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Gene Expression of Glycolysis Enzymes in MCF-7 Breast Cancer Cells Exposed to Warburg Effect and Hypoxia

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ABSTRACT

Hypoxia can cause significant changes in the glucose metabolism of cancer cells that prefer aerobic glycolysis for energy production instead of the conventional oxidative phosphorylation mechanism. In this study, breast cancer cells (MCF-7) were exposed to glucose (0-5.5-15-55 mM), during specific incubation periods (3, 6, 12, or 24 hours) under normoxic and hypoxic conditions. The expression levels of hypoxia-inducible factor-1α (HIF-1α), glucose transporter-1 (GLUT-1), and glycolytic enzymes at varying glucose concentrations in cells were investigated in the different oxygen environments. It was determined that glycolytic enzymes [Hexokinase 2 (HK2), Pyruvate Kinase M2 (PKM2), Glucose-6-phosphate dehydrogenase (G6PD), Lactate Dehydrogenase A (LDHA), Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH), and Phosphofructokinase M (PFKM)] increased at the transcriptional level, especially in the first hours. This increase indicates that major metabolic reprogramming in response to hypoxia probably occurs over a short period of time. The increase in G6PD gene expression under high glucose and hypoxia conditions suggests that the pentose phosphate pathway (PPP) is used by cancer cells to synthesize necessary precursors for the cell. The results of the study showed that there is a significant interaction between hypoxia and glycolytic metabolism in cancer cells. It is thought that metabolic pathways activated by hypoxia and related genes located in these pathways will contribute to the literature by offering the potential to be target molecules for therapeutic purposes.

Keywords: Glucose, glycolysis, gene expression, hypoxia, MCF-7, normoxia

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Introduction

Cancer is a complex disease that develops depending on the tissue origin and specific histological and genetic characteristics of each tumor. Cancer cells reprogram their metabolism to increase their energy and macromolecule requirements for survival and proliferation compared to normal cells (1). Mutations of the genes involved in cellular signaling pathways, cellular responses to changes in the tumour microenvironment, and many oncogenic changes that affect intracellular signaling pathways mediate this metabolic transformation (2).

Unlike normal cells, cancer cells show marked changes in glucose metabolism. Otto Warburg et al. observed in their study that, although the energy need in normal cells is predominantly met by mitochondrial oxidative phosphorylation, glucose can be metabolized to lactic acid even in the presence of oxygen in tumour cells, and this metabolic phenomenon is called "aerobic glycolysis" or the "Warburg effect" (3, 4). Most cancer cells increase their glucose consumption to meet their rapid proliferation, energy demands and biosynthesis needs (5). Glycolysis, which constitutes the first stage of carbohydrate metabolism and mediates many pathways activating glucose metabolism in cancer cells, is an essential biochemical process (6). The mechanism by which glycolysis activities may affect biological outcomes is complex. This biochemical process is linked to the activity of almost all other metabolic pathways. Despite its low bioenergetic nature, the glycolysis pathway chosen by cancer cells to generate ATP suggests that cells must adopt a model of increased glucose uptake to meet their energy needs (7). Glucose taken up by cells is also directed to the pentose phosphate pathway (PPP) for the biosynthesis of molecules such as glycerol-phosphate and serine/glycine/threonine (8). As the glycolytic intermediate glucose-6-phosphate (G6P) enters the PPP, which increases in the medium, the precursor metabolites necessary for the synthesis of macromolecules that are important for the proliferation and development of the cell and NADPH with a role in reducing biosynthesis and an important antioxidant function in protecting cells from reactive oxygen species (ROS) (9).

Hypoxia is another common feature of many cancer types. Hypoxia stress promotes cell survival and proliferation by triggering malignant progression and developing adaptive responses to the tumour microenvironment. (10). Hypoxia-inducible factor-1 (HIF-1) is an important transcription factor that plays a central role in the maintenance of O_2 homeostasis of the tumour microenvironment and the physiological adaptation of the cell (11). HIF-1 is rapidly stabilized in cells and regulates many target genes involved in metabolic events such as glucose homeostasis, angiogenesis, tumour progression, erythropoiesis, apoptosis, cellular proliferation, and tissue remodeling (10). It has been reported that HIF-1 up regulates the expression of all genes encoding glucose transporter molecules that perform glucose uptake by cells, glycolytic enzymes involved in converting glucose to pyruvate and then lactate, and enzymes that inhibit oxidative phosphorylation (OXPHOS) in the mitochondria. Thus, when cells are deprived of the oxygen required for OXPHOS, they can make a metabolic transition from OXPHOS to glycolysis for energy yield (12, 13). It has been reported that glucose uptake increases significantly in hypoxic cancer cells, accelerating the glycolytic flux and increasing the efficiency obtained from glycolytic metabolism. Cell survival is supported as a result of HIF-1 reprogramming glucose and energy metabolism under hypoxic conditions (14).

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It is important to understand how cancer cells' functions and metabolic properties are restructured to elucidate the basic mechanisms of tumorigenesis and observe trends in the therapy of malignant cells. For this purpose, our study was aimed to determining the gene expression levels of HIF-1α and glycolytic key enzymes in MCF-7 cells grown in environments with different concentrations of glucose in the presence of two different oxygen conditions [normoxia (20%) / hypoxia (1%)]. The effects of changes in oxygen and glucose levels on cancer cell glucose metabolism were attempted to be partially elucidated.

Materials and methods

Cell culture

In the study, the MCF-7 cell line in ADU Veterinary Faculty Biochemistry Laboratory stocks was used. MCF-7 cells cultured in Dulbecco's modified Eagle's medium DMEM; (Sigma, D6421) supplemented with 10% fetal bovine serum (FBS, Sigma) and antibiotics (penicillin, 10 U/mL and streptomycin, 10 µg/mL; Gibco) in a 37 °C humidified incubator with a mixture of 95% air and 5% CO_2. Before the experiments, cells were grown to~70-80% confluence, trypsinized with trypsin-EDTA (Gibco) and counted using a hemacytometer.

Glucose administration

Normal culture media with high glucose content (3.15 g/L glucose) were preferred so that the cells could initially grow rapidly. When cells cultured in the relevant cell culture plates in high glucose-containing DMEM medium (Sigma Aldrich) became approximately 60% confluent, the medium on them was replaced with glucose-free DMEM (Gibco) and cells were starved in a glucose-free medium for 24 h. After the removal of the glucose-free media, new media containing glucose concentrations of 0, 5.5, 15 and 55 mM were applied to the cells. A value close to the normal physiological concentration of glucose in human blood (5.5 mM) and a level of glucose that can be considered too severe for humans (15 and 55 mM) were selected based on the literatüre (6,12,15,16). After glucose application, the cells were transferred to normoxic and hypoxic conditions.

Hypoxic culture conditions/ creating a hypoxia model

Although many cells in the human body are exposed to lower O_2 levels, *in vitro* cultured cells are generally maintained in 20% O_2 (95% air and 5% CO_2), a concentration described as "normoxia" (17). Hypoxia is defined as a decrease in oxygen levels below normal (normoxia) (e.g., below 5%). In the study, cells were placed in a hypoxia environment after the addition of media containing different concentrations of glucose. Cells were exposed to normoxia (20% O_2) and hypoxia (1% O_2) conditions for 3, 6, 12, and 24 hours. The cells in the hypoxic group were incubated in a modular incubator chamber gassed 1%02 and 5% CO_2.

RNA isolation and cDNA synthesis

At the end of the incubation period (3, 6, 12, and 24 hours) of the cells treated with DMEM containing certain concentrations of glucose under normoxia/hypoxia conditions, the medium on them was discarded and then the total RNA was isolated using the Hybrid-R RNA Isolation Kit (GeneAll Biotechnology, South Korea) following the manufacturer's protocol. RNA (2 µg) was converted into cDNA using a HyperScript First Strand Synthesis Kit (GeneAll Biotechnology, South Korea) and quantified.

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Real-time quantitative polymerase chain reaction (RT-qPCR)

HK2, PKM2, G6PD, LDHA, PFKM, GAPDH, HIF-1α, GLUT1 (target genes) and β-actin (housekeeping gene) expression analyses were carried out using specific primers (Table 1) with the SYBR® Green PCR Master Mix and the Applied Biosystems kit on the quantitative real-time PCR (qPCR) LigthCycler®480 (Roche Diagnostics GmbH, Mannheim, Germany) appliance. These primers were designed using the Primer 3 program and controlled for specificity for the gene using the NCBI gene bank. The PCR protocol consisted of a preincubation step for denaturation of the cDNA (5 min, 95 °C), followed by 45 cycles consisting of denaturation (30 s, 95 °C), annealing (30 s, 55 °C), and extension steps (30 s, 72 °C). The relative expression levels of the target genes to the endogenous reference gene (β-actin) expression level were calculated using the delta cycle threshold (Ct) method. The protocol was performed in triplicate for two biological replicates.

Table 1. Primer sets for real-time PCR.

Gene names	Primer base sequences (5´→3´)	Amplicon (bp)
HIF-1α	F: TGTACCCTAACTAGCCGAGGAA R: AATCAGCACCAAGCAGGTCATA	153
GLUT1	F: CTGGCATCAACGCTGTCTTC R: GCCTATGAGGTGCAGGGTC	167
HK2	F: CAGTGGCAAAGGTGCAGC R: TGCTCAGACCTCGCTCCATT	158
PFKM	F: ATTCGGGCTGTGTTCTGG R: TGGCTAGGATTTTGAGGATGG	144
LDHA	F: CCCGAACTGGAAGTTGCTTAT R: AGGTAACGGAATCGGGCTGAAT	135
PKM2	F: CGTGGATGATGGGCTTATTTCTC R: TGCCTTGCGGATGAATGACG	220
GAPDH	F: GGTGTGAACCATGAGAAGTATGA R: GAGTCCTTCCACGATACCAAAG	123
β-ACTIN	F: AAACTGGAACGGTGAAGGTG R: AGTGGGGTGGCTTTTAGGAT	166
G6PD	F:CAACAGCCACATGAATGCCC R:CTTCTCCACGATGATGCGGT	151

Results

$2^{-\Delta\Delta CT}$ relative gene quantitative calculations were performed to see glucose concentration-dependent changes in the expression amount of HIF-1α, GLUT-1 and related glycolytic enzymes. It was observed that gene expression increases for all concentrations in molecules analyzed occurring in common at the 3rd and/or 24th hours, and the relevant molecules were downregulated at the 6th hour.

HIF-1α expression levels exhibited significant increases of 4.25, 4.21, and 2.29 (normoxia) and 2.7, 4.9, and 6.31 (hypoxia) in the normoxic and hypoxic treatment groups containing 5.5, 15 and 55 mM glucose, respectively, compared to the control group (0 mM) at 3 hours ($p<0.001$) (Figure 1). As shown in Figure 2 and Figure 3, unlike other enzymes, there was a 1-2.5 fold increase in the gene expressions of LDHA and PFKM in the application groups compared to the control group in the normoxic environment under the

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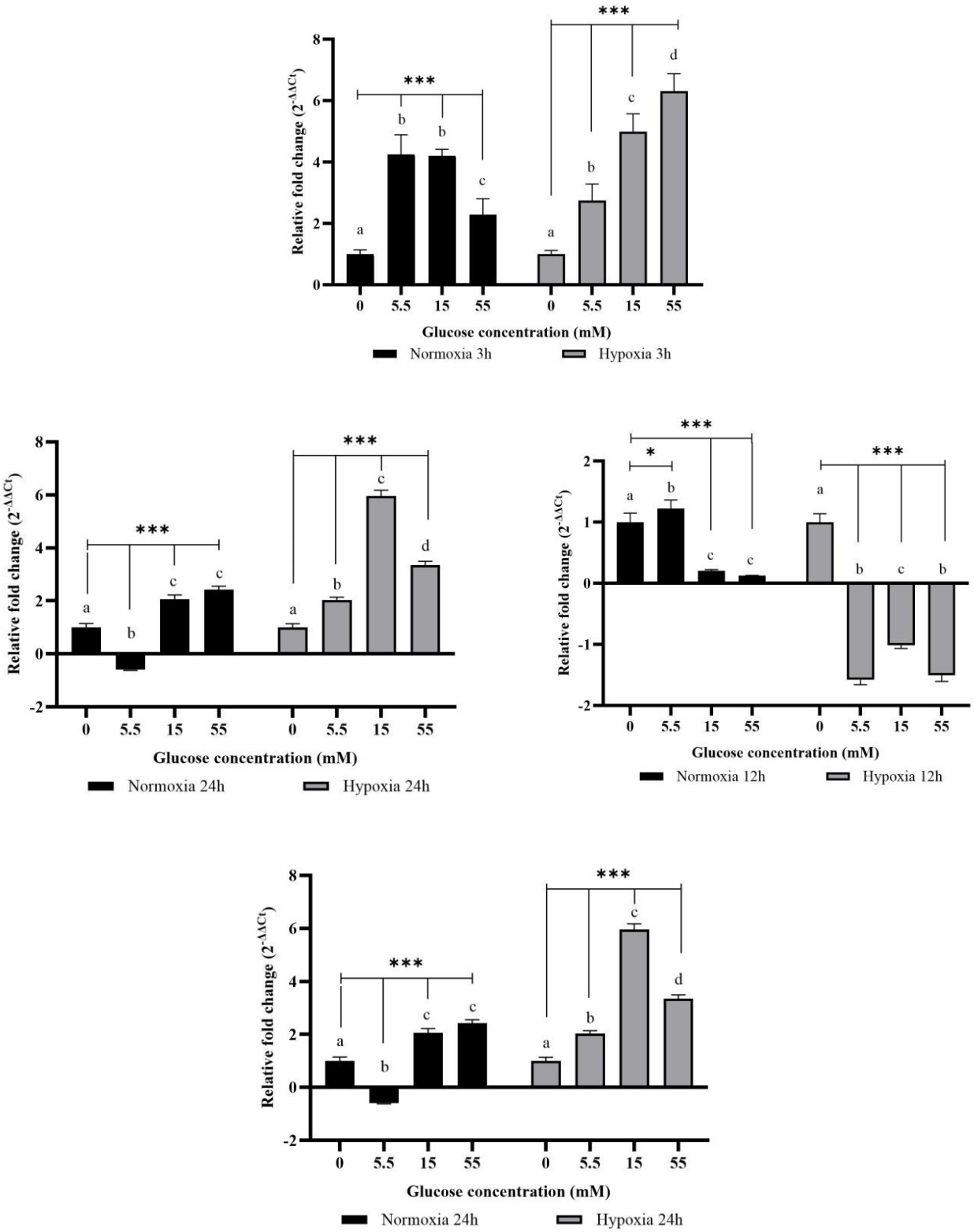

Fig. 1. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of HIF1α (control glucose-free medium) (***p<0.001, **p<0.05).

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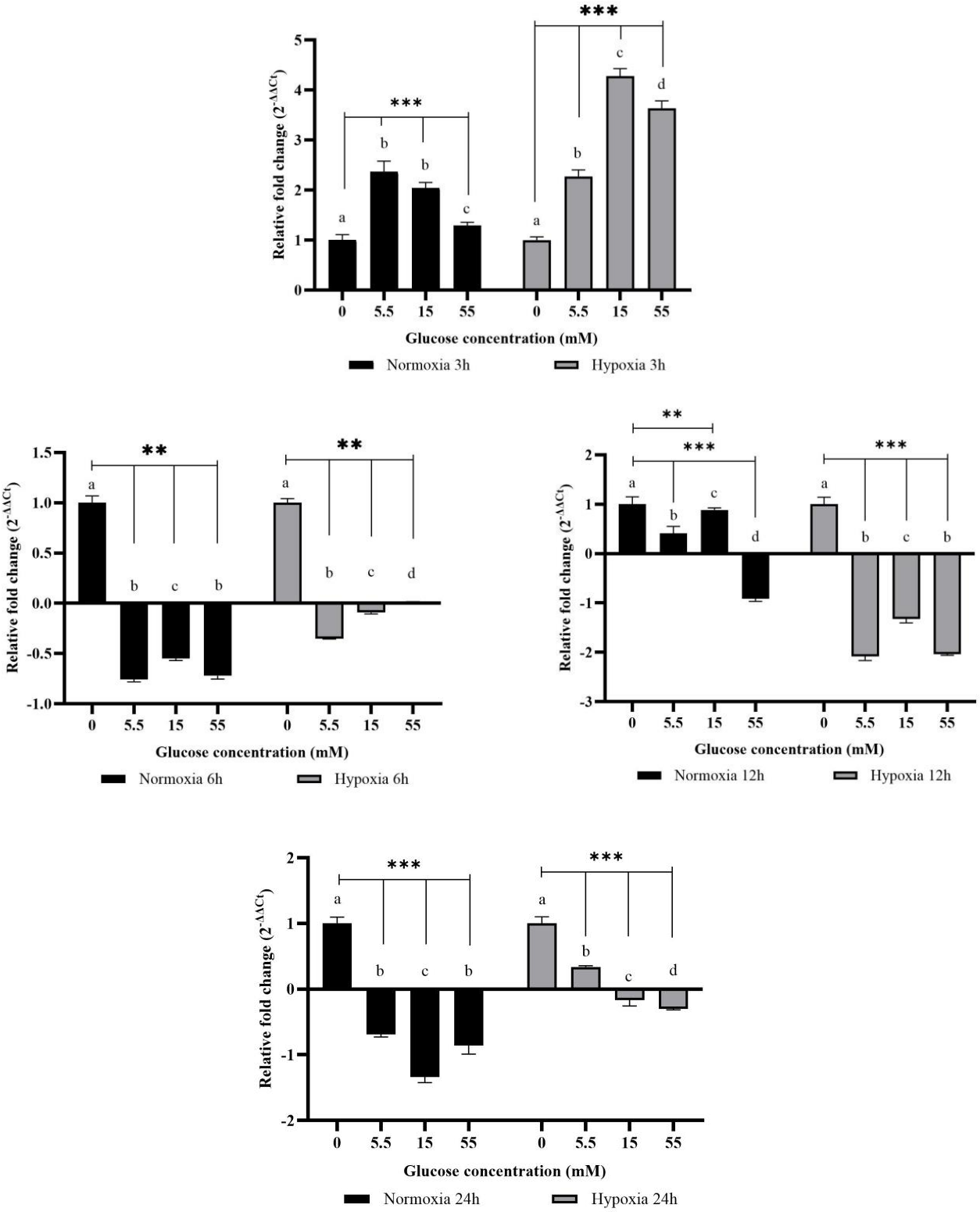

Fig. 2. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of LDHA (control glucose-free medium) (***p<0.001, **p<0.05).

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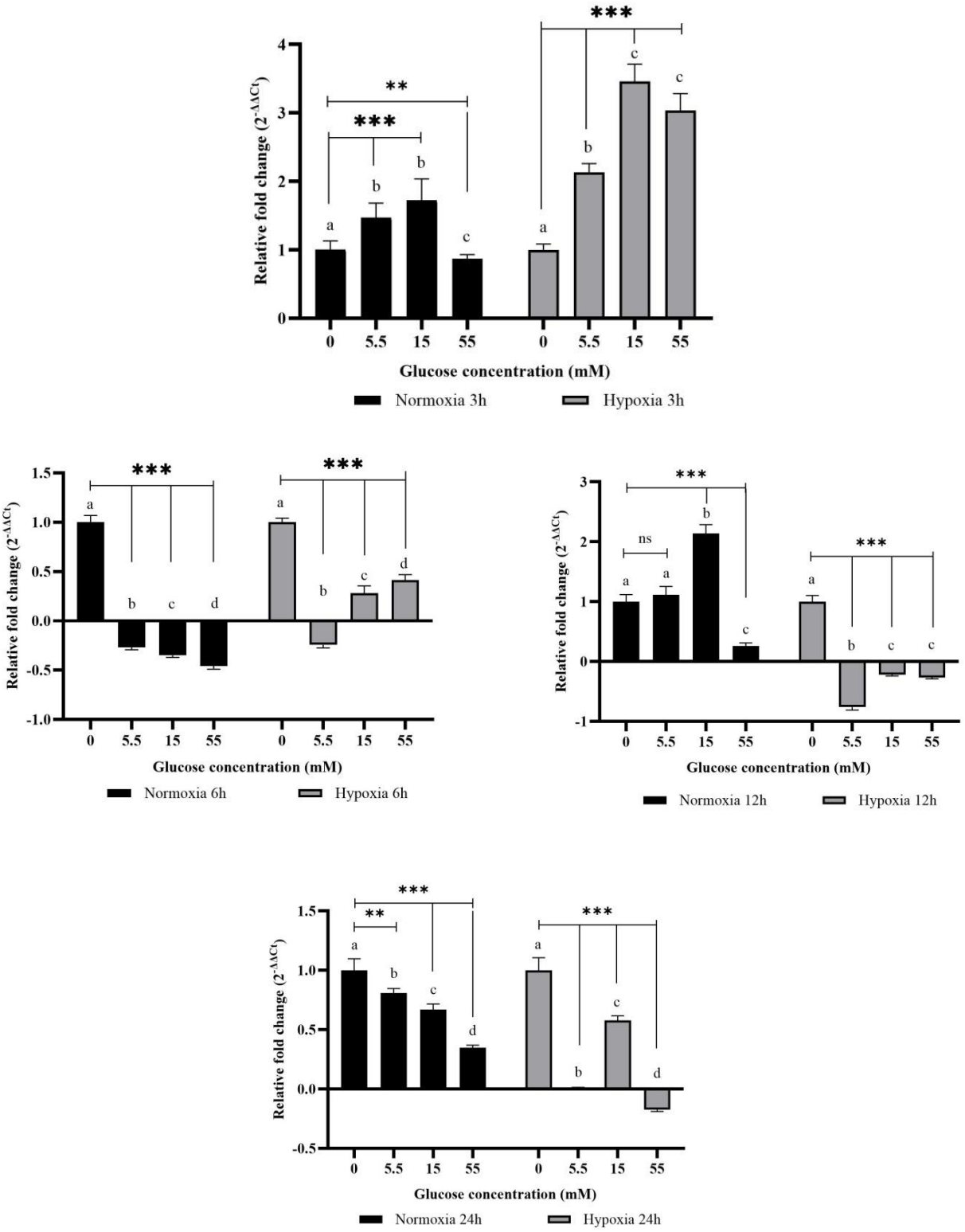

Fig. 3. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of PFKM (control glucose-free medium) ($^{***}p<0.001$, $^{**}p<0.05$).

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same incubation conditions ($p<0.001$). In parallel with the HIF-1α results, approximately 1.5-3 fold upregulation was observed in the gene expressions of GAPDH, GLUT1 and PKM2 enzymes at the 3rd hour in hypoxic conditions compared to glucose-free environments. These increases in gene expression levels are shown in Figure 4, Figure 5 and Figure 6. Under the same incubation conditions, a 3-4.5 fold upregulation of PFKM, LDHA and HK2 enzyme gene expressions was determined in hypoxic/hyperglycemic (15-55 mM) environments ($p<0.001$).

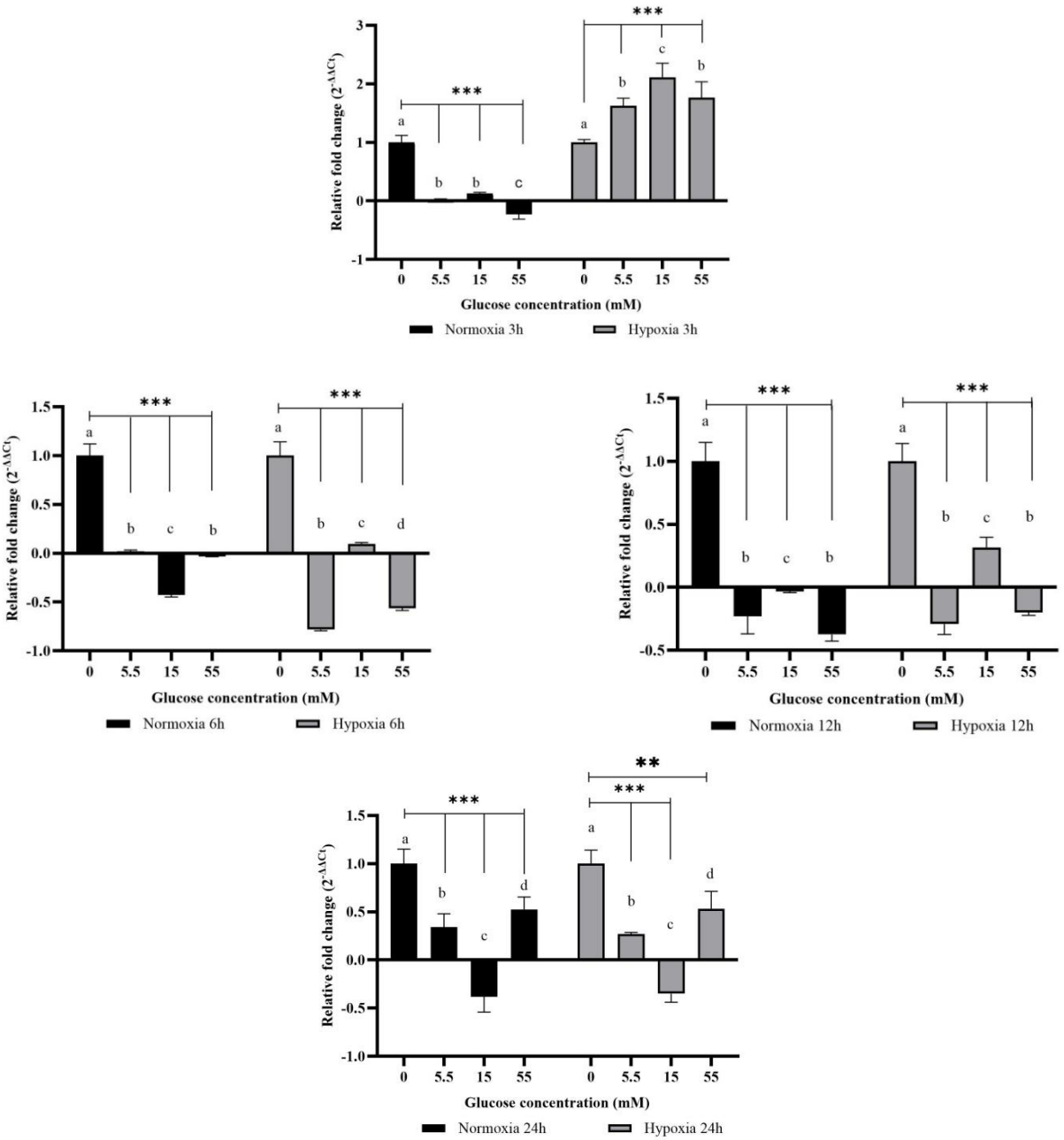

Fig. 4. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of GAPDH (control glucose-free medium) (***$p<0.001$, **$p<0.05$).

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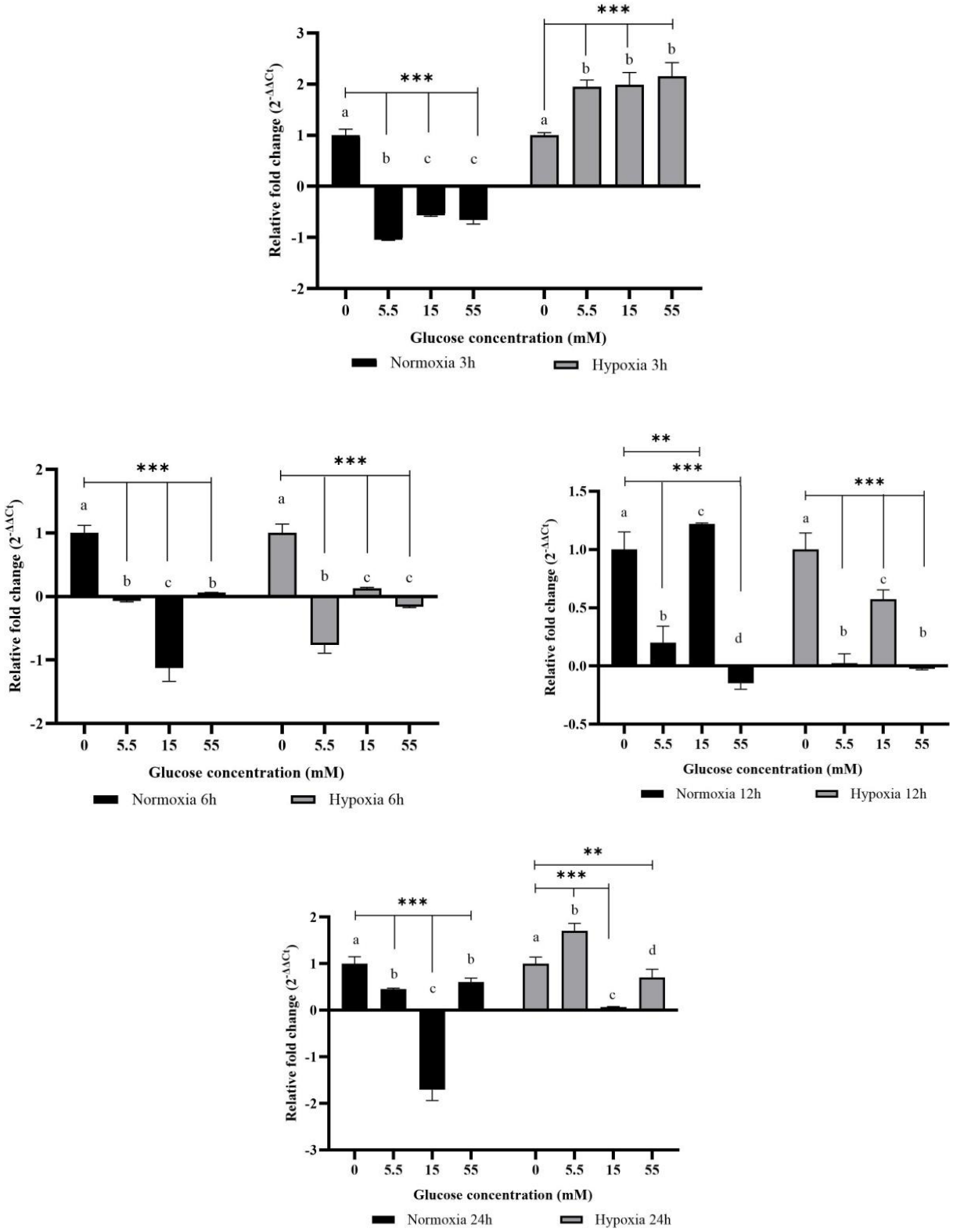

Fig. 5. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of GLUT1 (control glucose-free medium) ($^{***}p<0.001$, $^{**}p<0.05$).

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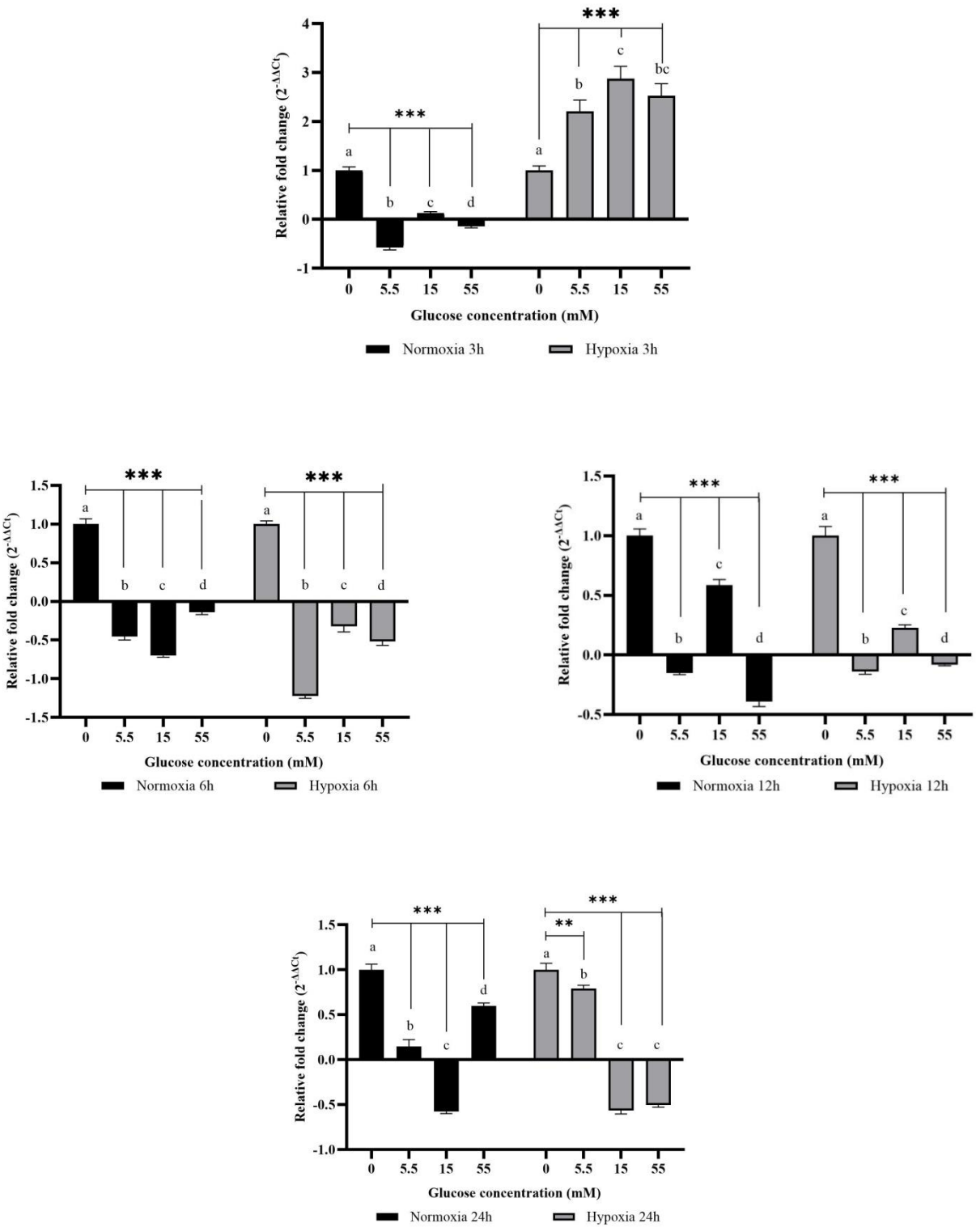

Fig. 6. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of PKM2 (control glucose-free medium) ($^{***}p<0.001$, $^{**}p<0.05$).

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At the 24th hour, it was observed that HK2 and G6PD gene expression levels increased by 1.7 and 1.8 times in normoxia and 1.6 and 1.5 times in hypoxia, respectively, in environments containing 55 mM glucose ($p<0.001$). These increases in gene expression levels are shown in Figure 7 and Figure 8. While HIF-1α expression levels were upregulated 2-6 fold under hypoxic conditions at 24 hours, there was a significant increase in GLUT1 (1.7 fold) and HK2 (2 fold) levels in the medium containing 5.5 mM glucose under the same conditions compared to the treatment groups containing other glucose concentrations ($p<0.001$).

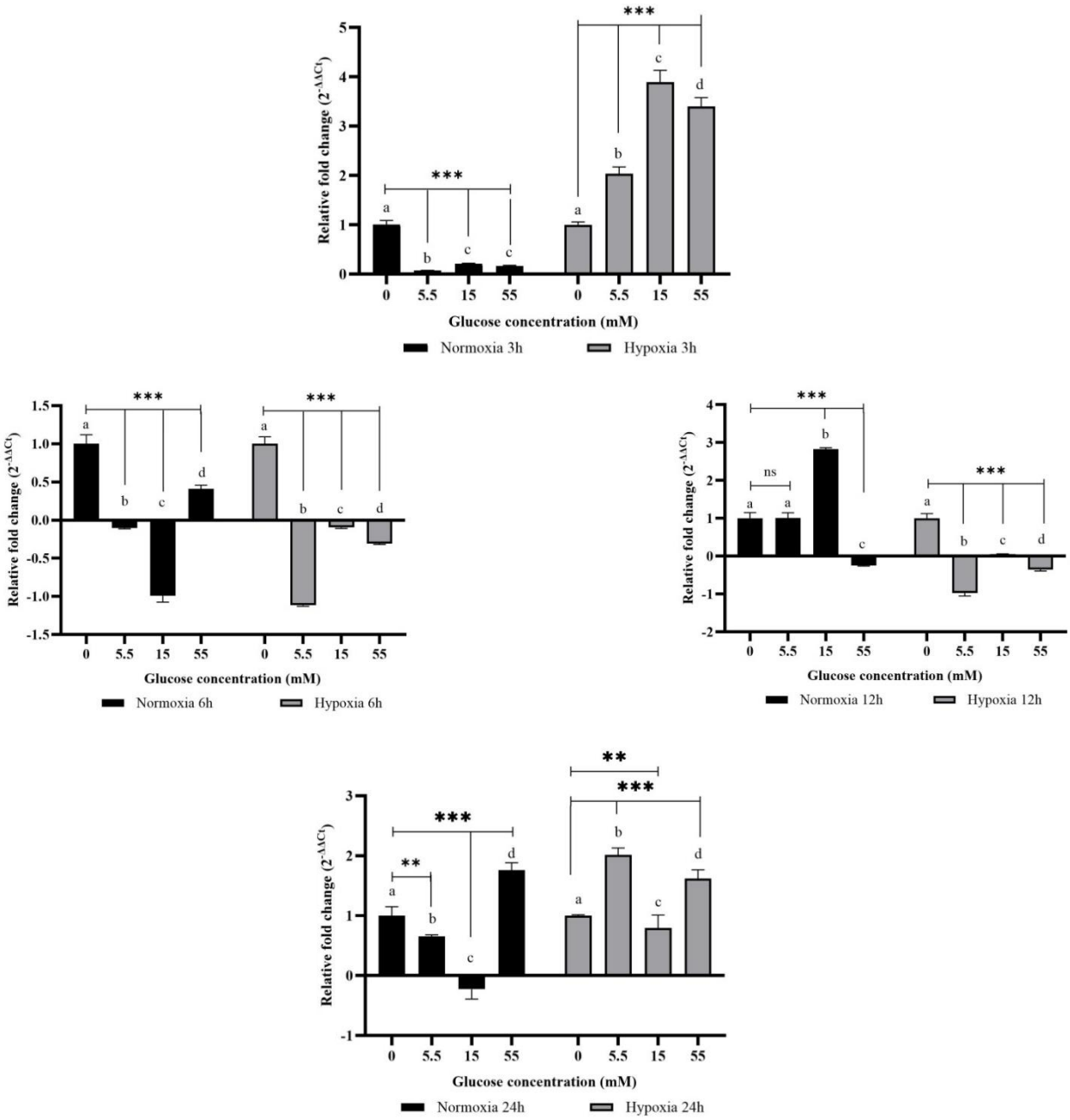

Fig. 7. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of HK2 (control glucose-free medium) (***$p<0.001$, **$p<0.05$).

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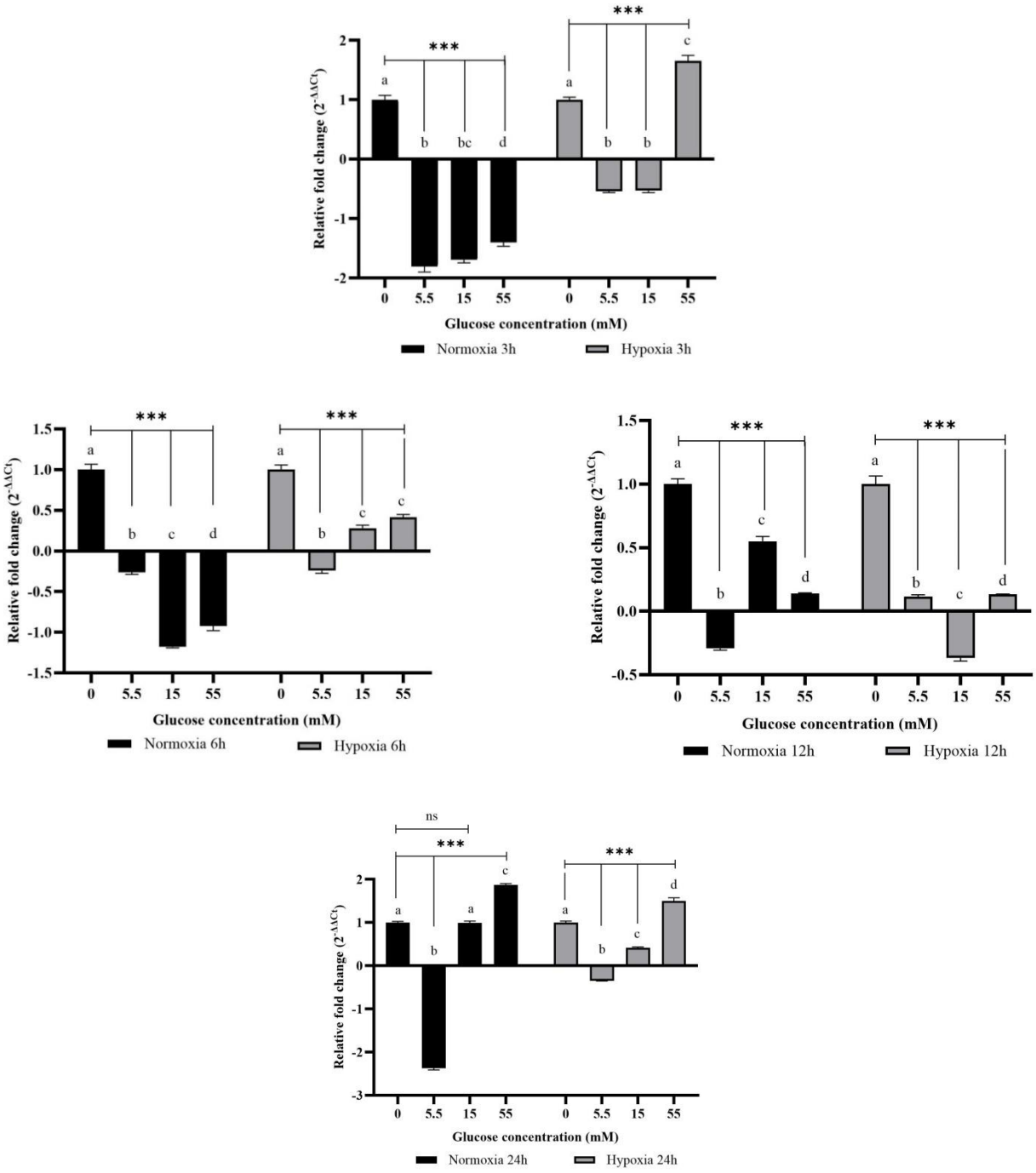

Fig. 8. $2^{-\Delta\Delta CT}$ relative gene quantitative calculations of glucose concentration-dependent changes in the expression amount of G6PD (control glucose-free medium) (***p<0.001, **p<0.05).

At the 12th hour, there was an increase in gene expression of enzymes, especially in environments containing 15 mM glucose (p<0.001). HK2 (1.2 fold) and PFKM (2.1 fold) expression levels obtained from cells in normoxic medium containing 15 mM glucose at the end of the 12th hour increased (p<0.001).

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Discussion

The main carbohydrate pathways of metabolism depend on glucose conversions. Glucose is the primary source of energy and carbon for cancer cells. Cancer cells that need more energy and nutrients than normal cells have different ways of uptaking and using glucose. Studies have also proven that glucose use is very important for fast-growing cancer cells to survive and proliferate. Significant increases in cell proliferation have been recorded due to the increase in glucose concentration in various breast cancer cell lines grown in media containing different glucose concentrations (15, 16, 18). Similar effects of glucose have also been observed in pancreatic and endometrial cancer cell lines (6, 19). The present study investigated the effects of normoxia/hypoxia media and glucose concentrations on MCF-7 cells at the level of gene expressions of glycolytic enzymes and HIF-1α and GLUT-1 proteins.

Hypoxia increasing in cancer cells may result in decreased cell cycle arrest, cell proliferation, and/or apoptosis. Many of these hypoxia-activated processes are regulated by a family of hypoxia-inducible factors (HIFs), specifically the HIF-1 isoform, which mediates the best-identified mechanisms of hypoxic responses (20). The transport of glucose across the plasma membrane is the first rate-limiting step for glucose metabolism. It is mediated by facilitative glucose transporters (GLUTs) (21). GLUT-1 is a widely expressed form in all tissues, with a high affinity for glucose and meeting the basal glucose requirement of cells (21, 22). It has been suggested that GLUT-1 expression level may be a convenient marker of hypoxia and glucose metabolism that can be simply measured as part of a routine histological evaluation of tumours (23-25). It has been reported that HIF-1 can activate transcriptions of several genes encoding glucose transporters and glycolytic enzymes to reprogram cancer metabolism (26).

In order for the cell to adapt to the environment, hourly changes occur during the self-renewal phase of metabolism. HIF1α expression in hypoxia-treated cells increased by 2.7, 4.9, and 6.3 times (3rd hour) and by 2, 5.9, and 3.3 times (24th hour), respectively, depending on the glucose concentration content (5.5, 15, and 55 mM), which increased at the 3rd and 24th hours, and the increase in glucose concentration with hypoxia caused an increase in HIF-1α gene expression (Fig 3). There were approximately 2-fold expression increases in other groups containing glucose compared to the 0 mM treatment group (control) in hypoxic cells at the 3rd hour (short term). (Fig 2). Our findings suggest that relatively short-term hypoxia is more effective than long-term stable hypoxia for energy metabolism reprogramming.

HK2, one of the important key enzymes, directs the metabolic flow of glucose required for anabolic activities in cancer cells by catalyzing the first stable step in cellular metabolism after glucose uptake into the cell. It has been reported that anabolic metabolism, which exhibits a faster flow in cancer cells, may need to increase HK activity and induce HK expression (27, 28). HK2 overexpression has been observed in some tumour tissues and is associated with a poor prognosis (29-32). In our study, it was observed that the expression of the HK2 enzyme increased depending on glucose levels in a short-term hypoxic environment (Fig 4). In addition, at the 12th hour, it was determined that HK2, GLUT1 and PFKM gene expression levels increased compared to the control in normoxic medium containing 15 mM glucose. In these conditions, although there is sufficient oxygen in the environment, it can be thought that the cells are prone to aerobic glycolysis (Warburg effect).

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In some studies, the findings regarding the way hypoxia and glucose exposure affect the expressions of genes encoding the related enzymes and molecules vary. Liu et al. revealed that elevated extracellular glucose- stimulated HK2 expression in normoxic wt-MiaPaCa2 and hypoxic wt-MiaPaCa2/si-MiaPaCa2 cell lines (12). Additionally, it was reported that a low glucose level in tumour cell cultures supported a significant increase (2-3-fold) in mRNA levels of genes encoding GLUT1, GLUT3, HK2, and PFK2 (11, 33, 34). It was indicated that LDHA activity and HK2 and PFKP expressions were significantly upregulated under hyperglycemic conditions in pancreatic cancer BxPC-3 cells (35). A decreased expression of pyruvate dehydrogenase and an increased expression of LDHA were observed in groups containing high glucose (25 mM) in ECC-1 and Ishikawa endometrial cell lines (6).

It was reported that the inactive dimeric form of PKM2, which plays a fundamental role in glycolytic energy regeneration, is characterized by a low PEP affinity, is common in cancer cells, and this enzyme form supports the channeling of glucose to the oxidative PPP (36, 37). In tumour cell metabolism, PKM2 is vital in terms of creating a balance between glycolytic energy regeneration and the synthesis of essential building blocks for the cell (37, 38). PKM2 was also reported to support the Warburg effect by acting as a transcriptional coactivator for HIF-1 in cancer cells (39). The HK2, PKM2, PFKM and LDHA expression increases obtained in the range of 2.5-5 times at the 3rd hour under hypoxic/hyperglycemic conditions compared to the glucose-free medium indicating that short-term hypoxia and high glucose treatment synergistically induce an increase in gene expression.

PPP, separated from glycolysis as the first branched step of glucose metabolism, is the pathway where the synthesis of pentose phosphates necessary for the cell is provided and NADPH is produced, which is essential for both fatty acid synthesis and cell survival under various stress conditions and supports its antioxidant effect, and G6PD in the oxidative branch of the pathway plays an important role as a rate-limiting enzyme (9, 40). The activity of G6PD directly reflects the flow of the oxidative PPP. Thus, its activity and expression in cells must be tightly controlled (41). It has been reported that the active PPP flow plays a role in cancer progression and increasing resistance to anti-cancer treatments (42). Comparisons made with glucose-free media revealed that high glucose (15-55 mM) concentration could significantly increase enzyme expression levels at the 24th hour. It is observed that long-term high-concentration glucose treatment not only induces the glycolytic flux in the cell but also enables the PPP to be used effectively. It has been concluded that the expression of G6PD is increased to prevent ROS accumulation and cell death that may be caused by hypoxic induction in cells exposed to hypoxia. Other glycolytic enzyme expression findings obtained from normoxic media in the study also support this hypothesis.

The mechanisms for the structural regulation of molecules involved in aerobic glycolysis, which cancer cells prefer despite the fact of oxygen, have not been fully elucidated. Many genes play roles in the regulation of cancer cell metabolism. Studies on cancer metabolism show that cells undergo complex metabolic reprogramming to remove the macromolecules necessary for cell proliferation and increased energy demands. Changes in the oxygen level of the glycolytic pathway enzymes, which are responsible for the entry of glucose into the cell and the metabolic pathway it follows, and changes in the transcription level depending on the amount of glucose in the medium will enable us to see differences in glycolytic regulation more clearly.

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Our results demonstrated that the transcriptional response to hypoxia most likely occurred shortly after the exposure of cells to stress, and environmental conditions might cause differences in mRNA levels depending on the synthesis and degradation processes. The increased gene expression of many of the glycolytic enzymes upon short-term exposure to hypoxia led us to conclude that HIF-1α stimulates these genes in response to hypoxia. Considering the mRNA results of the G6PD enzyme, it was concluded that cancer cells can use PPP, especially when exposed to hypoxic stress for a long time.

It is clear that changes in mRNA and proteins may not always reflect changes in enzyme activities and, most importantly, metabolic fluxes, especially for uncontrolled steps in metabolic pathways. It was predicted that all functional parameters should be measured to establish a better correlation with transcription data. To better understand the final and measurable effects of transcriptional changes that occur under hypoxia on energy metabolism, their effects over 24 hours should also be investigated.

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