Brief Note–Hypothesis

Possible Roles of the Pancreatic D-cell in the Normal and Diabetic States

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SUMMARY

The A-, D-, and B-cells—the islet cells that contain, respectively, immunoreactive glucagon, somatostatin, and insulin—are distributed within a specialized heterocellular region of the islets of Langerhans as if to permit heterologous contacts between all three cell types. Inasmuch as each one of the three secretory products of these three cell types influences the secretion of at least one of its neighboring cells, "paracrine" influence on islet hormone secretion becomes a reasonable hypothesis. Glucagon stimulates both insulin and somatostatin release, while insulin and somatostatin both inhibit glucagon release, providing the basis for a feedback relationship through which A-cell secretion may be restrained. In addition, glucagon-mediated insulin secretion may be restrained by glucagon-stimulated somatostatin release. Such intercellular relationships could help determine the composition of the insulin and glucagon mixtures released within a given metabolic setting. DIABETES *26*:241-44, March, 1977.

In all forms of diabetes, A-cell secretion is characteristically unrestrained, and in all forms of diabetes the normal heterocellular relationships are disrupted. In the hypoinsulinemic forms of diabetes insulin-containing B-cells are sparse, and lack of locally secreted insulin in the vicinity of the A-cells could be the cause of the hyperglucagonemia, which can be promptly corrected by large doses of exogenous insulin. In the hyperinsulinemic forms of diabetes, by contrast, it is the somatostatin-containing D-cells that are sparse while insulin-containing cells are abundant; here lack of locally secreted somatostatin in the vicinity of the A-cells could be the cause of the hyperglucagonemia, which, interestingly, is not corrected by even very large doses of exogenous insulin. Thus, the D-cell and the heterocellular region of the islet may well play an important role in normal islet-cell function, the disruption of which may contribute to certain anomalous manifestations of the diabetic state.

Recent immunocytochemical studies of the topographic interrelationships of the A-cells, D-cells, and B-cells of the endocrine pancreas of man and of the rat have defined a heterocellular region in the islets of Langerhans in which these three cell types are in direct contact with one another.[1,2] When this fact is considered in the light of recent demonstrations that each of their respective secretory products—glucagon, somatostatin, and insulin—can modify the secretory activity of at least one of their neighboring cells,[3-8] the existence of a "paracrine" system of secretory control that directs local actions of these secretory products[2] becomes an attractive hypothesis.

EVIDENCE FOR NORMAL PARACRINE RELATIONSHIPS

Samols et al. first reported that glucagon stimulates insulin secretion[3] and that insulin inhibits glucagon secretion,[4] and he proposed an A-cell—B-cell feedback circuit.[5] Subsequently, the immunoreactivity of somatostatin,[6] a powerful suppressor of both insulin[4,5,7-9] and glucagon release,[8,9] was identified in the pancreatic islets[10-12] and localized to the

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D-cells,[13-15] which in man and in the rat are situated between the outer A-cell mantle and the inner mass of B-cells[1,2] (figure 1, left upper panel). And most recently it has been reported that glucagon (but not insulin) stimulates immunoreactive somatostatin release from the isolated perfused dog pancreas.[16] Thus, the secretory products of each of the three cell types can influence the secretion of one or more of the nearby cell types. The recently reported arginine-induced stimulation of somatostatin release from the isolated perfused dog pancreas[17] could, at least in part, be mediated by local glucagon release and, in turn, influence the magnitude of the secretory responses of its neighboring cells.

The direct paracrine peptide-cell relationships depicted in figure 1 (left lower panel) are, therefore, theoretically possible. By virtue of their unique location in juxtaposition to both B- and D-cells, the A-cells of the normal islet may be under the restraining influence of insulin and of somatostatin released in response to a rise in local glucagon concentration. Additionally, glucagon-mediated somatostatin release may serve to reduce glucagon-stimulated insulin secretion (figure 1, left lower panel), thus preventing an outpouring of insulin and hypoglycemia during aminogenic stimulation of glucagon secretion. By modulating both insulin and glucagon secretion, the D-cell may influence their relative concentrations in pancreatic effluent.

ABNORMAL PARACRINE RELATIONSHIPS IN DIABETES

Pancreatic A-cell function is abnormal in diabetes mellitus.[18-20] Plasma glucagon levels are elevated despite hyperglycemia,[18,19] rise paradoxically following an oral glucose load,[21] and respond excessively to arginine[18] and to a protein meal.[22] Such abnormalities could well reflect loss of the restraining influence on the A-cell exerted by insulin and/or somatostatin released from neighboring B- and D-cells.

Cellular relationships in hypoinsulinemic diabetes. In the hypoinsulinemic forms of diabetes, such as juvenile-type diabetes of man,[1] severe streptozotocin diabetes in rats,[1] and spontaneous diabetes of mice (db/db on a BL/Ks background),[23] morphometric analyses of islets have demonstrated an excess of A-cells and D-cells coupled with an absence or striking reduction in B-cells (figure 1, upper center panel). It can be assumed that in such forms of diabetes insulin is absent or low in the intercellular spaces surrounding the numerous A-cells. While there is an increase in somatostatin-containing cells in such islets,[1,2,23] distortion of normal intercellular relationships could leave many A-cells without direct D-cell contacts. However, the most striking abnormality is lack of B-cells, and the major deficit in these forms of diabetes would seem to be within-islet insulin, as postulated by Weir et al.[24] (figure 1, lower center panel). It is noteworthy, therefore, that in human

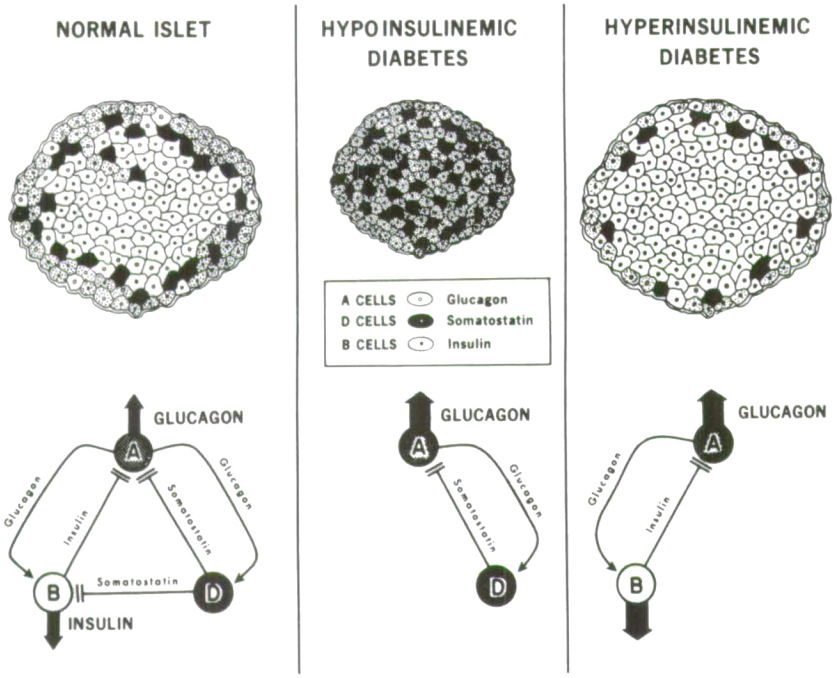

FIGURE 1

Upper panels—The topographic relationships of A-, D-, and B-cells in the normal islet, the islet of hypoinsulinemic diabetes, and the islet of hyperinsulinemic diabetes (see text). Lower panels—Schematization of possible paracrine relationships of the three secretory products of these cells—glucagon, somatostatin, and insulin—on the secretory activity of adjacent cells in the normal state, in hypoinsulinemic diabetes, and in hyperinsulinemic diabetes. An endocrine role for somatostatin, though not depicted here, cannot be excluded as a possibility.

juvenile-type diabetics the manifestations of unrestrained A-cell activity are correctable by insulin in doses[25-27] that are supraphysiologic in terms of plasma levels of insulin but not in terms of the concentrations of insulin presumably present in the intercellular spaces of the nondiabetic islet.

Cellular relationships in hyperinsulinemic diabetes. At the opposite end of the diabetic spectrum is the hyperinsulinemic form of diabetes, also characterized by unrestrained secretory activity of A-cells. Although the cellular composition of the islets of hyperinsulinemic diabetics has yet to be studied in man, morphometric analyses of the islets of hyperinsulinemic diabetic mice carrying the db or ob gene on a BL/6J background reveal a striking abundance of B-cells and a reduction in the number of D-cells.[23] In hyperinsulinemic diabetes, A-cells have ample contact with insulin-secreting cells but lack sufficient contacts with somatostatin-secreting cells (figure 1, right lower panel). In this form of diabetes the exaggerated glucagon response to arginine, which normally elicits a release of pancreatic somatostatin,[17] might be a consequence of inadequate local somatostatin release despite the insulin abundance. Indeed, in such patients the administration of supraphysiologic doses of insulin fails to improve their exaggerated response to arginine,[22] in sharp contrast to its effectiveness in hypoinsulinemic diabetes. Moreover, the excessive insulin responses in the hyperinsulinemic form of diabetes might also be, in part, the consequence of the dearth of somatostatin-producing cells in contact with B-cells.

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REFERENCES

[1]Orci, L., Baetens, D., Rufener, C., Amherdt, M., Ravazzola, M., Studer, P., Malaisse-Lagae, F., and Unger, R. H.: Hypertrophy and hyperplasia of somatostatin-containing D-cells in diabetes. Proc. Natl. Acad. Sci. USA *73*:1338-42, 1976.

[2]Orci, L., and Unger, R. H.: Hypothesis: Functional subdivisions of islets of Langerhans and possible role of D-cells. Lancet *2*:1243-44, 1975.

[3]Samols, E., Marri, G., and Marks, V.: Promotion of insulin secretion by glucagon. Lancet *2*:415, 1965.

[4]Samols, E., and Harrison, J.: Intraislet negative insulin/glucagon feedback. Metabolism *25* (Suppl.):1443-47, 1976.

[5]Samols, E., Tyler, J. M., and Marks, V.: Glucagon-insulin interrelationships. *In* Glucagon. Molecular Physiology, Clinical and Therapeutic Implications. Lefebvre, P. J., and Unger, R. H., Eds. Amsterdam, Pergamon Press, 1972, p. 151.

[6]Brazeau, P., Vale, W., Burgus, R., Ling, N., Butcher, M., Rivier, J., and Guillemin, R.: Hypothalamic polypeptide that inhibits the secretion of immunoreactive growth hormone. Science *179*:77-79, 1973.

[7]Alberti, K. G. M. M., Christensen, N. J., Christensen, S. E., Hansen, A. P., Iversen, J., Lundbaek, K., Seyer-Hansen, K., and Orskov, H.: Inhibition of insulin secretion by somatostatin. Lancet *2*:1299-1301, 1973.

[8]Koerker, D. J., Ruch, W., Chideckel, E., Palmer, J., Goodner, C. J., Ensinck, J., and Gale, C. C.: Somatostatin: Hypothalamic inhibitor of the endocrine pancreas. Science *184*:482-83, 1974.

[9]Mortimer, C. H., Turnbridge, W. M. G., Carr, D., Yeomans, L., Lind, T., Coy, D. H., Bloom, S. R., Kastin, A., Mallinson, C. N., Besser, G. M., Schally, A. V., and Hall, R.: Effects of growth hormone release-inhibiting hormone on circulating glucagon, insulin, and growth hormone in normal, diabetic, acromegalic, and hypopituitary patients. Lancet *1*:697-701, 1974.

[10]Luft, R., Efendic, S., Hokfelt, T., Johansson, O., and Arimura, A.: Immunohistochemical evidence for the localization of somatostatin-like immunoreactivity in a cell population of the pancreatic islets. Med. Biol. *52*:428-30, 1974.

[11]Dubois, M. P.: Immunoreactive somatostatin is present in discrete cells of the endocrine pancreas. Proc. Natl. Acad. Sci. USA *72*:1340-43, 1975.

[12]Arimura, A., Sato, H., Dupont, A., Nishi, N., and Schally, A. V.: Somatostatin: Abundance of immunoreactive hormone in rat stomach and pancreas. Science *189*:1007-09, 1975.

[13]Orci, L., Baetens, D., Dubois, M. P., and Rufener, C.: Evidence for the D-cell of the pancreas secreting somatostatin. Horm. Metab. Res. *7*:400-02, 1975.

[14]Polak, J. M., Pearse, A. G. E., Grimelius, L., Bloom, S. R., and Arimura, A.: Growth hormone release-inhibiting hormone in gastrointestinal and pancreatic D-cells. Lancet *1*:1220-22, 1975.

[15]Pelletier, G., Leclerc, R., Arimura, A., and Schally, A. V.: Immunohistochemical localization of somatostatin in the rat pancreas. J. Histochem. Cytochem. *23*:699-701, 1975.

[16]Patton, G., Dobbs, R., Orci, L., Vale, W., and Unger, R. H.: Stimulation of pancreatic immunoreactive somatostatin (IRS) release by glucagon. Metabolism *25*(Suppl.):1499, 1976.

[17]Patton, G., Ipp, E., Dobbs, R. E., Orci, L., Vale, W., and Unger, R. H.: Response of pancreatic immunoreactive somatostatin to arginine. Life Sci. *19*:1957-60, 1976.

[18]Unger, R. H., Aguilar-Parada, E., Müller, W. A., and Eisentraut, A. M.: Studies of pancreatic alpha cell function in normal and diabetic subjects. J. Clin. Invest. *49*:837-48, 1970.

[19]Müller, W. A., Faloona, G. R., Unger, R. H., and Aguilar-Parada, E.: Abnormal alpha cell function in diabetes: Response to carbohydrate and protein ingestion. N. Engl. J. Med. *283*:109-15, 1970.

[20]Müller, W. A., Faloona, G. R., and Unger, R. H.: The effect of experimental insulin deficiency on glucagon secretion. J. Clin. Invest. *50*:1992-99, 1971.

[21]Buchanan, K. D., and McCarroll, A.M.: Abnormalities of glucagon metabolism in untreated diabetes mellitus. Lancet *2*:1394-95, 1972.

[22]Raskin, P., Aydin, I., and Unger, R. H.: The effect of

insulin on the exaggerated glucagon response to arginine stimulation in diabetes mellitus. Diabetes *25*:227-29, 1976.

[23]Baetens, D., Coleman, D. L., and Orci, L.: Islet cell population in ob/ob and db/db mice. Diabetes *25*:344, 1976.

[24]Weir, G. C., Knowlton, S. S., Atkins, R. F., McKennan, K. X., and Martin, D. B.: Glucagon secretion from the perfused pancreas of streptozotocin-treated rats. Diabetes *25*:275-82, 1976.

[25]Raskin, P., Fujita, Y., and Unger, R. H.: Effect of insulin-glucose infusions on plasma glucagon levels in fasting diabetics and nondiabetics. J. Clin. Invest. *56*:1132-38, 1975.

[26]Gerich, J. E., Tsalikian, E., Lorenzi, M., Schneider, V., Bohannon, N. V., Gustafson, G., and Karam, J. H.: Normalization of fasting hyperglucagonemia and excessive glucagon responses to intravenous arginine in human diabetes mellitus by prolonged infusion of insulin. J. Clin. Endocrinol. Metab. *41*:1178-80, 1975.

[27]Aydin, I., Raskin, P., and Unger, R. H.: Role of insulin lack in the abnormal glucagon (IRG) response in human diabetes. Clin. Res. *25*:31A (abstr.), 1977.