STUDY OF GASTRIC AND ENTERIC FACTORS ON REGULATION OF PLASMA CALCIUM

THESIS
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By
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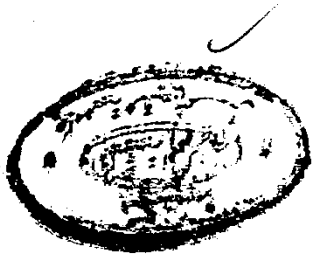

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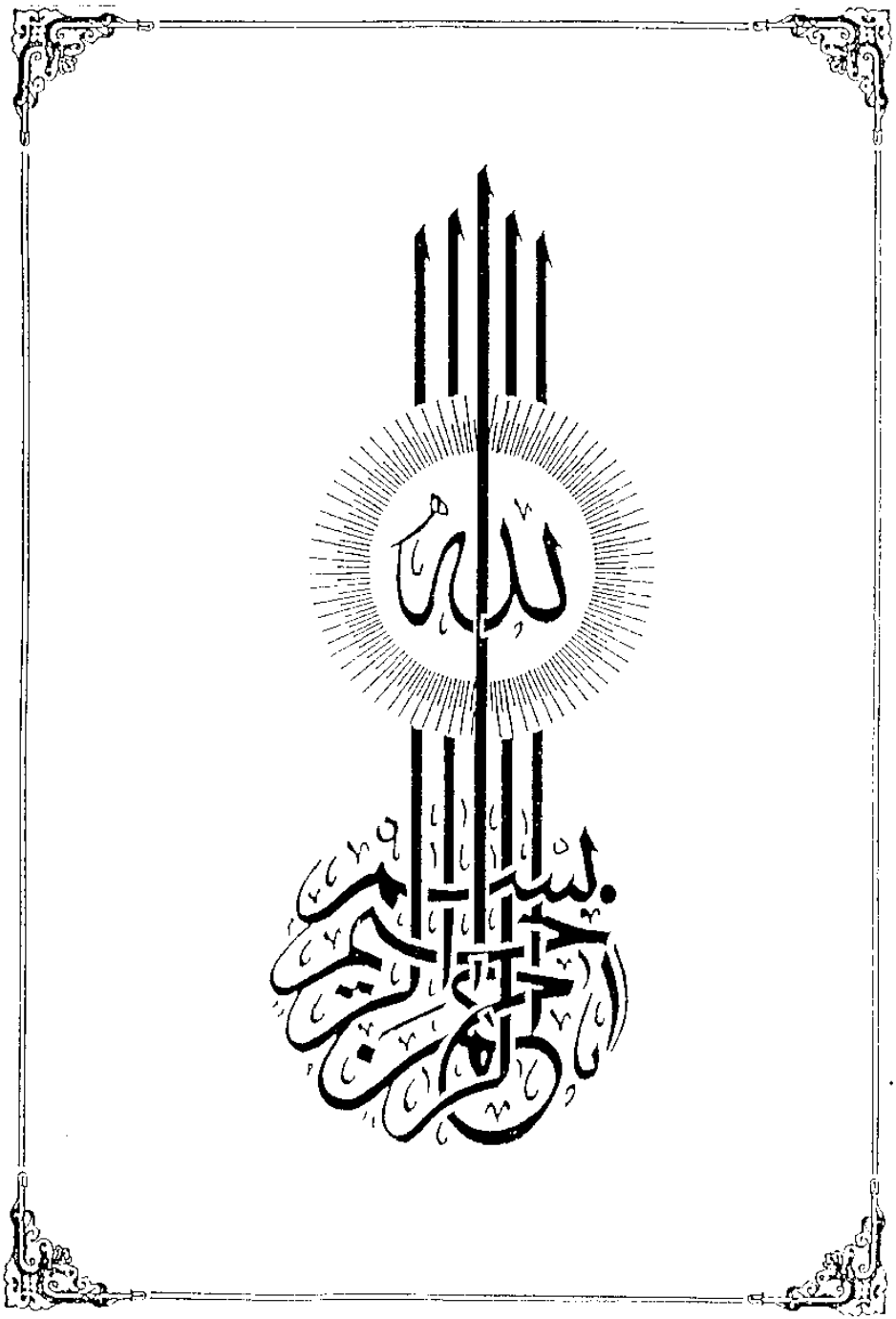

C O N T E N T S

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INTRODUCTION

This may help to throw more light on this ever interesting subject, and provides a deeper look to other gastrointestinal factors affecting calcium homeostasis.

CALCIUM HOMEOSTASIS

General considerations:

The concentration of calcium in extracellular fluid is normally controlled within very narrow limits,and so too, therefore, is the calcium concentration in the plasma. The plasma calcium-normally about 10 mg per 100 ml comprises non ionized(protein-bound)and ionized fractions Nordin, (1976) reported a mean serum ionized calcium concentration in 69 normal subjects of 4.64 mg per 100 ml. plasma calcium concentration in the steady state is the concentration at which the rate of calcium entry into the plasma has come into equilibrium with the rate at which it leaves.(Nordin,1976)

Calcium clearly enters plasma by absorption from the gastrointestinal tract and by resorption from bone. It leaves via the digestive juices into the gastrcintestinal tract,into bone by mineralization, and via the kidneys into the urine. In the steady state, net input must equal urinary calcium.(Nordin 1976).

Calcium participates in every known biological function. It has clearly been implicated in transmission of nerve impulses, in contractile mechanisms of skeletal,cardiac

neuromuscular excitability in the form of in voluntary tremors and spasm of skeletal and smooth muscle i.e. tetany (Martin,1976)

The daily requirement for the human adult has been placed at between 600 and 1000 mg. Requirements are increased during pregnancy and lactation, and positive calcium balance is needed to sustain growth and skeletal repair (Martin 1976).

Calcium is absorbed from the small intestine by active processes. The rate of uptake is controlled primarily by vitamin D metabolites. Uptake is enhanced by the presence of hydrochloric acid, amino acids,and citrate, and decreased by large amounts of fat and by substances(e.g., phytic and oxalic acids).

It has been estimated that all of the extracellular fluid calcium is removed 40-50 times a day (Martin,1976).

C A L C I T O N I N

In 1961 Copp demonstrated that there was a plasma calcium lowering hormone calcitonin as well as hormone that raised plasma calcium PTH which was already well known Copp and his colleagues(Copp et al,1962), perfused the thyroid and parathyroids of dogs with blood high in calcium, the resulting fall in systemic calcium observed proved to be more rapid than that produced by removal of the parathyroid glands themselves. From this it was deduced that the fall in plasma calcium provoked by hypercalcaemic perfusion was not due to inhibition of parathyroid hormone secretion alone. Foster,et al,(1964 a) demonstrated that the hypercalcaemic perfusion of an external parathyroid induced no fall in systemic plasma calcium. However,when the thyroid was included in the perfused area, striking hypocalcaemia occurred. The presence of a calcium lowering substance withen the thyroid was confirmed by the demonstration that an extract of this gland produced a similar fall in plasma calcium. It must be emphasized that since the discovery of this new hypocalcaemic substance, all would agree that calcitonin of ultimo branchial origin in lower animal species e.g. reptiles, fish, birds, are more effective in lowering serum calcium than those produced by the thyroid parafollicular cells or C cells of

mammals, (Irving,1973).

Cellular origin:

Foster et al (1964 b) found that a second thyroid cell type, distinct from that known to secrete the classical thyroid hormones, might exist. Evidence that these cells, now generally referred to as "C" cells contained calcitonin was provided by studies in which the presence of intra-cellular hormone was detected by immunofluorescent techniques using anticalcitonin antibody(Bussolati and Pearse,1967; Bussolate et al 1969,Kalina et al.,1970).

The cells secreting calcitonin are morphologically distinct from follicular cells,their most characteristic feature being electron-dense granules within the cytoblasm. These granules appear to be the secretory product and are discharged when stimulated with hypercalcaemic blood(Pearse, 1966,Cameron,1968,Pearse and Welsch,1968). In some instances C cells may occur outside the thyroid because the cells from the last branchial pouch,which migrate to the thyroid are cytochemically identical to calcitonin- secreting cells (Pearse and Carvalberia, 1967). So it is concluded that the ultimobranchial gland,which exists as a separate organ in fishes,amphibians,reptiles and birds, was a calcitonin

secreting endocrine organ.

Again ,in man, calcitonin-like activity is extractable from both parathyroid and thymus(Galante et al,1968). This was also proved by immunofluorescent techniques(Welsch and Pearse,1969).

Chemistry:

Pure calcitonin was first isolated from pig thyroid in 1968 (Potts et al,1968). It is a straight-chain peptide containing 32 amino-acid residues. Human calcitonin has also been isolated & synthesized,(Copp,et al.,1962).All the calcitonin so far isolated have the same basic structure containing 32 amino-acids with a seven membered disulphide ring at the NH_2-terminus and prolinamide at the COOH-terminus. There is also an aromatic amino-acid(tyrosine or phenylalanine) at position 22 and glycine at position 28. The difference in the intermediate amino acids are considerable between the porcine, salmon,human calcitonin. The entire molecule appeers to be essential,since removal of the amide group at the COOH terminus or shortening the chain by a single amino acid appears to result in almost complete loss of biological activity.

Since only nine residues, seven of these situated

within the first nine amino-acid residues,are common to the amino-acid sequences of calcitonin in all species so far known ,it suggests that this region of the molecule must be intimately related to biological activity. Salmon calcitonin is 100-200 times more active in the human (Neer et al,1970).

The difference in the activity depends on 3 factors(a) the concentration of the hormone in the receptor compartment which determined by both its rate of absorption and destruction.(b)the fit of the hormone at its receptor (c) the responsiveness of the receoptor site at the hormone itself.

Factors affecting secretion:

The principle stimulus for secretion of calcitonin is calcium. However, secretion or release may be affected by a variety of factors including other hormones,antibiotics and possibly magnesium. Copp et al.(1962) and Kumar et al, (1963) demonstrated that this hormone is secreted under conditions in which the plasma levels of calcium are high. So, the direct relationship between plasma calcium concentration and the rate of secretion of calcitonin is now well established A marked rise in the peripheral concentration of the hormone in the order of three-to fifteen fold have been detected following infusion of calcium.

Cyclic AMP is a potent stimulus for the release of the hormone (Avioli et al,1969). As the metabolic effects of glucagon are mediated through the activation of cyclic AMP (Sutherland and Robison,1966). Since the concentration of cyclic AMP is affected by sympathetic nervous activity (Murad et al,1962,Sutherland and Robison,1966). So,Alpha and beta adrenergic blockade abolish the response to glucagon but not to caclium.

Prostaglandins are potent secretagogues for calcitonin in porcine thyroid slice(Bell.,1975 & Meyer and Coworkers1975).Antibiotics as streptomycin and related compounds also release the hormone(Galante et al,1970) Imidazole, an activator of phosphodiesterase, inhibits this action suggesting that cyclic AMP may be involved in calcitonin release (Galante et al.,1970).

ACTION OF CALCITONIN

Calcitonin is far more effective in young than in old animals, and in children rather than adults, since sensitivity to calcitonin is related to rates of bone turnover (Sturtridge and Kumar, 1968). The hypocalcaemic response was obtained in parathyroidectomized rats. It also, occurs in eviscerated and nephrectomized rats(Kenny and Heiskell, 1965), so, it is reasonable to assume that its primary action is on bone.

Action of calcitonin on bone:

Bone resorption:

The fundumental action of calctionin is to inhibit bone resorption(Foster et al, 1972).

This has been demonstrated by many workers both in vivo and in vitro. Aliapoulios et al, (1966) using bone culture system, found the bone resorption caused by parathyroid hormone to be inhibited as well as that caused by vitamin A, Calcitonin thus acting on a basic site of bone resorption. Reynolds and Dingle(1970) also reported, that calcitonin inhibited the formation of new osteoclasts and the action of those already present when stimulated by either parathyroid

hormone or viatmin A in the medium.

Friedman and Raisz (1965),working in vitro,found osteoclast proliferation caused by parathyroid hormone to be inhibited.

They considered that calcitonin did not compete with parathyroid hormone for single site of action,but acted at a different site of the mechanisms of bone resorption. Klein and Talmage (1968) found that extracellular hydroxyproline was reduced as was the release of calcium, so that calcitonin inhibited the entire process of bone catabolism. Hydroxy proline has been measured as an index of the rate of bone resorption.

Bone Apposition:

The evidence that calcitonin may increase bone formation is not strong (Foster et al,1972). Matrait-Denys, (1968)found an increase in number of osteoblasts in bones of rates chronically treated with calcitonin. Gaillard(1967) observed more osteobalsts in bones cultured in the presence of the hormone. However, neither Reynolds (1968) nor Friedman and Raisz (1965) were able to demonstrate osteoblastic proliferation in vitro systems.