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Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones

(tumor weight and volume reduction/somatostatin analogs/luteinizing hormone-releasing hormone analogs)

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ABSTRACT **Using animal models of acinar and ductal pancreatic cancer, we investigated the effect of analogs of hypothalamic hormones on tumor growth. In Wistar/Lewis rats bearing the acinar pancreatic tumor DNCP-322, chronic administration of [L-5-Br-Trp^8]somatostatin-14 significantly decreased tumor weights and volume. Somatostatin-28 and the cyclic hexapeptide analog of somatostatin cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe) failed to influence the growth of this tumor. The agonistic analog of luteinizing hormone-releasing hormone [D-Trp^6]LH-RH also significantly decreased tumor weight and volume in this model and reduced testosterone levels and the weights of the ventral prostate and testes. In Syrian hamsters bearing ductal type of pancreatic carcinoma, chronic administration of [L-5-Br-Trp^8]somatostatin diminished tumor weights and volume. The percentage change in tumor volume was significantly decreased when compared to control animals. In one experiment, cyclic hexapeptide of somatostatin also inhibited growth of this tumor. [D-Trp^6]LH-RH, given twice daily or injected in the form of microcapsules for constant controlled release, significantly decreased tumor weight and volume and suppressed serum testosterone levels. Hamsters castrated 4 days after transplantation of the pancreatic tumors showed a significant decrease in weight and volume of these tumors. This suggests that pancreatic cancers may, at least in part, be sex hormone sensitive. [D-Trp^6]LH-RH may decrease the growth of pancreatic carcinomas by suppressing androgens. Somatostatin analogs reduce the growth of pancreatic ductal and acinar cancers, probably by inhibiting the release or stimulatory action of gastrointestinal hormones on tumor cells (or both). Inhibition of animal models of pancreatic tumors by chronic administration of somatostatin analogs and [D-Trp^6]LH-RH suggests that these compounds should be considered for the development of a new hormonal therapy for cancer of the pancreas.**

The development of new methods for the treatment of pancreatic cancer in man has been hampered by the lack of suitable experimental models of this disease. Recently, several animal models of transplantable pancreatic tumors with acinar and ductal phenotypic characteristics have been developed (1–3).

Regulation of growth of the exocrine pancreas appears to be hormonal in nature. The gastrointestinal hormones cholecystokinin (CCK) and secretin are the chief endocrine stimulants of pancreatic exocrine secretions (4). An important, recently established action of CCK, secretin, and gastrin is their ability to stimulate the growth of the exocrine pancreas (4–7). The role that these gastrointestinal hormones play in the development and growth of pancreatic cancer is not clearly understood, but it is likely that they may influence the growth of malignant cells of the pancreas (8). Townsend *et al.* (8) have shown that caerulein, which is structurally related to CCK, and secretin stimulate the *in vivo* growth of hamster pancreatic cancer. CCK, secretin, and gastrin can also stimulate the growth of rat stomach cancer cells in tissue cultures (9).

Somatostatin may also be important in regulating the activities of the gastrointestinal tract and the endocrine and exocrine pancreas (10). Studies carried out in several species, including human beings, have shown that somatostatin and its analogs exert inhibitory actions on the endocrine and exocrine pancreas as well as on the stomach and gut. These actions include inhibition of the release of insulin and glucagon and suppression of the secretion or action (or both) of gastrin, secretin, and CCK (11–14). Clinical studies have demonstrated that somatostatin or its analogs inhibit insulin secretion in patients with insulinomas and glucagon release in cases of glucagonomas (11, 15, 16). The secretions of ectopic endocrine tumors of the pancreas, including gastrin secreted from gastrinomas and vasoactive intestinal peptide (VIP) released from vipomas, are also suppressed by somatostatin or its analogs (17, 18).

Sex steroids may also play a role in the growth of normal and cancerous pancreas (19–21). The incidence of carcinoma of the pancreas is greater in males, indicating that this neoplasia may be androgen sensitive. The presence of specific receptors for estrogen and androgen in pancreatic cells indicates that sex hormones may influence neoplastic cell processes (19–21). All of these findings suggest that pancreatic adenocarcinomas may be sensitive to both gastrointestinal and sex hormones.

Inhibition of the growth of endocrine-dependent mammary, prostate, and pituitary tumors by analogs of hypothalamic hormones has recently been demonstrated (22–24). We have also reported that chronic administration of analogs of somatostatin-14 or the agonistic analog of luteinizing hormone-releasing hormone [D-Trp^6]LH-RH inhibits the growth of Swarm chondrosarcoma (25). The purpose of this current study was to determine whether [D-Trp^6]LH-RH or analogs of somatostatin could inhibit the growth of two histologically distinct transplantable pancreatic tumors.

MATERIAL AND METHODS

Wistar/Lewis rats with transplantable, well-differentiated acinar pancreatic tumor DNCP-322 (CA-20948) were a gift from D. Longnecker (Dartmouth Medical School, Hanover, NH). Golden Syrian hamsters bearing the well-differentiated (WD), chemically induced ductal adenocarcinoma were kindly provided by D. G. Scarpelli (Northwestern University, Chicago).

Donor tumor tissue from both species was removed, washed in ice-cold Hanks' buffered saline (pH 7.4), sliced

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Abbreviations: LH-RH, luteinizing hormone-releasing hormone; CCK, cholecystokinin; GH, growth hormone; RIA, radioimmunoassay; VIP, vasoactive intestinal peptide; [L-5-Br-Trp^8]SS, [L-5-Br-Trp^8]somatostatin; b.i.d., twice a day.

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into small pieces, and passed through a no. 30 stainless steel screen. The resulting slurry was centrifuged and washed twice with cold buffer. The pellet was resuspended in buffer and 1- to 2-mg aliquots of tumor tissue were injected subcutaneously into the middle back region of weanling male animals of the respective model—i.e., Wistar/Lewis rats or LAS Syrian hamsters.

Peptide Analogs of LH-RH and Somatostatin. [D-Trp^6]LH-RH was synthesized by solid-phase methods as described (26) and supplied by Debiopharm (Lausanne, Switzerland). [L-5-Br-Trp^8]Somatostatin ([L-5-Br-Trp^8]SS) and somatostatin-28 were also synthesized by solid-phase methods (27). Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe) (28) (cyclohexapeptide minisomatostatin analog) was made in our laboratory or supplied by J. Sandow and R. Geiger (Hoechst, Frankfurt).

The peptides were dissolved in saline/10% polyvinylpyrrolidone and injected subcutaneously in doses of 5–30 μg in a volume of 0.2 ml for 21–30 days. In some experiments the peptide was given twice a day (b.i.d.). In one experiment the hamsters were injected once with a microcapsule formulation of [D-Trp^6]LH-RH in poly(D,L-lactide-co-glycolide), which liberated a constant dose of about 25 μg/day for 30 days. These microcapsules were kindly provided by T. Tice (Southern Research Institute, Birmingham, AL, and Debiopharm). Control animals with tumors were injected with the vehicle solutions.

The animals were housed 5 or 6 to a cage in a temperature- and light-controlled room. Rats and hamsters were sacrificed 2 hr after the last injection of the experimental peptide and trunk blood was collected.

Tumors and organs from the animals were cleaned of any adhering tissue and weighed. Pieces of the tumor were quickly removed and frozen on dry ice. Estimation of tumor growth was made by measuring tumor volume twice a week with microcalipers (22–25).

Serum levels of growth hormone and prolactin were measured by double-antibody radioimmunoassays (RIAs) using materials supplied by the National Hormone and Pituitary Program. Serum testosterone levels were measured by a RIA kit supplied by Radioassay Laboratories (Carson, CA). All data are expressed as the mean ± SEM. Statistical evaluations of RIAs and tumor and organ weights were made using Duncan's new multiple-range test or Student's *t* test or both (29, 30).

RESULTS

The effects of chronic administration of analogs of LH-RH and somatostatin on the growth of the acinar pancreatic DNCP-322 tumor in male Wistar/Lewis rats are shown in Table 1. Chronic administration of 30 μg b.i.d. of [L-5-Br-Trp^8]SS for 21 days significantly decreased tumor volume and weight (67% and 51% reduction, respectively) but did not affect body and organ weights. Somatostatin-28 had no effect on the growth of this tumor. Administration of 30 μg b.i.d. of [D-Trp^6]LH-RH also significantly diminished tumor weight and volume (75% and 55% decrease, respectively). Testes and ventral prostate weights were also reduced in this group as compared to control animals, but body and anterior pituitary weights were not affected by treatment with [D-Trp^6]LH-RH.

In the second experiment, male rats bearing acinar pancreatic tumors were treated for 30 days with several analogs of hypothalamic hormones, as shown in Table 2. Administration of 30 μg of [L-5-Br-Trp^8]SS b.i.d. for 30 days significantly decreased tumor weight (64%) and volume (61%) in agreement with the results of experiment 1. Cyclic hexapeptide analog of somatostatin failed to change tumor weight or volume and had no significant effect on body or organ weights as compared to control animals. Treatment with [D-Trp^6]-LH-RH again induced a significant decrease in tumor weight and volume (56% and 51%, respectively) as compared to control animals that received the vehicle. The weights of the ventral prostate and testes were also significantly reduced as compared to control rats.

Serum levels of growth hormone (GH), prolactin, and testosterone in the two experiments with pancreatic acinar tumors in rats are recorded in Table 3. GH levels fell in rats receiving somatostatin-28 (experiment 1) but rose in rats given [L-5-Br-Trp^8]SS (experiments 1 and 2) or cyclic hexapeptide of somatostatin (experiment 2). Somatostatin-28 is a long-acting peptide, whereas [L-5-Br-Trp^8]SS has a much shorter action. The elevation in GH after injection of [L-5-Br-Trp^8]SS and cyclic hexapeptide is most likely due to a rebound phenomenon that is commonly seen with somatostatin or its short-acting analogs (11, 16–18, 27). A significant decrease in serum prolactin was seen in both experiments in tumor rats treated with [D-Trp^6]LH-RH and in experiment 2 in rats given [L-5-Br-Trp^8]SS or the cyclic hexapeptide of somatostatin. Testosterone levels fell significantly in both experiments in rats treated with [D-Trp^6]LH-RH but not with somatostatin-28 or [L-5-Br-Trp^8]SS.

Table 4 shows the effects of somatostatin analogs and [D-Trp^6]LH-RH on the growth of the WD ductal pancreatic adenocarcinoma in male LAS Syrian hamsters. Chronic treatment with [L-5-Br-Trp^8]SS, at a dose of 20 μg b.i.d. for 21 days, diminished tumor weights by 44% and tumor volume by 22%. Percentage change in tumor volume was significantly decreased as compared to control animals. Body and other organ weights remained unchanged except for a slight reduction in testes weight. When the cyclic somatostatin hexapeptide was injected for 21 days into hamsters bearing the ductal pancreatic tumor, there was a significant reduction in tumor weight and volume in this model in contrast to the rat DNCP-322 pancreatic acinar carcinoma. Chronic administration of [D-Trp^6]LH-RH, at a dose of 20 μg b.i.d. for 21 days, significantly reduced tumor weight and volume (by

Table 1. Effect of administration of analogs of LH-RH and somatostatin on the growth of the pancreatic acinar tumor DNCP-322 in Wistar/Lewis rats

Treatment	Dose, μg/b.i.d. for 21 days	Weight					Tumor volume, mm^3	% change in tumor volume
		Final body, g	Anterior pituitary, mg	Testes, g	Ventral prostate, mg	Tumor, g		
Control	—	273 ± 12	5.73 ± 0.68	2.48 ± 0.77	224.7 ± 55	15.18 ± 4	785 ± 97	88 ± 21
[L-5-Br-Trp^8]SS	30	260 ± 9	5.78 ± 1.2	2.51 ± 0.62	232.8 ± 36	5.08 ± 0.6	386 ± 55	14 ± 9
		NS	NS	NS	NS	$P < 0.05$	$P < 0.01$	$P < 0.05$
Somatostatin-28	15	266 ± 13	5.44 ± 0.61	2.59 ± 0.22	221.3 ± 37	14.05 ± 4	584 ± 76	87 ± 28
		NS	NS	NS	NS	NS	NS	NS
[D-Trp^6]LH-RH	30	243 ± 5	5.41 ± 0.35	1.58 ± 0.33	159.9 ± 18	3.79 ± 0.8	355 ± 21	28 ± 11
		NS	NS	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.01$	$P = 0.05$

Results are mean ± SEM. Each group contained six or seven rats. NS, not significant. *P* values were calculated by Duncan's new multiple-range test.

Table 2. Effect of chronic administration of analogs of LH-RH and somatostatin on tumor weight and volume and organ weights in Wistar/Lewis male rats bearing the DNCP-322 pancreatic acinar tumor

Treatment	Dose, μg/b.i.d. for 30 days	Weight						Tumor volume, mm^3	% change in tumor volume
		Final body, g	Anterior pituitary, mg	Adrenal, mg	Ventral prostate, mg	Testes, g	Tumor, g		
Control	—	305 ± 8	6.08 ± 0.19	38.6 ± 2.5	339.7 ± 73	2.44 ± 0.08	1.73 ± 0.16	176 ± 15	934 ± 166
[L-5-Br-Trp^8]SS	30	293 ± 17	5.55 ± 0.20	35.8 ± 1.3	219.4 ± 12	2.50 ± 0.04	0.62 ± 0.04	69 ± 7	318 ± 21
		NS	NS	NS	$P < 0.05$	NS	$P = 0.01$	$P < 0.01$	$P = 0.01$
Cyclic hexapeptide-SS	30	273 ± 8	5.62 ± 0.23	36.6 ± 4.0	250.9 ± 12	2.51 ± 0.07	1.75 ± 0.50	170 ± 20	755 ± 31
		NS	NS	NS	NS	NS	NS	NS	NS
[D-Trp^6]LH-RH	30	278 ± 16	6.01 ± 0.32	45.4 ± 2.2	138.9 ± 8	1.37 ± 0.13	0.76 ± 0.11	86 ± 7	292 ± 26
		NS	NS	NS	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.01$	$P < 0.01$

Results are mean ± SEM. Each group contained five to seven rats. NS, not significant. P values were calculated by Duncan's new multiple-range test. Cyclic hexapeptide-SS, cyclic hexapeptide analog of somatostatin.

58% and 51%, respectively) as compared to control animals. The percentage change in tumor volume observed in hamsters treated with [D-Trp^6]LH-RH was only about one-third of that found in control animals ($P < 0.01$). Ventral prostate and testes weights were also decreased in this group. Syrian hamsters castrated 4 days after transplantation of the pancreatic tumor showed a highly significant decrease in tumor weight and volume.

In the second experiment with hamsters bearing the ductal pancreatic adenocarcinoma (Table 5), administration of [L-5-Br-Trp^8]SS, at a dose of 20 μg b.i.d. for 30 days, decreased tumor weight and significantly reduced tumor volume. The percentage increase in tumor volume was only 47% of that found in control animals ($P < 0.01$). [D-Trp^6]LH-RH, injected b.i.d. at a dose of 12.5 μg, reduced tumor weight by 48% and volume by 37% ($P < 0.01$). Hamsters that received [D-Trp^6]LH-RH in the form of microcapsules designed for constant controlled release of about 25 μg/day for 30 days revealed only a 21% decrease in tumor weight but showed a significant decrease in tumor volume and percentage change in tumor volume as compared to control animals. Testes weights decreased in both groups treated with [D-Trp^6]LH-RH. Surgical castration of the hamsters 4 days after transplantation of the tumor significantly reduced tumor weight and volume and ventral prostate weights.

Testosterone levels were not affected by administration of [L-5-Br-Trp^8]SS (experiments 1 and 2) but were significantly decreased in hamsters treated either with a b.i.d. injection of [D-Trp^6]LH-RH (experiments 1 and 2) or with the microcapsule formulation of this drug (experiment 2) (Table 6). In castrated hamsters, serum testosterone fell to undetectable levels.

DISCUSSION

Development of experimental ductal pancreatic tumors in the rat has been hindered by the resistance of the rat ductal epithelium to carcinogens (31). However, a ductal pancreatic adenocarcinoma model has been developed by Scarpelli and Rao (3) by chronic administration of *N*-nitrobis(2-oxopropyl)amine to inbred Syrian golden hamsters. This neoplasm is a well-differentiated adenocarcinoma with cytological features characteristic of ductal epithelial cells and resembles neoplasms encountered most frequently in humans (1–3, 31). Azaserine is a carcinogen used by Longnecker *et al.* (2) to induce pancreatic carcinomas in rats. Histologically this tumor has been characterized as a well-differentiated carcinoma that has retained acinar and tubular configuration in many areas. Similar foci of atypical acinar cells may be present in a high proportion of human pancreases. This tumor is transplantable and has been described to be locally invasive with metastasis to the lung and liver in some recipients (2).

Recent findings indicate that some gastrointestinal hormones can exert potent trophic effects on the growth of the exocrine pancreas (4–7). CCK and the structurally related caerulein increase not only the growth of exocrine pancreas but also pancreatic DNA and RNA content and DNA synthesis (5–7). Although secretin is not as potent as CCK, it also increases pancreatic weight, DNA, RNA, and protein content (7). Similarly, gastrin has a potent trophic effect on the exocrine pancreas and the mucosa of the large and small

Table 3. Serum GH, prolactin, and testosterone levels in rats bearing the pancreatic acinar tumor DNCP-322 after treatment with various analogs of hypothalamic hormones

Experiment	Treatment	Dose, μg/b.i.d.	GH, ng/ml	Prolactin, ng/ml	Testosterone, ng/ml
1	Control	—	29.3 ± 10.6	41.5 ± 7.6	2.81 ± 0.63
	[L-5-Br-Trp^8]SS	30	46.4 ± 16.7	26.4 ± 5.6	3.23 ± 0.78
			NS	NS	NS
	Prosomatostatin	15	6.7 ± 0.3	27.7 ± 4.7	2.68 ± 0.66
			NS	NS	NS
	[D-Trp^6]LH-RH	30	28.3 ± 6.8	17.2 ± 3.2	1.13 ± 0.07
			NS	$P < 0.01$	$P = 0.05$
2	Control	—	13.1 ± 2.7	33.7 ± 8.6	1.71 ± 0.27
	[L-5-Br-Trp^8]SS	30	25.2 ± 14.6	15.7 ± 4.4	1.34 ± 0.09
			NS	$P < 0.01$	NS
	Cyclic hexapeptide-SS	30	42.4 ± 13.7	6.9 ± 1.5	0.89 ± 0.05
			NS	$P < 0.01$	$P < 0.01$
	[D-Trp^6]LH-RH	30	10.8 ± 2.1	9.8 ± 1.2	0.45 ± 0.04
			NS	$P < 0.01$	$P < 0.01$

Results are mean ± SEM. Each group contained five to seven rats. NS, not significant. P values were calculated by Duncan's new multiple-range test. Cyclic hexapeptide-SS, cyclic hexapeptide analog of somatostatin.

Table 4. Effect of chronic administration of analogs of somatostatin and LH-RH on the growth of the WD ductal pancreatic tumor and body and organ weights in Syrian Golden hamsters

Treatment	Dose, μg/b.i.d. for 21 days	Weight						Tumor volume, mm^3	% change in tumor volume
		Final body, g	Anterior pituitary, mg	Adrenal, mg	Ventral prostate, mg	Testes, g	Tumor, g		
Control	—	90 ± 3	2.24 ± 0.14	25.8 ± 1	35.7 ± 2	2.24 ± 0.07	6.75 ± 2	451 ± 86	813 ± 134
[L-5-Br-Trp^8]SS	20	95 ± 5	2.57 ± 0.14	28.0 ± 1	33.2 ± 1	1.93 ± 0.07	3.78 ± 0.32	353 ± 81	388 ± 150
		NS	NS	NS	NS	$P < 0.05$	NS	NS	$P < 0.05$
Cyclic hexapeptide-SS	5	87 ± 3	2.16 ± 0.11	25.9 ± 1	32.9 ± 0.8	2.30 ± 0.07	3.14 ± 0.39	218 ± 35	287 ± 52
		NS	NS	NS	NS	NS	$P < 0.05$	$P < 0.05$	$P < 0.01$
[D-Trp^6]LH-RH	20	77 ± 2	2.23 ± 0.16	25.7 ± 0.95	29.6 ± 1	1.77 ± 0.1	2.84 ± 0.78	221 ± 46	246 ± 64
		$P < 0.05$	NS	NS	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.05$	$P < 0.01$
Castrate	—	83 ± 0.5	3.36 ± 0.16	21.0 ± 1	22.0 ± 2	—	2.28 ± 0.83	201 ± 58	309 ± 84
		NS	$P < 0.01$	$P < 0.01$	$P < 0.01$		$P < 0.01$	$P < 0.05$	$P < 0.05$

Results are mean ± SEM. Each group contained five to seven hamsters. NS, not significant. P values were calculated by Duncan's new multiple-range test. Cyclic hexapeptide-SS, cyclic hexapeptide analog of somatostatin.

bowel. Chronic administration of pentagastrin to antrectomized rats prevents the decrease in pancreatic and colonic weight (6, 7).

The effects of gastrointestinal hormones on the growth of pancreatic tumors have been studied by Townsend *et al.* (8). They were able to demonstrate stimulation of the growth of ductal carcinoma by administration of high doses of caerulein in hamsters, alone or in combination with secretin (8). The mechanisms through which these hormones stimulate growth of these tumors are not fully understood. CCK is the major hormonal regulator of pancreatic acinar cell function. CCK receptors have been found in intact pancreatic acini and in particulate fractions prepared from the whole pancreas (32). Secretin is rapidly and specifically bound to pancreatic membranes and exerts its greatest effect on the pancreatic ducts (3). Binding of ^{125}I-labeled secretin to ductal pancreatic tumors of hamsters has also been demonstrated (3).

Somatostatin inhibits not only the liberation of insulin and glucagon but also the release or action (or both) of secretin, gastrin, CCK, and other gastrointestinal peptides such as VIP and motilin (11–18). Somatostatin has been shown to suppress exocrine pancreatic secretion in rats, dogs and humans (11, 12, 14, 18).

The inhibitory effects of somatostatin analogs on the growth of pancreatic carcinoma in our study may be partially explained by the inhibition of the release of gastrointestinal hormones. However, a direct effect of somatostatin analogs on pancreatic tumors cannot be ruled out. The relationship between endocrine and gastrointestinal inhibitory activity of somatostatin analogs and their antitumor activity is not yet clear, although [L-5-Br-Trp^8]SS, which is essentially equipotent with somatostatin in gastric acid suppression assays (33), was a powerful inhibitor of the growth of the pancreatic acinar and ductal tumors.

There is increasing evidence to suggest that the intact normal pancreas and pancreatic tumors are sex steroid sensitive. The steadily increasing incidence of carcinoma of the pancreas in men also suggests that this disease may be in part sex dependent. Sandberg and Rosenthal (19) described the presence of estrogen receptors in the pancreas of the dog, baboon, and man and suggested that estrogens may play a role in the regulation of exocrine function of the pancreas. The presence of androgen receptors in pancreatic tissue was demonstrated by Pousette (20) in castrate male and female rats. Recently, Greenway *et al.* (21) have found elevated levels of high-affinity estrogen receptors in cytosolic and nuclear fractions of tumor tissue in patients with pancreatic adenocarcinoma but not in normal pancreas. They also demonstrated the presence of two sex steroid biosynthetic enzymes, aromatase and 5-α reductase, in pancreatic tumor tissue (34) and found that testosterone levels were significantly reduced in patients with pancreatic carcinoma when compared to controls, possibly due to the uptake and metabolism within the tumor (34, 35). The findings that pancreatic adenocarcinomas might be sex steroid dependent are supported by evidence from xenografts of human pancreatic adenocarcinomas in *nude* mice (36). Testosterone stimulated tumor growth rate, whereas cyproterone, an antiandrogen, significantly inhibited it (36). Estrogen receptors have also been demonstrated in 7,12-dimethylbenz[*a*]anthracene-induced pancreatic carcinomas in rats and in human pancreatic carcinomas (37).

Table 5. Effect of administration of analogs of LH-RH and somatostatin on tumor weights and volume and body organ weights in Syrian Golden hamsters bearing WD ductal pancreatic tumors

Treatment	Dose, μg/b.i.d. for 30 days	Weight						Tumor volume, mm^3	% change in tumor volume
		Final body, g	Anterior pituitary, mg	Adrenal, mg	Ventral prostate, mg	Testes, g	Tumor, g		
Control	—	67 ± 3	2.09 ± 0.09	22.2 ± 0.9	19.5 ± 1	1.73 ± 0.05	2.36 ± 0.2	219 ± 22	1,377 ± 103
[L-5-Br-Trp^8]SS	20	69 ± 3	2.37 ± 0.06	23.7 ± 0.6	20.5 ± 1	1.59 ± 0.11	1.89 ± 0.2	153 ± 19	649 ± 102
		NS	NS	NS	NS	NS	NS	$P < 0.01$	$P < 0.01$
[D-Trp^6]LH-RH	12.5	72 ± 3	2.40 ± 0.11	21.2 ± 0.7	19.0 ± 1	1.35 ± 0.07	1.23 ± 0.2	139 ± 13	631 ± 56
		NS	NS	NS	NS	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
[D-Trp^6]LH-RH microcapsules	25*	65 ± 2	2.23 ± 0.06	19.7 ± 0.4	19.0 ± 0.6	1.19 ± 0.08	1.86 ± 0.2	176 ± 5	791 ± 76
		NS	NS	NS	NS	$P < 0.01$	NS	$P = 0.05$	$P < 0.01$
Castrate	—	72 ± 3	3.91 ± 0.16	18.7 ± 0.9	8.8 ± 0.9	—	1.18 ± 0.2	128 ± 3	654 ± 52
		NS	$P < 0.01$	$P < 0.01$	$P < 0.01$		$P < 0.01$	$P < 0.01$	$P < 0.01$

Results are mean ± SEM. Each group contained five to seven hamsters. NS, not significant. P values were calculated by Duncan's new multiple-range test.
*Daily release.

Table 6. Serum testosterone levels in Syrian Golden hamsters bearing the pancreatic ductal tumor after treatment with analogs of hypothalamic hormones

Experiment	Treatment	Dose, μg/b.i.d.	Testosterone, ng/ml
1	Control	—	1.79 ± 0.22
	[L-5-Br-Trp^8]SS	20	1.29 ± 0.20 NS
	Cyclic hexapeptide-SS	5	1.98 ± 0.34 NS
	[D-Trp^6]LH-RH	20	0.57 ± 0.15 $P < 0.01$
	Castrate	—	ND $P < 0.01$
2	Control	—	1.66 ± 0.27
	[L-5-Br-Trp^8]SS	20	1.48 ± 0.30 NS
	[D-Trp^6]LH-RH	12.5	0.18 ± 0.04 $P < 0.01$
	[D-Trp^6]LH-RH microcapsules	25*	0.14 ± 0.01 $P < 0.01$
	Castrate	—	ND $P < 0.01$

Results are mean ± SEM. Each group contained five to seven hamsters. NS, not significant; ND, not detectable (<0.1 ng/ml). P values were calculated by Duncan's new multiple-range test. Cyclic hexapeptide-SS, cyclic hexapeptide analog of somatostatin.
*Dose in μg/day.

The findings reported here support the view that both acinar and ductal pancreatic tumors may be sex hormone sensitive. Surgical castration of animals bearing these pancreatic tumors or medical castration by chronic administration of the agonist [D-Trp^6]LH-RH resulted in an inhibition, but not a complete suppression, of tumor growth.

It is apparent from our data that dual mechanisms may be involved in the control of growth of these pancreatic tumors. One mechanism may operate through gastrointestinal hormones that exert trophic effects on pancreatic tumor growth. Administration of somatostatin analogs slows the growth of the pancreatic tumor by inhibiting the release or action (or both) of gastrointestinal hormones. The second mechanism might involve stimulation of pancreatic tumor by sex steroids. Surgical or medical castration decreases tumor growth by eliminating the stimulating effect of sex steroids.

It is possible that a more efficacious method of inhibition of pancreatic carcinoma could result from a combination of somatostatin analog with [D-Trp^6]LH-RH or with an antagonistic analog of LH-RH. In the future it should be possible to administer such combinations in the form of polymeric microcapsules for constant controlled release. In any event, the findings reported here could be of clinical importance and might lead to the development of a new method for the treatment of pancreatic carcinoma based on administration of some analogs of somatostatin, [D-Trp^6]LH-RH, or combinations thereof.

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