ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

The Role Of Glucose Transporters In Skeletal Muscle, Liver, And Adipose Tissue In Metabolic Health And Disease

Jyoti Batra[1], Ayush Manral[2], Juhi Aggarwal[3] , Aarushi Batra[4]

1. Professor, Department of Biochemistry, Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad
2. MBBS-I year, Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad, Uttar Pradesh -201009
3. Professor, Department of Biochemistry, Santosh Medical College and Hospital, Santosh deemed to be University, Ghaziabad
4. MBBS final year, LLRM Medical College Merrut, UP

ABSTRACT

A family of facilitative glucose transporters (GLUTs) is involved in regulating tissue-specific glucose uptake and metabolism in the liver, skeletal muscle, and adipose tissue to ensure homeostatic control of blood glucose levels. Reduced glucose transport activity results in aberrant use of energy substrates and is associated with insulin resistance and type 2 diabetes. It is well established that GLUT2, the main regulator of hepatic hexose flux, and GLUT4, the workhorse in insulin- and contraction-stimulated glucose uptake in skeletal muscle, are critical contributors in the control of whole-body glycemia. However, the molecular mechanism how insulin controls glucose transport across membranes and its relation to impaired glycemic control in type 2 diabetes remains not sufficiently understood. An array of circulating metabolites and hormone-like molecules and potential supplementary glucose transporters play roles in fine-tuning glucose flux between the different organs in response to an altered energy demand.

Keywords: Crosstalk .Exercise . Insulin resistance .NAFLD . Type 2 diabetes.

INTRODUCTION

The primary energy source for the majority of bodily tissues is glucose. As a result, a sophisticated regulatory system comprising numerous tissues is responsible for maintaining whole-body glucose homeostasis. Distribution of dietary components according to the distinct needs of each organ is ensured by inter-organ crosstalk via a variety of circulating substances such hormones and neuropeptides [84]. Glucose transporters (GLUTs) from the SLC2A gene family, sodium-glucose symporters (SGLTs), and SWEETs are the three kinds

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

of eukaryotic sugar transporters currently known [32]. Absorption, distribution, and excretion/recovery are just a few of the crucial processes that the wide family of GLUTs, evolutionary conserved facilitative glucose transporters, is engaged in when handling glucose and other hexoses. After the glucose is absorbed from the intestine, consumption of carbohydrates causes an instantaneous rise in blood glucose levels. Pancreatic beta cells directly react to the increased blood glucose levels by secreting more insulin as a result of a GLUT2-dependent mechanism. Due to the acute translocation of GLUT4 transporter vesicles to the plasma membrane and the suppression of hepatic gluconeogenesis, insulin binding to its receptors results in increased glucose transfer into skeletal muscle, adipose tissue, and the heart. Together, the two regulatory processes cause the bloodstream to be cleared of glucose. Insulin resistance is a condition in which peripheral tissues are comparatively unable to respond appropriately to rising insulin levels in the blood, leading to persistently high blood glucose levels. Type 2 diabetes mellitus, a significant health burden on contemporary society, is known to be characterised by a progressive rise in peripheral insulin resistance, followed by beta cell death and, as a result, hypoinsulinemia. This state of hyperglycemia is known to be a hallmark of type 2 diabetes mellitus. Although the pathogenesis of this metabolic condition is not fully understood, there is compelling evidence that various GLUT family members play a critical role in the onset and progression of insulin resistance and type 2 diabetes.

The function of the GLUT family in the liver, muscles, and adipose tissue is highlighted in this article, as well as how specifically GLUTs contribute to systemic glucose homeostasis and energy metabolism in both a healthy and diabetic condition. On the structure-function relationship of GLUTs [32, 93], insulin signalling [83], and the control of the insulin- and contractionresponsive GLUT4 trafficking, several recent studies offer excellent and complete overviews.

The liver

The liver is the main organ for glucose storageand essential for the regulation of glucosehomeostasis.

By making it easier for the activity of numerous glycogen production enzymes, such as phosphofructokinase and glycogen synthase, to be suppressed, glycogenolysis can be prevented [173]. Although the precise mechanisms underlying insulin's direct role in

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

regulating hepatic gluconeogenesis remain unknown, various indirect regulatory pathways have been shown to exist. There are numerous mechanisms and various different organs involved in the indirect control of insulin on HGP. Reduced levels of circulating free fatty acids and glycerol are the outcome of insulin-mediated suppression of lipolysis in adipose tissue. In addition, insulin prevents pancreatic alpha cells from producing glucagon. In the postprandial state, these procedurestherefore result in decreased hepatic glucose output, sustaining normoglycemia [33].

Liver insulin resistance is a major feature of type 2 diabetes pathophysiology

Reduced insulin-stimulated signal transduction pathways for hepatic glucose synthesis, including insulin receptors and downstream mediators, have been described as the hallmark of hepatic insulin resistance. It is known that a number of variables can lead to the development of insulin resistance in the liver. For instance, type 2 diabetes incidence and the advancement of hepatic insulin resistance are both substantially correlated with infections with the hepatitis C virus (HCV). According to the mechanism, the HCV core protein causes an increase in inflammatory indicators such tumour necrosis factor (TNF-), which finally results in less insulin signalling activation downstream [36]. Additionally, HCV core protein promotes lipid accumulation and hepatic steatosis by impairing mitochondrial activity and endoplasmic reticulum (ER) function in hepatocytes.

Several members of the GLUT family are relevant in liver metabolism

In the liver, almost all GLUTs' gene expression has been verified. However, GLUT1, GLUT2, GLUT5, GLUT8, and GLUT9 are highly prevalent in this tissue.

- GLUT1: marker for oncogenic and metabolic diseases in the liver.
- GLUT2: major glucose transporter required for glucose sensing and hepatic glucose output.
- GLUT5: main mammalian fructose transporter.
- GLUT8: intracellular hexose transporter regulating hepaticoxidative metabolism.
- GLUT9: a high-capacity uric acid transporter compensatingfor GLUT2.
- GLUT10: high hepatic expression levels but so far enigmaticfunction.

Glucose transporters with minor expression levels or absentin the liver: GLUT3, GLUT4, GLUT6, GLUT7, GLUT11, GLUT12,and GLUT13 (HMIT)

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

Skeletal muscle and adipose tissue

Skeletal muscle is the main tissue controlling postprandial glucose disposal: Skeletal muscle plays a critical role in maintaining blood glucose homeostasis. In actuality, after a meal, skeletal muscle serves as the primary glucose sink. Approximately 75% of the glucose that is removed from the body once it has been infused into it goes through the muscle, and this process is severely hampered in an insulin-resistant state [47, 48]. Exercise increases muscle insulin sensitivity, and insulin and exercise work together to improve skeletal muscle glucose clearance [46]. Blood glucose levels have been demonstrated to decrease with both aerobic and resistance exercise training, which is at least partially attributable to enhanced glucose transport activity and glucose metabolism in skeletal muscle. Although the mechanism underlying the health benefits of exercise is not fully known, it probably involves changes in the metabolic and signal transduction pathways in numerous organs.

Adipose tissue regulates systemic glucose metabolism: Adipose tissue is a highly dynamic organ with a high capacity \sfor remodelling to meet the demands of changing nutritional \sconditions. Additionally, adipose tissue is a significant endocrine organ that produces vital hormones and elements that regulate the entire body's metabolism, systemic insulin sensitivity, and homeostasis of energy. Both the lack and excess of adipose tissue may lead to serious abnormalities of glucose homeostasis and diabetes. White adipose tissue harbours mature \sadipose cells and progenitor cells, but also other cell types \srelated to its innervation and vascularization. The fact that it comprises a variety of immune cell types, which are essential for adipocyte function and can dynamically adapt to changes in fat depot size, is most crucial. Adipose cells from diverse \sorigins, e.g., from subcutaneous or visceral depots, exhibit distinct metabolic characteristics and growth dynamics [82]. In \srodents, but also in humans, the brown adipose tissue is specialised to disperse energy as heat. As a result of these \sstructural intricacies, studies on glucose transport in adipose cells usually focus on a narrow subset of conditions \srelevant in adipocyte biology. The equilibrium of glucose and lipids is mostly regulated by adipose tissue, and the metabolism of both substances is interwoven. The contribution \sof adipose cells to glucose elimination is substantially smaller compared \sto skeletal muscle [47, 48]. However, research utilising transgenic and knockout mice with excess or defective glucose transporters have shown the crucial part adipose tissue plays in maintaining glucose homeostasis.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

Multiple GLUT isoforms are expressed in skeletal muscle and adipocytes: Skeletal muscle has a profound capacity for taking up glucosefrom the extracellular medium. While samples from humanand rodent skeletal muscle tissue have been found to expressmultiple glucose transporters belonging to both gene families,GLUTs and SGLTs, the corresponding copy numbers of therespective messenger RNAs (mRNAs) differed over 3 ordersof magnitude.

- GLUT1: major glucose transporter regulating basal glucose transport into skeletal muscle and adipocytes.
- GLUT3: contributor to basal glucose uptake in skeletal muscle.
- GLUT4: the workhorse for insulin- and contraction-responsive glucose transports in skeletal muscle and adipocytes.
- GLUT8: intracellular transporter with links to developmental insulin signaling and autophagy.
- GLUT8: intracellular transporter with links to developmental insulin signaling and autophagy.
- GLUT10: enigmatic glucose transporter also expressed in skeletal muscle and adipose tissue.
- GLUT11: fructose transporter specific for muscular tissues.
- GLUT12: compensatory glucose transporter upon GLUT4 deficiency in skeletal muscle.
- Glucose transporters with minor abundance or absent in skeletal muscle and adipocytes: GLUT2, GLUT5, GLUT6, GLUT7, GLUT9, and GLUT13 (HMIT)

In skeletal muscle and adipose cells, RabGAPs relayinsulin/contraction signaling to the GLUT4translocation machinery.

TBC1D1 and TBC1D4 are associated with metabolic traits and diseases

Mutations in TBC1D1 have been linked to features related to obesity in mice [29, 55, 88] and humans. Additionally, TBC1D4 mutations have been associated to human insulin resistance [40]. The Greenlandic Inuit group has a widespread loss-of-function mutation in TBC1D4 (p.Arg684Ter), and homozygous bearers of the mutant allele exhibit markedly delayed postprandial disposal of glucose and a more than 10-fold increased risk of developing type 2

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

diabetes. In actuality, TBC1D4 (p.Arg684Ter) seems to be the primary genetic contributor to type 2 diabetes in both Canadian and Greenlandic Inuit.

Physical exercise improves glycemic control through enhancing glucose transport

Exercise training increased skeletal muscle GLUT4 protein levels, which in turn boosted whole-body insulin-mediated glucose clearance in obese type 2 diabetes patients. Additionally, it has been demonstrated that increased GLUT4 translocation to the cell surface, which is independent of insulin signalling, is what causes the increased muscle insulin sensitivity of glucose transport during exercise [87]. The primary function of GLUT4 in this tissue was demonstrated to significantly boost glucose transport in skeletal muscle of wild-type mice but not in GLUT4 mutant animals during exercise and contraction.

Role of glucose transporters in intra-organ crosstalk

Homozygous global knockout mice with a lower abundance of GLUT4 in skeletal muscle and adipose tissue showed a more severe metabolic phenotype than heterozygous global knockout mice. This was linked to compensating mechanisms, which although still unclear, may enable survival. But conditional GLUT4 deletion in either adipose or skeletal muscle leads to systemic insulin resistance and has significant metabolic impacts on other tissues. While adipose-specific GLUT4 deletion causes insulin resistance in the liver and skeletal muscle, muscle-specific GLUT4 deficit reduced insulin sensitivity in adipose tissue and the liver [268]. It should be mentioned that compared to skeletal muscle, adipose cells contribute much less to the body's overall ability to dispose of glucose.

In muscle-specific GLUT4 mutant animals, overexpression of GLUT4 in adipose tissue (driven by the aP2 promoter) reversed whole-body insulin resistance without restoring glucose transport in skeletal muscle [25].

The etiology of insulin resistance is unknown

Skeletal muscle and adipose tissue have reduced insulin-stimulated glucose uptake as a result of type 2 diabetes and insulin resistance. Since GLUT4 translocation is necessary for maintaining glycemic homeostasis, overexpression of GLUT4 but not GLUT1 in skeletal muscle normalises insulin sensitivity and glucose tolerance in mice. The molecular causes of the decreased insulin activity are not entirely understood, yet. It has been proposed that changes in lipid metabolism and the production of harmful metabolites, such as DAGs ,

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

ceramides [31], and ROS, as well as inflammation, block the phosphorylation of the insulin receptor (IR), insulin receptor substrate 1 (IRS1), and downstream effectors, thereby inhibiting insulin signalling towards GLUT4. However, this idea has lately been called into question because experimental insulin resistance can happen without changes to IR and IRS1 signalling [65].Together, insulin resistance and diabetes are linked to significant changes in cellular glucose transport, but it is yet unknown what causes the decreased insulin-stimulated glucose transport and what effects it has on the aetiology of the illness.

CONCLUSION

In the liver, skeletal muscle, and adipose tissue, numerous distinct GLUT isoforms have been effectively discovered in earlier studies. There is still a lot to learn, as evidenced by the high level of substrate variety, intricate expressional control, and varied activity patterns of the isoforms. Future research may be particularly interesting in the impact of various lifestyle factors, such as high-fructose diets and exercise, on GLUT function in energy metabolism. For insulin-regulated glucose transport in adipose cells and for insulin- and contraction-stimulated glucose uptake in skeletal muscle, GLUT4 continues to be the workhorse. The idea that defective GLUT4 translocation plays a significant role in the genesis of insulin resistance and type 2 diabetes has been confirmed by a number of research.This process' mechanical structure is incredibly intricate, and it's going to be a hot issue for years to come.To balance glucose uptake and substrate metabolism in insulin-sensitive tissues in response to various physiological cues and/or increasing energy demand, other non-classical GLUTs, such as GLUT12, may also play a role in addition to GLUT4. In addition, additional GLUTs, such GLUT8, may offer inducible glucose transport capability throughout various stages of cellular development, which may help to cause the emergence of insulin resistance in adolescence. As demonstrated by the uric acid transporter GLUT9, other glucose transporters, including GLUT6, GLUT10, and GLUT11, may not even be significant for hexose transfer. An essential part of the fight against metabolic illnesses will be comprehending the intricate connections between these metabolic networks and organ crosstalk.

REFERENCES

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

1. Abel ED, Peroni O, Kim JK, Kim YB, Boss O, Hadro E, Minnemann T, Shulman GI, Kahn BB (2001) Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature 409:729–733. https://doi.org/10.1038/35055575
2. Aerni-Flessner LB, Otu MC, Moley KH (2011) The amino acids upstream of NH(2)-terminal dileucine motif play a role in regulating the intracellular sorting of the class III transporters GLUT8 and GLUT12. MolMembrBiol 28:30–41. https://doi.org/10.3109/09687688.2010.508196
3. Al-Hasani H, Hinck CS, Cushman SW (1998) Endocytosis of the glucose transporter GLUT4 is mediated by the GTPase dynamin. J BiolChem 273:17504–17510
4. Al-Hasani H, Kunamneni RK, Dawson K, Hinck CS, MullerWieland D, Cushman SW (2002) Roles of the N- and C-termini of GLUT4 in endocytosis. J Cell Sci 115:131–140
5. Alwahsh SM, Xu M, Seyhan HA, Ahmad S, Mihm S, Ramadori G, Schultze FC (2014) Diet high in fructose leads to an overexpression of lipocalin-2 in rat fatty liver. World J Gastroenterol 20: 1807–1821. https://doi.org/10.3748/wjg.v20.i7.1807
6. Andersen G, Rose CS, Hamid YH, Drivsholm T, Borch-Johnsen K, Hansen T, Pedersen O (2003) Genetic variation of the GLUT10 glucose transporter (SLC2A10) and relationships to type 2 diabetes and intermediary traits. Diabetes 52:2445–2448. https://doi. org/10.2337/diabetes.52.9.2445
7. Augustin R (2010) The protein family of glucose transport facilitators: it's not only about glucose after all. IUBMB Life 62:315– 333. https://doi.org/10.1002/iub.315
8. Augustin R, Carayannopoulos MO, Dowd LO, Phay JE, Moley JF, Moley KH (2004) Identification and characterization of human glucose transporter-like protein-9 (GLUT9): alternative splicing alters trafficking. J BiolChem 279:16229–16236. https://doi.org/ 10.1074/jbc.M312226200
9. Augustin R, Riley J, Moley KH (2005) GLUT8 contains a [DE]XXXL[LI] sorting motif and localizes to a late endosomal/ lysosomal compartment. Traffic 6:1196–1212. https://doi.org/10. 1111/j.1600-0854.2005.00354.x
10. Basaranoglu M, Basaranoglu G, Bugianesi E (2015) Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

Hepatobiliary SurgNutr 4:109–116. https://doi. org/10.3978/j.issn.2304-3881.2014.11.05

11. Berry GT, Baynes JW, Wells-Knecht KJ, Szwergold BS, Santer R (2005) Elements of diabetic nephropathy in a patient with GLUT 2 deficiency. Mol Genet Metab 86:473–477. https://doi.org/10. 1016/j.ymgme.2005.09.010
12. Bian H, Yan H, Zeng M, Rao S, Yao X, Zhou J, Jia W, Gao X (2011) Increased liver fat content and unfavorable glucose profiles in subjects without diabetes. Diabetes TechnolTher 13:149–155. https://doi.org/10.1089/dia.2010.0101
13. Bibert S, Hess SK, Firsov D, Thorens B, Geering K, Horisberger JD, Bonny O (2009) Mouse GLUT9: evidences for a urate uniporter. Am J Physiol Renal Physiol297:F612–F619. https:// doi.org/10.1152/ajprenal.00139.2009
14. Bickel PE (2004) Metabolic fuel selection: the importance of being flexible. J Clin Invest 114:1547–1549. https://doi.org/10. 1172/JCI23745
15. Bilan PJ, Mitsumoto Y, Maher F, Simpson IA, Klip A (1992) Detection of the GLUT3 facilitative glucose transporter in rat L6 muscle cells: regulation by cellular differentiation, insulin and insulin-like growth factor-I. BiochemBiophys Res Commun 186:1129–1137. https://doi.org/10.1016/0006-291x(92)90864-h
16. Block NE, Menick DR, Robinson KA, Buse MG (1991) Effect of denervation on the expression of two glucose transporter isoforms in rat hindlimb muscle. J Clin Invest 88:1546–1552. https://doi. org/10.1172/JCI115465
17. Boden G, Homko C, Barrero CA, Stein TP, Chen X, Cheung P, Fecchio C, Koller S, Merali S (2015) Excessive caloric intake acutely causes oxidative stress, GLUT4 carbonylation, and insulin resistance in healthy men. SciTransl Med 7:304re307. https://doi. org/10.1126/scitranslmed.aac4765
18. Borglykke A, Grarup N, Sparso T, Linneberg A, Fenger M, Jeppesen J, Hansen T, Pedersen O, Jorgensen T (2012) Genetic variant SLC2A2 [corrected] is associated with risk of cardiovascular disease - assessing the individual and cumulative effect of 46 type 2 diabetes related genetic variants. PLoS One 7:e50418. https://doi.org/10.1371/journal.pone.0050418
19. Brozinick JT Jr, McCoid SC, Reynolds TH, Nardone NA, Hargrove DM, Stevenson RW, Cushman SW, Gibbs EM (2001) GLUT4 overexpression in db/db mice dose-

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

dependently ameliorates diabetes but is not a lifelong cure. Diabetes 50:593–600. https://doi.org/10.2337/diabetes.50.3.593

20. Burcelin R, Dolci W, Thorens B (2000) Glucose sensing by the hepatoportal sensor is GLUT2-dependent: in vivo analysis in GLUT2-null mice. Diabetes 49:1643–1648. https://doi.org/10. 2337/diabetes.49.10.1643
21. Burcelin R, Dolci W, Thorens B (2000) Portal glucose infusion in the mouse induces hypoglycemia: evidence that the hepatoportal glucose sensor stimulates glucose utilization. Diabetes 49:1635– 1642. https://doi.org/10.2337/diabetes.49.10.1635
22. Byrne FL, Olzomer EM, Brink R, Hoehn KL (2018) Knockout of glucose transporter GLUT6 has minimal effects on whole body metabolic physiology in mice. Am J PhysiolEndocrinolMetab315:E286–E293. https://doi.org/10.1152/ajpendo.00082.2018
23. Carayannopoulos MO, Chi MM, Cui Y, Pingsterhaus JM, McKnight RA, Mueckler M, Devaskar SU, Moley KH (2000) GLUT8 is a glucose transporter responsible for insulinstimulated glucose uptake in the blastocyst. Proc Natl AcadSci U S A 97:7313–7318. https://doi.org/10.1073/pnas.97.13.7313
24. Cartee GD, Young DA, Sleeper MD, Zierath J, WallbergHenriksson H, Holloszy JO (1989) Prolonged increase in insulin-stimulated glucose transport in muscle after exercise. Am J Physiol256:E494–E499. https://doi.org/10.1152/ajpendo.1989. 256.4.E494
25. Carvalho E, Kotani K, Peroni OD, Kahn BB (2005) Adiposespecific overexpression of GLUT4 reverses insulin resistance and diabetes in mice lacking GLUT4 selectively in muscle. Am J PhysiolEndocrinolMetab289:E551–E561. https://doi.org/10. 1152/ajpendo.00116.2005
26. Castorena CM, Arias EB, Sharma N, Cartee GD (2014) Postexercise improvement in insulin-stimulated glucose uptake occurs concomitant with greater AS160 phosphorylation in muscle from normal and insulin-resistant rats. Diabetes 63:2297–2308. https://doi.org/10.2337/db13-1686
27. Caulfield MJ, Munroe PB, O'Neill D, Witkowska K, Charchar FJ, Doblado M, Evans S, Eyheramendy S, Onipinla A, Howard P, Shaw-Hawkins S, Dobson RJ, Wallace C, Newhouse SJ, Brown M, Connell JM, Dominiczak A, Farrall M, Lathrop GM, Samani NJ, Kumari M, Marmot M, Brunner E, Chambers J, Elliott P, Kooner J, Laan

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

M, Org E, Veldre G, Viigimaa M, Cappuccio FP, Ji C, Iacone R, Strazzullo P, Moley KH, Cheeseman C (2008) SLC2A9 is a high-capacity urate transporter in humans. PLoS Med 5:e197. https://doi.org/10.1371/journal.pmed.0050197

28. Chadt A, Immisch A, de Wendt C, Springer C, Zhou Z, Stermann T, Holman GD, Loffing-Cueni D, Loffing J, Joost HG, Al-Hasani H (2015) Deletion of both Rab-GTPase-activating proteins TBC1D1 and TBC1D4 in mice eliminates insulin- and AICARstimulated glucose transport. Diabetes 64:746–759. https://doi. org/10.2337/db14-0368
29. Chadt A, Leicht K, Deshmukh A, Jiang LQ, Scherneck S, Bernhardt U, Dreja T, Vogel H, Schmolz K, Kluge R, Zierath JR, Hultschig C, Hoeben RC, Schurmann A, Joost HG, AlHasani H (2008) Tbc1d1 mutation in lean mouse strain confers leanness and protects from diet-induced obesity. Nat Genet 40: 1354–1359. https://doi.org/10.1038/ng.244
30. Charron MJ, Kahn BB (1990) Divergent molecular mechanisms for insulin-resistant glucose transport in muscle and adipose cells in vivo. J BiolChem 265:7994–8000
31. Chavez JA, Summers SA (2012) A ceramide-centric view of insulin resistance. Cell Metab 15:585–594. https://doi.org/10.1016/ j.cmet.2012.04.002
32. Chen LQ, Cheung LS, Feng L, Tanner W, Frommer WB (2015) Transport of sugars. Annu Rev Biochem 84:865–894. https://doi. org/10.1146/annurev-biochem-060614-033904
33. Cherrington AD, Liljenquist JE, Shulman GI, Williams PE, Lacy WW (1979) Importance of hypoglycemia-induced glucose production during isolated glucagon deficiency. Am J Physiol 236: E263–E271. https://doi.org/10.1152/ajpendo.1979.236.3.E263
34. Choi YJ, Yoon Y, Lee KY, Hien TT, Kang KW, Kim KC, Lee J, Lee MY, Lee SM, Kang DH, Lee BH (2014) Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. FASEB J 28:3197– 3204. https://doi.org/10.1096/fj.13-247148
35. Copeland RJ, Bullen JW, Hart GW (2008) Cross-talk between GlcNAcylation and phosphorylation: roles in insulin resistance and glucose toxicity. Am J PhysiolEndocrinolMetab295:E17– E28. https://doi.org/10.1152/ajpendo.90281.2008

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

36. Copps KD, White MF (2012) Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia 55:2565–2582. https://doi.org/ 10.1007/s00125-012-2644-8
37. Corpe CP, Eck P, Wang J, Al-Hasani H, Levine M (2013) Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. J BiolChem 288:9092–9101. https://doi.org/10.1074/jbc.M112.436790
38. Cushman SW, Wardzala LJ (1980) Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. Apparent translocation of intracellular transport systems to the plasma membrane. J BiolChem 255:4758–4762
39. Darakhshan F, Hajduch E, Kristiansen S, Richter EA, Hundal HS (1998) Biochemical and functional characterization of the GLUT5 fructose transporter in rat skeletal muscle. Biochem J 336(Pt 2): 361–366. https://doi.org/10.1042/bj3360361
40. Dash S, Sano H, Rochford JJ, Semple RK, Yeo G, Hyden CS, Soos MA, Clark J, Rodin A, Langenberg C, Druet C, Fawcett KA, Tung YC, Wareham NJ, Barroso I, Lienhard GE, O'Rahilly S, Savage DB (2009) A truncation mutation in TBC1D4 in a family with acanthosis nigricans and postprandial hyperinsulinemia. Proc Natl AcadSci U S A 106:9350–9355. https://doi.org/10.1073/ pnas.0900909106
41. Davey JR, Humphrey SJ, Junutula JR, Mishra AK, Lambright DG, James DE, Stockli J (2012) TBC1D13 is a RAB35 specific GAP that plays an important role in GLUT4 trafficking in adipocytes. Traffic 13:1429–1441. https://doi.org/10.1111/j.1600-0854.2012.01397.x
42. Dawson PA, Mychaleckyj JC, Fossey SC, Mihic SJ, Craddock AL, Bowden DW (2001) Sequence and functional analysis of GLUT10: a glucose transporter in the type 2 diabetes-linked region of chromosome 20q12-13.1. Mol Genet Metab 74:186–199. https://doi.org/10.1006/mgme.2001.3212
43. DeBosch BJ, Chen Z, Finck BN, Chi M, Moley KH (2013) Glucose transporter-8 (GLUT8) mediates glucose intolerance and dyslipidemia in high-fructose diet-fed male mice. MolEndocrinol 27:1887–1896. https://doi.org/10.1210/me.2013-1137
44. Debosch BJ, Chen Z, Saben JL, Finck BN, Moley KH (2014) Glucose transporter 8 (GLUT8) mediates fructose-induced de novo lipogenesis and macrosteatosis. J BiolChem 289:10989– 10998. https://doi.org/10.1074/jbc.M113.527002

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

45. DeBosch BJ, Kluth O, Fujiwara H, Schurmann A, Moley K (2014) Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. Nat Commun 5:4642. https:// doi.org/10.1038/ncomms5642
46. DeFronzo RA, Ferrannini E, Sato Y, Felig P, Wahren J (1981) Synergistic interaction between exercise and insulin on peripheral glucose uptake. J Clin Invest 68:1468–1474. https://doi.org/10. 1172/jci110399
47. DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J (1985) Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. J Clin Invest 76:149–155. https://doi.org/10.1172/JCI111938
48. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP (1981) The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes 30:1000–1007. https://doi.org/10.2337/ diab.30.12.1000
49. Dentin R, Denechaud PD, Benhamed F, Girard J, Postic C (2006) Hepatic gene regulation by glucose and polyunsaturated fatty acids: a role for ChREBP. J Nutr 136:1145–1149. https://doi. org/10.1093/jn/136.5.1145
50. Deshmukh AS, Murgia M, Nagaraj N, Treebak JT, Cox J, Mann M (2015) Deep proteomics of mouse skeletal muscle enables quantitation of protein isoforms, metabolic pathways, and transcription factors. Molecular & Cellular Proteomics: MCP 14: 841–853. https://doi.org/10.1074/mcp.M114.044222
51. Didyk RB, Anton EE, Robinson KA, Menick DR, Buse MG (1994) Effect of immobilization on glucose transporter expression in rat hindlimb muscles. Metabolism 43:1389–1394. https://doi. org/10.1016/0026-0495(94)90033-7
52. Doege H, Bocianski A, Joost HG, Schurmann A (2000) Activity and genomic organization of human glucose transporter 9 (GLUT9), a novel member of the family of sugar-transport facilitators predominantly expressed in brain and leucocytes. Biochem J 350(Pt 3):771–776.
53. Doege H, Bocianski A, Scheepers A, Axer H, Eckel J, Joost HG, Schurmann A (2001) Characterization of human glucose transporter (GLUT) 11 (encoded by SLC2A11), a novel sugartransport facilitator specifically expressed in heart and

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

skeletal muscle. Biochem J 359:443–449. https://doi.org/10.1042/0264-6021:3590443

54. Doege H, Schurmann A, Bahrenberg G, Brauers A, Joost HG (2000) GLUT8, a novel member of the sugar transport facilitator family with glucose transport activity. J BiolChem 275:16275– 16280. https://doi.org/10.1074/jbc.275.21.16275
55. Dokas J, Chadt A, Joost HG, Al-Hasani H (2016) Tbc1d1 deletion suppresses obesity in leptin-deficient mice. Int J Obes (Lond) 40: 1242–1249. https://doi.org/10.1038/ijo.2016.45
56. Dokas J, Chadt A, Nolden T, Himmelbauer H, Zierath JR, Joost HG, Al-Hasani H (2013) Conventional knockout of Tbc1d1 in mice impairs insulin- and AICAR-stimulated glucose uptake in skeletal muscle. Endocrinology 154:3502–3514. https://doi.org/ 10.1210/en.2012-2147
57. Donovan CM, Hamilton-Wessler M, Halter JB, Bergman RN (1994) Primacy of liver glucosensors in the sympathetic response to progressive hypoglycemia. Proc Natl AcadSci U S A 91:2863– 2867. https://doi.org/10.1073/pnas.91.7.2863
58. Douen AG, Ramlal T, Klip A, Young DA, Cartee GD, Holloszy JO (1989) Exercise-induced increase in glucose transporters in plasma membranes of rat skeletal muscle. Endocrinology 124: 449–454. https://doi.org/10.1210/endo-124-1-449
59. Douen AG, Ramlal T, Rastogi S, Bilan PJ, Cartee GD, Vranic M, Holloszy JO, Klip A (1990) Exercise induces recruitment of the "insulin-responsive glucose transporter". Evidence for distinct intracellular insulin- and exercise-recruitable transporter pools in skeletal muscle. J BiolChem 265:13427–13430
60. Enogieru OJ, Ung PMU, Yee SW, Schlessinger A, Giacomini KM (2019) Functional and structural analysis of rare SLC2A2 variants associated with Fanconi-Bickel syndrome and metabolic traits. Hum Mutat 40:983–995. https://doi.org/10.1002/humu.23758
61. Espelage L, Al-Hasani H, Chadt A (2020) RabGAPs in skeletal muscle function and exercise. J MolEndocrinol 64:R1–R19. https://doi.org/10.1530/JME-19-0143
62. Esteves JV, Enguita FJ, Machado UF (2017) MicroRNAsmediated regulation of skeletal muscle GLUT4 expression and translocation in insulin resistance. J Diabetes Res 2017: 7267910–7267911. https://doi.org/10.1155/2017/7267910

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

63. Evans PL, McMillin SL, Weyrauch LA, Witczak CA (2019) Regulation of skeletal muscle glucose transport and glucose metabolism by exercise training. Nutrients 11. https://doi.org/10. 3390/nu11102432
64. Fazakerley DJ, Krycer JR, Kearney AL, Hocking SL, James DE (2019) Muscle and adipose tissue insulin resistance: malady without mechanism? J Lipid Res 60:1720–1732. https://doi.org/10. 1194/jlr.R087510
65. Flores-Opazo M, Raajendiran A, Watt MJ, Hargreaves M (2019) Exercise serum increases GLUT4 in human adipocytes. ExpPhysiol 104:630–634. https://doi.org/10.1113/EP087495
66. Fushiki T, Wells JA, Tapscott EB, Dohm GL (1989) Changes in glucose transporters in muscle in response to exercise. Am J Physiol256:E580–E587. https://doi.org/10.1152/ajpendo.1989. 256.5.E580
67. Gamberucci A, Marcolongo P, Nemeth CE, Zoppi N, Szarka A, Chiarelli N, Hegedus T, Ritelli M, Carini G, Willaert A, Callewaert BL, Coucke PJ, Benedetti A, Margittai E, Fulceri R, Banhegyi G, Colombi M (2017) GLUT10-lacking in arterial tortuosity syndrome-is localized to the endoplasmic reticulum of human fibroblasts. Int J MolSci 18. https://doi.org/10.3390/ ijms18081820
68. Garvey WT, Maianu L, Huecksteadt TP, Birnbaum MJ, Molina JM, Ciaraldi TP (1991) Pretranslational suppression of a glucose transporter protein causes insulin resistance in adipocytes from patients with non-insulin-dependent diabetes mellitus and obesity.JClin Invest 87:1072–1081. https://doi.org/10.1172/JCI115068
69. Gastaldelli A, Toschi E, Pettiti M, Frascerra S, Quinones-Galvan A, Sironi AM, Natali A, Ferrannini E (2001) Effect of physiological hyperinsulinemia on gluconeogenesis in nondiabetic subjects and in type 2 diabetic patients. Diabetes 50:1807–1812. https:// doi.org/10.2337/diabetes.50.8.1807
70. 71. Gaster M, Franch J, Staehr P, Beck-Nielsen H, Smith T, Schroder HD (2000) Induction of GLUT-1 protein in adult human skeletal muscle fibers. Am J PhysiolEndocrinolMetab279:E1191– E1195. https://doi.org/10.1152/ajpendo.2000.279.5.E1191
71. 72. Gaster M, Handberg A, Schurmann A, Joost HG, Beck-Nielsen H, Schroder HD (2004) GLUT11, but not GLUT8 or GLUT12, is expressed in human skeletal muscle

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

in a fibre type-specific pattern. Pflügers Arch 448:105–113. https://doi.org/10.1007/s00424- 003-1219-4

72. 73. Gawlik V, Schmidt S, Scheepers A, Wennemuth G, Augustin R, Aumuller G, Moser M, Al-Hasani H, Kluge R, Joost HG, Schurmann A (2008) Targeted disruption of Slc2a8 (GLUT8) reduces motility and mitochondrial potential of spermatozoa. MolMembrBiol 25:224–235. https://doi.org/10.1080/ 09687680701855405
73. 74. Gerrits PM, Olson AL, Pessin JE (1993) Regulation of the GLUT4/muscle-fat glucose transporter mRNA in adipose tissue of insulin-deficient diabetic rats. J BiolChem 268:640–644
74. 75. Ghosh S, Watanabe RM, Valle TT, Hauser ER, Magnuson VL, Langefeld CD, Ally DS, Mohlke KL, Silander K, Kohtamaki K, Chines P, Balow J Jr, Birznieks G, Chang J, Eldridge W, Erdos MR, Karanjawala ZE, Knapp JI, Kudelko K, Martin C, MoralesMena A, Musick A, Musick T, Pfahl C, Porter R, Rayman JB (2000) The Finland-United States investigation of non-insulindependent diabetes mellitus genetics (FUSION) study. I. An autosomal genome scan for genes that predispose to type 2 diabetes. Am J Hum Genet 67:1174–1185
75. 76. Gorboulev V, Schurmann A, Vallon V, Kipp H, Jaschke A, Klessen D, Friedrich A, Scherneck S, Rieg T, Cunard R, VeyhlWichmann M, Srinivasan A, Balen D, Breljak D, Rexhepaj R, Parker HE, Gribble FM, Reimann F, Lang F, Wiese S, Sabolic I, Sendtner M, Koepsell H (2012) Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucosedependentincretin secretion. Diabetes 61:187–196. https://doi. org/10.2337/db11-1029
76. 77. Gorovits N, Cui L, Busik JV, Ranalletta M, Hauguel de-Mouzon S, Charron MJ (2003) Regulation of hepatic GLUT8 expression in normal and diabetic models. Endocrinology 144:1703–1711. https://doi.org/10.1210/en.2002-220968
77. 78. Goto M, Yoshioka T, Battelino T, Ravindranath T, Zeller WP (2001) TNFalpha decreases gluconeogenesis in hepatocytes isolated from 10-day-old rats. Pediatr Res 49:552–557. https://doi. org/10.1203/00006450-200104000-00018
78. 79. Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB (2006) Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med 354:2552–2563. https://doi.org/10.1056/NEJMoa054862

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

79. 80. Guillam MT, Burcelin R, Thorens B (1998) Normal hepatic glucose production in the absence of GLUT2 reveals an alternative pathway for glucose release from hepatocytes. Proc Natl AcadSci U S A 95:12317–12321. https://doi.org/10.1073/pnas.95.21. 12317
80. 81. Guillam MT, Hummler E, Schaerer E, Yeh JI, Birnbaum MJ, Beermann F, Schmidt A, Deriaz N, Thorens B (1997) Early diabetes and abnormal postnatal pancreatic islet development in mice lacking Glut-2. Nat Genet 17:327–330. https://doi.org/10.1038/ ng1197-327
81. 82. Gustafson B, Hedjazifar S, Gogg S, Hammarstedt A, Smith U (2015) Insulin resistance and impaired adipogenesis. Trends EndocrinolMetab 26:193–200. https://doi.org/10.1016/j.tem. 2015.01.006
82. 83. Haeusler RA, McGraw TE, Accili D (2018) Biochemical and cellular properties of insulin receptor signalling. Nature Reviews Molecular Cell Biology 19:31–44. https://doi.org/10.1038/nrm. 2017.89
83. 84. Han HS, Kang G, Kim JS, Choi BH, Koo SH (2016) Regulation of glucose metabolism from a liver-centric perspective. ExpMol Med 48:e218. https://doi.org/10.1038/emm.2015.122
84. 85. Handberg A, Kayser L, Hoyer PE, Vinten J (1992) A substantial part of GLUT-1 in crude membranes from muscle originates from perineurial sheaths. Am J Physiol262:E721–E727. https://doi.org/ 10.1152/ajpendo.1992.262.5.E721
85. 86. Hansen PA, Gulve EA, Marshall BA, Gao J, Pessin JE, Holloszy JO, Mueckler M (1995) Skeletal muscle glucose transport and metabolism are enhanced in transgenic mice overexpressing the Glut4 glucose transporter. J BiolChem 270:1679–1684. https:// doi.org/10.1074/jbc.270.5.1679
86. 87. Hansen PA, Nolte LA, Chen MM, Holloszy JO (1998) Increased GLUT-4 translocation mediates enhanced insulin sensitivity of muscle glucose transport after exercise. Journal of Applied Physiology 85:1218–1222. https://doi.org/10.1152/jappl.1998. 85.4.1218
87. 88. Hargett SR, Walker NN, Keller SR (2016) Rab GAPs AS160 and Tbc1d1 play nonredundant roles in the regulation of glucose and energy homeostasis in mice. Am J PhysiolEndocrinolMetab 310: E276–E288. https://doi.org/10.1152/ajpendo.00342.2015