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HYPERINSULINEMIA AND ATHEROSCLEROTIC VASCULAR DISEASE

THESIS

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By

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The Candidate

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INTRODUCTION

Clinical and experimental studies suggest hyperinsulinemia could be a risk factor for atherosclerotic vascular disease. An early observation prompted to hypothesize that high levels of circulating insulin are related to the pathogenesis of atherosclerosis *(Stout and Vallance-Owen; 1969)*. They pointed out that most of the patients with ischemic heart disease had elevated insulin responses to glucose regardless of fasting insulin levels. These abnormalities were even found to be in non-obese patients who had experienced a myocardial infarction *(Stout and Vallance-Owen;1699)* .In contrast, the South African Bantu, who have an extremely low incidence of ischemic heart disease, have 50 % of the insulin response to an oral glucose load that is normally reported for white subjects *(Rubenstien et al; 1969)*. The best evidence linking hyperinsulinemia and atherosclerotic vascular disease comes from prospective epidemiological studies of ischemic heart disease conducted in Helsinki *(Pyorala,1979)*. Paris *(Ducimentiere et al; 1980)*, and Busselton,Western Australia These studies found a significant association between insulin concentrations and the development of ischemic heart disease independent of other risk factors including lipids, blood pressure, and smoking*(Stout,1987)*. Additional studies have found a striking relationship between high insulin concentrations and cardiovascular disease in normal individuals and patients with non-insulin dependent diabetes mellitus (NIDDM). Patients with NIDDM controlled by diet

and oral hypoglycemics were also found to have a significant correlation between the incidence of coronary heart disease and C-peptide levels. However, NIDDM patients treated with insulin experienced the highest incidence of cardiovascular disease while having the lowest C-peptide levels *(Standl and Janka,1985)*. Although mechanisms explaining the association of atherosclerosis with hyperinsulinemia are incompletely understood, several possibilities have been proposed. First, a high insulin level may directly promote the formation of the atheroma in the arterial wall through its effects on several cellular and metabolic processes *(Stout,1977)*. Second, hyperinsulinemia is associated with high blood pressure levels *(Laakso and Barrett-connor,1989)*, low HDL cholesterol, and high VLDL triglyceride concentrations *(Laakso and Barrett-connor,1989)*. Third, insulin resistance could be the primary abnormality related to atherosclerosis, with hyperinsulinemia as only a secondary compensatory mechanism *(Zavaroni et al; 1989)*. This third hypothesis is supported by the recent observation that asymptomatic atherosclerosis is associated with insulin resistance characterized by reduced whole - body and nonoxidative glucose uptake *(Zavaroni et al; 1989)*.

The overall objective of this study is to determine the effect of hyperinsulinemia as an independent risk factor for atherosclerotic arterial disease. This objective will be accomplished by rendering non-diabetic dogs hyperinslinemic by selective diversion of pancreatic venous outflow and then inducing atherosclerotic lesions. Progress of the atherosclerotic lesions will be compared in normal controls, hyperinsulinemic animals. In all animals native vessel lesions and

atheromatous changes in venous interposition grafts will be studied by surgical histology.

AIM OF THE WORK

This study is designed to examine the effects of hyperinsulinemia and insulin resistance in a non diabetic canine model on the progression of atherosclerotic vascular disease. Thus, the specific aims are:

1. To test the effects of hyperinsulinemia on vascular intimal regeneration and the development of atherosclerotic lesions.
2. To test the effects of hyperinsulinemia on myointimal hyperplasia of vein grafts

INSULIN SECRETION AND METABOLISM

Insulin was first isolated from the pancreas in *1922 by Banting and Best.* The pancreas of human being has 1 to 2 million islets of Langerhans. The islets contain three major types of cells, alpha, beta, delta, cells which are distinguished from one another by their morphologic and staining characteristics. The beta cells, constituting about 60 % of all the cells, lie mainly in the middle of each islet and secrete insulin. The alpha cells, about 25% of the total, sercrete glucagon and the delta cells, about 10% of the total, secrete somatostatin, In addition, at least one other type of cell, the PP cell, is present in small numbers in the islets and secretes a hormone of uncertain function called pancreatic polypeptide (PP) *(Guyton,1991).*

Insulin is composed of two unbranched peptide chains joined together by two disulfide bridges (Fig.1). The two chains of insulin and their disulfide cross bridges are formed as a single chain proinsulin molecule from which the connecting peptide is excised by a trypsin-like enzyme. Conversion of proinsulin to insulin takes place slowly within storage granules, which contain the necessary endopeptidase. The connecting peptide, therefore, accumulates within granules in equimolar amounts with insulin. Insulin is secreted by exocytosis. The entire contents of storage granules are disgorged into extracellular fluid. Consequently, peptidase, connecting peptide, and any remaining proinsulin are released into the circulation whenever insulin is secreted.

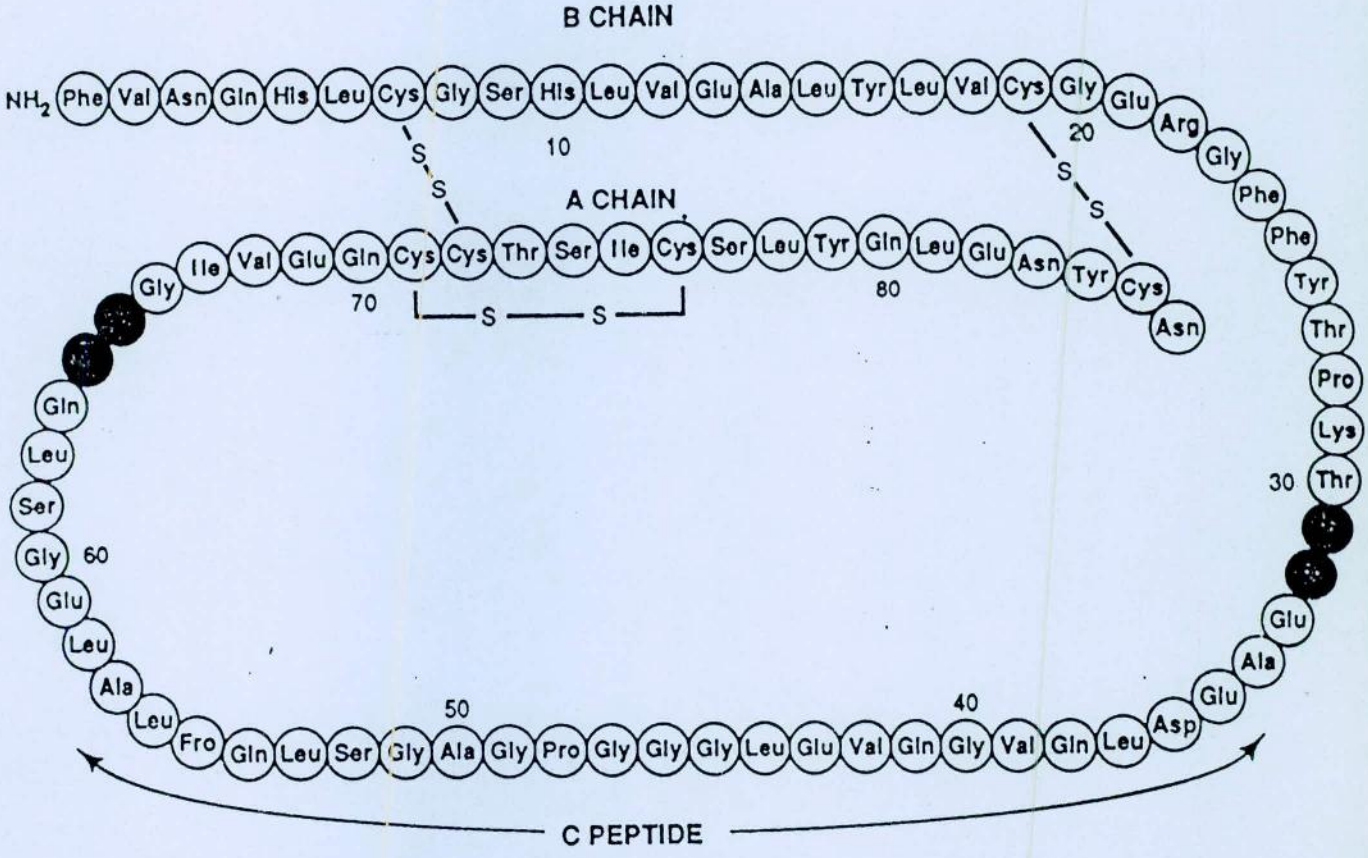

Fig.1 Amino acid sequence of human proinsulin. A pair of basic amino acids shown as open circles at both ends of connecting peptide are removed during the cleavage process, which separates the A chain of insulin (amino acids 1 to 30) from the B chin (amino acids 66 to 86). S-S, disulfide bridge. (Goodman, 1992).

When secretion is rapid, proinsulin comprise as much as 20 % of the circulating peptides detected by insulin antibodies, but it contributes little biological activity *(Goodman, 1992)*.

Insulin, with a half life of less than 10 min, is cleared rapidly from the circulation and is destroyed by a specific enzyme system, insulinase, that is present in liver, muscle, kidney, and other tissues. Proinsulin has a half-life that is at least twice as long and is not converted to insulin outside the pancreas. The liver may inactivate as much as 40 % of the insulin that reaches it in hepatic portal blood and thus has the potential for regulating the amount of insulin that enters the systemic circulation. Normally, little or no insulin is found in urine *(Goodman, 1992)*.

Effect of insulin on carbohydrate metabolism

Immediately after a high carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin which in turn causes rapid uptake, storage, and use of glucose by almost all tissues of the body, but especially by the muscles, adipose tissue, and liver *(Guyton, 1991)*.

Effects of Insulin in promoting glucose metabolism in muscle

During much of the day, muscle tissue depends on fatty acids for its energy. The principal reason for this is that the normal resting muscle membrane is only slightly permeable to glucose except when the muscle fiber is stimulated by insulin; and between meals, the amount of insulin secreted is too small to promote significant amounts of glucose entry

into the muscle cells. However, under two conditions the muscles do utilize large amounts of glucose. One of these is during periods of moderate to heavy exercise. This usage of glucose does not require large amounts of insulin because exercising muscle fibers, for reasons not understood, become highly permeable to glucose even in the absence of insulin because of contraction process itself. The second condition for muscle usage of large amounts of glucose is during the few hours after a meal. At this time the blood glucose concentration is high; also, the pancreas is secreting large quantities of insulin, and the extra insulin causes rapid transport of glucose into the muscle cells. This causes the muscle cell during this period of time to utilize carbohydrates, and to do so preferentially over fatty acids because the flow of fatty acids from adipose tissue is strongly inhibited by insulin. If the muscles are not exercising during the period following a meal and yet glucose is transported into the muscle cells in abundance, then most of the glucose is stored in the form of muscle glycogen instead of being used for energy, up to a limit of about 2 % concentration. The glycogen can later be used for energy by the muscle. It is especially useful for short periods of extreme energy for a few minutes at a time by glycolytic breakdown of the glycogen to lactic acid, which can occur even in the absence of oxygen *(Guyton, 1991)*.

Insulin increases uptake of glucose by muscle and directs its intracellular metabolism toward the formation of glycogen. It activates glycogen synthesis by a mechanism that is independent of cAMP, but that may involve other second messenger. Because it comprises about 50 % of body mass, uptake by muscle accounts for a major fraction of the glucose that disappears from blood after injection of insulin. In