STUDIES ON THE ROLE OF ANGIOTENSIN AND ANTIDIURETIC HORMONE ON THE CONTROL OF RENAL RESPONSES TO VARIATIONS IN THE ELECTROLYTE BALANCE

THESIS

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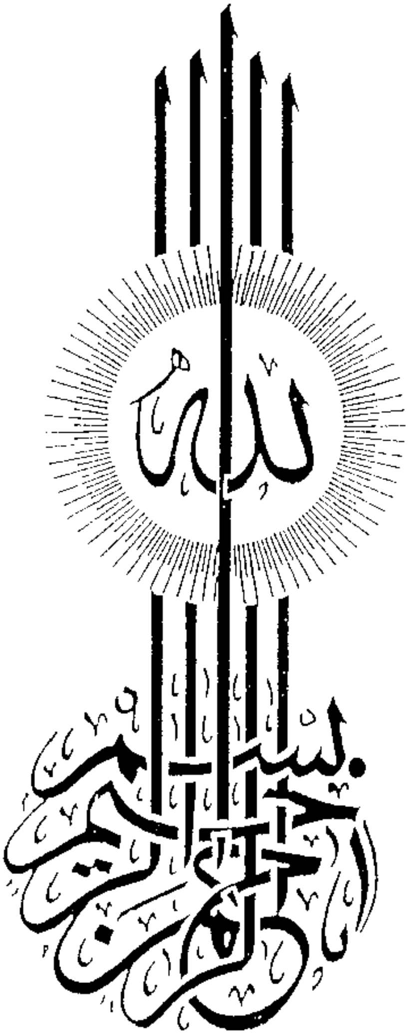
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INTRODUCTION

Life evolved in the sea, and all biological organisms still consist primarily of water. Since all life processes in some way or another require water, there must be a constant supply to assure survival. As long as the organism is surrounded by water, this presents no problem. As it vantures onto dry land, mechanisms must be evolved to maintain an internal environment that is essentially similar to the sea in an external medium that is often almost totally devoid of water.

This is not a single problem because water is continually lost due to:

a. Evaporation from the lungs and body surface

b. Secretion by sweat glands, which play an essential role in cooling the body.

c. Excretion of waste products by urination and defecation.

Moreover, the body fluids are stored in true compartments, the intercellular compartment referes to the water found inside the cells of the body. It is separated by a semipermeable membrane, the cell wall, from the extracellular compartment, which includes the fluids that surrounds all of the cells of the body, as well as the fluids found in the blood vessels. There is a constant exchange of fluids, as well as solids between these two compartments because the extracellular fluids provide the nutrients for and remove the waste products of all cellular activity.

Both fluid compartments contain substances other than water and some of these, having large molecules, cannot pass through the semipermeable membrane that separates the two compartments. This is important because the presence of solutions of unequal concentrations on opposite sides of a semipermeable membrane produces an osmotic pressure gradient.

In the body, both the intracellular and extracellular compartments contain some salts at all times, but their concentrations often differ. When this is true, water moves either into or out of the cells to reestablish the equilibrium of the two solutions. The absolute osmotic pressure i.e. the pressure that given solution would exert against pure water, measures the concentration of salts, relative osmotic pressure i.e., the pressure that exists between two solutions that are separated by a semipermeable membrane. As a rough generalization it can be stated that the volume and the distribution of the fluids of the body are determined by its content of water, and shortage or excess of either, upset the balance and compensatory mechanisms are brought into play. What happens during water deprivation.?

The animal continue to urinate, sweat, and evaporate water from the lungs and body surface, their concentrations are normally quite a bit lower than that of the body fluids. Deprivation increases the concentration of salt in the extracellular fluid compartment (i.e. increases its absolute osmotic pressure).

In turn, sets up relative pressure gradients between the two compartments that force water out of the cells. When deprivation continues for prolonged periods of time, the cells become unable to give up water to the extracellular compartment because water is an essential medium for all cellular reactions. The absolute osmotic pressure of the extracellular compartment then rises sharply, and a relative pressure gradient between the two compartments is maintained. When water is ingested, the absolute osmotic pressure of the extracellular fluids falls.The relative osmotic pressure gradient between the two compartments remains until extra water has been moved into the cell to reestablish an equilibrium between the salt concentrations in the extra and intracellular fluid compartments. How does the organism regulate this important process ?.

Firstly,the organism must measure not only the absolute level of its fluid stores but also the concentration of salts in them. The response of the organism to this state is to feel thirsty and drink. Some earlier theories suggested that water deprivation might increase the viscosity of blood, this in turn, was thought to stimulate receptors in the mouth and throat, Darwin (1801), and Dumas, (1803). Mayer (1900) demonstrated that water deprivation did indeed increase the absolute osmotic pressure of the blood. He suggested that the hypertonicity of the blood might irritate receptors in the walls of the blood vessel.

Wettendorff (1901) suggested that thrist could not be due to a metering of the absolute osmotic pressure of the extracellular fluid compartment because this pressure did not change fast enough. Instead, he proposed that thirst might be related to the movement of water out of the cell. Cells might be sensitive to the change in cell size or membrane tension and signal this informations to some coordinating centers in the brain . As we shall see, we are not get entirely sure whether cell size, the movement of water through the cell wall, or a relative osmotic pressure gradient may be stimulus for thirst.

The osmometric theory is supported by the observation that the ingestion or intravenous injection of hypertonic salt solution induces intense thirst in man (Arden, 1934) and water intake in experimental animals (Holmes and Gregersen, 1947).

That relative rather than absolute osmotic pressure are monitored, is indicated by the observation that injections of substances such as urea that increase the sbsolute osmotic pressure of the extracellular fluid but fail to set up relative pressure gradients (because they pass readily through the cell membrane) do not induce thirst or water intake (Gilman, 1937). An alternative interpretation of this finding that thirst might be related specifically to the absolute concentration of sodium chloride in the blood has been disproved in experiments that demonstrated that interavenous injections of hypertonic solutions of sorbital (which does not cross the cell membrane and consequently set up relative osmotic pressure gradients but actually reduces the absolute concentration of Na and Cl in the blood) induces intense thirst (Holmes and Gregersen, 1950).

The osmometric theory also supported by the discovery of cells in the hypothalamus that appears to be selectively activated by hypertonic solutions. Some of the hypothalamic osmoreceptors seem to control fluid intake, others regulate water loss by urinary excretion. This might be one of the mechanisms by which the body regulates its fluid balance. This was first suggested by the observation that injections of hypertonic saline solution into the diencephalic blood supply increase the secretion of antidiuretic hormone (ADH) and decrease urinary water loss.

The experimental evidence that more specifically supports a cellular dehydration theory of thirst, the picture is not quite as consistent. Strictly speacking, such a theory (Dill, 1938) suggested that thirst is related to the movement of water out of the cell and the resultant shrinkage in cell size and the satiety is related to the movement of water into the cell.

An acute depletion of NaCl from the extracellular fluid has in fact, been shown to produce a long lasting depression of fluid intake (Huang, 1955).

These observations present some difficulties for the cellular dehydration theory of thirst and suggest that the osmoreceptors may be sensitive not only to a decrease in cellular size but perhaps to any significant change in cellular size. It has been known for sometime that a substantial loss of blood produces thirst. The osmometric or cellular dehydration theories of thirst cannot readily account for this phenomenon, because blood is part of the body's extracellular fluid and its depletion does not produce any change in the osmotic pressure gradients between the body's fluid compartments. Since an osmometric theory also cannot explain the extreme thrist of patients on a salt-deficient diet.

Several investigators have examined the posibility that the osmometric system might be supplemented by volumetric mechanism that responds to changes in the quantity of extracellular fluid. These experimental analysis have shown that 10 to 15% decrease in blood plasma volume always produces thrist (Fitzsimons, 1961) The loss of blood plasma not only deplets the body's water store but also causes a significant reduction in total salt content. The effects of hypovolemia and cellular dehydration appear to be additive (Fitzsimons and oatley, 1968) but an increase in blood volume (hypervolemia) does not inhibit drinking in water deprived animals, suggesting that the osmometric and volumetric mechanisms operate essentially independently (Corbit, 1967).

Volume receptors that are specifically related to the hypovolemic thirst have not been demonstrated.

Water deprivation reduces both cellular and extracellular fluid volume (Hall & Blass, 1975, Ramsay, Rolls and Wood, 1977).

It has been suggested that plasma volume might be metered directly by pressure receptors in the blood