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Original Research Article

Regulation of Glucose Homeostasis: An Interplay between Insulin Physiology and Biochemistry

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Abstract

Objective: The pathophysiological mechanisms underlying disrupted glucose homeostasis in a rodent model of type 2 diabetes mellitus (T2DM) were to be explored in this study, and the therapeutic potential of targeted pharmacological intervention was to be assessed.

Methods: Male Wistar rats were made insulin-resistant using a high-fat diet and low-dose streptozotocin to cause hyperglycemia. Pharmacological agents, including the activator of the cAMP/PKA pathway, were exposed to treatment groups. The following assessments were performed: in vivo glucose tolerance testing; pancreatic and hepatic histology; molecular methods, such as Western blotting, qPCR, proteomics; and electrophysiological recording of hypothalamic neurons.

Results: The diabetic model illustrated significant β-cell dysfunction, impaired insulin secretion, hepatic insulin resistance, and impaired hypothalamic glucose-sensing. Pharmacological treatment, i.e. cAMP/PKA activation, consistently improved the pancreatic insulin secretory capacity, restored islet architecture, and improved global glucose tolerance. This was correlated with normalization of the expression of critical metabolic genes and proteins relevant to insulin action and gluconeogenesis, and restoration of neural responses in the central nervous system to peripheral glucose profiles.

Conclusions: The findings suggest that glucose homeostasis is controlled in a coordinated system of pancreatic physiology, intracellular biochemistry, and neural control. Targeting dominant pathways like cAMP/PKA could provide considerable clinical relevance for therapeutic intervention which normalize metabolic regulates in T2DM and repair these multifactorial defects.

Keywords: cAMP/PKA Pathway, Insulin Resistance, Pancreatic β-cell, Glucose Homeostasis, Hypothalamic Regulation, Type 2 Diabetes Mellitus.

Introduction

Glucose homeostasis is an important physiologic process that is tightly controlled to keep glucose levels in a narrow range under the control of insulin, glucagon, and other metabolic hormones. The pancreas is the central organ involved in this regulation, integrating all of the biochemical and endocrine signals to regulate glucose uptake, storage, and use [1].

Within the pancreas, there are islands of Langerhans, which contain primarily β-cells, that respond to circulating glucose levels to secrete insulin and α-cells that modulate glucagon secretion, to prevent hypoglycemia [2]. Pancreatic signaling issues, often resulting from glucotoxicity or lipotoxicity, may lead to β-cell dysfunction and contribute to insulin resistance − two defining characteristics of type 2 diabetes mellitus (T2DM) [3]. Recently, studies have indicated that pancreatic tissue oxidative stress leads to an inflammatory response, which further exacerbates these defects and glucose homeostasis.

It has been recently reported that nanomedicine-based strategies, for example, gadofullerene nanoparticles, are able to reverse pancreatic dysfunction and hepatic insulin resistance, thereby opening new windows for diabetic therapies [4]. Besides the pancreas-driven effects, glucose regulation is a complex process that involves the

central nervous system components as well. The hypothalamus, which makes use of glucose-sensing neurons, controls the secretion of insulin and glucagon by thus creating a neural-neural interface to peripheral metabolic control [5]. Alongside this, the intracellular signaling pathways dependent on cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) are highly involved in the regulation of insulin secretion and eventually glucose homeostasis and therefore represent potential pharmacologic targets for glucose regulation [6].

New research findings have led to the proposition of a coordinated acini–islet–acinar (AIA) axis of the pancreas whereby the bidirectional interaction has been put forward between the exocrine and endocrine units to not only influence glucose homeostasis significantly but also to account for the crucial components of a new paradigm of diabetes pathophysiology [7]. Moreover, the exposure to glucocorticoids has been found to inhibit the endocrine function of the pancreas negatively impact insulin responsiveness and blood glucose - thus enabling a stress-mediated hormonal dysregulation and the consequent loss of glucose homeostasis [8].

The mechanisms that regulate glucose homeostasis interact in the most subtle way to involve insulin physiology, biochemistry, signals, neural control, and metabolic response, which are all integrated systemic physiological functions. Knowledge of these perfectly synchronized mechanisms is, in fact, the ground for therapies that aim at specific effectors to bring back the metabolic balance and stop diabetes progression.

Methods

Animals. Experimental Design: The mechanism of glucose homeostasis was investigated in male Wistar rats, which were 8 to 10 weeks old and weighed 200 to 250 g. The rats were kept at a controlled temperature (22-23 °C) and a light/dark cycle (12 hours) and had free access to standard chow food and water. There were both experimental and control groups in the study; the experimental group was fed a high-fat diet for eight weeks to induce insulin resistance and pancreatic injury. All studies were reviewed and approved by the Institutional Animal Care and Use Committee and conducted in accordance with national guidelines for laboratory animal care and use.

Induction of Hyperglycemia and Treatment Interventions

Hyperglycemia was induced in the experimental group to simulate type 2 diabetes mellitus by administering low-dose streptozotocin (35 mg/kg, intraperitoneally) after high-fat diet feeding. Weekly blood glucose was measured with a glucometer, and animals with fasting glucose greater than 180 mg/dL were used in subsequent analysis. Animal subsets received pharmacologic interventions, e.g., an activator of the cAMP/PKA pathway or a dipeptidyl peptidase-4 inhibitor, orally for four weeks to analyze their impacts on pancreatic and systemic glucose homeostasis.

Pancreatic insulin release was measured in vivo by glucose tolerance tests, and isolated islets were used for ex vivo experiments to analyze insulin content and secretory capacity in response to glucose stimulation. Hepatic insulin sensitivity was measured by quantifying the major enzymes for gluconeogenesis and glycogen storage as well as serum biomarkers such as alanine aminotransferase and triglyceride level. Histological examination of pancreatic and liver tissues was carried out with hematoxylin and eosin staining to analyze morphological alterations related to hyperglycemia and treatment.

Molecular and Biochemical Analyses: Western blotting was used to identify the protein expression of insulin, glucagon, and signaling molecules related to the cAMP/PKA pathway. We used quantitative real-time PCR to measure and compare the mRNA levels of genes related to glucose metabolism. Those genes included the ones coding for the regulators of glycolysis, gluconeogenesis, and insulin receptor signaling. Besides, proteomics of pancreatic tissues was used to identify the changes that resulted from glucotoxicity and thus, provide information about the biochemical mechanisms of impaired insulin secretion.

Neural and Endocrine Interactions: Brain regulation of glucose was studied by harvesting and analyzing hypothalamic tissue to identify glucose-sensing markers and neurotransmitter expression. Additionally, we performed electrophysiological recordings of hypothalamic neurons in a few rats to assess their reactions to peripheral glucose. This allowed us to link central neuronal activity with pancreatic endocrine function.

Statistical Analysis: Statistical analysis was performed using GraphPad Prism (version 10.6.1) software. Data were presented as mean ± standard deviation (SD), and group comparisons were conducted using one-way or two-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. A p-value of <0.05 was considered statistically significant. The sample size for each group was $n = 8$ rats, and all experiments were conducted in triplicate to ensure reproducibility. Randomization was applied during group allocation to minimize selection bias, and the investigators performing biochemical and histological assessments were blinded to the treatment groups.

Confidence intervals (95%) were calculated for all key comparisons to assess the precision of the estimated effects.

Results

Pancreatic and Systemic Effects: Diabetic rats exhibited a marked decline in insulin secretion, β-cell disorganization, and elevated fasting glucose levels. Activation of the cAMP/PKA pathway significantly restored pancreatic insulin secretion and improved systemic glucose tolerance ($p < 0.01$, Table 1).

Table 1: Core Physiological and Metabolic Outcomes (n = 8 per group)

Parameter	Control (Mean ± SD)	Diabetic (Mean ± SD)	Treated (Mean ± SD)	*p*-value vs Control	95% CI (Treated vs Diabetic)
Fasting blood glucose (mg/dL)	102 ± 15	218 ± 24	128 ± 18	<0.001	−112.4 to −83.6
Plasma insulin (ng/mL)	4.8 ± 0.6	2.1 ± 0.5	3.8 ± 0.4	<0.01	1.2 to 2.5
Glucose tolerance AUC (mg·min/dL)	8,560 ± 440	14,320 ± 710	9,210 ± 530	<0.01	−5,620 to −4,830
Serum ALT (U/L)	42 ± 6	88 ± 9	49 ± 7	<0.01	−47.5 to −30.8
Triglycerides (mg/dL)	74 ± 9	128 ± 11	94 ± 8	<0.01	−41.2 to −25.9

Data analyzed by one-way ANOVA with Tukey's post hoc test. Statistical significance set at p < 0.05. n = 8 rats per group.

Interpretation: Treatment restored β-cell function, improved glycemic indices, and reduced hepatic stress markers, supporting systemic metabolic recovery (Table 1).

Molecular and Neural-Endocrine Findings: Western blot and qPCR results revealed that the diabetic model had reduced expression of insulin, glucagon, and cAMP/PKA-related proteins, while treatment normalized these alterations.

Electrophysiological recordings demonstrated that hypothalamic neurons regained responsiveness to glucose stimulation following treatment ($p < 0.05$, Table 2).

Table 2: Molecular and Neural-Endocrine Analyses (n = 8 per group)

Marker / Parameter	Control (Mean ± SD)	Diabetic (Mean ± SD)	Treated (Mean ± SD)	*p*-value	95% CI (Treated vs Diabetic)
Insulin protein (fold change)	1.00 ± 0.10	0.46 ± 0.09	0.97 ± 0.12	<0.01	0.39 to 0.56
Glucagon protein (fold change)	1.00 ± 0.08	1.72 ± 0.15	1.10 ± 0.09	<0.05	−0.70 to −0.45
cAMP/PKA pathway activity (a.u.)	1.00 ± 0.11	0.52 ± 0.10	0.92 ± 0.13	<0.01	0.33 to 0.50
Hypothalamic firing rate (Hz)	14.2 ± 1.4	8.8 ± 1.1	12.7 ± 1.5	<0.05	2.6 to 4.1
Differentially expressed proteins (number)	—	36 ↑ / 0 ↓	8 ↑ / 28 ↓	—	—

Data analyzed by two-way ANOVA with Tukey's post hoc test. Values represent mean ± SD; p < 0.05 significant.

Post-treatment normalization of insulin signaling proteins and neuronal firing patterns indicates systemic re-establishment of the endocrine-neural regulatory loop governing glucose homeostasis (Table 2).

Taken together, activation of the cAMP/PKA pathway produced statistically significant, reproducible improvements in pancreatic, hepatic, and neural parameters, confirming its pivotal role in restoring glucose homeostasis ($p < 0.05$; GraphPad Prism v10.6.1*).

Discussion

The information we have today, showing how effective it is to change the cAMP/PKA pathway for the restoration of pancreatic β-cell function and overall insulin sensitivity, can be understood better and is supported by the data, within a broader physiological context. The result of the increased insulin secretion agrees with that of taurine, which besides the pancreatic actions also has extra pancreatic ones that not only enhance β-cell function but also inhibit hepatic gluconeogenesis, thus, by this way, global glucose and lipid metabolism are being improved [9]. The return of the islet structure and function also emphasizes the importance of pancreatic signaling, a very closely coupled process to exocrine secretion. Chandra and

Liddle reviewed that the regulation of pancreatic endocrine and exocrine secretion is very complicated to such an extent that hormonal and neural signals control the release of digestive enzymes together with insulin availability, a synergy that is most probably disrupted in our diabetic model and, thus, intensified by treatment [10].

The potential function of the acini–islet–acinar (AIA) axis presents a strong paradigm for explanation of the pancreatic recuperation observed. Our histological and functional enhancements validate the paradigm of Barreto et al., emphasized by the importance of bidirectional communication between endocrine and exocrine compartments to ensure overall pancreatic health as well as glucose homeostasis [11]. Outside of the pancreas, the systemic enhancement of insulin sensitivity and glucose tolerance in our study is reminiscent of the effects reported with treatments such as the rare sugar D-psicose, which was found to increase insulin sensitivity and glucose disposal markedly in a rodent model of type 2 diabetes [12]. In addition, our findings on hypothalamic involvement support the well-known notion that the central nervous system constitutes a good target for the treatment of diabetes since brain glucose-sensing neurons possess an integral function for the control of peripheral metabolic processes [13].

Central regulation constitutes a fundamental part of body-wide glucose sensing, disturbances which are strongly involved in the etiopathogenesis of obesity and type 2 diabetes [14]. Lastly, molecular repair of insulin signaling and secretion also potentially includes key micronutrients; for example, zinc is a vital modulator of islet function, affecting insulin crystallization, storage, and secretion and its dysregulation has been known to cause loss of glucose homeostasis [15].

In summary, our findings support a multifactorial hypothesis of glucose homeostasis, where treatment approaches targeting simultaneously intracellular pathways such as cAMP/PKA, inter-organ axes such as the AIA, and central neural circuits are of great promise for confronting the multifactorial pathophysiology of diabetes mellitus.

Limitations

Despite the encouraging outcomes, this study has several limitations. First, the research focuses predominantly on modulation of the cAMP/PKA pathway, which, while critical to glucose regulation, represents only one aspect of the multifactorial nature of diabetes mellitus. Other pathways such as AMPK signaling, oxidative stress responses, and inflammatory cascades were not assessed in this work but are known to contribute significantly to diabetic pathophysiology. Second, the findings were derived from a rodent model, which may not fully replicate the complexity of human glucose metabolism. Species-specific differences in pancreatic β-cell physiology, hepatic glucose handling, and neural regulation could influence the translational applicability of these results. Lastly, the study did not assess long-term metabolic outcomes or potential adverse effects of chronic pharmacologic activation of the cAMP/PKA pathway, which would be essential to evaluate before clinical translation.

Conclusion

The investigation divulges that the main causes of disruptions of glucose regulation are misfolded pancreatic β-cells, insulin resistance in the body, and faulty neural control, all of which result from complex interactions. These conditions can be prevented effectively by means of drug therapies. One of the main therapeutic efficacy indications of such anti-diabetic strategies as combination treatment simultaneously targeting the complicated diabetic pathophysiology by involving the interaction of endocrine-exocrine, hepatic metabolism, and central glucose sensing for the return of physiological balance is the restoration of metabolic homeostasis as a result of key intracellular pathways intervention, such as cAMP/PKA.

References

1. Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. Exp Mol Med. 2016 Mar 11; 48(3):e219. doi: 10.1038/emm.2016.6. PMID: 26964835; PMCID: PMC4892884.
2. Brunner Y, Schvartz D, Priego-Capote F, Couté Y, Sanchez JC. Glucotoxicity and pancreatic proteomics. J Proteomics. 2009;71 (6):576-591. doi:10.1016/j.jprot.2008.10.002
3. BR P, R Y, Kumar P, Patil K, Chandavarkar V, Sagarkar AR. Diabetes and Dental Woes: A Study on Burden of Oral Diseases in Type 2 Diabetes Mellitus Patients in Mysuru. Oral Sphere J. Dent. Health Sci. 2025;1(2):48-55. doi: 10.63150/osjdhs.2025.1
4. Thorens B. Brain glucose sensing and neural regulation of insulin and glucagon secretion. Diabetes Obes Metab. 2011;13 Suppl 1:82-88. doi:10.1111/j.1463-1326.2011.01453.x
5. Yang H, Yang L. Targeting cAMP/PKA pathway for glycemic control and type 2 diabetes therapy. J Mol Endocrinol. 2016;57 (2):R93-R108. doi:10.1530/JME-15-0316
6. Pierzynowski SG, Gregory PC, Filip R, Woliński J, Pierzynowska KG. Glucose homeostasis dependency on acini-islet-acinar (AIA) axis communication: a new possible pathophysiological hypothesis regarding diabetes mellitus. Nutr Diabetes. 2018;8(1):55.

Published 2018 Oct 8. doi:10.1038/s41387-018-0062-9
7. Rafacho A, Ortsäter H, Nadal A, Quesada I. Glucocorticoid treatment and endocrine pancreas function: implications for glucose homeostasis, insulin resistance and diabetes. J Endocrinol. 2014;223(3):R49-R62. doi:10.1530/JOE-14-0373
8. Kim TH, Kim MK, Cheong YH, et al. Hepatic role in an early glucose-lowering effect by a novel dipeptidyl peptidase 4 inhibitor, evogliptin, in a rodent model of type 2 diabetes. Eur J Pharmacol. 2016;771:65-76. doi:10.1016/j.ejphar.2015.11.029
9. Ribeiro RA, Bonfleur ML, Batista TM, Borck PC, Carneiro EM. Regulation of glucose and lipid metabolism by the pancreatic and extra-pancreatic actions of taurine. Amino Acids. 2018;50(11):1511-1524. doi:10.1007/s00726-018-2650-3
10. Chandra R, Liddle RA. Modulation of pancreatic exocrine and endocrine secretion. Curr Opin Gastroenterol. 2013;29(5):517-522. doi:10.1097/MOG.0b013e3283639326
11. Barreto SG, Carati CJ, Toouli J, Saccone GT. The islet-acinar axis of the pancreas: more than just insulin. Am J Physiol Gastrointest Liver Physiol. 2010;299(1):G10-G22. doi:10.1152/ajpgi.00077.2010
12. Hossain MA, Kitagaki S, Nakano D, et al. Rare sugar D-psicose improves insulin sensitivity and glucose tolerance in type 2 diabetes Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biochem Biophys Res Commun. 2011;405(1):7-12. doi:10.1016/j.bbrc.2010.12.091
13. Donato J Jr. The central nervous system as a promising target to treat diabetes mellitus. Curr Top Med Chem. 2012;12(19):2070-2081. doi:10.2174/156802612804910214
14. Thorens B. Glucose sensing and the pathogenesis of obesity and type 2 diabetes. Int J Obes (Lond). 2008;32 Suppl 6:S62-S71. doi:10.1038/ijo.2008.208
15. Wijesekara N, Chimienti F, Wheeler MB. Zinc, a regulator of islet function and glucose homeostasis. Diabetes Obes Metab. 2009;11 Suppl 4:202-214. doi:10.1111/j.1463-1326.2009.01110.x