Journal of the North for Basic and Applied Sciences, Vol. (8), Issue (1), (May 2023/ Shawwal 1444 H) 22-27

KINGDOM OF SAUDI ARABIA
Northern Border University (NBU)
Journal of the North for Basic & Applied Sciences(JNBAS)
p - ISSN : 1658 -7022 / **e-ISSN: 1658 - 7014**
www.nbu.edu.sa
s.journal@nbu.edu.sa

Review Article

Glucose Transporter 1 in Health and Disease

Saeed Awad M. Alqahtani

(Received 2/1/2023 ; accepted 31/5/2023)

Abstract: Glucose transporter 1 (GLUT1) is a protein that is responsible for the transport of glucose from the bloodstream into cells. It is found in the cell membranes of many tissues in the body, including the brain, muscles, and red blood cells. Dysregulation of GLUT1 function has been implicated in several diseases, including cancer, neurological disorders, and cardiovascular disease. In this review, we will discuss the role of GLUT1 in these diseases and the potential for targeting GLUT1 as a therapeutic strategy.

Key words: glucose transporter 1, GLUT1, diabetes, cancer, neurological disorders, therapeutic intervention

DOI: 10.12816/0061501

* **Corresponding Author:**
Associate Professor, Department of Physiology, College of Medicine,Taibah University, Medina, Saudi Arabia.
e-mail: dr_alqahtani@hotmail.com

المملكة العربية السعودية
جامعة الحدود الشمالية (NBU)
مجلة الشمال للعلوم الأساسية والتطبيقية (JNBAS)
طباعة ردمد: 1658-7022/ إلكتروني – ردمد: 1658-7014
www.nbu.edu.sa
s.journal@nbu.edu.sa

بحث مرجعي

ناقل الغلوكوز-1 في الصحة والمرض

سعيد عوض القحطاني

(قدم للنشر في 1444/6/9؛ وقبل للنشر في 1444/11/11هـ)

مستخلص البحث: ناقل الغلوكوز-1 هو بروتين مسؤول عن نقل الغلوكوز من الدم إلى الخلايا. وتواجد في كثير من خلايا الأنسجة في جسم الإنسان، بما في ذلك الدماغ والعضلات وخلايا الدم الحمراء. هذا الناقل له علاقة في حدوث عدد من الأمراض ، بما في ذلك مرض السكري والسرطان والاضطرابات العصبية والأمراض القلبية الدموية. حيث وجدت الدراسة ارتباطه باضطراب خلايا بيتا البنكرياس التي تنتج الأنسولين بمرض السكري من النوع الثاني. كما تم ربطه عند اختلاله بنمو الخلايا السرطانية وتكاثرها فضلا عن الحالات العصبية مثل الصرع ومرض الزهايمر. لذلك تجدر الاشارة الى ان دراسة مثل هذا الناقل بشكل مكثف لمعرفة كيف كيف يساهم في حدوث بعض الأمراض سببا لمعرفة كيفية العلاج المحتملة.

كلمات مفتاحية: ناقل الغلوكوز-1، داء السكرى، السرطان، اضطرابات عصبية، التدخل العلاجى.

للمراسلة:
أستاذ مشارك بقسم علم وظائف الأعضاء بكلية الطب ، جامعة طيبة ، المدينة المنورة ، المملكة العربية السعودية.

e-maildr_alqahtani@hotmail.com

DOI: 10.12816/0061501

1.INTRODUCTION:

Glucose is a primary source of energy for cells in the body, and the uptake and utilization of glucose is regulated by a complex network of proteins which called glucose transporters (Hantzidiamantis & Lappin, 2022). Sodium-glucose co-transporters and glucose-mediated transporters (GLUTs) are the two categories of glucose transporters (Scheepers, Joost, & Schurmann, 2004). The glucose transporter family consists of fourteen members (Augustin & Mayoux, 2014). Different tissues produce GLUT differently and it works across the plasma membrane in the direction of the glucose gradient (Wilson-O'Brien, Patron, & Rogers, 2010). Class I, II, and III are the three subclasses that make up the GLUT family. High-affinity GLUT1, low-affinity GLUT3, GLUT4, GLUT14, and GLUT2 are all members of type I (Byers, Howard, & Wang, 2017). GLUT5, GLUT7, GLUT9, and GLUT11 are class II transporters with very low affinity for glucose. The class III transporters are GLUT6, GLUT8, GLUT10, and GLUT12 (formerly known as GLUT-X1). Sodium-glucose co-transporters move glucose in opposition to its gradient of concentration (Wright, Hirayama, & Loo, 2007).

GLUT1 plays a crucial role in glucose homeostasis (Palacin, Estevez, Bertran, Zorzano & Marsol,1998) and expressed in many tissues in the body, including the brain, muscles, and red blood cells, and it is regulated by a variety of factors including insulin, glucose levels, and substrate availability (Wang, Wang, Shen, & Zhang, 2016). GLUT1 is encoded on the short arm of chromosome 11 and is synthesized in the endoplasmic reticulum (Wilcox, 2005). Dysregulation of GLUT1 has been linked to a variety of diseases, including diabetes, cancer, and neurological disorders, making it a potential target for therapeutic intervention (Vulturar, Chiș, Pintilie, Farcaș, Botezatu, Login, Sitar-Taut, et.al. 2022)

While GLUT1 is essential for normal physiological function, dysregulation of GLUT1 has been implicated in a number of diseases. For example, abnormal expression of GLUT1 has been observed in cancer cells, and targeting GLUT1 has been proposed as a potential therapeutic strategy for cancer treatment (Santra et al., 2020). In addition, GLUT1 has been implicated in neurological disorders such as epilepsy and Alzheimer's disease (Bazinet, Al-Haidari, Bains, & Wurtman, 2014 ; Lu et al., 2015). Dysregulation of GLUT1 has also been linked to cardiovascular disease, as reduced GLUT1 expression has been observed in the endothelial cells of individuals with atherosclerosis (Iwamoto, Tamura, & Kataoka, 2020).

In this review, I will discuss the role of GLUT1 in these diseases and the potential for targeting GLUT1 as a therapeutic strategy. We will also consider the current state of the literature on GLUT1 in these diseases and highlight areas for future research.

The research aiming to clarify the effect of GLUT-1 in cases of health and diseases and study the drawbacks and benefits of its uses in different diseases.

2.METHODS:

Focusing on the significance of GLUT1 in the etiology of diseases and potential therapeutic approaches, a thorough assessment of the literature was carried out primarily utilizing Google Scholar and PubMed databases. These diseases include diabetes, cardiovascular illness, neurological conditions, and cancer. Search terms included GLUT1, glucose transporter, cancer, neurological problems, cardiovascular disease, and therapeutic approach. The search was restricted to recent English-language publications.

3.RESULTS AND DISCUSSION:

High blood glucose levels are the hallmark of the chronic condition known as diabetes. GLUT1 has been identified as a possible therapeutic target for the management of diabetes. The expression of GLUT1 in the pancreatic beta cells that produce insulin has been connected to the emergence of type 2 diabetes (Zhou, Qi, & Zhang, 2011). In animal models of type 1 diabetes, inhibition of GLUT1 has been found to increase insulin

sensitivity and glucose tolerance (Shen, Wang, Xu, Ma, & Zhang, (2014). One study found that targeting GLUT1 with a small molecule inhibitor improved glucose homeostasis in a mouse model of type 1 diabetes. GLUT1 has also been addressed as a therapeutic intervention for type 1 diabetes (Bansal, Chaudhary, & Dhawan, 2016).

Cardiovascular illness has also been associated with GLUT1 dysregulation. Individuals with atherosclerosis have been found to have reduced GLUT1 expression in their endothelial cells, and this reduced GLUT1 expression has been associated with decreased glucose absorption and utilization in these cells (Iwamoto et al., 2020). Atypical GLUT1 expression has also been connected to the emergence of hypertension and other cardiovascular illnesses. Furthermore, GLUT1 has been demonstrated to play a role in the regulation of blood pressure and vascular function (Iwamoto et al., 2020).

Additionally, GLUT1 has been linked to the emergence of cancer, with cancer cells frequently exhibiting high levels of GLUT1 expression (Pawar, Mhatre, & Kucuk, 2011). It has been demonstrated that GLUT1 contributes to the development, proliferation, and survival of cancer cells (Lin, Lin, Chen, & Hsieh, 2013). Cancer cells' growth and viability have been demonstrated to decrease when GLUT1 is inhibited, both in vitro and in vivo (Wang et al., 2016). Breast, ovarian, and pancreatic cancer are only a few cancer types where abnormal GLUT1 expression has been noted (Santra et al., 2020). GLUT1 is frequently overexpressed in cancer cells, which results in enhanced glucose absorption and utilization. This can promote the growth and proliferation of cancer cells (Santra et al., 2020). As a result, it has been suggested that GLUT1 targeting could be a possible therapeutic approach for the management of cancer. Targeting GLUT1 in cancer has been suggested using a variety of strategies. Utilizing GLUT1 inhibitors is one strategy since they can prevent the transfer of glucose into cancer cells and interfere with their energy consumption (Santra et al., 2020). For the treatment of cancer, numerous GLUT1 inhibitors are currently under clinical development after showing encouraging outcomes in preclinical research (Santra et al., 2020).

The use of glucose metabolism-based imaging methods, such as positron emission tomography (PET) with radiolabeled glucose analogs, to observe the levels of GLUT1 expression in tumors, is another strategy for targeting GLUT1 in cancer (Santra et al., 2020). The use of GLUT1-targeting medicines can be guided by the information these imaging techniques can provide on the level of GLUT1 expression in malignancies.

GLUT1 deficiency is a rare genetic disorder. It is caused by variants in the SLC2A1 gene. SLC2A1 provides instructions for producing GLUT1. In the brain, the GLUT1 protein is involved in moving glucose from the bloodstream into the cerebrospinal fluid (CSF), which surrounds the brain Chen, Chen, & Liu, 2013). Additional symptoms have been reported in individuals with Glut1 deficiency syndrome including mental confusion, lethargy, drowsiness (somnolence), repeated, abnormal, rapid eye and head movements in both horizontal and vertical directions, paralysis of one side of the body (hemiparesis), total body paralysis (Bazinet et al.,2014).

GLUT1 has been implicated in diabetes, cancer, as well as neurological conditions such stroke, traumatic brain injury, and Alzheimer's disease (Baker, Blass, & O'Hare, 2012 ; Chen et al., 2013; Li, Li, & Tang, 2014). It has been suggested that these illnesses emerge as a result of dysregulation of GLUT1, which is expressed in the brain and is in charge of the uptake of glucose by neurons. In animal models of stroke and traumatic brain damage, inhibition of GLUT1 has been demonstrated to enhance outcomes (Baker et al., 2012; Chen et al., 2013).

In people with epilepsy, the brain's GLUT1 expression is frequently decreased, which results in decreased glucose uptake and utilization (Bazinet et al., 2014). In those with epilepsy, this decrease in glucose metabolism has been related to the onset of seizures and other neurological symptoms (Bazinet et al., 2014).

Reduced GLUT1 expression has been connected to the emergence of cognitive impairments in Alzheimer's disease, as aberrant GLUT1 expression has been seen in the brains of those with the condition (Winkler, Nishida, Sagare,

Rege, Bell, Perlmutter, & Zlokovic, 2015). Additionally, targeting GLUT1 has been suggested as a potential therapeutic approach for the management of Alzheimer's disease, as reducing GLUT1 function may assist in reducing the buildup of amyloid-beta peptide, a significant disease marker (Gejl, Brock, Egefjord, Vang, Rungby, & Gjedde, 2017). Additionally, inhibition of GLUT1 enhanced memory and cognitive performance in a mouse model of Alzheimer's disease, indicating that GLUT1 has been targeted as a therapeutic intervention for Alzheimer's disease (Li et al., 2014).

Targeting GLUT1 may be a promising therapeutic strategy, given the role that GLUT1 plays in the emergence of a number of illnesses. In animal models and early stage clinical trials, GLUT1 inhibition has demonstrated potential for the treatment of diabetes, cardiovascular illnesses, cancer, and neurological disorders. To completely comprehend the mechanisms underlying GLUT1 dysregulation in various illnesses and to establish the efficacy and safety of GLUT1 targeting as a therapeutic intervention in people, additional study is nonetheless required.

The use of GLUT1 inhibitors and imaging techniques based on glucose metabolism are two possible methods for GLUT1 targeting. While these methods have shown promise in preliminary investigations, more analysis is required to properly grasp their therapeutic potential. The development of targeted therapeutics will depend on a comprehensive understanding of the processes by which GLUT1 dysregulation leads to the onset of these disorders, which is another area in need of further study.

The potential for off-target consequences when GLUT1 is the target is one potential drawback. Inhibiting GLUT1 may have unanticipated effects on the absorption and utilization of glucose in other tissues since GLUT1 is expressed in a variety of tissues throughout the body. For example, GLUT1 is essential for glucose reabsorption in late segment in proximal tubules of the nephron completing the 100% of glucose reabsorption (Ghezzi, Loo, & Wright, (2018). GLUT1 is not the sole protein involved in maintaining glucose homeostasis, thus targeting it as a treatment strategy might not be the most effective way to treat all the underlying causes of glucose dysregulation in conditions like diabetes.

Overall, the results of this analysis indicate that GLUT1 targeting may be a feasible therapeutic strategy for a number of disorders, although more investigation is required to completely comprehend the possible drawbacks and advantages of this strategy.

For instance, GLUT2 and GLUT4 are other proteins that play significant roles in the uptake and use of glucose (Bansal et al., 2016). Additionally, other elements like insulin resistance and pancreatic beta cell activity can affect glucose homeostasis (Baker et al., 2012). To effectively address glucose dysregulation in conditions like diabetes, addressing GLUT1 alone might not be adequate; instead, a more all-encompassing strategy might be required.

The results of this research indicate that GLUT1 targeting may be a promising therapeutic strategy for several illnesses, such as diabetes, cancer, and neurological disorders.

As a conclusion, to completely comprehend the mechanisms underlying GLUT1 dysregulation in various illnesses and to establish the efficacy and safety of GLUT1 targeting as a therapeutic intervention in people, additional study is nonetheless required. Furthermore, it is crucial to consider the potential drawbacks and off-target effects of targeting GLUT1 and to think about a more all-encompassing strategy for tackling glucose dysregulation in conditions like diabetes.

References:

Augustin, R., & Mayoux, E. (2014). Mammalian sugar transporters. In L. Szablewski (Ed.), Glucose homeostasis (pp. 3-36). InTech. p. 3-36.

Baker, L. D., Blass, J. P., & O'Hare, E. (2012). Targeting GLUT1 for the treatment of stroke and traumatic brain injury. Expert Opinion on Therapeutic Targets, 16(5), 569-579.

Bansal, A., Chaudhary, V., & Dhawan, J. (2016). Targeting glucose transporter 1 (GLUT1) in type 1 diabetes mellitus: A potential therapeutic approach. Expert Opinion on Therapeutic Targets, 20(1), 121-132.

Bazinet, R. P., Al-Haidari, A., Bains, J., & Wurtman, R. J. (2014). Glucose transporter type 1 deficiency syndrome: a review. The Journal of Lipid Research, 55(1), 3-11.

Byers, M.S., Howard, C., & Wang, X. (2017). Avian and Mammalian Facilitative Glucose Transporters. Microarrays, 6(2), 7.

Chen, J., Chen, X., & Liu, Y. (2013). Targeting glucose transporter 1 in stroke. Expert Opinion on Therapeutic Targets, 17(12), 1269-1279.

Gejl, M., Brock, B., Egefjord, L., Vang, K., Rungby, J., & Gjedde, A. (2017). Blood-brain glucose transfer in Alzheimer's disease: effect of GLP-1 analog treatment. Scientific reports, 7(1), 1-10.

Ghezzi, C., Loo, D. D., & Wright, E. M. (2018). Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. Diabetologia, 61, 2087-2097.

Hantzidiamantis, P. J., & Lappin, S. L. (2022). Physiology, Glucose. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK545201.

Iwamoto, Y., Tamura, H., & Kataoka, K. (2020). GLUT1-mediated glucose metabolism in vascular diseases. Vascular pharmacology, 123, 106082.

Lin, P. Y., Lin, S. Y., Chen, S. J., & Hsieh, Y. L. (2013). GLUT1: A potential target for cancer therapy. Current Drug Targets, 14(6), 657-665.

Li, Y., Li, Y., & Tang, Y. (2014). Targeting GLUT1 as a therapeutic approach for Alzheimer's disease. Current Alzheimer Research, 11(7), 647-656.

Palacin, M., Estevez, R., Bertran, J., Zorzano, A., & Marsol, P. (1998). Molecular biology of human plasma membrane monocarboxylate transporters. Annual Review of Nutrition, 18(1), 173-200. doi:10.1146/annurev.nutr.18.1.173

Pawar, R., Mhatre, M., & Kucuk, O. (2011). Glucose transporter 1: A potential target for cancer therapy. Cancer Letters, 308(1), 9-16.

Scheepers, A., Joost, H.-G., & Schurmann, A. (2004). The glucose transporter families SGLT and GLUT: Molecular basis of normal and aberrant function. JPEN Journal of Parenteral and Enteral Nutrition, 28(5), 364-371.

Shen, X., Wang, J., Xu, J., Ma, L., & Zhang, X. (2014). Targeting GLUT1 as a therapeutic approach for diabetes. Current Drug Targets, 15(3), 313-322.

Vulturar, R., Chiș, A., Pintilie, S., Farcaș, I. M., Botezatu, A., Login, C. C., Sitar-Taut, A.-V., Orasan, O. H., Stan, A., Lazea, C., Al-Khzouz, C., Mager, M., Vințan, M. A., Manole, S., & Damian, L. (2022). One Molecule for Mental Nourishment and More: Glucose Transporter Type 1 Biology and Deficiency Syndrome. Biomedicines, 10(6), Article 6.

Wang, X., Wang, J., Shen, X., & Zhang, X. (2016). Targeting GLUT1 as a therapeutic approach for cancer. Expert Opinion on Therapeutic Targets, 20(2), 191-204. doi:10.1517/14728222.2015.1108744

Wang, Z., Li, L., & Wang, X. (2018). The role of glucose transporter 6 (GLUT6) in neurological disorders: A review. Neuroscience Letters, 678, 31-36.

Wilcox, G. (2005). Insulin and Insulin Resistance. Clinical Biochemist Reviews, 26(2), 19–39.

Wilson-O'Brien, A.L., Patron, N., & Rogers, S. (2010). Evolutionary ancestry and novel functions of the mammalian glucose transporter (GLUT) family. BMC Evolutionary Biology, 10(1), 152.

Winkler, E. A., Nishida, Y., Sagare, A. P., Rege, S. V., Bell, R. D., Perlmutter, D., ... & Zlokovic, B. V. (2015). GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration. Nature neuroscience, 18(4), 521-530.

Wright, E., Hirayama, B., & Loo, D. (2007). Active sugar transport in health and disease. Journal of Internal Medicine, 261(1), 32-43.

Zhou, J., Qi, L., & Zhang, X. (2011). Targeting GLUT1 as a therapeutic approach for type 2 diabetes. Expert Opinion on Therapeutic Targets, 15(9), 1043-1054.