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# Regulation of water and electrolyte metabolism during dehydration and rehydration in camels

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Regulation of water and electrolyte metabolism during dehydration and rehydration in camels

by

Ali Abdullah Al-Qarawi

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in partial fulfillment of the requirements for the degree of

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Ames, Iowa

1997

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ACKNOWLEDGEMENTS

**LIST OF ABBREVIATIONS**

AII	Angiotensin II (pg/ml)
AI	Angiotensin I (pg/ml)
ACTH	Adrenocorticotrophic Hormone (pg/ml)
AVP	Arginine Vasopressin (pg/ml)
AQP	Aquaporins
BUN	Blood Urea Nitrogen (mg/dl)
Cl	Plasma Chloride (mmol/L)
CO	Cortisol (ng/ml)
CR	Plasma Creatinine (mg/dl)
CRF	Corticotrophin-Releasing Factor
ECF	Extracellular Fluid
GLU	Plasma Glucose (mg/dl)
HB	Hemoglobin (g/dl)
JG	Juxtaglomerular
ICF	Intracellular Fluid
K	Plasma Potassium (mmol/L)
Na	Plasma Sodium (mmol/L)
NTS	Nucleus Tractus Solitarius
OSMO	Plasma Osmolality (mosm/L)

OVL	Organum Vasculosum of the Lamina Terminalis
PA	Plasma Aldosterone (pg/ml)
PCV	Packed Cell Volume (%)
PCV	Packed Cell Volume (%)
PRA	Plasma Renin Activity (ng AI/ml/h)
PVN	Paraventricular Nucleus
SFO	Subfornical Organ
SON	Supraoptic Nucleus

**ABSTRACT**

The present study was undertaken to examine the effect of severe dehydration and rapid rehydration on electrolytes and body fluids homeostasis in the arabian camel (Camelus dromedarius), and to find out which pathway is responsible for the secretion of aldosterone in the dehydrated camel; either the renin-angiotensin axis or ACTH axis. In the first experiment ten dromedary camels were studied for a total of 29 days; 7 days under control conditions, 15 days of water deprivation and 7 days of rehydration in Bureidah (Saudi Arabia) during summer, 1996. Plasma electrolyte concentrations, plasma osmolality, packed cell volume (PCV), blood hemoglobin concentrations, plasma concentrations of glucose, creatinine, blood urea nitrogen (BUN), total protein, plasma renin activity (PRA), angiotensin II, aldosterone, arginine-vasopressin (AVP), adrenocorticotrophic hormone (ACTH) and cortisol were determined during both periods. During the second trial ACTH and enalapril, an angiotensin-converting enzyme inhibitor (ACE-I), were utilized in two separate experiments during dehydration and control (hydration) periods. Enalapril (0.2  $\mu\text{g}/\text{kg}$ ) induced a sharp decrease in plasma  $\text{Na}^+$  and an increase in plasma  $\text{K}^+$  concentrations in the dehydrated camels but not in the control camels.

Plasma osmolality decreased significantly in both dehydrated and control camels after ACE-I administration. ACE-I induced a sharp decrease in plasma angiotensin II and aldosterone concentrations in the dehydrated camels. In the control camels however, ACE-I induced a decrease in plasma aldosterone concentrations but not in plasma angiotensin II.

Plasma renin activity (PRA) increased significantly in the dehydrated camels. In the second experiment, ACTH administration (0.4 IU/kg) had no significant effect on plasma electrolytes and osmolality on the dehydrated and control camels. The administration of ACTH induced a sharp increase in plasma cortisol concentrations in the dehydrated and control camels. Plasma aldosterone concentrations, however, increased only in the dehydrated camels. The present study clearly shows that both angiotensin II and ACTH stimulate aldosterone secretion during dehydration in camels. However, due to the parallel increase in PRA, plasma angiotensin II and plasma aldosterone in dehydrated camels without any parallel changes in plasma cortisol or ACTH, the effect of angiotensin II on aldosterone secretion seems to be dominant over ACTH.

## **GENERAL INTRODUCTION**

### **Dissertation Organization**

This dissertation is written in an alternate thesis format. It includes a research objective, a general introduction, two manuscripts to be published in the American Journal of Physiology and a general summary and conclusions.

### **Research Objectives**

The purpose of the present study was to examine the effect of severe dehydration and rapid rehydration in electrolytes and body fluids homeostasis of the arabian camel (Camelus dromedarius), and to determine which pathway is responsible for the secretion of aldosterone in the dehydrated camel; either the renin-angiotensin axis or ACTH axis.

### **Background and Literature Review**

Water accounts for approximately 70% of the total body weight. Age, sex, species, and nutritional state are among the important factors affecting the total body water. Since the water content of the fat tissue is lower than that of other tissues, increasing amounts of fat tissue reduces the fraction of the total body weight due to water; thus the total water content of the obese animal will be lower than that of the lean animal. For example; in obese cattle,

total body water accounts for only about 40%, while in very thin cattle about 70% of body weight is water. In the newborn infant water constitutes about 75% of the body weight, this ratio declines to the adult value of 60% by the age of one year. In the newborn animal the water content is very high, it declines rapidly at first, and then declines slowly (Berne and Levy, 1993; Ganong, 1993; Swenson and Reece, 1993).

The total body water is distributed between two major compartments, water included within the cells is called intracellular fluid (ICF); it comprises approximately 2/3 of the total body water and the remaining 1/3 is located outside the cells is called extracellular fluid (ECF). The ECF is again divided into interstitial fluid and plasma. The interstitial fluid, which represents the fluid surrounding the cells in the various tissues of the body, comprises 3/4 of the ECF volume. Water within the bone and dense connective tissue is included in the interstitial fluid. The remaining 1/4 of the ECF is represented by the plasma volume. The cerebrospinal fluid, synovial fluid, urine, aqueous humor of the eye, and bile are also subdivision of ECF. These fluids are called transcellular fluids. Water in the alimentary canal is usually considered as ECF. In the lean animal, approximately 50% of the total body water is located in the cells, 15% in the interstitial spaces, and 5% in blood plasma (Berne and Levy, 1993; Swenson and Reece, 1993).

The free movement of water across the capillary endothelium is determined by two main forces; the osmotic pressure of the plasma proteins (oncotic pressure), and hydrostatic pressure (generated by the heart). On the other hand, the net pressure difference in osmotic pressure and hydrostatic pressure between ECF and ICF is the only factor allowing the movement of fluid across the cell membrane. A rapid shift of water will occur between body

fluid compartments, when an osmotic or hydrostatic pressure gradient occurs. However, if there is no appreciable hydrostatic pressure involved, the result of the water movement will be to equalize the osmoconcentrations of the fluids (Berne and Levy, 1993; Swenson and Reece, 1993).

The ionic compositions of the two compartments of the ECF (interstitial fluid and plasma) are similar because these compartments are separated only by the capillary endothelium, and this barrier is freely permeable to small ions. The major difference between the interstitial fluid and plasma is that the plasma has an appreciable amount of protein. The differential concentrations of protein in the interstitial fluid and plasma can affect the cation and anion distribution between these compartments. Plasma proteins have a net negative charge and tend to increase the cation concentrations and reduce the anion concentration in the plasma compartment. However, this effect is small, and the ionic compositions of the interstitial fluid and plasma can be considered to be identical (Berne and Levy, 1993; Ganong, 1993; Swenson and Reece, 1993).

Sodium ion is the major cation,  $\text{Cl}^-$  and  $\text{HCO}_3^-$  are the major anions of the ECF. Because of its abundance,  $\text{Na}^+$  (and its attendant anions, primarily  $\text{Cl}^-$  and  $\text{HCO}_3^-$ ) is the major determinant of the osmolality of the ECF. In contrast to the ECF, the  $[\text{Na}^+]$  of the ICF is extremely low;  $\text{K}^+$  is the predominant cation of the ICF. The major ICF anions are phosphates, organic anions, and protein. The capillaries are freely permeable to both water and electrolytes. The cell membrane does not permit the free movement of electrolytes, and thus the increased osmoconcentration of the ECF would cause a cellular dehydration (Berne and Levy, 1993; Ganong, 1993; Swenson and Reece, 1993).



In order to understand the important role of the endocrine system in regulating the body fluid and electrolytes homeostasis, we have to consider the role of arginine vasopressin, thirst mechanism, and the renin-angiotensin-aldosterone system.

### **Arginine Vasopressin**

Arginine vasopressin (AVP) is the determinant of the final renal water excretion and hence performs an important role in body fluid homeostasis. The magnocellular neurons of the supraoptic nuclei (SON) and paraventricular nuclei (PVN) in the hypothalamus are the major sites for AVP synthesis. In addition to the magnocellular neurons, smaller neurons (parvocellular) synthesizing AVP are present in the supraoptic and PVN. There are three main vasopressinergic neuronal projections arise from the SON and PVN. The main pathway originates from the SON and traverses to the posterior lobe of the pituitary gland (the neurohypophysis). Another important pathway terminates in the zona externa of the median eminence, these fibers arise from the medial parvocellular paraventricular nucleus and the final pathway projects to the forebrain, brain stem, and spinal cord. Complex neuronal interconnections exist between PVN and SON, the brain stem nuclei, the nucleus of tractus solitarius, and the locus coeruleus, via dorsal and ventral ascending noradrenergic bundles. After synthesis, AVP is stored in the nerve endings, where it is secreted in response to the electrical activity in these endings (Ganong, 1993; Leslie et al., 1995).

### Control of secretion

**Osmoregulation.** Osmotic regulation is mediated by osmoreceptors located in the anterior hypothalamus, which sense changes in body fluid osmolality. These receptors appear to be located in the circumventricular organs, outside the blood brain barrier, most likely in the organum vasculosum of the lamina terminalis (OVLT), or the subfornical organ (SFO). The osmoreceptors have direct projections to AVP magnocellular neurons in the PVN and the SON, this pathway involves angiotensin II as a neurotransmitter (Leonard, 1996).

There is a direct linear correlation between plasma osmolality and plasma AVP concentrations. When plasma osmolality changes by as little as one percent, substantial changes in plasma AVP occur. When the effective osmotic pressure of the plasma increases above the osmotic threshold, of 285 and 295 mOsm/kg in human and rats respectively, AVP secretion increases. In healthy humans, the infusion of concentrated NaCl (855 mM) to steadily increase plasma osmolality results in progressive rises in peripheral plasma AVP concentrations.

Osmoreceptors are very sensitive to changes in plasma Na<sup>+</sup> concentration and other solutes. The response of the osmoreceptor to solutes other than NaCl is variable. In the presence of insulin, moderate hyperglycemia fails to stimulate AVP secretion, but diabetic rats release AVP with severe hyperglycemia. Furthermore, urea has about one third the stimulatory effect of NaCl on AVP release. As plasma AVP rises, water retention occurs and urine becomes concentrated increases. Maximum diuresis occurs at plasma concentrations of AVP  $\leq$  0.5 pM. In response to rising plasma osmolality from 284

mOsm/kg (osmotic threshold for AVP release), plasma AVP concentration increases progressively to achieve increases in water retention. The osmoregulatory system for thirst and AVP secretion maintains plasma osmolality within the narrow limits of about 284 to 295 mOsm/kg in human (Ganong, 1993; Leslie et al., 1995).

***Baroregulation.*** Blood volume and pressure are widely recognized to influence AVP secretion. In contrast to the simple direct linear correlation between plasma osmolality and plasma AVP concentration, there is an inverse relationship between AVP secretion and the rate of discharge in afferents from stretch receptors in the high- and low-pressure portions of the vascular system. The blood volume is regulated by low pressure receptors in the left atrium, great veins, and pulmonary vessels, whereas arterial blood pressure regulation is mediated by baroreceptors located in the aortic arch and the carotid sinus. Afferent information is transmitted from the cardiac receptors and aortic arch baroreceptors by the vagi and from the carotid sinus baroreceptors by the glossopharyngeal nerves to the nucleus tractus solitarius (NTS) in the medulla. Input from the left atrial stretch receptors and the sinoaortic baroreceptors is inhibitory for AVP secretion; whereas, activation of the ventricular receptors is presumed to be stimulatory. Baroreceptor-mediated inhibition of the AVP secretion occurs via a pathway from the NTS to the A1 area (Ganong, 1993; Leslie et al., 1995).

***Other regulatory mechanisms affecting AVP secretion.*** In addition to osmoregulation and baroregulation there are other stimuli promoting AVP release. These stimuli include nausea, surgical stress, pain, some emotions, and a variety of drugs, including large

doses of barbiturates, morphine, and nicotine. Nausea and emesis are extremely powerful stimuli to AVP secretion. During nausea in primates, circulating AVP values  $\geq 500$  pM have been recorded, which are independent of osmotic and hemodynamic input. Traction on the intestines during surgery, for example, is a similar powerful nonosmotic stimulus for AVP release. Both phenomena probably contribute to the high plasma AVP values observed after gastrointestinal surgery and cause hyponatremia if excess fluid is administered in the postoperative period. Whether AVP is a true stress hormone remains controversial (Ganong, 1993; Leslie et al., 1995).

#### Vasopressin actions

The AVP actions are mediated via two kinds of receptors ( $V_1$  and  $V_2$ ) which are coupled to a GTP-binding protein (G-protein). The  $V_1$  receptors are classified into  $V_{1a}$  and  $V_{1b}$ , each of which is coupled to the phospholipase C and thus increases the formation of inositol 1,4,5-triphosphate ( $IP_3$ ), which increases the intracellular  $Ca^{2+}$  concentrations by promoting  $Ca^{2+}$  release from the endoplasmic reticulum and  $Ca^{2+}$  influx via  $Ca^{2+}$  channels. The vasoconstrictive activities of AVP are mediated by  $V_{1a}$  receptors, which are located in blood vessels. The  $V_{1b}$  receptors on the other hand are found in the pituitary corticotroph, pancreatic islets, and adrenal medulla. The  $V_2$  receptors are coupled to the G protein coupling to adenylate cyclase ( $G_s$ ) and is found principally in the kidney (Ganong, 1993; Leslie et al., 1995).

**Renal effects.** Two well-recognized sites of action of AVP have been located in the mammalian kidney, the collecting duct and the medullary thick ascending limb of Henle's

loop. AVP may also act on other parts of the nephron, including the glomerulus. Its effect on the collecting duct is to concentrate urine and this effect is dependent upon a solute gradient across the tubular cells, which arises from a hypertonic renal interstitium and hypotonic luminal fluid in the tubule. The hypertonic interstitium results from the active transport of solute from the Henle's loop, which acts as a countercurrent multiplier. The vasa recta following the course of the loop functions as the countercurrent exchanger. Consequently, a small solute gradient is created between ascending and descending limbs of Henle's loop, which allows the formation of a progressively more concentrated interstitium from the corticomedullary junction to the papilla. In the presence of AVP, the water permeability of the collecting duct that pass through the hypertonic interstitium increases. This enables water to move along the gradient from lumen to renal medulla, resulting in a decrease in urine output (Ganong, 1993; Leslie et al., 1995).

The increase in water permeability is mediated by a complicated cascade of intracellular events, starting with activation of adenylate cyclase to increase intracellular cAMP concentrations. Stimulation of a cAMP-dependent protein kinase (protein kinase A) rearranges the intracellular microfilaments and microtubules in response to AVP, but the precise nature and sequence of these events are obscure. The final step involves the insertion of aggregates of water-conducting particles into the luminal membrane of the collecting tubule. These aggregates arise from cytoplasmic tubular structures that fuse with the luminal membrane (Leslie et al., 1995).

Some epithelia of the renal tubules exhibit an extremely high water permeability that is mediated via specialized protein pores named water channels, which are now referred to as

“aquaporins” (AQP). AQP2 (WCH-CD) is a membrane-bound glycoprotein that appears in both nonglycosylated (28 kDa) and glycosylated forms (40-60 kDa). AQP2 is a water channel restricted to the apical domain of the renal collecting duct principal cells, and its localization is strongly enhanced in the renal medulla of dehydrated rats (due to the effect of AVP). In rats treated with AVP for up to 30 minutes the water channels are located into a dense apical band in principal cells. In the absence of AVP, however, these channels reside in cytoplasmic vesicles diffusely scattered in the apical cytoplasm of collecting duct principal cells. In the presence of AVP, the vesicles that contain the water channels move toward the apical membrane and, via a process of exocytosis, fuse with and insert water channels into the apical membrane. This results in an increased permeability of the apical plasma membrane to water. In the absence of stimuli, water channels are removed from the apical membrane via clathrin-mediated endocytosis (Sabolic and Brown, 1995).

In addition to AVP-sensitive water channels in the terminal collecting duct, there is a distinct AVP-regulated urea transporter in the distal collecting duct of the mammalian kidney. By recycling urea into the renal interstitium, urea is conserved to contribute to the osmotic gradient essential for the water channels (Leslie et al., 1995).

The other major renal site of AVP action is the medullary thick ascending limb of Henle's loop, which possesses, in some species,  $V_2$ -receptors. Clear evidence exists that  $Na^+$  can be actively transported into the renal interstitium following AVP-stimulation of the thick ascending limb. The effect of AVP on this part of the nephron assists in the generation of a hypertonic interstitial renal medulla and increases the osmotic gradient across the collecting duct, resulting in augmentation of its antidiuretic action (Leslie et al., 1995).

**Cardiovascular effects.** Although AVP is a potent vasopressor, plasma concentrations which are required to increase arterial blood pressure in healthy humans are many times higher than those observed under normal basal conditions. Nevertheless, AVP can produce considerable constriction of numerous regional arteries and arterioles (e.g., splanchnic, renal, hepatic) at nearly physiological plasma concentrations (10 pM). Using specific  $V_{1a}$  receptor antagonists as pharmacologic tools, the importance of endogenous AVP in maintaining blood pressure in mild volume depletion has emerged. The pressor effect of AVP varies according to the vascular bed, and differential pressor effects on intrarenal vessels account for the shunting of blood from the medulla to the cortex under the influence of AVP (Ganong, 1993; Leslie et al., 1995).

**Effect on the pituitary.** The release of ACTH from the anterior pituitary is under a synergistic action of corticotrophin-releasing factor (CRF) and AVP. AVP, synthesized in the parvocellular part of the PVN, is released from the median eminence into the portal blood to supply the anterior pituitary gland.  $V_{1b}$  receptors are found in abundance in the corticotrophic cells of the anterior pituitary gland. Following adrenalectomy in rats, CRF and AVP were found to be elevated in the PVN, where the two peptides are co-localized within the same cell. Corticosteroid administration, however, reverses the effect of adrenalectomy (Ganong, 1993; Leslie et al., 1995).

### **Thirst Mechanism**

Thirst is an extremely powerful sensation that drives the seeking and drinking of water. It is regulated by osmoreceptors and baroreceptors in the same way that AVP is

regulated. An increase in effective osmotic pressure of the plasma and a decrease in plasma volume are potent stimuli affecting water intake. A simple direct linear correlation exists between thirst and plasma osmolality, and small changes in blood tonicity are readily corrected by thirst. As mentioned above, osmoreceptors are specialized structures located in the anterior hypothalamus, most probably in the organum vasculosum of the lamina terminalis (OVLT), and the subfornical organ (SFO). Despite wide individual variations in the value of the thirst osmotic threshold, it remains remarkably consistent within individuals (Ganong, 1993; Leslie et al., 1995).

Stimulation of thirst by extracellular volume depletion can be partially mediated by renin-angiotensin system. Hypovolemia stimulates angiotensin II formation, which in turn acts on the SFO and probably on the OVLT to stimulate the neural areas concerned with thirst. Underfilling of the low-pressure thoracic circulation leads to drinking in animals, an effect probably mediated by the left atrium via the vagus nerve (Ganong, 1993).

### **Renin**

Renin is an acid protease (aspartyl protease) synthesized and secreted by the juxtaglomerular apparatus of the kidney (Ganong, 1993). The juxtaglomerular (JG) apparatus consists of three distinct groups of cells: (1) the juxtaglomerular cells (2) lacis cells and (3) the macula densa. The JG cells are epithelioid cells located in the media of the afferent arterioles as they enter the glomeruli; lacis cells on the other hand, are agranular cells located in the junction between the afferent and efferent arterioles, and finally the macula densa is a



modified region of tubular epithelium formed at the point where the tubule of the nephron touches the arterioles (at the point where the afferent arteriole enters the glomerulus and the efferent arteriole leaves it) of the glomerulus (Ganong, 1993; Guyton and Hall, 1996; Leslie et al., 1995; Swenson and Reece, 1993). The secreted renin cleaves its substrate, angiotensinogen (or renin substrate), a circulating  $\alpha_2$ -globulin synthesized by the liver, to produce angiotensin I, a biological inactive decapeptide, which appears to be only the precursor of angiotensin II without any other established function. Angiotensin-converting enzyme cleaves two terminal amino acids from angiotensin I, to form angiotensin II, an octapeptide. Angiotensin-converting enzyme is present in most endothelial cells, but lung endothelial cells have the highest concentration of it. Thus, more than 80% of the angiotensin I conversion to angiotensin II occurs during its passage through the lung. It is also found in vascular endothelial cells of renal arteries, and there is substantial conversion of angiotensin I to angiotensin II in the renal circulation (Ganong, 1993; Guyton and Hall, 1996; Leslie et al., 1995). Angiotensin III is formed when angiotensin II undergoes N-terminal degradation to form the heptapeptide (des-aspartyl)-angiotensin II. Angiotensin III has the same influence on aldosterone secretion as angiotensin II, however, it shows considerably less pressor activity (Ganong, 1993; Leslie et al., 1995).

#### Control of renin secretion

Many factors influence renin secretion, including renal perfusion pressure, sympathetic nervous system activity, and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) are stimulatory while dopamine, atrial natriuretic peptide (ANP), vasopressin (AVP), and angiotensin II are inhibitory (Ganong, 1993; Leslie et al., 1995).

Decreased perfusion pressure, sensed by stretch of the afferent arteriolar wall (intra-renal baroreceptor mechanism), is a major factor controlling renin release. Through this mechanism the main feedback control occurs to increase aldosterone secretion when extracellular fluid volume has not been normalized. But, when the intra-arteriolar pressure at the level of JG cells increases, the renin secretion decreases (Ganong, 1993; Leslie et al., 1995). The other major factor controlling renin secretion is based on the composition of the tubular fluid that passes through the macula densa. Therefore, an increase in the delivery of  $\text{Na}^+$  and  $\text{Cl}^-$  to the distal tubules is associated with a decrease in renin secretion and vice versa (Ganong, 1993; Leslie et al., 1995).

Sympathetic nervous system activity increases renin secretion. Both circulating catecholamines and renal sympathetic nerves are responsible for this increase. The sympathetic effects on renin secretion are mostly mediated by  $\beta_1$ -adrenergic receptors and to a lesser degree by  $\alpha$ -adrenergic receptors (Ganong, 1993). Activation of  $\beta_1$ -receptors increases renin secretion, whereas, activation of  $\alpha$ -receptors decreases renin secretion (Leslie et al., 1995). Prostaglandin ( $\text{PGI}_2$ ) has a direct influence on the JG cells to stimulate renin secretion (Ganong, 1993; Leslie et al., 1995). Plasma  $\text{K}^+$  has an inverse relationship with renin secretion (Ganong, 1993; Leslie et al., 1995).

Vasopressin has been shown to have inhibitory effects on renin release (Ganong, 1993). Angiotensin II directly inhibits renin secretion through its short feedback loop, and this inhibition is not mediated through changes in volume or blood pressure. This effect of angiotensin II have been shown by using converting enzyme inhibitors which lead to an

elevation in renin secretion, whereas, angiotensin infusion leads to the termination in renin secretion (Leslie et al., 1995).

In addition to the circulating renin-angiotensin system, a number of tissues have been shown to have local renin-angiotensin systems, including submaxillary glands, testes, ovaries, smooth muscle cells, pituitary, brain, and adrenal cortex. These local renin-angiotensin systems may stimulate aldosterone secretion from the adrenal cortex.

The local adrenal renin-angiotensin system and the circulating system have different regulatory mechanisms (Leslie et al., 1995; Gulati and Lall, 1996). Even though, the reduction in plasma  $\text{Na}^+$  elevates the production of angiotensin II in the circulating system and the adrenal gland, a high- $\text{K}^+$  diet decreases the circulating but increases the adrenal system. High dietary  $\text{K}^+$  intake influences the adrenal renin-angiotensin system via an increase in aldosterone secretion and adrenal sensitivity. Captopril, a converting enzyme inhibitor, blocks both increases (Leslie et al., 1995).

### **Angiotensins**

The angiotensins are a group of peptides produced by the action of renin from the inactive precursor, angiotensinogen. Angiotensin II is a remarkably potent vasoconstrictor. However, this effect is reduced during  $\text{Na}^+$  depletion and in some other diseases such as cirrhosis. The reason behind the reduction in angiotensin II pressor activity in these cases is due to the increase in circulating angiotensin II, which in turn downregulates its receptors in

the vascular smooth muscles; thus, the injected angiotensin II will have less pressor effect (Ganong, 1993).

Angiotensin II is the major secretagogue involved in regulating aldosterone secretion by glomerulosa cells of the adrenal cortex in response to changes in plasma  $\text{Na}^+$  and/or volume (Ganong, 1993; Leslie et al., 1995). Angiotensin II and III have similar activity in stimulating aldosterone synthesis and release, initiating their action by binding to the type I angiotensin receptor. Blood pressure and aldosterone secretion increase dramatically after angiotensin II infusion. The vascular smooth muscle appears to be less sensitive than the adrenal cortex, this can be seen clearly by the substantial increase in plasma aldosterone concentrations with angiotensin II infusion at rates insufficient to produce a measurable increase in circulating levels (Leslie et al., 1995).

In addition to its effect on aldosterone secretion, angiotensin II helps the kidney retain water and salt through its direct effect on renal blood vessels. It constricts the mesangial cells (stellate cells located between the basal lamina and the endothelium of the renal arterioles) thereby diminishing glomerular filtration rate. The slow flow of the blood in the peritubular capillaries also reduces their pressure, which allows rapid osmotic reabsorption of fluid from the tubules. Thus, for both of these reasons, less urine is excreted (Ganong, 1993; Guyton and Hall, 1996).

Angiotensin II acts on the circumventricular organs, four small structures in the brain that are outside the blood-brain barrier in order to reduce blood pressure, increase water intake, and increase the secretion of AVP and ACTH (Ganong, 1993).

Angiotensin II has four types of receptors (AT 1-4) that may mediate its diverse functions. AT1 receptor, a serpentine receptor, is the most well known receptor that preferentially binds angiotensin II and angiotensin III. The AT1 receptors appear to mediate the classic known influences of the Angiotensin II concerned with the body water balance and the maintenance of blood pressure. They are found in many organs, including the adrenal cortex, the walls of blood vessels, the brain, and many other organs. There is an opposite regulation of the AT1 receptors located in the adrenal cortex and the arterioles: an excess of angiotensin II upregulates the adrenocortical receptors, making the gland more sensitive to the aldosterone-stimulating effect of the peptide, at the same time it downregulates the vascular receptors. AT1 receptors are found to be coupled by a G protein (Gq) to phospholipase C. The cytosolic free  $\text{Ca}^{2+}$  concentration is increased by angiotensin II. Less is known about the AT2 receptor which also binds angiotensin II and angiotensin III, and is found in abundance in fetal and neonatal life, but in the adults AT2 receptors remain in the brain and other organs, and may play a role in vascular growth. No second messengers are yet known for AT2 receptors. Recently, AT3 receptors have been discovered in cultured neuroblastoma cells and AT4 receptors that preferentially bind angiotensin IV. It has been implicated in memory acquisition and retrieval and in the regulation of blood flow (Ganong, 1993; Gulati and Lall, 1996).

## **Aldosterone**

Aldosterone, secreted from the adrenal cortex, has an important role in body fluid and electrolyte regulation by increasing  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion in many of body tissues, including the kidney, sweat glands, salivary glands, and colon. Aldosterone is the major mineralocorticoid synthesized and secreted by the glomerulosa cells of the adrenal cortex, and its rate of secretion fluctuates in a manner consistent with its regulatory function. It varies inversely with changes in  $\text{Na}^+$  intake (Ganong, 1993; Guyton and Hall, 1996; Leslie et al., 1995).

### Aldosterone actions

In the kidney, the major site of aldosterone action is on the cortical collecting duct. It also has important actions on other regions of the nephron including: the medullary collecting duct, where it directly stimulates  $\text{H}^+$  secretion, and the thick ascending limb of Henle's loop, where it stimulates  $\text{Na}^+$  reabsorption indirectly. Mineralocorticoid receptors are localized almost exclusively in the cortical collecting duct and other subdivisions of the collecting tubule; specific aldosterone binding is negligible in more proximal segments of the nephron (Leslie et al., 1995).

Aldosterone acts to stimulate  $\text{Na}^+$  reabsorption as well as  $\text{K}^+$  and  $\text{H}^+$  ion secretion in the cortical collecting duct. The renal cortical collecting duct is composed of at least two types of epithelial cells: The principal cells, which comprise of about 75% of the cells, are primarily responsible for  $\text{Na}^+$  and  $\text{K}^+$  transport, and the intercalated cells which regulate  $\text{H}^+$  ion or  $\text{HCO}_3^-$  absorption or secretion. Each of these latter functions is carried out in a distinct

subtype of the intercalated cells, both responsive directly or indirectly to the stimulatory action of aldosterone. In addition, the medullary collecting duct is engaged exclusively in the secretion of  $H^+$  ions and this function also is stimulated directly by aldosterone (Leslie et al., 1995).

The cortical collecting duct response to aldosterone is characterized by an early phase, with an onset of one to two hours,  $Na^+$  transport in this phase is increased by the addition of more  $Na^+$  channels at the apical cell membrane, causing greater  $Na^+$  influx. The late phase, on the other hand, is characterized by enhancement in  $Na^+$  transport by the synthesis of new  $Na^+$  pumps,  $Na^+$ ,  $K^+$ -ATPase, in the basolateral cell membrane. The activation of the latent pre-existent channels is the reason behind this increase in sodium channels, and this activation, nevertheless, does require protein synthesis. During the late phase, the up-regulation of  $Na^+$ ,  $K^+$ -ATPase is due to a direct stimulation of synthesis of the enzyme via aldosterone. The synthesis of  $Na^+$ ,  $K^+$ -ATPase due to an increase in aldosterone concentration is a slow process having a variable latent period depending upon aldosterone level: around 1 to 3 hours in adrenalectomized animals and 24 hours in animals with intact adrenals (Leslie et al., 1995).

The transport of  $Na^+$  and  $K^+$  resulting from  $Na^+$ ,  $K^+$ -ATPase activity is tightly coupled. During the early phase of aldosterone action,  $Na^+$ ,  $K^+$ -ATPase activity increases due to the increased  $Na^+$  influx at the apical cell membrane. Thus  $Na^+$  extrusion and  $K^+$  entry are elevated at the basolateral membrane. The increase in  $K^+$  entry combined with depolarization of the apical membrane provides a favorable electrochemical gradient for  $K^+$  secretion into the lumen through existing apical membrane  $K^+$  channels. During the late phase,  $K^+$  secretion

is greatly augmented by increased pump activity resulting from synthesis of new  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase and also by the up-regulation of  $\text{K}^+$  channels in both the apical and basolateral cell membranes (Leslie et al., 1995).

The effects of aldosterone on the sweat and salivary glands are the same as its effects on the renal tubules. Both these glands form a primary secretion that contains large quantities of NaCl, but much of the NaCl, on passing through the excretory ducts, is reabsorbed, whereas  $\text{K}^+$  and  $\text{HCO}_3^-$  ions are secreted. The reabsorption of NaCl and the secretion of  $\text{K}^+$  by the ducts are markedly increased by aldosterone. In hot environments, the effect of aldosterone on the sweat glands is important in order to conserve body salt, and its effect on the salivary glands is necessary to conserve salt when excessive quantities of saliva is lost.

Aldosterone also greatly enhances  $\text{Na}^+$  absorption by the intestines, especially in the colon, which prevents the loss of  $\text{Na}^+$  in the stool. On the other hand, in the absence of aldosterone,  $\text{Na}^+$  absorption can be poor, leading to a failure to absorb  $\text{Cl}^-$  and other anions and water as well. The unabsorbed NaCl and water then lead to diarrhea, with further loss of salt from the body (Guyton and Hall, 1996).

### Mechanism of aldosterone action

The mechanism of aldosterone action is briefly discussed here. Aldosterone as a mineralocorticoid has two terms of effects: the first one is the long-term effects, which is considered as a genomic, and late onset actions and can be blocked by inhibitors of transcription or translation, such as actinomycin D and cycloheximide respectively (Wehling, et al., 1993). When aldosterone binds to the mineralocorticoid receptors, a family of



intracellular steroid receptors, the binding interaction results in transformation of the receptor. The transformed receptor is translocated to the cell nucleus and is rendered capable of binding to specific DNA sites, thereby initiating expression or repression of regulated genes involved in the synthesis of proteins that mediate the effects of aldosterone. The principal new protein is a  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase which provides the target cells with more  $\text{Na}^+$  pumps. Aldosterone also appears to increase the abundance of amiloride-inhibitable  $\text{Na}^+$  channels in the membranes of target cells and to increase the  $\text{H}^+$  pump activity in cortical collecting ducts. In addition, there may be a small number of  $\text{Na}^+$ - $\text{H}^+$  antiporters in the distal as well as the proximal portions of the nephrons, and the activity of the distal antiporters may be increased by aldosterone (Ganong, 1993). The synthesis of a new protein is a long process; it takes 10-30 minutes (Ganong, 1993), 30-45 minutes (Guyton and Hall, 1996), and Wehling, et al., 1993, reported that the genomic effects of aldosterone are characterized by a latency of action lasting between 2-8 hours, and this can clearly explain why it takes long time to see the start of aldosterone effects on  $\text{Na}^+$  excretion, even when it is directly injected into the renal artery (Ganong, 1993).

The second mechanism of aldosterone action is the short-term effects. Studies in extrarenal non-epithelial cells such as smooth muscle cells and easily accessible human lymphocytes have demonstrated that aldosterone not only produces classical genomic effects, but also rapid non-genomic effects on transmembrane electrolyte movements. These involve the activation of the  $\text{Na}^+$ - $\text{H}^+$  antiporters of the cell membrane with an acute initiation within 1 to 2 minutes, which cannot be explained as a genomic effects. The mechanisms underlying these fast aldosterone electrolyte effects have been studied extensively in human

lymphocytes and rat vascular smooth muscle cells representing attractively valuable tools in the delineation of the receptor-effector mechanisms involved. This includes the demonstration of membrane binding sites in lymphocytes which are highly specific for aldosterone and transmit the rapid non-genomic responses to aldosterone, as suggested by the intriguing similarities of binding kinetics and pharmacology in the receptor and effector assays. The unique characteristics of this new pathway for steroid action includes its rapid time course, 10,000-fold selectivity for aldosterone over cortisol, and the ineffectiveness of spironolactones, the classical mineralocorticoid cytosolic receptor antagonist (Wehling, 1995).

The rapid effects of aldosterone on intracellular  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ , cell volume and the  $\text{Na}^+$ -proton-antiport have been described in human mononuclear leukocytes and rat vascular smooth muscle cells. These nongenomic effects are signaled through membrane receptors with a high affinity for aldosterone, but not for cortisol. The rapid intracellular signaling for aldosterone in rat vascular smooth muscle cells is through phospholipase C, diacylglycerol (DAG) and protein kinase C (PKC) in addition to  $\text{Ca}^{2+}$  and inositol-1,4,5-trisphosphate in human lymphocytes, cultured vascular smooth muscle, and endothelium (Christ et al., 1995).

### Control of secretion

Many factors have been shown to be involved in the control of aldosterone secretion. Many would argue that angiotensin II is the major secretagogue involved in the regulation of aldosterone secretion (Ganong, 1993; Griffin and Ojeda, 1992; Guyton and Hall, 1996; Leslie et al., 1995).

In humans, the changes in ECF volume and/or NaCl balance are accompanied by comparable changes in plasma renin activity and aldosterone secretion. Moreover, aldosterone secretion in humans is stimulated by angiotensin II, and the resultant increments are sustained during prolonged stimulation. These observations support the assumption that the aldosterone responses to changes in salt balance or volume status are regulated by the renin-angiotensin system (Leslie et al., 1995). The usage of converting enzymes inhibitors such as captopril and enalapril, that block the conversion of angiotensin I to angiotensin II has opened another scope to this inquiry. In conscious Na<sup>+</sup> depleted sheep the effects of captopril together with dexamethasone (to minimize pituitary secretion of ACTH) suggests that angiotensin II is a primary stimulus to aldosterone during Na<sup>+</sup> depletion. Nevertheless, in the absence of a functional angiotensin II, other factors can become dominant and can restore aldosterone secretion to levels appropriate for the degree of Na<sup>+</sup> depletion (McDougall, 1987).

In spite of the fact that plasma aldosterone secretion is regulated mainly by angiotensin II, it also is influenced by many other factors. A small increase in plasma K<sup>+</sup> concentration is able to cause a distinct increase in aldosterone secretion. The zona glomerulosa cells are extremely sensitive to the changes in plasma K<sup>+</sup> concentrations. *In vivo*, stimulatory effects on aldosterone secretion start with changes in plasma K<sup>+</sup> concentration as little as 0.2 mM. Stimulation of aldosterone secretion by K<sup>+</sup> is due to its direct effect on glomerulosa cells, as aldosterone levels rise in response to oral K<sup>+</sup> loading plasma renin activity is depressed. Even though angiotensin II facilitates the aldosterone response to K<sup>+</sup>, the stimulatory effect of K<sup>+</sup> concentration is blunted in dogs when angiotensin II is reduced

by captopril (ACE-I) (Leslie et al., 1995). Although the aldosterone response to  $\text{Na}^+$  restriction is mediated mostly by angiotensin II,  $\text{K}^+$  can exert an additional stimulatory effect independently. Changes in plasma  $\text{Na}^+$  concentration may have a direct influence in aldosterone secretion (Leslie et al., 1995).

The regulation of aldosterone secretion under the influence of ACTH is still controversial. In humans with chronic pituitary insufficiency and after hypophysectomy, the secretion of aldosterone may be decreased. Elevated aldosterone levels of caval-constricted dogs are sharply reduced by hypophysectomy. In humans with hypopituitarism and in hypophysectomized animals, aldosterone secretion remains responsive to salt deprivation or other physiological stimuli (Leslie et al., 1995).

Aldosterone secretion is unresponsive to small doses of ACTH, however, large doses of ACTH have shown to stimulate aldosterone secretion, but the response is transient and declines after the first 24 hours in spite of the continuous administration of ACTH. Several fragments of the 31-kDa ACTH processor polypeptide pro-opiomelanocortin (POMC), such as  $\beta$ -lipotropin,  $\beta$ -melanocyte-stimulating hormone, and  $\beta$ -endorphin, have shown to stimulate aldosterone secretion (Leslie et al., 1995).

To summarize the ACTH role in aldosterone secretion, during the pathological circumstances ACTH, or other pituitary factors, that possibly derived from POMC, may be a dominant stimulus to aldosterone secretion. However, ACTH has a lesser part under normal circumstances (Ganong, 1993; Griffin and Ojeda, 1992; Leslie et al., 1995).

## **Dehydration and Its Pathogenesis**

Dehydration occurs when there is a disturbance in body fluid balance in which more fluid is lost from the body than is absorbed, which in turn results in a reduction in circulating blood volume. The excessive loss of water and the failure of water intake are the principal cause of dehydration. Diarrhea, vomiting, polyuria, skin wounds, and copious sweating are the most common causes of dehydration when excessive fluid is lost. On the other hand, water deprivation, esophageal obstruction, and the lack of thirst due to toxemia are common causes of dehydration when there is a failure in water intake (Radostits et al., 1994). The interference with tissue metabolism due to the depression of the tissue fluid levels and the reduction in the blood volume are the main factors involved in dehydration pathogenesis. Dehydration is considered serious when it involves the loss of water as well as electrolytes (Swenson and Reece, 1993).

Dehydration due to water deprivation under severe environmental conditions is considered in this study. Fluid withdrawal from the tissues to maintain normal blood volume is the first response to the disturbance in water balance. The shift of fluids mainly comes from the intravascular compartment and the interstitial space. The second response to the disturbance in water balance is the reduction in blood volume, which in turn leads to hemoconcentration, and consequently an increase in hematocrit value and serum protein concentration (Radostits et al., 1994). Plasma osmolality and plasma  $\text{Na}^+$  concentration increase during water deprivation. As ECF is reduced in the beginning of dehydration the increased concentrations of  $\text{NaCl}$  appear in the urine. By the end of a long period of

dehydration, there is a depletion in water as well as the principal electrolytes.

Hemoconcentration increases plasma viscosity which in turn, impedes blood flow. During water deprivation, the kidney compensates effectively via decreasing urine output. In addition, water can be preserved via producing a very dry feces. Dehydration also affects tissue metabolism via increasing the breakdown of fat, then carbohydrate and finally protein, in order to produce water. Acidosis develops due to the formation of acid metabolites.

The reduction in urine output and the increase in the metabolism, causes a moderate increase in plasma levels of non-protein nitrogen, usually urea and creatinine (Radostits et al., 1994). Blood urea nitrogen (BUN) concentrations are inversely proportional to glomerular filtration rates (GFR). Urea is subject to passive reabsorption in the tubules, and this occurs to a greater extent at slower tubular flow rates, which occur during dehydration and volume depletion (Ettinger and Feldman, 1995). Creatinine, on the other hand, is a nonenzymatic breakdown product of phosphocreatine in muscle, and daily production of creatinine in the body is determined largely by the muscles mass of the animal. Young animals have lower concentrations whereas males and well-muscled animals have higher concentration of creatinine. Creatinine is not metabolized and is excreted by the kidneys almost entirely by glomerular filtration. The rate of creatinine excretion is relatively constant in the steady state, and its concentration varies inversely with GFR. Therefore, creatinine clearance determination provides a good estimate of GFR ( Ettinger and Feldman, 1995). Due to the reduction in fluids that is necessary to maintain the loss of heat via evaporation, there is a slight increase in body temperature during dehydration. In addition, there is a delay in the onset of sweating. Dehydration is also accompanied by a loss in body weight and a lack of

appetite. The resistance to the loss in body weight as water before the occurrence of death varies largely according to dietary and environmental conditions. For instance, in humans, the loss in body weight may vary between 15-25 % (Radostits et al., 1994; Swenson and Reece, 1993).

### **Dehydration and Rehydration in Camels and Other Animal Species**

Regulation of body fluid homeostasis within narrow limits depends mainly on the maintenance of a balanced water economy. The capability of maintaining body fluids under a wide range of environmental conditions is known to be controlled primarily by the concentration of plasma arginine vasopressin (AVP), which regulates renal water absorption, and also by the thirst mechanism. It has been shown that several mammalian species increase the excretion of  $\text{Na}^+$  in urine as they become dehydrated (McKinley, 1992). The conservation of solutes, particularly  $\text{Na}^+$ , is as vital to the animal as the conservation of water.  $\text{Na}^+$  content is controlled primarily by aldosterone (Choshniak and Shaham, 1990).

The ability of the arabian camel (Camelus dromedarius) to endure heat stress and water deficiency has been supported by experimental studies (Achaaban et al., 1992; Finberg et al., 1978; Macdonald, 1984; Schmidt-Nielsen, 1964). The unique physiological ability to withstand drought conditions and to survive on poor quality fibrous vegetation, makes the camel well suited to desert areas (Higgins, 1985). It can survive on dry vegetation for two weeks or more, depending on the environmental temperature (Yagil, 1985).

The dromedary camels have various ways to conserve body fluids. They can produce a greatly reduced volume of an extremely concentrated urine. The long of Henle's loops in the camel's kidneys entitle the reabsorption of a large amounts of water via the countercurrent multiplier system. In addition, they have considerable ability to produce very dry feces (Swenson and Reece, 1993; Yagil, 1985).

The remarkable water metabolism is also accounted for by a low respiratory rate (which reduces the evaporative water losses), water retention in the rumen, and the capability of increasing their body temperature during the day when they are heat stressed. The advantage of increasing body temperature is to save the water that would have been required to dissipate this heat (Higgins, 1985; Swenson and Reece, 1993; Yagil, 1985). The body temperature of the normally hydrated camel is varies by about 2 °C, between 36 °C and 38 °C (Schmidt-Nielsen, 1990). This fluctuation in body temperature is remarkably increased by dehydration (Yagil, 1985). The body temperature of the dehydrated camel is extremely low in the early morning, 34 °C, however, it might surpass 42 °C in the late afternoon. The most important route of evaporative heat dissipation in camel is through sweating; however, they do not sweat until their body temperature exceeds 42 °C (Yagil, 1985).

Finally, the rapid rehydration capability of the camel is one of the most important adaptation features. Camels have lost more than a third of their body weight in water after 2-3 weeks of water deprivation without suffering any ill-effects (MacFarlane et al., 1971; Schmidt-Nielsen, 1964; Yagil, 1985 ). The camel can consume more than one-fourth of the body weight as water in a few minutes and their body fluids become promptly diluted. The plasma osmodilution due to rapid intake of water usually causes hemolysis of red blood cells



in man and other mammals, but the oval biconcave erythrocytes of the camel are extremely resistant to such hemolysis (Swenson and Reece, 1993; Yagil, 1985; Yagil et al., 1974a).

Intake of water and the end product of cellular metabolism are the main sources of body water, which can be lost through urine, alimentary canal (in the feces), from the skin, with expired gases, and also through the milk in lactating animals. Most of these routes of water loss or gain are not controlled with respect to body water content. Water intake and urinary water excretion are the only routes to be controlled in order to regulate body water volume (Swenson and Reece, 1993). The major role in adjusting body fluid balance is maintained by kidneys (Ganong, 1993; Swenson and Reece, 1993; Yagil, 1985).

In the kangaroo rat, a desert rodent, metabolic water plays an important role in their water balance and may constitute 100 % of their water intake (Swenson and Reece, 1993). However, Yagil et al. (1974c) have shown that in the camel metabolic water is not the ideal source that can be relied upon, particularly during water deprivation when basal metabolic rate is reduced. Consequently, alimentary water of the dehydrated camel is the most important source of body water (Yagil, 1985).

The absorption of water and electrolytes from the kidneys and the gut is under the influence of plasma AVP and aldosterone (Ganong, 1993; Swenson and Reece, 1993). These two hormones are directly responsible for the maintenance of electrolytes and body fluids homeostasis. In addition, AVP plays an important role in maintaining blood pressure due to its vasoconstrictive activity (Ganong, 1993; Yagil, 1985).

Finberg et al. (1978) studied the effects of 8-10 days of water deprivation in five young female camels during cool spring ( 23.5 °C) and hot summer ( 36.9 °C) weather, and

found that dehydration was accompanied by an increase in plasma  $\text{Na}^+$  concentration from  $138 \pm 3.7$  to  $147 \pm 2.5$  (mean  $\pm$  SEM) mEq/l during spring, and from  $146 \pm 1.3$  to  $157 \pm 1.14$  mEq/l after two days of dehydration and stayed at a similar concentration throughout the 8-10 days during summer. Plasma  $\text{Na}^+$  returned to its control level after 15 minutes of rehydration on spring, on the other hand, plasma  $\text{Na}^+$  decreased slightly by 2-3 hours of rehydration and returned to its control level after 24 hours on summer. There were no changes in plasma  $\text{K}^+$  concentration during dehydration in both seasons. However,  $[\text{K}^+]$  decreased slightly 15 minutes to 3 hours during rehydration in summer and increased by 0.58 mEq/l after 24 hours of rehydration in the spring. There were significant increases in plasma renin activity (PRA) and plasma aldosterone concentration (PA) in both seasons, but, the increases were greater in the summer. Soon after rehydration PRA, returned to its control levels, however, it returned slower in the summer. In contrast to PRA, PA showed a further increase after rehydration, and 24 hours after rehydration, a marked elevation was observed in both seasons, but, the increases were remarkable in the summer. There were no significant differences in cortisol levels during dehydration and rehydration in both seasons.

In another study, three young female camels were subjected to 14 days of water deprivation and 10 days of rehydration in hot, dry summer weather ( $40^\circ\text{C}$ , 25% Relative Humidity) of Tadla, Morocco. Water restriction was accompanied by a profound reduction in urine output (82%), a significant increase in plasma AVP concentration and plasma osmolality. Urine output increased slightly in the first 24 hours of rehydration, then rapidly to beyond the control level after 48 to 72 hours. During rehydration, AVP concentrations fell slowly in the initial 24 hours, and remaining very low thereafter (Achaaban et al., 1992).

Water deprivation for 72-96 hours in ewes induces hypovolemia and a marked increase in plasma AVP concentration and osmolality (Agnew et al., 1993; Bell et al., 1991; Dodd et al., 1992), and an increase in plasma  $\text{Na}^+$  and  $\text{Cl}^-$  (Dodd et al., 1992). After 24 hours of water deprivation in castrated rams, there was no change in plasma cortisol concentration, but there was a significant reduction in the hematocrit (Thornton et al., 1987). In the water-deprived sheep, there was a reduced in the glomerular filtration rate (Leng et al., 1987). During rehydration plasma AVP decreased rapidly, and reached the basal level within 5 minutes (Bell et al., 1991) in comparison to the gradual decrease in plasma osmolality (Agnew et al., 1993). Thus satiation was not necessary for rapid inhibition of AVP release after drinking, but satiation was necessary for this inhibition to be maintained. The initial inhibition was associated with falls in hematocrit and plasma total protein but not plasma osmolality (Blair-West et al., 1987). Plasma sodium and osmolality returned to predehydration levels within 6 hours of satiation (Bell et al., 1991). Dehydration for 48 hours in sheep increased total plasma protein and plasma renin activity (PRA) (Dahlborn and Holtenius, 1990). Blair-West et al. (1972) found that plasma renin concentrations increased in the dehydrated sheep and it reached the highest concentration 12 hours of rehydration. Twenty four hours after drinking, renin concentrations remained elevated. It was suggested that the stimulus for renin secretion was the reduction in  $\text{Na}^+$  concentrations in the macula densa.

During 4 days of dehydration in unrestrained steer calves, there was a progressive increase in plasma osmolarity (posm) with hypernatremia, packed cell volume (PCV) (Bell et al., 1985; Doris and Bell, 1984a; Doris and Bell, 1984b). Associated with these changes

was a progressive increase in plasma AVP concentration (Becker et al., 1985; Doris and Bell, 1984b), and plasma angiotensin II (AII) (Bell et al., 1985). By 3 hours rehydration, plasma AVP concentrations dropped dramatically (Becker et al., 1985).

Water deprivation in goats was accompanied by about 30% drop of their initial body weight, a decrease in urine flow, GFR and effective renal plasma flow (ERPF). On the other hand, there was an increase in plasma osmolality, total plasma protein concentration, plasma vasopressin (AVP) concentration (Dahlborn et al., 1988), plasma renin activity (PRA), and plasma aldosterone (PA) (Wittenberg et al., 1986). Following rehydration, the urine flow, GFR and ERPF of the recently rehydrated goats dropped further and even after the 3 hours of the continuous recording that followed rehydration all three parameters did not exceed the predrinking level (Wittenberg et al., 1986). A further increase was recorded in PRA and PA following rehydration (Dahlborn et al., 1988; Wittenberg et al., 1986). At the same time plasma osmolality, Na<sup>+</sup> and AVP fell, but remained above control levels (Dahlborn et al., 1988). On the other hand, Hossaini et al. (1994) studied the effects of dehydration and rehydration, in the black Moroccan goat, and found that, after rehydration, the elevated plasma osmolality as well as Na<sup>+</sup> and total protein concentrations returned to basal values within 2-3 hr, indicating a rapid absorption of the ingested water, but urine excretion did not increase.

Sneddon et al. (1993) investigated the change in plasma AVP and aldosterone concentrations in desert-adapted horses, the Namib horses and in control horses from a subtropical region, during 72 hours of water deprivation and during rehydration. During dehydration, AVP concentrations increased in both groups of horses, but the increase was

greater in Namib horses than in control horses. During rehydration, AVP levels fell, but fell less in Namib horses than control horses. The change in vasopressin concentration correlated significantly with plasma osmolality, and the relationship between these two variables was the same for both groups of horses during the dehydrated and rehydrated states. Aldosterone concentrations fell up to 48-h dehydration in both groups, but decreased significantly more in desert horses. From 48-h dehydration and during rehydration, aldosterone concentrations increased and the increase was sustained longer in Namib than in control horses. Changes in plasma osmolality did not correlate significantly with changes in aldosterone concentration. During dehydration, the Namib horses sustained higher plasma osmolalities and consequently elevated AVP levels than the control horses. From these data it was concluded that plasma osmolality in conjunction with these two hormones plays a significant role in water homeostasis in horses. Naylor et al. (1993), studied the effects of dehydration on horses and found a reduction in plasma volume, an increase in hematocrit, total plasma protein concentration, and plasma  $\text{Na}^+$  and  $\text{Cl}^-$  concentrations. On the other hand, plasma  $\text{K}^+$  concentration was lowered. Pony mares deprived of water showed significant increases in plasma AVP and plasma osmolality. When water was made available the ponies drank rapidly and corrected their fluid deficits precisely. The horse differs from rodents and humans, but is similar to pigs in that AVP levels do not fall before osmolality returns to normal (Haupt et al., 1989).

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## REGULATION OF WATER AND ELECTROLYTE METABOLISM DURING DEHYDRATION AND REHYDRATION IN CAMELS

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### Abstract

The present study was undertaken to examine the effect of severe dehydration and subsequent rapid rehydration on electrolytes and body fluids homeostasis in the arabian camels (Camelus dromedarius). Ten dromedary camels were studied for 29 days under control conditions (7 days), during water deprivation (15 days) and rehydration (7 days) in Bureidah, Saudi Arabia during summer, 1996. Plasma electrolyte concentrations ( $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$ ), plasma osmolality, packed cell volume (PCV), Hemoglobin, plasma concentrations of glucose, creatinine, blood urea nitrogen (BUN), total protein, plasma renin activity (PRA), angiotensin II, aldosterone, arginine-vasopressin (AVP), adrenocorticotrophic hormone (ACTH) and cortisol were determined at specific intervals during both periods. Dehydration was associated with a 25% decrease in calculated plasma volume and a concomitant rise in plasma  $\text{Na}^+$  concentration and plasma osmolality. These changes were accompanied by increases in plasma concentrations of AVP, PRA, angiotensin II, and aldosterone. The changes in plasma ACTH and cortisol concentrations were not parallel to those in the other hormones. However, plasma concentrations of cortisol and ACTH increased at the end of

dehydration. Most of these parameters decreased significantly within ½ hour of rehydration indicating a rapid absorption of water, except for plasma aldosterone, ACTH, and cortisol which increased further. Plasma aldosterone and angiotensin II concentrations were highly correlated ( $r = 0.99$ ) during the first 10 days of dehydration, whereas plasma aldosterone and ACTH concentrations were not ( $r = 0.57$ ). During rehydration plasma aldosterone and ACTH concentrations were highly correlated ( $r = 0.90$ ), whereas plasma aldosterone and angiotensin II were not ( $r = 0.21$ ). Plasma concentrations of AVP and plasma osmolality were highly correlated ( $r = 0.99$ ) during dehydration, whereas during the first 24 hours of rehydration they were less correlated ( $r = 0.75$ ). Our results suggest that aldosterone secretion during dehydration in camels is mainly due to angiotensin system, whereas, during rehydration ACTH seems to dominate. High AVP secretion during dehydration is mainly due to high plasma osmolality, whereas low AVP secretion during rehydration is mainly due to the sudden increase in plasma volume.

### **Introduction**

The ability of the arabian camel (Camelus dromedarius) to endure heat stress and water deficiency has been supported by experimental studies (Achaaban et al., 1992; Finberg et al., 1978; Macdonald, 1984; Schmidt-Nielsen, 1964). The unique physiological ability to withstand drought conditions and to survive on poor fibrous vegetation, makes the camel well suited to desert areas (Higgins, 1985). It can survive on dry vegetation for two weeks or more, depending on the environmental temperature (Yagil, 1985).

The dromedary camels have various ways to conserve body fluids. They can produce a greatly reduced volume of an extremely concentrated urine. The long of Henle's loops in the camel's kidneys enable the reabsorption of a large amount of water via the countercurrent multiplier system. In addition, they have considerable ability to produce very dry feces (Swenson and Reece, 1993; Yagil, 1985).

The remarkable water metabolism is also accounted for by a low respiratory rate (which reduces the evaporative water losses), water retention in the rumen, and the capability of increasing their body temperature during the day when they are heat stressed. The advantage of increasing body temperature is to save the water that would have been required to dissipate this heat (Higgins, 1985; Swenson and Reece, 1993; Yagil, 1985). The body temperature of the normally hydrated camel is varies by about 2 °C, between 36 °C and 38 °C (Schmidt-Nielsen, 1990). This fluctuation in body temperature is remarkably increased by dehydration (Yagil, 1985). The body temperature of the dehydrated camel is extremely low in the early morning, 34 °C, however, it might surpass 42 °C in the late afternoon. The most important route of evaporative heat dissipation in camel is through sweating; however, they do not sweat until their body temperature exceeds 42 °C (Yagil, 1985).

Finally, the rapid rehydration capability of the camel is one of the most important adaptation features. The camel can consume more than one-fourth of the body weight as water in a few minutes and their body fluids become promptly restored. The plasma osmodilution due to rapid intake of water usually causes hemolysis of red blood cells in man and other mammals, but the oval biconcave erythrocytes of the camel are extremely resistant to such hemolysis (Swenson and Reece, 1993; Yagil, 1985; Yagil et al., 1974a).

In the kangaroo rat, a desert rodent, metabolic water plays a very important role in their water balance and may constitute 100 % of their water intake (Swenson and Reece, 1993). However, Yagil et al. (1974c) have shown that in the camel metabolic water is not the ideal source that can be relied upon, particularly during water deprivation when basal metabolic rate is reduced. Consequently, the water that comes from dry food is thought to be the most important source of body water in the dehydrated camel (Yagil, 1985).

The absorption of water and electrolytes from the kidneys and the gut is under the influence of plasma arginine vasopressin (AVP) and aldosterone (Ganong, 1993; Swenson and Reece, 1993). These two hormones are directly responsible for the maintenance of electrolytes and body fluid homeostasis. In addition, AVP plays an important role in maintaining blood pressure due to its vasoconstrictive activity (Ganong, 1993).

It has already been shown that water deprivation increases plasma AVP, osmolality, and  $\text{Na}^+$  concentrations in camels (Achaaban et al., 1992; Finberg et al., 1978; Yagil and Etzion, 1979). There were no changes in plasma  $\text{K}^+$  concentration during dehydration in camels (Ben-Goumi et al., 1993; Finberg et al., 1978). The secretion of plasma renin activity (PRA) and plasma aldosterone increased during water deprivation in camels (Finberg et al., 1978; Yagil and Etzion, 1979). However, Ben-Goumi et al. (1993) found no significant changes in plasma aldosterone concentrations in camels during dehydration.

Shortly after rehydration plasma AVP dropped dramatically, whereas, plasma osmolality and plasma  $\text{Na}^+$  concentrations decreased gradually (Ben-Goumi et al., 1993; Finberg et al., 1978). Plasma  $\text{K}^+$  concentrations decreased slightly 15 minutes after the onset of rehydration (Finberg et al., 1978). Soon after rehydration PRA returned to its control

levels (Finberg et al., 1978). Ben-Goumi et al. (1993), found that PRA concentrations decreased after rehydration but, did not return to control values until 7 days after rehydration. In contrast to PRA, plasma aldosterone concentrations showed a further increase after rehydration (Finberg et al., 1978). Ben-Goumi et al. (1993), found no significant changes in plasma aldosterone concentrations following rehydration. There were no significant differences in cortisol levels during dehydration and rehydration in camels (Finberg et al., 1978).

While reviewing the literature on this topic in camels, we did not find a single publication that utilized adequate control groups to evaluate the changes of plasma electrolytes and body fluids during dehydration and rehydration. In addition, there were no measurements of plasma angiotensin II or plasma ACTH in the camel. The present study was conducted to study the integrative homeostatic changes that occur in the camel during dehydration and rehydration that include the measurement of: plasma AII and ACTH.

### **Materials and Methods**

Preliminary work and techniques were conducted in the Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, Iowa State University. The actual animal experimentation was carried out in the Department of Veterinary Medicine, Faculty of Agriculture and Veterinary Medicine, King Saud University, AlQassem, Bureidah, Saudi Arabia during June and July 1996. Environmental temperature varied between 31 and 42.5°C and relative humidity varied between 20 and 30 %.



Animals: Ten male one-humped camels (Camelus dromedarius) of 4-5 years old weighing  $484 \pm 23$  kg (mean  $\pm$  SEM) were used. The camel's ages were determined by dentition marks and the records of the owner. The camels were kept confined on a special farm, with no available shade. They were fed a daily ration of 5 kg barley and 3 kg hay, and water was provided *ad libitum*. Camels were randomly assigned to two groups of 5 camels each, and assigned to either: 1) the dehydration group (water deprivation) or 2) the control group (free access to water).

Experimental procedure: The experimental group was treated as follows : one week as a control period (water was provided *ad libitum*), followed by 15 days of water deprivation and then 7 days of rehydration (water was provided *ad libitum*). Water was provided to the control group *ad libitum*.

Blood samples were taken from the two groups by an external jugular vein puncture on -7, 0 (control period), 3, 5, 7, 10, 14, and 15 days (dehydration), and  $\frac{1}{2}$ , 1, 2, 4 hours, and 1, 2, 3, 5, and 7 days after rehydration.

Ten mls of blood were collected in heparinized tubes for measurements of plasma concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , osmolality, total protein, blood urea nitrogen (BUN), creatinine, and glucose.

The plasma was separated from the blood by centrifugation ( $1,000 \times g$ ) at  $4^\circ\text{C}$  and analyzed within 24 hours. Plasma concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , glucose, creatinine, BUN and total protein were analyzed using Beckman autoanalyzer Synchron CX-5 Clinical System

(Beckman). Plasma osmolality was measured by freezing point depression using advanced 3C2 Osmometer (Advanced Instruments, MA).

For hormone analyses,  $5 \times 10$  mls of blood were collected into prechilled tubes containing  $K_3$ -EDTA. After hemoglobin and PCV measurements, the blood was centrifuged at  $4^\circ\text{C}$  and the plasma was stored at  $-20^\circ\text{C}$  until assay.

Packed cell volume (PCV) was estimated using the Clay Adams microhematocrit centrifuge. Plasma hemoglobin concentrations were determined by the cyanmethemoglobin method (Tietz, 1984).

Percentage changes in plasma volume ( $\% \Delta \text{PV}$ ), i.e., control (day 0) (c) to dehydration (day 15) (d) were calculated from PCV and hemoglobin (Hb) according to the equation by Ben-Goumi et al. (1993):

$$\% \Delta \text{PV} = 100 \left( \left( \frac{\text{Hb}_c}{\text{Hb}_d} \right) \left( \frac{1 - \text{PCV}_d}{100} \right) / \left( \frac{1 - \text{PCV}_c}{100} \right) \right) - 100$$

Radioimmunoassay (RIA) kits were used to determine plasma AVP and angiotensin II (Buhlmann, Basel, Switzerland), aldosterone (Diagnostic Products, Los Angeles, CA), plasma renin activity (PRA), cortisol and adrenocorticotrophic hormone (ACTH) (INCSTAR, Stillwater, MN).

### Statistical analyses

Values are expressed as means  $\pm$  SEM. Analysis of variance (ANOVA) was used to determine the treatment and day (or time) effect. The treatment  $\times$  day (or time) interaction

used to determine the effect of day (or time). The conservative F value was used to establish significance for the effect of treatment and day (time). Tukey's test was used to test for differences between means of end points for which the ANOVA indicated a significant ( $p < 0.05$ ) F ratio.

## Results

### **Effects of dehydration and rehydration on body weight, plasma volume, PCV, and blood hemoglobin**

The effects of dehydration on body weight, PCV, and hemoglobin are shown in Fig.

1. Water deprivation induced approximately 25% decrease in calculated plasma volume.

Body weight decreased significantly from  $482.8 \pm 23.3$  kg at day 0 to  $368.4 \pm 19.8$  by the end of dehydration. PCV fluctuated during dehydration and increased significantly from  $31.0 \pm 1.0$  to  $36.0 \pm 0.6$  % at the end of dehydration. Hemoglobin increased significantly from  $13.2 \pm 0.3$  to  $16.3 \pm 0.3$  g/dl at the end of dehydration.

The effects of rehydration on body weight, PCV, and hemoglobin are shown in Fig. 2.

After 15 days of dehydration the camels drank an average initial quantity of water ( $80.0 \pm 16.0$  liters) and their body weights rose sharply within  $\frac{1}{2}$  hour of rehydration and reached  $443.0 \pm 21.34$  kg. PCV and hemoglobin decreased significantly within  $\frac{1}{2}$  hour of rehydration. PCV and hemoglobin decreased further at one hour of rehydration and returned to control levels within 4 hours of rehydration.

### **Effects of dehydration and rehydration on plasma osmolality and electrolytes**

Effects of dehydration on plasma osmolality and electrolytes are shown in Fig. 3 and Fig. 4, respectively. Water deprivation induced a significant increase in plasma osmolality, Na<sup>+</sup>, and Cl<sup>-</sup> concentrations, 25, 20, and 12 %, respectively of the day 0 level. Plasma K<sup>+</sup> concentrations fluctuated during dehydration but increased significantly ( $4.40 \pm 0.13$  to  $5.50 \pm 0.07$  mmol/L) on the last day of dehydration.

Effects of rehydration on plasma osmolality and electrolytes are shown in Fig. 5 and Fig. 6, respectively. Plasma osmolality and plasma Na<sup>+</sup> concentrations decreased significantly within ½ hour of rehydration, but were still significantly higher than the control levels. Plasma osmolality and plasma Na<sup>+</sup> concentrations then decreased slowly and gradually and reached the control levels after 24 hours of rehydration. Plasma Cl<sup>-</sup> and K<sup>+</sup> concentrations decreased significantly within ½ hour of rehydration and reached the control levels 1-2 hours later.

### **Effects of dehydration and rehydration on plasma creatinine, BUN, protein and glucose**

Effects of dehydration on plasma creatinine, BUN, protein and glucose are shown in Fig. 7 and Fig. 8, respectively. Dehydration induced a significant increase on plasma creatinine (from  $1.4 \pm 0.2$  to  $2.9 \pm 0.1$  mg/dl), BUN (from  $12.4 \pm 1.1$  to  $32.4 \pm 1.1$  mg/dl), protein (from  $6.5 \pm 0.1$  to  $8.7 \pm 0.2$  g/dl) and glucose from a basal level of  $109.6 \pm 4.8$  mg/dl, to a peak of  $154.4 \pm 4.2$  mg/dl. Plasma glucose concentrations, however, decreased to that below the control levels during the last days of dehydration.

Effects of rehydration on plasma creatinine, BUN, protein and glucose are shown in Fig. 9 and Fig. 10, respectively. Within  $\frac{1}{2}$  hour of rehydration, plasma glucose concentrations decreased significantly to below the control levels and returned to the control levels within 4 hours of rehydration. Plasma BUN decreased significantly  $\frac{1}{2}$  hour of rehydration and reached the control levels within 2 hours of rehydration. Total plasma protein showed a significant decrease within one hour of rehydration; however, they were still significantly higher than the control levels. Plasma protein then decreased gradually and reached the control levels within 24 hours of rehydration. Plasma creatinine concentrations decreased significantly 4 hour after the onset of rehydration and reached the control levels.

#### **Effects of dehydration and rehydration on plasma hormone concentrations**

Components of the plasma renin-angiotensin-aldosterone system significantly increased during dehydration ( Fig. 11). On day 0 the basal level of plasma renin activity (PRA) were  $0.9 \pm 0.1$  and increased after 15 days of water deprivation to a peak of  $7.6 \pm 0.2$  ng Angiotensin I / ml /h, plasma angiotensin II concentrations increased from  $1.2 \pm 0.1$  to  $10 \pm 0.1$  pg /ml, and plasma aldosterone increased from  $30.4 \pm 1.6$  to  $137.4 \pm 3.0$  pg /ml. Water deprivation induced a sharp and prompt increase ( $P < 0.05$ ) in plasma AVP concentrations from the basal level of  $0.7 \pm 0.0$  to  $7.4 \pm 0.2$  pg /ml at the end of dehydration (Fig. 3). Plasma ACTH and cortisol concentrations increased significantly at the end of dehydration from the basal level of  $11.0 \pm 0.2$  and  $24.2 \pm 1.3$  to  $16.9 \pm 0.2$  pg /ml and  $127.8 \pm 8.2$  ng /ml, respectively (Fig. 13).

PRA and plasma concentrations of angiotensin II decreased significantly within  $\frac{1}{2}$  hour of rehydration and reached the control levels within 2 hours of rehydration (Fig. 12). Plasma aldosterone concentrations, however, increased significantly from  $137.4 \pm 3.0$  to  $220.0 \pm 5.0$  pg/ml within two hours of rehydration. Within 48 hours, plasma aldosterone concentrations returned to control levels (Fig. 12). Plasma concentrations of AVP decreased significantly within  $\frac{1}{2}$  hour of rehydration and returned to control levels after four hours of rehydration (Fig. 5). Rehydration induced an increase ( $P < 0.05$ ) in plasma ACTH and cortisol concentrations from  $16.9 \pm 0.2$  to  $40.3 \pm 0.9$  pg/ml and from  $127.8 \pm 8.2$  to  $331.4 \pm 12.5$  ng/ml, respectively (Fig. 14). Both plasma ACTH and cortisol concentrations returned to control values after 24 hours of rehydration. Multiple regression was utilized to study the relationship between plasma aldosterone and angiotensin II concentrations, plasma aldosterone and ACTH concentrations, and between plasma concentrations of AVP and plasma osmolality during dehydration and rehydration. Plasma aldosterone and angiotensin II concentrations were highly correlated ( $r = 0.99$ ) during the first 10 days of dehydration, whereas plasma aldosterone and ACTH concentrations were not ( $r = 0.57$ ). During rehydration plasma aldosterone and ACTH concentrations were highly correlated ( $r = 0.90$ ), whereas plasma aldosterone and angiotensin II were not ( $r = 0.21$ ). Plasma concentrations of AVP and plasma osmolality were highly correlated ( $r = 0.99$ ) during dehydration, whereas during the first 24 hours of rehydration they were less correlated ( $r = 0.75$ ).

## Discussion

The present study was performed to investigate the effect of severe dehydration and rapid rehydration on the dromedary camels. Water deprivation for 15 days induced approximately a 25% decrease in mean body weight, predominantly due to the loss of body fluid. The reduction in body weight was accompanied by a 25% decrease in calculated plasma volume. Ben-Goumi et al. (1993) reported a 43% decrease in calculated plasma volume on camels subjected to dehydration for 14 days. MacFarlane et al. (1963), however, reported a decrease of less than 10 % in plasma volume after a 20 % decrease in camels' body weight. Siebert and MacFarlane. (1971) reported a 5% maximal decrease in plasma volume in camels after 10 days of dehydration; the latter however, seems to be far less than what would be expected after a 20-30 % decrease in body weight. In the present study, the significant increase in PCV and hemoglobin concentrations at the end of dehydration is consistent with that found in camels by Ben-Goumi et al. (1993) and Siebert and MacFarlane. (1971), but, differ from obtained by Yagil et al. (1974b) who found a decrease in PCV and hemoglobin concentrations after 7 days of dehydration in camels. However, these data were from only one female camel. The rapid decrease in PCV and hemoglobin concentrations after rehydration is consistent with that found in camels by Ben-Goumi et al. (1993), but, differ from that of Yagil et al. (1974b) who found an increase in PCV ½ hour after rehydration. These data are inconsistent with the expectation that a decrease in PCV should occur following the entrance of large amount of water into the blood stream. The rapid decline in

PCV and hemoglobin concentrations after rehydration suggests a rapid absorption of water from the alimentary tract.

Water deprivation induced a severe hypernatremia in camels. These results are consistent with those in camels by others (Ben-Goumi et al., 1993; MacFarlane, 1968; Siebert and MacFarlane, 1971) but, differ from those of Finberg et al. (1978) who found a small increase in plasma  $\text{Na}^+$  concentrations after 8-10 days of dehydration in camels. It seems that 8 days of dehydration were not sufficient to induce high plasma  $\text{Na}^+$  concentrations in the latter study. Plasma  $\text{Na}^+$  concentrations began to decline  $\frac{1}{2}$  hour after rehydration, but, were still significantly elevated 24 hours after rehydration which can be explained by a concomitant increase in plasma aldosterone concentrations during the same period (Finberg et al., 1978; Ben-Goumi et al., 1993; Yagil, 1985). Hyperosmolality also was induced in the dehydrated camels. After  $\frac{1}{2}$  hours of rehydration, plasma osmolality began to decrease and reached the control levels following 24 hours of rehydration. These results are consistent with those of Ben-Goumi et al. (1993) in camels. Plasma  $\text{K}^+$  concentrations increased significantly on the last day of dehydration. These results are consistent with those of Siebert and MacFarlane. (1971) but, differ from those of Finberg et al. (1978) and Ben-Goumi et al. (1993), who found no significant changes in plasma  $\text{K}^+$  concentrations during dehydration in camels. The increase in plasma  $\text{K}^+$  concentrations was not expected in the presence of high plasma aldosterone concentrations. The increase in plasma  $\text{K}^+$  concentrations seems likely to be due to the hemoconcentration associated with water deprivation. In addition, this increase in plasma  $\text{K}^+$  concentrations seems to be of cellular origin due to the severe effect of dehydration on cellular metabolism and the shift of



water from the cells to the ECF (Swenson and Reece, 1993). Finally, the camel's kidney functions are very depressed toward the end of dehydration and seemed to be unresponsive to the high concentrations of plasma aldosterone. The rapid decline in plasma  $K^+$  concentration observed after rehydration in this study was also reported by Finberg et al. (1978). This can be explained by rapid return of the camel's kidneys to their normal function shortly after rehydration, and seems to become very responsive to the high concentrations of plasma aldosterone that were associated with the rehydration (Yagil, 1985).

The increases in plasma protein, creatinine, BUN, and glucose concentrations during dehydration were reported by Yagil, (1985) and Ben-Goumi. (1995). The decline in plasma glucose concentrations to those below control level during the last days of dehydration can be explained by a concomitant decline on food intake during the same period. The decrease in food intake in camels during dehydration was reported by Ben-Goumi et al. (1993).

During dehydration, the reduction in urine output causes an increase in plasma levels of non-protein nitrogen, usually urea and creatinine (Radostits et al., 1994). In order to conserve water during dehydration, camels have to decrease their renal blood flow (RBF) and glomerular filtration rate (GFR)( Yagil, 1985). Renal excretion of urea occurs by glomerular filtration, and blood urea nitrogen (BUN) concentrations are inversely proportional to GFR. Urea is subject to passive reabsorption in the tubules, and this occurs to a greater extent at slower tubular flow rates, which occur during dehydration (Ettinger and Feldman, 1995).

Creatinine is a nonenzymatic breakdown product of phosphocreatine in muscle. Creatinine is not metabolized and is excreted by the kidneys almost entirely by glomerular

filtration. The rate of creatinine excretion is relatively constant in the steady state. Therefore, creatinine clearance determination provides a good estimate of GFR (Ettinger and Feldman, 1995). The increase in creatinine and BUN in this study suggests a reduced GFR and a subsequent reduction in urine output in the dehydrated camel.

Plasma protein concentrations were still elevated 24 hours after rehydration and decreased to control levels within 48 hours. The decrease in plasma protein concentrations was parallel to that of plasma  $\text{Na}^+$  concentrations. This suggests that plasma protein concentrations remained elevated during the first 24 hours of rehydration in order to maintain body fluid tonicity and to prevent water intoxication. Most of the blood constituents started to decline  $\frac{1}{2}$  hour after rehydration and this can be explained by the rapid entrance of water into camel's blood stream. Within a few hours of rehydration camels were able to return to normal renal function (Yagil, 1985). This was demonstrated by the significant decrease in plasma creatinine concentrations within 4 hours of rehydration.

Water deprivation induced a sharp and prompt increase in plasma AVP concentration. These results are consistent with those in camels (Achaaban et al., 1992; Ben-Goumi et al., 1993; Finberg et al., 1978; Yagil and Etzion, 1979), horses (Haupt et al., 1989; Sneddon et al., 1993), cattle (Bell et al., 1985; Doris and Bell, 1984a; Doris and Bell, 1984b), sheep (Agnew et al., 1993; Bell et al., 1991; Dodd et al., 1992), and goats (Dahlborn et al., 1988; Wittenberg et al., 1986). Water intake induced a sharp decrease in plasma AVP concentrations, which returned to control levels four hours following the onset of rehydration. The decrease in plasma AVP concentrations was associated with the decrease in plasma osmolality even though the decrease of AVP was sharp and the decrease of plasma

osmolality was gradual. These results are consistent with those of previous studies in camels by others (Achaaban et al, 1992; Ben-Goumi et al.,1993) and horses (Sneddon et al., 1993). The secretion of AVP during dehydration in camels seems to be controlled mainly by the changes in plasma osmolality but not plasma volume. Support for this assumption can be found in the high correlation ( $r = 0.99$ ) between plasma concentrations of AVP and plasma osmolality during dehydration, whereas PCV did not increase significantly until the end of dehydration. These results are consistent with those in camels (Achaaban et al., 1992; Ben-Goumi et al.,1993) and horses (Sneddon et al, 1993). During the first 24 hours of rehydration plasma concentrations of AVP and plasma osmolality were less correlated ( $r = 0.75$ ). The rapid inhibition of AVP release after drinking seems to be caused by the sudden increase in plasma volume but not by the gradual decrease in plasma osmolality (Blair-West et al., 1987).

Water deprivation induced a significant increase in PRA concentrations in camels. These results are consistent with those in camels (Finberg et al., 1978; Ben-Goumi et al., 1993), sheep (Blair-West et al., 1972; Dahlborn and Holtenius, 1990), and goats (Wittenberg et al., 1986). PRA concentrations decreased dramatically after  $\frac{1}{2}$  hour of rehydration and reached control levels within 2 hours of rehydration. These results are consistent with those of Finberg et al. (1978) and Ben-Goumi et al. (1993) in camels. However, further increase in PRA concentrations was observed following drinking in goats (Dahlborn et al., 1988; Wittenberg et al., 1986), sheep (Blair-West et al., 1972). The decrease in  $\text{Na}^+$  concentrations in the macula densa is assumed to be the main stimulus for renin secretion during this period (Dahlborn et al., 1988).

Plasma angiotensin II significantly increased during dehydration. This finding is consistent with that of Bell et al. (1985) in cattle, and has not been previously demonstrated in camels. The decrease in PRA concentration was associated with a similar decrease in plasma angiotensin II concentrations after rehydration.

Plasma aldosterone concentration increased due to water deprivation. These results are consistent with those of Finberg et al. (1978) and Yagil and Etzion, (1979) in camels, Wittenberg et al. (1986) in goats, Houpt et al. (1989) and Sneddon et al. (1993) in horses. However, these results differ from those of Ben-Goumi et al. (1993) who found no significant changes in plasma aldosterone concentration in camels during dehydration even though PRA concentrations in their study were significantly increased. The increase in plasma electrolytes during dehydration is mainly due to the hemoconcentration but not under the influence of plasma aldosterone. The high levels of plasma aldosterone during dehydration seems to be not functioning well which can be attributed to the desensitization of aldosterone receptors and this need further study. Plasma aldosterone concentrations, however, increased further after rehydration. These data are consistent with those of Ben-Goumi et al. (1993), Finberg et al. (1978) and Yagil and Etzion, (1979) in camels, Dahlborn et al. (1988) and Wittenberg et al. (1986) in goats, Houpt et al. (1989) and Sneddon et al. (1993) in horses. The increase in plasma aldosterone during rehydration in camels would attenuate the decrease in plasma osmolality by maintaining high concentrations of plasma  $\text{Na}^+$  and thus the magnitude of water diuresis (Benlamlah et al., 1992)

Plasma ACTH and cortisol concentrations increased at the end of dehydration. Our report is the first one investigating ACTH in dehydration and rehydration in camels. The

increase in plasma ACTH and cortisol concentrations was associated with the lack of food intake during the same period, and was previously observed in dehydrated camels (Ben-Goumi et al., 1993). Plasma cortisol has been shown to increase due to starvation in goats, whereas heat stress has no effect on plasma cortisol concentration (Olsson et al., 1995). Plasma cortisol concentrations were not changed in camels during 8-10 days of dehydration (Finberg et al., 1978). Rehydration induced a further increase in plasma ACTH and cortisol concentrations. This increase could be attributed to the large and rapid water intake or the excitement of drinking. The high levels of plasma aldosterone during rehydration seems to be maintained by the high concentrations of plasma ACTH. A small increase in plasma cortisol concentration was reported in camels during rehydration (Finberg et al., 1978). In the present study plasma ACTH concentrations were still elevated 24 hours after rehydration. Both plasma ACTH and cortisol returned to control values within 24 hours of rehydration. The secretion of aldosterone is affected by renin-angiotensin system, ACTH, and plasma  $K^+$  (Ganong, 1993). The increase in plasma ACTH concentrations during the 24 hours of rehydration was highly correlated with the increase in plasma aldosterone concentrations. In addition, there was a decrease in PRA and angiotensin II concentrations during the same period. This suggests that during rehydration in camels the nexus between the renin-angiotensin system and aldosterone was impaired; whereas the nexus between the ACTH and aldosterone appears to be activated. It is likely that the increase in plasma aldosterone concentration during rehydration in camels is under the influence of ACTH. Further studies are needed to prove or disprove this hypothesis. One approach would be using dexamethasone, a long-acting potent glucocorticoid, to decrease ACTH secretion. During

dehydration in camels, aldosterone secretion seems to be maintained by renin-angiotensin system and not by plasma ACTH. This hypothesis is supported by the high correlation between plasma aldosterone and angiotensin II and the absence of a correlation between plasma aldosterone and ACTH.

### **Acknowledgment**

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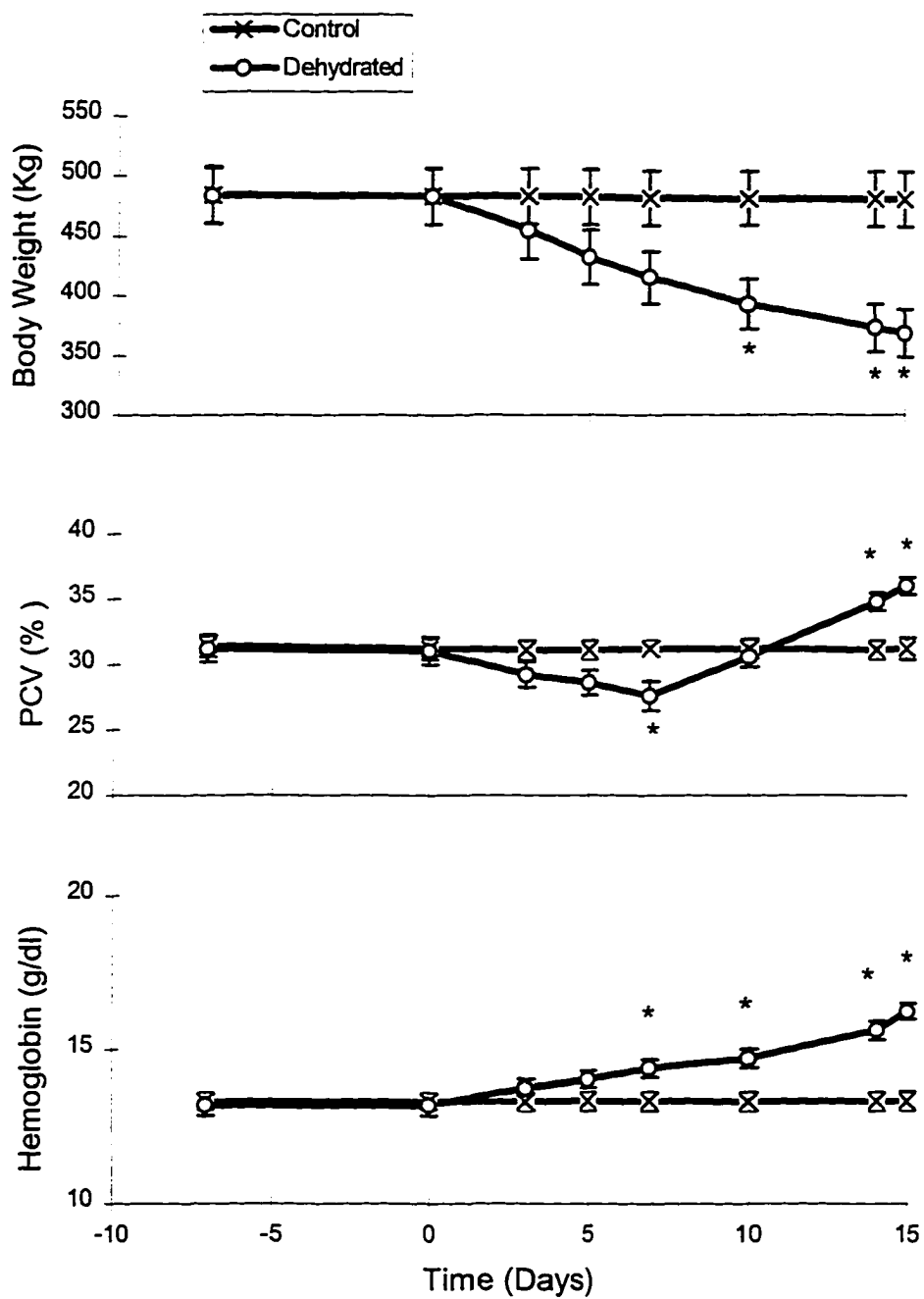


Fig. 1. Changes of body weight, packed cell volume (PCV), and hemoglobin in dehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM. \*P < 0.05, compared with the day 0 value in the dehydrated group.

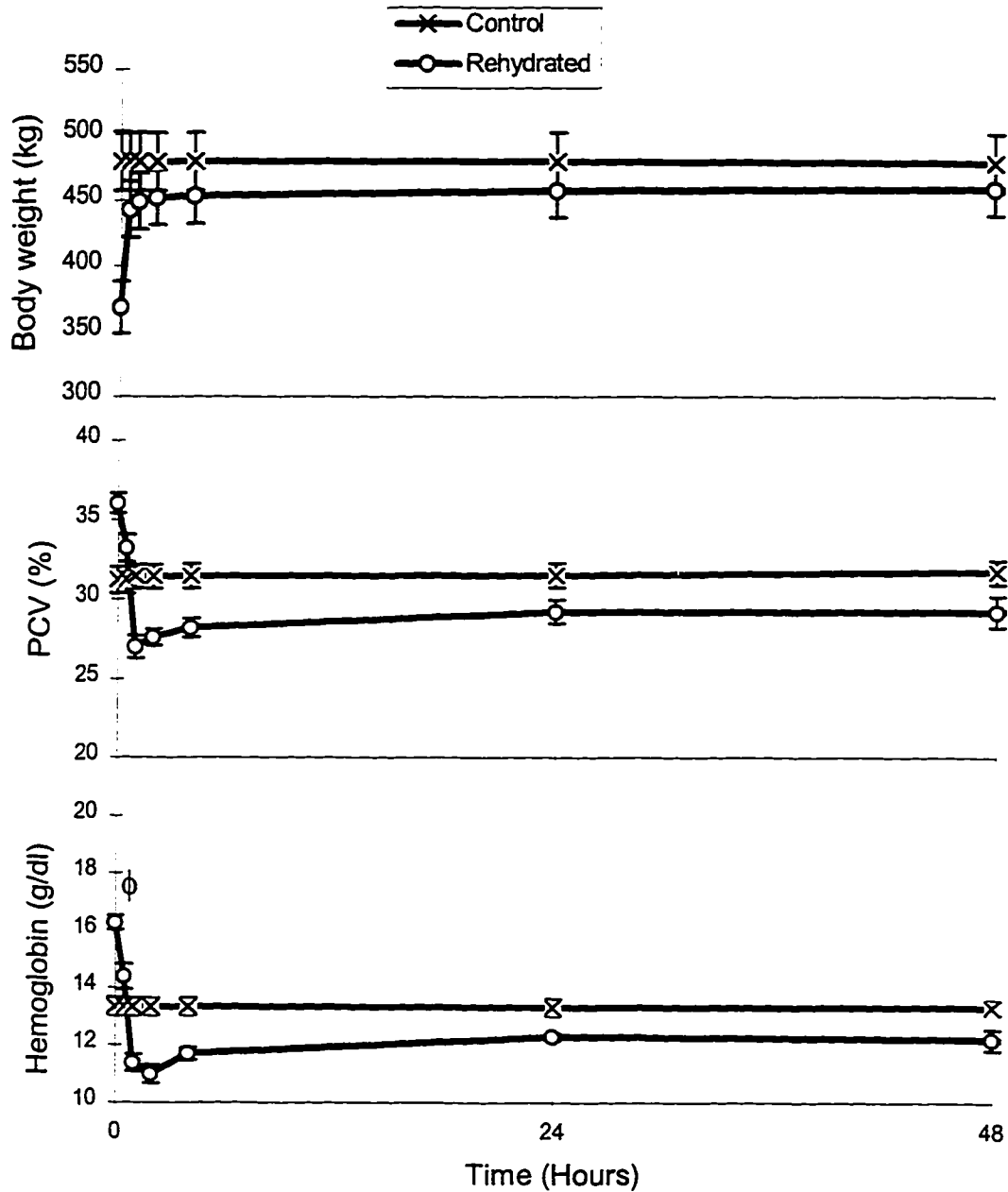


Fig. 2. Changes of body weight, packed cell volume (PCV), and hemoglobin in rehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM.  $^*P < 0.05$ , compared with the rehydrated group at the corresponding time. In the dehydrated group, rehydration induced significant ( $P < 0.05$ ) changes at all time points when compared with the time 0 value.

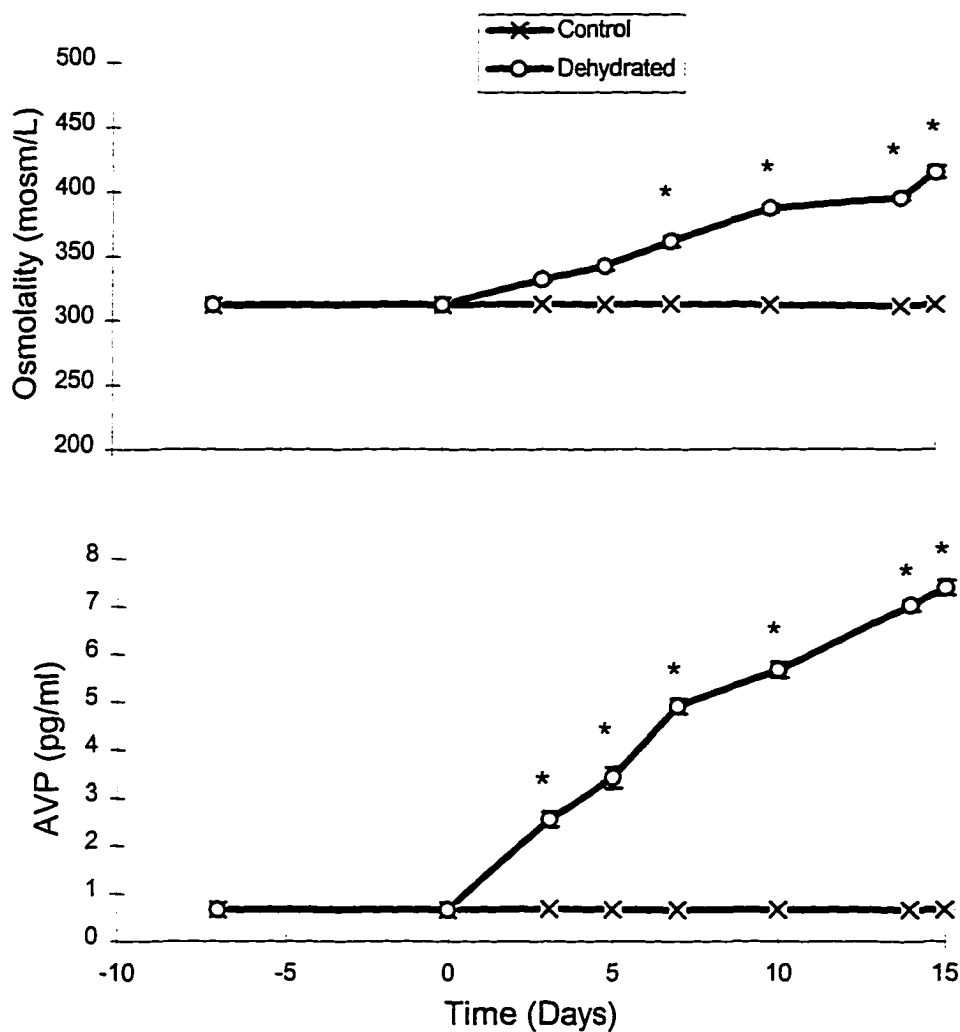


Fig. 3. Changes of plasma osmolality and plasma arginine vasopressin (AVP) in dehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM. \*P < 0.05, compared with the control group at the corresponding day.

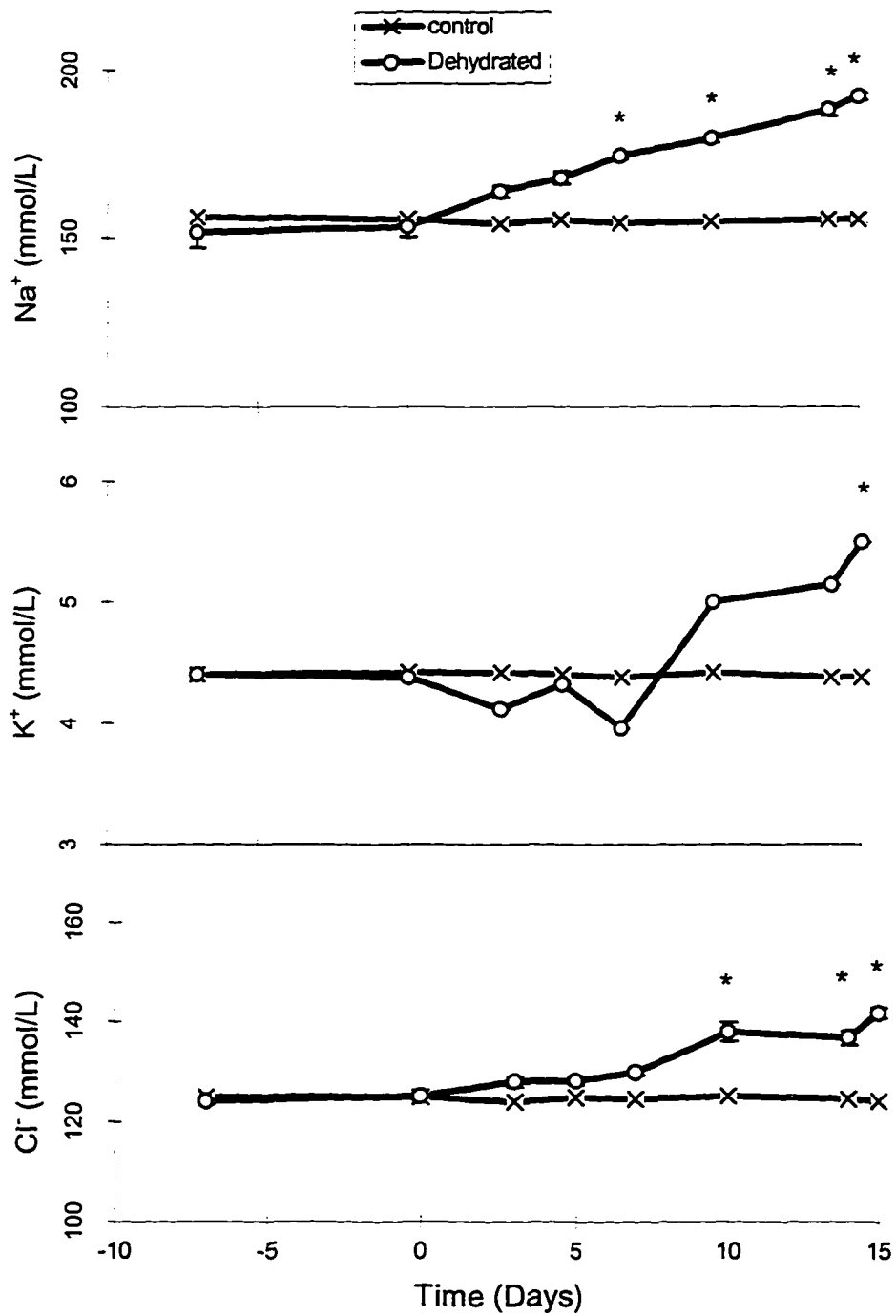


Fig. 4. Changes of plasma electrolytes in dehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM. \* $P < 0.05$ , compared with the control group at the corresponding day.

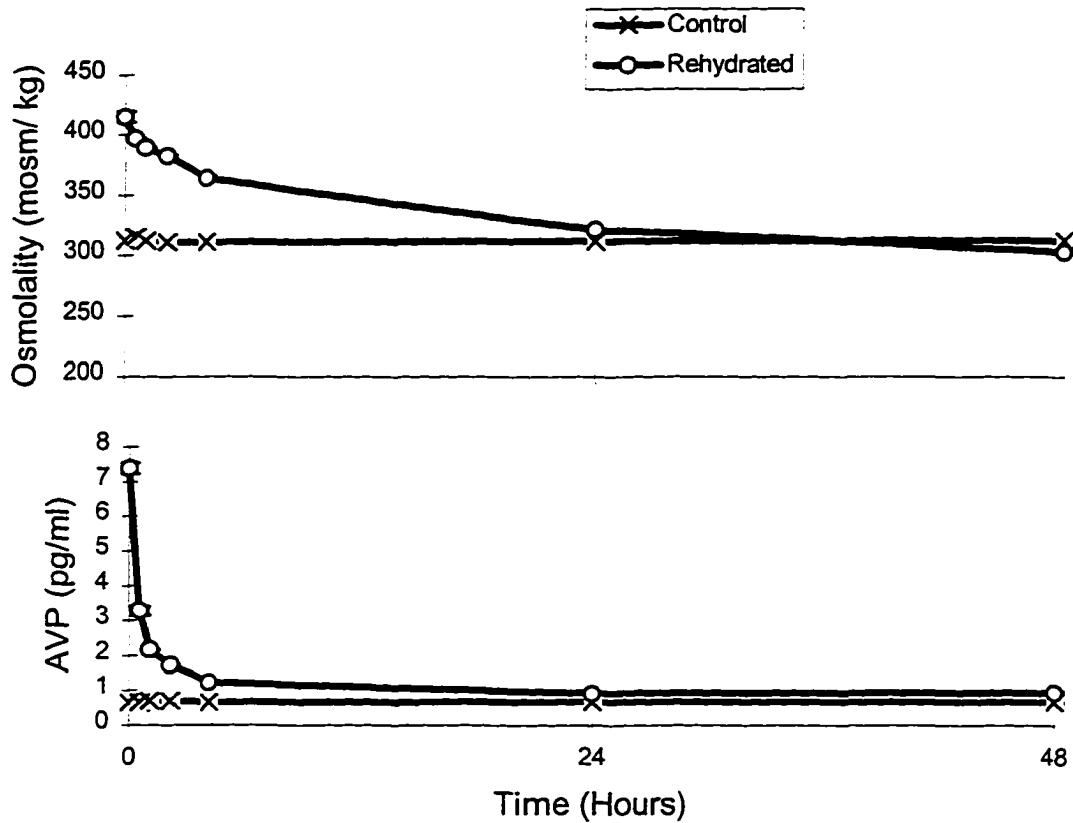


Fig. 5. Changes of plasma osmolality and plasma arginine vasopressin (AVP) in rehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM. The rehydrated group was still different ( $P < 0.05$ ) from the control group up to 4 hours for both parameters. In the dehydrated group, rehydration induced significant ( $P < 0.05$ ) changes at all time points when compared with the time 0 value.



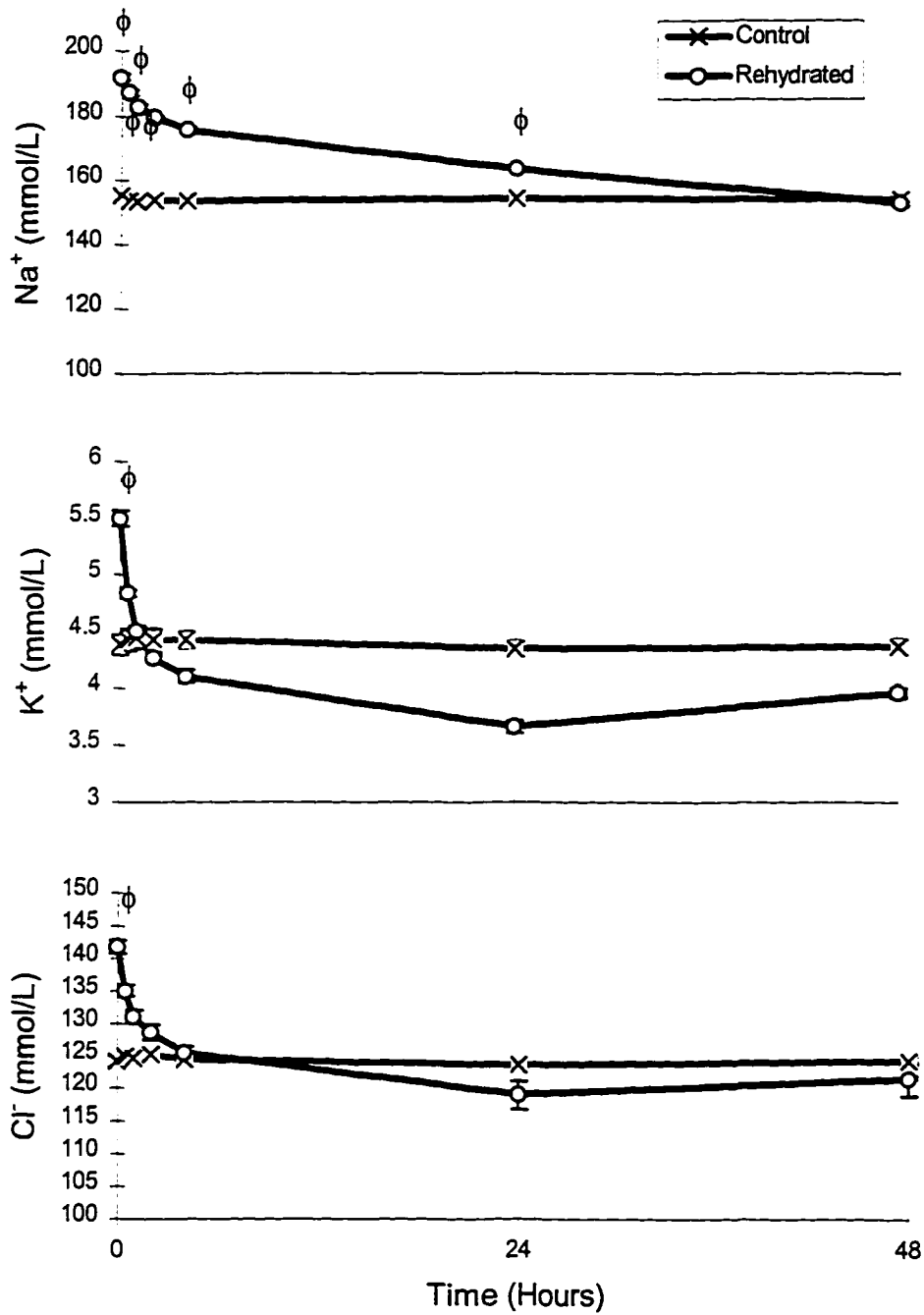


Fig. 6. Changes of plasma electrolytes in rehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM.  $\phi P < 0.05$ , compared with the rehydrated group at the corresponding time. In the dehydrated group, rehydration induced significant ( $P < 0.05$ ) changes at all time points when compared with the time 0 value.

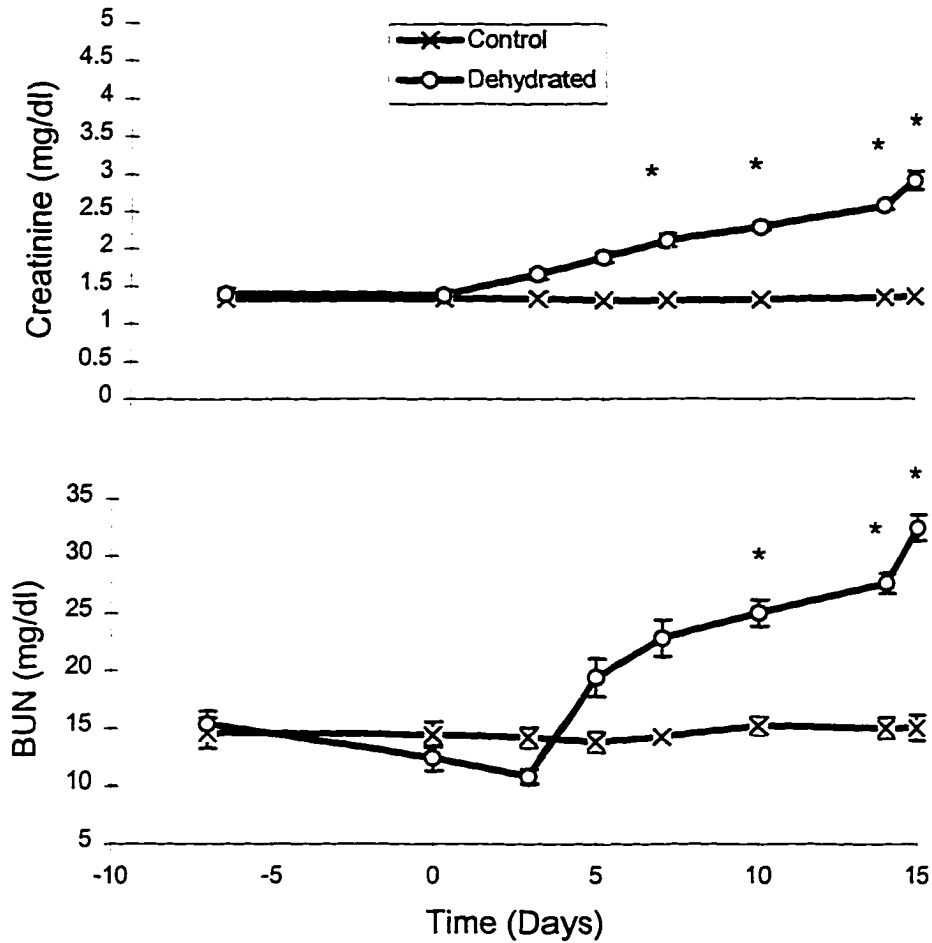


Fig. 7. Changes of plasma creatinine and blood urea nitrogen (BUN) in dehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM. \*P < 0.05, compared with the control group at the corresponding day.

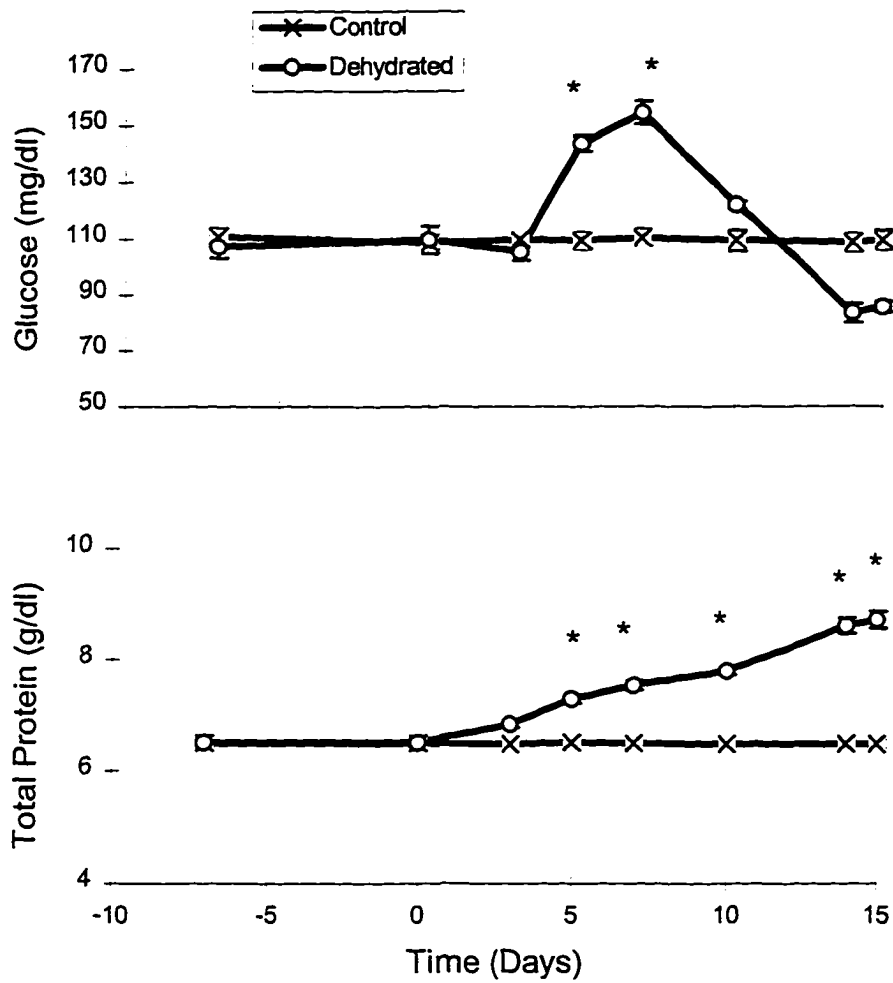


Fig. 8. Changes of plasma glucose and total plasma protein in dehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM. \*P < 0.05, compared with the control group at the corresponding day.

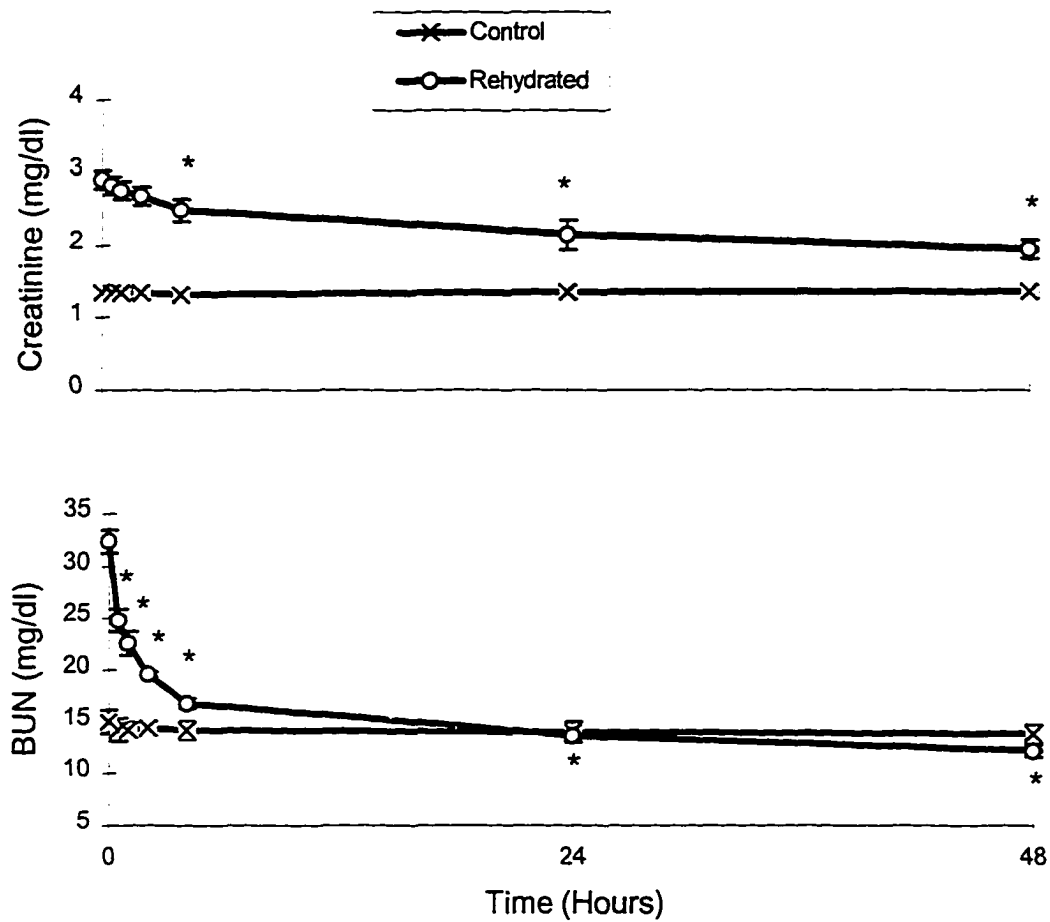


Fig. 9. Changes of plasma creatinine and blood urea nitrogen (BUN) in rehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM. The rehydrated group was still different ( $P < 0.05$ ) from the control group up to 4 hours and 1 hour for plasma creatinine and BUN, respectively. \* $P < 0.05$ , compared with the time 0 value in the rehydrated group.

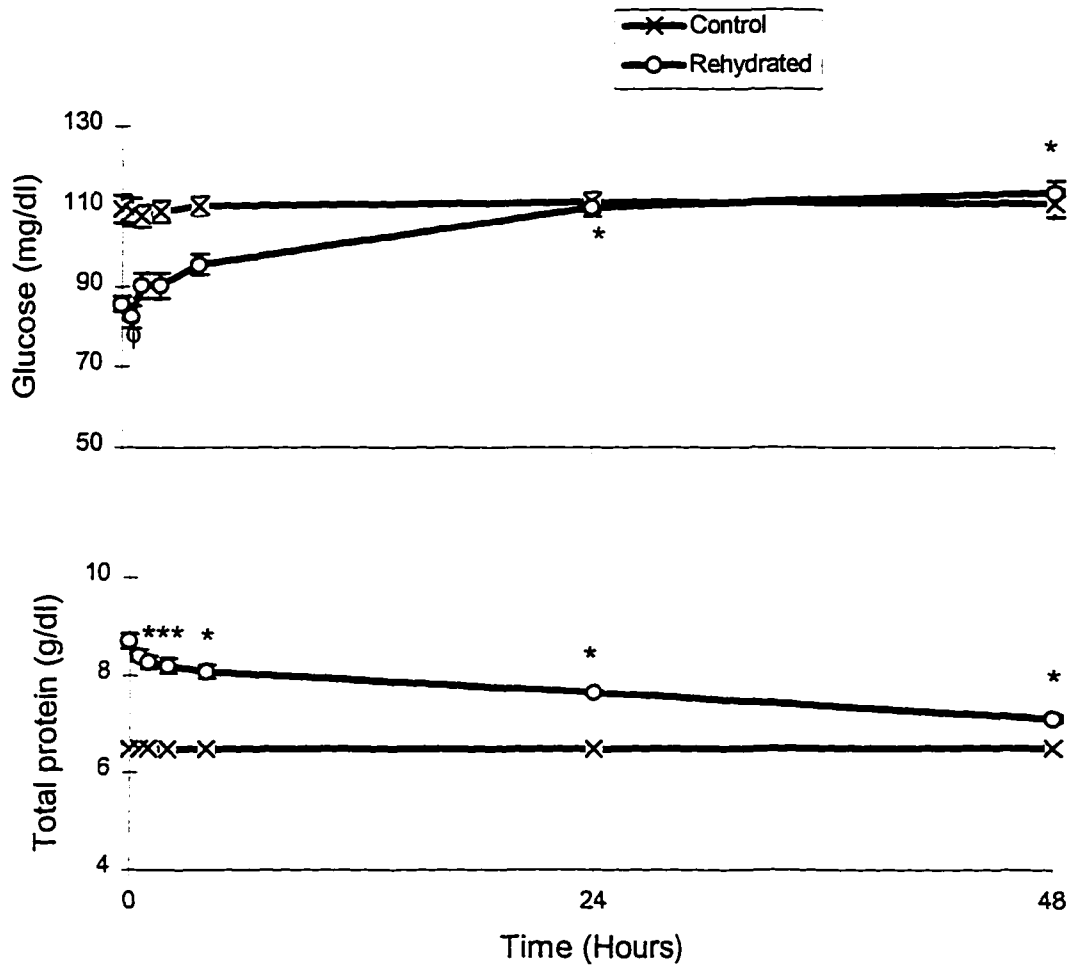


Fig. 10. Changes of plasma glucose and total plasma protein in rehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM. \* $P < 0.05$ , compared with the rehydrated group at the corresponding time. For total plasma protein the rehydrated group was still different ( $P < 0.05$ ) from the control group up to 24 hours. \* $P < 0.05$ , compared with the time 0 value in the rehydrated group.

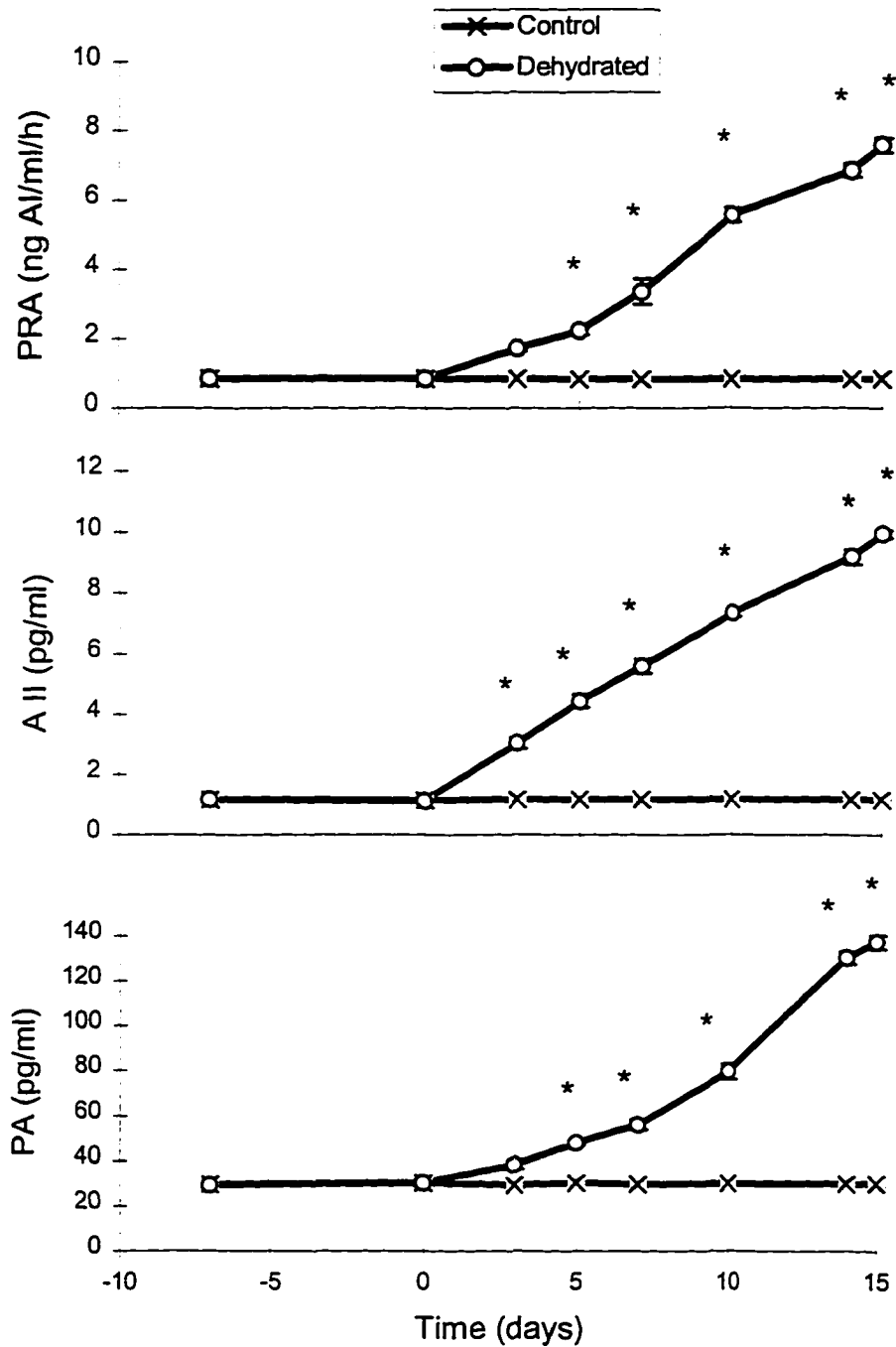


Fig. 11. Changes of plasma renin activity (PRA), plasma angiotensin II (A II), and plasma aldosterone (PA), in dehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM. \*P < 0.05, compared with the control group at the corresponding day.

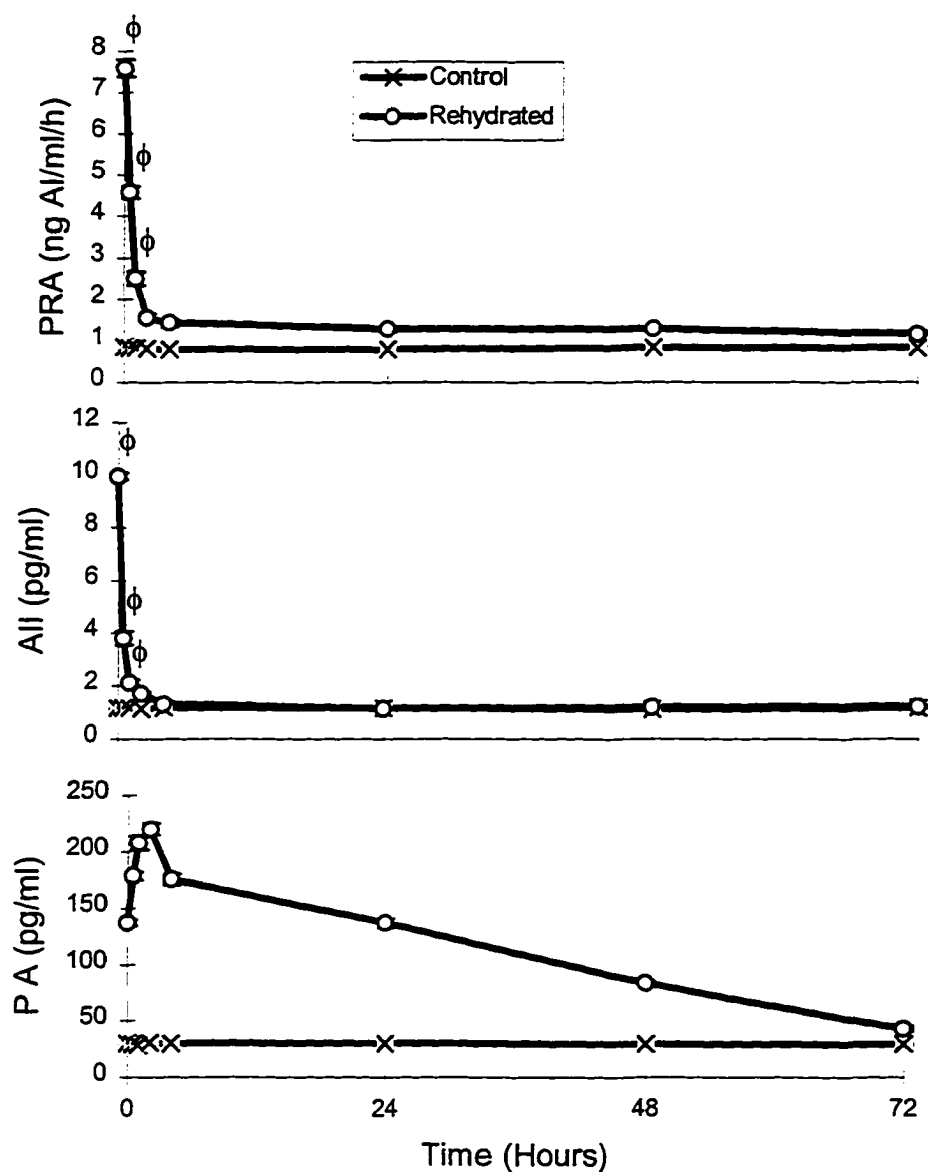


Fig. 12. Changes of plasma renin activity (PRA), plasma angiotensin II (A II), and plasma aldosterone (PA) in rehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM. \* $P < 0.05$ , compared with the rehydrated group at the corresponding time. For PA the rehydrated group was still different ( $P < 0.05$ ) from the control group up to 48 hours. In the dehydrated group, rehydration induced significant ( $P < 0.05$ ) changes at all time points when compared with the time 0 value.

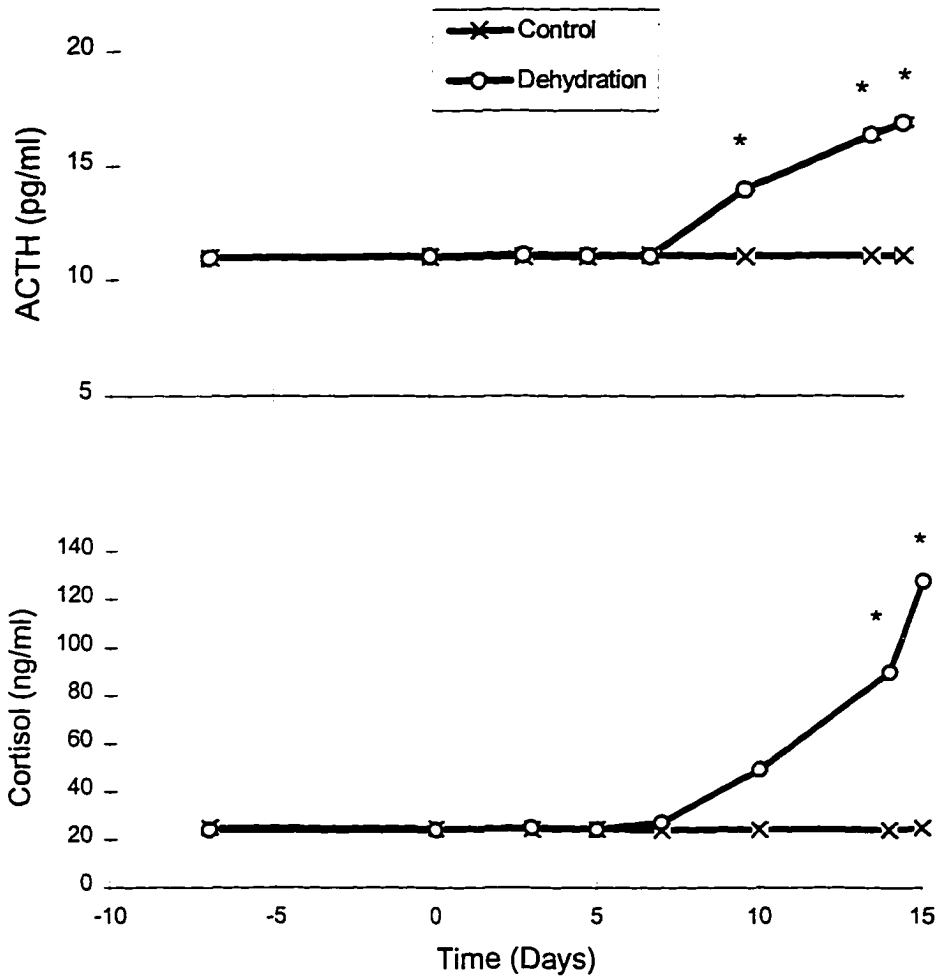


Fig. 13. Changes of plasma adrenocorticotrophic hormone (ACTH) and plasma cortisol in dehydrated and control camels (n = 5). Data are expressed as means  $\pm$  SEM. \*P < 0.05, compared with the control group at the corresponding day.



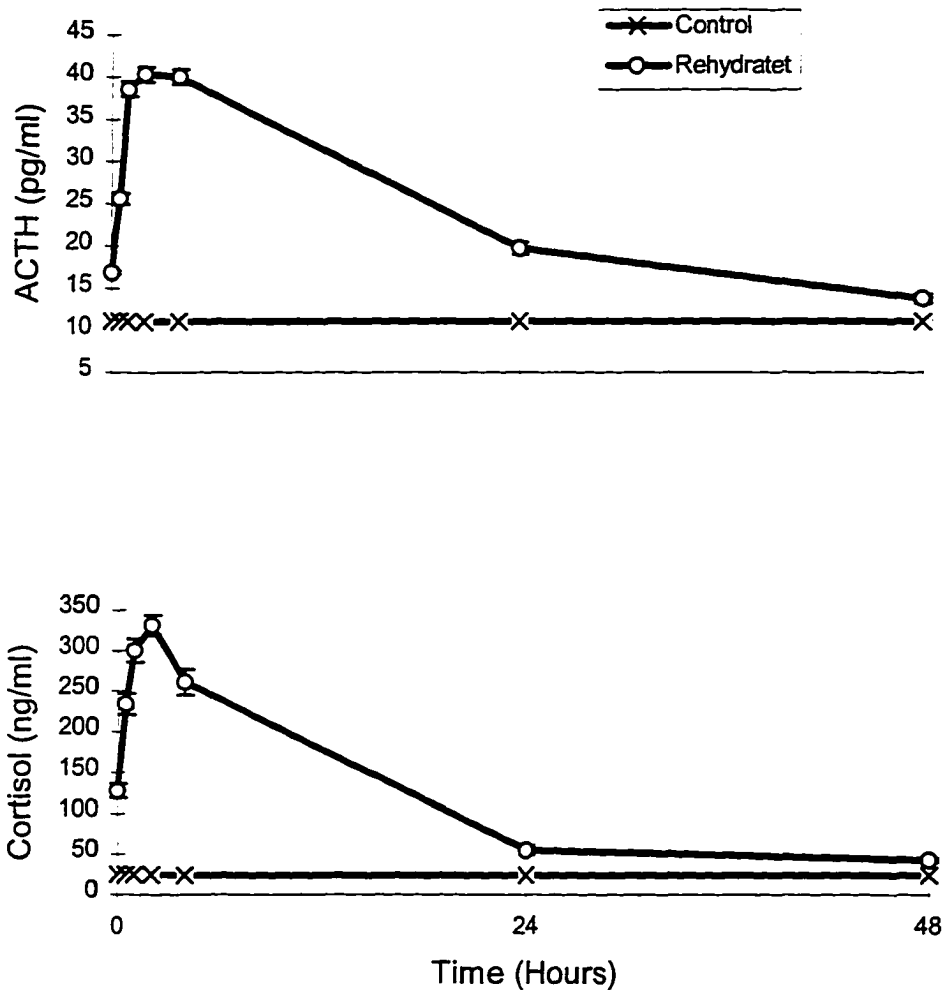


Fig. 14. Changes of plasma adrenocorticotrophic hormone (ACTH) and plasma cortisol in rehydrated and control camels ( $n = 5$ ). Data are expressed as means  $\pm$  SEM. The rehydrated group was still different ( $P < 0.05$ ) from the control group up to 24 hours and 4 hours for plasma ACTH and cortisol, respectively. In the dehydrated group, rehydration induced significant ( $P < 0.05$ ) changes at all time points when compared with the time 0 value.

## REGULATION OF ALDOSTERONE SECRETION DURING DEHYDRATION IN CAMELS

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### Abstract

The mineralocorticoid hormones especially aldosterone have an important role in regulating body electrolyte balance by increasing  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion; thereby, assisting in the regulation of the body fluid volume. The present study was undertaken to determine which pathway is responsible for the secretion of aldosterone in the dehydrated camel; either the renin-angiotensin axis or the ACTH axis. Adrenocorticotrophic hormone (ACTH) and enalapril, an angiotensin-converting enzyme inhibitor (ACE-I), were utilized in two separate experiments in dehydrated and control (hydration) arabian camels (Camelus dromedarius). Forty 3-5 year one-humped camels (Camelus dromedarius), (20 males; 20 females) were used. In the first experiment the camels were randomly assigned to four groups of 5 camels each: 1) hydration (free access to water), 2) hydration plus enalapril, 3) dehydration (10 days of water deprivation), and 4) dehydration (10 days of water deprivation) plus enalapril.

Enalapril (0.2  $\mu\text{g}/\text{kg}$ ) induced a sharp decrease in plasma  $\text{Na}^+$  and an increase in plasma  $\text{K}^+$  concentrations in the dehydrated camels but not in the hydrated camels.

After enalapril administration, plasma osmolality decreased significantly in both dehydrated and hydrated camels. Enalapril administration induced a decrease in plasma aldosterone concentrations in both the dehydrated and hydrated camels. Plasma angiotensin II concentrations decreased in the dehydrated camels but not the hydrated camels after enalapril administration. Plasma renin activity (PRA) increased significantly in the dehydrated camels after enalapril administration but not in hydrated animals. In the second experiment, ACTH administration (0.4 IU / kg) had no significant effects on plasma electrolytes and osmolality in either the dehydrated or hydrated camels. The administration of ACTH induced a sharp increase in plasma cortisol concentrations in both the dehydrated and hydrated camels. Plasma aldosterone concentrations, however, increased only in the dehydrated camels and declined in 24 hours in the presence of continuous administration of ACTH. The present study clearly shows that both angiotensin II and ACTH stimulate aldosterone secretion during dehydration in camels. However, due to the parallel increase in PRA, plasma angiotensin II and plasma aldosterone in dehydrated camels without any parallel changes in plasma cortisol or ACTH, the effect of angiotensin II seems to be dominant over ACTH.

### **Introduction**

Aldosterone is the major mineralocorticoid secreted by the glomerulosa cells of the adrenal cortex. It has an important role in regulating electrolyte balance by increasing  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion in many tissues, including the kidney, sweat glands, salivary

glands, and colon; thus, aldosterone aids in the regulation of the body fluid volume (Ganong, 1993; Leslie et al., 1995; Swenson and Reece, 1993).

Many factors have been shown to be involved in the control of aldosterone secretion including: angiotensin II, adrenocorticotrophic hormone (ACTH), high plasma  $K^+$  concentrations and to a lesser extent, low plasma  $Na^+$  concentrations (McDougall, 1987). Many, however, would argue that angiotensin II is the major secretagogue involved in the regulation of aldosterone secretion (Ganong, 1993; Griffin and Ojeda, 1992; Leslie et al., 1995). It has been demonstrated that water deprivation causes an increase in plasma aldosterone concentrations in goats (Wittenberg et al., 1986), horses (Haupt et al., 1989; Sneddon et al, 1993), and camels (Al-Qarawi et al., 1997; Finberg et al, 1978; Yagil and Etzion, 1979).

Plasma renin activity (PRA) also increased during water deprivation in camels (Al-Qarawi et al., 1997; Finberg et al., 1978; Ben-Goumi et al., 1993), sheep (Blair-West et al., 1972; Dahlborn and Holtenius, 1990), and goats (Wittenberg et al., 1986). In addition, plasma angiotensin II increased during dehydration in camels (Al-Qarawi et al., 1997), sheep (Yesberg et al., 1984), and cattle (Bell et al., 1985). Plasma cortisol concentrations did not change in camels during 8-10 days of dehydration (Finberg et al, 1978). Al-Qarawi et al. (1997), however, found an increase in plasma concentrations of ACTH and cortisol at the end of dehydration period when the dehydration was associated with a lack of food intake during the same period. Finberg et al. (1978) and Ben-Goumi et al. (1993), found no changes in plasma  $K^+$  concentrations during dehydration. Al-Qarawi et al. (1997) however, found a significant increase in plasma  $K^+$  concentration on day 15 of dehydration. In view of the

available literature it seems that in the dehydrated camels the nexus between the renin-angiotensin system and aldosterone is very active, whereas the nexus between either ACTH or plasma  $[K^+]$  and aldosterone appears to be impaired during dehydration. Aldosterone secretion is normally under the control of angiotensin II, and of plasma  $K^+$  and ACTH concentrations to a lesser degree, whereas the effect of ACTH is powerful but short-lived (Griffin and Ojeda, 1992). Yagil (1985) and Yagil and Etzion (1979), speculated that aldosterone secretion in the dehydrated camel was not via the renin-angiotensin axis but rather via the AVP-ACTH axis. However, this remains a speculation since they did not measure plasma concentrations of angiotensin II or ACTH during dehydration in camels. Their hypothesis was as follows: the release of ACTH from the anterior pituitary is under a synergistic action of corticotrophin-releasing factor (CRF) and AVP. AVP secretion is initiated by the loss of water, which directly induces ACTH secretion, followed by aldosterone secretion, even if plasma  $Na^+$  concentrations are high. Although the physiological role of ACTH on aldosterone secretion is limited, during ACTH insufficiency, the zona glomerulosa may atrophy and be less able to respond to other stimuli (Griffin and Ojeda, 1992).

This study was undertaken to determine which pathway is responsible for aldosterone secretion in the dehydrated camel; either the renin-angiotensin axis or the ACTH axis.

## Materials and Methods

**Animals:** Forty 3-5 year one-humped camels (Camelus dromedarius), (20 males; 20 nonpregnant, nonlactating females) weighting  $468 \pm 31$  kg (mean  $\pm$  SEM) were used. The camel's ages were determined by dentition marks and the records of the owner. The camels were kept confined in a special farm, with no available shade. They were fed a daily ration of 5 kg barley and 3 kg hay, and water was provided *ad libitum*.

### Experiment design

**Experiment 1:** The camels were randomly assigned to four groups of 5 camels each: 1) hydration (free access to water), 2) hydration plus enalapril, 3) dehydration (10 days of water deprivation), and 4) dehydration (10 days of water deprivation) plus enalapril.

Enalapril, (0.2  $\mu$ g/kg) (SIGMA, St. Louis, MO) an angiotensin-converting enzyme inhibitor (ACE-I), was administered intramuscularly (IM) as a bolus dose at noon on day 10 of dehydration. Blood samples were taken from the external jugular vein immediately before the treatment and at  $\frac{1}{2}$ , 1, 2, 4, 8, 12, and 24 hours post-treatment for measurements of plasma concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ , angiotensin II, aldosterone, PRA and osmolality.

**Experiment 2:** The camels were randomly assigned to four groups of 5 camels each; 1) hydration (free access to water), 2) hydration plus ACTH, 3) dehydration (10 days of water deprivation), and 4) dehydration (10 days of water deprivation) plus ACTH.

ACTH (SIGMA, St. Louis, MO) was administered intramuscularly (IM, 0.4 IU/kg) at 0, 12, and 24 hours. Blood samples were taken from the external jugular vein immediately before the treatment and 6, 12, 18, 24, 30, and 36 hours after treatment for the measurement of plasma concentrations of Na<sup>+</sup>, K<sup>+</sup>, aldosterone, cortisol and osmolality.

Blood (10 ml) was collected into heparinized tubes for the measurement of plasma concentrations of Na<sup>+</sup>, K<sup>+</sup>, and osmolality. The plasma was separated by centrifugation (1,000 × g) at 4 °C and analyzed within 24 hours.

Plasma concentrations of Na<sup>+</sup> and K<sup>+</sup> were analyzed using Beckman autoanalyzer Synchron CX-5 Clinical System (Beckman). Plasma osmolality was measured by freezing point depression using an advanced 3C2 Osmometer (Advanced Instruments, MA). For hormone analysis, 50 ml of blood were collected into prechilled tubes containing K<sub>3</sub>-EDTA. The blood was centrifuged at 4 °C and the plasma was stored at -20 °C until assay.

Radioimmunoassay (RIA) kits were used to determine plasma angiotensin II (Buhlmann, Basel, Switzerland), aldosterone (Diagnostic Products, Los Angeles, CA), plasma renin activity (PRA), cortisol and adrenocorticotrophic hormone (ACTH) (INCSTAR, Stillwater, MN).

### Statistical analyses

Values are expressed as means ± SEM. Analysis of variance (ANOVA) was used to determine the treatment and time effect. The treatment × time interaction used to determine the effect of time. The conservative F value was used to establish significance for the effect

of treatment and time. Tukey's test was used to test for differences between means of end points for which the ANOVA indicated a significant ( $p < 0.05$ ) F ratio.

## Results

Effects of water deprivation on plasma electrolytes concentrations, plasma osmolality concentrations and renin-angiotensin-aldosterone system are shown in Fig. 1 and Fig. 2, respectively. Water deprivation for 10 days induced a significant increase in PRA and plasma concentrations of angiotensin II, aldosterone,  $\text{Na}^+$  and osmolality. Water deprivation, however, induced a significant decrease in plasma  $\text{K}^+$  concentrations. The effects of enalapril on plasma electrolytes and osmolality are shown in Fig. 1. Enalapril administration induced a sharp decrease in plasma  $[\text{Na}^+]$  and an increase in plasma  $[\text{K}^+]$  ( $P < 0.05$ ) in the dehydrated camels but not in the control camels. These changes became apparent one hour after the enalapril administration. Plasma osmolality decreased significantly in both dehydrated and control camels.

The effects of enalapril on PRA, plasma angiotensin II and aldosterone are shown in Fig. 2. It induced a sharp decrease in plasma angiotensin II and aldosterone concentrations ( $P < 0.05$ ) in the dehydrated camels. In the control camels ACE-I induced a significant decrease in plasma aldosterone concentrations, but did not change plasma angiotensin II concentrations. These changes began  $\frac{1}{2}$  hour after the ACE-I administration and remained decreased ( $P < 0.05$ ) for 24 hours in the dehydrated camels. PRA concentrations increased significantly in the dehydrated camels. The increase in PRA concentrations in the control



camels was not significantly different. The increase in PRA in the dehydrated camels began one hour after enalapril administration and remained significantly elevated for 12 hours.

The effects of water deprivation on plasma concentrations of electrolytes, osmolality, ACTH and cortisol are shown in Fig. 3 and Fig. 4, respectively. Water deprivation for 10 days induced a significant increase in plasma concentrations of ACTH, cortisol, Na<sup>+</sup> and osmolality. Water deprivation, however, induced a significant decrease in plasma K<sup>+</sup> concentration. The effects of ACTH administration on plasma electrolytes and osmolality are shown in Fig. 3. ACTH had no significant effects on plasma electrolytes and osmolality in both the dehydrated and control camels.

The effects of ACTH on plasma aldosterone and cortisol are shown in Fig. 4. ACTH induced a sharp increase on plasma cortisol concentrations ( $P < 0.05$ ) in both the dehydrated and control camels. Plasma aldosterone concentrations, however, increased only in the dehydrated camels in response to ACTH.

## Discussion

In the present study, enalapril, an ACE-I, induced a decrease in plasma angiotensin II and aldosterone concentrations in the dehydrated camels. The decrease in plasma angiotensin II in the control camels, however, was not significant. PRA increased significantly in the dehydrated camels but not in the control camels. Similar findings are seen in humans (Davidai et al., 1984; Morganti et al., 1987; Wade et al., 1987) and sheep (McDougall, 1987). The decrease in plasma angiotensin II during converting enzyme inhibition interrupts the

short feedback loop existing between plasma angiotensin II and renin and causes an increase in plasma PRA (Leslie et al., 1995). The changes in plasma electrolytes and osmolality after ACE-I administration in this study are consistent with those in sheep (McDougall, 1987). The high concentrations of plasma angiotensin II in the dehydrated camels seem to enhance the effect of ACE-I in this study.

In the present study, ACTH did not significantly affect either plasma electrolytes or osmolality. These results are consistent with those of Raff et al. (1986) in dogs, but differ from those of Tarjan et al. (1995) in rabbits. ACTH increased plasma cortisol concentrations in both the dehydrated and control camels. These results are consistent with those of Tarjan et al., (1995) in rabbits, Alam et al. (1986) and Roth et al. (1982) in cows. ACTH increased plasma aldosterone concentrations only in the dehydrated camels. Aldosterone declined after the first 24 hours in the presence of consecutive administration of ACTH. These results are consistent with those of Davidai et al. (1984) and Leslie et al. (1995) in humans.

The influence of plasma ACTH and plasma  $K^+$  on aldosterone secretion is enhanced by plasma angiotensin II. The stimulatory effect of  $K^+$  is blunted in dogs when angiotensin II formation is reduced by captopril (Leslie et al., 1995). The increase in plasma aldosterone concentrations in human by ACTH administration was blunted by captopril (Davidai et al., 1984; Morganti et al., 1987). These data support the view that normal aldosterone secretion is achieved by action of the renin-angiotensin system. This also can explain the significant increase in plasma aldosterone in the dehydrated camels but not in the control camels. Water deprivation caused an increase in plasma angiotensin II in camels (Al-Qarawi et al., 1997),

which in turn enhances the action of ACTH on the zona glomerulosa cells (Leslie et al., 1995)

Our data clearly show that both angiotensin II and ACTH stimulate aldosterone secretion during dehydration in camels. However, the parallel increase in PRA, plasma angiotensin II and plasma aldosterone in dehydrated camels, which have been observed in this study and also reported previously (Al-Qarawi et al., 1997; Finberg et al., 1978) without any parallel changes in plasma cortisol or ACTH (Al-Qarawi et al., 1997), suggests that the effect of angiotensin II in stimulating aldosterone secretion seems to be dominant over that of ACTH.

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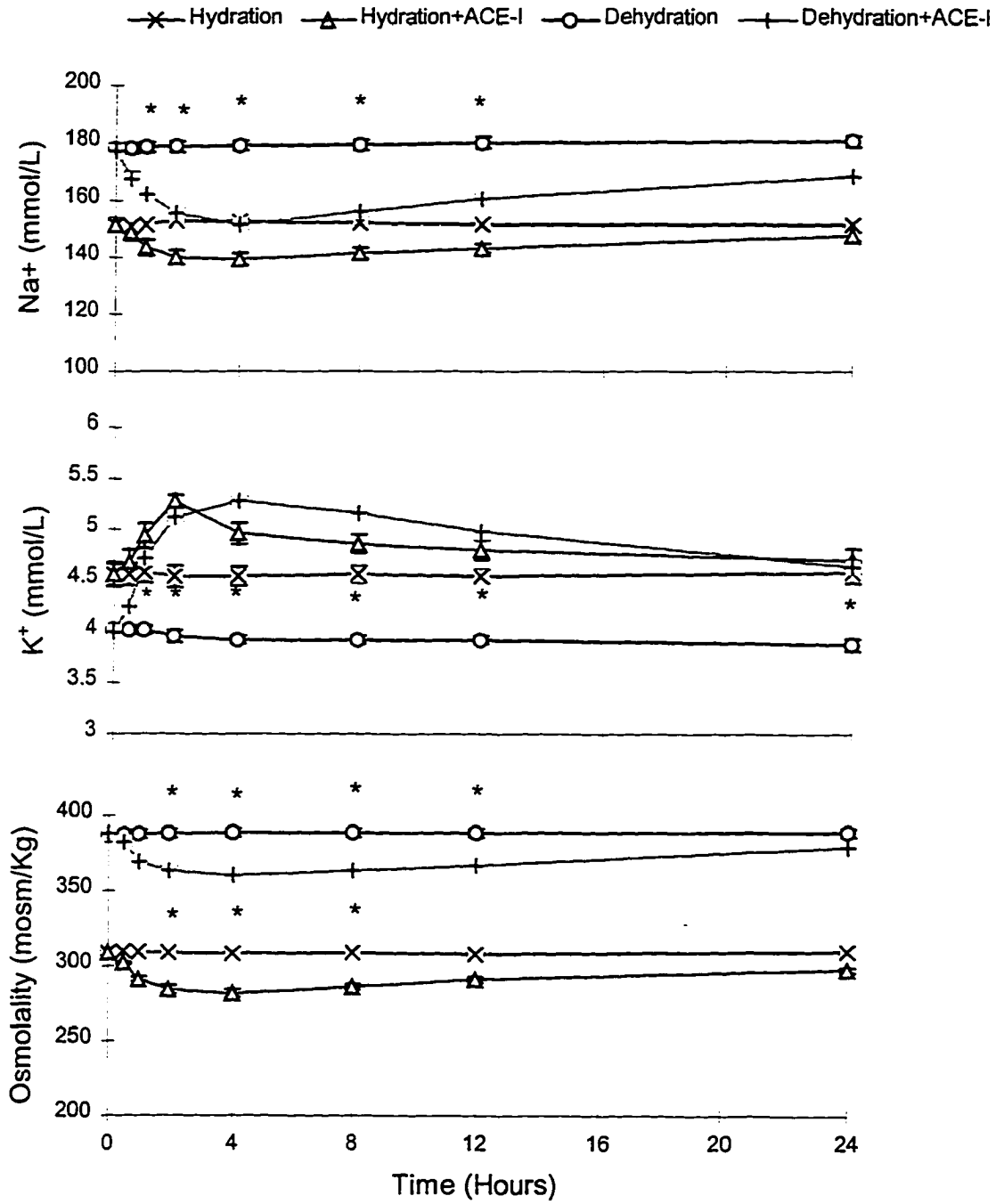


Fig. 1. Changes of plasma electrolytes and osmolality in dehydrated and control camels following ACE-I administration (n = 5). Data are expressed as means  $\pm$  SEM; \*P < 0.05, compared with the respective group at the corresponding time.

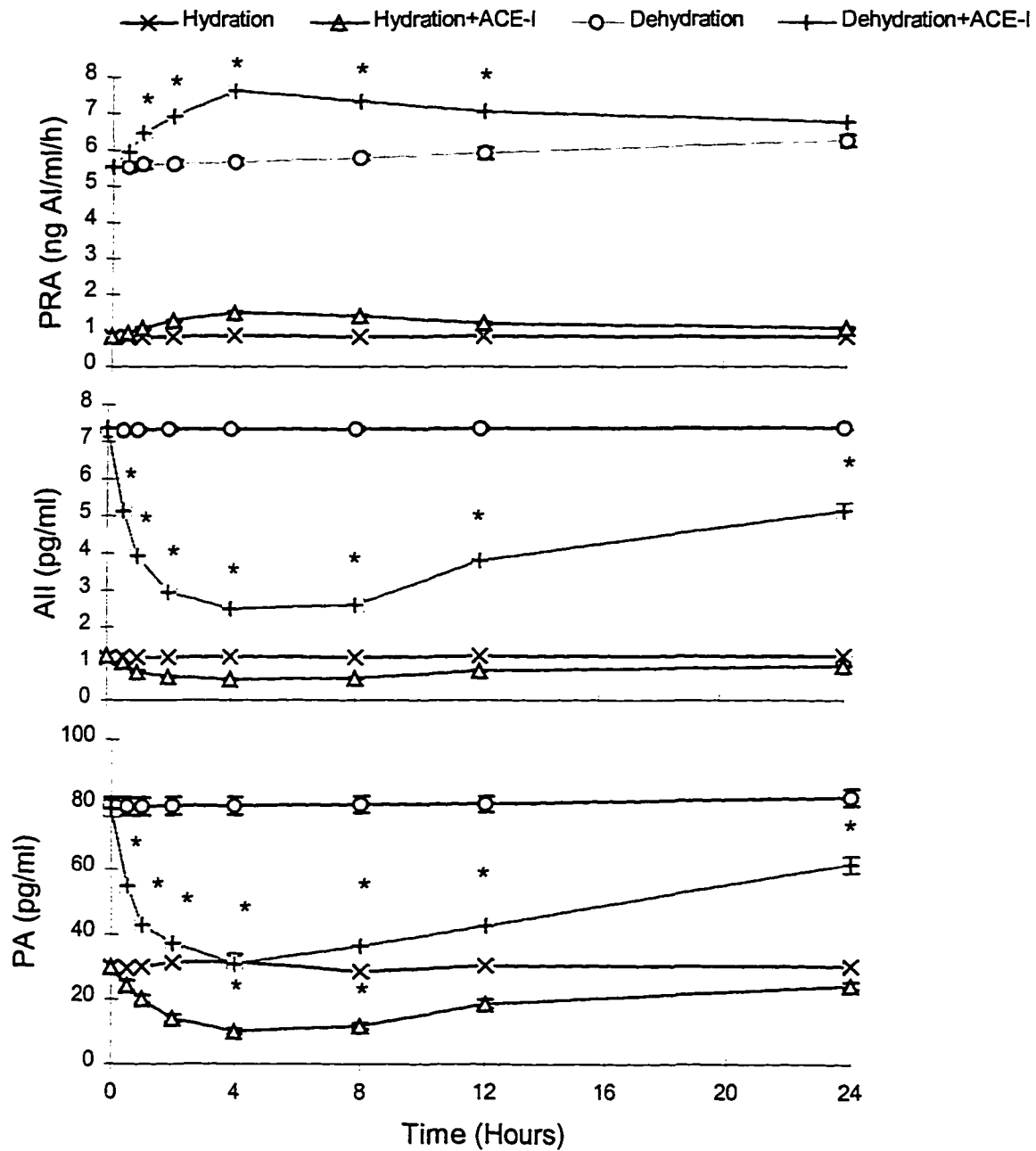


Fig. 2. Changes of plasma renin activity (PRA), plasma angiotensin II (A II), and plasma aldosterone (PA) in dehydrated and control camels following ACE-I administration (n = 5). Data are expressed as means  $\pm$  SEM; \*P < 0.05, compared with the respective group at the corresponding time.



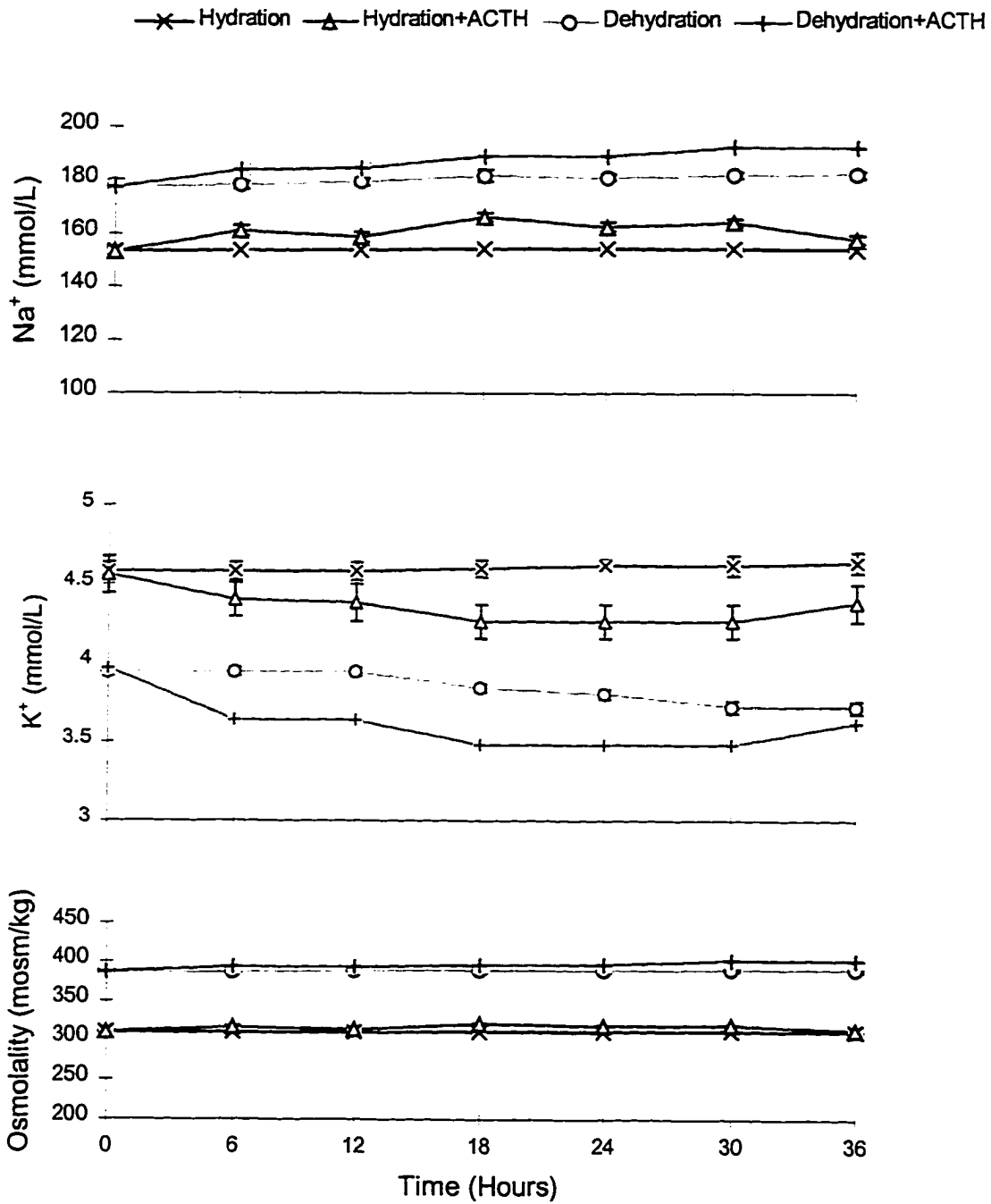


Fig. 3. Failure of ACTH administration in changing plasma electrolytes and osmolality in dehydrated and control camels during (n = 5). Data are expressed as means  $\pm$  SEM

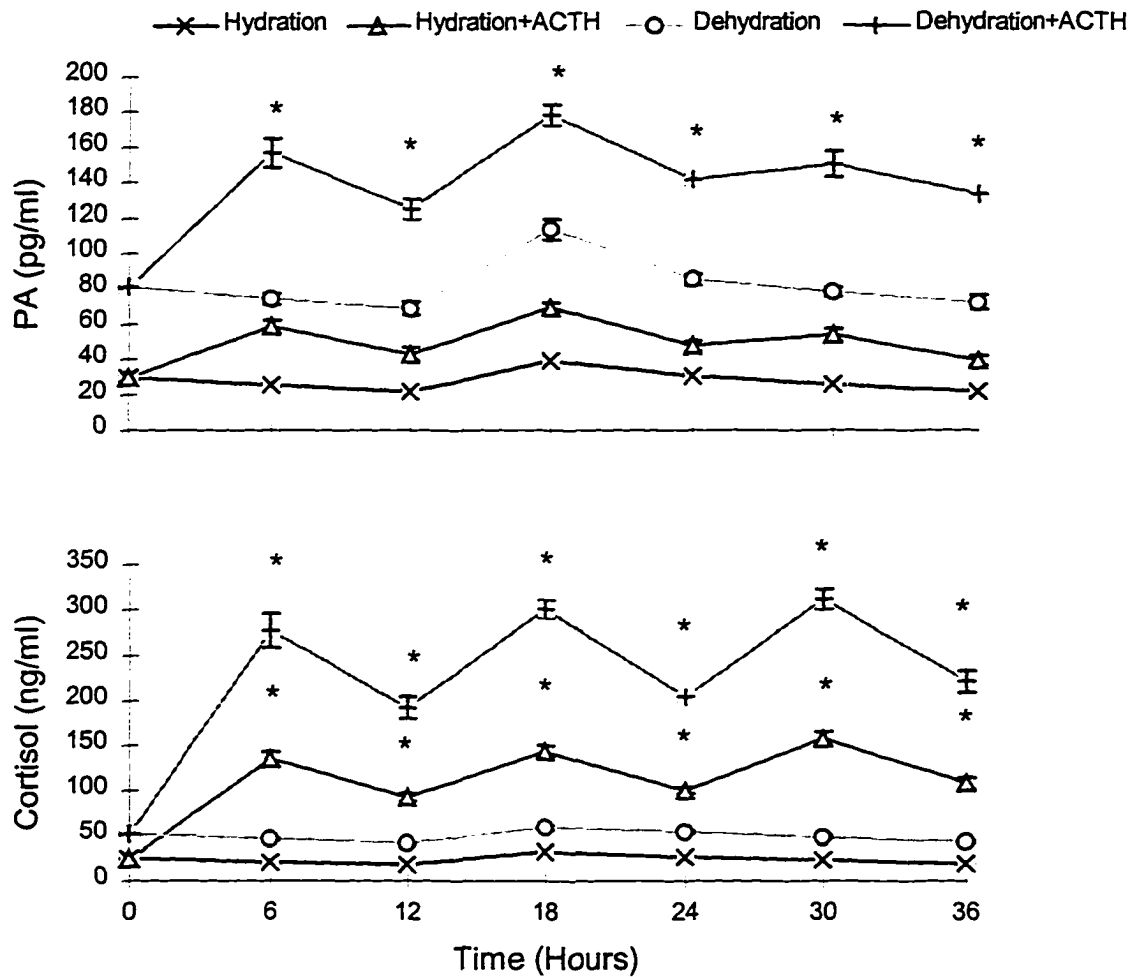


Fig. 4. Changes of plasma aldosterone (PA) and plasma cortisol in dehydrated and control camels following ACTH administration ( $n = 5$ ). Data are expressed as means  $\pm$  SEM; \* $P < 0.05$ , compared with the respective group at the corresponding time.

## GENERAL SUMMARY AND CONCLUSIONS

The present study was undertaken to examine the effect of severe dehydration and rapid rehydration in electrolytes and body fluids homeostasis of the arabian camel (Camelus dromedarius), and to determine which pathway is responsible for the secretion of aldosterone in the dehydrated camel; either the renin-angiotensin axis or ACTH axis.

Water deprivation induced a 25% decrease in calculated plasma volume. Body weight decreased significantly from  $482.8 \pm 23.3$  kg at day 0 to  $368.4 \pm 19.8$  by the end of dehydration. PCV fluctuated during dehydration and increased significantly from  $31.0 \pm 1.0$  to  $36.0 \pm 0.6$  % (at the end of dehydration). Hemoglobin increased significantly from  $13.2 \pm 0.3$  to  $16.3 \pm 0.3$  g/dl (at the end of dehydration).

After 15 days of dehydration the camels drank an average initial quantity of water ( $80.0 \pm 16.0$  liters) and their body weights rose sharply within  $\frac{1}{2}$  hour of rehydration and reached  $443.0 \pm 21.34$  kg. PCV and hemoglobin decreased significantly within  $\frac{1}{2}$  hour of rehydration. PCV and hemoglobin decreased further one hour of rehydration and returned to control levels within 4 hours of rehydration.

Water deprivation induced a significant increase in plasma osmolality,  $\text{Na}^+$ , and  $\text{Cl}^-$  concentrations, 25, 20, and 12 %, respectively. Plasma  $\text{K}^+$  concentrations fluctuated during dehydration but increased significantly ( $4.40 \pm 0.13$  to  $5.50 \pm 0.07$ ) by the last day of dehydration.

Plasma osmolality and plasma  $\text{Na}^+$  concentrations decreased significantly within  $\frac{1}{2}$  hour of rehydration, but they were still significantly higher than the control levels. Plasma

osmolality and plasma  $\text{Na}^+$  concentrations then decreased slowly and gradually, which reached the control levels after 24 hours of rehydration. Plasma  $\text{Cl}^-$  and  $\text{K}^+$  concentrations decreased significantly within  $\frac{1}{2}$  hour of rehydration, which reached the control levels 1-2 hours later.

Dehydration induced a significant increase on plasma protein (from  $6.5 \pm 0.1$  to  $8.7 \pm 0.2$  g/dl), creatinine (from  $1.4 \pm 0.2$  to  $2.9 \pm 0.1$  mg/dl), BUN (from  $12.4 \pm 1.1$  to  $32.4 \pm 1.1$  mg/dl), and glucose from a basal level of  $109.6 \pm 4.8$  mg/dl, to a peak of  $154.4 \pm 4.2$  mg/dl. Plasma glucose concentrations, however, decreased to those below the control levels during the last days of dehydration.

Within  $\frac{1}{2}$  hour of rehydration, plasma glucose concentrations decreased significantly to those below the control levels and returned to the control levels at 4 hours. Plasma BUN decreased significantly within  $\frac{1}{2}$  hour of rehydration and reached the control levels within 2 hours after rehydration. Total plasma protein showed a significant decrease one hour of rehydration. However, plasma protein concentrations were still significantly higher than the control levels. Plasma protein then decreased gradually and reached the control levels within 24 hours of rehydration. Plasma creatinine concentrations decreased significantly 4 hour after the onset of rehydration and reached the control levels afterward.

On day 0 the basal levels of plasma renin activity (PRA) were  $0.86 \pm 0.04$  and increased after 15 days of water deprivation to a peak of  $7.6 \pm 0.2$  ng Angiotensin I / ml /h, plasma angiotensin II concentrations from  $1.2 \pm 0.1$  to  $10 \pm 0.1$  pg /ml, and plasma aldosterone from  $30.4 \pm 1.6$  to  $137.4 \pm 3$  pg /ml. Water deprivation induced a sharp and prompt increase ( $P < 0.05$ ) in plasma AVP concentrations from a basal levels of  $0.67 \pm 0.02$

to  $7.4 \pm 0.2$  pg /ml at the end of dehydration. Plasma ACTH and cortisol concentrations increased significantly at the end of dehydration from a basal levels of  $11.0 \pm 0.2$  and  $24.2 \pm 1.3$  to  $16.9 \pm 0.2$  pg /ml and  $127.8 \pm 8.2$  ng /ml, respectively.

PRA and plasma concentrations of angiotensin II decreased significantly within  $\frac{1}{2}$  hour of rehydration and reached the control levels within 2 hours of rehydration. Plasma aldosterone concentrations, however, increased significantly and reached a value of  $220.0 \pm 5.0$  (pg /ml) within two hours of rehydration. Within 48 hours, plasma aldosterone concentrations returned to control levels. Plasma concentrations of AVP decreased significantly within  $\frac{1}{2}$  hour of rehydration and returned to control levels after four hours of rehydration. Rehydration induced an increase ( $P < 0.05$ ) in plasma ACTH and cortisol concentrations to  $40.3 \pm 0.9$  pg /ml and  $331.4 \pm 12.5$  ng /ml, respectively. Both plasma ACTH and cortisol concentrations returned to control values after 24 of rehydration. Plasma aldosterone and angiotensin II concentrations were highly correlated ( $r = 0.99$ ) during the first 10 days of dehydration, whereas plasma aldosterone and ACTH concentrations were not ( $r = 0.57$ ). During rehydration plasma aldosterone and ACTH concentrations were highly correlated ( $r = 0.90$ ), whereas plasma aldosterone and angiotensin II were not ( $r = 0.21$ ). Plasma concentrations of AVP and plasma osmolality were highly correlated ( $r = 0.99$ ) during dehydration, whereas, during the first 24 hours of rehydration they were less correlated ( $r = 0.75$ ).

In this study ACE-I administration induced a sharp decrease in plasma  $[Na^+]$  and an increase in plasma  $[K^+]$  ( $P < 0.05$ ) in the dehydrated camels but not in the control camels. These changes became apparent one hour after the ACE-I administration. Plasma osmolality

decreased significantly in both dehydrated and control camels. ACE-I induced a sharp decrease in plasma angiotensin II and aldosterone concentrations ( $P < 0.05$ ) in the dehydrated camels. In the control camels ACE-I induced a significant decrease in plasma aldosterone concentrations, but did not change plasma angiotensin II concentrations. These changes began  $\frac{1}{2}$  hour after the ACE-I administration and remained decreased ( $P < 0.05$ ) for 24 hours in the dehydrated camels. PRA concentrations increased significantly in the dehydrated camels, but not in the control camels. The increase in PRA in the dehydrated camels started one hour after ACE-I administration and remained significantly elevated 12 hours later.

ACTH administration did not cause a significant changes in plasma electrolytes or osmolality in both the dehydrated and control camels. ACTH induced a sharp increase in plasma cortisol concentrations ( $P < 0.05$ ) in both the dehydrated and control camels. Plasma aldosterone concentrations however, increased only in the dehydrated camels in response to ACTH.

Camels in this study were able to conserve water during dehydration decreasing their renal blood flow (RBF) and glomerular filtration rate (GFR). The increase in creatinine and BUN in this study gives a very good indication of a reduced GFR and a subsequent reduction in urine output in the dehydrated camel. Within  $\frac{1}{2}$  hour of rehydration most of blood parameters decreased significantly indicating a rapid reabsorption of water to the blood stream. Camels in this study were able to restore their normal renal functions within 4 hours of rehydration. This can be shown by the return of plasma creatinine to the control values 4 hours of rehydration. The decrease in plasma protein concentrations were parallel to those of

plasma  $\text{Na}^+$  concentrations. It seems that they remained elevated during the first 24 hours of rehydration in order to maintain body fluid tonicity and to prevent water intoxication.

The secretion of AVP during dehydration in camels seems to be controlled mainly by the changes in plasma osmolality but not plasma volume due to the high correlation ( $r = 0.99$ ) between plasma concentrations of AVP and plasma osmolality during dehydration, whereas PCV did not increase significantly until the end of dehydration. During the first 24 hours of rehydration plasma concentrations of AVP and plasma osmolality were less correlated ( $r = 0.75$ ). The rapid inhibition of AVP release after drinking seems to be caused by the sudden increase in plasma volume but not by the gradual decrease in plasma osmolality. The increase in plasma ACTH concentrations during the 24 hours of rehydration was highly correlated with the increase in plasma aldosterone concentrations. In addition, there was a decrease in PRA and angiotensin II concentrations during the same period. This suggests that during rehydration in camels the nexus between the renin-angiotensin system and aldosterone is impaired, whereas the nexus between the ACTH and aldosterone appears to be activated. It is likely that the increase in plasma aldosterone concentrations during rehydration in camels is under the influence of ACTH even though it needs more studies to prove or disprove this hypothesis by using dexamethasone, a long-acting potent glucocorticoid, to minimize ACTH secretion. During dehydration in camels, aldosterone secretion seems to be maintained by renin-angiotensin system but not plasma ACTH due to a high correlation between plasma aldosterone and angiotensin II concentrations but not between plasma aldosterone and ACTH concentrations.

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