

PRELIMINARY NOTE

Growth-Hormone and Somatostatin Effects on [⁷⁵Se]Selenomethionine Uptake by the Pancreas

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The imaging of the pancreas with [⁷⁵Se]selenomethionine has a low rate of reliability. This study was carried out in order to elucidate some factors that may be important in affecting the degree of uptake of the tracer by the pancreas. Studies were carried out in animals to observe the effects of growth-hormone (GH), somatostatin (SRIF), L-DOPA, and apomorphine administration on the distribution of [⁷⁵Se]selenomethionine. Intravenously administered GH significantly depressed pancreatic uptake of Se-75 in mice and dogs and depressed the pancreas-to-liver concentration ratio (P/L). The effect of i.p. GH in mice was to decrease the P/L ratio, but the decrease in pancreatic uptake was not statistically significant. There was also a greater effect of GH in dogs than in mice, with pancreatic uptake decreasing from $5.60 \pm 2.17\%$ to $1.24 \pm 0.96\%$ and the P/L from 4.78 ± 1.85 to 0.97 ± 0.73 . L-DOPA and apomorphine produced effects similar to GH in mice. SRIF in small doses had little effect, but in larger doses it enhanced pancreatic uptake, although not affecting P/L. The results indicate that hypothalamic factors may be important in affecting the function of the exocrine pancreas. Both L-DOPA and apomorphine are known to stimulate GH production through hypothalamic-pituitary pathways. In addition to suppressing GH release, SRIF may have direct effects on the exocrine pancreas.

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Somatotrophin (growth-hormone, GH) stimulation of insulin and glucagon release from the endocrine pancreas is well known (1). Although somatotrophin-release inhibiting factor (somatostatin, SRIF) exerts an opposite effect and, in addition, has demonstrated effects on the exocrine pancreas (2,3), there has been no report of GH effect on pancreatic acinar function.

Moreover, stimulation of GH is known to occur after administration of L-DOPA and apomorphine in the treatment of Parkinsonism (4). Growth-hormone release occurs after electrical stimulation of the ventromedial nucleus of the hypothalamus (5). This same nucleus is destroyed by administration of gold thioglucose to mice, resulting in loss of appetite regulation and thus followed by obesity (6).

Studies with radiolabeled zinc thioglucose have demonstrated a significant increase in pancreatic uptake of the radiolabel following growth-hormone

administration (7). Because the mechanism of uptake of zinc thioglucose is unknown, we decided to investigate growth-hormone effects on a commonly used pancreatic imaging agent, selenomethionine labeled with selenium-75, in order to see whether similar effects would occur.

METHODS

Swiss albino mice weighing approximately 25 g were used. In all studies mice were killed 1 hr following the i.v. administration of [⁷⁵Se]selenomethionine (~3 μ Ci). The pancreas, liver, kidneys, and intestinal tract were excised and weighed. Radioactivity was assayed in a sodium iodide well counter and the data were expressed as percentage of injected dose, per organ and per gram of tissue. Growth-hormone (GH, 4 international units) and somatostatin (SRIF, 4.4 μ g) were administered intraperitoneally in two divided doses, one just before selenomethionine administration and the second half an hour later. In other animals, GH and SRIF were given by i.v. infusion, starting about 5 min before the selenomethionine and lasting 40 min. The infusion delivered 4 units of GH in 5% dextrose in

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TABLE 1. EFFECT OF INTRAPERITONEAL ADMINISTRATION OF GROWTH HORMONE AND SOMATOSTATIN ON [⁷⁵Se] SELENOMETHIONINE DISTRIBUTION IN MICE (% DOSE/ORGAN ± S.D)

	Control (n = 14)	Growth hormone, 4 I.U. (n = 10)	P	Somatostatin, 4.4 μg (n = 10)	P
Pancreas	7.42 ± 1.41	6.44 ± 0.84	n.s.†	8.92 ± 1.91	0.05-0.02
Liver	20.88 ± 3.33	21.49 ± 2.30	n.s.	18.72 ± 2.74	n.s.
Intestines	20.06 ± 2.60	18.60 ± 1.31	n.s.	20.73 ± 5.44	n.s.
Kidneys	3.69 ± 0.85	3.17 ± 0.33	n.s.	3.05 ± 0.31	0.05-0.025
Pancreas/liver*	3.03 ± 0.54	2.02 ± 0.27	<0.001	3.13 ± 0.70	n.s.

* Ratio of concentrations in % dose/g.

† n.s. = not significant

TABLE 2. EFFECT OF GROWTH HORMONE AND SOMATOSTATIN INFUSIONS ON [⁷⁵Se] SELENOMETHIONINE DISTRIBUTION IN MICE (% DOSE/ORGAN ± S.D.)

	Control n = 11	Growth hormone, 4 I.U. n = 9	P	Somatostatin, 6 μg n = 16	P
Pancreas	8.14 ± 0.79	5.10 ± 1.84	<0.001	7.30 ± 1.88	n.s.
Liver	19.25 ± 2.74	21.58 ± 3.04	n.s.	18.72 ± 3.68	n.s.
Intestines	16.99 ± 1.92	17.92 ± 2.21	n.s.	18.40 ± 3.73	n.s.
Kidneys	3.79 ± 0.89	4.46 ± 1.07	n.s.	4.06 ± 1.06	n.s.
Pancreas/liver*	3.31 ± 0.49	2.03 ± 0.61	<0.001	3.61 ± 1.49	n.s.

* Ratio of concentrations in % dose/g.

water (D/W), or 6 μg SRIF in normal saline. An additional group of mice received 40 μg SRIF in saline by infusion. The total infusate delivered was 1.2 ml.

L-DOPA (0.5 mg/g) and apomorphine (2 μg/g) were administered by intraperitoneal injection 1 hr before [⁷⁵Se]selenomethionine injection, and the animals were killed as above.

Beagles weighing approximately 25 kg were given infusions of 16.5 international units of GH in 150 ml of 5% D/W, or of SRIF (50 μg in 150 ml normal saline), starting 5 min before i.v. [⁷⁵Se]selenomethionine (~7 μCi) administration and continuing for 40 min.

An additional group of dogs received an infusion of 1 mg SRIF in 250 ml normal saline. Control animals received infusions of 5% D/W (n = 2) or normal saline (n = 3). Organs were obtained by sacrifice at 1 hr, were weighed, and two to three samples from each organ were obtained for radioassay. The data were expressed as percentage injected dose, per organ and per gram of tissue. P/L ratios were calculated from the percentage dose per gram for the pancreas and liver of each animal separately.

All animals were maintained on a standard laboratory diet. Mice were fed ad libitum. Dogs were fasted overnight. All studies were begun in mid-morning.

Autoradiography was performed on sections of pancreas in mice that had received ~10 μCi

[¹⁴C]methionine. One mouse served as a control, one had a pre-injection of 2 μg/g apomorphine, and one received an infusion of 40 μg SRIF. The mice were killed at 1 hr after administration of [¹⁴C]methionine and the pancreas was fixed in 10% buffered formalin. The tissues were dehydrated in ascending grades of alcohol (50%, 70%, 80%, 95%, and absolute) and infiltrated for 48 hr with a 1:1 solution of absolute alcohol and solution A*. The tissues were infiltrated again with solution A alone, then embedded with 25 parts of solution A and 1 part of solution B* and covered with liquid paraffin overnight to ensure total polymerization. Sections were cut with a thickness of 2 μ. The autoradiographic process involved dipping of the sections into NTB-2 dipping emulsion† at (45°C) and exposure for different periods (3, 7, and 10 days) at 4°C. The sections were then developed using developer

TABLE 3. EFFECT OF 40-μg INFUSION OF SOMATOSTATIN ON [⁷⁵Se] SELENOMETHIONINE DISTRIBUTION IN MICE (% DOSE/ORGAN ± S.D.)

	Control (n = 11)	Somatostatin (n = 11)	P
Pancreas	7.83 ± 0.69	9.46 ± 0.73	<0.001
Liver	20.85 ± 1.88	20.49 ± 2.75	n.s.
Intestines	18.49 ± 2.74	18.03 ± 2.00	n.s.
Kidneys	4.47 ± 0.64	4.63 ± 0.66	n.s.
Pancreas/liver*	3.23 ± 0.42	3.66 ± 0.58	n.s.

* Ratio of concentrations in % dose/g.

TABLE 4. EFFECT OF L-DOPA ON [⁷⁵Se] SELENOMETHIONINE DISTRIBUTION IN MICE (% DOSE/ORGAN ± S.D.)

	Control (n = 7)	L-DOPA, 0.5 mg/g i.p. (n = 7)	P
Pancreas	6.83 ± 0.58	5.74 ± 0.76	0.02–0.01
Liver	16.02 ± 1.33	17.30 ± 1.65	n.s.
Intestines	19.78 ± 1.27	18.07 ± 2.57	n.s.
Kidneys	5.80 ± 0.70	5.97 ± 0.88	n.s.
Pancreas/liver*	3.59 ± 0.24	2.87 ± 0.36	0.005–0.001

* Ratio of concentrations in % dose/g.

TABLE 5. EFFECT OF APOMORPHINE ON [⁷⁵Se] SELENOMETHIONINE DISTRIBUTION IN MICE (% DOSE/ORGAN ± S.D.)

	Control (n = 5)	Apomorphine, 2 μg/g i.p. (n = 6)	P
Pancreas	7.35 ± 0.88	4.87 ± 1.30	0.01–0.005
Liver	16.95 ± 1.13	17.89 ± 2.83	n.s.
Intestines	18.37 ± 0.94	16.66 ± 1.41	n.s.
Kidneys	4.29 ± 0.40	3.72 ± 0.39	n.s.
Pancreas/liver*	3.47 ± 0.38	2.33 ± 0.33	<0.001

* Ratio of concentrations in % dose/g.

at 19°C and stained with hematoxylin and eosin. Photomicrographs of the sections were obtained at a magnification of 375–600×.

The silver grains in a unit area in the tissue sections were counted using a bacterial-colony counter. Ten areas on three sections for each mouse were counted and averaged.

RESULTS

The effects of intraperitoneal administration of growth-hormone and of somatostatin can be seen

in Table 1. The slight decrease in pancreatic uptake, and the increase in liver uptake, were not significant but the resultant decrease in pancreas-to-liver concentration ratio (P/L) was highly significant: from 3.03 to 2.02. Somatostatin, in the dose used, caused a significant increase in pancreatic uptake and a decrease in kidney radioactivity, but had no statistically significant effect on the P/L ratio.

Growth-hormone administered by infusion had a marked effect, decreasing pancreatic uptake and P/L ratio, whereas a low dose (6 μg) of somatostatin by infusion showed no significant effect (Table 2). However, a much larger (40 μg) dose of somatostatin did significantly increase pancreatic uptake (7.83% to 9.46%) while apparently exerting a lesser but not significant effect on P/L (3.23 to 3.66; Table 3).

Both L-DOPA and apomorphine had effects similar to growth-hormone administration, with a decrease in both pancreatic concentration and P/L ratios (Tables 4 and 5).

The results in dogs were more striking (Table 6). Growth-hormone reduced pancreatic uptake from 5.60 ± 2.17% to 1.24 ± 0.96%; increased liver uptake from 13.13 ± 1.42% to 18.55 ± 2.93%; and decreased the P/L ratio from 4.78 ± 1.85 to 0.97 ± 0.73. There was also a slight increase in kidney uptake. Somatostatin had no significant effect, even in larger doses. The 1-mg dose was lower on a body-weight basis than the 40-μg dose in the mice.

The silver grains in the autoradiograms were distributed both in the pancreatic acini and the islets. The acinar cells (pyramidal zymogenic and centroacinar cells) showed comparatively more grain uptake than the cells of the islets of Langerhans. The grains were located mainly in the cytoplasm of the cells, but some grains were also seen around the nuclear membrane and within the cell nuclei. Grains also localized in the cells of the intralobular ducts, and a large number of grains were seen in the lumina of the ducts (Fig. 1).

TABLE 6. EFFECT OF GROWTH HORMONE AND SOMATOSTATIN ON [⁷⁵Se] SELENOMETHIONINE DISTRIBUTION IN DOGS (% DOSE/ORGAN ± S.D.)

	Control (n = 5)	Growth hormone, 16.5 I.U. (n = 5)	P	Somatostatin, 50 μg n = 8	P	Somatostatin, 1 mg n = 4	P
Pancreas	5.60 ± 2.17	1.24 ± 0.96	0.01–0.005	4.11 ± 1.22	n.s.	5.95 ± 0.65	n.s.
Liver	13.13 ± 1.42	18.55 ± 2.93	0.01–0.005	12.39 ± 1.65	n.s.	16.01 ± 2.64	n.s.
Intestines	18.00 ± 4.20	14.69 ± 4.94	n.s.	15.58 ± 1.35	n.s.	18.95 ± 2.57	n.s.
Kidneys	2.44 ± 0.54	3.16 ± 0.28	0.05–0.025	2.07 ± 0.27	n.s.	2.49 ± 0.47	n.s.
Pancreas/liver*	4.78 ± 1.85	0.97 ± 0.73	0.005–0.001	4.02 ± 1.07	n.s.	3.87 ± 0.76	n.s.

* Ratio of concentrations in % dose/g.

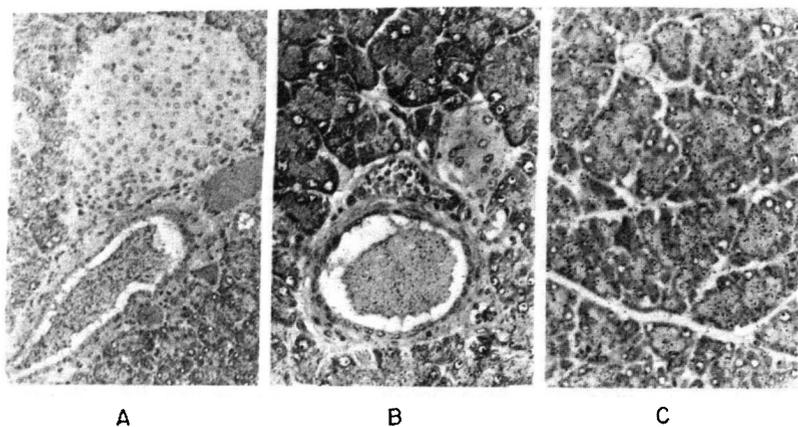


FIG. 1. Autoradiograms of pancreas of mice one hour after administration of [14 C]methionine. (A) Control (B) Pre-injection with apomorphine (C) Pre-injection with SRIF.

Quantitative grain counts with the bacterial-colony counter revealed that the highest grain density was in the pancreas of the mouse treated with SRIF, followed by control mouse, and last by mouse treated with apomorphine (68.86 ± 9.53 counts/unit area, 50.83 ± 8.95 C/A, and 29.90 ± 2.67 C/A for SRIF, control, and apomorphine, respectively).

DISCUSSION

The significant depression of [75 Se]selenomethionine uptake by the exocrine pancreas under the influence of GH was entirely unexpected. The suppression of uptake after administration of L-DOPA is probably due to stimulation of GH release by the pituitary rather than to a direct competitive effect of the amino acid L-DOPA on uptake, because apomorphine administration had a similar effect. Apomorphine is known to stimulate GH secretion through its dopaminergic properties (6). Growth-hormone levels were not obtained in this study. Repeat studies on hypophysectomized animals might resolve the question of whether L-DOPA and apomorphine effects are direct or mediated by the pituitary.

Somatostatin is known to have an effect by inhibiting secretion of gastrin and secretin (3,8-10). Those effects are in addition to the inhibition of insulin and glucagon release by the pancreatic islets. In these experiments we used two different dose levels, although the higher dose in dogs (1 mg) was not equivalent to the 40- μ g dose in mice. It was not practical to use more than 1 mg in dogs because of the very high cost.

Since both GH and SRIF production are under control of the hypothalamus, this portion of the brain may play a role in the quality of pancreatic imaging with labeled amino acids. Stimulation of the ventromedial nucleus (VMN) leads to increased growth-hormone production (5). Destruction of the VMN results in decreased GH blood levels as well

as loss of appetite regulation in rodents (11-13). The interrelationship of the VMN, the pituitary, and the pancreas merits further investigation.

FOOTNOTES

* J-B4 methacrylate embedding medium, Polyscience, Warrington, PA

† Eastman Kodak Co., Rochester, NY

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