THE PANCREATIC B-CELL AS A VOLTAGE-CONTROLLED OSCILLATOR.

J.V. Sánchez-Andrés and B. Soria.

Dept. de Fisiología. Instituto de Neurociencias. Univ. Alicante. Aptdo. 374, 03080 Alicante. Spain. Phone: (346) 565 98 11; Fax: (346) 565 85 39; E-mail: andres@EALIUN11

ABSTRACT

We recorded the intracellular activity of pancreatic B-cells. The B-cells are the biological elements of the glucose control system. The action of glucose on the pancreatic B-cells take place in a two step fashion: 1) concentrations lower than 6 mM glucose induces a progressive depolarization, 2) for higher concentrations the cells start to oscillate. This oscillation develops between two levels of potential that remain stable independently of the glucose concentration. The effect of increased glucose concentrations is transduced in terms of modulation of frequency of the oscillations rather than in a sustained depolarization. We stress the analogies between this control system and a voltage-controlled oscillator fed by a comparator.

1. INTRODUCTION.

The absorption of glucose by the majority of the tissues in the organisms is controlled by the hormone insulin. These tissues use glucose or other metabolites as a function of the insulin levels in blood. The more remarkable exception is the nervous tissue: glucose penetrates inside the neurons with independence of insulin. Additionally, neurons are unable to use other substrates apart from glucose as metabolic substrates. The abnormalities in these parameters produce the diabetes when chronically installed, and hypo- and hyper-glycemic commas when installed acutely. The deleterious consequences of the last syndromes over the brain come from the deviations of the glucose levels far away of the physiological levels (for a review see ref. 5).

Insulin is produced in the endocrine pancreas, consisting of several thousands groups of cells called islands of Langerhans distributed inside the exocrine pancreas (Fig 1A). Each island contains 2-3000 cells, 80% out of them are insulin-secretors (B-cells) (Fig 1B). Pancreatic B-cells are equipped with a series of specific membrane channels which have now been well-defined in microelectrode and patch-clamp studies. So far, a Na⁺ channel, two types of voltage-activated Ca²⁺ channels, referred to as fast and slowly inactivating, three types of K⁺ channels, referred to as ATP-sensitive, Ca²⁺ activated and delayed rectifier, and a voltage independent but glucose sensitive Ca²⁺ channel have been identified in normal B-cells (14). These channels provide the basis for the excitatory behavior of the B-cells. On the other hand, the same type of channels have been described in neurons, underlying the same functions. Under this scope the pancreatic B-cells turns out to be a potentially interesting cell model for neuronal simulations as far as: a) they are endowed with sets of channels, very like regular neurons, but b) they lack the geometrical complexity provided by the
dendritic and axonal branching. The glucose sensitivity is coupled to the electrical pattern and to the insulin secretion process through a chain of metabolic biophysics steps. Briefly, when a resting pancreatic B-cell is challenged with glucose (or other metabolic substrate), the sugar interacts with a tissue-specific glucose transporter, enters the cell and is rapidly phosphorylated. The ATP generated by glucose metabolism blocks the $K^+$ channel controlling resting membrane potential. As these channels close, the cells depolarize, causing the opening of voltage-activated $Ca^{2+}$ channels, which, in turn, lead to $Ca^{2+}$ entry. The increased intracellular calcium concentration triggers insulin release (9, 15), which stimulates glucose absorption by tissues, then, reducing blood glucose concentration. The whole process constitutes a loop of negative feed-back, permitting the control of the blood glucose concentration (Fig. 3).

Islands of Langerhans constitute an unique example of electrically and metabolically coupled network. As a system they show several prominent properties: a) B-cells into an island constitute an heterogeneous population coupled through gap-junctions, b) they are able to respond with an oscillatory pattern in given experimental conditions (1), and c) the electrical pattern is synchronic for every cell into an islet (4).

Although there are evidences supporting that the whole islet works as a functional unit or "syncithium", studies with isolated B-cells have shown a high degree of heterogeneity with respect to insulin biosynthesis (10), glucose-induced intracellular calcium ($[Ca^{2+}]_i$) changes (12) and insulin release (11). We have recently shown that, at intermediate glucose concentrations (7-16 mM), $[Ca^{2+}]_i$ measured in single islets undergo oscillations which are due to glucose-induced bursting of electrical activity (13, 9) indicating that the whole islet is simultaneously active. Despite their heterogeneous responses to glucose the whole population of B-cells has the ionic mechanisms that lead to a rise of $[Ca^{2+}]$: when ATP-regulated $K^+$ channels are blocked (14). Under the framework of a coupled tissue, cell-to-cell differences have attenuated functional consequences (13). B-cells grouped in island of Langerhans constitute an unique example of paraneural network in which electrical and metabolic coupling through gap junctions permits to build homogeneous responses from an heterogeneous population of cells. On the other hand, the islands of Langerhans have a rich inervation that provides the possibility of a precise regulation from the nervous system (7, 8).

The aim of this paper is to show the parallelism between the functionality of an island of Langerhans and a voltage-controlled oscillator (VCO).