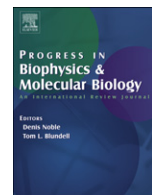
Progress in Biophysics and Molecular Biology 107 (2011) 224–235

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio



Review

Electrophysiology of pancreatic β-cells in intact mouse islets of Langerhans

Patrik Rorsman [a,b,*], Lena Eliasson [c], Takahiro Kanno [d], Quan Zhang [a,b], Sven Gopel [e]

[a] Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford OX3 7LJ, UK
[b] Alberta Diabetes Institute, 5-126B LKS Centre, University of Alberta, Edmonton, AB T6G 2E1, Canada
[c] Lund University Diabetes Centre, Clinical Research Center, 205 02 Malmö, Sweden
[d] Department of Blood Transfusion and Transplantation Immunology, School of Medicine, Fukushima Medical University, 1 Hikariga-oka, Fukushima 960-1295, Japan
[e] AstraZeneca R&D, Pepparedsleden 1, 43183 Mölndal, Sweden

ARTICLE INFO

Article history:
Available online 6 July 2011

Keywords:
Pancreas
Beta-cell
Insulin
Ion channels
Glucose
Electrical activity

ABSTRACT

When exposed to intermediate glucose concentrations (6–16 mol/l), pancreatic β-cells in intact islets generate bursts of action potentials (superimposed on depolarised plateaux) separated by repolarised electrically silent intervals. First described more than 40 years ago, these oscillations have continued to intrigue β-cell electrophysiologists. To date, most studies of β-cell ion channels have been performed on isolated cells maintained in tissue culture (that do not burst). Here we will review the electrophysiological properties of β-cells in intact, freshly isolated, mouse pancreatic islets. We will consider the role of ATP-regulated K^+-channels (K_{ATP}-channels), small-conductance Ca^{2+}-activated K^+-channels and voltage-gated Ca^{2+}-channels in the generation of the bursts. Our data indicate that K_{ATP}-channels not only constitute the glucose-regulated resting conductance in the β-cell but also provide a variable K^+-conductance that influence the duration of the bursts of action potentials and the silent intervals. We show that inactivation of the voltage-gated Ca^{2+}-current is negligible at voltages corresponding to the plateau potential and consequently unlikely to play a major role in the termination of the burst. Finally, we propose a model for glucose-induced β-cell electrical activity based on observations made in intact pancreatic islets.

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Contents

1. Introduction 225
2. Methodological considerations: single-cell vs. whole-islet studies 226
3. Results 226
 3.1. The K_{ATP}-channel: the resting glucose-dependent conductance of the β-cell 226
 3.2. Reactivation of glucose-inhibited K_{ATP}-channels by electrical activity 227
 3.3. Spontaneous oscillations of K_{ATP}-channel activity 227
 3.4. A depolarizing cation-dependent inward current 228
 3.5. β-cell Ca^{2+}-current in intact islets: activation, inactivation and reactivation 229
  3.5.1. Biphasic inactivation of β-cell Ca^{2+}-current 229
  3.5.2. Time-dependent recovery of the β-cell Ca^{2+}-current from inactivation 230
  3.5.3. Ca^{2+}-dependent and -independent inactivation of β-cell Ca^{2+}-current 230
 3.6. Voltage-gated K^+-currents 230
 3.7. Role of voltage-gated Na^+-currents in mouse β-cells 231

Abbreviations: BK, large-conductance Ca^{2+}-activated K^+-channel; GΩ, giga-ohm; I, membrane current; IC_{50}, concentration producing half-maximal inhibition; K_{ATP}, ATP-sensitive K^+-channel; K_{slow}, slowly developing K^+-current evoked by electrical activity; Kv2.1, voltage-dependent K^+-channel (Shab-related subfamily, member 1); mV, millivolt; nA, nanoampere; nS, nanosiemens; pA, picoampere; pS, picosiemens; SK3, small-conductance Ca^{2+}-activated K^+-channel, subtype 3 (K_{Ca}2.3); SUR1, sulphonylurea receptor subtype 1 (K_{ATP}-channel subunit); V_h, voltage at which inactivation is half-maximal; V_r, reversal potential; Trp, transient receptor potential; τ, time constant (tau); TEA, tetraethylammonium.

* Corresponding author. Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK.
E-mail addresses: patrik.rorsman@drl.ox.ac.uk (P. Rorsman), lena.eliasson@med.lu.se (L. Eliasson), btkanno@fmu.ac.jp (T. Kanno), quan.zhang@drl.ox.ac.uk (Q. Zhang), sven.gopel@astrazeneca.com (S. Gopel).

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doi:10.1016/j.pbiomolbio.2011.06.009

4. General discussion ... 231
4.1. Role of Ca^{2+}-channel inactivation in β-cell electrical activity ... 231
4.2. K_{ATP}-channels: more than a stable resting conductance? ... 233
4.3. A model for glucose-induced β-cell electrical activity ... 233
Acknowledgements ... 234
References ... 234

1. Introduction

The insulin-secreting β-cells play a central role in systemic glucose homeostasis. Insulin secretion depends on the initiation of electrical activity in the β-cells (Henquin and Meissner, 1984). Patch-clamp analyses have revealed that the β-cell contains several types of ion channel (Ashcroft and Rorsman, 1989). It is well established that the ATP-sensitive K^+-channels represent the glucose-sensitive conductance of the β-cell. The K_{ATP}-channels are spontaneously active at low glucose and efflux of positively charged K^+ through these channels generates an excess of negative charges inside the β-cell and thereby accounts for the negative membrane potential of the unstimulated β-cell.

Glucose produces a concentration-dependent inhibition of K_{ATP}-channel activity with an IC_{50} of 2–3 mmol/l in isolated β-cells (Ashcroft et al., 1988; Ashcroft and Rorsman, 1989). At a glucose concentration of 5 mmol/l, the glucose concentration in a fasted mouse, channel activity is reduced by ~90% but the remaining <10% of channel activity (<0.5 nS at the whole-cell level) is sufficient to keep the β-cell sufficiently repolarised to prevent action potential firing (Smith et al., 1990a). When glucose is elevated to 8–10 mmol/l, close to the plasma glucose concentration in fed mice, K_{ATP}-channel activity is completely suppressed. This leads to membrane depolarization to the threshold for action potential firing (between −60 and −50 mV). Over the physiological range of glucose concentrations, this electrical activity consists of oscillations in membrane potential between depolarised plateaux (lasting ~10 s), on which bursts of action potentials are superimposed, separated by repolarised electrically silent intervals (Cook et al., 1991). With increasing glucose concentrations there is a progressive increase in the relative duration of the active phase at the expense of the silent intervals until continuous action potential firing occurs at glucose concentrations above 20 mmol/l (Henquin and Meissner, 1984).

The depolarizing phase of the β-cell action potential depends on voltage-gated Ca^{2+}-channels (Rorsman and Trube, 1986; Satin and Cook, 1985). Mouse β-cell expresses at least three types of voltage-gated Ca^{2+}-channel (L-, R- and P/Q-type). L-type Ca^{2+}-channels account for >60% of the whole-cell Ca^{2+}-current (Schulla et al., 2003). Somewhat surprisingly, pharmacological blockade of L-type Ca^{2+}-channels with nifedipine only transiently suppresses action potential firing (Rosario et al., 1993; Vasseur et al., 1987). The relatively weak effect on electrical activity contrasts with the strong suppression of glucose-induced insulin secretion (Gopel et al., 2004; Schulla et al., 2003). This dichotomy between electrical activity and insulin secretion may reflect the important role of L-type Ca^{2+}-channels in rapid (action potential-dependent) exocytosis (Barg et al., 2001; Wiser et al., 1999). R-type Ca^{2+}-channels account for ~20% of the β-cell Ca^{2+}-current. They have, based on observations made in Cav2.3$^{-/-}$ (R-type) knockout mice, been proposed to play a role in 2nd phase insulin secretion (Jing et al., 2005); possibly by producing the global increase in $[Ca^{2+}]_i$ required for refilling of the readily releasable pool of granules. The P/Q-type and N-type Ca^{2+}-channels account for only ~10% (Schulla et al., 2003) of the β-cell whole-cell Ca^{2+}-current. The significance of these channels in mouse β-cells (if any) remains obscure but in human β-cells Ca^{2+}-entry via P/Q-type channels plays a central role in depolarization-evoked exocytosis (Braun et al., 2008).

Action potential repolarization depends on activation of a delayed outward K^+-current. The initial experiments suggested in reflected the activation of delayed rectifying K^+-channels with a conductance of ~10 pS (Rorsman and Trube, 1986; Smith et al., 1990b). At the molecular level, the delayed rectifying K^+-channels present in mouse β-cells are of the Kv2.1 subtype (MacDonald et al., 2002). Electrical activity in β-cells from Kv2.1-deficient mice (Kv2.1$^{-/-}$) resembles that of wildtype β-cells in the presence of the selective Kv2.1 blocker stromatoxin (Jacobson et al., 2007). However, a stromatoxin-resistant and Kv2.1-independent current is also present in mouse β-cells. This residual current, which is sufficient to repolarise the β-cell action potential, was later identified to flow through large-conductance Ca^{2+}-activated K^+-channels (BK-channels) (Houamed et al., 2010; Jacobson et al., 2010). A rapidly activating transient outward K^+-current component dependent on Ca^{2+}-entry was in fact first described in mouse β-cells more than 20 years ago (Satin et al., 1989; Smith et al., 1990b) but its significance was not fully appreciated following an early report that the specific blocker charybdotoxin was without effect on glucose-induced electrical activity (Kukuljan et al., 1991).

The oscillatory nature of β-cell electrical activity reviewed above, first described by Dean and Matthews more than 40 years ago (Dean and Matthews, 1968), has never stopped to intrigue (and vex!) β-cell electrophysiologists. Experimental and theoretical considerations have led to the proposal of numerous hypotheses. These include (but are not limited to) inactivation of the voltage-gated Ca^{2+}-current (Satin et al., 1994), activation of K_{ATP}-channels via oscillations in the intracellular ATP/ADP-ratio driven by metabolism (Larsson et al., 1996), activation of Ca^{2+}-activated K^+-channels by mobilization of intracellular Ca^{2+}-stores (Ammala et al., 1991), activation of large-conductance (BK) Ca^{2+}-activated K^+-channels by Ca^{2+}-influx during β-cell electrical activity (Atwater et al., 1983) and opening of a depolarizing store-operated conductance (Worley et al., 1994). It has turned out remarkably difficult to conclusively establish the mechanisms involved. This may be because isolated β-cells maintained in tissue culture (the favourite preparation for patch-clamp experiments) do not generate the typical bursting electrical activity observed in membrane potential recordings from intact pancreatic islets. Rather, electrical activity in isolated cells consists of uninterrupted action potential firing (Ammala et al., 1991; Rorsman et al., 1991), very brief bursts consisting of two or three action potentials (Kinard et al., 1999) or very long (5–10 min) (Smith et al., 1990a). The absence of the normal bursting pattern of electrical activity in isolated β-cells may reflect the loss of electrical coupling with other β-cells and/or auto/paracrine interactions. Changes in β-cell electrical activity following islet dissociation may also be a consequence of changes in gene expression, glucose metabolism and intracellular Ca^{2+} handling.

The finding that the normal oscillatory electrical activity is not maintained in isolated β-cells led us to explore whether it is feasible to perform patch-clamp analyses of β-cells in freshly isolated intact

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