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Original Article

Glycogen synthase kinase-3 (GSK-3) a magic enzyme: it's role in diabetes mellitus and glucose homeostasis, interactions with fluroquionlones. A mini-review

Glicogênio sintase quinase-3 (GSK-3), uma enzima mágica: seu papel no diabetes mellitus e na homeostase da glicose: interações com fluoroquinolonas. Uma mini-revisão

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Abstract

Diabetes mellitus (DM) is a non-communicable disease throughout the world in which there is persistently high blood glucose level from the normal range. The diabetes and insulin resistance are mainly responsible for the morbidities and mortalities of humans in the world. This disease is mainly regulated by various enzymes and hormones among which Glycogen synthase kinase-3 (GSK-3) is a principle enzyme and insulin is the key hormone regulating it. The GSK-3, that is the key enzyme is normally showing its actions by various mechanisms that include its phosphorylation, formation of protein complexes, and other cellular distribution and thus it control and directly affects cellular morphology, its growth, mobility and apoptosis of the cell. Disturbances in the action of GSK-3 enzyme may leads to various disease conditions that include insulin resistance leading to diabetes, neurological disease like Alzheimer's disease and cancer. Fluoroquinolones are the most common class of drugs that shows dysglycemic effects via interacting with GSK-3 enzyme. Therefore, it is the need of the day to properly understand functions and mechanisms of GSK-3, especially its role in glucose homeostasis via effects on glycogen synthase.

Keywords: Diabetes mellitus, Glycogen Synthase Kinase-3 (GSK-3), Glucose homeostasis, Fluoroquinolones.

Resumo

O diabetes mellitus (DM) é uma doença não transmissível em todo o mundo, na qual existe nível glicêmico persistentemente alto em relação à normalidade. O diabetes e a resistência à insulina são os principais responsáveis pelas morbidades e mortalidades de humanos no mundo. Essa doença é regulada principalmente por várias enzimas e hormônios, entre os quais a glicogênio sintase quinase-3 (GSK-3) é uma enzima principal e a insulina é o principal hormônio que a regula. A GSK-3, que é a enzima-chave, normalmente mostra suas ações por vários mecanismos que incluem sua fosforilação, formação de complexos de proteínas e outras distribuições celulares e, portanto, controla e afeta diretamente a morfologia celular, seu crescimento, mobilidade e apoptose do célula. Perturbações na ação da enzima GSK-3 podem levar a várias condições de doença que incluem resistência à insulina que leva ao diabetes, doenças neurológicas como a doença de Alzheimer e câncer. As fluoroquinolonas são a classe mais comum de drogas que apresentam efeitos disglicêmicos por meio da interação com a enzima GSK-3. Portanto, é necessário hoje em dia compreender adequadamente as funções e mecanismos da GSK-3, principalmente seu papel na homeostase da glicose via efeitos na glicogênio sintase.

Palavras-chave: diabetes mellitus, Glicogênio Sintase Quinase-3 (GSK-3), homeostase da glicose, fluoroquinolonas.

1. Introduction

Diabetes mellitus (DM), a non-communicable disease was considered as a disease of minor significance to the world health in past (Barroso et al., 1999), but in 21st century DM is the most life threatened disease to the human health (Amos et al., 1997), (Zimmet, 2001). DM is the fifth leading cause of death worldwide (Sandu et al.,

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2016) and every 7 seconds, a person dies due to Diabetes (Baker et al., 2016).In 2018 about 150-220 million people worldwide were suffering from diabetes and that may raise up to 300 million in 2025 (King et al., 1998). Due to the poor sedentary life style of people in the developing countries like Pakistan there is a maximum increase of DM in the last decade (IADPSG, 2010). DM is classified into two classes *i.e.* Type I and Type II. Type I Diabetes mellitus is about 5-10% that is mainly due to absolute insulin deficiency and autoimmune destruction of pancreatic beta cell of islets of Langerhans (Defronzo, 1997). Type II DM is about 90- 5% and caused due to defective insulin secretion or insulin action or both (Fajans et al., 2001).This is due to single gene disorders affecting the beta cell of the pancreas to secrete sufficient amount of insulin (Fajans et al., 2001; Taylor and Arioglu, 1999), or the ability of body cells to respond to insulin action leading to insulin resistance (Barroso et al., 1999; Ali et al., 2001).

GSK-3 is playing a vital role in resistance of insulin and glucose homeostasis. (GSK-3) is a serine threonine kinase comprising of two encoded different genes isoforms *i.e* GSK3a and GSK-3b with molecular weights 51 kDa and 46 kDa, respectively in mammals. These two isoforms have similar kinase domains sequences and they showing 85% homology at the level of amino acids with each other's (Bijur and Jope, 2003). GSK-3 is known for wide regulatory activities and cell functioning and has a lot of substrates and showing a great relationship toward glycogen synthase and thus involved in glycogen metabolism (Muyllaert et al., 2008). Besides, its functions in the glycogen regulation, (GSK-3), is also involved in some other biological activities including tumorogenesis, cell survival and developmental patterning. Thus, they are used for various therapeutic purposes including treatment of cancer, bipolar disorders, neurological diseases, stroke, diabetes and various inflammatory disease (Jope and Johnson, 2004) .The various substrates that are responsible for GSK-3 function includes glycogen synthase (GS), beta catenin proteins and tau protein (Eldar-Finkelman, 2002; Patel et al., 2004). Based upon the above various functions of GSK-3 the development of GSK-3 inhibitors will be successful to treat diabetes mellitus and cancer (Jope and Johnson 2004; Henriksen and Dokken, 2006).

2. GSK-3 A Unique Multi-Tasking Kinase

As the GSK-3 have several substrates (Figure 1) and is involved in several diverse pathways. Of these pathways one of the important one is GSK-3 role in insulin signaling and canonical Wnt signaling. In the insulin signaling, GSK-3 causes the inhibition of Glycogen Synthase that causes the decrease glycogen synthesis and thus by the inhibition of GSK-3 causes the activation of GS thus there will be increase in glycogen synthesis and ultimately there will be increase in insulin sensitivity and hypoglycemia (Woodgett, 1990; Lee and Kim, 2007) .

3. Isoforms of GSK-3

The two isoforms of GSK-3 are GSK3a/b that is encoded by two different genes. These two isoforms have similar substrate specificity and functions (Phiel and Klein, 2001). Modern research elaborates the role

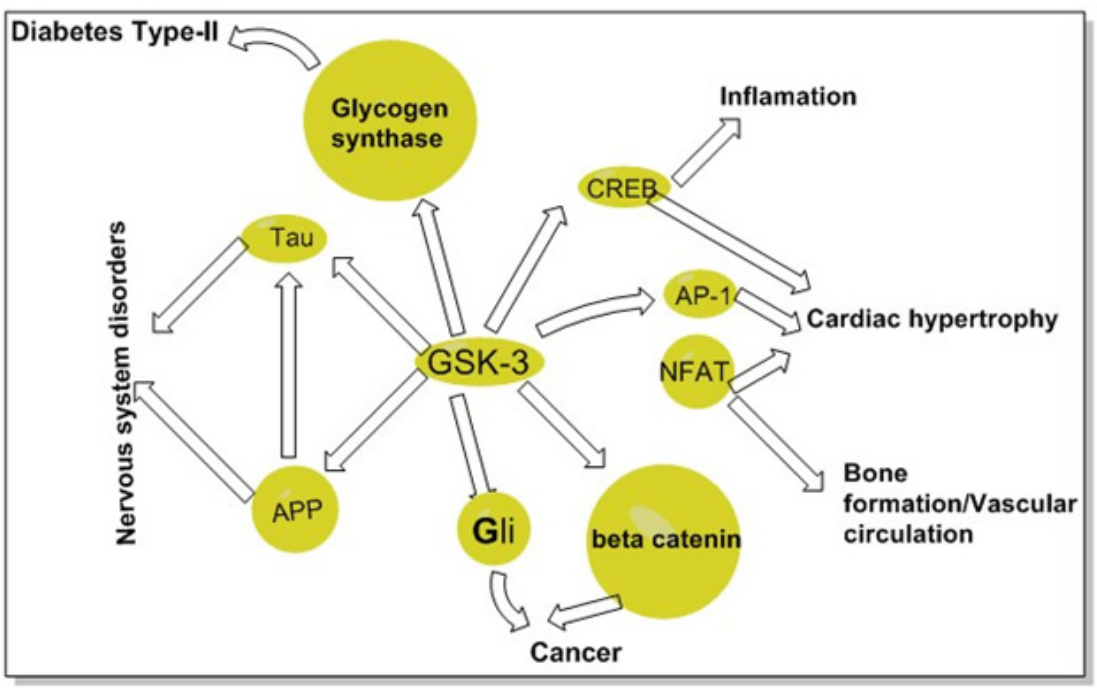

Figure 1. Showing the effects of GSK-3 on various substrates.

of GSK-3 in the treatment of Cancer, Bipolar disorders, Chronic inflammatory diseases, Alzheimer's disease (MacAulay et al., 2007), Insulin resistance and glucose metabolism (Bouche et al., 2004) may change the course.

4. GSK-3 Role in Homeostasis of Blood Glucose

The efficient blood glucose homeostasis is achieved by effective absorption of glucose and the storage of extra glucose as glycogen in liver and skeletal muscles. A Profound dysregulation of these processes may results to cause insulin resistance and ultimately causes increase in fasting and random/Postprandial glucose levels. Resistance of insulin is one of the main underlying causes for the development of type II diabetes mellitus (T-II-DM) (Eldar-Finkelman and Ilouz, 2003). In insulin resistance the tissues that are sensitive to insulin become non respondent to the action of insulin and thus they become unable to clear efficiently the blood glucose level leading to decrease hepatic glucose output and peripheral tissues glucose uptake is decreased (Nikoulina et al., 2000).

5. Insulin Signal Transduction Involves Various Steps

The binding of insulin with receptors causes the stimulation of insulin receptor (Sandu et al., 2016) that causes auto-phosphorylation of various tyrosine parts in insulin receptor. The mentioned processes of phosphorylation causes a cascade events of phosphorylation in which insulin receptor substrates 1(IRS1) and insulin receptor substrates 2 (IRS2) recognize and bind to the phosphorylated insulin receptors and become auto phosphorylated. Activated phosphoinositol 3 kinase causes the conversion of phosphatidylinositol bisphosphate to phosphatidylinositol triphosphate, ultimately causes stimulation and activation of PKB. The next step in the insulin signaling events involves the conversion of activated PKB to phosphorylate GSK-3 leading to its inactivation (Eldar-Finkelman et al., 1999). This inactivation of GSK-3 causes a decrease in the phosphorylation of GS that leads to its activation. Beside from GS, eIF2B is also activated in a similar manner that leads to an elevation in protein synthesis and glycogen synthesis. In the T-II-DM patients there is increased expression and activity of GSK-3 in their skeletal muscle (Meijer et al., 2000; McManus et al., 2005) this suggests that dysregulation of GSK-3b might result in impaired insulin signaling and hence causes the diabetes. This hypothesis is also supported by using the pharmacological inhibitors of GSK-3 that causes the improvement in the insulin signaling and thus ultimately causes the decrease in glucose levels in animal models of diabetes (Hanashiro and Roach, 2002). Inactivation of GSK-3 leads to the activation of GS by insulin. Data suggests that GS activation by glucose in the liver is via activation of a PP, protein phosphatase besides the Ser 21/Ser 9-mediated inactivation of GSK-3 isoforms (Nikoulina et al., 2002). Besides, the GSK-3 inhibitors are responsible for stimulation of hepatic GS and thus cause the decrease in the blood glucose level due to this GSK-3 inhibition. In skeletal muscle and liver activity of GS is regulated by GSK-3a and b and insulin (Summers et al., 1999). Prolonged use of GSK-3 pharmacological inhibitors causes the inactivation of Glycogen Synthase in muscle and causes increase in glucose uptake by the skeletal muscles and elevated IRS1 levels (Srinivasan et al., 2005). Apart from Skeletal muscles the GSK-3 also plays a vital role in the metabolism of glucose in the adipocytes and thus contributes to regulation of insulin by the synthesis of glycogen and not at the level of transport of glucose and glucose transporter 4 (GLUT4) translocation (Ryves and Harwood, 2001). GSK-3 is also playing a vital role in endoplasmic reticulum stress in beta cells of pancreatic, and thus the down-regulation of GSK-3 can protect the cells from disruption and death (Rossetti, 1989).

Lithium is a GSK-3 inhibitor, showing its action by competing with magnesium and inhibits GSK3and thus used for the treatment of manic depression and bipolar disorders (Phiel and Klein, 2001).Lithium also stimulates the glucose uptake by muscles and peripheral tissues, thus enhances the glycogen synthesis and increases the sensitivity insulin (Shakoori et al., 2007). It is noteworthy that lithium is non-selective inhibitor of GSK-3 and also inhibit certain other enzymes protein kinase-2 (Ye, 2013) inositol monophosphate and polyphosphate 1-phosphatase (Petrie et al., 1996). GSK-3 also plays a vital role in the treatment of cancer, and nowadays novel GSK-3 inhibitors are novel class of drugs for the treatment of colon cancer (Mulnier et al., 2008).

6. Insulin resistance

Hypertension and dyslipidemia are the main concomitant diseases associated side by side to insulin resistance (Henriksen and Dokken, 2006). Insulin resistance in endothelium causes decrease nitric oxide production and causes vasodilatation. In adipose tissues insulin resistance, causes the activation of hormone sensitive lipase which causes an elevated level of free fatty acid generation that causes hepatic triglyceride synthesis and thus causes the alteration of the composition of increase in LDL and decrease in HDL level (Lee and Kim, 2007), thus enhances the risk of myocardial infarction in diabetes patients (Harwood, 2001).

GSK-3 shows its role by several pathways specially its role in insulin signaling and canonical Wnt signaling. GSK-3 regulates insulin signaling via inhibition of GS leading to decreased glycogen synthesis and hence inhibition of GSK3 leads to increase in glycogen synthesis and increase in insulin sensitivity (Doble and Woodgett, 2003; Pearce et al., 2004). Unlike other kinases the enzyme is constitutively active and is then inactivated in response to cellular signals (Summers et al., 1999).

7. GSK-3 Role in Pancreas

It has been proposed that the GSK-3 is playing a vital role in the in regulation of Glycogen Synthase in muscle. Over expression of GSK3-b in the skeletal muscle suggesting that GSK3-b is the main important kinase

regulating GS in the muscle. GSK3-a is the primarily regulator of hepatic glycogen metabolism and not in the skeletal muscle using GSK-3 .Glycogen synthase kinase-3 is contributing to the regulation of insulin by glycogen synthesis and not contributing to the glucose transport and glucose transporter 4 (GLUT4) translocation (Gfeller et al., 2013). From the Swiss target prediction model of various fluoroquinolones it is evident that the FQs inhibits GSK-3 both their alpha and beta isoforms and shows glucose hemostasis disturbances (Gfeller et al., 2013).

8. Conclusion

From this review article it is concluded that GSK-3 is playing a vital role in glucose homeostasis and have many more substrates like fluoroquinolones. Thus GSK-3 inhibitors can be used for the treatment of a lot number of diseases i.e. Cancer, neurological and bipolar disorders like schizophrenia and Diabetes Mellitus type II.

Competing interests

The authors declared no competing interests.

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