Effect of Insulin in Hypertriglyceridemia. (30509)

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The frequent occurrence of carbohydrate intolerance, either latent(1-7) or overt(8-10) in some forms of hyperglyceridemia has suggested that an abnormality of insulin action may be involved in the pathogenesis of these syndromes(11,12). Daily insulin administration to some patients who have combined hyperglyceridemia and hyperglycemia results in an impressive fall in plasma triglycerides (12,13). This effect is not necessarily associated with changes in blood sugar.

The following studies were undertaken in order to examine the acute effect of insulin on plasma triglyceride levels in patients with hyperglyceridemia. The hyperglyceridemics studied fall into the type 4 or 5 categories, described by Fredrickson *et al*(6). Not included are subjects with hyperchylomicronemia ("fat induced" hyperlipemia) or hyper-β-lipoproteinemia (essential hypercholesterolemia). Also excluded from this report are subjects with as yet unclassifiable forms of hyperglyceridemia, and subjects who, with the amount of insulin used, developed significant hypoglycemia, since the secondary epinephrine-glucagon release made interpretation difficult or impossible.

Materials. In the first study, 8 subjects with plasma triglyceride levels ranging from 280 to 4650 mg per 100 ml were evaluated. In 3, hyperglyceridemia was associated with occult carbohydrate intolerance (abnormal glucose tolerance or cortisone glucose tolerance with normal fasting blood sugar and no glycosuria); 5 exhibited various degrees of fasting hyperglycemia and glycosuria under conditions of average dietary intake. After an overnight fast, regular insulin in a concentration of 20 units per litre of normal saline solution was infused intravenously at a rate of 2 units per hour for 8 hours. Blood was obtained hourly for determination of blood sugar, plasma free fatty acids and triglycerides. Food or smoking was not allowed during this period. A control infusion with normal saline solution was performed under identical conditions on a separate day.

In the second study, 6 hyperglyceridemic subjects were studied in a similar manner. Regular insulin and protamine sulfate were infused simultaneously, at the rates of 2 units and 100 mg per hour, respectively. Blood sugar, plasma free fatty acids and triglycerides were again measured at hourly intervals.

Results. Fig. 1 demonstrates the effect of these infusions on plasma triglyceride levels in this group of hyperglyceridemic subjects. It is apparent that administration of insulin under these conditions resulted in a significant decrease in plasma triglyceride levels during the period of the study as compared to the control infusion. The blood sugar decreased during the insulin infusion to an average of 60% of initial values. Free fatty acids were depressed to approximately 50% of initial level during the first several hours of the infusion with a slow rise thereafter.

It can be seen from Table I that combined infusion of insulin and protamine resulted in (a) as great a fall in blood sugar and plasma free fatty acids as with insulin alone; (b) no decrease (actually some increase) in plasma triglycerides. It seems probable that this selective inhibition of insulin effect by protamine is attributable to the known inhibitory effect of the latter on lipoprotein lipase(14).

Discussion. From the foregoing it appears that infusion of exogenous insulin into many subjects with essential hyperglyceridemia results in a significant decrease of plasma glyceride levels as compared to the values in the same subjects receiving a control infusion.

This effect of insulin in essential hyperglyceridemia probably differs, partially or completely, from its effect upon the hyperglyceridemia associated with progressive diabetic ketoacidosis(15). In this latter condition, as the result of complete insulin lack, fatty acid mobilization is accelerated with resultant increase in glyceride and ketone formation by the liver.

TABLE I. BS, FFA, and Plasma TG During Insulin-Protamine Infusion in 6 Hyperglyceridemic Subjects.

Time in hr	0	1	2	3	4	5	6	7	8
BS	100	76 ± 17	69 ± 16	62 ± 12	62 ± 13	57 ± 12	60 ± 12	56 ± 15	57 ± 15
FFA	100	47 ± 13	42 ± 15	54 ± 15	53 ± 12	67 ± 9	60 ± 12	72 ± 25	92 ± 22
TG	100	112 ± 9	124 ± 19	128 ± 26	124 ± 25	122 ± 21	121 ± 29	122 ± 31	112 ± 20

Values as % of levels at time 0, ± S.D.
BS = blood sugar. FFA = free fatty acids. TG = triglycerides.

It is also well to mention that hyperglyceridemia does not occur to any significant extent in the average adult onset (non-proketotic) diabetic, even under conditions of serious and prolonged hyperglycemia, indicating that the hyperglyceridemia seen in this type of essential hyperlipemia is not "secondary to hyperglycemia" *per se.*

In the primary hyperglyceridemics here described, lowering of plasma glycerides by exogenous insulin could be the result of decreased release of very low density lipoproteins from the liver and/or increased removal of glyceride by peripheral tissues, with particular reference to adipose tissue. The combined insulin-protamine observations appear to provide support for the latter concept.

It is generally accepted that the removal of plasma triglyceride by adipose tissue depends upon initial extracellular hydrolysis followed by intracellular re-esterification. Such re-esterification is dependent upon glucose catabolism with resultant availability of alpha glycerol phosphate. Havel(16) showed that in normal subjects the level of plasma glycerides following a 16-hour fast was significantly reduced when glucose was administered. Administration of glucose to dogs(17) and man(18) has been shown to diminish or abolish the alimentary lipemia which occurs

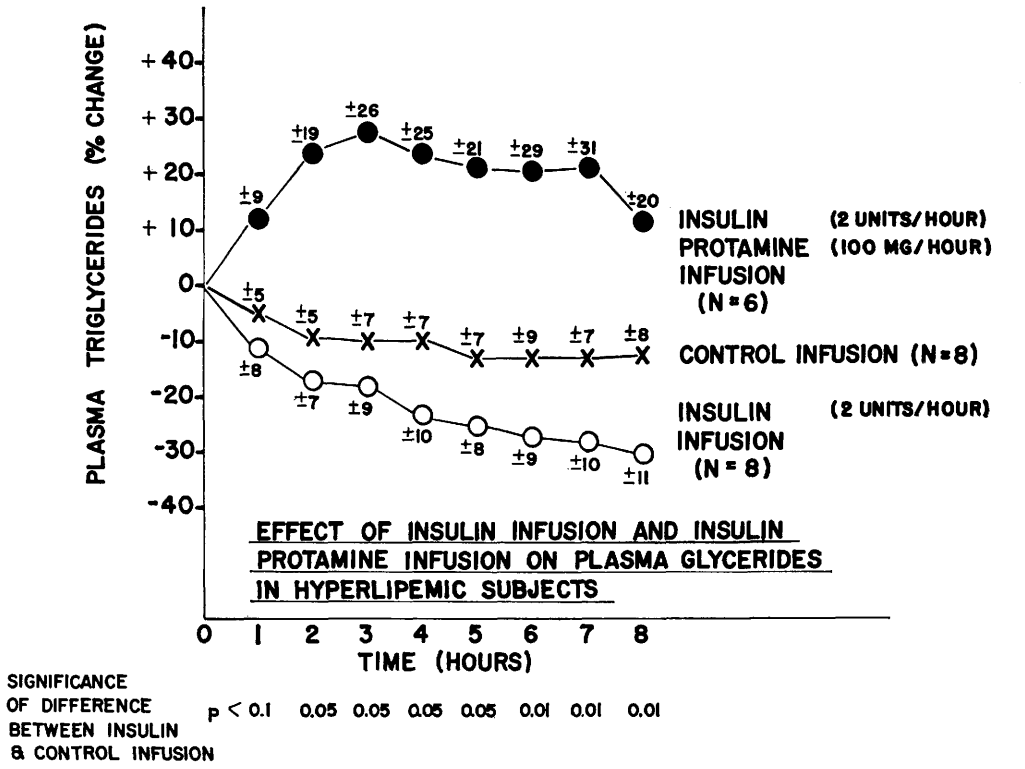

FIG. 1

after a fatty meal. Very possibly both of these effects are in part attributable to the same mechanism responsible for the decrease in endogenous plasma glycerides noted by us during administration of insulin. Also apropos is the postulation by Kessler(19) of lipoprotein lipase activation by insulin.

Thus it seems most probable that in suitable subjects administration of insulin accelerates the rate of glyceride removal by peripheral tissues, including particularly, adipose tissue. This does not negate the possibility of an effect of insulin upon formation or release of very low density lipoproteins by the liver.

Since subjects with this variety of hyperglyceridemia have been shown to have normal or increased amounts of circulating insulin (3,7,11), one may postulate either that endogenous insulin is in some way modified, perhaps during its initial passage through the liver, whereas exogenous insulin is enabled to produce its effects on peripheral tissues prior to such modification, or that there is peripheral resistance to the hypoglyceridemic effect of endogenous insulin which is partially overcome by the insulin infusion.

Summary. Infusion of insulin to hyperglyceridemic subjects results in decreased plasma glyceride levels as compared to control infusions. Protamine can prevent this insulin-induced decrease. It is tentatively concluded that insulin accelerates removal of glycerides from the plasma by peripheral tissues.

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