THE EFFECT OF GLUCAGON ON THE CARDIOVASCULAR SYSTEM IN EXPERIMENTAL ANIMALS

THESIS

Submitted for the Degree of Ph. D. (Pharmacology)

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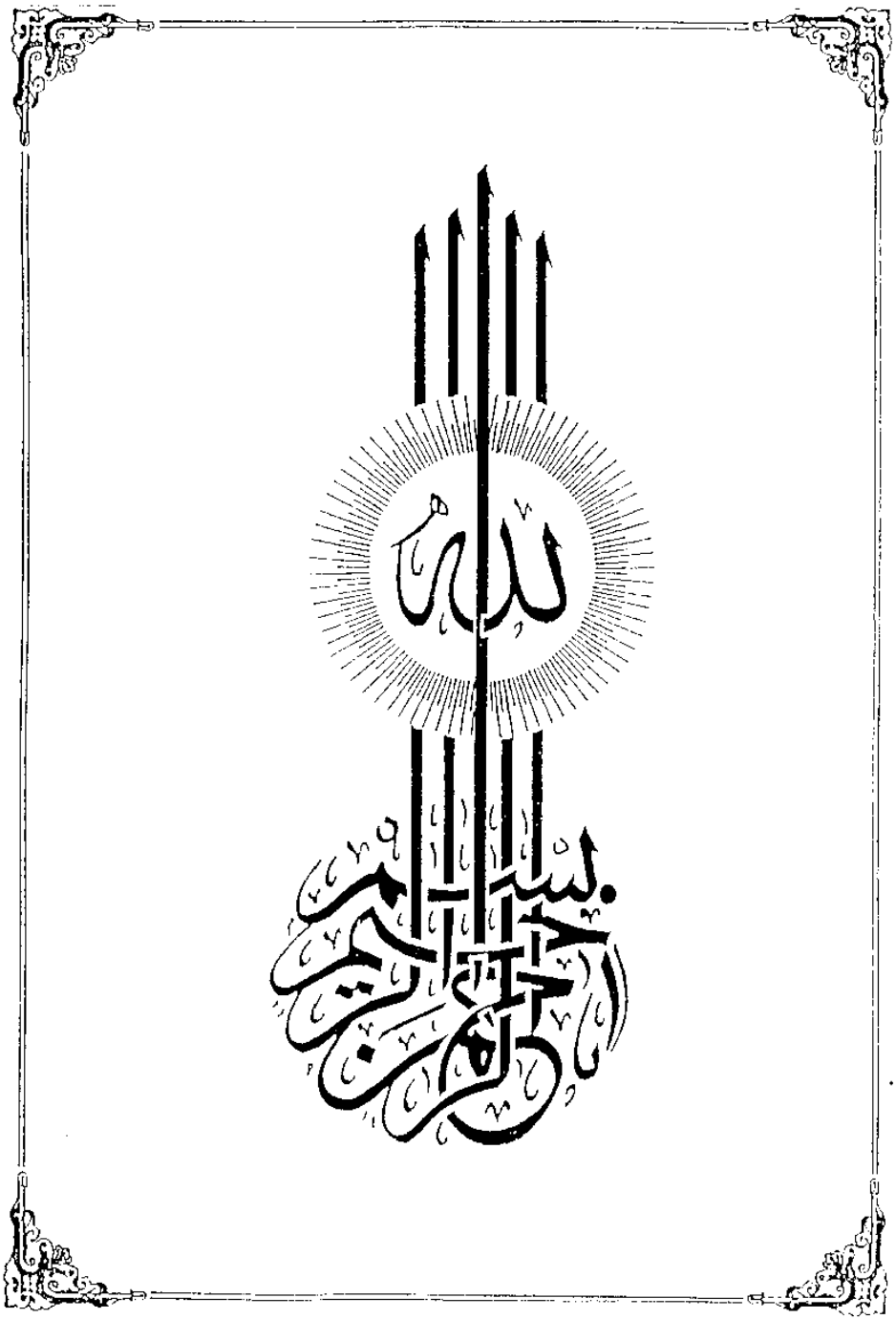

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INTRODUCTION

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INTRODUCTION

The cardiac actions of the pancreatic hormone glucagon a known hyperglycemic, hypoaminoacedemic and lipolytic agent have received recent attention.

Farah (1939) reported that certain isulin preparations were capable of increasing myocardial contractility and heart rate. Farah suggested that these effects of insulin are due to contamination of the insulin preparations with glucagon.

In 1960 Farah and Tuttle have reported that several preparations of glucagon have epinephrine - like effects on isolated heart and intestine, and that these effects are most likely due to glucagon rather than some contaminant of the glucagon preparations.

Regan et al., (1964) reported that purified preparations of insulin delivered into the left coronary artery of dogs have no influence upon the left ventricular contractility, despite enhanced glucose uptake.

Since crystalline glucagon has become available in a highly purified form (Wunsch and Weignes, 1972), interest developed in determining its effects on the cardiovascular system.

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Glucagon was discovered by Murlin et al., (1923) two years after the discovery of insulin. Glucagon was of little interest, its discoverers received little recognition, and the hormone was not purified extensively until over 30 years had passed (Staub et al., 1955).

Glucagon is a polypeptide originating in the alpha cells of the pancreas, It is composed of 29 amino acids with a molecular weight of 3485 Daltons. The amino acids are arranged in a straight chain. The sequence of the amino acids in the chain has beer determined (Bromer et al., 1956), and the molecule has been completely synthesized (Weignes et al., 1969). Histidine is the N-terminal amino acid and therionine is the C-terminal amino acid. In contrast to insulin, glucagon contains no cystine, proline, or isoleucine but does contain considerable amounts of methionine and tryptophan. Further, it can be crystallized in the absence of zinc or other metals. The structure of the glucagon polypeptide is shown in Fig. (1).

Glucogon is now recognized as an important hormone involved in the rapid mobilization of hepatic glucose (Sutherland and Cori, 1948), and to a lesser extent in the mobilization of fatty acids from adipose tissue (Lefebvre, 1966 ; Butcher and Sutherland, 1967).

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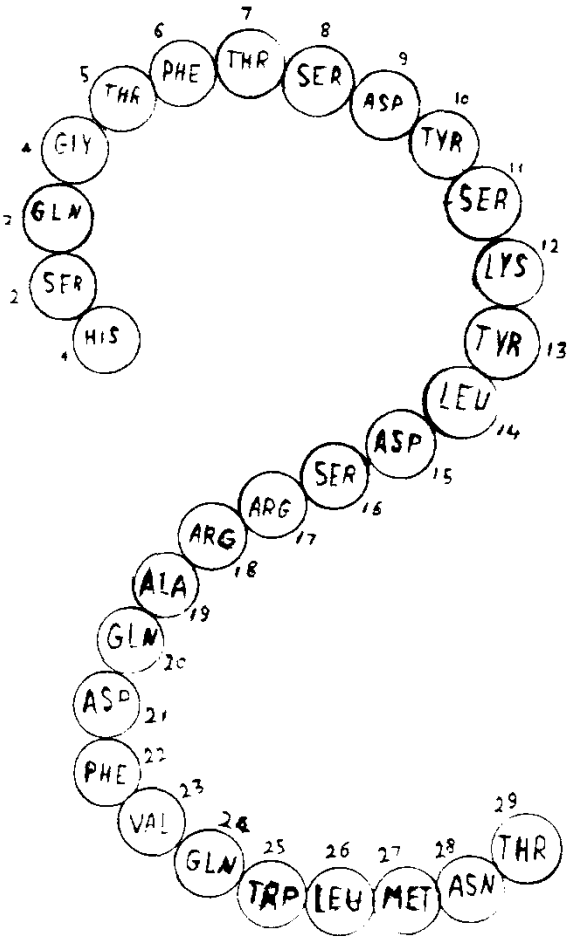

Fig. (1). Glucagon polypeptide

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In normal humans, the mean fasting blood level is 150 μμ per milliter (Aguilar - Parada et al., 1969). At this concentration its propable major action is the induction of hepatic glycogenolgsis to sustain blood glucose levels. The same investigators in 1970 have reported that the post-tabsorptive glucagon plasma level is approximately 100 μμ per milliter.

Pancreatic glucagon is released in response to hypoglycemia reversing this situation by raising blood glucose (Unger et al., 1968). It may assure adequate insulin level after glucose ingestion, as it has been shown to affect directly insulin release (Samol et al., 1965) and (Marks, 1968).

Assan, Rosselin and Dolais (1967) reported that Starvation, Pancreozymin and Aminoacedemia, notably argininemia cause release of the pancreatic glucagon, as well as hypoglycemia. Thus an additional role for pancreatic glucagon has been postulated to prevent hypoglycemia during aminoacedemia of carnivorous diets (Assan et al., 1967).

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Increased blood glucose is acheived (hereafter called "glucagon") through increasing phosphorylase activity to lyse glycogen in the liver (Sutherland and Cori, 1951 and Sokal, 1966) and also in the heart (Kreisberg and Williamson, 1964).

Sutherland (1968) showed that the adenyl cyclase receptor sites in the liver are sensitive to glucagon, and after the presentation of glucagon to the liver the cyclic AMP level increase. The cyclic AMP in turn activates the enzyme dephosphorylase kinase, and an increase in the active phosphorylase results. Glucagon also, increases the conversion of pyruvate to glucose via phosphoenol - pyruvate, and promotes as well hepatic deamination (Garcia et al., 1968).

Butcher and Sutherland (1967) have shown an increase in the cyclic AMP levels of adipose tissue under the effect of glucagon.

Lefebvre and Presse (1969) have reported that glucagon directly causes release of parathormone and release of catecholamines from the adrenals, the latter has provided the basis for a provocative test for pheochromocytoma (Sheps and Maher, 1968).

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Core (1969) and Bell (1970) reported that glucagon causes release of growth hormone, thyroid hormone and thyrocalcitonin, through direct Stimulation apparently independent of its other actions (glycogenolysis and insulin release).

Through recently available techniques of radiommunoassay, Unger (1969) reported that a substance immunologicaly similar, though not identical with the pancreatic glucagon, has been shown to be present in the gastric and duodenal mucosa. They reported that this glucagon like hormone (enteroglucagon) is released after ingestion of glucose load. Furthermor, it is less active than the pancreatic glucagon in stimulating the adenyl cyclase and therefore cannot duplicate many of the actions of the pancreatic hormone. Only it shares with it the ability to cause hepatic glycogenolysis and insulin release. Through their study they explained why oral glucose loads stimulate insulin release more effectively than glucose administered intravenously.

Additional properties of glucagon include supression of gastric secretion (Clark et al., 1967), stressed pancreatic exocrine secretion (Dyck et al., 1969), and decrease

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in the bile flow as well as a diminution in the release of the other digestive enzymes (Daniell and Henderson, 1970).

The findings of endogenous hyperglucagonemia in diabetic persons has led to a postulated diabetogenic role for glucagon (Muller et al., 1970).

Glasgow (1970) has reported that exogenous glucagon administered with commercial insulin as a contaminant has been cited as rarely responsible for insulin resistance.

Glucagon is degraded in the liver and Kidney as well as in the plasma and at its tissue receptor sites in plasma membranes. The enzymatic destruction of glucagon is by proteolysis, and the removal of the amino-terminal histidine leads to loss of biological activity (Duckworth and Kitabchi, 1974).

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Cardiac actions of glucagon :

After the observations made by Farah (1939) and confirmed again by Farah and Tuttle (1960) that the positive inotropic and chronotropic effects of certain insulin preparations were due to contamination by the hormone glucagon. And since this demonstrated properties like those of the sympathomimetic hormones, a series of investigations were carried on to explore its cardiovascular actions.

Farah and Tuttle (1960) first demonstrated the positive inotropic and chronotropic effects of glucagon in heart - lung preparations, and in isolated atria of dog, rat, cat and guinea-pig. They reported that these effects resemble those of epinephrine, however some differences were observed. Glucagon effects were more slowly manifested and lasted a longer time than the effects of epinephrine. The possibility that glucagon may act by the liberation of catacholamines, had been considered by these investigators. However they reported that pretreatment of dogs with reserpine, did not eliminate the cardiostimulatory effects of glucagon.

In their study Farah and Tuttle have also reported that the beta blocker dichloroisoproterenol which is a specefic antagonist to the positive inotropic and chronotropic effects

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of epinephrine and norepinephrine, reduced the actions of the crystalline glucagon on mycardial contractility and heart rate. They suggested that this hormone acts on beta receptor sites.

Regan and associates (1964) demonstrated the positive inotropic and chronotropic effect of glucagon on intact dogs. They reported that pretreatment with reserpine in sufficient doses to produce lethergy failed to affect the contractile activity of glucagon. They also demonstrated the inhibition of the contractile force produced by glucagon by the adminstration of dichloroisoproterenol.

Whitehouse and James (1966) studied the chronotropic effect of glucagon by infusing the hormone directly into the sinus node artery of dogs. They reported that it significantly increased the heart rate.

Glick et al., (1968) studied the cardiovascular effects of glucagon on both intact and open-chest dogs. They reported that glucagon strikingly augmented the contractile state of the myocardium , and increased the heart rate. Depletion of catecholamines by pretreament with reserpine did not alter the cardiovascular response to glucagon.

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