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Circulating Somatostatin Acts on the Islets of Langerhans by Way of a Somatostatin-Poor Compartment

Abstract. *Somatostatin perfused in canine pancreases at 10 to 20 picograms per milliliter or 10 to 20 percent of the pancreatic vein somatostatin concentration inhibited insulin and glucagon secretion. This suggests that the high local concentration of endogenous somatostatin is not in contact with somatostatin receptors of the islets. The integrity of this separation may determine the sensitivity of islet cells to circulating somatostatin.*

It is generally believed that the interstitial space of the islets of Langerhans consists of a single compartment throughout which the islet hormones diffuse freely. If this were true, islet cell receptors for insulin, glucagon, and somatostatin would be continually exposed to maximum concentrations of those hormones, in which case only a relatively large change in their arterial concentration could have a biological effect on islet cells. Yet there is evidence that relatively small changes in the concentrations of exogenous insulin (*1*), glucagon (*2*), and somatostatin (*3*) can affect the secretion of islet cells. If a small change in arterial concentration of an islet hormone that is well below the concentration in the pancreatic vein could affect the secretion of other islet hormones, it would suggest that the hormone secreted into the venous circulation did not have access to the interstitial space containing the "arterial-side" receptors of the affected islet cells. We, therefore, systematically determined the relation between the venous efflux concentration and the minimal biologically effective concentration of two islet hormones: somatostatin, which is secreted by the D cells of the islets (*4*) and inhibits insulin (*5*) and glucagon secretion (*6*), and glucagon, which is secreted by the A cells of the islets and stimulates both insulin (*7*) and somatostatin (*8*) secretion. We used the isolated perfused canine pancreas preparation of Iversen and Miles (*9*).

In this system the baseline concentration of endogenous somatostatin in the venous effluent averaged ~ 100 pg/ml. Fujita (*10*) estimates that in the dog about 70 percent of the pancreatic venous effluent consists of blood that has not passed through islets; if this is so, the concentration of somatostatin in the islet interstitium near the D cells must be approximately 300 pg/ml or greater. We tested the effects of somatostatin in concentrations from 10 to 4000 pg/ml, that is, from 10 to 400 percent of the baseline somatostatin level in the venous effluent, upon insulin and glucagon secretion. Somatostatin significantly suppressed insulin secretion at a concentration of only 10 pg/ml, or 10 percent of the venous level (Fig. 1). Glucagon was significantly suppressed by a somatostatin concentration of 20 pg/ml, or 20 percent of the venous level (Fig. 1). Thus, exogenous somatostatin was biologically active on B cells at an arterial concentration that was only 10 percent of the level of endogenous somatostatin in the venous effluent—perhaps 3 percent or even less of the concentration of endogenous somatostatin in the interstitium surrounding the D cells. It seems unlikely that A and B cells could have responded to so small a rise in the arterial concentration of somatostatin had their somatostatin receptors been in contact with even the 100 pg/ml concentrations of endogenous somatostatin present in the venous effluent. Rather, it seems more plausible to suggest that the endogenous somatostatin that enters the venous circulation is secreted into a space that is separate from the space that contains the somatostatin

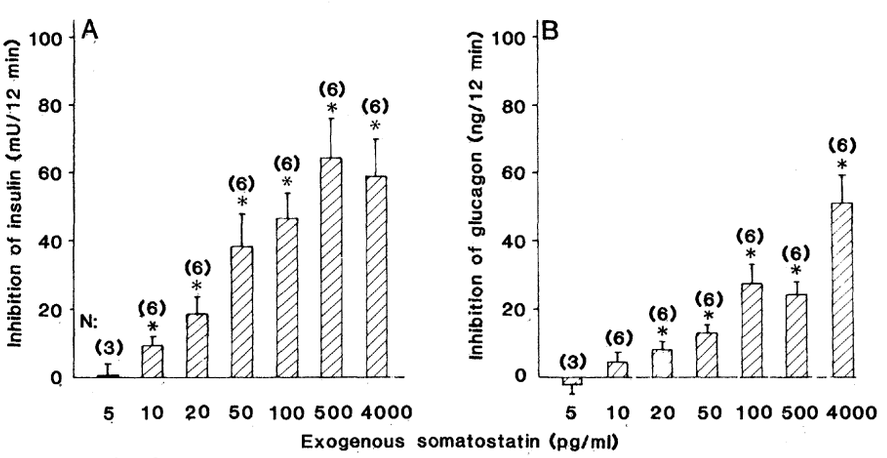

Fig. 1. Degree of inhibition of (A) insulin and (B) glucagon secretion by perfusion of various doses of somatostatin into isolated dog pancreas. The perfusate consisted of a Krebs-Ringer bicarbonate solution containing 4 percent dextran T-70 (Pharmacia Fine Chemicals), 0.2 percent bovine serum albumin, 5.5 m*M* glucose, and 10 m*M* arginine. The pancreatic effluent was collected at 1-minute intervals and frozen for subsequent radioimmunoassay for insulin (*15*), glucagon (*16*), and somatostatin (*17*) after a 40-minute equilibration period. Samples for determining basal concentrations of hormone secretion were collected for 15 minutes; somatostatin was perfused for the next 15 minutes. Inasmuch as the inhibitory effects of somatostatin on the hormone secretion required 3 minutes to reach a plateau, the degree of inhibition was calculated as a decrease in total insulin and glucagon secretion from the preceding basal secretion for the final 12 minutes of each 15-minute infusion period. The baseline concentration of endogenous somatostatin was ~ 100 pg/ml. Differences relative to the initial value (at 5 pg/ml) were regarded as statistically significant if Student's t (d.f. = 8) exceeded the $P = .05$ level (indicated by *).

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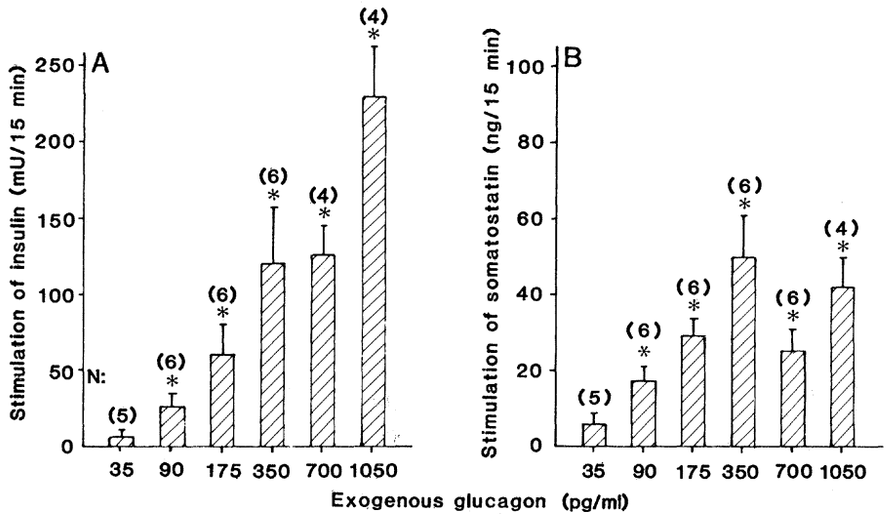

Fig. 2. Degree of stimulation of (A) insulin and (B) somatostatin secretion by perfusion of various doses of glucagon into isolated dog pancreas. The experiment was performed by the same method as in Fig. 1, except that the influx medium contained 11 m*M* glucose and 10 m*M* arginine. The degree of activation was calculated as the increase in total insulin and somatostatin secretion from the preceding basal secretion for each 15 minutes. The baseline concentration of endogenous glucagon was ~ 100 pg/ml. Differences relative to the initial value (at 35 pg/ml) were regarded as statistically significant if Student's *t* [d.f. = 7 (or 9)] exceeded the $P = .05$ level (indicated by *).

receptors of the A and B cells. Alternatively, somatostatin, which lowers portal blood flow in dogs when infused at a rate of 80 to 400 ng per kilogram of body weight per minute (*11*), might have caused a reduction in islet blood flow. However, that infusion rate is calculated to produce somatostatin concentrations from 280 to 3200 times those used in this study.

Glucagon and insulin do not have such effects on portal blood flow. We tested the effects of glucagon in concentrations of 35 to 1050 pg/ml on endogenous insulin and somatostatin secretion. The baseline level of endogenous glucagon in the venous effluent was ~ 100 pg/ml. A significant increase in insulin and somatostatin secretion was first noted at a perfusate concentration of 90 pg/ml (Fig. 2), approximately the same concentration as in the venous effluent. However, if, as estimated by Fujita (*10*), 70 percent of the total pancreas effluent consists of effluent that has not passed through glucagon-secreting islets, the concentration of endogenous glucagon in the interstitium surrounding the A cells would, at the very least, be 300 pg/ml and could be much greater, and 90 pg/ml would still constitute a rather modest fraction of the glucagon level within the islets, although substantially closer to the local level than in the case of somatostatin. (Perhaps the difference is explained by less complete separation of the glucagon receptors of D and B cells from locally secreted glucagon under the experimental conditions used.)

The minimum concentration of insulin required to suppress glucagon was not determined in this study. However, we have previously reported that an increase of as little as 40 μU of insulin per milliliter, a small fraction of the estimated pancreatic venous level, causes significant suppression of glucagon in normal humans (*1*).

Barring a vascular effect with redistribution of pancreatic blood flow away from the islets, the relative sensitivity of the islets to small changes in perfused somatostatin is best explained by compartmentalization of the interstitium of the islets of Langerhans. The anatomical "substrate" for compartmentalization of the interstitial space is the tight junction (*12*). In a tight junction, the outer leaflets of adjacent membranes are fused, thus introducing a seal on the diffusion of substances in the interstitium, a device used extensively in tubular or cavitary epithelia to prevent material secreted into the lumen from mixing with the interstitial fluid. Tight junctions are present among all islet cell types, and their development can be modulated by various experimental conditions (*13, 14*). Thus the anatomical requirements for variable compartmentalization of the interstitium certainly exist, provided that (i) regions of the cell where exocytosis occurs are at least temporarily sealed from nonexocytotic areas so as to deny to the secreted hormone access to its receptors on other islet cells via the interstitium; (ii) the exocytosis-related interstitial space has access to the venous capillaries, which must carry the hormone out of the islet, denying it access to its receptors on other islet cells; and (iii) nonexocytotic membrane areas are accessible to circulating hormones entering from the arterial side of the capillary.

These prerequisites could be fulfilled by an appropriate disposition of modulable tight junctions around the cell periphery. In this way, an "exocytotic-venous capillary pathway" might be kept separate from an "arterial-receptor pathway" and account for the extraordinary sensitivity of endocrine islet cells to certain circulating islet cell hormones. Loss of this compartmentalization could result in high interstitial concentrations of certain hormones and apparent "resistance" of groups of islet cells to changes in the arterial concentrations of these hormones.

KOICHI KAWAI
ELI IPP
Department of Internal Medicine, Veterans Administration Medical Center and *University of Texas Health Science Center, Dallas 75235*
LELIO ORCI
ALAIN PERRELET
Department of Morphology, Institute of Histology and Embryology, University of Geneva, Geneva, Switzerland
ROGER H. UNGER
Department of Internal Medicine, Veterans Administration Medical Center and *University of Texas Health Science Center, Dallas*

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