Crimson Publishers
Wings to the Research

Review Article

Role and Regulation of Glycogen Synthase Kinase-3 in Obesity-Induced Metabolic Perturbations

Jacob J Lemon and Manisha Gupte*

Department of Biology, Austin Peay State University, Clarksville, TN 37040

ISSN: 2637-8019

***Corresponding author:** Manisha Gupte, Department of Biology, Austin Peay State University, Clarksville, TN 37040

Submission: March 07, 2022

Published: April 29, 2022

Volume 3 - Issue 3

How to cite this article: Jacob J Lemon and Manisha Gupte*. Role and Regulation of Glycogen Synthase Kinase-3 in Obesity-Induced Metabolic Perturbations. Glob J Endocrinol Metab. 3(3). GJEM. 000563. 2021.
DOI: 10.31031/GJEM.2021.03.000563

Abstract

Metabolic Syndrome which encompasses of hypertension, hyperlipidemia, insulin resistance, and obesity increases the risk of diseases such as cardiovascular diseases, Type 2 Diabetes Mellitus (T2DM), and cancer to list a few. The mechanisms leading to this syndrome have not been fully understood due to the multifaceted pathologies associated with this syndrome. While numerous molecules are being investigated in the etiology of metabolic syndrome, a number of studies have looked at the association of Glycogen Synthase Kinase-3 (GSK-3) and metabolic syndrome given the data that GSK-3 activity is increased with obesity and T2DM. The GSK-3 family consists of two isoforms, alpha (α) and beta (β). GSK-3α/β expression and activity has been found to be significantly elevated in muscle biopsies of T2DM patients and administration of GSK-3 inhibitors to rodent models of obesity and T2DM have improved insulin sensitivity and glucose homeostasis. Thus, GSK-3 is a promising therapeutic target for the management of metabolic diseases including T2DM. Numerous studies using either a pharmacological approach or animal models have investigated the role of GSK-3 in obesity-associated metabolic perturbations including glucose clearance However, this has been a daunting task given its ubiquitous expression, complex signaling, and the two very similar isoforms with some unique as well as redundant functions. Hence, as yet, the precise molecular mechanisms via which GSK-3 causes metabolic perturbations including obesity-induced glucose intolerance, diabetic cardiomyopathy, or cardiac dysfunction are yet unknown.

Introduction

Obesity has reached epidemic proportions worldwide and is associated with increased incidence of numerous pathologies including hypertension, Type 2 Diabetes Mellitus (T2DM), and heart failure to list a few [1]. Thus, current available therapies to counter the onslaught of metabolic diseases associated with obesity are inadequate, hence a need to identify new molecular targets to combat obesity-associated pathologies. Numerous studies in humans and animal models have implicated Glycogen Synthase Kinase-3 (GSK-3), a ubiquitously expressed serine threonine kinase in glucose intolerance and peripheral insulin resistance which are hallmarks of Type 2 Diabetes Mellitus (T2DM) [2-6]. Identified in 1980 it was shown to regulate Glycogen Synthase (GS), a rate limiting enzyme of glycogen synthesis [7]. However, now it is becoming clear that GSK-3 is critical for the regulation of many other signaling pathways of glucose homeostasis [8-11]. GSK-3 has two isoforms: α and β which share 98% sequence homology in their kinase domain but differ in their N and C terminal [12]. Overall, the two isoforms are 85% identical and hence it is not surprising that a number of studies indicate a distinct and overlapping effects of the two GSK-3 isoforms in various pathologies. Another interesting feature of this kinase is that it is constitutively active in unstimulated state and becomes inactive by phosphorylation in response to external stimuli including insulin [12]. Numerous studies using either a pharmacological approach or animal models have been conducted to determine the role of GSK-3 in obesity-associated metabolic perturbations including glucose clearance [13-28]. However, this has been a

daunting task given its ubiquitous expression, complex signaling, and the two very similar isoforms. As yet, we do not know the precise molecular mechanisms via which GSK-3 causes metabolic perturbations including obesity-induced glucose intolerance, diabetic cardiomyopathy, or cardiac dysfunction. Additionally, the role of specific GSK-3 isoforms (α and β) in peripheral tissues critical for glucose homeostasis is yet unclear. Hence numerous studies including those from our group are investigating the role and regulation of specific GSK-3 isoforms in tissues such as heart, liver, skeletal muscle, pancreas, and adipose tissue in High-Fat Diet (HFD) induced glucose intolerance, a hallmark of T2DM.

Regulation of GSK-3 in Heart

Heart metabolic pathophysiology has been linked to increased lipid accumulation and higher saturated fatty acids found in HFD, which increases the risk of Heart Failure (HF) and cardiovascular disease (CVD). The most common form of HF is Cardiomyopathy, where obesity induces lipotoxic cardiomyopathy by causing lipid accumulation in Cardiomyocytes (CM) leading to cardiac dysfunction [29]. CVD and HF are associated with abnormal GSK-3 activity, such as regulating cardiomyopathy and angiogenesis. For instance, pigs induced with metabolic syndrome symptoms and cardiovascular ischemia while on a high-fat diet demonstrated elevated myocardial perfusions ratios and capillary and arterolic density after using the GSK-3ß inhibitor IM-12 [30]. Furthermore, in obesity-related cardiac dysfunction, GSK-3α mediates lipid accumulation in the heart by stimulating fatty acid uptake and storage by phosphorylating the nuclear receptor peroxisome proliferative-activated receptor alpha (PPARα) [31]. GSK-3ß's role in obesity-induced cardiac dysfunction has been studied using Cre-loxP genetic recombination in mouse cardiomyocytes, which shows contrasting phenotypes whether the deletion occurs before or after establishing chronic obesity. On a control diet, CM-specific GSK-3β-KO mice exhibit no alteration in cardiac function. Interestingly, CM-GSK-3α compensated for the loss of CM-GSK-3β, as evident by significantly reduced GSK-3αs21 phosphorylation (activation) resulting in a preserved canonical β-catenin ubiquitination pathway and cardiac function. However, this protective compensatory mechanism is lost with HFD, leading to excessive accumulation of β-catenin in HFD-fed CM-GSK-3β-KO hearts, resulting in adverse ventricular remodeling and cardiac dysfunction. These results suggest that cardiac GSK-3β is crucial to protect against obesity-induced adverse ventricular remodeling and cardiac dysfunction [32]. In stark contrast to the developing obesity model, deleting CM-GSK-3β in obese animals did not adversely affect the GSK-3αS21 phosphorylation (activity) and maintained canonical β-catenin degradation pathway and cardiac function. Importantly, deleting GSK-3β in CMs improved glucose clearance in obese CM-GSK-3β KO animals compared to the controls [33].

Regulation of GSK-3 in Skeletal Muscle

Numerous studies have indicated a role of GSK-3 in insulin-responsive peripheral tissue such as Skeletal Muscle (SM) with total GSK-3 activity elevated in T2DM human skeletal muscle [13]. Importantly, GSK-3 inhibition in skeletal muscle of insulin resistant ZDF rats enhanced insulin action on glucose transport, oral glucose tolerance, whole body insulin sensitivity, and IRS-1-dependent insulin signaling [5,17]. Tissue and isoform specific experimentation reveals skeletal muscle specific GSK-3β KO mice, in contrast to the liver-deleted animals, display improved glucose tolerance that is coupled with enhanced insulin-stimulated glycogen synthase regulation and glycogen deposition [11]. In addition, in human non-diabetic skeletal muscle, siRNA against GSK-3ß led to 60-70% reduction in expression and increased glycogen synthase activity in absence of insulin and increased insulin action [34]. Unlike GSK-3α, GSK-3ß directly regulates both GS activity in the absence of added insulin and through control of insulin action [34]. Furthermore, mice fed a HFD and given a GSK-3ß inhibitor had higher glucose infusion rates, GS activity ratios and net glycogen synthesis, higher plasma glucose disappearance, improved peripheral insulin sensitivity, and lower endogenous glucose production compared to HF only [35].

Regulation of GSK-3 in Pancreas

Pancreatic activity and GSK-3's role in T2DM are interconnected when understanding glucose tolerance and insulin effectiveness. Insulin is generated by the ß-cells found in the pancreas, and this secreted peptide hormone enters the bloodstream to lower blood glucose levels under normal conditions. When insulin resistance becomes chronic, partial ß-cell mass reduction in the pancreas occurs, which is a hallmark sign in T2DM patients [36]. Previous research shows GSK-3ß deletion in pancreatic ß-cell mice increased ß-cell mass leading to higher insulin levels and improved glucose tolerance even when fed a HFD [10]. Similarly, using isolated, human adult pancreatic islets, GSK-3 inhibition enhanced pancreatic ß-cell proliferation by reducing p27 expression, which is an important cell cycle regulatory protein to halt cell division [36].

Regulation of GSK-3 in Adipose Tissue

Obesity is associated with excessive adipose accumulation that can lead to worsening pathologies. Glucose intolerance and insulin resistance arising from obesity can lead to T2DM, but how GSK-3 is involved in these conditions is still being considered. Mice fed a HFD exhibit an increase in GSK-3 activity in adipose tissue and a rapid increase in plasma blood glucose levels, indicating that excessive adipose accumulation can lead to glucose intolerance and insulin resistance [6]. Weight-loss on the other hand is demonstrated to reduce both GSK-3 isoform expressions in adipose tissue [37]. Current understanding in lipid accumulation can be seen with mice exhibiting hypercortisolism from excess glucocorticoids and GSK-3 levels. Elevated adipose GSK3β and H6pdh expression were seen to contribute to 11ß-HSD1 mediating hypercortisolism associated with visceral adiposity [38].

Systemic Regulation of GSK-3

The above studies have utilized non-isoform specific inhibition or tissue-specific genetic models to investigate the role of GSK-3 in obesity-associated pathologies, but these are of limited value to predict the clinical outcome of systemic inhibition. To investigate the isoform specific role of GSK-3 in HFD-induced metabolic

perturbations, we created a novel global conditional GSK-3-KO mouse model that allowed us to delete the gene globally in an isoform-specific and temporal manner. On an HFD, GSK-3α- KO mice had a significantly lower body weight and modest improvement in glucose tolerance compared to their littermate controls. In contrast, GSK-3β-deletion-mediated improved glucose tolerance was evident much earlier in the timeline and extended up to 12 weeks post-HFD. However, this protective effect was blunted after chronic HFD (16 weeks) when GSK-3β KO mice had a significantly higher body weight compared to controls. Importantly, GSK-3β KO mice on a control diet maintained significant improvement in glucose tolerance even after 16 weeks. In summary, our novel mouse models allowed us to delineate the isoform-specific role of GSK-3 in obesity and glucose tolerance and indicates the importance of maintaining a healthy weight in patients receiving lithium therapy, which is thought to work by GSK-3 inhibition mechanisms [39].

Conclusion

GSK-3 is a critical enzyme that has shed light into further understanding metabolic pathologies that underlie metabolic syndrome and related diseases. Many studies have examined whole enzyme inhibition to demonstrate its roles in glucose disposal, insulin sensitivity, and cardiac physiology [40]. Genetically deleting or enzymatically inhibiting each isoform has brought forth isoform-specific roles of GSK-3 in specific tissues and organs, such as heart, adipose, skeletal muscle, and pancreas. Systemic GSK-3 inhibition is a crucial advancement in delineating the isoform-specific roles of GSK-3 in glucose metabolism under a HFD, but homozygous genetic deletion is different from the level of inhibition seen with pharmacological agents. Therefore, future studies examining systemic heterozygous deletion in animal models are warranted (Table 1).

Table 1:

Tissue Type	Genetic Model	Pathology	Phenotype(s)	Mechanism	Reference
Adipose	C57BL/6J and A/J mice	Obesity, High-fat diet	GSK-3 activity and plasma blood glucose levels rapidly increase	Total GSK-3 activity	[6]
Adipose	Human healthy, obese, and obese type II diabetic	Obesity and Type II Diabetes	Weight-loss in adipose tissue reduces both GSK-3 isoform expressions	Total GSK-3 activity	[38]
Adipose	C57/BL6J mice	Hypercortisolism	Elevated adipose GSK3β and H6pdh expression contribute to 11ß-HSD1 mediating hypercortisolism associated with visceral adiposity	GSK-3ß activity	[39]
Skeletal Muscle	Humans skeletal muscle biopsy	Type 2 Diabetes	Basal and insulin stimulated total GSK-3 activity was elevated	GSK-3 inhibition	[13]
Skeletal Muscle	ZDF rats	Obesity, insulin resistance	Enhanced insulin action on glucose transport	GSK-3 inhibition	[5]
Skeletal Muscle	ZDF rats	Insulin resistant, prediabetic	Enhanced oral glucose tolerance, whole body insulin sensitivity, and improved IRS-1-dependent insulin signaling	GSK-3 inhibition	[17]
Skeletal Muscle	R1 Embryonic stem cell line	N/A	Improved glucose tolerance that is coupled with enhanced insulin-stimulated glycogen synthase regulation and glycogen deposition	GSK-3ß deletion	[11]
Skeletal Muscle	C57/BL6J mice	Obesity and insulin-resistance High-fat diet	GSK-3ß inhibited had higher glucose infusion rates, glycogen synthase activity ratios, net glycogen synthesis, higher plasma glucose disappearance, improved peripheral insulin sensitivity, and lower endogenous glucose production compared to high-fat fed only	Hight-fat fed mice vs. High-fat fed + L803-mts GSK3 inhibitor	[35]
Skeletal Muscle	Human non-diabetic skeletal muscle	N/A	siRNA against GSK-3ß led to 60-70% reduction in expression and increased glycogen synthase activity in absence of insulin and increased insulin action	GSK-3ß inhibition	[34]
Vascular Smooth Muscle Cells	Rat LEF cell R7r5	N/A	Twofold increase in glucose uptake due to a similar increase in protein expression of the facilitative glucose transporter 1 (GLUT1). GSK-3 was found to reduce glucose uptake by suppressing GLUT1 expression.	GSK-3 inhibition	[40]
Liver	GSK-3α KO mice	N/A	Enhanced glucose and insulin sensitivity, reduced fat mass, increased fasted and glucose- stimulated hepatic glycogen content.	GSK-3α deletion	[3]
Liver	B6.Cg-Tg(Alb-Cre)21Mgn/J mice	N/A	Viable, glucose and insulin tolerant, and display "normal" metabolic characteristics and insulin signaling	GSK-3β deletion	[11]

Pancreas	Human pancreatic islets	N/A	Enhanced pancreatic ß-cell proliferation by reducing p27 expression.	GSK-3 inhibition	[36]
Pancreas	Mice with beta cell deficiency of GSK-3β (Gsk3b]−/−)	High-fat diet	Improved glucose tolerance and expanded beta cell mass with increased proliferation	GSK-beta deletion	[10]
Heart	Yorkshire Swine Cardiomyocytes	High-fat diet and ischemia with Metabolic Syndrome	Elevated myocardial perfusions ratios and capillary and arterolic density.	GSK-3ß Inhibition	[30]
Heart	C57BL/6 Cardiomyocytes	High-fat diet	GSK-3α mediates lipid accumulation in the heart by stimulating fatty acid uptake and storage by phosphorylating the nuclear receptor peroxisome proliferative-activated receptor alpha (PPARα).	GSK-3α/ß heterozygous deletion	[31]
Heart	C57BL/6 Cardiomyocytes	Chronic obesity	Control-fed mice had increased GSK-3α activity, which compensated for the loss of GSK-ß and protected the heart from cardiac dysfunction. HFD-fed mice lost protective effect, and GSK-3α could not compensate leading to an increase in cardiac ß-catenin accumulation.	GSK-3ß deletion before established obesity	[32]
Heart	C57BL/6 Cardiomyocytes	Chronic obesity	HFD-fed mice had improved systemic glucose tolerance, normal cardiac function, and GSK-3α was able to compensate for GSK-3ß loss and not allow ß-catenin accumulation.	GSK-3ß deletion after established obesity	[33]
Systemic	Global conditional homozygous GSK-3α/ßfl+/+Cre+/-	High-fat diet	GSK-3α KO: lower body weights and modest improvement in glucose tolerance GSK-3β KO: improved glucose tolerance much earlier and extended up to 12 weeks post-HFD but diminished after 16 weeks after a significantly higher body weight Control fed GSK-3β KO: maintained significant improvement in glucose tolerance even after 16 weeks.	GSK-3α/ß homozygous deletion	[39]

References

1. Wolfgang R, Guido G (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27(10): 2568-2569.
2. Liu Z, Tanabe K, Permutt MA, Mizrachi EB (2008) Mice with beta cell overexpression of glycogen synthase kinase-3beta have reduced beta cell mass and proliferation. Diabetologia 51: 623-631.
3. Liu Z, Tanabe K, Permutt MA, Mizrachi EB (2008) Mice with beta cell overexpression of glycogen synthase kinase-3beta have reduced beta cell mass and proliferation. Diabetologia 51: 623-631.
4. Kaidanovich O, Eldar-Finkelman H (2002) The role of glycogen synthase kinase-3 in insulin resistance and type 2 diabetes. Expert Opin Ther Targets 6(5): 555-561.
5. Henriksen EJ, Kinnick TR, Harrison SD, Mary KT, Matthew PK, et al. (2003) Modulation of muscle insulin resistance by selective inhibition of GSK-3 in Zucker diabetic fatty rats. Am J Physiol Endocrinol Metab 284(5): 892-900.
6. Eldar-Finkelman H, Schreyer SA, Krebs EG (1999) Increased glycogen synthase kinase-3 activity in diabetes- and obesity-prone C57BL/6J mice. Diabetes 48(8): 1662-1666.
7. MacAulay K, Woodgett JR (2008) Targeting glycogen synthase kinase-3 (GSK-3) in the treatment of Type 2 diabetes. Expert Opin Ther Targets 12(10): 1265-1274.
8. Frame S, Zheleva D (2006) Targeting glycogen synthase kinase-3 in insulin signalling. Expert Opin Ther Targets 10(3): 429-444.
9. Chen H, Abdul F, Miriam H, Bingbing Z, Erwin DS, et al. (2016) PI3K-resistant GSK3 controls adiponectin formation and protects from metabolic syndrome. Proc Natl Acad Sci U S A 113(20): 5754-5759.
10. Liu Y, Tanabe K, Baronnier D, Patel S, Woodgett J, et al. (2010) Conditional ablation of Gsk-3β in islet beta cells results in expanded mass and resistance to fat feeding-induced diabetes in mice. Diabetologia 53(12): 2600-2610.
11. Patel S, Doble BW, Woodgett JR, Katrina M, Elaine MS, et al. (2008) Tissue-specific role of glycogen synthase kinase 3beta in glucose homeostasis and insulin action. Mol Cell Biol 28(20): 6314-6328.
12. Prital Patel, James R Woodgett (2017) Curernt topics in developmental biology. PP. 277-302.
13. Nikoulina SE, Ciaraldi TP, Henry RR (2000) Potential role of glycogen synthase kinase-3 in skeletal muscle insulin resistance of type 2 diabetes. Diabetes 49(2): 263-271.
14. Flepisi TB, Lochner A, Huisamen B (2013) The consequences of long-term glycogen synthase kinase-3 inhibition on normal and insulin resistant rat hearts. Cardiovasc Drugs Ther 27(5): 381-392.
15. Nikoulina SE, Henry RR, Ciaraldi TP, Carter L, Park KS, et al. (2001) Impaired muscle glycogen synthase in type 2 diabetes is associated with diminished phosphatidylinositol 3-kinase activation. J Clin Endocrinol Metab 86(9): 4307-4314.
16. Cline GW, Johnson K, Shulman GI, Werner R, Pascale P, et al. (2002) Effects of a novel glycogen synthase kinase-3 inhibitor on insulin-stimulated glucose metabolism in Zucker diabetic fatty (fa/fa) rats. Diabetes 51(10): 2903-2910.
17. Dokken BB, Henriksen EJ, Julie AS (2005) Acute selective glycogen synthase kinase-3 inhibition enhances insulin signaling in prediabetic insulin-resistant rat skeletal muscle. Am J Phys Endo Metab 288(6): 1188-1194.
18. McManus EJ, Alessi DR, Kei S, Laura JA, Leah R, et al. (2005) Role that phosphorylation of GSK3 plays in insulin and Wnt signalling defined by

knockin analysis. EMBO J 24(8): 1571-1583.

19. Zhou J, Ahmad F, Lal H, Force T, Shan P, et al. (2016) Loss of adult Cardiac myocyte GSK-3 leads to mitotic catastrophe resulting in fatal dilated cardiomyopathy. Circ Res 118(8): 1208-1222.

20. Lal H, Force T, Firdos A, James W (2015) The GSK-3 family as therapeutic target for myocardial diseases. Circ Res 116(1): 138-49.

21. Ahmad F, Lal H, Force T, Jibin Z, Ronald JV, et al. (2014) Cardiomyocyte-specific deletion of Gsk3alpha mitigates post-myocardial infarction remodeling contractile dysfunction and heart failure. J Am Coll Cardiol 64(7): 696-706.

22. Fontes MS, Kessler EL, Goldschmeding R, van Veen TA, Leonie VS, et al. (2015) CTGF knockout does not affect cardiac hypertrophy and fibrosis formation upon chronic pressure overload. J Mol Cell Cardiol 88: 82-90.

23. Zhou J, Freeman TA, Lal H, Force T, Firdos A, et al. (2013) GSK-3alpha is a central regulator of age-related pathologies in mice. J Clin Invest 123(4): 1821-1832.

24. Zhou J, Lal H, Force T, Chen X, Shang X, et al. (2010) GSK-3alpha directly regulates beta-adrenergic signaling and the response of the heart to hemodynamic stress in mice. J Clin Invest 120(7): 2280-2291.

25. Jung EM, Ka M, Kim WY (2015) Loss of GSK-3 causes abnormal astrogenesis and behavior in mice. Mol Neurobiol 53(6): 3954-3966.

26. Tolosa E, Litvan I, Del Ser T, Gunter UH, David B, et al. (2014) A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. Mov Disord 29(4): 470-478.

27. Lovestone S, Boada M, Del Ser T, Bruno D, Michael H, et al. (2015) A Phase II Trial of Tideglusib in Alzheimer's Disease. J Alzheimers Dis 45(1): 75-88.

28. Kaidanovich-Beilin O, Woodgett JR (2011) GSK-3: Functional insights from cell biology and animal models. Front Mol Neurosci 4: 40.

29. Nakamura M, Liu T, Husain S, Zhai P, Warren JS, et al. (2019) Glycogen synthase kinase-3α promotes fatty acid uptake and lipotoxic cardiomyopathy. Cell metabol 29(5): 1119-1134.

30. Potz BA, Sabe AA, Elmadhun NY, Clements RT, Robich MP, et al. (2016). Glycogen synthase kinase 3beta inhibition improves myocardial angiogenesis and perfusion in a swine model of metabolic syndrome. J Am Heart Assoc 5(7): e003694.

31. Nakamura M, Liu T, Husain S, Zhai P, Warren JS, et al. (2019) Glycogen synthase kinase-3α promotes fatty acid uptake and lipotoxic cardiomyopathy. Cell metabol 29(5): 1119-1134.

32. Gupte M, Tumuluru S, Sui JY, Singh AP, Umbarkar P, et al. (2018) Cardiomyocyte-specific deletion of GSK-3β leads to cardiac dysfunction in a diet induced obesity model. Int J Cardiol 259: 145-152.

33. Gupte M, Umbarkar P, Singh AP, Zhang Q, Tousif S, et al. (2020) Deletion of cardiomyocyte glycogen synthase kinase-3 beta (gsk-3β) improves systemic glucose tolerance with maintained heart function in established obesity. Cells 9(5): 1120.

34. Ciaraldi TP, Carter L, Mudaliar S, Henry RR (2010) GSK-3beta and control of glucose metabolism and insulin action in human skeletal muscle. Mol Cell Endocrinol 315(1-2): 153-158.

35. Rao R, Hao CM, Redha R, Wasserman DH, McGuinness OP, et al. (2007) Glycogen synthase kinase 3 inhibition improves insulin-stimulated glucose metabolism but not hypertension in high-fat-fed C57BL/6J mice. Diabetologia 50(2): 452-460.

36. Stein J, Milewski WM, Hara M, Steiner DF, Dey A (2011) GSK-3 inactivation or depletion promotes β-cell replication via down regulation of the CDK inhibitor, p27 (Kip1). Islets 3(1): 21-34.

37. Ciaraldi TP, Oh DK, Christiansen L, Nikoulina SE, Kong AP, et al. (2006) Tissue-specific expression and regulation of GSK-3 in human skeletal muscle and adipose tissue. Am J Physiol Endocrinol Metab 291(5): 891-898.

38. Yan C, Yang H, Wang Y, Dong Y, Yu F, et al. (2016) Increased glycogen synthase kinase-3β and hexose-6-phosphate dehydrogenase expression in adipose tissue may contribute to glucocorticoid-induced mouse visceral adiposity. Int J obes (Lond) 40(8): 1233-1241.

39. Gupte M, Tousif S, Lemon JJ, Toro Cora A, Umbarkar P, et al. (2022) Isoform-specific role of GSK-3 in high fat diet induced obesity and glucose intolerance. Cells 11(3): 559.

40. Buller CL, Loberg RD, Fan MH, Zhu Q, Park JL, et al. (2008) A GSK-3/TSC2/mTOR pathway regulates glucose uptake and GLUT1 glucose transporter expression. Am J Physiol Cell Physiol 295(3): 836-843.