STUDY OF GLUCAGON IN DIABETIC PATIENTS WITH AUTONOMIC NEUROPATHY

THESIS

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by

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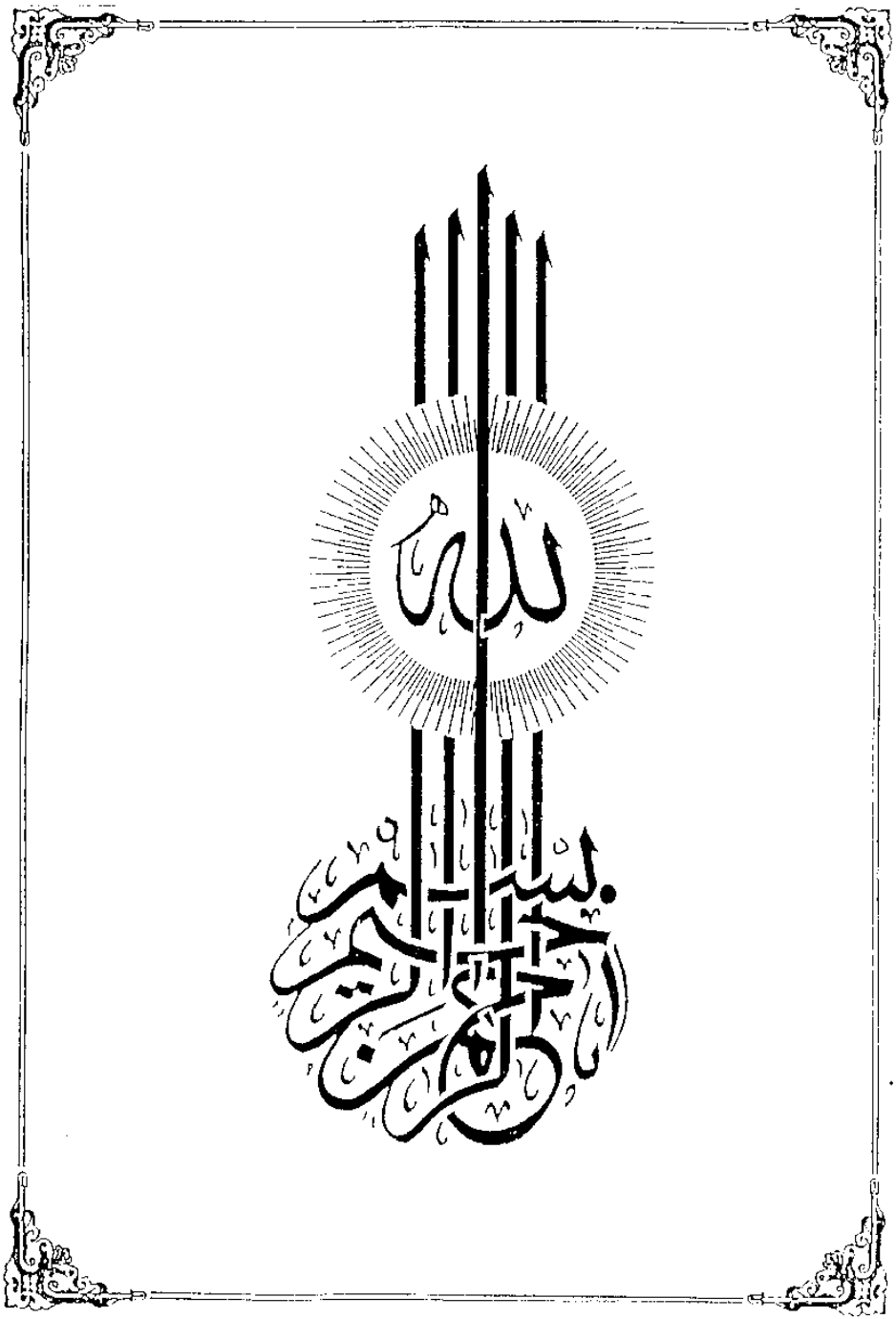

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INTRODUCTION

INTRODUCTION

Human diabetes mellitus is charactarized by exessive glucagon secretion as well as deficient insulin secretion.

In recent years the role of glucagon, a polypeptide hormone secreted from the alpha cells of the pancreas, has become a great deal of interest to investigators in the field of glucose metabolism.

Glucagon plays an antagonistic role with insulin in the regulation of blood glucose level. Thus, its presence acts as a hormone of energy releas raising blood sugar levels by glycogenolysis and gluconeogesis .

Although recent studies indicate that hyperglucagonemia may itself account for at least 25% of the fasting plasma glucose value found in patients with insulin dependent diabetes.

Diabetic neuropathy and other long-term complecations of diabetes in human result from the interaction of multiple metabolic, genetic and other factors of which the most important is chronic hyperglycemia.

Anumber of observation have led to the conclusion that chronic insulin deficiency and/or hyperglcemia inflence the development of diabetic neuropathy.

Glucagon responses to hypoglycemia have been reported to be diminshed in juvenile-onset diabetes.

Maher et al. ,(1977) found that glucagon releas

during hypoglycemia was diminshed in juvenile-onset diabetics without autonomic neuropathy and was absent in diabetics with autonomic neuropathy.

REVIEW OF LITERATURE

GLUCAGON

HISTORY:

The first crude insulin preparation were made in 1921 by (Banting and Bast).

After injection into volunteears these caused a profound fall in the blood glucose level. It was noticed, however that this was preceded by a rise in glucose level.

Kimball and Murlin (1924), were able to isolate a fraction that was responsible for this rise and they called it glucagon.

It was not fully purified until 1953 (Stanb et al.,)

Source of glucagon:

Glucagon is secreted from A cells of islets of langerhans. The islets of L. are ovoid 75x175 Mm. their numbers have ranged from 100,000 to 2,500,000 islets in a total pancreas, making up 1-3% of total pancreatic mass. The tail of pancreas contains more islets than the head (Port and Halter 1981).

In a normal man, the islets are composed of at least four types of cells: A, B, D, and pancreatic polypeptide (F) cells. A cells secrete glucagon and B cells secrete insulin. D cells contain and secrete somatostatin. F cells contain and secrete pancreatic polypeptide.

The composition of islets varies from the head

to the tail, with glucagon rich islets in tail and pancreatic polypeptide rich islets in the head.

A cells differ from B cells in that the concentration of the A granules are greater and the golgi complex is smaller, the A cells have smaller granules and a more ovoid nucleus. Both sympathetic and parasympathetic nerve ending have been identified in islet cells, and these nerves function as part of insulin, glucagon, somatostatin, and pancreatic polypeptide control system (Port and Halter 1981).

A cells are largely situated in the outer rim of the islet, and constitude approximatly 25% of total islet cells (Orci and Unger 1975 a, Orci et al., 1976).

Ssomatostatin acts as suppressor of both insulin and glucagon (Kocher et al.,1974) and its cells D cellsare located between A and B cells.

The A granules for glucagon storage,are relatively uniform cells (Ganong 1980).

Chemistry of glucagon:

Human glucagon is a linear polypeptide with a molecular weight of 3485 with 29 amino acids residues (Thomsen J., et al. 1972).

Traces of zinc and other metals are associated with glucagon but these metals do not form an integral part of the crystal as they do in insulin (Port and Halter 1981).

Glucagon is relatively insoluble in water, its isoelectric point is between 7.5 and 8.5. Electrolytes decrease its solubility but mildly acidic and basic conditions increase it, tryptophan and methionine are constituents of glucagon but not insulin, while cystine, isoleucine and proline are components of insulin but not of glucagon - the integrity of the glucagon molecule is required for physiologic acvivity (Port and Halter 1981).

There is some evidence for the formation of glucagon from a larger polypeptide precursor "proglucagon" in the A cells of the pancreas (Ganong 1980)

									NH_2				NH_2				NH_2	
r.	Lys.	Tyr.	Leu.	Asp.	Ser.	Arg.	Arg.	Ala.	Glu.	Asp.	Phe.	Val.	Glu.	Tyr.	Leu.	Met.	Asp.	T
1	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	2

						NH_2			
y.	Asp.	Ser.	Thr.	Phe.	Thr.	Gly.	Glu.	Ser.	His.
	9	8	7	6	5	4	3	2	1

Fig. (1) : Amino acid sequence of human glucagon , showing the site of cleavage by dipeptidyl aminopeptidase I

(After Porte and Halter 1981).

Plasma immunoreactive glucagon (IRG) :

Valvered et al. (1975) : identified four IRG fractions in plasma, three corresponds to IRG components present in glucagon secreting tissues :-

1- IRG : 2000

2- IRG : 3485 presumed to be true glucagon.

3- TRG : 9000 thought to correspond to proglucagon.

4- The fourth is big plasma glucagon.

The normal fasting level of glucagon in man is about 100 pg/ml. (Ghareeb A., and Ghaliongi P.,1978).

Metabolism :

The half time of disappearance of endogenous true glucagon is 3 minutes - whereas that of IRG 9000 is 16 minutes (Valvered et al.,1975).

The glucagon is degradated within the liver by a glucagon degradation enzyme and also excreted in the bile.

The kidneys appear to be the major site of glucagon removal. Recent work suggests that proglucagon is diproportionately increased in patients with chronic renal failure (Kuku et al., 1976). This was confirmed by Norbert Freinkel (1977), which explains hyperglucagonemia of renal failure.

This raises the possibility that impaired convertion of proglucagon to glucagon may contribute to high IRG level of renal failure patients.

Rise in prepheral blood glucagon levels produced by excitatory stimuli is exagerated in patients with cirrhosis, because of decreased hepatic degradation of the hormone (Ganong 1980).

Mode of action of glucagon :

Glucagon is an important regulator of carbohydrate metabolism. Itsmajor site of action is the liver. In physiologic amounts it increases intracellular cyclic AMP in the liver and in pharmacologic doses can cause similar increases in other organs (Port and Halter 1981)

Glucagon is a hyperglycemic agent that acts by mobilising hepatic glycogen which is released into the blood as glucose.

Glucagon acts as the first messenger by activating the enzyme adenyl cyclase to produse an increased intracellular concentration of cyclic AMP. which then acts as the second messenger to affect the series of biological processes. (Port and Halter 1981)

Regulation of secretion :

STIMULATORS	INHIBITORS
-Amino acids (particularly glucogenic amino acids)	- Glucose
-CCK, gastrin	- Secretin
- Acetyl choline	- F.F.A.
- B adrenergic stimulators	- Ketones
- Theophylline	- Phnenytoin
- Cortisol	- A adrenergic stimulators
- Exercise	-Somatostatin
- Infections	
- Calcium	
- Other stresses	

Glucose :

There is an inverse relationship between glucagon output and glucose concentration & hyperglycemia supress glucagon secretion and hypoglycemia augment it, (Port and Halter 1981).

Hyperglycemia is the most potent physiological supressor of glucagon, and this inhibitory effect requires the presence of insulin, thus, the A cells appear to be an insulin-dependent tissue (Norbert Frei-nkel. 1977).