

Diabetes & its Complications

Association of Mitochondrial Dysfunction, Impaired ATP Metabolism, Increased Basal Sympathetic Activity, and Insulin Resistance

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ABSTRACT

Background: Insulin resistance is a major pathophysiological feature of type 2 diabetes mellitus (T2DM), but the precise cellular mechanisms underlying impaired glucose uptake remain incompletely understood. Mitochondrial dysfunction and altered cellular energy (ATP) metabolism have been increasingly implicated in insulin resistance. This review explores the potential association between mitochondrial dysfunction, impaired ATP metabolism, increased basal sympathetic activity, and insulin resistance.

Methods: We reviewed published evidence to examine the relationship between impaired mitochondrial ATP production, increased basal sympathetic activity, and insulin resistance. We focused on the role of ATP-dependent insulin signaling, PI3K–AKT pathways, GLUT4 translocation, and sympathetic regulation of cellular energy demand.

We also assessed the central concept of imbalance between cellular ATP availability and energy demand, which contributes to impaired insulin signaling and glucose utilization.

Results: GLUT4 transporters on the cell surface are necessary for facilitated diffusion of glucose from the extracellular fluid (ECF) into the intracellular fluid (ICF). This transport process does not directly require ATP; however, ATP is required to support insulin signaling and the cellular processes involved in GLUT4 translocation and PI3k–AKT activation. Mitochondrial dysfunction can reduce ATP production, impair fatty acid oxidation, increase reactive oxygen species (ROS) generation, and alter mitochondrial dynamics. These alterations may contribute to impaired insulin signaling and insulin resistance. We propose that persistent sympathetic activation may increase cellular metabolic activity and ATP demand, potentially resulting in an ATP demand–supply mismatch. This mismatch may adversely affect insulin signaling and GLUT4 trafficking.

Conclusion: An association between impaired mitochondrial energy metabolism, ATP demand–supply mismatch, impaired GLUT4 translocation to the cell surface, increased basal sympathetic activity & insulin resistance has been suggested. Chronic psychological stress may contribute to sustained sympathetic activation. Further experimental and clinical studies are required to establish causality and to determine whether improving mitochondrial ATP availability or reducing sympathetic activity can enhance insulin sensitivity.

Keywords

Type 2 diabetes mellitus, Insulin resistance, Mitochondrial dysfunction, ATP metabolism, Sympathetic nervous system, GLUT4 translocation, PI3K–AKT signaling, Energy demand–supply imbalance.

Introduction

The global burden of type 2 diabetes mellitus (T2DM) and its associated microvascular and macrovascular complications is rising continuously [1-3]. Mitochondrial dysfunction and impaired ATP availability have been increasingly implicated in the pathogenesis of diabetes [4,5]. Drugs such as Imeglimin, which may improve mitochondrial function and cellular energy metabolism, have been reported to improve glycemic control [6].

The American Diabetes Association (ADA) diagnostic criteria for diabetes include an HbA1c level of $\geq 6.5\%$, a fasting plasma glucose level of ≥ 126 mg/dL, a 2-hour plasma glucose level of ≥ 200 mg/dL during an oral glucose tolerance test, or a random plasma glucose level of ≥ 200 mg/dL in individuals with classic symptoms of hyperglycemia [7,8].

Glucose homeostasis involves two major processes: the secretion of insulin from the pancreas and the uptake of glucose into insulin-sensitive cells [9]. Insulin resistance refers to an impaired ability of the body to respond effectively to insulin, resulting in inadequate glucose uptake by peripheral tissues despite the presence of insulin. This may lead to hyperglycemia and compensatory hyperinsulinemia [10].

Several factors contribute to insulin resistance, including visceral obesity, aging, physical inactivity, nutritional imbalance, glucotoxicity, lipotoxicity, and genetic predisposition [11]. Insulin resistance can occur in several insulin-sensitive tissues, including adipose tissue, skeletal muscle, and the liver [12]. Insulin resistance is closely linked with increased sympathetic activity, endothelial dysfunction, and associated cardiovascular morbidities [13,14]. Despite extensive research into the mechanisms underlying insulin resistance, the precise cellular mechanisms responsible for impaired glucose uptake remain incompletely understood. Glucose transport from the extracellular fluid (ECF) into the intracellular fluid (ICF) in skeletal muscle and adipose tissue is facilitated primarily by the glucose transporter type 4 (GLUT4) [15,16]. In response to insulin stimulation, GLUT4-containing intracellular vesicles translocate to the plasma membrane, thereby facilitating glucose uptake. This review examines the potential role of cellular ATP availability in GLUT4 translocation and glucose uptake, the contribution of mitochondrial dysfunction to impaired cellular energy availability, and the factors that may underlie mitochondrial dysfunction [16-20].

Methods

This review explores the pathophysiology of insulin resistance based on findings from previously published studies [1-96]. The mechanisms are discussed under the following sections:

1. Normal mechanism of glucose uptake into the cell and the indirect role of ATP (**established mechanisms**)
2. Mechanisms involved in the development of insulin resistance and impaired glucose uptake (**evidence- supported associations**)
 - o 2a. Mitochondrial dysfunction
 - o 2b. Impaired ATP availability and ATP mismatch
3. Potential causes of ATP mismatch: the role of increased basal sympathetic activity (**proposed hypothesis**)
4. Potential mechanisms underlying increased basal sympathetic activity: the central role of the brain (**proposed hypothesis**)

Normal Mechanism of Glucose Uptake into the Cell: The Indirect Role of ATP

The normal mechanism of glucose uptake into insulin-sensitive cells is a complex, multistep process. In skeletal muscle and adipose tissue, glucose uptake is primarily mediated by the GLUT4 transporter. Under basal conditions, GLUT4 is predominantly located in intracellular vesicles. After insulin stimulation, GLUT4-containing vesicles translocate to the plasma membrane, where GLUT4 facilitates glucose transport from the extracellular to the intracellular compartment.

Glucose transport through GLUT4 is a facilitated diffusion process and does not directly require ATP. However, the intracellular signaling cascade that regulates GLUT4 translocation is energy-dependent. Therefore, ATP may indirectly support glucose uptake by fueling the cellular processes involved in insulin signaling and GLUT4 trafficking.

Following its release from the pancreas, insulin reaches its receptors in insulin-sensitive tissues, including skeletal muscle, adipose tissue, and the liver. Insulin binds to the insulin receptor, a receptor tyrosine kinase, thereby initiating a series of intracellular signaling events. One major pathway activated by insulin is the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway, which ultimately promotes translocation of GLUT4-containing vesicles to the plasma membrane and facilitates glucose uptake into the cell.

GLUT4 translocation to the plasma membrane enables glucose to enter the cell via facilitated diffusion, moving down its concentration gradient from the extracellular to the intracellular compartment. Thus, while the actual movement of glucose through GLUT4 is not directly dependent on ATP, the cellular signaling and vesicular trafficking processes that facilitate GLUT4 translocation require energy [21-28].

The following are key steps in the insulin signaling cascade involved in GLUT4 translocation:

PI3K activation

Following insulin receptor activation, intracellular signaling activates phosphoinositide 3-kinase (PI3K). PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to

phosphatidylinositol 3,4,5-trisphosphate (PIP3) by adding ATP, & initiating downstream signaling events

AKT recruitment and activation

PIP3 formation facilitates AKT recruitment to the cell membrane. AKT is subsequently activated through phosphorylation by upstream kinases. These phosphorylation reactions require ATP as a phosphate donor.

Downstream signaling and GLUT4 translocation

Once activated, AKT phosphorylates several downstream target proteins involved in regulating glucose metabolism and GLUT4 trafficking. These signaling events ultimately promote the translocation of GLUT4-containing vesicles to the plasma membrane, facilitating glucose uptake [29-34].

Glucose enters insulin-sensitive cells through GLUT4-mediated facilitated diffusion, moving down its concentration gradient from the extracellular fluid (ECF) to the intracellular fluid (ICF). This final step of glucose transport is energy-independent and does not directly require ATP. Under basal conditions, GLUT4 is predominantly stored in intracellular vesicles. Following insulin stimulation, GLUT4-containing vesicles translocate to the plasma membrane, increasing the number of GLUT4 transporters available at the cell surface and thereby facilitating glucose uptake [35-39]. (Figure 1).

Insulin Resistance: An Important Step in the Development of Diabetes

Insulin resistance refers to a reduced biological response to insulin,

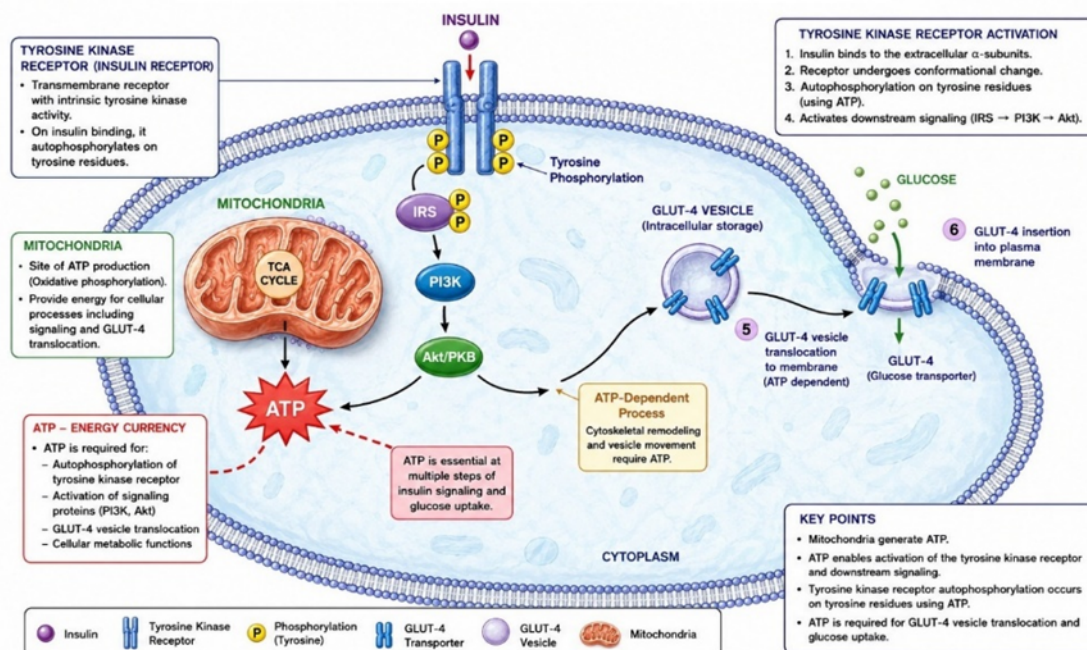
resulting in impaired glucose uptake and utilization despite insulin presence. It is a major component of the pathophysiology of type 2 diabetes mellitus and contributes to the development of hyperglycemia.

Mitochondrial Dysfunction and Impaired ATP Availability

The role of mitochondria in diabetes has attracted considerable attention, as growing evidence suggests that mitochondrial dysfunction may contribute to the development and progression of metabolic disorders, including insulin resistance and type 2 diabetes mellitus.

Mitochondria are the primary organelles responsible for cellular energy production & generate ATP predominantly through oxidative phosphorylation, using reducing equivalents derived from metabolic pathways such as the tricarboxylic acid (TCA) cycle. ATP plays an important indirect role in cellular glucose uptake by supporting the energy-dependent processes involved in insulin signaling and GLUT4 translocation.

GLUT4 facilitates glucose transport from the extracellular to the intracellular compartment through facilitated diffusion. Therefore, although glucose movement through GLUT4 does not directly require ATP, adequate cellular energy may be necessary to support the signaling and vesicular trafficking required for GLUT4 translocation. Consequently, impaired mitochondrial function and altered cellular energy metabolism may contribute to impaired insulin signaling, defective GLUT4 trafficking, and reduced glucose uptake [39-51].



Increased sympathetic activity may also influence cellular energy metabolism by increasing ATP demand in multiple tissues. If cellular ATP demand exceeds the capacity of mitochondria to generate ATP, an imbalance between ATP demand and ATP production may occur. This proposed ATP mismatch could potentially contribute to impaired cellular energy availability and may influence processes involved in insulin signaling and glucose uptake [52,53].

Impaired mitochondrial energy metabolism is associated with insulin resistance & has been characterized by alterations in fatty acid oxidation, ATP production, oxidative stress, and mitochondrial dynamics. These abnormalities may promote the accumulation of lipid metabolites that interfere with insulin signaling in tissues such as skeletal muscle and the liver. Such alterations may contribute to impaired glucose uptake and the development or progression of insulin resistance and type 2 diabetes mellitus [54-58].

Key Effects of Impaired Mitochondrial Function

Mitochondrial dysfunction may affect cellular metabolism through several mechanisms:

Decreased ATP Production

Impaired mitochondrial respiration and oxidative phosphorylation may reduce ATP production, thereby affecting cellular functions that depend on adequate energy availability. Alterations in cellular energy metabolism may interfere with insulin signaling and other metabolic processes.

Reduced Fatty Acid Oxidation

Impaired mitochondrial fatty acid oxidation may contribute to the accumulation of lipid intermediates in non-adipose tissues, including skeletal muscle and the liver. Ectopic lipid accumulation may interfere with insulin signaling and contribute to insulin resistance.

Increased Reactive Oxygen Species

Dysfunctional mitochondria may generate increased levels of reactive oxygen species (ROS). Excessive ROS production can promote oxidative stress, cellular damage, and activation of stress-related signaling pathways that may contribute to impaired insulin signaling and insulin resistance.

Altered Mitochondrial Dynamics

Mitochondrial function is also influenced by the balance between mitochondrial fission and fusion; Disruption of this balance may alter mitochondrial network integrity, energy metabolism, and cellular function and may contribute to metabolic dysfunction [59-61].

Other Evidence Supporting a Role for Mitochondrial Dysfunction

Several lines of evidence suggest that improving mitochondrial function and cellular energy metabolism may be associated with improved insulin sensitivity and glycemic control. Pharmacological

interventions and nutritional strategies that influence mitochondrial metabolism have been investigated for their potential effects on insulin sensitivity and glucose homeostasis [62-64].

Similarly, interventions that improve mitochondrial function, including regular physical exercise and certain nutritional strategies, have shown potential benefits in improving insulin sensitivity and metabolic health. However, the precise relationship between improvements in mitochondrial ATP production and insulin sensitivity remains complex and may involve multiple mechanisms.

Potential Cause of “ATP demand- supply mismatch”: The Role of Sympathetic Activity

Increased sympathetic nervous system activity is associated with increased metabolic activity and energy demand in several tissues. It has been proposed that sustained sympathetic activation may increase cellular ATP demand and, under certain conditions, contribute to an imbalance between ATP demand and ATP production.

Some studies have also reported increased sympathetic nervous system activity in individuals with diabetes and metabolic disorders. Persistent sympathetic activation may therefore contribute to increased metabolic demands in multiple tissues and potentially influence cellular energy homeostasis [52-53,65].

Basal sympathetic activity refers to the ongoing activity of the sympathetic nervous system under resting conditions. This activity helps regulate cardiovascular function, vascular tone, and metabolic processes. When sympathetic activity is persistently elevated, the resulting increase in metabolic demand may place additional demands on cellular energy production.

The effects of increased sympathetic activity may vary among different tissues:

- **Skeletal muscle:** Increased sympathetic activity may influence muscle metabolism and energy expenditure through effects on contractile activity, glycogen metabolism, and blood flow.
- **Adipose tissue:** Sympathetic stimulation promotes lipolysis and alters fatty acid metabolism. These processes involve multiple energy-dependent cellular mechanisms.
- **Liver:** Sympathetic activation can influence hepatic glucose and lipid metabolism and may promote a shift toward increased metabolic activity under certain physiological conditions.
- **Heart:** Increased sympathetic activity enhances heart rate and myocardial contractility, thereby increasing myocardial energy requirements and ATP demand [65-81].

Overall, sustained sympathetic activation may increase metabolic and energetic demands across multiple tissues. It is proposed that, when ATP demand exceeds the capacity of mitochondrial ATP production, an ATP demand–supply mismatch may develop. This proposed ATP mismatch could potentially contribute to impaired cellular energy availability and metabolic dysfunction [51-52].

Central Mechanisms Potentially Underlying Increased Sympathetic Activity

The central nervous system plays an important role in regulating autonomic activity. The cerebral cortex and limbic system have extensive connections with hypothalamic and brainstem regions involved in autonomic regulation. The hypothalamus integrates signals from multiple brain regions, including areas involved in emotional processing and stress responses, and influences sympathetic outflow through downstream autonomic pathways.

Chronic psychological stress and mental fatigue have been associated in some studies with alterations in autonomic function, EEG activity, and sympathetic nervous system activity. Some studies have also reported associations between altered autonomic function and metabolic disorders, including diabetes [63-68].

These observations raise the possibility of chronic stress-related alterations in central autonomic regulation that may contribute to persistent sympathetic activation. Increased sympathetic activity could, in turn, influence metabolic processes and cellular energy demand.

However, the proposed relationship between psychological stress, alterations in cortical or EEG activity, increased sympathetic activity, mitochondrial ATP mismatch, and insulin resistance remains incompletely established. Further research is required to determine whether this represents a direct causal pathway or a complex association involving multiple interacting mechanisms [81-94].

Summary and Conclusion

Type 2 diabetes mellitus is characterized by impaired insulin secretion and insulin resistance, both of which contribute to the development and progression of hyperglycemia and diabetes-related complications.

Insulin resistance is associated with impaired glucose uptake in insulin-sensitive tissues and may involve defects in insulin signaling and GLUT4 translocation. Mitochondrial dysfunction and altered cellular energy metabolism may contribute to these abnormalities by affecting ATP availability, oxidative stress, lipid metabolism, and insulin signaling.

The present review proposes a potential link between increased sympathetic activity, mitochondrial energy metabolism, ATP demand–supply imbalance, and insulin resistance. Under this model, persistent sympathetic activation may increase metabolic and cellular energy demands. If mitochondrial ATP production is insufficient to meet these demands, an ATP demand–supply mismatch may develop, potentially affecting energy-dependent processes involved in insulin signaling and GLUT4 trafficking.

Impaired GLUT4 translocation may subsequently contribute to reduced glucose uptake, hyperglycemia, and the progression of insulin resistance. Chronic psychological stress and mental

fatigue may contribute to increased sympathetic activity; however, the causal relationship between these factors requires further investigation.

Suggestions and Future Perspectives

Strategies aimed at reducing chronic sympathetic activation, improving sleep and recovery, managing psychological stress, and promoting regular physical activity may benefit metabolic health. Nutritional strategies and interventions that support mitochondrial function may also improve insulin sensitivity.

However, further experimental and clinical studies are required to determine whether interventions that reduce sympathetic activity or improve cellular ATP availability can directly enhance GLUT4 translocation, improve insulin sensitivity, and reduce the risk or severity of type 2 diabetes.

References

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: IDF. 2021.
2. American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-Diabetes Care. 2026.
3. Kelley DE, He J, Menshikova EV, et al. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002; 51: 2944-2950.
4. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science*. 2005; 307: 384-387.
5. Petersen KF, Befroy D, Dufour S, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science*. 2003; 300: 1140-1142.
6. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J Clin Invest*. 2016; 126: 12-22.
7. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009; 58: 773-795.
8. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature*. 2001; 414: 799-806.
9. James DE, Stockli J, Birnbaum MJ. The etiology and molecular landscape of resistance. *Nat Rev Mol Cell Biol*. 2021; 22: 751-771.
10. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. *Nature Medicine*. 2017; 23: 804-814.
11. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unraveling the mystery. *Lancet*. 2010; 375: 2267-2277.
12. James DE, Stöckli J, Birnbaum MJ. The etiology and molecular landscape of insulin resistance. *Nat Rev Mol Cell Biol*. 2021; 22: 751-771.
13. Sartori C, Scherrer U. Insulin, nitric oxide and the sympathetic nervous system: at the crossroads of metabolic

- and cardiovascular regulation. *Journal of Hypertension*. 1999; 17: 1517-1525.
14. Kim JA, Montagnani M, Koh KK, et al. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006; 113: 1888-1904.
 15. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin Resistance. *Circ Res*. 2008; 102: 401-414.
 16. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin resistant states. *Cold Spring Harb Perspect Biol*. 2014; 6: a009191.
 17. Kahn BB. Facilitate glucose transporters regulatory mechanisms and dysregulation in diabetes. *J Clin Invest*. 1992; 89: 1367-1374.
 18. Kelley DE, He J, Menshikova EV, et al. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002; 51: 2944-2950.
 19. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol Rev*. 2013; 93: 993-1017.
 20. Hallakou-Bozec S, Vial G, Kergoat M, et al. Mechanism of action of imeglimin: A novel therapeutic agent for type 2 diabetes. *Diabetes Obes Metab*. 2021; 23: 664-673.
 21. Rorsman P, Ashcroft FM. Pancreatic β -cell electrical activity and insulin secretion: of mice and men. *Physiol Rev*. 2018; 98: 117-214.
 22. Klip A, McGraw TE, James DE. Thirty sweet bars of GLUT4. *J Biol Chem*. 2019; 294: 11369-11381.
 23. Jaldin-Fincati JR, Pavarotti M, Frendo-Cumbo S, et al. Update on GLUT4 vesicle traffic: a cornerstone of insulin action. *Trends Endocrinol Metab*. 2017; 28: 597-611.
 24. Watson RT, Kanzaki M, Pessin JE. Regulated membrane trafficking of the insulin-responsive glucose transporter 4 in adipocytes. *Endocr Rev*. 2004; 25: 177-204.
 25. Zaid H, Antonescu CN, Randhawa VK, et al. Insulin action on glucose transporters through molecular switches, tracks and tethers. *Traffic*. 2008; 9: 662-674.
 26. Bogan JS, Kandror KV. Biogenesis and regulation of insulin-responsive vesicles containing GLUT4. *Nat Rev Mol Cell Biol*. 2010; 11: 757-768.
 27. James DE, Brown R, Navarro J, et al. Insulin-regulatable tissues express a unique insulin-sensitive glucose transport protein. *Nature*. 1988; 333: 183-185.
 28. Furtado LM, Somwar R, Sweeney G, et al. Activation of the glucose transporter GLUT4 by insulin. *Biochem Cell Biol*. 2002; 80: 569-578.
 29. White MF. IRS proteins and the common path to diabetes. *Am J Physiol Endocrinol Metab*. 2002; 283: E413-E422.
 30. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signaling pathways: insights into insulin action. *Nat Rev Mol Cell Biol*. 2006; 7: 85-96.
 31. Electrical Stimuli Release ATP to Increase GLUT4 Translocation and Glucose Uptake via P13K-Akt-AS160 in Skeletal Muscle Cells. César Osorio-Fuentealba, Ariel E Contreras-Ferrat et al. *DIABETES*. 2013; 62.
 32. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harb Perspect Biol*. 2014; 6: a009191.
 33. Manning BD, Toker A. AKT/PKB signaling: navigating the network. *Cell*. 2017; 169: 381-405.
 34. Sano H, Kane S, Sano E, et al. Insulin-stimulated phosphorylation of a Rab GTPase-activating protein regulates GLUT4 translocation. *J Biol Chem*. 2003; 278: 14599-14602.
 35. Larance M, Ramm G, James DE. The GLUT4 code. *Mol Cell*. 2008; 31: 588-595.
 36. Jaldin-Fincati JR, Pavarotti M, Frendo-Cumbo S, et al. Update on GLUT4 vesicle traffic: a cornerstone of insulin action. *Trends Endocrinol Metab*. 2017; 28: 597-611.
 37. Martin OJ, Lee A, McGee SL, et al. Dissecting multiple steps of GLUT4 trafficking and identifying the sites of insulin action. *Cell Metab*. 2007; 5: 47-57.
 38. Stöckli J, James DE. Insulin action under arrest: AS160 steers GLUT4 vesicles. *Cell Metab*. 2009; 9: 115-116.
 39. Hoffman NJ, Elmendorf JS. Signaling mechanisms that regulate GLUT4 translocation. *J Cell Physiol*. 2011; 226.
 40. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J Clin Invest*. 2016; 126: 12-22.
 41. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009; 58: 773-795.
 42. Szendroedi J, Phielix E, Roden M. The role of mitochondria in insulin resistance and type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012; 8: 92-103.
 43. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science*. 2005; 307: 384-387.
 44. Kelley DE, He J, Menshikova EV, et al. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002; 51: 2944-2950.
 45. Petersen KF, Befroy D, Dufour S, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science*. 2003; 300: 1140-1142.
 46. Patti ME, Corvera S. The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocr Rev*. 2010; 31: 364-395.
 47. Hesselink MKC, Schrauwen-Hinderling VB, Schrauwen P. Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2016; 12: 633-645.
 48. Morino K, Petersen KF, Shulman GI. Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes*. 2006; 55: S9-S15.
 49. Højlund K. Mitochondrial dysfunction in type 2 diabetes and obesity. *Endocrine Connections*. 2008; 37: S123-S132.

50. Koves TR, Ussher JR, Noland RC, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab.* 2008; 7: 45-56.
51. Morino K, Petersen KF, Dufour S, et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J Clin Invest.* 2005; 115: 3587-3593.
52. Tarun Saxena, Sanjay Patidar, Shailesh Verma, et al. Endothelial Cells Strengthening: Improving Functions in Management of Acute Coronary Syndrome (A Double Blind Randomized Interventional Control Trial). *Clinical Cardiol Cardiovascular Med.* 2019; 3: 17-22.
53. Saxena T, Khichi G, Saxena M. Cell Death in Stroke: Role of Metabolism. *Austin J Cerebrovasc Dis Stroke.* 2017; 4: 1059.
54. Holloway GP, Bonen A, Spriet LL. Regulation of skeletal muscle mitochondrial fatty acid metabolism in lean and obese individuals. *Am J Clin Nutr.* 2009; 89: 455S-462S.
55. Zorzano A, Liesa M, Palacín M. Mitochondrial dynamics as a bridge between mitochondrial dysfunction and insulin resistance. *Arch Physiol Biochem.* 2009; 115: 1-12.
56. Yoon YS, Yoon DS, Lim IK, et al. Mitochondrial dynamics in diabetes. *Antioxid Redox Signal.* 2011; 14: 439-457.
57. Montgomery MK, Turner N. Mitochondrial dysfunction and insulin resistance: an update. *Endocr Connect.* 2015; 4: R1-R15.
58. García-Peña LM, Abel ED, Pereira RO. Mitochondrial dynamics, diabetes, and cardiovascular disease. *Diabetes.* 2024; 73: 151-161.
59. Anderson EJ, Lustig ME, Boyle KE, et al. Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *J Clin Invest.* 2009; 119: 573-581.
60. Way KL, Hackett DA, Baker MK, et al. The effect of regular exercise on insulin sensitivity in type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab J.* 2016; 40: 253-271.
61. Rabol R, Hojberg PM, Almdal T, et al. Hyperinsulinemia does not change mitochondrial function in patients with type 2 diabetes. *J Clin Invest.* 2009; 119: 2454-2463.
62. Bharat Saboo, Shambo SS, Anuj M, et al. Imeglimin in Indian Adults with Type 2 Diabetes: A Prospective Multicenter Real-World Cohort Study of Prescription Patterns, Glycemic Change, and Safety. *J Assoc Physicians India.* 2026; 74: 56-65.
63. EunhyunChoi, Junsang Oh, Gi-Ho Sung. Beneficial Effects of Cordyceps militaris on Exercise Performance via Promoting Cellular Energy Production. *Mycobiology.* 2020; 48: 512-517.
64. Gang Li, Guangxiang Luan, Yanfeng He, et al. Polyphenol Stilbenes from Fenugreek (*Trigonella foenum-graecum* L) Seeds Improve Insulin Sensitivity and Mitochondrial Function in 3T3-L1 Adipocytes. *Oxid Med Cell Longev.* 2018; 2018: 7634362.
65. Tarun KS, Sanjiv M, Manjari S. Aetiopathogenesis of Type 2 Diabetes Mellitus: Could Chronic Stress Play an Important Role. *J Assoc Physic India.* 2014; 62: 484-489.
66. Wangler S, Jarczok MN, Ennis M, et al. The autonomic nervous system in the regulation of glucose and lipid metabolism. *Nat Rev Endocrinol.* 2026; 22: 274-286.
67. Mancina G, Grassi G. The sympathetic nervous system and the metabolic syndrome. *J Hypertens.* 2007; 25: 909-920.
68. Kei Mizuno, Masaaki Tanaka, Kouzi Yamaguti, et al. Mental fatigue caused by prolonged cognitive load associated with sympathetic hyperactivity. *Behav Brain Funct.* 2011; 7: 17.
69. Masaaki Tanaka, Kel Mizuno, Seiki Tajima, et al. Central nervous system fatigue alters autonomic nerve activity. *Life Sci.* 2009; 84: 235-239.
70. Esler M, Straznicki N, Eikelis N, et al. Mechanisms of sympathetic activation in obesity-related hypertension. *Biochem Biophys Acta.* 2006; 1762: 90-99.
71. Grassi G, Seravalle G, Dell'Oro R, et al. Sympathetic activation in obesity: role, mechanisms, and clinical implications. *Hypertens Res.* 2010; 33: 130-136.
72. Tentolouris N, Liatis S, Katsilambros N. Sympathetic activity in obesity and metabolic syndrome. *Ann N Y Acad Sci.* 2006; 1083: 129-152.
73. Matsumura K, Abe I, Tsuchihashi T, et al. Chronic administration of insulin increases sympathetic nerve activity in rats. *Hypertension.* 1994; 24: 187-193.
74. Thorp AA, Schlaich MP. Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. *J Diabetes Investig.* 2015; 6: 645-648.
75. Esler M, Lambert G, Schlaich M. Point: Chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension. *J Appl Physiol.* 2010; 109: 1996-1998.
76. Shimazu T. Central nervous system regulation of liver and adipose tissue metabolism. *Diabetologia.* 1981; 20: 343-356.
77. Bartness TJ, Song CK. Sympathetic and sensory innervation of white adipose tissue. *J Neuroendocrinol.* 2007; 19: 654-668.
78. Eugene EL, Emily SS, Reiji K. Peripheral innervation in the regulation of glucose homeostasis. *Trends Neurosci.* 2021; 44: 189-202.
79. Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia.* 2002; 45: 1201-1210.
80. Moro C, Lafontan M. Remodeling of skeletal muscle lipid metabolism by physical activity: emphasis on adipose tissue lipolysis. *Exerc Sport Sci Rev.* 2013; 41: 213-220.
81. Wahren J, Ekberg K. Splanchnic regulation of glucose production. *Annu Rev Nutr.* 2007; 27: 329-345.
82. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. *Diabetologia.* 2000; 43: 533-549.
83. Lambert GW, Straznicki NE, Lambert EA, et al. Sympathetic nervous system activity in obesity and the metabolic

-
- syndrome-causes, consequences and therapeutic implications. *Pharmacol Ther.* 2010; 126: 159-172.
84. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci.* 2009; 10: 397-409.
85. Myers MG Jr, Affinati AH, Richardson N, et al. Central nervous system regulation of organismal energy and glucose homeostasis. *Nat Metab.* 2021; 3: 737-750.
86. Lam CKL, Chari M, Lam TKT. CNS regulation of glucose homeostasis. *Physiology Bethesda.* 2009; 24: 159-170.
87. Hackett RA, Steptoe A. *Type 2 diabetes mellitus and psychological stress-A modifiable risk factor.* *Nat Rev Endocrinol.* 2017; 13: 547-560.
88. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. *Diabetologia.* 2000; 43: 533-549.
89. Carnagarin R, Vance BM, Lakshini YH, et al. Autonomic Regulation of Glucose Homeostasis: a Specific Role for Sympathetic Nervous System Activation. *Curr Diab Rep.* 2018; 18: 107.
90. Tarun Saxena, Azeema O, Manjari S. Pathophysiology of Essential Hypertension: update. *Expert Rev Cardiovasc Ther.* 2018; 16: 879-887.
91. Tarun Saxena, Azeema Ozefa Ali, Manjari Saxena. Lifestyle Management in Diabetes. *Diabetes Complications.* 2019; 3: 1-2.
92. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol.* 2009; 5: 374-381.
93. Black PH. The inflammatory consequences of psychologic stress: relationship to insulin resistance, obesity, atherosclerosis and diabetes mellitus, type II. *Med Hypotheses.* 2006; 67: 879-891.
94. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet.* 1999; 354: 1435-1439.
95. Stamatakis KA, Punjabi NM. Effects of sleep duration on metabolic risk factors for diabetes. *Diabetes Care.* 2010; 33: 1481-1484.
96. Way KL, Daniel AH, Michael KB, et al. The effect of regular exercise on insulin sensitivity in type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab J.* 2016; 40: 253-271.