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EFFECT OF PHOTOBIOMODULATION THERAPY ON THE REGULATION OF GLUCOSE UPTAKE BY LYMPHOCYTES IN DIABETES MELLITUS (REVIEW)

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For most cells, including lymphocytes, glucose is a primary energy source, and, therefore, it is vital to understand the regulatory mechanisms that control the work of glucose transporters. Lymphocytes are pivotal for mediation of immune and inflammatory responses. A feature of lymphocytes is increasing glucose utilization during activation of the immune function, which is strongly dependent on glucose uptake. Some studies show that elevated glucose concentration in diabetes mellitus affects lymphocytes' glucose transporters expression, which correlates with impaired immune functions and may become one of the predisposing factors of contracting infectious diseases. Recent studies have focused on glucose transporters as therapeutic targets for a variety of diseases, including diabetes mellitus. This review demonstrates the effect of photobiomodulation therapy on glucose uptake by Na^+-coupled glucose carrier SGLT1 and facilitated diffusion glucose carriers of the GLUT family (GLUT1, GLUT3, GLUT4) in normal and diabetic lymphocytes.

Keywords: GLUT, SGLT1, photobiomodulation, lymphocytes, diabetes mellitus

ABBREVIATION LIST

AC – Adenylate cyclase;
Akt – Protein kinase B;
AMPK – AMP-activated protein kinase;
ATP – Adenosine triphosphate;
CAMKKβ – Ca^{+2}/calmodulin-dependent kinase kinase β;
cAMP – Cyclic adenosine monophosphate;
CREB – cAMP response element-binding protein;

Cyt *c* – Cytochrome *c* oxidase;
DM – Diabetes mellitus;
GLUT – Glucose transporter;
GPCRs – G-protein-coupled receptors;
HNF-1 – Hepatic nuclear factor 1;
IL-7 – Interleukin-7;
IL-7R – Interleukin-7 receptor;
IR – Insulin receptor;
IRS – Insulin receptor substrate;
JAK1/3 – Janus kinase 1/3;
MAP3K – Mitogen activated protein 3 kinase;
MKK3/6 – Mitogen-activated protein kinase kinase 3/6;
MSK1/2 – Mitogen- and stress-activated kinases 1/2;
mTORC1/2 – Mammalian target of rapamycin complex 1/2;
NFAT – Nuclear factor of activated T-cells;
NF-kB – Nuclear factor kappa-light-chain-enhancer of activated B cells;
p38 MAPK – p38 mitogen-activated protein kinases;
PBMT – Photobiomodulation therapy;
PDK1 – Pyruvate dehydrogenase kinase 1;
PI3K – Phosphoinositide 3-kinases;
PIP2 – Phosphatidylinositol 4,5-bisphosphate;
PIP3 – Phosphatidylinositol 3,4,5-triphosphate;
PMCA1/4 – Plasma membrane Ca^{2+} ATPase 1/4;
PTEN – Phosphatase and tensin homolog;
Rheb – Ras homolog enriched in brain;
ROS – Reactive oxygen species;
RS1 – Regulator of solute carriers 1;
S6K – S6 Kinase 1;
sAC – Soluble adenylyl cyclase;
SGK1 – Serum/glucocorticoid regulated kinase 1;
SGLT1 – Sodium-glucose linked transporter1;
SP1 – Specificity protein 1;
STAT3/5 – Signal transducer and activator of transcription 3/5;
TRPML1 – Transient receptor potential mucolipin-1;
TRPV – Transient receptor potential vanilloid;
Tsc1/2 – Tuberous sclerosis protein 1/2.

INTRODUCTION

ATP produced by glycolysis and the electron transport chain is the fuel for the activity and function of any cell. The activation of T cells is accompanied by changes in glucose metabolism. Naïve T lymphocytes are dependent on oxidative phosphorylation for energy, but after stimulation, they differentiate into effector T lymphocytes with the reprogramming of metabolic pathways to glycolysis, and this affects T cells proliferation, activation, and immune function (Zhou *et al.*, 2021). According to Lang *et al.* (2020), glucose uptake into lymphocytes across the cell membrane is accomplished by non-concentrative glucose carriers of the GLUT family (GLUT1, GLUT3, GLUT4) which mediate passive transport but are unable to operate against a chemical glucose gradient. Also, Kavanagh *et al.* (2018) demonstrated the co-expression of GLUT1, GLUT3,

GLUT4, and GLUT6 in human $CD4^+$ T cells after cell activation. Meanwhile, some of the data show that after naïve T lymphocytes differentiate into effector T cells, they significantly increase the expression of GLUT1 on cell membranes (Zhou *et al.*, 2021; Sinclair, Barthelemy, & Cantrell, 2020). Besides, there is a report that store-operated calcium entry controls T cell receptor (TCR)-induced proliferation of T lymphocytes by controlling the expression of GLUT1 and GLUT3, glycolytic enzymes, and proteins required for mitochondrial respiration after stimulation (Vaeth *et al.*, 2017). In this review, we will not pay attention to GLUT6 because there is a study in which authors conclude that GLUT6 does not mediate glucose uptake and localizes on lysosomal membranes (Maedera, Mizuno, Ishiguro, Ito, Soga, & Kusuhara 2019). Also, Byrne, Olzomer, Brink, & Hoehn (2018) showed that the knockout of glucose transporter GLUT6 has minimal effects on whole-body energy metabolism in mice. It is noteworthy that some studies demonstrates the influence of elevated glucose concentration in patients with diabetes on lymphocytes' GLUT expression by decreasing GLUT1, GLUT3 and GLUT4 levels, which was more significant for GLUT3 (Kipmen-Korgun, Bilmen-Sarıkçıoğlu, Altunbas, Demir, & Korgun 2009) and GLUT4 (Dou *et al.*, 2016). Facilitated diffusion glucose transporters differ in terms of their levels in cells and regulatory mechanisms that mediate their functioning. They play a vital role in cells' survival and physiological functioning, which makes them a promising therapeutic target for the treatment of diabetes mellitus (DM).

Likewise, there are some reports about Na^+ coupled glucose carrier SGLT1 mRNA expressions in the lungs, liver, pancreas, and T lymphocytes (Sano, Shinozaki, & Ohta, 2020). Additionally, Bhavsar *et al.* (2016) reveal that JAK3 up-regulates SGLT1 by increasing the carrier protein abundance in the cell membrane, an effect enforcing cellular glucose uptake into activated lymphocytes and thus contributing to the immune response. On the other hand, Sano *et al.* (2020) suggested the possibility of reducing postprandial hyperglycemia in patients with diabetes by reducing glucose absorption in the small intestine using an SGLT1 inhibitor. However, some studies on mice warn of the potential danger of using SGLT1 inhibitors for the treatment of diabetes because the inhibitors may, similarly to genetic knockout of the SGLT1 gene, compromise the macroorganism defense against bacteria and lead to lethal infections (Sharma *et al.*, 2017; Koepsell & Vallon, 2020). Though, whether humans are similarly sensitive to lack of SGLT1 as mice has not been proven for the time being.

Photobiomodulation therapy (PBMT), also known as low-level light therapy, is commonly used to promote diabetic wound healing (Rajendran, Houreld, & Abrahamse, 2021; Rahbar Layegh *et al.*, 2020; Oyebode, Houreld, & Abrahamse, 2021), decreasing inflammation (Ahmadi *et al.*, 2020; Moradi et al, 2020), and produce analgesia (De Freitas & Hamblin, 2016) using a low-power light source (lasers or light-emitting diodes). The most commonly used wavelength for PBMT was 630–660 nm. The PBMT photons were absorbed by endogenous chromophores that elicit photochemical events without thermal damage (Raizman & Gavish, 2020). Some data suggest that PBMT modulates gene transcription for protein synthesis and activates cellular signaling (Jere, Houreld, & Abrahamse, 2020; Rajendran, Houreld, & Abrahamse, 2021). On the other hand, there are a lot of data in which authors pay more attention to the ability of PBMT to either increase the activity of antioxidant enzymes such as superoxide dismutase (Sunemi *et al.*, 2021), catalase (Karkada, Maiya, Arany, Rao, Adiga, & Kamath, 2021), as well as the total antioxidant capacity of cells (Chen, Tu, Shi, Wang, Hou, & Wang, 2021) or to reduce the levels of the proinflammatory cytokine IL-6 and TNF-α in diabetic wound cells (Shaikh-Kader, Houreld, Rajendran, & Abrahamse, 2021). It was found that PBMT could affect cell

functions, such as differentiation (Mokoena, Houreld, Dhilip Kumar, & Abrahamse, 2019), migration, survival (Jere, Houreld & Abrahamse, 2021), and metabolism in different cell types, including red blood cells (Walski et al, 2018), endothelial cells (Colombo *et al.*, 2021), hepatic cells (Guo, Gong, Shen, & Xing, 2020), fibroblasts (Alexandria, de Silva, Maia Filho, Assis, & Tim 2020), stem cells, osteoblast (Houreld, 2019), and muscle cells (Gong, Zou, Liu, Guo, & Xin, 2021). Furthermore, several recent studies have concluded that PBMT improves the redox state of mitochondria in diabetic ulcers (Mehrvar *et al.*, 2021; Gopalakrishnan *et al.*, 2020). Additionally, Mussttaf's, Jenkins', & Jha's (2019) review mentioned that PBMT increases the ability of macrophages to act as phagocytes, stimulates a greater secretion of basic fibroblasts growth factors, and intensifies fibrin resorption as part of the demolition phase of wound healing. Similarly, the above review stated that after PBMT lymphocytes become activated, proliferate more speedily, and become more motile. On the other hand, Karmash, Liuta, Yefimenko, & Sybirna (2021) demonstrated a decrease in total NO synthase activity and an increased catalase activity in leukocytes of rats with diabetes under PBMT, which prevents the development of oxidative stress. Moreover, Karmash, Liuta, Korobov, & Sybirna (2020) found that irradiation of rats with DM causes normalization of advanced glycation end product levels in leukocytes. The authors also confirm the ability of PBMT at a wavelength of 630–660 nm to enhance glucose uptake in leukocytes of rats from both control and diabetic groups. It is noteworthy that Gong *et al.* (2021) showed a possible mechanism of action of PBMT to improve glucose uptake, which includes reactive oxygen species-induced activation of phosphatase and tensin homolog (PTEN)/protein kinase B (AKT)/GLUT4 translocation signaling pathway in skeletal muscle. However, cellular and molecular mechanisms of enhancing glucose uptake in leukocytes induced by PBMT are not fully understood, and further studies are necessary. This review aims to demonstrate an assumed effect of PBMT on signaling pathways that enhance glucose uptake by SGLT1, GLUT1, GLUT3, and GLUT4 in lymphocytes under both DM and healthy conditions.

Effect of photobiomodulation therapy on the regulation of Na^+-coupled glucose carrier SGLT1 in lymphocytes. Summarizing the analyzed literature sources, we created a scheme that visualizes hypothetical mechanisms of the influence of PBMT on the regulation of glucose uptake by SGLT1, both in normal and in diabetic wound lymphocytes (**Fig. 1**).

Hamblin (2018) and de Freitas & Hamblin (2016) considered the hypothetical mechanisms of the influence of PBMT on mitochondrial redox signaling. According to their reviews, the leading hypothesis to explain how exactly light increases cytochrome *c* oxidase enzyme activity is that nitrogen oxide can be photodissociated by absorption of a photon of red light at a wavelength of 630–660 nm. Cytochrome *c* oxidase is unit IV of the mitochondrial respiratory chain and can be inhibited by noncovalently binding with nitric oxide, which also explains why PBMT has greater effects in diseased or damaged cells in contrast to healthy cells. Thus, PBMT increases adenosine triphosphate (ATP) synthesis and causes resumption of respiration with the generation of reactive oxygen species (ROS) by increasing the mitochondrial membrane potential. One of the direct consequences of the higher level of ATP after PBMT is an increase in cyclic adenosine monophosphate (cAMP) concentration (Zhang, Shen, Wu, Zhang, & Xing, 2020). It is noteworthy that the generation of cAMP is regulated in two ways: first by adenylate cyclase (AC) in a G-protein-dependent manner, and second by soluble adenylyl cyclase (sAC), the activity of which is induced by Ca^{2+} with HCO_3^- in a G-protein-independent manner (Arumugham & Baldari, 2017; Zhang, Kong, Wang, Jiang, & Hua, 2020). Also, there is

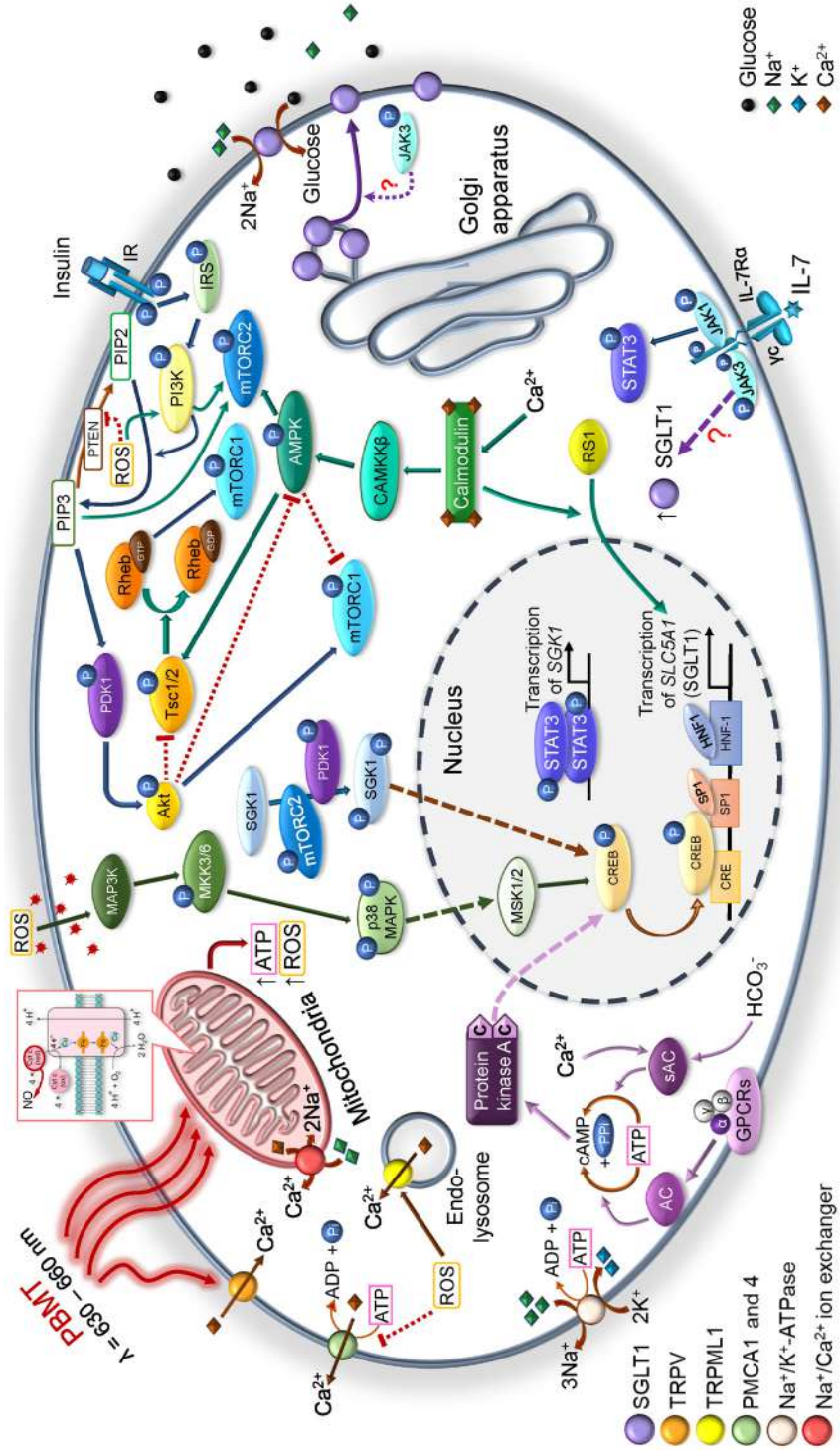

Fig. 1. Hypothetical mechanisms of the effect of photobiomodulation therapy on the regulation of glucose uptake by the Na^+-coupled glucose carrier SGLT1 in lymphocytes

Рис. 1. Гіпотетичні механізми впливу фотобіомодуляційної терапії на регулювання поглинання глюкози за допомогою Na^+-залежного транспортера глюкози SGLT1 у лімфоцитах

evidence that irradiation can induce cellular alkalinization, and as a consequence, can facilitate the opening of transient receptor potential vanilloid (TRPV) channels, which leads to an increase in intracellular Ca^{2+} as shown by fluorescent probes. However, there is a possibility that PBMT can directly activate TRPV channels (De Freitas & Hamblin, 2016). Besides, it is possible that there is another way to increase intracellular Ca^{2+} after the effect of PBMT on normal cells through transient receptor potential mucolipin-1 (TRPML1) activation, which is localized in the late endo-lysosome by ROS (Clement, Goodridge, Grimm, Patel, & Malmberg, 2020), although this needs to be confirmed. In return, under DM conditions a decreased ATP production affects Na^+/K^+ ATPase activity, so in an attempt to restore cellular pH, Na^+ is removed by the Na^+/Ca^{2+} ion exchanger causing a substantial influx of Ca^{2+} in lymphocytes (Takeuchi, Kim, & Matsuoka, 2020). As it is known, PBMT can increase ATP production and thus restore Na^+/K^+ ATPase activity, which also normalizes Na^+ and Ca^{2+} ions intracellular concentration under diabetes (Rhee, Moon, Jung, Oh, Ahn, & Chung, 2019; Liebert, Krause, Goonetilleke, Bicknell, & Kiat, 2017). Additionally, it is also possible that an increase in intracellular ATP level after PBMT can promote expelling Ca^{2+} from lymphocytes through the plasma membrane Ca^{2+} ATPase (PMCA) isoforms 1 and 4, but further studies are needed to confirm this hypothesis. Moreover, Bruce (2018) reviewed that PMCA can be directly inhibited not only by ATP depletion during metabolic stress but also by ROS, so one of the consequences of PBMT influence on normal cells can be inhibition of PMCA with consistent cytosolic Ca^{2+} increase. The effect of PBMT on the generation of cAMP and changes in intracellular Ca^{2+} and Na^+ ions concentration is shown on the left side of **Fig. 1**.

An increase in cytosolic Ca^{2+} by PBMT followed by Ca^{+2}/calmodulin-dependent kinase β (CaMKKβ) activation was reported in the study by Guo *et al.* (2020). CaMKKβ phosphorylates and activates AMP-activated protein kinase (AMPK) (Kazyken, Lentz, & Fingar, 2021), which can promote cell survival and metabolic homeostasis by increasing glucose uptake through direct activation of mTOR complex 2 (mTORC2) and inhibition of mTORC1 during energetic stress (Kazyken *et al.*, 2019). Moreover, AMPK can phosphorylate and activate Tsc1/2, which acts as a GTPase-activating protein for Rheb (Ras homolog enriched in brain) and inhibit Rheb activity with a corresponding decrease in mTORC1 activity in lymphocytes, which was demonstrated in the study by Zhang *et al.* (2019). The described mechanism is shown by green arrows in **Fig. 1**.

Several studies demonstrated that PBMT can stimulate signaling pathways involving protein kinase B (also known as Akt) in diabetic wound cells (Rajendran *et al.*, 2021; Jere, Houreld, & Abrahamse, 2019). On the other hand, there is a study by Hamblin (2018) in which the author assumed that the mechanism of Akt activation by PBMT can be related to an increase in ROS generation. Meanwhile, some articles described the ability of ROS to directly activate phosphoinositide 3-kinases (PI3K), amplify its downstream signaling and also concurrently inactivate PTEN, which negatively regulates the synthesis of phosphatidylinositol 3,4,5-triphosphate (PIP3) and thereby inhibits the activation of Akt (Zhang *et al.*, 2016). Another way to activate Akt by PBMT is the insulin signaling pathway. A recent review by Marks (2021) described the ability of PBMT to lower blood glucose concentration and reduce insulin resistance in various types of cells under DM, as well as in the norm. Furthermore, some authors insist that PBMT improved glucose tolerance through the insulin signaling pathway (Gong *et al.*, 2021; Silva *et al.*, 2018). The recent study by Sheccid (2021) demonstrated the capability of PBMT to enhance insulin secretion by β-cells. Increases in insulin secretion may affect lymphocytes through activation of IR (Insulin receptor) by hormone and, as a consequence, this increased levels of

activated PI3K, pyruvate dehydrogenase kinase 1 (PDK1), Akt. This mechanism is depicted above in **Fig. 1**. Among other things, recent findings by Dai & Thomson (2019) suggest that in lymphocytes, mTORC2 can be activated directly by PI3K. Importantly, the activation of Akt requires phosphorylation by mTORC2, but after activation, Akt positively regulates mTORC1 (Pollizzi *et al.*, 2015) and inhibits AMPK (Clement *et al.*, 2020).

On the other hand, there is data by Jere *et al.* (2020) that demonstrate the ability of PBMT to directly regulate genes that encode for proteins involved in the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, including Akt, JAK3, JAK1, STAT3, and STAT5. While Akt, JAK1, and STAT5 proteins can take part in mTORC1 activation, which we will explain later, some studies suggested that after phosphorylation of STAT3 mediated by JAK1 and nonreceptor kinases, activated STAT3 can regulate the expression of genes such as serum/glucocorticoid regulated kinase 1 (SGK1) (Zhu, Wang, & Rui, 2019) and thus take part in enhanced transcription of SGLT1. Moreover, other authors assumed that JAK3 could influence SGLT1 protein abundance in the cell membrane by direct phosphorylation of the carrier protein or by phosphorylation of other signaling molecules, which in turn up-regulated SGLT1 in lymphocytes (Bhavsar *et al.*, 2016). However, the molecular mechanism of the effect of JAK3 on the content of SGLT1 in cells needs to be studied; therefore, we indicated it with red question marks in **Fig. 1**. We mentioned earlier that the influence of PBMT upregulates JAK3 and JAK1. Also, according to Stabile *et al.* (2018), both of these proteins are phosphorylated by the interleukin-7 (IL-7) receptor. Phosphorylated JAK3 and JAK1 can stimulate downstream activation of STAT3 and STAT5 in lymphoid cells (Stabile *et al.*, 2018), these proteins are also upregulated by PBMT, so IL-7 can play a significant role in the JAK/STAT pathway activated by PBMT, especially in diabetes due to overproduction of IL-7 (Coulson, Bakhashab, Latief, & Weaver, 2021), although this also requires further research.

As shown in the review by Koepsell (2020), several factors that regulate the transcription of SGLT1 at the promoter region have been identified, for example, binding of hepatic nuclear factor 1 (HNF1), transcription factor SP1, and cAMP response element-binding protein (CREB) to the SGLT1 gene. Look at the nucleus shown in **Fig. 1**. Phosphorylation of CREB is catalyzed by SGK1 (Koepsell, 2017), which has been phosphorylated by PDK1 and mTORC2 (Saravia, Raynor, Chapman, Lim, & Chi, 2020). Mitogen- and stress-activated kinases (MSK) 1 and 2 are nuclear proteins activated downstream of the p38 MAPK pathways (Martínez-Limón, Joaquin, Caballero, Posas, & de Nadal, 2020), which is depicted using dark green arrows in **Figs. 1**. and **2**. MSK 1/2 play an important role in CREB activation in lymphocytes, as shown by Kaiser, Wiggin, Lightfoot, Arthur, & Macdonald (2007). p38 MAPK is activated by a wide range of environmental stimuli that also include oxidative stress (Martínez-Limón *et al.*, 2020). PBMT can increase the activity of enzymatic antioxidants and decrease total NO synthase activity, which leads to a corresponding decrease in the level of oxidative modification of proteins and other markers of oxidative stress in leukocytes of diabetic rats; nevertheless, in healthy animals, the effect of PBMT is the opposite (Karmash *et al.*, 2021; Karmash *et al.*, 2020). Thus, PBMT can influence the p38 MAPK pathway. Furthermore, there is an alternative way how PBMT can increase transcription of SGLT1, namely by increasing cAMP concentration (Hamblin, 2018) and binding of this second messenger to two regulatory subunits of the inactive protein kinase A (PKA) that results in the release and activation of the two catalytic subunits that are able to phosphorylate CREB (Zhang *et al.*, 2020). Additionally, an increase in Ca^{2+} by PBMT can regulate the nuclear abundance of RS1 (the regulator of solute carriers 1), which is

involved in confluence-dependent regulation of SGLT1 transcription, via nuclear shuttling domain that contains a Ca^{2+}-dependent calmodulin-binding site (Koepsell, 2020).

Thus, PBMT can enhance glucose uptake by the Na^+-coupled glucose carrier SGLT1 in lymphocytes of healthy humans by increasing the intracellular concentration of cAMP, Ca^{2+}, ROS and via activating some elements of the JAK/STAT pathway and insulin signaling pathway, ultimately affecting SGLT1 transcription. Possibly, in DM PBMT affects SGLT1 transcription in lymphocytes by reducing oxidative stress through increasing the activity of enzymatic antioxidants, as well as increasing the level of intracellular ATP required for Na^+/K^+ ATPase activity and therefore stable cells homeostasis. It is noteworthy that PBMT supports the carrier transcription by activating the cAMP/PKA pathway and other pathways mentioned earlier, but with lower intensity in comparison with processes occurring in diabetic wound cells, which may contribute to the normal cell-mediated protection of the macroorganism, but this requires further research.

Effect of photobiomodulation on the glucose transporters of the GLUT family in lymphocytes. Based on the literature, we created a scheme that demonstrates the hypothetical mechanisms of the influence of PBMT on the regulation of glucose uptake by GLUT1, GLUT3, and GLUT4 in leukocytes of rats from both control and diabetic groups (**Fig. 2**).

Previously, we noted that in lymphocytes from humans with DM, quantitative contents of GLUT1, GLUT3, and GLUT4 are lower than the content of these glucose transporters in lymphocytes from a healthy human. Furthermore, this difference is more significant for GLUT3 and GLUT4, which might be the cause of the reduced cell-mediated immunity. However, there is conflicting evidence suggesting that upon activation of B cells in DM, they upregulate GLUT1 which is dependent on the action of the transcription factor c-Myc (Wilson & Moore, 2020). NK cells in diabetes express elevated levels of GLUT4, and, as proposed, the cause of such changes is neutrophil-derived ROS (Daryabor, Atashzar, Kabelitz, Meri, & Kalantar, 2020). Thus, we consider that it is necessary to conduct more detailed studies of gene expression and exposure of GLUT family proteins on the plasma membrane in different lymphocyte subpopulations.

As discussed earlier, PBMT enhances the expression of JAK1, JAK3, and STAT5 proteins. JAK1 and JAK3 proteins link to the IL-7Rγc (gamma chain of the IL-7 receptor), phosphorylate each other to increase their kinase activity, and then phosphorylate the IL-7Rα (alpha chain of the IL-7 receptor), which provides STAT5 binding and phosphorylation (**Fig. 2**). Activation of the above JAK-STAT pathway promotes glucose uptake by GLUT1 in T (Di Dedda, Vignali, Piemonti, & Monti, 2019) and B cells (Wilson & Moore, 2020) that we will explain in more detail. Firstly, phosphorylation of STAT5 proteins results in their dimerization and translocation to the nucleus and finally in the transcription of target genes including c-Myc (González-García, García-Peydró, Alcain, & Toribio, 2012) and *SLC2A1* (GLUT1) (Di Dedda *et al.*, 2019). c-Myc itself also regulates gene expression of key metabolic enzymes (Kress, Sabò, Amati, 2015) and *SLC2A1* (Siska & Rathmell, 2015). Secondly, evidence suggests that STAT5 can directly bind to consensus sites within the Akt gene and enhance its transcriptional activation, but the phosphorylation of p38 negatively correlates with the phosphorylation of STAT5 (Tian *et al.*, 2020). At the same time, activation of Akt plays a central role in regulating GTUT1 vesicle trafficking (Di Dedda *et al.*, 2019) and stabilization (Avanzato *et al.*, 2018) at the plasma membrane, leading to an increase in GLUT1 surface exposure. Furthermore, induction of GLUT1 regulation on the transcriptional level in lymphocytes may occur through the PI3K-Akt-mTORC1 pathway that regulates the key metabolic transcription factor c-Myc (Shyer,

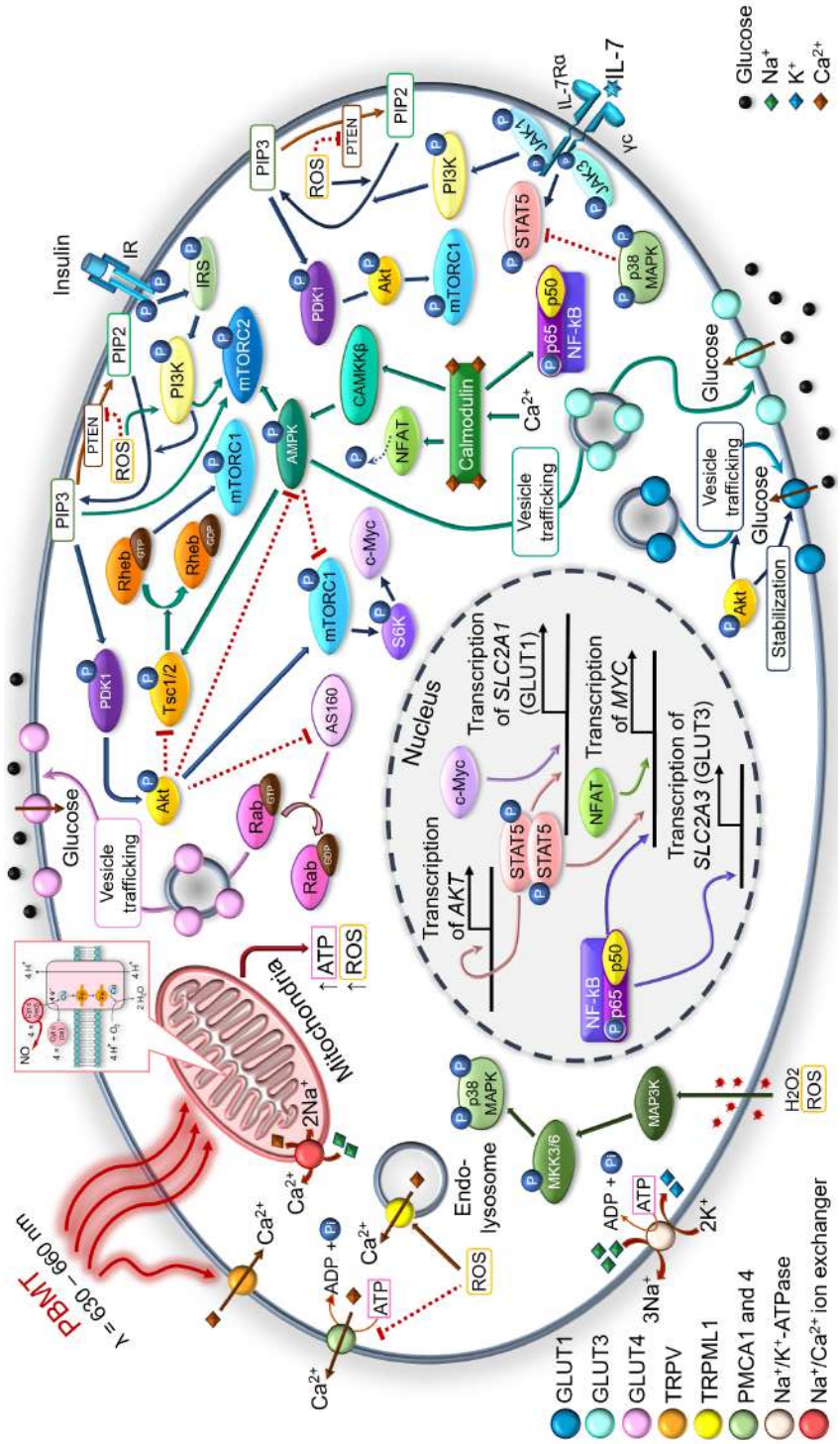

Fig. 2. Hypothetical mechanisms of the effect of photobiomodulation therapy on the regulation of glucose uptake by GLUT1, GLUT3, and GLUT4 in lymphocytes
Рис. 2. Гіпотетичні механізми впливу фотобіомодуляційної терапії на регулювання поглинання глюкози за допомогою GLUT1, GLUT3 та GLUT4 у лімфоцитах

Flavell, & Bailis, 2020). In particular, phosphorylation of mTORC1 substrate S6 Kinase 1 (S6K1) can mediate *MYC* mRNA stability, translation, and protein stability (Shorning, Dass, Smalley, & Pearson, 2020). Alternatively, in the review by de Barrios, Meler, & Parra (2020) it is mentioned that phosphorylated STAT5 may cooperate with JAK2 to maintain an elevated level of c-Myc by protecting it from ubiquitin-dependent degradation. Besides, one of the main pathways activated by JAK1 is the PI3K/Akt/mTORC1, where JAK1 induces phosphorylation of the IL-7Ra intracellular domain and promotes PI3K recruitment with consequent activation (Oliveira, Akkapeddi, Ribeiro, Melão, Barata, 2019).

Among the targets of intracellular Ca^{2+} in lymphocytes are Ca^{2+}-regulated transcription factors, including the Nuclear factor of activated T-cells (NFAT) and Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Berry, May, & Freedman, 2018). As has been found, the enhanced activity of NF-κB upregulates glucose transporters GLUT3 (Kawauchi, Araki, Tobiume, & Tanaka, 2008) and GLUT1 (Ziegler, Almos, McNeill, Jansch, & Lesch, 2020) in lymphocytes. While NF-κB stimulates GLUT3 transcription by binding to a specific NF-κB binding element located within the intron of the *SLC2A3* (GLUT3) (Ancey, Contat, & Meylan, 2018), the stimulation of GLUT1 transcription enhances upon the regulation of the c-Myc gene transcription by NF-κB and NFAT (Berry *et al.*, 2018). Look at the nucleus shown in **Fig. 2.** On the other hand, data by Berry *et al.* (2018) introduced a significant possibility that c-Myc expression in T cells is induced by NFAT-independent manner compared to the transcriptional regulation of the c-Myc gene by NF-κB/NFAT in B cells. According to Hogan, Chen, Nardone, & Rao (2003), Ca^{2+}/calmodulin-dependent serine phosphatase calcineurin dephosphorylates NFAT upon rising intracellular Ca^{2+} concentration, after which dephosphorylated NFAT translocate to the nucleus and become transcriptionally active, thus providing a direct link between intracellular Ca^{2+} and gene expression. On the contrary, calmodulin directly binds to NF-κB p65 and lets it translocate to the nucleus and act on its target genes in T and B lymphocytes, including *MYC* and *SLC2A3* (Berry *et al.*, 2018). In addition to an increase in transcriptions of GLUT1 and GLUT3, PBMT may also increase translocation of GLUT3 to the plasma membrane through activation of AMPK, because as has been shown by Chan, Burke, Gao, & Fish (2012), activated AMPK is also able to stimulate glycolysis through GLUT3 trafficking and phosphorylation/activation of the glycolytic enzymes.

Another way in which PBMT increases glucose uptake in leukocytes includes activation of Akt, which can inactivate the AS160 protein (Rab GTPase-activating protein) by phosphorylation that results in the translocation of GLUT4 containing vesicles on the cell surface according to the current understanding of GLUT4 translocation mechanisms by Wang, Wang, Hu, Huang, & Chen, (2020). This mechanism is depicted by pink arrows in Fig. 2. Also, there is evidence in support of this hypothesis in different cells, including adipocytes (Silva *et al.*, 2018), myocytes (Gong *et al.*, 2021), and lymphocytes (Karmash *et al.*, 2020).

Therefore, PBMT can increase intracellular ROS and Ca^{2+} concentration, enhance NF-kB translocation to the nucleus, mediate MYC mRNA transcription and protein stability in normal cells, which correspondingly upregulate GLUT1 and GLUT3 genes in lymphocytes. Additionally, PBMT improves vesicle trafficking for GLUT4 and GLUT1 transporters in cells from healthy groups via phosphorylated Akt in insulin-stimulated and IL-7-stimulated pathways. Although PBMT may increase translocation of GLUT3 to the plasma membrane through activation of AMPK by CAMKKβ, this mechanism may be insignificant compared to activation of AMPK by AMP, which is tightly associated with cell activation as a response to a substantial increase in energy need. Notably, activation of

AMPK by AMP is theoretically crucial for GLUT3 translocation, and so elevated ATP content in lymphocytes after PBMT contradicts this pathway. It is possible that in diabetes, PBMT has the opposite effect compared to the influence of therapy on the lymphocytes of a healthy body. Probably PBMT does not significantly affect GLUT3 gene expression and may reduce GLUT3 exposure on the plasma membrane in lymphocytes in DM because PBMT causes a decrease in NF-κB translocation into the nucleus, AMPK inhibition by Akt, and a rise in intracellular ATP concentration. Thus, this mechanism requires further research. On the other hand, the effect of PBMT on oxidatively stressed cells in diabetes reduces the level of ROS (Hamblin, 2017) and increases the level of phosphorylated Akt, which leads to increased vesicle trafficking of GLUT1 and GLUT4. Moreover, elevated levels of phosphorylated mTORC1 and STAT5 by PBMT provide GLUT1 upregulation through metabolic transcription factor c-Myc, as discussed earlier.

CONCLUSION

PBMT can significantly influence glucose uptake by various glucose transporters, including SGLT1, GLUT1, GLUT3, and GLUT4 in normal and diabetic lymphocytes. Many molecular mechanisms of glucose uptake regulation in lymphocytes are not fully understood and need further investigation, especially signaling pathways induced by PBMT.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, [S.N.O.; L.M.Ya]; methodology, [-]; validation, [-]; formal analysis, [-]; investigation, [M.A.O.]; resources, [M.A.O.; L.M.Ya; S.N.O]; data curation, [-]; writing – original draft preparation, [M.A.O.]; writing – review and editing, [S.N.O.; L.M.Ya]; visualization, [M.A.O.] supervision, [S.N.O.]; project administration, [S.N.O.]; funding acquisition, [-]. All authors have read and agreed to the published version of the manuscript.

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ВПЛИВ ФОТОБІОМОДУЛЯЦІЙНОЇ ТЕРАПІЇ НА РЕГУЛЮВАННЯ ПОГЛИНАННЯ ГЛЮКОЗИ У ЛІМФОЦИТАХ ЗА ЦУКРОВОГО ДІАБЕТУ (ОГЛЯД)

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Для більшості клітин, включаючи лімфоцити, глюкоза є основним джерелом енергії, а тому важливо зрозуміти регуляторні механізми, що контролюють роботу транспортерів глюкози. Лімфоцити – ключові клітини, які опосередковують імунну відповідь і запальні реакції. Особливістю лімфоцитів є посилення утилізації глюкози за активації імунної відповіді, що сильно залежить від поглинання глюкози. Деякі дослідження демонструють, як підвищена концентрація глюкози за цукрового діабету впливає на експресію транспортерів глюкози у лімфоцитах, що корелює з порушенням імунної відповіді та може стати одним із факторів схильності до зараження інфекційними захворюваннями. У нещодавніх дослідженнях приділяють велику увагу транспортерам глюкози як терапевтичним мішеням за умов різноманітних захворювань, включаючи цукровий діабет. У цьому огляді продемонстровано вплив фотобіомодуляційної терапії на поглинання глюкози Na^+-залежним ко-транспортером глюкози SGLT1, а також полегшеною дифузією транспортерами родини GLUT (GLUT1, GLUT3, GLUT4) в лімфоцитах у нормі та за цукрового діабету.

Ключові слова: GLUT, SGLT1, фотобіомодуляція, лімфоцити, цукровий діабет

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