https://www.mediresonline.org/

ISSN: 2836-502X

Open Access

Endocrine System and Diabetes

Mini Review

Calcium Signaling in Diabetes: Role of Ion Channels and Transporters

Nnodim Johnkennedy[1]*, Ozoemena Chimaoge Covenant[2]

[1]Department of Medical Laboratory science, Imo state university, Owerri, Nigeria
[2]Department of Chemical pathology,Faculty of Medical Laboratory Science, Federal University Otuoke, Bayelsa State

***Corresponding Author:** Nnodim Johnkennedy, Department of Medical Laboratory science, Imo state university, Owerri, Nigeria.

Received Date: 10 April 2026; **Accepted Date:** 29 April 2026; **Published Date:** 05 May 2026

Abstract

Calcium (Ca^{2+}) signalling is crucial for controlling physiological functions like insulin secretion, glucose balance, and metabolic signalling. Dysregulation of intracellular calcium dynamics is significantly implicated in the development of diabetes mellitus, especially in pancreatic β-cell dysfunction and insulin resistance. Ion channels and transporters are essential regulators of calcium inflow, efflux, and intracellular storage, therefore influencing calcium signalling dynamics. This study examines the molecular processes of calcium signalling in diabetes, emphasising the function of essential ion channels and transporters, including voltage-gated calcium channels, transient receptor potential (TRP) channels, store-operated calcium entry (SOCE) pathways, and calcium ATPases. The role of mitochondrial calcium management and endoplasmic reticulum stress in β-cell failure is also examined. Comprehending these pathways offers insights into prospective treatment targets for diabetes control.

Key words: Calcium Signaling, Diabetes, Ion Channels, Transporters

Introduction

Calcium ions (Ca^{2+}) are among the most flexible and ubiquitous intracellular messengers, influencing a vast array of physiological activities including secretion, metabolism, gene expression, and cell survival. In metabolic disorders like Type 2 Diabetes, disruptions in calcium signalling have become a primary mechanism responsible for both pancreatic β-cell impairment and peripheral insulin resistance. In recent decades, there has been a growing focus on comprehending the role of ion channels and transporters in regulating calcium homeostasis and how their malfunction leads to the development and advancement of diabetes mellitus [1].

Diabetes mellitus is a long-term metabolic disease that causes high blood sugar levels that don't go down because of problems with insulin secretion, insulin action, or both. The International Diabetes Federation says that diabetes is becoming more common around the world at an alarming rate, which is a big problem for healthcare systems everywhere. Conventional research has concentrated on glucose metabolism and insulin signalling pathways; however, recent findings suggest that calcium signalling is crucial in modulating these processes at both cellular and molecular levels [2].

A large concentration gradient between the inside and outside of cells is what makes calcium signalling work. Cytosolic calcium levels are tightly controlled at about 100 nM while the cell is at rest, but extracellular levels are much greater. This gradient makes it possible for intracellular calcium levels to rise quickly and temporarily when certain ion channels are opened. Calcium is a flexible signalling chemical because it can create complex spatiotemporal patterns, such as oscillations, waves, and localised microdomains. These patterns allow for fine regulation of how cells respond to signals [3].

Calcium signalling is essential for glucose-stimulated insulin secretion (GSIS) in pancreatic β-cells, a process that connects hormone release to metabolic activity. When glucose enters β-cells through glucose transporters, it goes through glycolysis and the tricarboxylic acid cycle, which raises the amounts of ATP inside the cells. This increase in ATP causes ATP-sensitive potassium (K_ATP) channels to close, which

makes the membrane depolarise. The depolarised membrane then opens voltage-gated calcium channels (VGCCs), which let calcium ions into the cell. The rise in calcium levels inside the cell is what causes insulin-containing granules to be released from the cell [4].

The way calcium signals work in β-cells is quite complicated and precise. Insulin secretion happens in two phases: a quick first phase and a longer second phase. Calcium is important in both phases because it controls the fusion of insulin granules with the plasma membrane and the movement of reserve granules. Oscillatory calcium signals are crucial for pulsatile insulin production, which is more successful in preserving glucose homeostasis than continuous insulin release. A sign that β-cells aren't working right in diabetes is that these oscillations stop.

Ion channels are essential for controlling the flow of calcium into cells and for signalling inside cells. Voltage-gated calcium channels are the main way that calcium gets into cells when the membrane depolarises. L-type calcium channels are very important for insulin release and are found in considerable amounts in pancreatic β-cells. Changes in the expression or function of these channels can cause calcium to flow in less, insulin to be released less, and eventually hyperglycemia. Long-term exposure to high glucose levels has been demonstrated to change how VGCCs work, which makes β-cell dysfunction even worse [5].

Transient receptor potential (TRP) channels, together with VGCCs, form a varied group of non-selective cation channels that facilitate calcium influx in response to different stimuli. Various TRP channel subtypes, such as TRPM2, TRPM5, and TRPV1, have been associated with β-cell physiology and the aetiology of diabetes. Oxidative stress activates TRPM2, which has been linked to β-cell death in cases of persistent hyperglycemia. TRPM5 helps control how easily the membrane can become excited and how much insulin is released. TRPV1, on the other hand, is implicated in inflammation and metabolic regulation. So, if TRP channel activity isn't working right, it might lead to oxidative stress, inflammation, and problems with insulin secretion.

Store-operated calcium entry (SOCE) is another key way for calcium to get into cells. It happens when calcium stores in the endoplasmic reticulum (ER) run out. The connection between stromal interaction molecule 1 (STIM1), a calcium sensor in the ER membrane, and Orai1, a calcium channel in the plasma membrane, is what causes SOCE. This route helps keep calcium signalling going by letting calcium reserves inside cells be refilled. SOCE is very important for keeping calcium levels stable and making sure that insulin is released properly in pancreatic β-cells. Problems with SOCE have been linked to problems with β-cell function and a higher risk of apoptosis [6].

Ion channels let calcium in, but calcium transporters and pumps keep the balance of calcium inside cells by controlling how it is stored and removed. The sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) is an important transporter that moves calcium from the cytosol to the ER. This keeps calcium levels from getting too high in the cytoplasm and keeps calcium stores full. In diabetes, diminished SERCA activity results in the depletion of endoplasmic reticulum calcium reserves, which induces endoplasmic reticulum stress and activates the unfolded protein response (UPR). Persistent endoplasmic reticulum (ER) stress leads to β-cell death and decreased insulin production, underscoring the significance of SERCA in sustaining cellular homeostasis [7].

The sodium-calcium exchanger (NCX) and the plasma membrane Ca^{2+}-ATPase (PMCA) are also very important for getting calcium out of the cell. PMCA uses ATP to aggressively pump calcium out of the cytosol, while NCX makes it possible for calcium to move in both directions, depending on the electrochemical gradient. These transporters are very important for bringing calcium levels back to normal once insulin is released and for keeping calcium levels stable. If PMCA or NCX doesn't work right, it might cause too much calcium to build up, oxidative stress, and damage to cells, which can make diabetes worse.

Mitochondria have a big role in calcium signalling and controlling metabolism. The mitochondrial calcium uniporter (MCU) brings calcium into mitochondria, which then activates important enzymes in the tricarboxylic acid cycle to make ATP. This pathway is necessary for linking insulin release in β-cells to metabolic activity. But too much calcium in the mitochondria can cause reactive oxygen species (ROS) to form, change the mitochondrial membrane potential, and start pathways that lead to cell death. Mitochondrial malfunction is a characteristic of both β-cell failure and insulin resistance, highlighting the dual function of calcium in cellular physiology and pathology [8].

The endoplasmic reticulum is a large storage space for calcium inside cells and is very important for folding and digesting proteins. Disruption of ER calcium homeostasis is a key characteristic of diabetes, especially in the context of persistent hyperglycemia and lipotoxicity. Calcium deficiency in the endoplasmic reticulum (ER) hinders protein folding, resulting in the buildup of misfolded proteins and the activation of the unfolded protein response. The UPR starts out as a way to safeguard cells, but if it stays on for too long, it can cause cells to stop working and die. Calcium-dependent signalling pathways are thus pivotal in the emergence of ER stress and its detrimental effects in diabetes [9].

Calcium signalling is also important for the development of insulin resistance in tissues outside of the pancreas. In skeletal muscle, increased intracellular calcium concentrations activate stress-related kinases, including protein kinase C (PKC) and c-Jun N-terminal kinase (JNK), which disrupt insulin signalling pathways. This causes less glucose to be taken in and the body's metabolism to work less well. Calcium controls the release of adipokines and the breakdown of fats in fat tissue. When this process goes wrong, it causes

inflammation and insulin resistance. In the liver, changes in calcium signalling also affect gluconeogenesis and glycogen metabolism, which leads to more glucose being made and high blood sugar levels [10].

Calcium signalling in diabetes is directly related to oxidative damage and inflammation. Increased amounts of calcium inside cells can lead to the creation of reactive oxygen species, which can then throw off calcium homeostasis and hurt parts of cells. Inflammatory cytokines make this process worse by changing how calcium channels and transporters work and how they are expressed. Calcium imbalance, oxidative stress, and inflammation all make each other worse, which makes the disease worse [11].

Because calcium signalling is so important in diabetes, targeting ion channels and transporters could be a good way to treat the disease. Pharmacological regulation of voltage-gated calcium channels has been demonstrated to affect insulin secretion, whilst the blockage of particular TRP channels may mitigate oxidative damage and inflammation. Increasing the activity of SERCA could be a way to bring calcium levels back to normal in the ER and relieve stress in the ER. Antioxidants that lower the amount of ROS generated can also assist calcium signalling work normally and protect cells from harm. New treatments that focus on increasing mitochondrial activity and calcium management may make metabolic results even better [12].

Recent progress in molecular biology and imaging technology has shed light on the intricacy of calcium signalling networks. High-resolution imaging techniques now enable the observation of calcium dynamics at the subcellular level, uncovering complex patterns of calcium signalling that were previously unrecognised. These advancements have created new opportunities for research and underscored the necessity for a more cohesive comprehension of calcium signalling in both health and disease [13].

Future research endeavours should concentrate on clarifying the tissue-specific functions of calcium signalling pathways and discovering innovative molecular targets for therapeutic intervention. The advancement of selective modulators for ion channels and transporters presents significant potential for diabetic treatment. Also, new gene editing technologies could make it possible to fix genetic problems in calcium-regulating proteins, which could lead to personalised treatment [14].

Conclusion

Calcium signalling is a key player in controlling insulin release and keeping the body's metabolism stable. Ion channels and transporters are very important for regulating calcium levels, and when they don't work right, they are a big part of what causes diabetes. The combination of calcium signalling, mitochondrial function, endoplasmic reticulum stress, oxidative stress, and inflammation highlights the complexity of this disease. To come up with new techniques to stop and treat diabetes mellitus, we need to learn more about how these pathways are linked.

References

1. Rutter, Guy A., and Paolo Pinton. "Mitochondria-associated endoplasmic reticulum membranes in insulin signaling." Diabetes 63, no. 10 (2014): 3163-3165.
2. Islam, M. Shahidul. "Calcium signaling in the islets." The Islets of Langerhans (2010): 235-259.
3. Eizirik, Décio L., Alessandra K. Cardozo, and Miriam Cnop. "The role for endoplasmic reticulum stress in diabetes mellitus." *Endocrine reviews* 29, no. 1 (2008): 42-61.
4. Ashcroft, Frances M., and Patrik Rorsman. "Diabetes mellitus and the β cell: the last ten years." *Cell* 148, no. 6 (2012): 1160-1171.
5. Henquin, Jean-Claude. "The dual control of insulin secretion by glucose involves triggering and amplifying pathways in β-cells." Diabetes research and clinical practice 93 (2011): S27-S31.
6. Prentki, Marc, and Christopher J. Nolan. "Islet β cell failure in type 2 diabetes." *The Journal of clinical investigation* 116, no. 7 (2006): 1802-1812.
7. Gilon, Patrick, Hee-Young Chae, Guy A. Rutter, and Magalie A. Ravier. "Calcium signaling in pancreatic β-cells in health and in Type 2 diabetes." Cell calcium 56, no. 5 (2014): 340-361.
8. Rorsman, Patrik, and Frances M. Ashcroft. "Pancreatic β-cell electrical activity and insulin secretion: of mice and men." Physiological reviews 98, no. 1 (2018): 117-214.
9. Wiederkehr, A. and Wollheim, C.B. (2012). Mitochondrial signals in insulin secretion. Diabetologia, 55(3), pp.613–621.
10. Yang, Shao-Nian, and Per-Olof Berggren. "The role of voltage-gated calcium channels in pancreatic β-cell physiology and pathophysiology." *Endocrine reviews* 27, no. 6 (2006): 621-676.
11. Guerrero-Hernandez, Agustin, and Alexei Verkhratsky. "Calcium signalling in diabetes." *Cell calcium* 56, no. 5 (2014): 297-301.
12. Jacobson, David A., and Show-Ling Shyng. "Ion channels of the islets in type 2 diabetes." *Journal of molecular biology* 432, no. 5 (2020): 1326-1346.
13. Zhu, Jia-Xuan, Zhao-Nan Pan, and Dan Li. "Intracellular calcium channels: Potential targets for type 2 diabetes mellitus?." *World Journal of Diabetes* 16, no. 4 (2025): 98995.
14. Vallon, Volker. "The proximal tubule in the pathophysiology of the diabetic kidney." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 300, no. 5 (2011): R1009-R1022.

Citation: Nnodim Johnkennedy, Ozoemena Chimaoge Covenant. Calcium Signaling in Diabetes: Role of Ion Channels and Transporters. *Endocr. Syst. Diabetes.* Vol. 4 Iss. 1. (2026) DOI: 10.58489/2836-502X/014