Acute Effects of Human Chorionic Somatomammotropin on Insulin and Glucagon Release in the Isolated Perfused Pancreas

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SUMMARY

Insulin and glucagon release from the isolated perfused pancreas of rats was measured following administration of human chorionic somatomammotropin (HCS). In the presence of low glucose levels there is a significant acute but short release of insulin and glucagon following HCS, which is not sustained despite continuous HCS infusion. The magnitude of HCS-induced insulin and glucagon release is closely related to the glucose concentration of the perfusion medium. At high glucose levels of 11 mM. there is no significant action on insulin or glucagon output by HCS. The short peaks of insulin and glucagon release are probably due to an HCS-induced membrane effect. The acute effects on α and β cells of the endocrine pancreas may indicate certain relationships between glycohomeostasis and HCS serum levels in pregnancy. DIABETES *21*:1072-76, November 1972.

Human chorionic somatomammotropin (HCS), or placental lactogen,[9] is a polypeptide hormone which participates actively in the regulation of metabolism in pregnancy. Besides its lactogenic activity, HCS exhibits diabetogenic properties[6] and is highly active in fat metabolism. In vitro studies on isolated fat cells[24] and on epididymal fat pads of rats show that HCS possesses both a lipolytic activity and the ability to increase glucose utilization for neolipogenesis.[17] The plasma concentration of HCS increases rapidly from nondetectable levels at the beginning of pregnancy up to 6.2 μg./ml. in the thirty-fifth week of pregnancy.[19] Since pregnancy constitutes a diabetogenic challenge to both normal[18] and diabetic subjects, it was postulated that HCS has a major responsibility for these metabolic alterations. Some studies have shown an increased early insulin response to glucose after a twelve-hour infusion of HCS,[2,18] and a marked increase in glucose-induced insulin secretion following administration of HCS to hypophysectomized rats.[14] Very few studies, however, have dealt with the acute effects of exogenous HCS on insulin release. Diurnal variations of several μg.-Eq. HCS/ml. plasma seem to be possible within a few hours.[12] We therefore report our findings as to immediate influences of HCS infusion on both insulin and glucagon release in the isolated perfused rat pancreas.

MATERIAL AND METHODS

In the present experiments, the isolated perfused rat pancreas[22] was used without any adjacent organs such as stomach or spleen.[5] Arterial flow was achieved by cannulation of the aorta. The perfusate was freely collected from the portal vein without recirculation at intervals of two minutes. The perfusion fluid consisted of an Umbreit buffer (pH 7.35) supplemented with 1 per cent albumin and equilibrated with 95 per cent oxygen, and 5 per cent carbon dioxide. A constant flow rate of 2.5 ml./min. was achieved by a pressure of about 40 mm. Hg. The temperature was adjusted to 38°C. The stimulating substances—human chorionic somatomammotropin (HCS), 10 μg./ml., and glucose, 2.75, 5.5 and 11 mM. in separate experiments—were infused for different periods into the tube leading to the cannula.

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At the end of each experimental run, 0.2 ml. of glucose 50 per cent was perfused through the rat pancreas to establish the viability of the organ. All samples were stored at —20° C. until used for radioimmunoassay in one batch. Twenty male Wistar rats (Fa. Thomae, Biberach), each weighing between 180 and 250 gm., were used for the experiments. The animals were fed a standard laboratory pellet chow (Altromin). The rats were fasted overnight prior to the pancreas perfusion. The blood glucose was estimated enzymatically.[21] Insulin (IMI) was measured immunologically.[16] Glucagon (IMG) was determined by means of a dextran charcoal technic.[8] The stability of glucagon was insured by adding 4,000 units of Trasylol to 1 ml. of perfusate; the deterioration rate was found to be negligible as controlled by samples of exogenous glucagon. HCS (provided by Fa. Behring Werke, Marburg) consisted of the two times crystallized lot S_1 and was found to be three times more potent than the original standard of the World Health Organization tested at the National Institute for Medical Research, Mill Hill, London, N.W. 7, 1970. Statistical evaluations were done according to Student's t test.

RESULTS

Perfusion of the isolated rat pancreas with a low glucose concentration of 2.75 mM. did not effect significant insulin releases, whereas glucagon levels rose up to 0.6 ng./min. (figure 1). Following HCS infusion, 10 μg./ml. for ten minutes, insulin and glucagon release exhibited an acute but short rise, similar to the pattern shown by amino acid stimulation. This acute release, however, is not sustained over the total period of HCS infusion but falls to a nadir within six to eight minutes.

Glucose in a concentration of 5.5 mM. shows the typical multiphasic pattern of insulin release, where a steady state is reached within twenty minutes (figure 2). Addition of HCS again caused an acute rise of insulin release (160 ± 18 to 355 ± 58 μU./min.) which was less pronounced, however, than in the presence of 2.75 mM. of glucose. Similarly, glucagon secre-

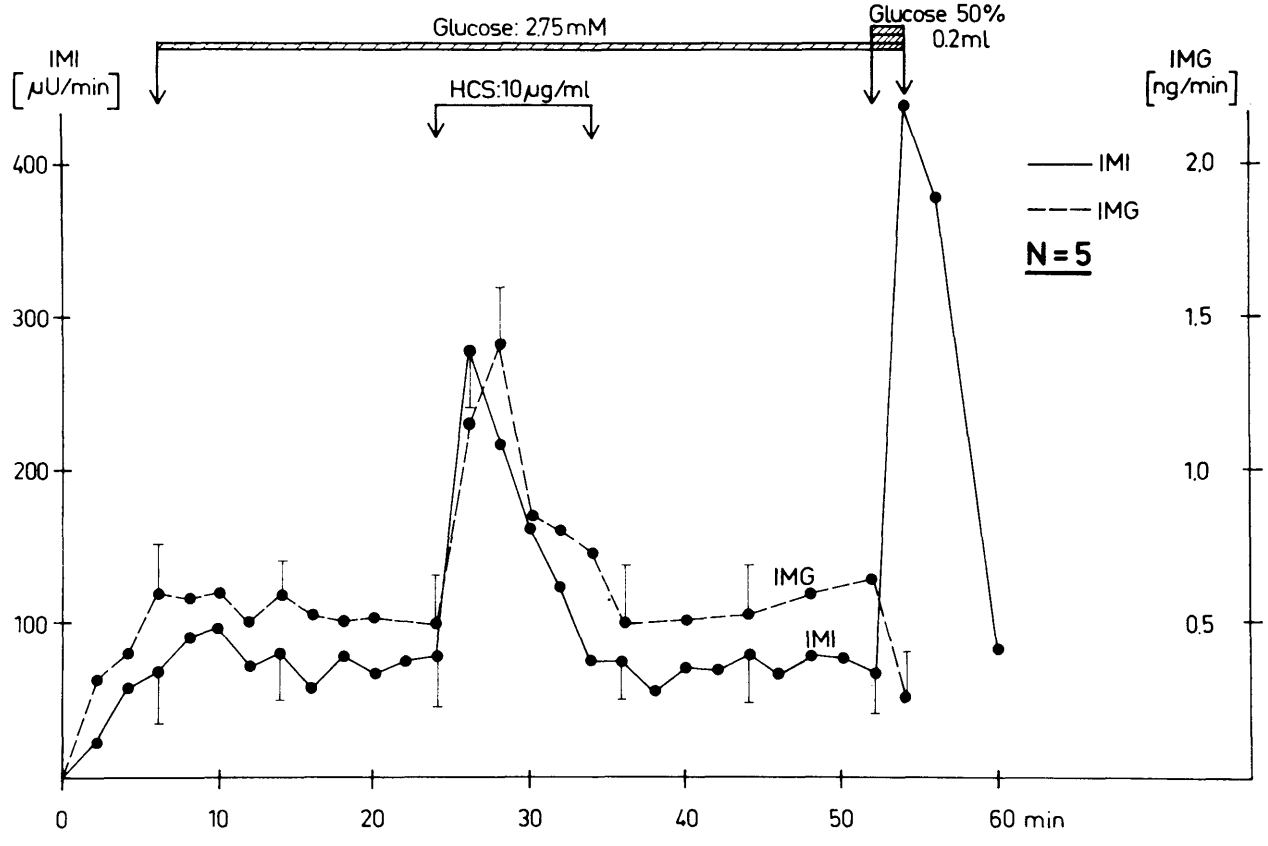

FIG. 1. Insulin and glucagon release from the isolated perfused pancreas (2.5 ml./min.), following infusion of human chorionic somatomammotropin (HCS) in the presence of glucose 2.75 mM. Values are mean ± S.E.M.

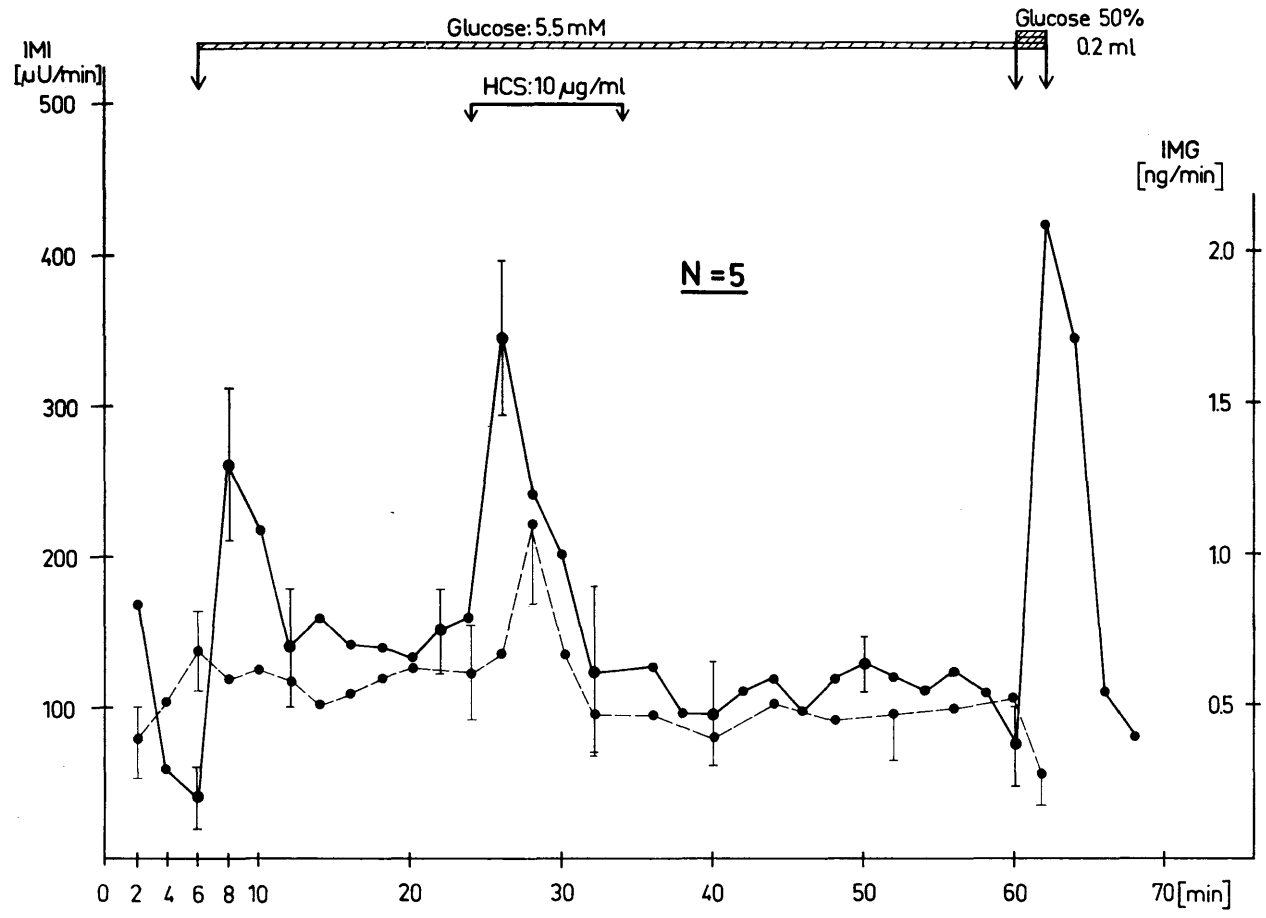

FIG. 2. Insulin and glucagon release from the isolated perfused pancreas following infusion of HCS in the presence of glucose 5.5 mM. Values are mean ± S.E.M.

tion increased rapidly (0.6 to 1.1 ng./min.) but less than in the presence of 2.75 mM. of glucose. Following perfusion with glucose, 11 mM., the initial rise of insulin release appears further accentuated (340 ± 58 µU./min.). The level of a steady state was significantly higher as compared with a glucose concentration of 5.5 mM. (figure 3). On the other hand, infusion of HCS resulted in only a small, insignificant additional insulin output, markedly lower than in the presence of low glucose concentrations. No significant glucagon release was noted following HCS infusion at high glucose concentrations.

DISCUSSION

Pregnancy is known to be a diabetogenic challenge.[13] Many metabolic and endocrine changes during pregnancy have been attributed to the combined effects of the three gestational hormones: human chorionic somatomammotropin (HCS), progesterone and estrogen.[3] However, the primary metabolic changes, which lead to the typical phenomena associated with pregnancy, are not yet fully understood.[19] Recent evidence suggests some relationship between serum HCS levels and insulin-glucose homeostasis.[4,15] Hyperinsulinism as found in the late stage of pregnancy or following prolonged HCS infusion has been observed by numerous workers.[1,2,10,11,14] Few, however, have tested the acute metabolic effects of exogenous HCS administration on insulin and glucagon release. The present results indicate that HCS by itself stimulates early insulin release from the isolated perfused pancreas. The secretion pattern exhibits a striking similarity in duration and shape to the initial peak of glucose-induced insulin release. The acute insulin release of the β cell is probably brought about by an emptying of different compartmental systems of already preformed and stored insulin pools.[7] The acute insulin release following HCS, however, has little in common with the progressive rises in insulin levels in

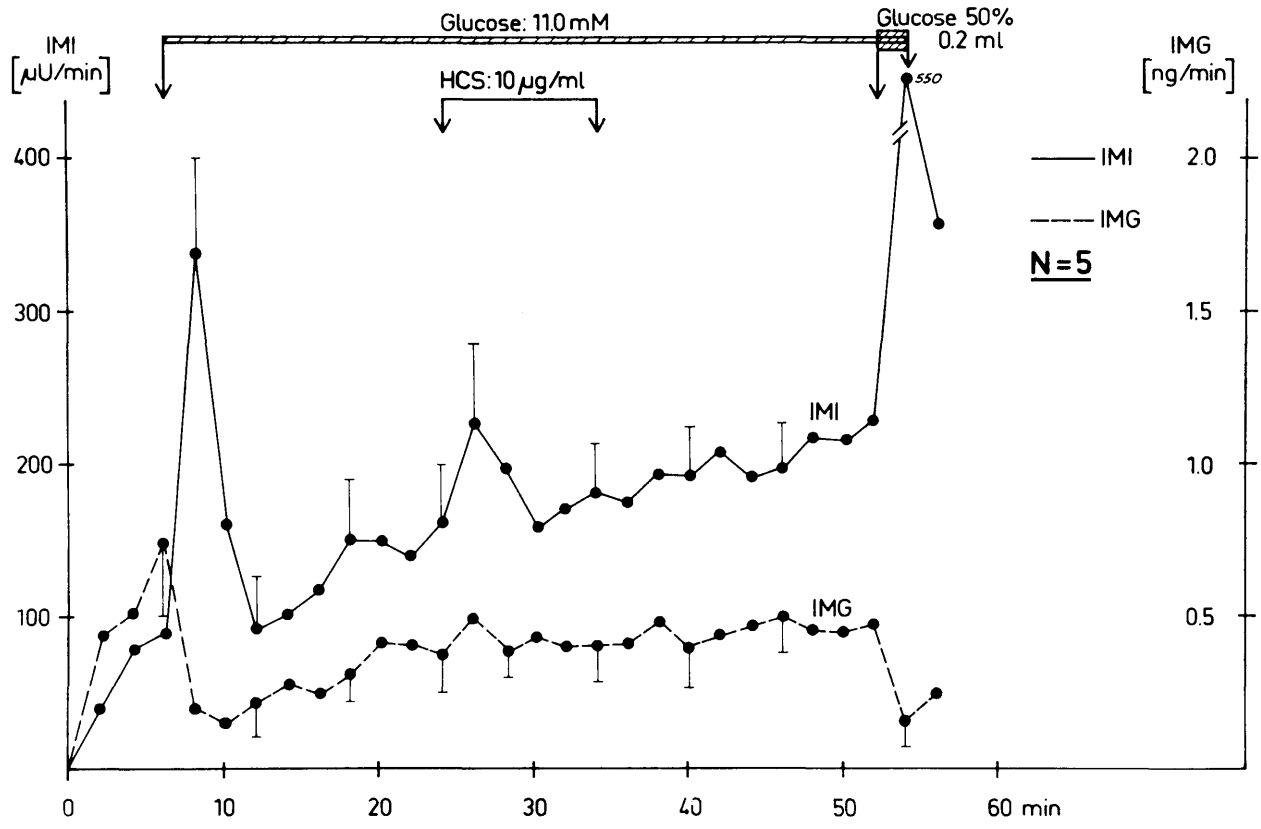

FIG. 3. Insulin and glucagon release from the isolated perfused pancreas following HCS infusion in the presence of glucose 11.0 mM. Values are mean ± S.E.M.

pregnant women.[20] The short peak is probably due to a membrane effect caused by change in either membrane permeability or the adenyl cyclase system of the cell membrane.[23] The magnitude of HCS-induced insulin release is closely related to the glucose concentration in the perfusion medium, being higher and more pronounced during perfusion with low glucose concentration. Initial hyperglycemia following intravenous glucose administration was found to depress HCS plasma concentration immediately;[4] this finding supports the idea of a glucose-homeostatic effect of HCS.

It is conceivable that HCS plasma levels adjust in order to meet changes in the glycolipid homeostasis of the mother. Diurnal variations from 5 to 8 µg.-Eq./ml. HCS activity were found in the blood of pregnant women at term.[12] Following HCS infusion, glucagon release from the isolated perfused pancreas, similar to that of insulin, is closely related to glucose concentration. At low glucose levels, there is a marked rise of glucagon output following HCS. Glucagon release, however, is rather short and not sustained over the whole period of HCS infusion. High glucose levels suppress any additional secretory action of the α cells stimulated by HCS. This again is suggestive of an HCS-induced membrane effect on the α cell. The metabolic role of HCS, in particular the elevated plasma level in diabetic pregnancy, the depression during high glucose concentrations and the direct stimulatory effect on insulin and glucagon at low glucose concentrations, is not yet fully understood. However, the acute effects on α- and β cells of the pancreas, as shown in the present study, are suggestive of a possible involvement of HCS in the regulation of glucose metabolism in pregnancy.

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