FURTHER STUDY ON THE EFFECT OF GASTROINTESTINAL MUCOSAL EXTRACTS ON BLOOD CALCIUM

THESIS
Submitted For The Degree Of Ph. D.
(PHYSIOLOGY)

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1986

A C K N O W L E D G E M E N T

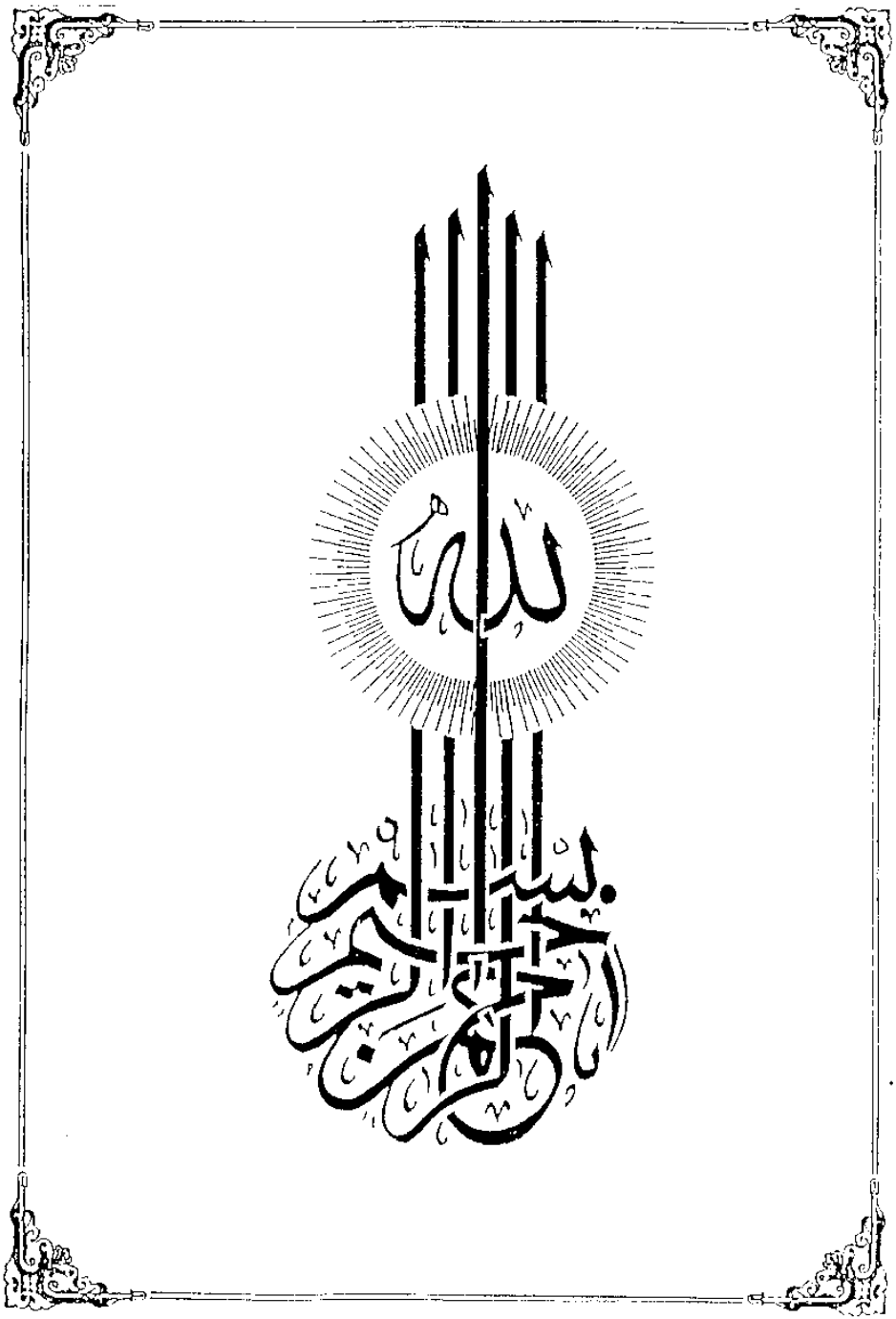
I wish to express my thanks to Professor Dr. MAHMOUD EL-KARIMY, Head of the Physiology Department, for his continuous encouragement, kind help and keen supervision .

I am deeply grateful to Dr. MAHMOUD HANI AYOBE , Professor of Physiology, for initiating, suggesting and planning this study, and for his help in solving the problems metwith throughout the work .

I am especially indebted to Dr. NABIL EL-DAMARAWY, Professor of Physiology, for his great contributions and suggestions that inspired life in the whole study . Without his kind meticulous guidance, wise counsel and faithful advice cordially offered to me, this work would not have been possible .

I wish to express my appreciation and gratitude for Prof. Dr. FATMA AHMED MOHAMED, Professor of Physiology, and Dr. LAILA EL-GUINDY, Assistant Professor of Physiology, for their continuous encouragement and kind cooperation .

I am deeply grateful to Dr. FARID EL-ASMAR, Prof. of Biochemistry, for his valuable advice and generous co-operation .



I am greatly indebted to Dr. KHADIGA GHONEIM , Professor of Biochemistry, for the tremendous amount of time and energy she spent assisting and encouraging as well as for patience and unyielding optimism .

I would like to express my great thanks to Dr. SALAH ABOU-SHANAB, for his generous help and co-operation .

Last but not least, I would also like to thank all the members of Physiology Department, for their interest and encouragement .

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INTRODUCTION

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In the last few years, several investigators were concerned with the role of gastrointestinal tract in calcium homeostasis . Beside its function in calcium absorption through a vitamin D-stimulated calcium binding protein (Wasserman and Taylor, 1966), there is considerable interest in the relationship between gut hormones and calcitonin .

In 1970, Gudmundsson et al. have shown that human calcitonin levels were higher after a meal . Also, the presence of calcium in the gastrointestinal tract increases calcitonin secretion eventhough circulating levels of calcium are not raised (Cooper and Deftos, 1970) .

In 1972, Sizemore et al. have reported greater increases of thyro-calcitonin in normal subjects after oral calcium than after i.v. calcium despite the fact that i.v. calcium produced much greater increases in the blood calcium level .

Orally ingested calcium, therefore, may act locally in the gut leading to release of gastrointestinal hormones which are calcitonin secretagogues (Cooper and Deftos , 1970 ; Care et al., 1971b; Hennessy et al., 1973) .

According to Boden (1981) , the gastrointestinal tract represents a large endocrine organ that contains many hormonal active peptides . Gastrointestinal endocrine cells , like other endocrine cells , contain secretory granules , that can be discharged into adjacent blood vessels in response to stimuli delivered from luminal contents , from nerves or through the blood . There are , however , important differences between the endocrine gut and other endocrine organs . In the gastrointestinal tract , single endocrine cells are dispersed between other mucosal cells . The scattering of these endocrine cells among other essential structures throughout the entire gastrointestinal tract has made it impossible to apply the classical endocrine approach to the study of hormonal actions i.e. to create hormonal deficiency by ablation of the endocrine organ under study . Consequently , no deficiency states are known for any of the gastrointestinal hormones (Boden , 1981) .

Study of the gastrointestinal mucosal extract represents , therefore , a plausible alternative approach in this respect .

In an earlier attempt (Awad , 1980) , we were able to demonstrate significant hypocalcemia in rats injected with mucosal extracts from rat stomachs and upper intestines .

Further studies are needed to identify the role of gastrointestinal mucosal extracts in calcium homeostasis .

REVIEW OF LITERATURE

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Role Of Gastrointestinal Hormones In Calcium Homeostasis

I. Gastrin :

The stimulatory effect of pentagastrin on calcitonin release was demonstrated by Care et al. (1971 b) and Care et al. (1971 a) and confirmed by Cooper and Mahgoub (1971) . This observation that pentagastrin is a calcitonin secretagogue was later documented and extended to include both synthetic human gastrin I and pure procine gastrin II (Care et al., 1971 b) . The latter hormone was shown to stimulate the secretion rate of calcitonin from thyroid preparation perfused in situ in anaesthetized pigs at concentrations similar to those found after stimulation of gastrin production by a meat extract placed in the stomach (Care et al., 1971 b) .

In 1971, Cooper et al. have reported that administration of a small intravenous dose of pentagastrin in the pig results in a marked rapid increase in thyrocalcitonin secretion as much as 40-fold . They also reported that stimulation of this magnitude by calcium alone requires a severe hypercalcemia (12 - 15 mg calcium/100 ml) .

In 1973, Hennessy et al have evaluated the calcitonin secretagogue action of pentagastrin in patients with

thyroid medullary carcinoma . The intravenous administration of pentagastrin (0.05 and 0.5 ug / kg) to two patients with metastatic medullary carcinoma of the thyroid was followed by a very rapid two to ten-fold rise in serum levels of immunoreactive thyrocalcitonin . The administration of calcium, either orally or intravenously, produced rises in calcitonin that were slower and much smaller magnitude . Oral calcium appeared to stimulate calcitonin secretion in these patients without producing a rise in serum calcium levels . The data are consistent with the hypothesis that pentagastrin influences secretion of thyrocalcitonin in man .

Cooper et al. (1972b) have demonstrated the hypocalcemic effect of gastrins in rats, systemic intravenous injection of synthetic pentagastrin and tetragastrin and of native procine gastrin in doses of 4 - 12 ug per 150 g rat produced modest hypocalcemia (fall of 6 - 12 %) , 15 - 30 minutes later . By 60 minutes after injection , normocalcemia was reestablished . Single injections of pentagastrin produced hypophosphatemia as well as hypocalcemia . The hypocalcemic effect of pentagastrin was abolished after acute removal of thyroid gland, suggesting that the secretion of thyrocalcitonin was involved . From the above data, Cooper et al.(1972b)suggested that gastrin may play a role in the physiological regulation of thyrocalcitonin secretion in the rat.

The relation of gastrin and calcitonin in patients with Zolinger-Elison syndrome and medullary carcinoma of thyroid was described by Sizemore et al. (1973) . Patients with Zolinger-Elison syndrome have high immunoreactive gastrin levels and mean levels of calcitonin are also high . On the other hand, mean serum immunoreactive gastrin was decreased significantly in patients with medullary carcinoma of the thyroid when the serum calcitonin was above normal . These results suggest a possible interhormonal relation between calcitonin and gastrin in man , calcitonin inhibiting gastrin secretion and conversely, gastrin stimulating calcitonin secretion .

The influence of gastrin on calcium homeostasis was studied in both thyroid intact and thyroparathyroidectomized rats by Schulak and Kaplan(1974) . Either synthetic human gastrin I or procine gastrin was injected intravenously into fasted, anaesthetized male 60-80 g rats. Venous blood was collected before gastrin administration and both at 30 and 60 minutes after injection. Gastrin at a dose of 12 - 50 ug / rat has induced a significant hypocalcemic response in thyroid intact rats . Similarly , they proved that gastrin at a dose of 12 - 25 ug / rat , also produced a significant decrease in serum calcium in thyroparathyroidectomized rats . On the basis of these

experiments, Schulak and Kaplan(1974) suggested that in the rat, while gastrin may act as a calcitonin secretagogue, it is unlikely that this is the sole mechanism of gastrin-induced hypocalcemia . Since removal of the thyroid gland does not abolish the hypocalcemic response of gastrin, a mechanism other than the release of thyroid calcitonin is likely .

Schulak and Kaplan (1975) have shown that the hypocalcemia following gastrin administration occurs in thyroparathyroidectomized as well as thyroid intact rats . They also reported that hypophosphatemia does not accompany the hypocalcemia induced by gastrin, and they suggested that a mechanism other than release of calcitonin from the thyroid gland may be involved in this response in the rat. They also reported that neither adrenalectomy, nephrectomy nor excision of the pancreas and small and large intestine altered the hypocalcemic response to gastrin . Their experiments have proven that gastrectomy, however, eliminated all hypocalcemia following administration of gastrin in both thyroid intact and thyroparathyroidectomized rats . They demonstrated that the removal of the antrum of the stomach did not influence the hypocalcemic response to gastrin while, resection of the proximal 75 % of the stomach, however, inhibited the hypocalcemic response to

gastrin as did total gastrectomy, thus, in the rat, the proximal stomach appears to play an important role in mediating this response . they concluded , from their work, that in the rat, an intact stomach is necessary in order for gastrin-induced hypocalcemia to occur . Thus, in this animal, the stomach may be more important than the thyroid gland in mediating the hypocalcemic response . The mechanism by which the stomach influences calcium homeostasis is unknown, whether or not this gastric response is secondary to a functional phenomenon related to gastric acid secretion is uncertain (Schulak and Kaplan, 1975) .

Cooper et al. (1977b) selected the suckling period, a time when rapid growth of the skeleton requires a retention of calcium, for investigation of a possible role for calcitonin in normal physiology . They examined serum concentration of calcium, phosphorus and immunoreactive calcitonin, in 14-day-old rat pups during fasting and suckling . Litters of 6 - 10 pups each litter were allowed to nurse ad libitum or were separated from their mothers (fasted) for 4 - 12 hour . After fasting, half of each litter was allowed to suckle for $\frac{1}{2}$ to 2 hours . Babies nursing ad libitum and with milk curds in the stomach showed a serum calcium of 10.5 mg / 100 ml and a high serum calcitonin of several thousand pg / ml . These values