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Studies on the Extrapancreatic Metabolic Effects of Somatostatin (39839)

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The ability of somatostatin (SRIF) to inhibit the release of insulin and glucagon from the rat pancreas is well documented (1-6). Other studies have shown effects of such inhibition of pancreatic endocrine function on glucose, free fatty acid (FFA), and ketone body metabolism (6-10). Somatostatin *in vivo* does not appear to have a direct effect on glycogenolysis or gluconeogenesis (6, 11, 12). It has been reported, however, that somatostatin inhibits glucagon stimulation of these two metabolic processes in isolated hepatocytes (13). Thus, the evidence for a direct extrapancreatic action of somatostatin has been contradictory (6, 11-13).

We studied the extrapancreatic effects of somatostatin on blood glucose, ketone body, FFA, cholesterol, amino acid, and urea metabolism in the eviscerated rat with a functional liver, after establishing the activity of our somatostatin preparation in the intact rat.

Materials and methods. In the first study, male Sprague-Dawley rats (200-250 g) were fasted overnight. They were then anaesthetized with sodium amobarbital (10 mg/100 g body wt), and a catheter was inserted into the femoral vein. Either somatostatin (100 μg/ml) or normal saline was administered (0.5 ml bolus and 0.5 ml constant infusion for 30 min). At 0, 10, 30, or 45 min of infusion, blood was collected via abdominal aortic puncture, and aliquots of whole blood or serum were frozen for later analysis.

In the second study, male Sprague-Dawley rats (200-250 g) were eviscerated with a functional liver maintained *in situ* by a method previously described (14). Twenty-four hours postoperatively these rats were infused (as described above), and blood samples were similarly collected.

Blood glucose (15), plasma FFA (16), blood ketone bodies (17), plasma total, free and esterified cholesterol (18), plasma amino nitrogen (19), and plasma urea nitrogen (20) were determined in all samples.

In another series of rats, similarly operated and infused, tail vein glucose and β-OH-butyrate were measured at 0, 10, 30, and 45 min. β-OH-butyrate levels were determined fluorimetrically (21).

Results. Table I shows the concentrations of blood glucose, ketone bodies, FFA, total, free, and esterified cholesterol, amino nitrogen, and urea nitrogen at different times during somatostatin infusion in intact 24-hr fasted animals. Blood glucose levels in control animals fell continuously during the infusion period. In somatostatin-infused animals, however, blood glucose rose slightly at 10 and 30 min and showed significantly higher values than saline controls.

Blood ketone bodies in somatostatin-infused animals showed a significant increase over controls at 30 min. Plasma FFA in somatostatin-infused animals was significantly lower as compared to control animals after 30 min. Total and esterified cholesterol and urea nitrogen levels were decreased in somatostatin-infused animals. No differences in free cholesterol were observed during the infusion as compared with control rats.

Table II shows the effect of somatostatin infusion on the above metabolites in the eviscerated animals with functional livers. No difference was observed between somatostatin-infused animals and controls.

Table III shows the changes in blood concentrations of β-OH-butyrate and glucose in the same eviscerated rat at each time period. In these experiments no differences between somatostatin-infused animals and saline controls were observed.

Discussion. The ability of somatostatin to block pancreatic secretion of glucagon and insulin in the intact rat is well established. It has been reported that somatostatin, at concentrations of 100 ng/ml, suppresses basal and epinephrine stimulated glucagon

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TABLE I. THE EFFECT OF SOMATOSTATIN INFUSION (0–30 MIN) ON BLOOD METABOLITES IN 24-HR FASTED RATS.[a]

		Time (min)			
		0	10	30	45
Glucose (mg/dl)	SAL	79.0 ± 5.6	70.2 ± 3.3	64.2 ± 3.7	78.4 ± 4.5
	SRIF		86.4 ± 4.1*	81.4 ± 6.1**	75.1 ± 4.0
Ketone bodies (mg/dl)	SAL	1.86 ± 0.38	2.14 ± 0.27	1.78 ± 0.28	0.56 ± 0.09
	SRIF		1.70 ± 0.16	4.33 ± 0.72*	0.67 ± 0.06
FFA (μEq/ml)	SAL	0.63 ± 0.06	0.83 ± 0.07	1.44 ± 0.19	0.84 ± 0.05
	SRIF		0.78 ± 0.10	0.93 ± 0.03**	0.74 ± 0.04
Total cholesterol (mg/dl)	SAL	84.9 ± 7.5	86.2 ± 14.8	94.9 ± 7.3	77.2 ± 8.9
	SRIF		75.8 ± 11.0	76.6 ± 6.4**	83.6 ± 11.7
Free cholesterol (mg/dl)	SAL	57.3 ± 4.23	40.8 ± 6.8	45.5 ± 7.2	38.1 ± 6.5
	SRIF		55.6 ± 9.9	41.1 ± 6.6	53.5 ± 5.7
Esterified cholesterol (mg/dl)	SAL	27.4 ± 5.2	50.0 ± 8.7	49.1 ± 5.7	40.1 ± 07.1
	SRIF		22.2 ± 3.5**	36.9 ± 6.4	41.1 ± 10.9
Amino nitrogen (mg/dl)	SAL	4.55 ± 6.4	3.80 ± 0.20	3.86 ± 0.45	3.48 ± 0.44
	SRIF		4.10 ± 0.44	3.85 ± 0.65	4.66 ± 0.42
Urea nitrogen (mg/dl)	SAL	28.5 ± 1.4	21.1 ± 1.1	29.6 ± 2.0	21.5 ± 0.7
	SRIF		17.3 ± 0.7*	25.8 ± 1.3	22.8 ± 1.3

* $p < 0.01$.
** $p < 0.05$.
[a] $N = 10$ at each time.

TABLE II. THE EFFECT OF SOMATOSTATIN INFUSION (0–30 MIN) ON BLOOD METABOLITES IN EVISCERATED RATS WITH FUNCTIONAL LIVERS.[a]

		Time (min)			
		0	10	30	45
Glucose (mg/dl)	SAL	270.4 ± 12.4	273.1 ± 16.6	245.8 ± 13.8	280.3 ± 15.9
	SRIF		261.0 ± 15.2	251.6 ± 9.1	263.4 ± 12.0
Ketone bodies (mg/dl)	SAL	6.69 ± 1.30	4.76 ± 0.92	7.35 ± 1.03	6.52 ± 0.68
	SRIF		5.19 ± 0.86	6.85 ± 1.45	6.57 ± 0.90
FFA (uEq/ml)	SAL	1.85 ± .09	1.95 ± 0.10	1.80 ± 0.13	1.90 ± 0.11
	SRIF		2.01 ± 0.11	1.92 ± 0.08	2.00 ± 0.07
Total cholesterol (mg/dl)	SAL	83.2 ± 10.9	78.4 ± 4.1	78.6 ± 5.2	71.6 ± 6.2
	SRIF		98.0 ± 10.6	86.2 ± 8.7	74.2 ± 5.0
Free cholesterol (mg/dl)	SAL	50.7 ± 5.1	35.9 ± 4.5	47.0 ± 3.72	40.6 ± 4.1
	SRIF		35.2 ± 2.9	42.9 ± 2.60	33.6 ± 3.1
Esterified cholesterol (mg/dl)	SAL	23.8 ± 5.7	19.1 ± 2.0	30.6 ± 3.50	31.0 ± 5.6
	SRIF		15.0 ± 2.0	43.2 ± 7.82	37.8 ± 6.0
Amino nitrogen (mg/dl)	SAL	10.96 ± 1.38	10.09 ± 0.63	10.50 ± 0.96	8.41 ± 1.75
	SRIF		10.95 ± 1.16	11.65 ± 0.90	9.82 ± 1.95
Urea nitrogen (mg/dl)	SAL	48.7 ± 3.9	33.8 ± 1.9	36.2 ± 2.5	42.9 ± 3.3
	SRIF		36.6 ± 2.2	36.3 ± 2.2	42.9 ± 3.1

[a] N = 10 at each time period.

TABLE III. EFFECT OF SOMATOSTATIN INFUSION (0–30 MIN) ON BLOOD GLUCOSE AND β-OH-BUTYRATE IN EVISCERATED RATS WITH FUNCTIONING LIVERS.

			Time (min)			
		N	0	10	30	45
Glucose (mg/dl)	SAL	8	285.3 ± 20.9	290.0 ± 21.0	283.9 ± 20.2	287.9 ± 19.1
	SRIF	8	282.5 ± 20.5	275.3 ± 23.2	272.6 ± 14.2	269.6 ± 14.2
β-OH-Butyrate (millimoles/liter)	SAL	8	5.73 ± 0.68	5.71 ± .76	5.70 ± .77	5.86 ± 0.84
	SRIF	8	6.85 ± 1.01	6.67 ± .95	6.85 ± .98	6.89 ± 1.02

release (2), as well as basal and glucose stimulated insulin release (4) from the isolated perfused rat pancreas. In other work, insulin and glucagon levels reportedly fell to undetectable levels in three out of four fasted intact baboons during a somatostatin infusion (7). Thus, at sufficiently high concentrations of somatostatin, a total pancreatic endocrine blockade can occur.

Very high doses of somatostatin were utilized in these experiments. Such a high concentration of somatostatin (8–12 μg/ml) presumably causes complete inhibition of insulin and glucagon release. Although plasma concentrations of IRI and IRG were not measured, the observed effects of somatostatin may have resulted from an acute suppression of pancreatic endocrine function.

The increased blood glucose levels observed in the intact rat during somatostatin infusion may be due to a blockade of insulin release which results in decreased glucose utilization. Gluconeogenesis also seems to be acutely imparied since urea levels are lowered. This may be due to somatostatin's inhibition of glucagon secretion. However, the net effect of somatostatin infusion is hyperglycemia due to decreased glucose utilization.

The decrease in plasma FFA observed during the somatostatin infusion could have resulted either from increased tissue utilization of lipid moieties or from a decrease in lipolysis resulting from the somatostatin inhibition of glucagon secretion. The drop in total cholesterol might be explained by an associated decrease in esterified cholesterol synthesis as fatty acid oxidation increased.

These metabolic alterations observed during a somatostatin infusion seem to be due to a bihormonal deficit of both insulin and glucagon. However, the metabolic consequences of insulin deficiency override the metabolic contribution of glucagon lack. The net effect observed under these circumstances is hyperglycemia and hyerketonemia.

Somatostatin has been shown to reduce the hyperglycemia produced under conditions of insulin deficiency by lowering circulating glucagon levels (8). In our eviscerated preparation, however, where both pancreatic and intestinal sources of glucagon, as well as insulin, were removed, no such effect of somatostatin on blood glucose was observed. The hyperglycemia and hyperketonemia already present before somatostatin infusion were unchanged by somatostatin. Somatostatin did not alter plasma levels of any of the other metabolites measured in our eviscerate preparation. A recent report suggested that somatostatin might selectively decrease alanine and increase glutamine release from muscle *in vitro* (22). We previously reported, however, that there was no significant effect of somatostatin on alanine release from perfused rat hind limb preparations (11).

Our data demonstrate, therefore, that infusion of somatostatin affects blood metabolites by altering the secretion of insulin and glucagon and not by any direct effect on metabolite production or utilization.

Summary. We studied the effect of somatostatin on various metabolic parameters in the fasted intact rat and in the eviscerated rat with a functional liver. In the fasted intact animal, high doses of somatostatin produced an elevation of blood glucose and ketone bodies together with a decrease in plasma FFA, total and esterified cholesterol, and urea nitrogen. We have postulated, therefore, that high levels of somatostatin (100 μg) may cause a functional endo-

crine pancreatectomy in normal rats. The metabolic consequences are due more to the insulin deficit than the lowered glucagon levels. Somatostatin had no effect on any of the parameters measured in eviscerated rats. We concluded that somatostatin has no extrapancreatic metabolic effects in this model.

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