Toward an Integrative Concept of Control of Total Body Sodium

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Total body sodium (TBSodium) is a major determinant of body water and arterial pressure. Several observations, in particular that of a “sodium memory,” indicate that TBSodium is a controlled variable. Various regulatory elements are involved, e.g., the renin-angiotensin-aldosterone system, atrial receptors, and renal arterial pressure. Balance studies in dogs provide new insights into their contributions to TBSodium control.

In mammals, the body contents of water and electrolytes, as well as the osmolality of body fluids, are kept constant within narrow limits over long periods of time. Mechanisms of osmo-control are well known: excess intake or loss of water, each of which alter osmotic pressure of body fluids, are compensated for by excretion or intake of water, respectively. Furthermore, it is known that the organism maintains its content of isotonic fluid by maintaining its electrolyte content (2). In particular, the control of isotonic volume, i.e., of total body water (TBWater), is achieved through control of total body sodium (TBSodium) and total body potassium (TBPotassium). TBSodium control is basically responsible for control of extracellular volume and plasma volume. Thus control of TBSodium and long-term control of arterial pressure are closely coupled (2).

However, it is unclear how the body controls TBSodium. For instance, how and where TBSodium is sensed remains unknown. Theoretically, sensing of sodium concentration and sensing of volume, i.e., TBWater, would provide this information. However, sodium and water are distributed within different fluid compartments, i.e., intracellular, interstitial, and intravascular compartments (plasma volume), and ions and water are often shifted among these compartments. Changes of extracellular sodium concentration are sensed by hypothalamic receptors (11). The hitherto known volume receptors are capable of sensing blood volume only. Thus how the organism may sense TBSodium remains unknown. However, in this review we will present indirect evidence that indicates that TBSodium is an independently controlled variable.

Although various regulatory elements of sodium homeostasis are well described, a complete feedback control system capable of maintaining TBSodium is as yet unknown. Maintenance of TBSodium requires equilibrium between sodium intake and excretion. Consequently, some regulatory elements contributing to control of TBSodium drive sodium intake (hunger for salt), whereas others impinge on renal sodium excretion. This review will focus on the latter only. New insight into the contribution of various regulatory elements for TBSodium control and their potency, hierarchy, and interactions has recently been obtained. This has been achieved through standardized balance studies, which allow exact measurements of changes in TBSodium.

TBSodium: checks and balances

Sodium balance is determined by sodium intake, renal sodium excretion, and extrarenal sodium losses. Thus all three variables must be measured or standardized in balance studies. Regarding sodium intake, this can be achieved by fixed oral intake, provided that the sodium content of the food, i.e., the total amount of sodium, is known and complete food intake is ensured. Likewise, renal sodium excretion can be measured, provided that urine is completely collected. Continuous measurement of extrarenal losses is hard to achieve. However, by means of standardized environmental conditions (constant room temperature, moisture, and light-dark cycle and prevention of significant changes in physical activity), extrarenal losses can be kept rather constant.

One should be aware that various elements of TBSodium control, e.g., renin release, are altered by stress, as may be induced by restraint or by the actions taken to conduct an experiment. We have developed methods that enable balance studies in chronically instrumented beagle dogs for several days. A swivel system allows free movement within a 9-m² kennel. Because of separation between the laboratory and the sound-protected animal room, the actions necessary to conduct the experiments (e.g., urine collection, blood sampling) can be taken without drawing the attention of the dogs. Intake is standardized with regard to amount (per kilogram of body weight) and feeding time. The amount of extrarenal loss is determined in time control experiments, wherein the difference between intake and renal excretion reflects extrarenal loss (for details, see Refs. 1, 10, and 12).

Fixed intake, assessed extrarenal losses, and measurement of urinary output allow exact determination of 24-h balances. If 24-h urinary excretion plus extrarenal losses exactly match oral intake, then 24-h balance is equilibrated. If less is excreted than ingested, then 24-h balance becomes positive (retention). If excretion exceeds intake, then 24-h balance becomes negative (deficit). As long as 24-h balances are equilibrated, intake determines the turnover (throughput). It should be noted that different amounts of sodium intake mean different turnover yet do not necessarily mean different

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TBSodium. A positive or a negative 24-h sodium balance represents a change in TBSodium. Long-term changes in TBSodium are determined by adding 24-h balances from consecutive days (cumulative balance). In the same manner, long-term changes of TBWater and TBPotassium are recorded.

**TBSodium as a controlled variable**

The sodium memory. Early studies in dogs (8, 11) provided circumstantial evidence indicating that TBSodium is a controlled variable. By means of peritoneal dialysis, a certain amount of sodium (7 mmol/kg body wt) was withdrawn. This deficit of TBSodium was achieved without primary changes of TBWater; thus a certain amount of body water became “osmotically free.” Plasma sodium concentration immediately decreased (8). Because of osmocontrol, 60%, but not all, of osmotically freed water was renally excreted within 24 h. However, concomitantly, sodium concentration returned to its control level. This was achieved through two mechanisms: water entered intracellular space, and sodium was mobilized from intracellular space (8). Hence, reduction of TBSodium results in changes within both compartments: intracellular sodium concentration is lowered, intracellular volume is increased, and extracellular volume is reduced. In the face of shifts of sodium and water among compartments, the only known volume receptors, which sense changes of plasma volume, cannot provide the required information for TBSodium control. However, when dogs receive small amounts of sodium through food (daily intake 2 mmol/kg body wt) some days after dialysis (11), this sodium is almost totally retained. Retention lasts for a couple of days, until 24-h sodium balances again become equilibrated. Intriguingly, the total amount of sodium retained matches the amount initially withdrawn. This result led to the hypothesis of a “sodium memory” and indicated that TBSodium is indeed a controlled variable (11). Furthermore, sodium retention was accompanied by water retention. Thus control of TBSodium eventually led to restoration of TBWater (control of isotonic volume) (8). Because restoration of TBSodium and TBWater includes reverse ion and water shifts among fluid compartments, it is conceivable that such shifts may contribute to sensing changes in TBSodium.

**Changes in TBSodium trigger compensatory mechanisms.** It is a characteristic feature of a controlled variable that its alterations activate compensatory mechanisms that counteract the primary disturbance. When osmodiuretic mannitol is given to dogs that are on a low-sodium diet, sodium excretion increases on day 1, which results in a deficit of TBSodium. On the following days, the same amount of mannitol does not result in natriuresis. Likewise, when TBSodium has been reduced by peritoneal dialysis, mannitol does not increase sodium excretion even on day 1 (11). It is concluded that a deficit in TBSodium triggers compensatory mechanisms that prevent further sodium loss.

Similar results have been obtained by Strauss et al. (15) in humans. When sodium intake was suddenly reduced to a very low level, an exponential fall in sodium excretion was observed. If a small amount of sodium was then given, it was excreted. The same small amount of sodium was retained, however, when additional sodium had been eliminated by diuretics. Strauss proposed a concept of TBSodium control, which was further developed by Hollenberg and Simpson (14). According to this concept, there is a basal level of TBSodium that is maintained by TBSodium control when sodium intake is very low (just sufficient to cover obligatory extrarenal losses). As long as sodium intake is greater than extrarenal losses, as it is even during commonly used low-sodium diets, TBSodium is above this basal level. While the amount of sodium above the basal level (extra sodium) is in the process of being excreted, TBSodium is constantly replenished by further intake of sodium. Thus, although TBSodium is running downhill toward the basal level all the time, it does not reach this level. Therefore, a commonly used low-sodium diet per se reduces the amount of extra sodium yet does not result in a true deficit of TBSodium. However, if TBSodium is forced below basal level, e.g., by diuretics, there is a state of sodium deficit. Any ingested sodium will be retained until the deficit is made up (14). The latter prediction of this concept was verified by the above-mentioned study in dogs after peritoneal dialysis [sodium memory (11)].

The well known mineralocorticoid escape phenomenon indicates that a primary increase in TBSodium activates compensatory mechanisms as well. Chronic elevation of mineralocorticoid activity initially results in sodium retention. This increase in TBSodium is accompanied by increase in mean arterial blood pressure. Although mineralocorticoids continue to act on renal tubules, 24-h sodium balances equilibrate after few days. Thus further increase in TBSodium is prevented. In summary, changes in TBSodium, deficit as well as surplus, trigger compensatory mechanisms, which counteract primary changes. Obviously, this counteraction is accomplished by regulatory elements involved in TBSodium control. Thus, if TBSodium is indeed a controlled variable, then primary alteration of TBSodium should feed back on these regulatory elements.

**Reduced TBSodium abolishes atrial natriuresis.** Atrial receptors were originally described by Gauer and Henry as part of a “volume reflex” because an increase in left atrial pressure resulted in water diuresis in anesthetized dogs. Subsequent studies in conscious dogs revealed that increasing left atrial pressure within the physiological range also results in natriuresis [“atrial natriuresis” (9)]. Intriguingly, left atrial pressure increases postprandially. Provided that water intake is constant, postprandial increase of left atrial pressure is positively related to sodium intake. Thus a significant role of atrial receptors in TBSodium control has been suggested (9). A controlled increase of left atrial pressure without primary change in TBSodium and plasma volume (open loop conditions) has been achieved by means of the reversible mitral stenosis technique [pursue string around the left atrium (9)]. Atrial natriuresis is abolished when
TBSodium is reduced: if elevation of left atrial pressure is applied for several hours, leading to a deficit in TBSodium, then natriuresis diminishes (see Fig. 1). After achieving a certain deficit of TBSodium, atrial natriuresis is abolished (9). In another study (9), left atrial pressure was elevated for 1 h each day on consecutive days, and the resulting deficit of TBSodium could not be replenished (low sodium intake). Atrial natriuresis decreased from day to day; on day 4 it was abolished. In conclusion, atrial receptors contribute to TBSodium control; however, the feedback of TBSodium on atrial natriuresis clearly indicates that other receptors of yet unknown site and nature play a major role in TBSodium control.

**TBSodium determines renin release.** The renin-angiotensin-aldosterone-system (RAAS), with its potent sodium-retaining hormones angiotensin II (ANG II) and aldosterone (Aldo), is a prime candidate for the regulatory system controlling TBSodium. Renal renin release is mainly determined by three physiological variables. Renin release is stimulated, firstly, by decreasing renal arterial pressure (pressure-dependent renin release) and secondly by increasing renal sympathetic nerve activity or circulating catecholamines. Thirdly, clinical as well as experimental observations suggest that changes in TBSodium impinge on renin release. Recently, we (13) systematically studied the influence of changes in sodium intake and the influence of experimental changes in TBSodium on renin release in conscious dogs. Because renin release is suppressed postprandially after a sodium-rich meal and is increased by stress and physical activity, the experiments took place during the postabsorptive state (20 h after last sodium intake) in the early morning (dark period, low physical activity). Changes of sodium intake per se, i.e., without major changes in TBSodium, did not significantly alter renin release during the postabsorptive state. Conversely, a deficit in TBSodium dramatically increased renin release, whereas a moderate surplus of TBSodium slightly inhibited renin release and a large surplus suppressed it almost totally (see Fig. 2). Thus an inverse relationship between TBSodium and renin release is found and is called TBSodium-dependent renin release (13).

The pathway by which changes of TBSodium impinge on renin release is uncertain. Our results (13) indicate that TBSodium-dependent renin release is not mediated by changes in plasma sodium concentration. Likewise, concomitant changes in TBWater, and thus in plasma volume, do not seem crucial. Despite the striking difference in the change in TBSodium between dogs with large surplus of TBSodium (~8 mmol/kg; see Fig. 2) and those with moderate surplus (~3 mmol/kg), change in TBWater was not different between these groups (13), because a certain amount of retained sodium was osmotically compensated by a loss of potassium in the group with large surplus of TBSodium (12). The notion that differences in plasma volume are not decisive for TBSodium-dependent renin release is supported by the fact that plasma concentrations of atrial natriuretic peptide (ANP) were not different between both of these groups (13). On the other hand, distal tubular sodium chloride load is known to influence renin release, whereby sodium movements across the membrane of macula densa cells are suggested to play a crucial role. On the basis of the above-mentioned sodium shifts after peritoneal dialysis (8), we hypothesize that such ion shifts may contribute to mediating TBSodium-dependent renin release.

The influence of decreasing renal perfusion pressure on TBSodium-dependent renin release was also studied (13). A pneumatic aortic cuff above the renal arteries, driven by a servo-controlled device, allowed us to reduce renal perfusion pressure stepwise (see Fig. 2). The inverse relationship between TBSodium and renin release is preserved despite different preset pressures. Thus TBSodium-dependent renin release is not mediated by changes in renal perfusion pressure. However, the lower that renal perfusion pressure is set, the steeper the relationship becomes, i.e., the TBSodium dependency of renin release is enhanced by low renal perfusion pressure (13).

The finding that TBSodium feeds back onto renin release supports the theory that TBSodium is a controlled variable.

**TBSodium control: the potencies of RAAS, atrial natriuresis, and renal perfusion pressure as regulatory elements**

Does a given regulatory element have the potency to restore normal TBSodium (set point), or at least to prevent further changes in TBSodium, when other control elements are altered?
NG II and Aldo reduces sodium excretion. Second, reducing renal perfusion pressure is known to induce sodium retention, thus increasing TBSodium. Two phenomena.

Reduction of renal perfusion pressure is known to reduce sodium excretion (4, 5). The intrarenal mechanism underlying pressure natriuresis and putative pressure antinatriuresis is still under investigation (2). However, a tight linking of blood pressure regulation and control of extracellular volume or TBSodium is assumed. According to Guyton’s concept, the renal body fluid pressure control system is capable of keeping constant both variables, arterial blood pressure and TBSodium, and the system displays an infinite feedback gain (4, 5). If one aims to determine the contribution of pressure natriuresis to control of TBSodium experimentally, one should be aware that changing renal perfusion pressure automatically induces sodium retention (partial escape), as demonstrated by a further study with additional low-dose ANG II supplementation (12). Sodium retention is markedly augmented, as shown in Fig. 3. Thus suppression of RAAS is a major compensatory mechanism in TBSodium control. Obviously, this downregulation is caused by elevation of TBSodium (12, 13).

Contributions and interactions of atrial natriuresis and other sodium-eliminating factors. The phenomenological term “atrial natriuresis” does not name the mediators by which elevation of left atrial pressure increases sodium excretion. Early studies (9) revealed that acute elevation of left atrial pressure decreases renin release (Fig. 1). Low-dose ANG II infusion abolished atrial natriuresis. Thus RAAS inhibition is involved in atrial natriuresis (9). With subsequent discovery of ANP, this peptide became a further candidate. However, studies in conscious, cardially denervated dogs revealed that atrial natriuresis depends on intact vagal afferent nerves. Elevation of left atrial pressure within the physiological range still resulted in significant increase of ANP, yet cardiac denervation prevented atrial natriuresis (3). Thus neither direct renal actions of ANP nor its possible inhibition of renin release seem to contribute to atrial natriuresis. This does not exclude the possibility that ANP may facilitate sodium excretion via its inhibitory effect on Aldo secretion. Since lowered Aldo levels take some hours to induce natriuresis, this effect of ANP is underestimated in acute studies. During pressure escape (10), continuous elevation in renal perfusion pressure per se, i.e., via the mechanism of pressure natriuresis/antinatriuresis, may reduce sodium excretion. In freely moving dogs, servocontrolled 20% reduction of renal perfusion pressure (↓RPP) for four consecutive days was combined with continuous angiotensin-converting enzyme inhibition (1). As shown in Fig. 3, the mechanism of pressure natriuresis does not result in sodium retention during reduction of renal perfusion pressure.

With intact RAAS, i.e., when pressure-dependent renin release increases ANG II and Aldo levels, ↓RPP results in sodium and water retention (Fig. 3) and systemic arterial pressure increases (10). Because of continued ↓RPP (open loop conditions), elevated systemic pressure is prevented from acting on the renal level via the pressure natriuresis mechanism. Nevertheless, beginning on day 2, 24-h sodium balances once again equilibrate. The initially retained sodium is not excreted; thus TBSodium remains elevated. Consequently, systemic pressure remains elevated as well. Thus retention of sodium and water caused elevation of systemic pressure. The reequilibration of 24-h sodium balances at an elevated level of TBSodium was called pressure escape, in analogy to mineralocorticoid escape (10).

Endogenous inhibition of RAAS is a major compensatory mechanism. Pressure escape is mainly accomplished through suppression of Aldo secretion. Concomitant with restoration of 24-h balances, the initially elevated Aldo declines to control values or takes on even lower values despite continued elevation of renin activity (10). Preventing the effect of reduced Aldo secretion by low-dose Aldo infusion abolished pressure escape (12). As shown in Fig. 3, sodium is continuously retained. Concomitantly, renal renin release, and thus ANG II, is suppressed. This contributes to a slight attenuation of sodium retention (partial escape), as demonstrated by a further study with additional low-dose ANG II supplementation (12). Sodium retention is markedly augmented, as shown in Fig. 3. Thus suppression of RAAS is a major compensatory mechanism in TBSodium control. Obviously, this downregulation is caused by elevation of TBSodium (12, 13).

Pressure antinatriuresis and RAAS: the pressure escape phenomenon. Reduction of renal perfusion pressure is known to induce sodium retention, thus increasing TBSodium. Two different mechanisms may be responsible. First, pressure-dependent renin release stimulates the RAAS, which via renal action of ANG II and Aldo reduces sodium excretion. Second, reduction of renal perfusion pressure (↓RPP) for four consecutive days was combined with continuous angiotensin-converting enzyme inhibition (1). As shown in Fig. 3, the mechanism of pressure natriuresis does not result in sodium retention during reduction of renal perfusion pressure.

With regard to several studies we (1, 10, 12) have performed under standardized conditions in freely moving dogs on high-sodium diets (5.5 mmol·kg body wt⁻¹·day⁻¹), the potencies of different effectors can be compared quantitatively.

A vast number of regulatory factors, i.e., humoral, neural, and physical forces, impinge on renal sodium excretion and may therefore contribute to TBSodium control. Here the following putative controllers of TBSodium are discussed: atrial natriuresis, the RAAS, and the renal body fluid pressure control system. The latter was proposed by A. C. Guyton (4, 5). The concept is based on two observations. First, an increase in TBSodium results in an increase in mean arterial blood pressure via increased plasma volume and, in turn, cardiac output (2). Second, an increase in arterial pressure, and thus of renal perfusion pressure, increases renal sodium excretion; likewise, a decrease in renal perfusion pressure is supposed to reduce sodium excretion (4, 5). The intrarenal mechanism of renal perfusion pressure, increases renal sodium excretion; thus suppression of RAAS is a major compensatory mechanism in TBSodium control. Obviously, this downregulation is caused by elevation of TBSodium (12, 13).
of ANP was observed, which may have contributed to inhibition of Aldo secretion.

Reduction of renal perfusion pressure plus prevention of endogenous suppression of RAAS (ANG II + Aldo infusion) results in continuous increase of TBSodium (Fig. 3). Edema formation and increase of systemic pressure up to 170 mmHg forced us to terminate several experiments prematurely. ANP increased dramatically (12). Although ANP cannot exert effects via RAAS inhibition under these circumstances, it may increase sodium excretion through direct renal effects. Likewise, various hormones, mediators, and physical factors are suggested to possess sodium-eliminating potency, e.g., prostaglandins, kinines, urodilatin, nitric oxide, and colloidosmotic pressure. In the face of the striking TBSodium increase, these factors are presumably highly stimulated.

A partial escape is accomplished, as shown in Fig. 3. Daily sodium accumulation is attenuated: compared with the amount retained on day 1, on day 4 only 60% is retained. Thus the continued sodium-retaining effect of ↓RPP plus ANG II and Aldo supplementation is partially compensated for (12). This effect is accomplished by an entity of all remaining sodium-eliminating factors, i.e., those not acting via RAAS inhibition or pressure natriuresis mechanism. It should be noted that even the sum of all does not prevent continuous retention.

Likewise, the contribution of atrial receptors to the maintenance of TBSodium appears relatively minor: the ability to equilibrate sodium balance following a large sodium load is not compromised in cardially denervated dogs. Similarly, cardiac denervation did not alter sodium retention after TBSodium was decreased by peritoneal dialysis (8).

Pressure natriuresis accomplishes escape but does not completely correct TBSodium. Reduction of renal perfusion pressure plus prevention of endogenous suppression of RAAS leads to continuous increase of TBSodium and thus of systemic arterial pressure. Within the first 24 h of this study (12), systemic pressure rose by ~25 mmHg. The question arises as to whether such a pressure elevation may compensate for sodium retention if it is permitted to act on the renal level through the mechanism of pressure natriuresis. If Guyton's theory of an "infinite gain principle" (4, 5) of the renal body fluid pressure control is applied, one may expect that the initially retained sodium is completely excreted. Thus TBSodium as well as arterial blood pressure would be assumed to be regulated "all the way back to normal" (5). This hypothesis was tested: after one day of ↓RPP plus low-dose infusions of ANG II and Aldo, reduction of renal perfusion pressure was released, i.e., elevated pressure was permitted to act through the pressure natriuresis mechanism; however, endogenous downregulation of RAAS was prevented by continuous infusion. As shown in Fig. 4, 24-h sodium balances became equilibrated at an elevated level of TBSodium. Thus elevation of renal perfusion pressure by ~25 mmHg accomplishes an escape (ANG II + Aldo escape). The surplus of TBSodium is not corrected, and as long as TBSodium is augmented, arterial blood pressure remains elevated.

Hall et al. (6, 7) performed studies on mineralocorticoid escape and ANG II escape in dogs. When the increase in renal perfusion pressure induced by sodium retention was counteracted by servo control, escape did not occur. This result agrees with the results of our study: if perfusion pressure
is elevated, then the pressure natriuresis mechanism prevents further sodium retention.

The relationship between mean arterial blood pressure and sodium excretion has been depicted as the chronic renal function curve (2, 4–6). These curves aim to characterize the dependence of sodium excretion on pressure during steady-state conditions (sodium excretion equals intake, i.e., equilibrated 24-h balances). When sodium excretion is primarily altered, e.g., because of elevated levels of ANG II or Aldo, then the relationship between sodium excretion and pressure (renal function curve) is shifted toward higher pressure (4–6). Our interpretation of such shifts is as follows. Before a new steady-state is achieved, i.e., during the transient time, sodium is retained. This increase in TBSodium caused the increase of arterial pressure. Thus the new steady state represents a complete escape.

Quantitative comparison and feedback gain. The quantitative effect of pressure natriuresis (see Fig. 4) is estimated by comparison between surplus of TBSodium, as it is achieved by ↓RPP and ANG II + Aldo infusion for 4 days (13 mmol/kg), and the remaining surplus of TBSodium after release of renal perfusion pressure (3.5 mmol/kg). Intriguingly, this effect is comparable with that exerted by endogenous suppression of RAAS during continuous ↓RPP: the remaining TBSodium surplus during pressure escape amounted to 3.5 mmol/kg (see Fig. 3). Thus both compensatory mechanisms, endogenous inhibition of RAAS and pressure natriuresis, possess similar potency.

The degree of effectiveness of a control system, its potency in compensating for disturbances, is determined by the gain of negative feedback. The “closed loop gain” (Gc) is defined as the part of an induced disturbance that is compensated (Gc = compensation/induced error). A theoretical open loop gain is calculated by the equation Go = –Gc/1 – Gc. For maintenance of TBSodium, daily sodium intake can be regarded as a disturbance that should be eliminated within 24 h. If the amount ingested is completely excreted by the kidneys, then Gc value is ~ 1.0 and Go value is close to ±∞. If applied to escape phenomena, calculation of gains reveals the following: on day 1, out of the sodium ingested (induced error), only a fraction is renally excreted (compensated) within 24 h, whereas the rest is retained (remaining error). For instance, out of 5.5 mmol sodium/kg ingested minus extrarenal losses of 0.5 mmol/kg, 3.0 mmol/kg are retained; thus, Gc = 0.40 and Go = –0.67. In contrast to day 1, the newly ingested sodium on day 2 is completely excreted during this day; thus, Gc = ~1.0 and Go is nearly (–) ∞. Hence, in accordance with Guyton’s infinite gain principle (4, 5), control without detectable error is achieved. However, this applies only to 24-h intake-output balances, which now equilibrate again (new steady state). When TBSodium is regarded as a controlled variable, then the error gained on day 1 (TBSodium surplus of 3.0 mmol/kg) remains uncompensated. Correction of TBSodium is only achieved if the action of all major controllers is undisturbed. In another study, ↓RPP plus low-dose infusions of ANG II and Aldo was applied for one day. Again, sodium was retained and systemic pressure was increased by ~25 mmHg (Fig. 4). Thereafter, reduction of renal perfusion pressure was released, and at the same time ANG II and Aldo infusions were stopped. This resulted in a striking increase of sodium excretion. Within 24 h, the amount of sodium ingested on this day was excreted, as well as the amount retained on day 1. Thus within 24 h the
control level of TBSodium was regained, and arterial pressure was back to normal. It is concluded that TBSodium as well as arterial pressure regain their set points only if the action of all compensatory mechanisms, especially those of pressure natriuresis and downregulation of RAAS, is undisturbed.

Integrating facts and concepts

TBSodium apparently constitutes a controlled variable. Reduction of TBSodium is quantitatively corrected by sodium retention (sodium memory), and TBSodium feeds back on sodium-eliminating and -retaining controllers. Control of TBSodium is not simply achieved by simultaneous control of sodium concentration of body fluids and control of TBWater. On the other hand, control of isotonic body fluid volume is mainly achieved through control of TBSodium. Thus TBSodium is a major factor in control of extracellular and plasma volume and, therefore, in long-term pressure control. Conversely, arterial pressure has differential effects on sodium excretion: significant pressure elevation facilitates sodium excretion via the pressure natriuresis mechanism, whereas pressure reduction per se does not reduce excretion.

Escape means that, in the face of continued stimulation of a sodium-retaining controller, sodium is initially retained; thereafter, 24-h sodium balances reequilibrate, but TBSodium remains elevated. During ANG II + Aldo escape, the major part of compensation is achieved through pressure natriuresis. During pressure escape, it is achieved through suppression of Aldo secretion. Partial escape occurs during reduction of renal perfusion pressure: significant pressure elevation facilitates sodium excretion independently of release of atrial peptides. Am J Physiol Regulatory Integrative Comp Physiol 250: R946–R950, 1986.


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