A STUDY ON PLASMA GLUCAGON LEVEL IN SOME VIRAL DISEASES

A THESIS

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By

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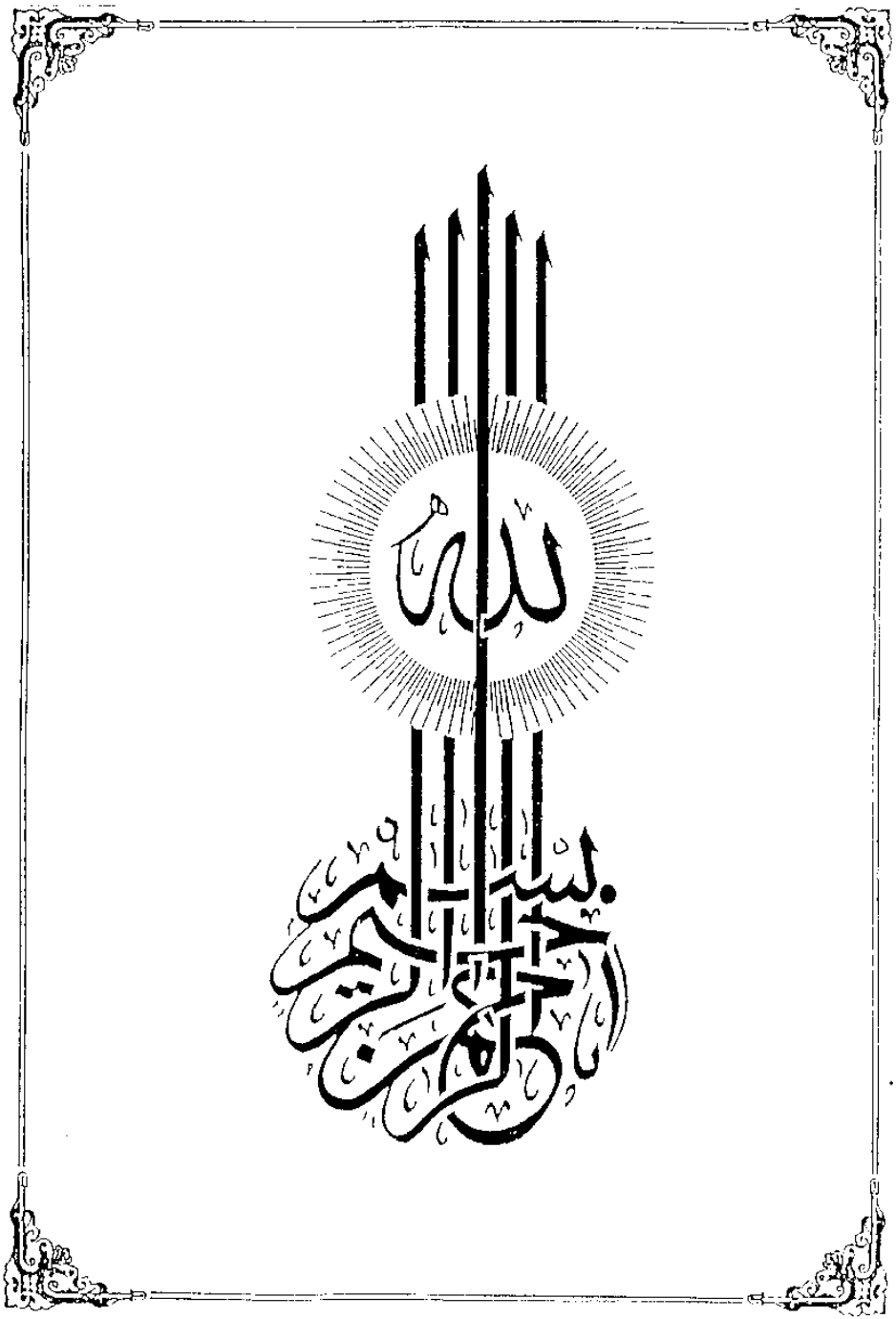

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INTRODUCTION AND AIM OF THE WORK

Glucagon is a hormone secreted from the alpha cells of islets of langerhans of the pancreas.

Glucagon is an important regulator of carbohydrate metabolism, its main site of action is the liver, (Porte and Halter 1981). It is a hyperglycaemic agent and its secretion is believed to be affected by many stimulators and inhibitors. Infection is one of these factors.

No studies have been made about the possible effect of viral infections on plasma glucagon level.

Viruses of a number of different classes have been proposed as an aetiologic agents.

The present work was carried on 10 cases as a control, 10 cases of acute infective hepatitis, 10 cases of measles infection and 10 cases of mumps infection, aiming to determine if these viral infections have an insulting effect on plasma glucagon level being produced from the alpha cells of the pancreas.

Review of Literature

Glucagon Hormone

History:

Shortly after the discovery of insulin 1921 by Banting and Bast. Kimball and Murlin (1923) described the presence of a substance in pancreatic extracts which causes an increase of blood glucose concentration when injected intravenously and which they named "glucagon".

Most commercial insulin preparations contain small amounts of this substances.

As a result, most studies of the metabolic effects of insulin were mixed with those of glucagon, (Bondy and Feling, 1974).

Source of glucagon:

Glucagon is secreted from A cells of islets of Langerhans of the pancreas. The islets of L. are ovoid 75 x 175 Mm. Their number ranges 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, (Porte 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, (Porte and Halter., 1981).

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

Somatostatin acts as suppressor of both insulin and glucagon, (Kocher et al., 1974), and its cells D cells are 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).

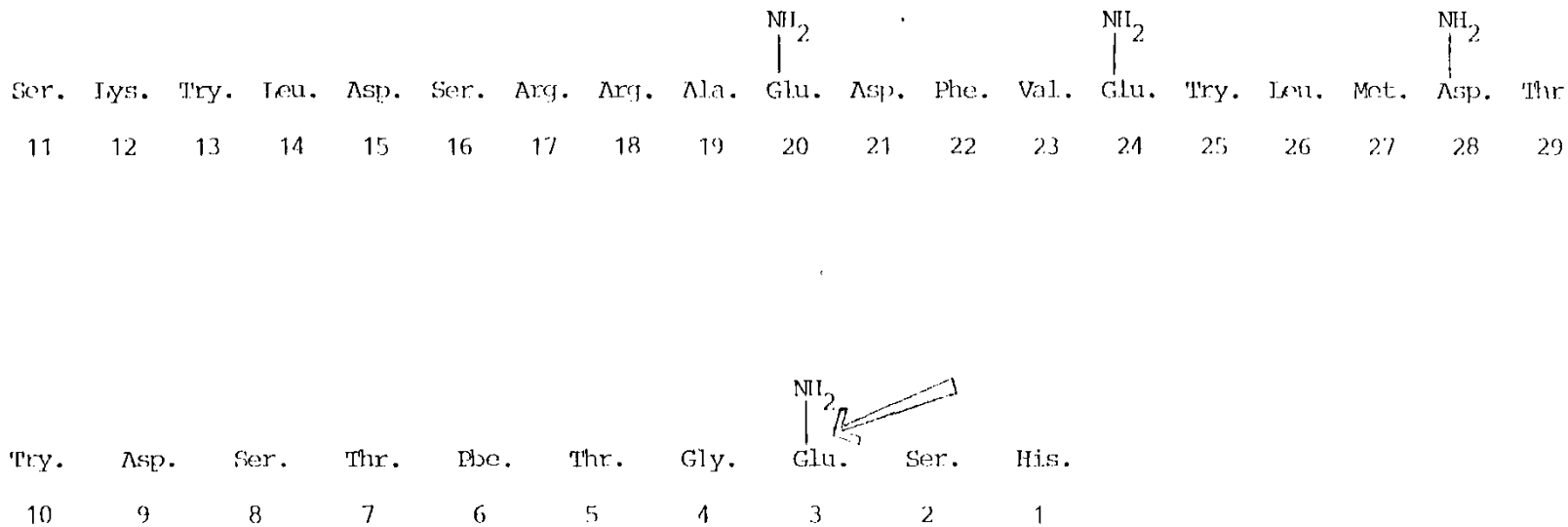

Fig. (1): Amino acid sequence of human glucagon, showing the site of cleavage by dipeptidyl aminopeptidase I

(After Porte and Halter, 1981)

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, (Porte 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 of insulin, while cystine, isoleucine and proline are components of insulin but not of glucagon, the integrity of the glucagon molecule is required for physiologic activity, (Porte 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).

Tissue immunoreactive glucagon:

Glucagon containing tissues such as pancreas and the fundus of stomach contains four major immunoreactive components:

1 - True biologically active glucagon of about 3485 daltons.
2 - An immunoreactive glucagon of about 2000 daltons.
3 - An immunoreactive glucagon of about 9000 daltons that does not bind to hepatic glucagon receptors or activate hepatic adenylate cyclase and corresponds to proglucagon.
4 - An immunoreactive glucagon of about 65000 present in extracts of canine fundus that binds to hepatic glucagon

receptors, activates adenylate cyclase, but it could not be detected in extracts of whole pancreas, (Norbert Freinkel., 1977).

Plasma immunoreactive glucagon (IRG):

Valverde 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 - IRG : 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 Ghaloungi P., 1978).

Metabolism:

The half time of disappearance of endogenous true glucagon is 3 minutes whereas that of IRG 9000 is 16 minutes, (Valverde 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 disproportionately increased in patients with chronic renal failure

(Kuku et al., 1976). This was confirmed by Norbert Freinkel (1977), which explains hyperglucagonaemia of renal failure. This raises the possibility that impaired conversion of proglucagon to glucagon may contribute to high IRG levels of renal failure patients. Rise in peripheral blood glucagon levels produced by excitatory stimuli is exaggerated 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. Its major 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, (Porte and Halter.,1981).

Glucagon is a hyperglycaemic 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 produce an increased intracellular concentration of (cyclic AMP). Which then acts as the second messenger to affect the series of biological processes. Porte and Halter (1981).

Regulation of secretion:

STIMULATORS	INHIBITORS
- Amino acids (particularly glucogenic amino acids).	- Glucose
- CCK, gastrin	- Secretin
- B-adrenergic stimulators	- F.F.A.
- Theophylline	- Ketones
- Cortisol	- Pheytoin
- Exercise	- ∝-adrenergic stimulators
- Infections	- somatostatin
- Other stresses	

Glucose:

There is an inverse relationship between glucagon output and glucose concentration & hyperglycaemia supress glucagon secretion and hypoglycaemia augment it, (Porte and Halter., 1981).

Hyperglycaemia is the most potent physiological supressor of glucagon, and this inhibitoryeffect requires the presence of insulin, thus, the A cells appear to be an insulin-dependent tissue, (Norbert Freinkel, 1977).

Amino acids:

Intravenous infusion of amino acids, particularly arginine, alanine and several others are powerful stimuli of pancreatic glucagon secretion, (Rocha D., et al., 1972).

The importance of these interaction is to prevent hypoglycaemia secondary to aminogenic insulin secretions, (Unger, R., et al., 1969).

A protein meal and infusion of various amino acids increase glucagon secretion. It seems appropriate that the glucogenic amino acids are more potent in this regard, since these are the amino acids that are converted to glucose in the liver, under the influence of glucagon, (Porte and Halter, 1981).

Following a protein meal glucagon secretion is increased, and since the amino acids stimulate insulin secretion, the secreted glucagon prevents the development of hypoglycaemia while insulin promotes storage of the absorbed carbohydrates, fats and lipids, (Ganong, 1980).

The glucagon response to oral administration of amino acids is greater than the response to intravenous infusion of amino acids suggesting that a glucagon stimulating factor is secreted from gastrointestinal mucosa.