PHYSIOLOGICAL ROLE OF PANCREATIC D CELLS (A MATHEMATICAL STUDY)

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The structure of the islets of Langerhans (IL) [13] and the presence of receptors for insulin, glucagon, and somatostatin on membranes of the islet cells [4, 14] are responsible for communication between A, B, and D cells within the islets. The ability of somatostatin to inhibit the secretion of insulin and glucagon is widely known [9, 14]. The D cells producing this hormone account for 5-15% of the total number of islet cells and they are located mainly between B and A cells [14]. The physiological role of pancreatic somatostatin is not absolutely clear [2]. Meanwhile an understanding of that role would provide the key to elucidation of the principles of function of the A-B-D-cell complex of IL as a biosystem.

The aim of this investigation was to study the role of pancreatic D cells by the use of a mathematical model.

EXPERIMENTAL METHOD

The mathematical model of functioning of pancreatic A-, B-, and D-cells is a system of six nonlinear first-order differential equations. The variables in the model are: the quantity of insulin, glucagon, and somatostatin secreted by each B, A, and D cell respectively; the concentrations of insulin, glucagon, and somatostatin in the intercellular space. The parameters of the model are: the number of A, B, and D cells and the glucose concentration in the intercellular fluid in the islet.

A detailed description of the mathematical model of functioning of IL was published previously [1, 3]. The works cited also contained data showing that the mathematical model is qualitatively adequate with respect to its biological prototype. No attempt was made at quantitative correlation of the data of the mathematical model with the results of experimental investigations in vitro and in vivo. The reason for this approach is that solution of the quantitative problem could not give any additional information essential for a fundamental understanding of the processes studied, and at the same time, it would be dependent on the surmounting of great technical difficulties.

The computer experiment simulated incubation of normal and somatostatin-deficient IL in solutions containing different concentrations of glucose. In the case of normal IL the ratio of A, B, and D cells was 20:70:10 [7]. In the case of somatostatin-deficient islets the number of A and B cells remained normal whereas the number of D cells was zero. In the course of each computer experiment, total insulin and glucagon secretion by IL was studied during time T in the presence of a fixed glucose concentration. Throughout the series of experiments the glucose concentration was varied from 0 to 4.5 conventional units (CU) with a step of 0.1 CU.

EXPERIMENTAL RESULTS

The data on insulin secretion by normal and somatostatin-deficient IL in the presence of different glucose concentrations are given. Somatostatin-deficient IL are characterized by higher insulin secretion in response to the glucose stimulus. Differences in the insulin-producing activity of normal and somatostatin-deficient islets depend on the glucose concentration. They are very small when the glucose level in the intercellular fluid is low. Rais-

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ing the glucose concentration leads to a gradual diminution of differences in insulin secretion by the two types of islets, and when the glucose level is 4.3 CU, somatostatin-deficient and normal IL secrete the maximal possible, and equal, amounts of insulin.

The results obtained by computer are analogous with those of an investigation by Taniguchi et al. [10], who used antisomatostatin antiserum in an experiment with real IL. They are also in good agreement with the hypothesis that D cells have a moderating influence on B cells, leading to more economical secretion of insulin in response to the glucose stimulus [6].

The phenomenon that the degree of the influence of D cells on B cells is determined by the glucose level can evidently be explained as follows. The secretory activity of both B and D cells is stimulated by glucose [5, 8, 9], However, half the maximal secretion of somatostatin is reached at lower blood glucose levels than half the maximal insulin secretion [3, 8]. Consequently, the possibility of counteracting the inhibitory effect of somatostatin on B cells with the stimulating effect of glucose on them is greatest when concentrations of the latter are low. As the glucose level in the intercellular space rises, the real effect of somatostatin decreases and gradually disappears.

Data are given on glucagon secretion by normal and somatostatin-deficient IL in the presence of different concentrations of glucose. Glucagon secretion by somatostatin-deficient IL exceeds its secretion by normal islets. The experiment thus showed that pancreatic somatostatin has a moderating influence not only on B cells, but also on A cells.

Unlike insulin secretion, to which the absence of D cells is connected only quantitatively glucagon secretion in the case of somatostatin-deficient IL undergoes both quantitative and qualitative changes.

Under normal conditions, with an increase in the glucose concentration from 0.5 to 1.5 CU, glucagon secretion fell. In the analogous situation somatostatin-deficient IL increased glucagon secretion. A further increase in the glucose concentration led to reduction of glucagon secretion both by normal and by somatostatin-deficient islets. Under normal conditions, however, this phenomenon was due to the inhibitory effect of somatostatin and insulin, whereas in the case of somatostatin-deficient islets a different mechanism was involved. The effect of inhibition of glucagon secretion by glucagon already secreted now began to exert a significant influence [1].

Increased glucagon secretion in response to an increase in the glucose concentration is known to be a characteristic hormonal response in diabetes [1, 3, 13]. The results of the present experiments can be regarded as confirmation of the hypothesis of a possible connection between some cases of diabetes mellitus and D-cell deficiency [13].

Differences in glucagon secretion by normal and by somatostatin-deficient IL can be explained on the grounds that the secretory activity of the A cells is inhibited both by insulin [13] and by somatostatin [9, 13]. Synergism of the effect of these two hormones on A cells [1], moreover, is reflected by a greater degree on IL function, the higher the glucose concentration.

It may be that the mechanism recently described by Veld and co-workers [15] may also lead to potentiation of the inhibitory effect of insulin and somatostatin on A cells in real IL. These workers showed that the number of polygonal forms of subunits of gap junctions between the cells, on which the degree of coupling between the function of islet cells evidently depends, changes directly proportionally to the glucose concentration [15].

The results of the present investigation show that D cells become, as it were, temporary allies of both B and A cells, depending on which hormone of the pancreatic islets, insulin or glucagon, is more essential to the body at that particular time. In the presence of low levels of glucose, they inhibit glucagon secretion only slightly, while significantly depressing the secretory activity of the B cells, i.e., they help to lower the insulin/glucagon ratio and, consequently, stimulate mobilization of biological fuel from the depots [11]. In the presence of high glucose concentrations, the inhibitory effect of D cells on the A cells is significant, whereas their inhibitory effect on B cells is relatively weak or absent. As a result of this the insulin/glucagon ratio is increased, and this is a signal for storage of biological fuel in the depots [11, 12].

The ratio between insulin and glucagon produced by normal and somatostatin-deficient islets was shown to be dependent on the glucose concentration, and the response of somatostatin-deficient islets to glucose was not only ineffective, but was indeed illogical from the point of view of the storage and mobilization of biological fuel. For instance, at the maximal

glucose level of 4.5 CU the insulin/glucagon ratio was only 4.8, whereas when the glucose concentration was much lower (0.6 CU) the ratio was 9.37. Under normal conditions the insulin/glucagon ratio increases with an increase in the glucose concentration.

The computer experiment thus showed that D-cell deficiency leads to quantitative and qualitative disturbances in IL function. As a result of these disturbances the IL are no longer able to carry out effective hormonal regulation of the functions of storage and mobilization of biological fuel. The D cells apparently coordinate functional activity of the A and B cells, and endow IL with some degree of inertia, which contributes to the maintenance of a high degree of resistance of the islets.

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