CALCIUM, CYCLIC AMP AND HYPERTENSION

THESIS

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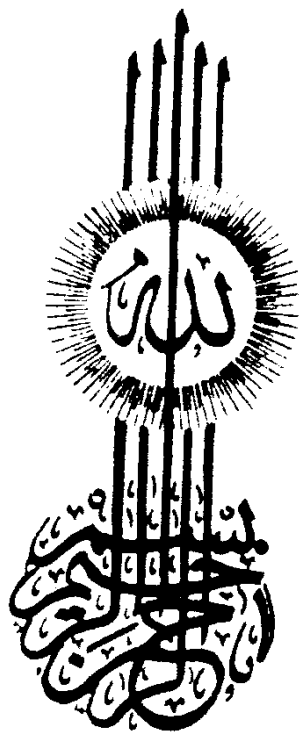

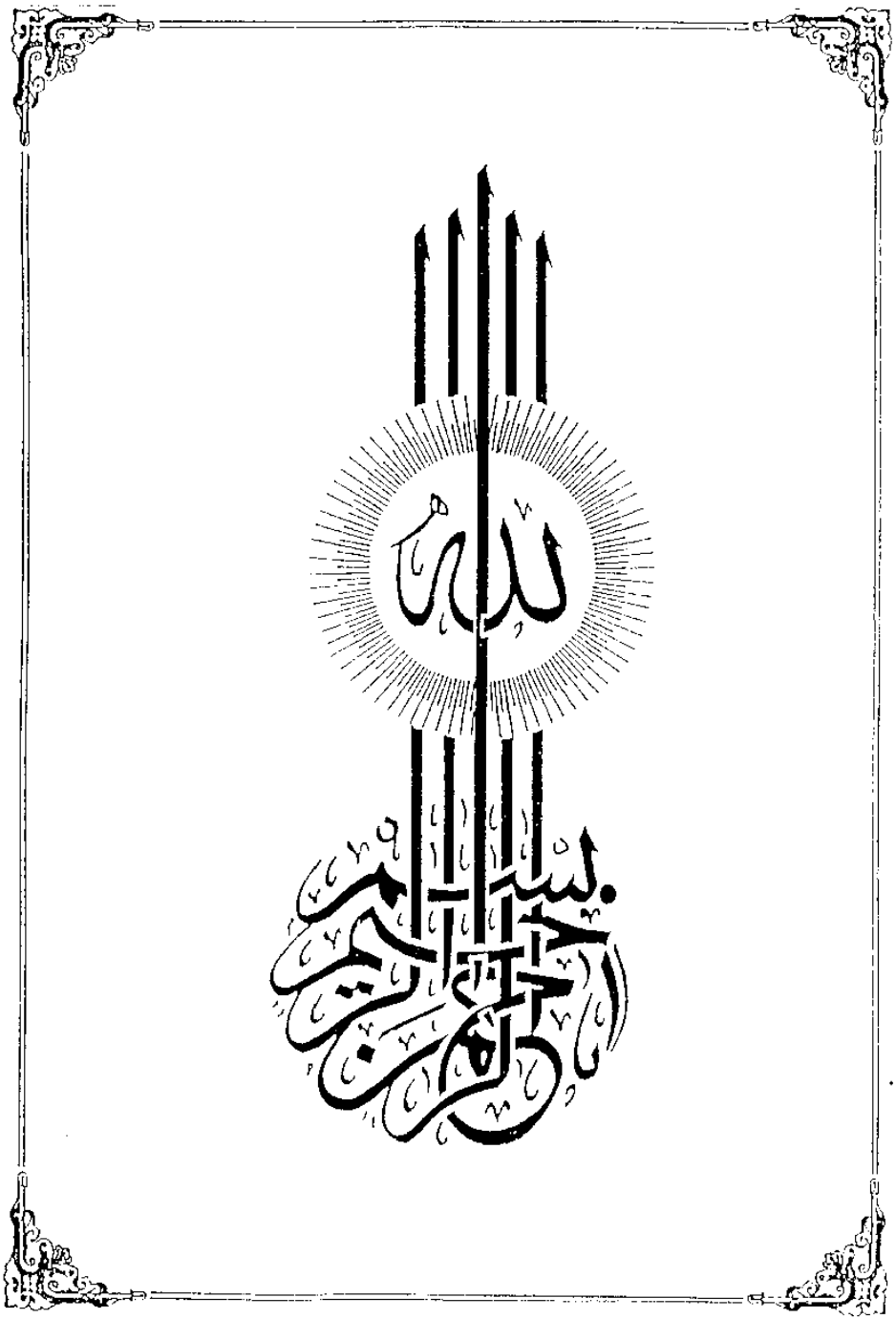

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C O N T E N T S

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INTRODUCTION AND AIM OF THE WORK

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Calcium is an important structural element in the body, it is an essential nutrient and is required for many body functions. It is important for normal function of vascular smooth muscle changes.

Little attension has been paid to the relation between calcium and blood pressure, but in recent theories concerning the pathogenesis of hypertension, intracellular calcium has been found to play an important role (Blaustein 1977).

In an epidemiological survey, Kesteloot and Geboers (1982) measured 24 hours urinary calcium excretion in hypertensive subjects and found that there is a highly significant correlation between serum calcium and both systolic and diastolic blood pressure. Moreover Belizais et al 1983 found an inverse relationship between calcium intake and blood pressure.

The aim of our work is to study the interrelationship between calcium, cyclic AMP and hypertension.

REVIEW OF LITERATURE

INTRACELLULAR CALCIUM HOMEOSTASIS

Calcium is an important structural element in the human body, it is an essential nutrient and is required for reproduction as well as growth.

At the cellular level it is necessary for the maintenance and regulation of many biological processes throughout the body i.e. the integrity and permeability of cell membranes, as a coupling factor between excitation and contraction in muscle, as a regulator of nerve excitability and as a regulator of secretions from exocrine and endocrine glands.

Since calcium is so vital to the body many mechanisms have been evolved to preserve the body stores of the ion and to regulate the level of calcium in body fluids.

A fine homeostatic control is necessary to ensure that the above processes operate with maximum effiency (Nordin 1976).

In animal cells the concentration of Ca^{+2} in the cytosol is in the range of 10^{-5} to 10^{-8} (Borle 1967), while its concentration in the extracellular fluid is

close to 10^{-3}, so the ratio of exterior Ca^{+2} to interior Ca^{+2} is 10^{2} to 10^{5} and the intracellular calcium concentration is more than extracellular one.

There are three calcium pumps orientated to remove ionized calcium from the cytosol either by ejecting calcium from the cell or by storing it in some bound form in the subcellular compartments (Nordin 1976). These pumps are:

pump in cell membrane, in mitochondrial membrane and in microsomal membranes.

Calcium pump in cell membrane:

As mentioned before the ratio of exterior Ca^{+2} to interior Ca^{+2} is 10^{2} to 10^{5}. However, the predicated ratio based on Nernst equation and a membrane potential of -80 m.volts (The intracellular negative with respect to extracellular) is approximately 10^{-2}. This means that calcium ion is not distributed according to its electrochemical potential across the plasma membrane, moreover radioactive calcium is exchangable in both directions across the cell membrane, so calcium enter the cell by passive diffusion and is pumped out by an active process, calcium pump, which require Ca^{+2} activated ATP in the plasma membrane.

In addition to being transported across the membrane, calcium is a key component of the membrane (Manery 1969).

Changes in calcium binding alter many properties of the membrane as its permeability to water and ions.

From variety of evidences (Holand 1969) a model of cell membrane activity has been constructed. The membrane is assumed to exist in one or two stable states, resting or calcium associated and active or calcium dissociated state. During active calcium is disociated and an action potential is produced and the permeability of Na^{+}, K^{+} and Ca^{+2} is increased. (Holland 1969).

Recently Rasmussen and his co workers (1970) have noted an apparent relationship between cyclic AMP and Ca^{+2} and concluded that exitation of the cell is followed by a rise of intracellular concentration of C-AMP and an increased uptake of calcium into the

cell. However, Ca^{+2} is not required for the stimulus to produce rise in intracellular C-AMP, yet the final physiological response is observed only if the bathing medium contains Ca^{+2}.

Subcellular calcium exchange:

Although the exchange of calcium across the cell membrane and its binding to this membrane are extremely important to cellular calcium homeostasis, they are not the sole means by which homeostasis is achieved.

Two cell organelles posses the ability to accumulate calcium, the mitochondria and microsomes, each organelle can reduce the calcium from the media and the bulk of accumulated calcium is sequesterated in a non ionized form.

The physiological significance of microsomal system is clear in skeletal muscles.

The sarcoplasmic reticulum is able to accumulate calcium by two mechanisms, by binding of calcium to

the membrane or by transport of calcium through the membrane (Inesi 1972).

The binding mechanism involves the formation of a complex between ATP and membrane enzyme

$$ATP + E \rightleftharpoons ATP - E$$

The formed complex binds calcium very rapidly (Ohnishi and Ebashi 1964) and induce conformational change around the active site of ATPase.

ATPase reaction produces a phosphorylated complex ($E \sim P$) and induces another change of the membrane structure as a result of which calcium is released and, the membrane becomes permeable to calcium.

$$ATP - E \rightleftharpoons E \sim P + ADP$$

ATPase isolated from the sarcoplasmic reticulum is correlated with calcium accumulation in microsomal vesicles (Feretos 1964) although the enzyme itself does not contain a significant number of binding sites for calcium.

More recently a calcium binding protein, which is not an enzyme has been extracted from the reticulum

and shown to be hydrophobically bounded to the interior of the vesicles (Maclennan and Wong 1971).

Although the sarcoplasmic reticulum being able to accumulate calcium, it can also release calcium on excitation so it fulfils both a regulator role for calcium concentration and controller of activation and relaxation of the muscles.

The released calcium initiate contraction, the calcium pump in the sarcoplasmic reticulum reaccumulates calcium and relaxation occurs (Hasselbach 1969).

The physiological role of mitochondrial system is not yet understood (Rassmussen 1970). It may involved in:

1. maintaining cytosol calcium at low concentration.
2. transcellular calcium transport.
3. acting as subsidary system for regulating calcium exchange in contractile and secretory cells.

The uptake of calcium by mitochondria requires ATP, Mg^{+2}, an oxidisable substrate such as succinate, citrate and in some instances in organic phosphate (Brierley et al. 1963).

Accumulation of calcium also involves electron transport and phosphorylation since inhibitors of electron transport and uncouplers of phosphorylation block calcium uptake (Deluca and Engstrom 1961, Pedersen and Coty 1972).

This suggests that calcium accumulation by the mitochondria is an energy dependent process driven either by respiration controlled electron transport or by hydrolysis of ATP and that ion transport may be coupled to the energy source through a nonphosphorylated high energy intermediate (Lehninger et al.,1967).

In absence of anions as phosphate, alternative mechanism Ca^{+} - H^{+} exchange may take place, and the respiration controlled electron transport establishes an H^{+} gradient across the mitochondrial membrane (Mitchell and Moyle 1965).

This supplies the drive for oxidative phosphorylation and calcium transport (Lehninger 1970).

The release of calcium from the mitochondria is couppled by the events at the cell surface, so the interaction of the first messenger (hormone) with its