EFFECTS OF SOMATOSTATIN INFUSION ON CARBOHYDRATE AND LIPID PROFILES IN INDUCED HYPOINSULINEMIC GOATS

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ABSTRACT: The study was performed at Zoology Department, University of Punjab, Lahore. The goats (n = 4) were made diabetic after the 2 consecutive administrations of streptozotocin at a rate of 33mg and 40mg/kg body weight. A group of normal goats (n = 4) were also maintained on same feeding regime for comparative study. Somatostatin was administered in a dose of 3.3g/kg body weight. In intact group, a significant ($P < 0.05$) hyperglycemia was observed following 2 hours of hormonal infusion. Remarkable decreasing trend in the concentration of long chain fatty acids was observed in both control and hypoinsulinemic goats. The control group exhibited invariable decline in concentration of volatile fatty acids, while hypoinsulinemic group demonstrated considerable increasing tendency in most of its fractions after hormonal treatment.

Key words: *Hypoinsulinemia, Goats, Glucose, Long chain fatty acids, Volatile fatty acids.*

INTRODUCTION

Somatostatin is a potent and so far universally effective inhibitor of both acute and chronic phases of stimulated insulin and glucagon secretion and the inhibitory effect is quickly reversible. It is suggested that the effect of somatostatin on blood glucose is mediated through its effect on blood glucagons. A somatostatin-induced fall in serum insulin levels did not prevent a decrease in hepatic glucose production (Chideckel *et al.*, 1975). The hypoglycaemic action of intravenous somatostatin depends exclusively upon the inhibition of hepatic glucose production (Blauth *et al.*, 1977). Somatostatin has no acute effects on glucose turnover other than those it induces perturbation of pancreatic hormone secretion (Cherrington *et al.*, 1976). Somatostatin is well known for its effects on release of endogenous pancreatic hormones, thus this character renders it important to observe in relation of insulin and glucagon effects. Somatostatin suppressed but did not completely inhibit insulin secretion in ewes (Leenanuruksa *et al.*, 1988). Somatostatin infusion for 100 minutes decreased glucagon significantly, insulin, cortisol, glucose and free fatty acids were also decreased (Krazer, 1988). During food deprivation in the rat, absolute concentration of somatostatin was found to be decreased (Janowski *et al.*, 1993). Injection of somatostatin caused elevation in plasma FFA within two minutes and remained elevated for 30-75 minutes in sheep. Studies of Hendrick *et al.* (1987) demonstrated that somatostatin directly or indirectly inhibits adipose tissue NEFA release and causes a decrease in the plasma NEFA level. Infusion of somatotrophin release inhibiting factor (SRIF) alone was associated with an increase in plasma FFA and glycerol concentrations, whereas hepatic glucose production and plasma glucose concentrations fell somewhat (Jeng *et al.*, 1993). The concentration of NEFA in plasma is believed to have direct modifying effects on insulin (Balent *et al.*, 2002). However, somatostatin lowers blood glucose concentrations as a secondary effect of inhibition of glucagon secretion. Somatostatin is not suitable for therapy in diabetes (Del Guercio *et al.*, 1976). Studies of Pagano *et al.* (2004) demonstrated that infusion of somatostatin slightly reduced insulin without affecting glucose concentration in rats. These results demonstrate that somatostatin may influence peripheral insulin and glucagon values by modifying their hepatic extraction and inhibiting their pancreatic secretion (Ishida *et al.*, 1980). The present study was carried out to determine the interaction of somatostatin and glucagon on carbohydrates and lipid targets in experimentally induced hypoinsulinemia in goats.

MATERIALS AND METHODS

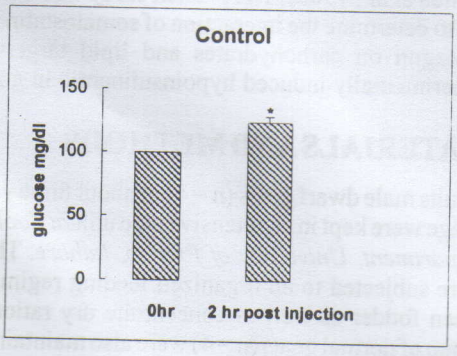
Adults male dwarf goats (n = 4) of about three years of age were kept in an intensive care unit *at Zoology Department, University of Punjab, Lahore*. These were subjected to an organized feeding regime of green fodder as well as concentrate dry ration. A group of normal goats (n = 4) were also maintained

on same feeding regime for comparative study. Goats were acclimated for seven days and than rendered diabetic, permanently, with two successive administrations of streptozotocin (STZ)(Sigma Chemical Company, U.S.A.) at a concentration of 33 and 40mg/ kg body weight in saline citrate buffer (pH 4.3) within four days. In an experiment, the goats were administered somatoatatin @ 3.3 µg/kg body weight intravenously and sampling was done just before and 2 hour post somatostatin treatments. Glycemia, long chain fatty acids lauric (C12), myristic (C14), palmitic (C16), stearic (C18:0), oleic (C18:1), and linoleic acid (C18:2) and volatile fatty acids were estimated following hormonal administration in control and hypoinsulinemic goats. Glucose was estimated with glucose oxidase (Barham and Trinder, 1972) and commercial kits (Randox Laboratories Ltd.) were used. For LCFAs, plasma FFAs were extracted from plasma by the method of Falholt *et al.* (1973) and esterified with boron triflouride (Morrison and Smith, 1964) and further extracted with benzene. Volatile fatty acids (VFAs) were estimated after the procedure of Remesy and Demigne (1974). A standard mixture from Supelco, Inc. GC Bulletin 748H was used for gas chromatography. Data were expressed as mean ± SEM. Differences were evaluated by student's t-test to compare means of control with experimental group.

RESULTS

Glucose

The pretreatment circulatory glucose level in intact and hypoinsulinemic goats were 68.43 4.4 and 175.93 25.02 mg/dl respectively. The glycemia was found to be significantly increased ($P < 0.05$) in intact group (Fig. 1). Whereas it remained almost in the same range in hypoinsulinemic group, when observed two hours after administration of the hypothalamic control hormone. Somatostatin, thus affected glycemia in intact group and hypoinsulinemic goats (Fig. 1).



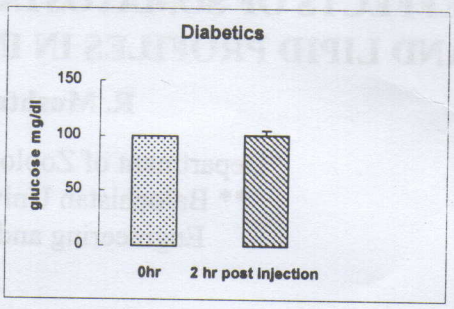


Fig. 1. Plasma glucose following somatostatin (3.3 g/kg) hypoinsulinemic goats, 0 hr pretreatment sample, * significant level at $P < 0.05$. administration in intact and streptozotocin induced

FREE FATTY ACIDS

LONG CHAIN FATTY ACIDS.

Initial concentration of lauric, myristic and stearic acid were 0.5331, 0.09582, and 0.2038g/ml respectively in intact group. All the fractions of lauric, myristic, palmitic, stearic, oleic, and linoleic acid) appeared in hypoinsulinemic goats in the concentration of 0.832, 1.5999, 1.059, 1.2553, 0.9165 and 1.14g/ml respectively. Two hours after somatostatin treatment, lauric and myristic acid disappeared, stearic acid decreased 23% and oleic acid had appeared (0.104 g/ml) in the circulation in the intact group. In hypoinsulinemic goats after somatostatin all the fractions which were in considerable amounts before treatment disappeared from the circulation except lauric acid that was also reduced markedly 83% (Fig. 2).

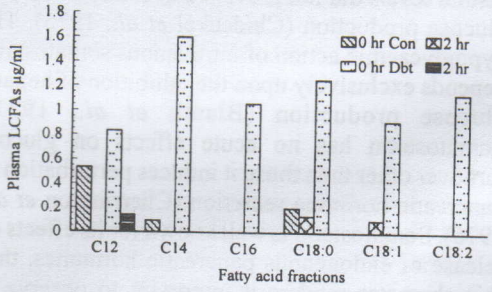


Fig. 2. Plasma LCFAs (g/ml) before and 2hours following somatostatin (3.3 g/kg) administration in intact and streptozotocin induced hypoinsulinemic goats, Con: Control, Dbt: Diabetic.

Somatostatin lowered LCFAs fractions both in intact and hypoinsulinemic goats; however, the intensity of the effect was greater in insulin deficient group. A lowering trend in long chain fatty acids was observed in both intact and hypoinsulinemic goats. 468 and 712% respectively compared to pretreatment levels (Fig. 3).

VOLATILE FATTY ACIDS

Before somatostatin administration the levels of formic, acetic, propionic, iso-butyric, iso-valeric, n-valeric, iso-caproic, n-caproic and heptanoic acid in intact group were 16.10, 200.232, 0.502, 0.2209, 0.8798, 0.0923, 0.6185, 0.0281 and 1.611 g/ml respectively. Two hours after somatostatin treatment, the fractions of formic and acetic acid remained unaffected while propionic iso-butyric iso-valeric n-valeric, iso-caproic and heptanoic acid decreased 61%, 85%, 49%, 12%, 44% and 11% and n-caproic acid enhanced 138%. The fraction of n-butyric acid was not detected in this group before and after the hormone treatment. In hypoinsulinemic goats, all the studied fractions of formic, acetic, propionic, iso-butyric, n-butyric, iso-valeric, n-valeric iso-caproic n-caproic and heptanoic acid were detected and at the concentrations of 76.44, 237.321, 0.283, 0.068, 0.1129, 1.106, 0.1132, 0.1854, 0.0547 and 2.61g/ml in the pretreatment samples. Two hour after somatostatin treatment, formic acid decreased 70%, acetic and n-caproic acid remained unaffected and propionic, iso-butyric, n-butyric, iso-valeric, n-valeric, iso-caproic and heptanoic acid were markedly greater 73, 135, 104, 26, 293,

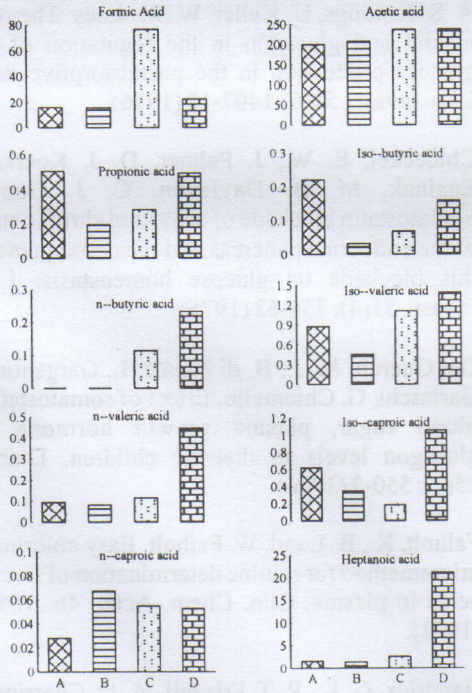


Fig. 3. Plasma VFAs (µgml) before and 2 hours following somatostatin (3.3 g/kg) administration in intact and streptozotocin induced hypoinsulinemic goats. (A) Pretreatment sample of control, (B) post two hour of control, (C) pretreatment sample of diabetics and (D) post two hour sample of diabetics.

DISCUSSION

Somatostatin is a potent and universally effective inhibitor of both acute and chronic phases of stimulated insulin and glucagon secretion as Krazer (1998) demonstrated that somatostatin infusion decreased glucagon significantly and insulin, cortisol, glucose and FFA were also decreased. In the present study in the goats somatostatin, significantly elevated glycemia in intact, however, failed to induce similar effect in hypoinsulinemic goats (Fig. 1). In the intact goats, somatostatin has affected in the presence of both of the pancreatic insulin and glucagon and in contrast to that in hypoinsulinemic state in the presence of glucagon only. Somatostatin has been reported to lower blood glucose concentrations as secondary effect of inhibition of glucagon secretion and the hypoglycemic action of intravenous somatostatin depends exclusively upon the inhibition of hepatic glucose production (Blauth *et al.*, 1977). It reveals that somatostatin in hypoinsulinemic goats effectively inhibited glucagon in its gluconeogenic role, however, this gluconeogenic inhibiting characteristic failed to express similarly in the presence of intact pancreatic β-cells. Chideckel *et al.* (1975) observed that in overnight fasted baboon, somatostatin–induced fall in serum insulin levels appeared to be unable to prevent a decrease in hepatic glucose production and accompanied increase in glycemia. Thus the effect of somatostatin in intact goats resembled to that of fasting non ruminant baboons. During food deprivation in the rat the absolute concentration of somatostatin was found to be decreased (Janowski *et al.*, 1993) which reduced its glycemic lowering effect as food deprivation already prevents insulin release. This may explain the mechanism of blunting the gluconeogenic role of glucagon with lack of glycemic raising effect in acute insulin deficiency of induced hypoinsulinemia. Despite elevated glycemia in the diabetes induced goats the cells are in state of starvation due to lack of glucose transport across the membrane.

A decreasing trend in long chain fatty acids concentrations following somatostatin treatment has been observed in both intact and hypoinsulinemic goats, however, the intensity of the effect is greater in insulin deficient group. Hendrick *et al.* (1987) demonstrated that somatostatin directly or indirectly inhibited adipose tissue NEFA release and caused a decrease in the plasma NEFA level. A large number of LCFAs that circulated in hypoinsulinemic state of the goat disappeared after somatostatin treatment compared to a contrasting response in the intact

goats. In intact goats a few disappeared and the rest were distinctly reduced. The disappearance of LCFAs following somatostatin treatment could be due to their transport into tissues from the circulation. The mechanism of disappearance of most of LCFAs from circulation following somatostatin infusion in hypoinsulinemic goats will be an interesting target of further investigations. Decreasing trend in long chain fatty acids concentrations following somatostatin treatment has been observed in both intact and hypoinsulinemic goats, however, the intensity of the effect is greater in insulin deficient group. Hendrick *et al.* (1987) demonstrated that somatostatin directly or indirectly inhibited adipose tissue NEFA release and caused a decrease in the plasma NEFA level. A large number of LCFAs that circulated in hypoinsulinemic state of the goat disappeared after somatostatin treatment compared to a contrasting response in the intact goats. In intact goats a few disappeared and the rest were distinctly reduced. The disappearance of LCFAs following somatostatin treatment could be due to their transport into tissues from the circulation. The mechanism of disappearance of most of LCFAs from circulation following somatostatin infusion in hypoinsulinemic goats will be an interesting target of further investigations. It is well established that volatile fatty acids in general and among these propionate, through gluconeogenesis, are largely converted for the supply of glucose (Brockman, 1990; Brockman & Greer, 1980; Shoji and Tsuda, 1980). In the present study most of the fractions of VFAs responded variably in both intact and hypoinsulinemic groups following somatostatin administration, however, most fractions were found decreased in intact and increased in hypoinsulinemic goats. The decrease in VFAs in intact goats may be accounted for their utilization in gluconeogeneic synthesis of glucose. The increase in VFAs in hypoinsulinemic goats, contrary to intact goats, thus reflects their non utilization in gluconeogenesis. These results additionally explain the elevation of glycemia following somatostatin in intact goats with lack of such response in hypoinsulinemic goats. The results also expound the role of insulin in utilization of VFAs in gluconegenesis as it failed to express similarly in hypoinsulinemic goats. The results of the study unveil the little understood role of somatostatin and insulin in a crucial mechanism of gluconeogensis in the ruminant model of the goat. Gluconeogensis is the only source of glucose availability in ruminants. Certainly further investigations on this axis will provide more useful information for better growth and reproduction in small ruminants.

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