INSULIN ANTAGONISTS

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It is known that insulin is antagonised by other hormones. This is an attempt to describe the functions of all these hormones but one (thyroxin).

Insulin: the storage hormone

Man eats intermittently and stores some food for periods of fasting. The digestive system limits the quanity of food that can be taken in at a time; but even before digestion of a meal is complete, renewed pangs of hunger may stimulate man to ingest more food. At times food is taken in excess, but all the food that is digested is absorbed and none of the food that is absorbed is lost.

Prevention of food loss is due to secretion of insulin in response to glucose absorption. Insulin specifically enhances glucose uptake by muscle and adipose tissue within minutes of its secretion. This specific action on cell membranes is not followed by specific action on glucose phosphorylation. Insulin does not act directly on glycogen turnover, but indirectly it favours glycogen synthesis by accelerating glucose uptake.

Excess glucose is incorporated in adipose tissue. The triglycerides of this tissue are in continuous breakdown and resynthesis (Fig. I). After breakdown, glycerol is released into the bloodstream; so that resynthesis has to make use of glycerol phosphate, and this is formed from glucose. Insulin enhances esterification of glycerides and inhibits release into the bloodstream of fatty acids that have been set free by breakdown of these glycerides. Hence, insulin favours glyceride synthesis as part of its overall function to preserve muscle and adipose tissue stores and to increment them.

Hydrocortisone: the stress hormone

Hydrocortisone inhibits glucose uptake by cell membranes, thereby reducing phosphorylation and formation of glycerol phosphate. Reduced supply of glycerol phosphate delays resynthesis of fatty acids in adipose tissue, so that fatty acids accumulate and are released into the blood stream. There follows a high concentration of non-esterified fatty acids or "NEFA" in plasma. It woul appear that high plasma NEFA concentrations inhibit glucose uptake by cell membranes, so that this action of hydrocortisone is reinforced by its own effect and plasma glucose concentration tends to rise. This rise of plasma glucose concentration is particularly useful during fasting, which is a form of stress.

It would appear that the main function of hydrocortisone is to maintain sufficient supplies of glucose to the brain during periods of stress without emergency, as during fasting. The central nervous system has a high metabolic rate whether one is awake or asleep, and glucose is its principal nutrient. The adult brain takes up about 65% of glucose that is available to the body, and of the glucose that is taken up, only 35% is used directly for oxidation. The rest is converted into aminoacids, lipids and proteins in a continuous process of breakdown and resynthesis of the brain constituents. Hence continuous supply of glucose to the brain is vitally important. Since there is no glucose or glycogen store in the brain, the blood stream supply must be uninterrupted and high, and this is taken care of by hydrocortisone.

The main action of hydrocortisone is on the liver, where it stimulates gluconeogenesis. In other terms hydrocortisone ensures a good depot of hepatic glycogen for secretion into the blood. Liver glycogen is not a store of carbodydrate in the same sense as muscle glycogen. Whereas muscle builds up its glycogen from the general plasma supply of glucose and will not give glucose back to plasma under any circumstances, the liver builds up its glycogen from several sources and supplies it

to the blood. Hence muscle glycogen is a local depot; but hepatic glycogen is a store for general use.

Sources of hepatic glycogen are several. Some of these are economical as glycerol or fatty acids derived from lipolysis, and as pyruvic or lactic acid overflowing into the blood stream from contracting muscle. But at times the source of hepatic glycogen is highly uneconomical, as amino-acids derived from tissue proteins, generally from proteins of peripheral supporting tissues. Gluconeogenesis is therefore potentially wasteful of valuable material, and may be harmful. It seems likely that hydrocortisone raises plasma NEFA concentration and plasma glucose concentration to reduce gluconeogenesis from amino-acids as much as possible. During intestinal absorption of glucose, gluconeogenesis becomes superfluous. It is therefore inhibited by insulin, which is secreted in response to glucose absorption. Insulin rebuilds the stores of carbohydrate and triglyceride that hydrocortisone had reduced; and it seems likely that it promotes amino-acid incorporation into protein to repair faults to body tissues which fasting may have caused.

Adrenaline: the emergency hormone

Adrenaline is generally released under emergency conditions, and one of its functions is to supply additional glucose to the blood stream for use by essential tissues, including brain. This additional supply is obtained from the liver, where adrenaline provokes glycogenolysis by maintaining a larger proportion of phosphorylase than usual in its active form, thus increasing the effective concentration of the enzyme mainly responsible for glycogen breakdown. Adrenaline also enhances release of fatty acids by adipose tissue. In this way it provides economical material for gluconeogenesis, and by reducing material for resynthesis of triglycerides it spares the glycerol phosphate, which is derived from glucose.

Adrenaline causes also rapid muscular contraction for which rapid supply of energy is required. Yet adrenaline may decrease the uptake of glucose by muscle, thereby impairing glucose phosphorylation. This means that muscle has to rely on its local glycogen store for contraction. Because the supply of energy has to be rapid and abundant, muscle uses anaerobic glycolysis, with accumulation of pyruvic and lactic acid. These products overflow into the blood stream and provide more material for gluconeogenesis, so that the additional supply of glucose which adrenaline brings about into the plasma from the liver, is not obtained from uneconomical sources. Adrenaline therefore provides for rapid muscular contraction without curtailment of glucose available for use in other tissues and without inducing gluconeogenesis at the expense of supporting tissues.

Glucagon

The function of this hormone is difficult to understand. Like adrenaline, glucagon increases glycogenolysis and like adrenaline it exerts this effect by increasing the effective concentration of phosphorylase in the liver. Both hormones mediate their effect on glycogen metabolism by the initial formation of adenine — ribose, 3, 5 — phosphate, but glucagon affects only hepatic glycogen.

The growth hormone

Like hydrocortisone, this hormone acts on cell membranes by reducing muscle uptake of glucose, as has been confirmed in man with acromegaly. There results a high plasma NEFA concentration and some rise of plasma glucose concentration. Growth hormone presumably obtains these effects to provide economical material for neoglucogenesis and spare amino-acids which are essential for growth.

Cushing's syndrome

It is clear that each and everyone of the above hormones has a definite specific function to perform. They all affect carbohydrate and glyceride metabolism, and excess of hormone may provoke a metabolic state with reduced glucose tolerance,

which insulin administration cannot correct well.

The most typical of these states is Cushing's syndrome. This is due to overproduction of hydrocortisone by gross overacting of the adrenal cortex or gross overstimulation by ACTH. Hydrocortisone in physiological doses does not lead to fat deposition in the subcutaneous tissues or elsewhere; indeed it mobilises fatty acids from glyceride depots and its physiological effect is characterised by increased plasma NEFA concentration and by inhibition of glucose storage. But hydrocortisone stimulates also neoglucogenesis and the hyperglycaemia which follows the oversecretion of hepatic glucose into the blood stream provokes a response by the pancreatic islets with overproduction of insulin. Hence Cushing's syndrome may give rise to severe glycosuria; but more frequently, in the presence of an adequate reserve of insulin, it produces excessive deposition of glycerides in adipose tissue. The hyperglycaemia of Cushing's syndrome is produced by liver secretion at the expense of sources of glycogen which include amino-acids derived from body tissue proteins. Hence there is mobilisation of peripheral supporting tissue with muscle weakness and fatigueability, osteoporosis, cutaneous striae and weakening of vascular tissue with easy bruising at sites of mild trauma. In addition there are hypertension, emotional changes and androgenic changes which apparently are independent of the effects of hydrocortisone on food metabolism. It is evident from this picture that the antagonism of insulin to hydrocortisone does not correct the pathological effects.

FIGURE I

Glucose - Fatty Acid Cycle