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Abstracts

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THE INFLUENCE OF CELL NUMBER ON Ca^{2+} OSCILLATIONS IN CLUSTERS OF β CELLS

F.C. Jonkers, P. Gilon and J.C. Henquin. Unité d'Endocrinologie et Métabolisme, University of Louvain, Brussels, Belgium.

During continuous stimulation with glucose, intact islets display regular oscillations of cytosolic $[\text{Ca}^{2+}]_i$, whereas the oscillations are inconsistent and variable in single β cells. Here, we tested the hypothesis that a minimum number of β cells must be coupled for appearance of regular oscillations. Normal mouse islets were dispersed into single cells and clusters of different sizes, and cultured for 1-4 days. $[\text{Ca}^{2+}]_i$ was then measured by the fura-2 technique during continuous stimulation with 15 mmol/l glucose. One third of single cells were unresponsive. In responsive cells, $[\text{Ca}^{2+}]_i$ oscillations had a mean frequency of 0.16/min, and were variable in amplitude and duration. 90% of cell doublets showed oscillations of greater regularity but still low frequency (0.20/min). In small (3-5 cells) or large (up to 50 cells) clusters, all cells showed $[\text{Ca}^{2+}]_i$ responses, usually characterized by regular oscillations. However, the frequency plateaued at ~0.25/min. Mean $[\text{Ca}^{2+}]_i$ did not increase with the cluster size. Extending the culture from 1 to 4 days did not affect the characteristics of the response in single cells, but caused appearance of sustained rises in $[\text{Ca}^{2+}]_i$ in 20% of the clusters. In cell doublets, both regular and irregular oscillations of $[\text{Ca}^{2+}]_i$ were synchronous in the two cells. In larger clusters, both adjacent and non-adjacent cells displayed synchronous $[\text{Ca}^{2+}]_i$ changes. In no cluster could an irregular or sustained elevation of $[\text{Ca}^{2+}]_i$ be ascribed to asynchronous responses in different cells. In conclusion, the heterogeneity of glucose-induced $[\text{Ca}^{2+}]_i$ changes in single β cells disappears when the cells form small clusters. However, an increase in cluster size hardly affects the frequency of the oscillations, which is similar to that of the slow oscillations present in intact islets.

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PARTIAL INHIBITION OF THE Na/K PUMP UNMASKS Na^+ OSCILLATIONS IN GLUCOSE-STIMULATED PANCREATIC β -CELLS
E. Grapengiesser. Department of Medical Cell Biology, Uppsala University, Sweden.

The importance of the Na/K pump for the cytoplasmic concentration of Na^+ ($[\text{Na}^+]_i$) in glucose-stimulated mouse β -cells was analyzed using dual-wavelength microfluorometry and the indicator SBFI. Under conditions known to induce large-amplitude oscillations of cytoplasmic Ca^{2+} (11 mmol/l glucose) $[\text{Na}^+]_i$ usually remained low and stable at 10-14 mmol/l. Partial suppression of the Na/K pump with 50 $\mu\text{mol/l}$ ouabain resulted in oscillations of $[\text{Na}^+]_i$ in 65% of the cells (frequency $0.13 \pm 0.01 \text{ min}^{-1}$; amplitudes $4.4 \pm 0.3 \text{ mmol/l}$). The oscillations were unaffected by the presence of tetrodotoxin but disappeared when the medium was depleted of Ca^{2+} or supplemented with methoxyverapamil. The analysis of the ouabain effect was facilitated by replacing extracellular Ca^{2+} with 5 mmol/l Sr^{2+} . In the Sr^{2+} -containing medium oscillations of $[\text{Na}^+]_i$ were seen in > 70 % of the β -cells exposed to 11 mmol/l glucose. Ouabain (50 $\mu\text{mol/l}$) modified these oscillations by increasing their amplitudes almost threefold and reducing the frequency from once every 3 min to once every 10 min. A relationship between oscillations of cytoplasmic Sr^{2+} and Na^+ was apparent both from observations of similar frequencies and for the modifications obtained with ouabain. It is concluded that the glucose-induced oscillations of cytoplasmic Ca^{2+} result in a rhythmic entry of Na^+ usually balanced by the Na/K pump.

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PROTEIN KINASE A AS DETERMINANT FOR SLOW AND FAST Ca^{2+} OSCILLATIONS IN β -CELLS AND PANCREATIC ISLETS

E. Gylfe and Y.J. Liu. Dept. of Medical Cell Biology, Uppsala University, Sweden

Pancreatic β -cell and islets of Langerhans commonly respond to 11 mM glucose with slow oscillations ($0.3\text{-}0.9 \text{ min}^{-1}$) of the cytoplasmic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$). In islets a regular fast pattern ($2\text{-}7 \text{ min}^{-1}$) is often superimposed on the slow oscillations. Agents increasing cAMP promote the fast islet pattern and also induce less regular fast $[\text{Ca}^{2+}]_i$ oscillations and pronounced $[\text{Ca}^{2+}]_i$ spiking in the individual β -cells. We have now tested the effect of the protein kinase A inhibitor Rp-cAMPs on oscillatory Ca^{2+} signalling. Rp-cAMPs was found to inhibit the fast oscillations in islets transforming the mixed oscillatory pattern into a slow one. However, at high concentrations Rp-cAMPs also suppressed the slow oscillations. Since such an effect may be due loss of cell coordination after inhibition of gap-junctional coupling we tested the effects of Rp-cAMPs on individual β -cells. It was found that the individual β -cells sometimes reacted to high concentrations of Rp-cAMPs with attenuation of the slow oscillations. The data indicate that the disappearance of the fast oscillatory signalling in islets is due to inhibition of intracellular Ca^{2+} release after desensitization of inositol 1,4,5-trisphosphate receptors. Further studies will have to clarify if the attenuation of the slow oscillations in individual cells represents an effect on the voltage-dependent Ca^{2+} channels *per se* or on determinants of the membrane potential.

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ROLE OF VOLTAGE-DEPENDENT Na^+ CHANNELS FOR RHYTHMIC Ca^{2+} SIGNALLING IN GLUCOSE-STIMULATED PANCREATIC β -CELLS.

M. Eberhardsson, E. Grapengiesser. Dept. of Medical Cell Biology, Uppsala University, Sweden

The role of voltage-dependent Na^+ channels for glucose induction of rhythmic Ca^{2+} signalling was studied in mouse pancreatic β -cells using dual wavelength fluorometry and the indicator fura-2. A rise of glucose from 3 to 11 mmol/l induced slow oscillations ($0.2\text{-}0.5 \text{ min}^{-1}$) of the cytoplasmic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$), which persisted when adding the Na^+ channel blocker tetrodotoxin. However, in the presence of the Na^+ channel agonist veratridine (1-10 $\mu\text{mol/l}$), the glucose-induced oscillations were replaced by repetitive and pronounced transients of $[\text{Ca}^{2+}]_i$ ($1.7\text{-}3.5 \text{ min}^{-1}$) arising from the basal level. This effect of veratridine was reversed by tetrodotoxin. The $[\text{Ca}^{2+}]_i$ transients obtained in the presence of veratridine were amplified by increasing extracellular Ca^{2+} and disappeared in Ca^{2+} -deficient medium or when blocking the voltage-dependent Ca^{2+} channels by methoxyverapamil. The intracellular Ca^{2+} -ATPase inhibitor thapsigargin caused a slight amplification of the transients. When the β -cells were depolarized with 100 $\mu\text{mol/l}$ tolbutamide or 10 mmol/l ketosacproate, veratridine induced transients of $[\text{Ca}^{2+}]_i$ similar to those obtained in glucose-stimulated cells but failed to do so in β -cells depolarized with 100 $\mu\text{mol/l}$ quinine or 30 mmol/l K^+ . The results indicate that the Ca^{2+} oscillations normally observed in glucose-stimulated β -cells occur without involvement of voltage-dependent Na^+ channels. However, the activation of such channels might represent a useful approach in the development of drugs promoting insulin secretion.