhibition of central vasopressin release by portal hyposmolality [24]. These portal osmoreceptors can signal changes in blood osmolality well before water intake impacts systemic blood osmolality.

Because of the confines of the skull, brain cell tolerance to volume changes is very narrow and only a small degree of brain swelling or shrinkage is compatible with life. As underlined recently by Sterns [1], although osmotic disturbances affect all cells, clinical manifestations of hyponatremia and hypernatremia are primarily neurologic, and rapid changes in plasma sodium concentrations in either direction can cause severe, permanent, and sometimes lethal brain injury. Tonicity changes as small as 1–2% alter vasopressin release with a threshold around 280 mOsm/kg in humans and a progressive increase with increasing osmolality. Under a value of 280 mosm/kg, plasma vasopressin concentration is below the detection limit of sensitive radio-immunoassays. The threshold of thirst sensation, using a visual analogue scale, has been reported for a long time to be 10 mOsm/kg higher than the vasopressin release one, i.e. 290–295 mOsm/kg [4, 11, 24, 25]. However, recent data strongly suggest that both are very close. As observed with vasopressin release, thirst sensation increases linearly with the increase

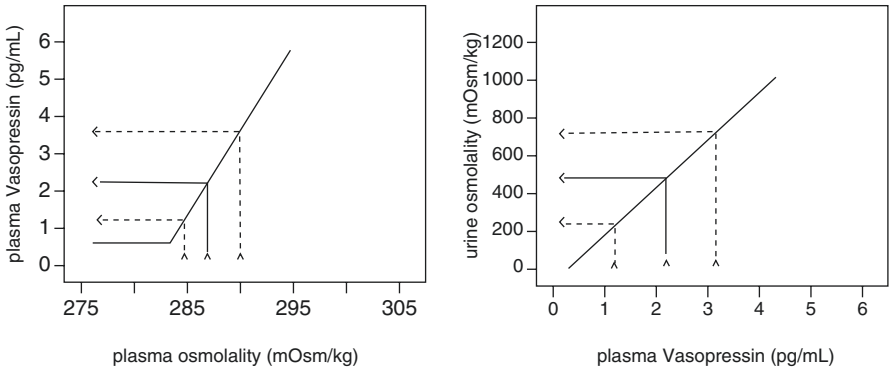



**Fig. 1.4** Schematic representation of the effect of small alterations in the basal plasma osmolality on (*left*) plasma vasopressin and (*right*) urinary osmolality in healthy adults. Modified from Robertson GL et al. [68] with permission

in systemic tonicity [30]. The exquisite sensitivity and gain of the osmoreceptor–AVP–renal reflex is given by the following example (Fig. 1.4). A normally hydrated man may have a plasma osmolality of 287 mmol/kg, a plasma vasopressin concentration of 2 pg/mL and a urinary osmolality of 500 mmol/kg. With an increase of 1% in total body water, plasma osmolality will fall by 1% (2.8 mmol/kg), plasma AVP will decrease to 1 pg/mL and urinary osmolality will diminish to 250 mmol/kg. Similarly, it is only necessary to increase total body water by 2% to suppress the plasma AVP maximally (<0.25 pg/mL) and to maximally dilute the urine (<100 mmol/kg). In the opposite direction, a 2% decrease in total body water will increase plasma osmolality by 2% (5.6 mmol/kg), plasma AVP will rise from 2 to 4 pg/mL and urine will be maximally concentrated (>1000 mmol/kg). Thus, in the context of these sensitivity changes, a 1 mmol rise in plasma osmolality would be expected to increase plasma AVP by 0.38 pg/mL and urinary osmolality by 100 mmol/kg. Such a small change in plasma osmolality (measured by freezing point depression) or plasma AVP (by radioimmunoassay) may be undetectable yet of extreme physiological importance. For example, a patient with a 24-h urinary solute load of 600 mmol must excrete 6 l of urine with an osmolality of 100 mmol/kg to eliminate the solute; however, if the urine osmolality increases from 100 to 200 mmol/kg (due to an undetectable rise of 1 mmol in plasma osmolality and 0.38 pg/mL in plasma AVP), the obligatory 24-h urine volume to excrete the 600 mmol solute load decreases substantially from 6 to 3 l. The upper limit for water intake is dependent of the total osmoles to be excreted and of the minimal urine osmolality: 24 liters per day could be excreted if minimal urine osmolality is 60 with 1200 mOsm to be excreted. During dehydration, with the same osmotic load to be excreted and a maximal urine osmolality of 1200 mOsm, 1 l of urine will be excreted. As a consequence, the development of severe systemic hypertonicity is rare, except in case of primary abnormalities of thirst sensation (hypo- or adipsia) or in patients who have no access to water (coma, digestive aspiration).

There are differences in sensitivity of VP release depending on the sex. It is now well established that male presents a higher osmotic sensitivity than female, regardless their menstrual cycle. Despite an accepted role of gonadal steroids hormones,

the precise mechanism of these differences remain complex. Testosterone has been reported to increase VP synthesis and release, while estrogen seems to confer opposite effects. This could be in relation with the presence of two types of estrogen receptors in the magnocellular neurons (ER α and β) and the level of exposure to both oestradiol and progesterone. However, estrogen lowers renal tubular sensitivity to VP in the same time. Vasopressin release and thirst are not equally sensible to all solutes. Indeed sodium and its cations confer a strongest osmotic powerful stimulation than non ionic osmoles (glucose for example).

#### 1.3.1.2 Baroregulation

It is now well established that afferent neural impulses arising from stretch receptors in the left atrium, carotid sinus and aortic arch inhibit the secretion of vasopressin. Conversely, when the discharge rate of these receptors is reduced, vasopressin secretion is enhanced (for review, see Norsk [26]). Moreover, the relative potency of the cardiac and sino-aortic reflexes in the release of vasopressin appears to vary among species. For example, the increase in plasma vasopressin that occurs during moderate hemorrhage in the dog is attributable primarily to reflex effects from cardiac receptors; sino-aortic receptors appear to exert only minor influences on vasopressin release in this situation. In contrast, sino-aortic receptors appear to play the dominant role in eliciting vasopressin secretion during blood loss in nonhuman primates and humans [26]. In humans, blood pressure reductions of as little as 5%, induced by the ganglion blocking agent trimetaphan, significantly altered plasma arginine vasopressin concentration [27]. Furthermore, an exponential relationship between plasma vasopressin and the percentage decline in mean arterial blood pressure has been observed with large decreases in blood pressure (Fig. 1.5). Since an interdependence exists between osmoregulated and baroregulated arginine

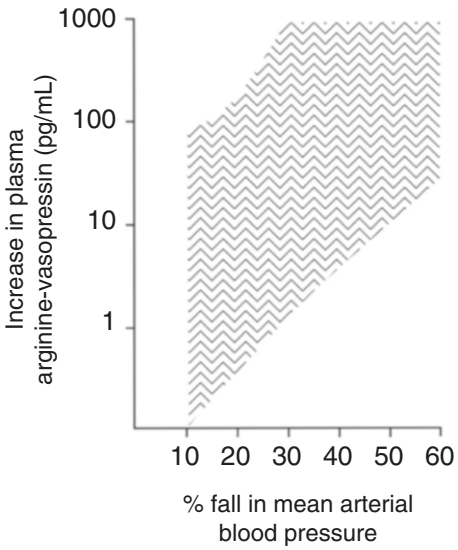



**Fig. 1.5** Increase in plasma arginine vasopressin AVP during hypotension. Note that a large diminution in blood pressure in normal humans induces large increments in AVP. Reproduced from Zerbe GL et al. [69] with permission

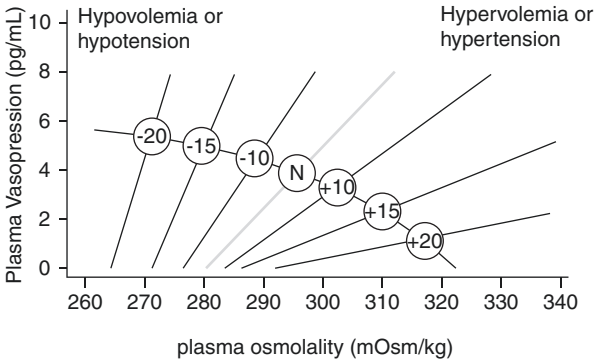



**Fig. 1.6** Schematic representation of the relationship between plasma vasopressin and plasma osmolality in the presence of differing states of blood volume and/or pressure. The line labeled N represents normovolemic normotensive conditions. Minus numbers to the left indicate percent fall, and positive numbers to the right, percent rise in blood volume or pressure. Reproduced from Vokes TP et al. [70] with permission

vasopressin secretion [28] (Fig. 1.6), under conditions of moderate hypovolemia, renal water excretion can be maintained around a lower set-point of plasma osmolality, thus preserving osmoregulation. As hypovolemia becomes more severe, plasma arginine vasopressin concentrations attain extremely high values and baroregulation overrides the osmoregulatory system. An enhanced osmoreceptor sensitivity, but blunted baroregulation, has been described in elderly subjects [29].

### 1.3.1.3 Hormonal Influences on the Secretion of Vasopressin

Studies on the direct effects of various peptides and other biological substances on the release of vasopressin may be confounded by the hemodynamic effects of these substances, which indirectly modulate vasopressin release via the cardiovascular reflexes. For example, the infusion of pressor doses of norepinephrine increases both arterial blood pressure and left atrial pressure. Each of these changes is capable of eliciting a reflex inhibition of vasopressin release which should reduce plasma vasopressin. However, the inhibitory effects of the sino-aortic and cardiac reflexes on vasopressin release seem to be offset by the direct stimulatory effect of circulating norepinephrine. A similar situation may exist with the possible stimulation of vasopressin release by angiotensin. The direct stimulatory effect of angiotensin may be offset by inhibitory influences elicited from the cardiovascular reflexes. Angiotensin is a well-known dipsogen and has been shown to cause drinking in all the species tested [30]. Morton et al. [31] submitted six normal subjects to a 3-day diet containing 10 mmol of sodium and 60 mmol of potassium per day. The mean cumulative sodium loss (±SD) for the six subjects was 208 ± 94 mmol. Sodium restriction had no effect on serum sodium concentrations. Sodium depletion increased the circulating concentrations of angiotensin II more than fivefold ($p < 0.001$), but had no effect on plasma arginine vasopressin concentrations. In short, physiologic concentrations of angiotensin II do not cause an increase in plasma vasopressin concentration in normal subjects.

The presence of endogenous opioid peptides and opioid receptors in the neural lobe has led to the suggestion that opioid peptides play a role in the release of neurohypophyseal hormones [32]. It is now recognized that opioid drugs exert their pharmacologic effects through an interaction with specific receptors. These receptors are classified into several types: μ, δ, σ and κ. μ Agonists such as morphine and methadone are responsible for the classical opiate effects of analgesia, respiratory depression, and physical dependence. They typically cause an antidiuresis in hydrated animals and humans [33]. In contrast, κ agonists have analgesic properties, but do not cause respiratory depression nor physical dependence at the dose required for analgesia. They have been shown to cause a water diuresis in experimental animals and in humans, probably by the inhibition of vasopressin secretion [34]. *K* opioid agonists could have potential therapeutic benefits in the treatment of hyponatremia secondary to increased arginine vasopressin secretion.

Neuropeptides such as neurotensin or cholecystokinine activates the stretch-inactivated cation channels mainly by a G-protein cellular transductive message and cause vasopressin release and thirst. A very rapid and robust release of arginine vasopressin is seen in humans after cholecystokinin (CCK) injection [35]. Nitric oxide is an inhibitory modulator of the hypothalamo–neurohypophysial system in response to osmotic stimuli [36]. Vasopressin secretion is under the influence of a glucocorticoid-negative feedback system and the vasopressin responses to a variety of stimuli (haemorrhage, hypoxia, hypertonic saline) in normal humans and animals appear to be attenuated or eliminated by pretreatment with glucocorticoids [37]. Finally, nausea and emesis are potent stimuli of arginine vasopressin release in humans and seem to involve dopaminergic neurotransmission [38]. The osmotic stimulation of arginine vasopressin release by dehydration or hypertonic saline infusion, or both, is regularly used to test the arginine vasopressin secretory capacity of the posterior pituitary (Fig. 1.7a). This secretory capacity can be assessed directly by comparing the plasma arginine vasopressin concentration measured sequentially during a dehydration procedure with the normal values and then correlating the plasma arginine vasopressin with the urinary osmolality measurements obtained simultaneously [39]. Copeptin, the C-terminal part of the arginine vasopressin precursor peptide, has been found to be a stable surrogate marker of arginine vasopressin release [40] and a useful measurement in the differential diagnosis of polyuric states [41]. The AVP release can also be assessed indirectly by measuring plasma and urine osmolalities at regular intervals during the dehydration test [42] (Fig. 1.7b). The maximum urinary osmolality obtained during dehydration is compared with the maximum urinary osmolality obtained after the administration of 1-desamino[8-D-arginine]vasopressin [desmopressin (dDAVP]) (1–4 μg sc or intravenously during 5–10 min). The nonosmotic stimulation of AVP release can be used to assess the vasopressin secretory capacity of the posterior pituitary in a rare group of patients with the essential hypernatremia and hypodipsia syndrome [43]. Although some of these patients may have partial central diabetes insipidus, they respond normally to nonosmolar AVP release signals such as hypotension, emesis, and hypoglycemia. In all other cases of suspected central diabetes insipidus, these nonosmotic stimulation tests will not give additional clinical information.

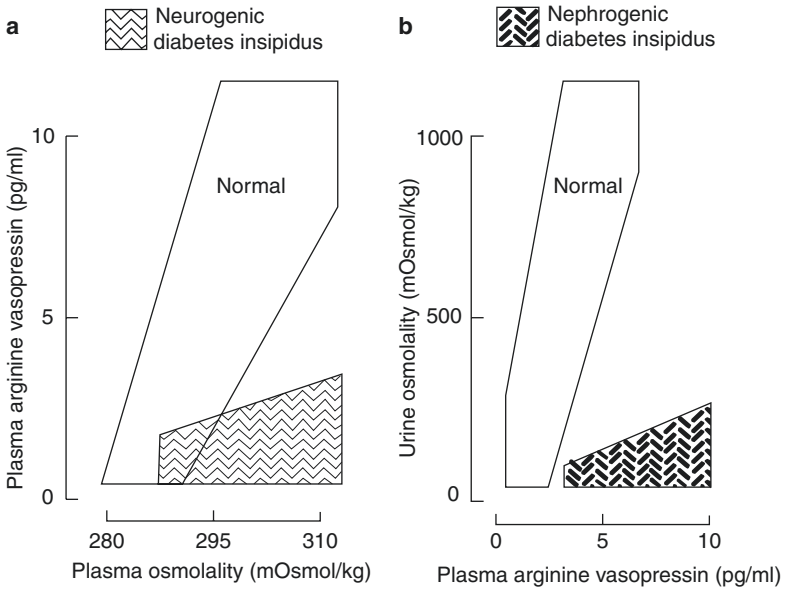



**Fig. 1.7** Direct, measurements of vasopressin, and indirect, measurements of urine osmolality, evaluations of vasopressin secretion during dehydration (**a**) or hypertonic saline infusions testing (**b**)

In summary, vasopressin secretion and thirst perception and quenching, and the ability of the kidney to respond to vasopressin are key regulators of water balance. In the thirst centers, cell shrinking during dehydration is mechanically coupled to the activation of Transient Receptor Potential Vanilloid (TRPV) channels and lead to the depolarization of vasopressin neurosecretory neurons and to the central and systemic release of vasopressin. These tonicity and vasopressin producing cells are outside the blood brain barrier and angiotensin II is augmenting the gain of osmoreceptors cells, that is, augmenting vasopressin release for the same osmotic stimulus. Low blood pressure and its perception by other stretch receptors is also a potent baro-regulator of vasopressin release during hypotension or low effective arterial blood volume. Thus, over and above the multifactorial processes of excretion water balance is dependent of a complex multiple control system orchestrated by the brain.

### 1.3.2 Regulation of Renal Water Excretion by Vasopressin

After its release in the systemic circulation, VP is delivered to the kidneys to control water excretion via urine output. Water reabsorption in the proximal convoluted tubule is passive, but the cell membrane becomes impermeable in the distal tubule while sodium reabsorption persists. Vasopressin activates an active free-water reabsorption by renal cells of the limb of Henle and distal tubule thanks to a binding with three types of

receptor [44]. Vasopressin acts mainly through renal V2 receptors (V2R), which are located on the basal cell membrane of the collecting duct. Vasopressin binding to these receptors is coupled with a G-protein activation. This promotes a cascade of reactions resulting in an increased intracellular cyclic AMP (cAMP) production and the expression of water channels; i.e. aquaporins. Aquaporins were first identified in the 1990s [45]. This large ubiquitous family of transmembrane proteins is mainly involved in water and neutral solute trafficking. Based on their functional properties and their primary aminoacid sequences, AQPs are divided into three subgroups: (1) AQP 0, 1, 2, 4, 5, 6, 8 are water channels; (2) AQP7 is an aquaglyceroporin permeable to small neutral molecules; (3) AQP3, 7, 9, 10 are implicated in urea, glycerol, and water movements; (4) AQP11, 12 are superaquaporins [46, 47] (Fig. 1.8). All of the AQPs are characterized by a common tetrameric structure which includes six transmembrane domains, an alpha helix connected by five loops, intracellular amino- and carboxyl-terminal domains associated with twofolded loops. This represents the intrasubunit of each subunit. Water passes essentially through the central pore in the middle of the tetramer subunit, while ions may cross the channel through individual subunit pore pathways [8, 46, 48].

Vasopressin-regulated channels responsible for water permeability of collecting duct are AQP2. They are highly selective and specific water channels (Fig. 1.9).

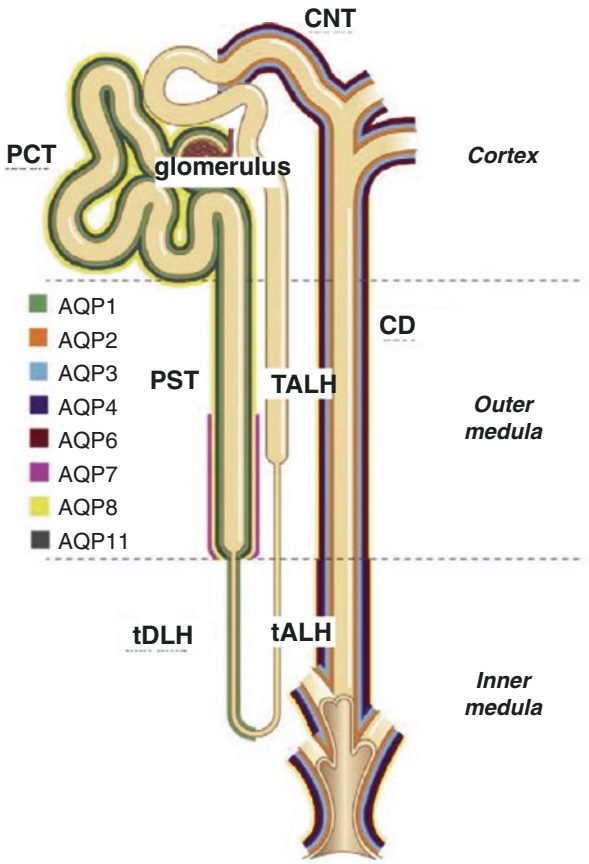



**Fig. 1.8** Expression of renal aquaporins along the nephron. *CD* collecting duct, *CNT* connecting tubule, *PCT* proximal convoluted tubule, *PST* proxima straight tubule, *tALH* thin ascending loop of henle, *tDLH* thin decending loop of Henle, *TALH* thick ascending loop of Henle. Modified from Kortenoeven ML et al. [50] with permission

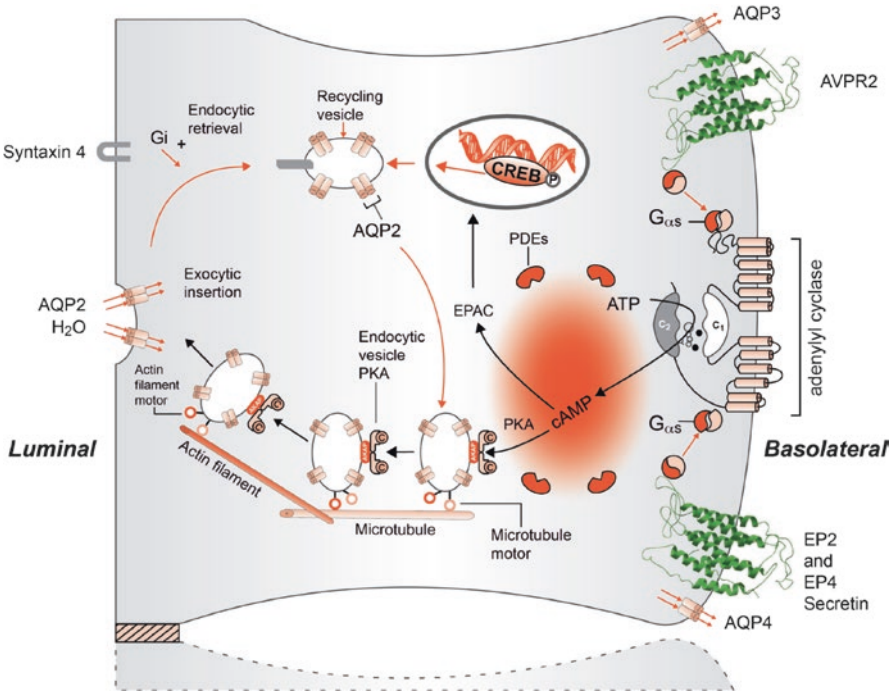



**Fig. 1.9** Schematic representation of the effect of arginine vasopressin (AVP) to increase water permeability in the principal cells of the collecting duct. AVP is bound to the $V_2$ receptor (a G-protein-linked receptor) on the basolateral membrane. The basic process of G-protein-coupled receptor signaling consists of three steps: a hepta-helical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein that dissociates into alpha subunit bound to GTP and beta and gamma subunits after interaction with the ligand-bound receptor, and an effector (in this case, adenylyl cyclase) that interacts with dissociated G-protein subunits to generate small-molecule second messengers. AVP activates adenylyl cyclase increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP). The topology of adenylyl cyclase is characterized by two tandem repeats of six hydrophobic transmembrane domains separated by a large cytoplasmic loop and terminates in a large intracellular tail. Generation of cAMP follows receptor-linked activation of the heteromeric G-protein ($G_s$) and inter-action of the free $G_{as}$-chain with the adenylyl cyclase catalyst. Protein kinase A (PKA) and possibly the Exchange factor directly activated by cAMP (EPAC) are the target of the generated cAMP. On the long term, vasopressin also increases AQP2 expression via phosphorylation of the cAMP responsive element binding protein (CREB), which stimulates transcription from the AQP2 promoter. Cytoplasmic vesicles carrying the water channel proteins (represented as homotetrameric complexes) are fused to the luminal membrane in response to AVP, thereby increasing the water permeability of this membrane. Microtubules and actin filaments are necessary for vesicle movement toward the membrane. The mechanisms underlying docking and fusion of aquaporin-2 (AQP2)-bearing vesicles are not known. The detection of the small GTP binding protein Rab3a, synaptobrevin 2, and syntaxin 4 in principal cells suggests that these proteins are involved in AQP2 trafficking [71]. When AVP is not available, water channels are retrieved by an endocytic process, and water permeability returns to its original low rate. Internalized AQP2 can either be targeted to recycling pathways or to degradation via lysosomes. AQP3 and AQP4 water channels are expressed on the basolateral membrane)

VP exerts its regulation in two ways. The short-term regulation is the result of AQP2 trafficking and relocation in the renal cell membrane. Under normal conditions, AQP2 channels are restricted within the cytoplasm. VP-V2R binding first activates the expression of AQP3 on the basal membrane of renal cells. This triggers the transport of AQP2 located in intracellular vesicles (exocytosis) [44, 49, 50]. Therefore, the activated phosphorylated AQP2 on the apical membrane allows water reabsorption through the pore [8, 44, 46, 48, 51, 52]. The long-term regulation of AQP2 related to vasopressin occurs as a result of an increased half-life and abundance of AQP2 by increasing its transcription [44, 51–53].

In summary, renal AQP2 activation following vasopressin secretion represents the central key for controlling urine dilution/concentration and consequently water balance. Thus, the collecting duct permeability to water varies according to plasma vasopressin concentration: in case of a low concentration of vasopressin, urines are highly diluted (minimal urinary osmolality is about 100 mosm/L); if vasopressin release increases, urinary concentration in a linear fashion with vasopressin due to a large amount of water reabsorption. However, despite a continuous increase in vasopressin concentration, urine concentration reaches a maximum value of 1000–1200 mosm/L. Usually, the kidney is able to equilibrate a 1000–2000 mL per day of water ingestion through urine concentration/dilution. Urea, sulfates, phosphates and other substrates issued from the cellular metabolism are responsible for a 600 mosm per day which requires an obligatory and minimal water excretion of 500 mL per day by the kidney. AQP2 dysregulation is recognised to be responsible for various water disorders: mutations of V2R or AQP2 cause polyuric pathologies, especially nephrogenic diabetes insipidus; increased AQP2 expression leads to abnormal water retention as observed in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [10, 53–56].

Vasopressin enables also to control water balance through the activation of various solutes co-transporters [44, 57]. The bumetamide-sensitive sodium-chloride cotransporter is located in the thick ascending limb of Henle. vasopressin stimulates its activity leading to increase the active reabsorption of sodium-chloride. The resulting medullary interstitial accumulation of solutes promotes water reabsorption from renal ducts. Vasopressin also promotes water reabsorption by triggering the epithelial sodium channel (ENaC) activity in the collecting duct, in an aldosterone-independent way [58] (see infra). The subsequent increase in sodium reabsorption facilitates water reabsorption [44, 58–60].

## 1.4 Body Sodium Balance and Its Regulation

### 1.4.1 Sodium Balance

Sodium is a monovalent cation and a strong base. Its molecular weight is 23, chloride molecular weight is 35.4 and 1 g of NaCl contains 17 mmol of Na. Total body

sodium is 60 moles per kg. Forty percent is located in the bones [61]. Plasma sodium concentration is 140 ± 2 mmol/L and 144 ± 2 mmol/L in the interstitial compartment and freely crosses the capillary membrane. Intracellular sodium concentration varies but remains very low (<20 mmol/L) due to $Na^+$-$K^+$-ATPase enzyme activity which continuously extrudes sodium from cells. Due to its high extracellular content, sodium is the prime determinant of the volume of this compartment. In other words, body sodium content regulates the ECV and arterial pressure, while natremia, which is the plasma sodium concentration, determines plasma tonicity and consequently the ICV. In pathological situations, the presence of oedema indicates an increased ECV (interstitial), due to the accumulation of Na (and water). It is important to underline that interstitial and EABV ("volemia") vary in an opposite way in most clinical situations. For example, patients with congestive cardiac or renal insufficiency or ascitic cirrhosis present oedema and low EABV. In these situations, ECV volume is abnormally high due to the increased sodium content in the interstitial volume, while EABV is low. The treatment of these water and electrolyte abnormalities is difficult because sodium vascular loading is essential to maintain effective circulation, but worsens oedema.

In physiological situations, the exogenous oral intake of Na is higher than the needed one. The difference depends on food habits. The obligatory losses by the skin and the intestinal tractus correspond to the minimal intake required (10 mmoles per day). Despite variations in Na intake, total Na balance is usually constant due to an equilibrium between sodium intake and renal excretion. The kidney represents the key organe of this tight regulation [62]. Total sodium renal elimination is >95% of that excreted. Quantitatively, this represents 500 g of sodium extracted from plasma per day. This regulatory mechanism is the major energetic and expenditure challenge of the tubular epithelium (Fig. 1.10).

As reviewed recently, the kidney filters vast quantities of Na at the glomerulus but excretes a very small fraction of this Na in the final urine [62]. Although almost every nephron segment participates in the reabsorption of Na in the normal kidney, the proximal segments (from the glomerulus to the macula densa) and the distal segments (past the macula densa) play different roles. The proximal tubule and the thick ascending limb of the loop of Henle interact with the filtration apparatus to deliver Na to the distal nephron at a rather constant rate. This involves regulation of both filtration and reabsorption through the processes of glomerulotubular balance and tubuloglomerular feedback. The more distal segments, including the distal convoluted tubule (DCT), connecting tubule, and collecting duct, regulate Na reabsorption to match the excretion with dietary intake.

Sodium filtration is passive, while its reabsorption is an energy-consuming process. The total sodium entering the glomerus is filtered, i.e. 25 moles per day. Sixty to seventy percent is reabsorbed along the proximal convoluted tubule (PCT). This isotonic process is performed by $Na^+/H^+$ exchangers (NHE3) [60]. The thick ascending limbs of the loop of Henle (TALH) are responsible for 25–35% of sodium reabsorption. This active process is mediated by Na-K-2Cl (NKCC) cotransporters. Only 8–10% of sodium filtered enters the distal convoluted tubule (DCT) and 6–10% is finally reabsorbed. The pathways of sodium transport differ according to the part of DCT: in the proximal part, reabsorption is performed by Na-Cl (NCC)

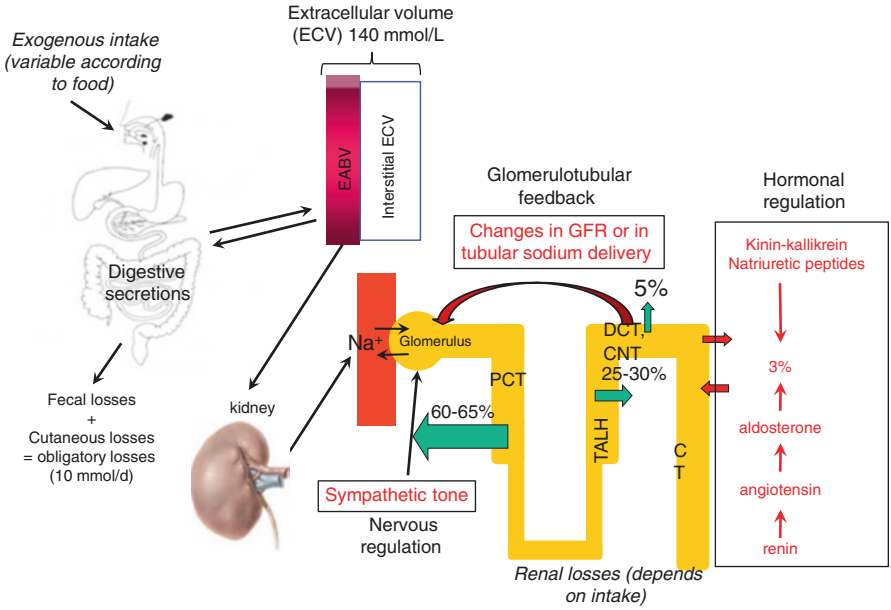



**Fig. 1.10** Sodium balance and its major regulating mechanisms in a 70 kg adult. Sodium intake coming essentially from the exogenous food is equilibrate by urinary sodium output. By regulating sodium excretion, kidney plays an essential role in total sodium balance. After its ingestion, sodium is massively reabsorbed by the gastrointestinal system and is further distributed in body compartments. Sodium homeostasis is mainly maintained thanks to the hormonal renin angiotensin aldosterone system axis which globally triggers renal sodium reabsorption in the collecting tubule. Natriuretic peptides and the kinin-kallikrein systems behaves as natriuretic effectors. Besides the hormonal system, sodium balance regulation is controlled by the glomerulotubular feedback which is mediated by sodium tubular delivery and glomerular filtration rate (GFR), and a sympathetic nervous pathway. *CNT* connecting tubule, *CT* collecting tubule, *DCT* distal convoluted tubule, *EABV* effective arterial blood volume, *ECV* extracellular volume, *PCT* proximal convoluted tubule

cotransporters; in the distal tubule sodium is reabsorbed through the Epithelial sodium channel (ENaC). In the final, a very low content of filtered sodium reaches the collecting duct (CD). However, due to large variations in sodium excretion, the CD plays a major role to maintain sodium balance. The intestinal tract participates strongly in sodium exchanges: sodium excretion through biliary, pancreatic and intestinal secretion are important. But, in physiological situations, almost all excreted sodium is reabsorbed. This phenomenon explains why patients presenting severe intestinal losses (gastric suctioning or intestinal fistula) are hypovolemic.

### 1.4.2 Regulation of Sodium Balance

The mechanisms involved in sodium balance regulation consist in loops (Table 1.3): a peripheral or central signal activates receptors which trigger an afferent

**Table 1.3** Major factors and mechanisms of sodium balance regulation

| | Afferent mechanisms | stimuli | Efferent mechanisms | Effects |
|---|---|---|---|---|
| Hormonal factors | | | | |
| – angiotensin | – decrease in renal perfusion pressure | – renin | – increase in the sympathetic nerve tone | – renal Na PCT reabsorption |
| | | – hyperkalemia | – increase in GFR | – renal Na DCT and CD reabsorption |
| | | | – aldosterone release | |
| – aldosterone | – renin | – angiotensin | – activation of the epithelial channel ENaC | – renal Na DCT and CD reabsorption |
| | | | – activation of the Na-K-ATPase pump | – renal K DCT and CD excretion |
| | | | – activation of the epithelial channel ROMK | = Antinatriuretic and kaliuretic effect |
| – natriuretic peptides | – hypertension | – sympathetic nervous tone | – systemic and renal vasoconstriction | = hypotensive effect |
| | – hypervolemia | | – increase in GFR | = natriuretic effect |
| | | | – decrease in PCT and CD Na reabsorption | |
| – bradykinin | – kallicrein | | – systemic and renal vasodilation | |
| – prostaglandins | – sympathetic nervous tone | – PGE2, PGI2 | – modulation of GFR and RBF | = modulation of natriuresis and urine output |
| Mechanical factors | | | | |
| – GFR | – decrease in renal perfusion pressure | | – stimulation of renin and aldosterone | = antinatriuretic effect |
| | | | – inhibition of angiotensin | |
| | | | – decrease in the SRAA activation | |
| – tubuloglomerular feedback | | – decrease in tubular Na delivery | | = natriuretic effect |

*CT* collecting tubule, *ENaC* epithelial sodium channel, *GFR* glomerular filtration rate, *K* potassium, *Na* sodium, *DCT* distal convoluted tubule, *PCT* proximal convoluted tubule.

transmission to a central or peripheral command; an efferent transduction of the signal through efferent pathways reaches effectors (organs). Kidneys and vessels are the most important.

#### 1.4.2.1 Afferent Pathways

Two pathways are activated [6]:

– the activation/inhibition of mechanoreceptors which depends on volemia and arterial pressure. In case of hypervolemia or arterial hypertension, these stretch receptors are activated, leading to an inhibition of the central signal and consequently to decrease the neurendocrine and sympathetic response. Baroreceptors are located in the high pressure arterial system (aortic arch, carotid sinus) and sensored modifications in pressure. Various organs contain low pressure receptor: pulmonary artery circulation, atrial and ventricular walls and portal vessels (voloreceptors). Regardless their situation, these receptors are activated or inhibited by changes in parietal stretch. The signal issued from the systemic arterial circulation is conducted along the vagus (X) and the glossopharyngial (IX) nerves to the central nervous system (Fig. 1.11).

mechanical mechanisms such as a decrease in GFR or in sodium delivery in the tubule. An increased amount of sodium delivered in the juxtaglomerular apparatus

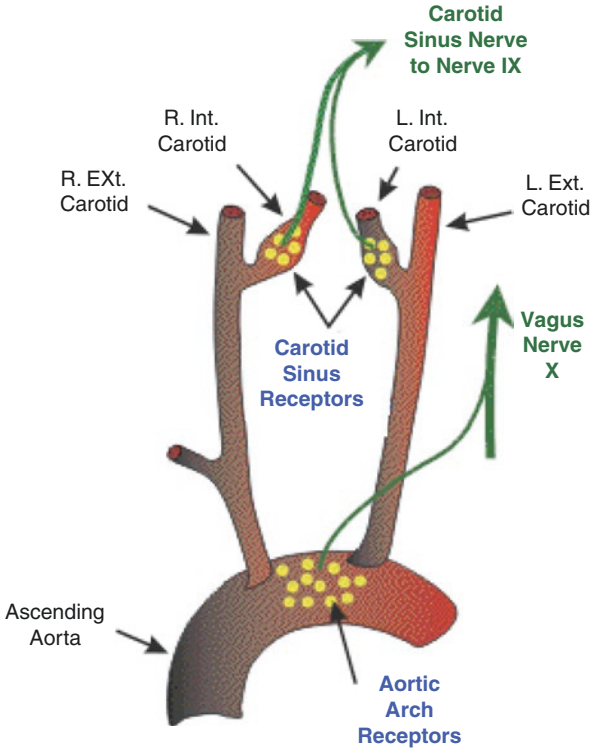



**Fig. 1.11** Major peripheral mechanoreceptors and pathways implicated in the renin-angiotensin-aldosterone and vasopressine release. *Ext* external, *I* internal, *L* left, *R* right

induces a decrease in GFR, leading in return to a decrease in sodium delivery. This is the famous "tubuloglomerular feedback" which is mediated by a vasoconstriction of glomerular afferent arterioles.

### 1.4.2.2 Efferent Pathways

The transmission (transduction) of the signal is conducted through three pathways: the hormonal, neuronal pathways and the sodium and potassium dietary.

- *The hormonal system* plays a key role in the regulation of sodium balance. Sodium excretion is precisely controlled thanks to several hormone systems responsible in sodium renal reabsorption or excretion.
  - Renin-Angiotensin-Aldosterone system (RAAS) axis: this is the most important system of sodium balance regulation. Renin is synthetized by the epithelial cells of the afferent arteriole of the juxtaglomerular apparatus located in the DCT. Renin release is mainly activated by a decrease in renal perfusion pressure which triggers the receptors located on the juxtaglomerular afferent arterioles. Hyperkalemia, hyponatremia and an increase in sympathetic nerve activity also stimulate renin synthesis. Non active angiotensinogen is synthetized by the liver, then converted into the inactive angiotensin I in the kidney thanks to renin. The converting enzyme allows the conversion of angiotensin I into the active angiotensin II. This latter molecule binds to specific transmembrane receptors and triggers consequently several peripheral and central effects: release of aldosterone, thirst, vasoconstriction (Fig. 1.12). The final results is always to control sodium

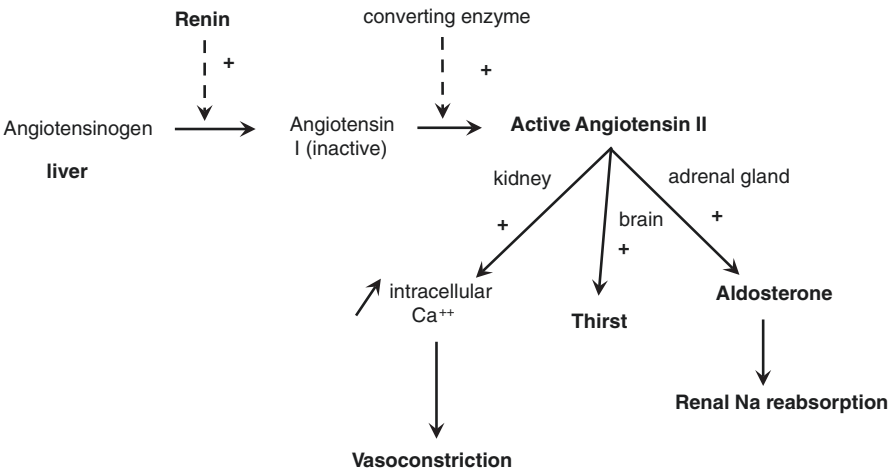



**Fig. 1.12** The renin-angiotensin-aldosterone system axis. Renin is synthetized by renal cells of the juxtaglomerular apparatus, angiotensinogen is synthetized by the liver and aldosterone by the adrenal gland. The activation of renin synthesis and release by hypovolemia/arterial hypotension converts angiotensinogen (inactivate molecule) in angiotensin 1 (inactivate molecule). The converting enzyme conducts to the release of the active angiotensin II. This latter triggers several effects on different organs: vasoconstriction, renal sodium reabsorption and thirst