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Insulin Hormone Role in the Organizing of Mitochondrial Functions: A review

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ABSTRACT

Insulin is one of the important hormones in human body, it contributed in different cellular processes included mitochondria, in present review the role of insulin organizing of mitochondrial biogenesis, degradation, and function was discussed, the impact of insulin impairment in type 1 and insulin resistance in type 2 have mischievous influences on mitochondrial role, foremost in skeletal muscle and in several organs like liver heart, kidneys, and the brain. Deficient in secretion of insulin level and action may elucidate many of the variations in mitochondrial functions that noticed in diabetes types, and in fact demonstrate how the changes mitochondrial function can participate to variety pathologies in diabetes. From this can be concluded that there were linked between insulin and mitochondria at different cellular functions.

Keywords: Insulin hormone, organizing, mitochondria functions

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INTRODUCTION

The mitochondria are cellular compartments that generate the plurality of a cell's Adenosine triphosphate (ATP) from nutrients using two pathways ; the oxidative phosphorylation (OXPHOS) and the cellular respiration, The Mitochondria's major functions in addition to cellular respiration, is in fact linked with variety of assignments like β-oxidation , removal toxic materials and diversion of acetyl-CoA that formation in the fatty acids (FAs), glucose molecules, AA oxidation during the cycle of tricarboxylic acid (TCA); the chain of mitochondrial electron transport (ETC) complicated actions , and finally generation of reactive oxygen species (ROS) (1, 2).

Mitochondria having nearly about 1000- 1,500 preponderantly proteins which genomic DNA encoded in addition to 13 proteins found in mitochondrial DNA, about 37 genes, included 22 genes encoded to tRNA and two subunits of RNA in human , and all are crucial to preserve the mitochondrial role (3). The mitochondrial process like replication, biogenesis including the transcription, translation, balance of proteomic, and the role of mitochondria is tightly organized and extremely intricate.

As roughly all cellular operations demand the presence of ATP, it is expected that the pathological and physiological variations in energy requirements and fuel alimentation effects the roles of mitochondria , involving the mitochondrial dynamics (incorporation and cleavage), biogenesis, and mitophagy (4).

Variety of mitochondrial labors in insulin-deficient and insulin-resistant states

The occurrence worldwide of diabetes disease, particularly the diabetes mellitus type 2 (T2D), and related international economic concern are fundamental and fast mounting, with counteractive effects on social security and health systems (5). In spite of identified T2D by the resistance of insulin and imperfect secretion of insulin and type 1 diabetes (T1D) diagnosed via ultimate insulin incompetence, both types have different etiologies (6), deeply disrupt fuel metabolism, involving glucose metabolism, fat, and amino acids (AAs), the major fuel provenance to cell processes.

Furthermore, well-authenticated up organization of oxygen exhaustion in T1D and T2D refers the elevation expenditure of resting energy in non-treated patients (7, 8). Emerging evidence clearly refers that the changes in the energy metabolism can be traced to the mitochondria.

Insulin considered the predominant hormone in the metabolism of fuel, is contributed in variety of assignments in the cells, include the turnover of proteins, a robustly ATP-dependent operation; Furthermore, insulin deteriorations in diabetes is connected with changed energy metabolism.

The primary goal is to largely highlight the impact of insulin impairment in type 1 and insulin resistance in type 2 have mischievous influences on mitochondrial role, foremost in skeletal muscle and in liver, kidney, adipose tissue, heart and the brain. (9-13).

Insulin hormone role in mitochondrial processes

The signaling of insulin pathway and it connects with receptor (IR) enhancing the IR auto phosphorylation, persuading insulin receptor substrate (IRS) adaptor proteins, and AKT pathway energizing (14). The insulin/IRS/AKT passageway is focal to glucose balance and adjusts diversified ATP-dependent operations involving catalyzing the uptake of glucose in muscles and adipose tissue, suppressing glucose emission and glycogenesis, enhancing lipid storage and production in both adipose tissue and liver, in addition to coordinating protein production and dissolution. The insulin-IRS-AKT passageway's organizations of mammalian target of rapamycin (mTOR) efficacy and FOXO transcription factors which have role inclusions for assignment of mitochondria, as mTOR (15, 16) and FOXO1 (17,18) organize oxidative role of mitochondria through the organization of PPARγ co-activator 1α (PGC1A).

PGC1A is a prime governor of the biogenesis of mitochondria through both nuclear respiratory factor 1 (NRF1) and NRF2, that organizes the nuclear and mitochondrial-encoded genes by transcription factor A of mitochondria (TFAM) (19). All mitochondrial proteins

encoded in genomic DNA imported into the mitochondria after produced in ribosomes, while mitochondrial ribosomes produce about 13 mitochondrial proteins (20). The compounds of mitochondria generated from both the imported nuclear and proteins encoded by mitochondrial genome Insulin's duty in the outer and inner mitochondrial membrane transporters and complexes productions stays vague, Mitochondrial protein production and rotation are crucial for preserving the protein characteristics and role (21- 23).

Insulin's impacts on protein production highly differ between various tissues and proteins (24). Stump and others (25) proved that the elevation in physiological level of insulin casting in the normal individuals raised the ATP generation in real time secluded mitochondria from skeletal muscle of human. In similar way, insulin casting elevated mRNA of mitochondrial genes like NADH dehydrogenase subunit IV (*MT-ND4*) and genomic genes encoding the proteins of mitochondrial such as cytochrome *c* oxidase subunit IV (*COX4*) raised mitochondrial protein generation, and raised the effectiveness of the clef metabolic enzymes COX and citrate synthase (CS) in muscle.

In the normal individuals, the high insulin concentricity trigger production of mitochondrial protein in muscles, but only when co infused with amino acids (26), as intense insulin pouring out reduces the plasma amino acids concentrations via inhibiting protein degeneration (27, 28). Similar to the mitochondrial protein production, elevation in the enzyme actions of mitochondria and ATP generation also rely on amino acids availability. In adults insulin casting without amino acids complementation intake up regulated the *COX3*, *PGC1A*, and *NRF1* gene expression though, insulin alone flopped to increased protein production in mitochondria of muscles, COX and CS action, generation of ATP, in addition to phosphorylation of the protein assembly enhancers 4EBP1, p70S6K in addition to mTOR (29). In a Similar manner, Ling *et al.* (30) linked elevated the *PGC1A* mRNA with raised oxidation of glucose pursuing insulin casting but noticed that PGC1A protein scale was unchanged in the muscles.

These oversights (25, 26, 29, 31) referred to that insulin triggers the transcription of a special genes with prospect impacts on the function of mitochondria, but only induces the expression and mission of mitochondrial proteins when proper amino acids concentrates are existing.

Insulin suppresses not only the degeneration of endogenous proteins but fat preserving too. So, when carbohydrates alone are digested, the insulin signaling enhances utilization of carbohydrate for energy demands, maintaining the fat and protein storage. Although of both amino acids and insulin are required for protein production, carbohydrate or fat alone is improbable to enhance protein generation.

So, it's expected that protein digestion is connected with higher thermogenesis than carbohydrate and fat consuming, probable due to synthesis of proteins higher ATP request (32). (34). It stays infirm whether carbohydrate-stimulate raises in the insulin signaling flop to trigger protein production in muscle (particularly in mitochondria) so as to keep amino acids for the assembly of substantial proteins, like the clotting factors in liver, when amino acids availability is restricted. Genetic manipulation studies in mice have applied molecular associations between mitochondrial role and insulin signaling.

Investigations found that the removal of IR in the heart muscles and brain reduces the mitochondrial respiration and oxidative stress elevation in addition to inhibit generation of ATP and fatty acid oxidation (FAO) in heart (33-35). The knockout of Adipose-specific IR lowers mitochondrial purport and oxygen exhaustion in brown adipose tissue (BAT), whilst the lowering white adipose tissue (WAT) bloc by upon 90% (36).

In a similar manner, synthesis of ATP is lowered in β cell–specific IR-knockout mice in spite of raised oxygen consuming, and retrieving the expression of IR in β cells iterated the defect in mitochondrial ATP synthesis, proposing that the insulin hormone organizes function of mitochondrial β cell (37).

The cardio myocyte-specific removal of *Irs1* and *Irs2* lowered ADP-enhanced consumed of oxygen and ATP generation accompanied with down regulation of FAO and OXPHOS genes in mitochondria (38). Similar lowering found in FAO and morphology of mitochondria in heart followed double knockout (DKO) of IR and IGF1 receptor (*Igf1r*), that signaling cascades get together at IRS proteins (39).

Researches in *Irs1/2*–DKO mice applied mechanistic associations between hepatic insulin function and mitochondrial role. Plugging hepatic insulin signaling in *Irs1/2*–DKO mice causes resistance to insulin and FOXO1 hyper activation, which ruptured ETC combinations and minimized NAD+ level (40). As a result, the NAD+-dependent protein deacetylase SIRT1 lowers its de acetylation of PGC1A, reducing mitochondrial biogenesis and drastically inhibiting mitochondrial coupling and ATP generation (17). So, insulin thought of promote the functions of mitochondria by PGC1A redox regulation, studies present that insulin enhances mitochondrial respiration in isolated cortical neurons from healthy mice but not Alzheimer's disease–prone (AD-prone) apo lipoprotein E ε4–knock in mice (41). Given that 80% of AD patients present inhibited glucose tolerance or T2D (42), and the AD brain shows insulin resistance and inhibited mitochondrial function (43, 44), strategies that promote insulin sensitivity in diabetes may also have therapeutic value in AD. Collectively, these data prove importance of insulin for normal mitochondrial function in multiple tissues.

Sergi et al (45) suggested that the dysfunction of Mitochondria is linked to the insulin resistance pathogenesis in the T2D, but this relation still under investigations whilst some evidences suggests that enhancing the function of mitochondria may elucidate a valuable therapeutic tool for insulin sensitivity enhancing. Also they exhibited the mechanistic pathway of insulin resistance with mitochondrial dysfunction in skeletal muscle alongside the intracellular pathways orchestrating mitochondrial bioenergetics.

REFERENCES

1. Dr◌ge W. Free radicals in the physiological control of cell function. Physiol Rev. 2002;82(1):47–95.
2. Liesa M, Palacٍn M, Zorzano A. Mitochondrial dynamics in mammalian health and disease. Physiol Rev. 2009;89(3):799–845.
3. Anderson S, et al. Sequence and organization of the human mitochondrial genome. Nature. 1981;290(5806):457–465.
4. Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 2013;17(4):491–506.

5. Bommer C, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. Diabetes Care. 2018;41(5):963–970.
6. American Diabetes Association. Position statement: 2. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(suppl 1):S8–S16.
7. Bogardus C, Taskinen MR, Zawadzki J, Lillioja S, Mott D, Howard BV. Increased resting metabolic rates in obese subjects with non-insulindependent diabetes mellitus and the effect of sulfonylurea therapy. Diabetes. 1986;35(1):1–5.
8. Ravussin E, et al. Thermic effect of infused glucose and insulin in man. Decreased response with increased insulin resistance in obesity and noninsulin-dependent diabetes mellitus. J ClinInvest. 1983;72(3):893–902.
9. Cheng Z, Tseng Y, White MF. Insulin signaling meets mitochondria in metabolism. Trends Endocrinol Metab. 2010;21(10):589–598.
10. Hesselink MK, Schrauwen-Hinderling V, Schrauwen P. Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. Nat Rev Endocrinol. 2016;12(11):633–645.
11. Koliaki C, Roden M. Alterations of mitochondrial function and insulin sensitivity in human obesity and diabetes mellitus. Annu Rev Nutr. 2016;36:337–367.
12. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012;148(6):1145–1159.
13. Wai T, Langer T. Mitochondrial dynamics and metabolic regulation. Trends Endocrinol Metab. 2016;27(2):105–117.
14. De Meyts P. The insulin receptor and its signal transduction network. In: De Groot LJ, et al., eds. Endotext. South Dartmouth, Massachusetts, USA: MDText.com, Inc.; 2000.
15. Cunningham JT, Rodgers JT, Arlow DH, Vazquez F, Mootha VK, Puigserver P. mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex. Nature. 2007;450(7170):736–740.
16. Schieke SM, et al. The mammalian target of rapamycin (mTOR) pathway regulates mitochondrial oxygen consumption and oxidative capacity. J Biol Chem. 2006;281(37):27643–27652.
17. Cheng Z, et al. Foxo1 integrates insulin signaling with mitochondrial function in the liver. Nat Med. 2009;15(11):1307–1311.
18. Daitoku H, Yamagata K, Matsuzaki H, Hatta M, Fukamizu A. Regulation of PGC-1 promoter activity by protein kinase B and the forkhead transcription factor FKHR. Diabetes. 2003;52(3):642–649.
19. Scarpulla RC. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Biochim Biophys Acta. 2011;1813(7):1269–1278.
20. Wiedemann N, Frazier AE, Pfanner N. The protein import machinery of mitochondria. J Biol Chem. 2004;279(15):14473–14476.
21. Barrett EJ, Schwartz RG, Francis CK, Zaret BL. Regulation by insulin of myocardial glucose and fatty acid metabolism in the conscious dog. J Clin Invest. 1984;74(3):1073–1079.
22. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J. Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients. J Clin Invest. 1995;95(6):2926–2937.
23. James HA, O'Neill BT, Nair KS. Insulin regulation of proteostasis and clinical implications. Cell Metab. 2017;26(2):310–323.
24. Jaleel A, et al. Differential effects of insulin deprivation and systemic insulin treatment on plasma protein synthesis in type 1 diabetic people. Am J Physiol Endocrinol Metab. 2009;297(4):E889–E897.
25. Stump CS, Short KR, Bigelow ML, Schimke JM, Nair KS. Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. Proc Natl Acad Sci U S A. 2003;100(13):7996–8001.
26. Robinson MM, et al. High insulin combined with essential amino acids stimulates skeletal muscle mitochondrial protein synthesis while decreasing insulin sensitivity in healthy humans. J Clin Endocrinol Metab. 2014;99(12):E2574–E2583.
27. Chow LS, Albright RC, Bigelow ML, Toffolo G, Cobelli C, Nair KS. Mechanism of insulin's anabolic effect on muscle: measurements of muscle protein synthesis and breakdown using aminoacyl-tRNA and other surrogate measures. Am J Physiol Endocrinol Metab. 2006;291(4):E729–E736.
28. Gelfand RA, Barrett EJ. Effect of physiologic hyperinsulinemia on skeletal muscle protein synthesis and breakdown in man. J Clin Invest. 1987;80(1):1–6.
29. Barazzoni R, Short KR, Asmann Y, Coenen-Schimke JM, Robinson MM, Nair KS. Insulin fails to enhance mTOR phosphorylation, mitochondrial protein synthesis, and ATP production in human skeletal muscle without amino acid replacement. Am J Physiol Endocrinol Metab. 2012;303(9):E1117–E1125.
30. Ling C, et al. Multiple environmental and genetic factors influence skeletal muscle PGC-1α and PGC-1β gene expression in twins. J Clin Invest. 2004;114(10):1518–1526.
31. Asmann YW, et al. Skeletal muscle mitochondrial functions, mitochondrial DNA copy numbers, and gene transcript profiles in type 2 diabetic and nondiabetic subjects at equal levels of low or high insulin and euglycemia. Diabetes. 2006;55(12):3309–3319.
32. Nair KS, Halliday D, Garrow JS. Thermic response to isoenergetic protein, carbohydrate or fat meals in lean and obese subjects. Clin Sci. 1983;65(3):307–312.
33. Boudina S, et al. Contribution of impaired myocardial insulin signaling to mitochondrial dysfunction and oxidative stress in the heart. Circulation. 2009;119(9):1272–1283.
34. Franko A, et al. Complete failure of insulintransmitted signaling, but not obesity-induced insulin resistance, impairs respiratory chain function in muscle. J Mol Med. 2012;90(10):1145–1160.
35. Kleinridders A, et al. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. Proc Natl Acad Sci U S A. 2015;112(11):3463–3468.
36. Boucher J, et al. Differential roles of insulin and IGF-1 receptors in adipose tissue development and function. Diabetes. 2016;65(8):2201–2213.
37. Liu S, et al. Insulin signaling regulates mitochondrial function in pancreatic beta-cells. PLoS One. 2009;4(11):e7983.

38. Riehle C, et al. Insulin receptor substrate signaling suppresses neonatal autophagy in the heart. J Clin Invest. 2013;123(12):5319–5333.
39. Laustsen PG, et al. Essential role of insulin and insulin-like growth factor 1 receptor signaling in cardiac development and function. Mol Cell Biol. 2007;27(5):1649–1664.
40. Dong XC, et al. Inactivation of hepatic Foxo1 by insulin signaling is required for adaptive nutrient homeostasis and endocrine growth regulation. Cell Metab. 2008;8(1):65–*76.*
41. Zhao N, et al. Apolipoprotein E4 impairs neuronal insulin signaling by trapping insulin receptor in the endosomes. *Neuron*. 2017;96(1):115–129.e5.
42. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*. 2004;53(2):474–481.
43. Talbot K, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest*. 2012;122(4):1316–1338.
44. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*. 2006;443(7113):787–795.
45. Sergi D, Naumovski N, Heilbronn LK, Abeywardena M, O'Callaghan N, Lionetti L and Luscombe-Marsh N (2019) Mitochondrial (Dys)function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet.Front. Physiol. 10:532. doi: 10.3389/fphys.2019.00532.