PATHOGENETIC ROLE OF SIGMA-1 RECEPTORS IN THE DEVELOPMENT OF PANCREATIC DYSFUNCTION IN METABOLIC SYNDROME

BUKOVINIAN STATE MEDICAL UNIVERSITY

Filipec N.D., Olentyr S.S.

Bukovinian State Medical University, Chernivtsi, Ukraine



BACKGROUND

Metabolic syndrome (MetS) is characterized by a combination of insulin resistance, disturbances in carbohydrate and lipid metabolism, chronic low-grade inflammation, and oxidative stress. Prolonged metabolic overload is accompanied by a compensatory increase in the functional activity of pancreatic β-cells, which, as the pathological process progresses, may be replaced by β-cell dysfunction and a decline in their secretory reserve. A promising direction for investigating the mechanisms underlying these alterations is the study of sigma-1 receptors (σ1R), which are involved in regulating cellular responses to metabolic stress.

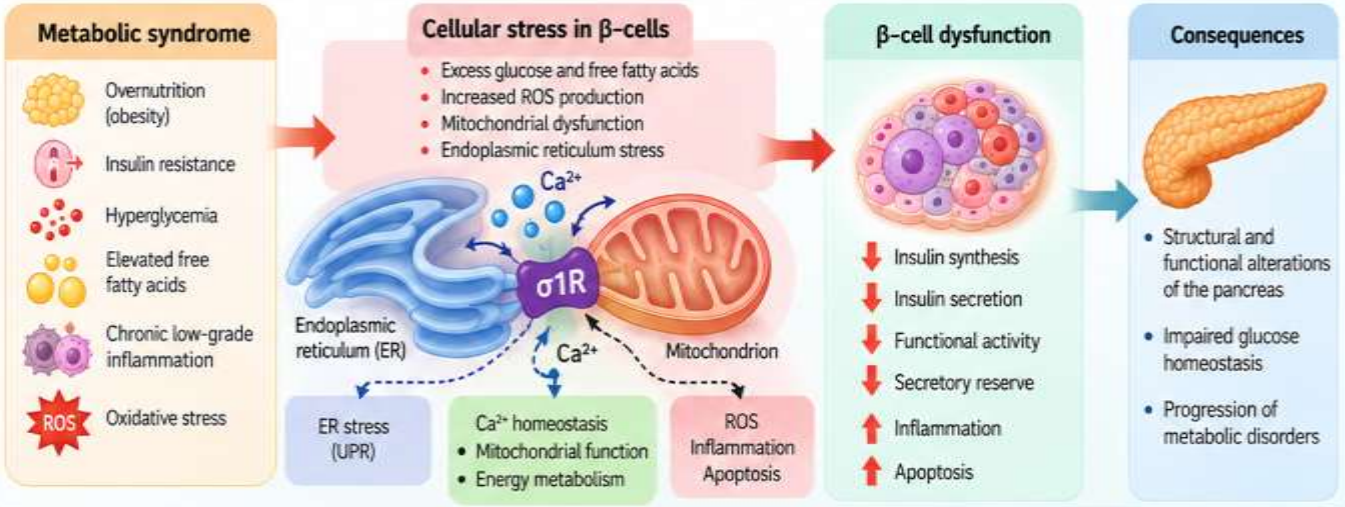
OBJECTIVE

To summarize current knowledge regarding the potential pathogenetic role of sigma-1 receptors in the development of structural and functional alterations of the pancreas in metabolic syndrome.

KEY MECHANISMS AND ROLE OF σ1R

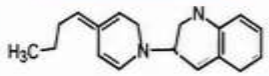
1. **Localization and function**
   Sigma-1 receptor is an intracellular chaperone protein, mainly localized at the endoplasmic reticulum–mitochondria contact sites. It is involved in the regulation of intracellular Ca^{2+} signaling, mitochondrial function, energy metabolism, and adaptive cellular responses to stress.
2. **Cytoprotective effects in β-cells**
   σ1R may maintain ER–mitochondria interactions, stabilize Ca^{2+} homeostasis, and support mitochondrial function.
3. **Modulation of pathological processes**
   σ1R activity may affect the intensity of oxidative stress, inflammatory responses, and mechanisms of cell death.
4. **Impaired σ1R-dependent adaptation**
   Disruption of σ1R-dependent mechanisms may contribute to the progression of pancreatic islet dysfunction under conditions of prolonged metabolic overload.

SCHEMATIC OVERVIEW



PHARMACOLOGICAL ACTIVATION OF σ1R

PRE-084



Selective σ1R agonist

- May serve as a useful experimental tool for elucidating the role of σ1R in maintaining cellular homeostasis.
- Potentially capable of reducing oxidative stress, inflammation and apoptosis, and supporting β-cell function.

FUTURE RESEARCH DIRECTIONS

- Comprehensive analysis of σ1R expression in pancreatic tissue in MetS.
- Correlation of σ1R expression with parameters of carbohydrate metabolism, insulin resistance, and oxidative stress.
- Study of morphological changes in the islets of Langerhans.
- Evaluation of the therapeutic potential of σ1R agonists in models of metabolic syndrome.

CONCLUSIONS

Sigma-1 receptors may represent an important component of the adaptive response of pancreatic cells to metabolic stress. Their involvement in the regulation of endoplasmic reticulum–mitochondria interactions, Ca^{2+} homeostasis, oxidative stress, and cell survival mechanisms provides a rationale for further investigation of σ1R in the pathogenesis of β-cell dysfunction in metabolic syndrome. Pharmacological modulation of σ1R may be considered a promising experimental approach in the search for strategies to prevent the progression of metabolically induced pancreatic injury.

KEYWORDS

metabolic syndrome, sigma-1 receptor, pancreas, β-cells, insulin resistance, mitochondrial dysfunction, oxidative stress.

REFERENCES

1. Kourrich S, Su TP, Fujimoto M, Bonci A. The sigma-1 receptor: roles in neuronal plasticity and disease. Trends Neurosci. 2012;35(12):762–771. doi:10.1016/j.tins.2012.09.007.
2. Hayashi T. The Sigma-1 Receptor in Cellular Stress Signaling. Front Neurosci. 2019;13:733. doi:10.3389/fnins.2019.00733.
3. Ke M, Lin F, Wang H, He G, Feng J, Song L, Xu Y, Liu J. Sigma-1 receptor overexpression promotes proliferation and ameliorates cell apoptosis in β-cells. Mol Med Rep. 2022;25(5):170. doi:10.3892/mmr.2022.12666.
4. Resende R, Fernandes T, Pereira AC, Marques AP, Pereira CF. Endoplasmic Reticulum-Mitochondria Contacts Modulate Reactive Oxygen Species-Mediated Signaling and Oxidative Stress in Brain Disorders: The Key Role of Sigma-1 Receptor. Antioxid Redox Signal. 2022;37(10–12):758–780. doi:10.1089/ars.2020.8231.