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A comparative gene expression study of sarcoplasmic/endoplasmic reticulum calcium ATPase1 (SERCA-1) in rabbit muscle cells

Subham Kumar Puntia

Department of Biotechnology, Utkal University, Bhubaneswar, Odisha, India

ABSTRACT

Sarcoplasmic/Endoplasmic Reticulum Ca^{2+} ATPase-1 (SERCA-1) is a P-type ATPase responsible for maintaining intracellular calcium homeostasis by transporting Ca^{2+} ions from the cytoplasm into the sarcoplasmic reticulum. Ca^{2+} regulation plays a vital role in excitation–contraction coupling, muscle relaxation, cellular metabolism, and thermogenesis. Different expression of SERCA isoforms has been reported in muscle tissues. But comparative expression profiling of SERCA-1 across diverse rabbit muscle tissues remains insufficient. The present study aims to comparatively assess the gene expression profile of SERCA-1 in different rabbit muscle tissues to understand tissue-specific variation associated with functional and metabolic requirements.

Total RNA was isolated from six rabbit muscle tissues which included tibialis anterior (TA), extensor digitorum longus (EDL), soleus, trapezius, gastrocnemius (GCN), and ventricle using TRIzol reagent. RNA integrity was confirmed by agarose gel electrophoresis and quantified using spectrophotometry. Complementary DNA (cDNA) was synthesized using reverse transcription, followed by amplification through real-time quantitative PCR (RT-qPCR) using gene-specific primers for SERCA-1 with 18S rRNA as control. Relative expression levels were analyzed based on amplification and melt curve profiles.

SERCA-1 expression was identified in all six muscle tissues, showing differential transcriptional regulation. The melt curve analysis confirmed primer specificity, indicating amplification of target gene sequences. The study provides insight into Ca^{2+} regulatory mechanisms in skeletal muscle physiology and provides details for further investigation into muscle metabolism and pathophysiological conditions.

KEY WORDS

SERCA-1 expression; Ca^{2+} regulation; Muscle fiber metabolism; Gene expression profiling; RT-qPCR analysis; Tissue-specific variation

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Introduction

Intracellular Ca^{2+} homeostasis is a basic determinant of cellular survival, signalling fidelity, and contractile function beyond virtually all eukaryotic cell types. In striated and smooth muscle, precise regulation of cytosolic Ca^{2+} concentration is essential for the coupling of membrane excitation to mechanical contraction and subsequent relaxation [1]. Central to this regulatory architecture is the SERCA, a P-type ATPase that actively transfers two Ca^{2+} ions from the cytoplasm into the lumen of the sarcoplasmic reticulum (SR) per molecule of ATP hydrolyzed, thereby restoring resting cytosolic Ca^{2+} levels following each excitation-contraction cycle.

In mammals, the SERCA family is encoded by three distinct genes ATP2A1, ATP2A2, and ATP2A3 each fabricating a set of highly homologous pump proteins designated SERCA1, SERCA2, and SERCA3, respectively. Phylogenetic analyses disclose that these three principal isoforms show fundamentally divergent expression patterns across tissue types: SERCA1 is typically expressed in fast-twitch skeletal muscle fibres, SERCA2 covers the broadest functional spectrum, and SERCA3 is broadly present in non-muscle tissues. Further isoform heterogeneity emerges through tissue- and developmental stage-specific alternative splicing of primary transcripts. The SERCA2 gene gives rise to at least four splice variants (SERCA2a–2d), among which SERCA2a often referred to as the "cardiac isoform" is expressed in cardiac muscle, slow-twitch skeletal muscle, and smooth muscle cells, while SERCA2b comprise of ubiquitously expressed variant found across both muscle and non-muscle lineages [2,3]. The SERCAl primary transcript is similarly subject to developmental regulation, retaining its penultimate exon in adult fast-twitch fibres while splicing it out during the neonatal period.

By re-sequestering Ca^{2+} ions from the cytosol into the SR/ER at the expense of ATP hydrolysis, SERCA pumps are ubiquitous membrane proteins found in all eukaryotic cells. They are well-known parts of the calcium transport machinery involved in a variety of physiological processes, including muscle contraction, energy metabolism, secretion, synaptic transmission, cell survival, and fertilization.

From a structural standpoint, SERCA is a single polypeptide of 994 amino acid residues categorize into ten transmembrane helices (M1–M10) and three cytoplasmic domains, the actuator (A), nucleotide-binding (N), and phosphorylation (P) domains which collectively mediate catalytic activity [4]. The catalytic mechanism proceeds through a well-characterized E1/E2 conformational transition: in the E1 state, the enzyme binds two Ca^{2+} ions with high affinity at transmembrane sites I and II; phosphorylation of Asp-351 by the γ-phosphate of ATP then drives conformational alteration to the E2-P state, wherein Ca^{2+} affinity is markedly reduced and luminal release is assisted [5].

***Correspondence:** Mr. Subham kumar Puntia, Department of Biotechnology, Utkal University, Bhubaneswar, Odisha, India,
e-mail: Subhamkumarpuntia9@gmail.com

The 181TGES signature sequence of the A domain offers the catalytic assistance required for hydrolytic cleavage of the phosphoenzyme intermediate.

The physiological significance of SERCA increases well beyond the maintenance of muscle tonicity. Pathological conditions linked with aging, neurodegeneration, and muscular dystrophy significantly lower the SERCA function, with the potential to reduce intracellular Ca^{2+} homeostasis and further contribute to muscle atrophy and weakness. At the level of the myocardium, changes in the activity of SR Ca^{2+}-cycling proteins, particularly SERCA2a, are responsible for the modification of Ca^{2+} cycling observed in failing hearts, rendering SERCA2a one of the most intensively investigated therapeutic targets in cardiovascular medicine [6]. Additionally, to heart failure, dysregulated SERCA activity has been involved in Brody disease, Darier disease, myotonic dystrophy type 1, and different forms of limb-girdle muscular dystrophy.

A mechanistically informative parallel exists between SERCA and the mammalian copper-transporting P-type ATPases ATP7A and ATP7B. Both enzyme families engage in phosphoenzyme intermediate (E-P) formation to achieve vectorial cation transport yet divide considerably with respect to the kinetics of ATP utilization, phosphoenzyme processing, and the role of metal chelation in reverse phosphorylation [7,8]. Understanding these comparative biochemical features not only illuminates the mechanistic diversity within the P-type ATPase superfamily but also updates the rational design of isoform-selective modulators with therapeutic potential.

Allosteric control of SERCA pumps is essential for both health and illness, and control of SERCA activity has become a therapeutic strategy for the management of neurological, metabolic, cardiovascular, and muscle disorders [9]. The current studies aims to provide a comprehensive and current perspective on the molecular architecture, catalytic mechanism, isoform-specific expression, and pathophysiological significance of SERCA, with specific emphasis on its comparative features relative to copper-transporting ATPases and the emerging therapeutic landscape targeting SERCA-mediated Ca^{2+} homeostasis.

Materials and Methods

Tissue procurement and storage

Six different skeletal and cardiac muscle tissue types were obtained from the New Zealand White rabbit (Oryctolagus cuniculus), specifically: EDL, TA, soleus, trapezius, left ventricular myocardium, and GCN. All tissues were obtained under appropriate institutional protocols from the laboratory of Dr. Naresh Bal, Department of Biotechnology, Kalinga Institute of Industrial Technology (KIIT), Bhubaneswar, India. After dissection, tissues were quickly snap-frozen and stored at −80°C till further processing to stop RNA degradation. Before homogenization, tissues were weighed to ensure uniformity of input mass across all experimental groups.

Tissue homogenization and total RNA extraction

Total RNA was isolated from about 50 mg of each frozen tissue using TRIzol® reagent (Invitrogen Life Technologies, Carlsbad, CA, USA), a monophasic solution of phenol and guanidinium isothiocyanate that enable real-time disruption of biological membranes and inhibition of endogenous RNases. All homogenization steps were carried out under RNase-free conditions. The rotor was pre-chilled at 4°C before processing. Frozen tissue was kept into a 1.5 mL microcentrifuge tube containing a stainless-steel bead. TRIzol® was added in three sequential aliquots (350 µL, 150 µL, and 500 µL) with intervening mechanical homogenization cycles of 30–35 seconds each using a bead mill homogenizer, yielding a final homogenate volume of 1,000 µL. Between homogenization steps, samples were centrifuged at low speed (500 × g, 5–10 seconds) to collect the lysate. This stepwise addition strategy was acquired to maximize tissue disruption and ensure complete lysis, particularly important for fibrous skeletal muscle tissue.

After homogenization, 200 µL of chloroform was added to the homogenate, and the mixture was centrifuged vigorously for 20–30 seconds to promote phase separation. Samples were then incubated at room temperature for 3 minutes before centrifugation.

RNA isolation and quality assessment

The homogenate was centrifuged at 5,400 × g for 15 minutes at 4°C to attain three-phase separation: an upper aqueous phase (containing total RNA), an interphase (containing DNA), and a lower organic phase (containing proteins and lipids). The aqueous phase was thoroughly studied and transferred to a fresh microcentrifuge tube, avoiding contamination from the interphase. Total RNA was precipitated by the addition of an equal volume of ice-cold isopropanol followed by centrifugation. The resulting RNA pellet was washed twice with 75% (v/v) ethanol at 4°C to remove residual guanidinium salts and phenol contaminants. The pellet was air-dried for 5–10 minutes at room temperature and subsequently released in nuclease-free water (Ambion, Austin, TX, USA).

RNA concentration and purity were evaluated spectrophotometrically using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Samples with an A_{260}/A_{280} ratio ≥ 1.8 and an A_{260}/A_{230} ratio ≥ 1.5 were considered of acceptable purity for downstream applications. RNA integrity was also confirmed by denaturing agarose gel electrophoresis, where the presence of two discrete 28S and 18S ribosomal RNA bands at an approximate intensity ratio of 2:1 was taken as indicative of intact, non-degraded total RNA. Skeletal muscle samples were snap-frozen and stored at −80°C until RNA extraction; RNA integrity was assessed by visualization of 28S and 18S rRNA bands, with the intensity of 28S being approximately twice that of 18S indicating intact RNA suitable for downstream analysis.

cDNA synthesis

First-strand cDNA was synthesized from total RNA using a two-step reverse transcription protocol with the PrimeScript™ Reverse Transcriptase System (TaKaRa Bio Inc., Shiga, Japan) and random hexamer primers to ensure unbiased representation of all RNA species, which include non-polyadenylated transcripts such as 18S rRNA.

Template denaturation

For each reaction, 3.3 µL of total RNA template was combined with 2 µL of random hexamer primers and 2 µL of dNTP mix (10 mM each), with the volume adjusted to 10 µL with nuclease-free water. This mixture was incubated at 65°C for 5 minutes in a thermal cycler to denature RNA secondary structures and subsequently placed on ice to prevent reannealing.

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Reverse transcription

The denatured RNA-primer mixture was supplemented with 4.4 µL of 5× PrimeScript buffer, 2 µL of RNase inhibitor (RNaseOUT™, Invitrogen), and 2 µL of PrimeScript Reverse Transcriptase (SSII RT), with nuclease-free water added to a final reaction volume of 20 µL. The reverse transcription reaction was carried out under the following thermal conditions: 30°C for 10 minutes (primer annealing), followed by 42°C for 60 minutes (cDNA elongation), and enzyme inactivation at 95°C for 5 minutes. Synthesized cDNA was stored at −20°C until use. One microgram of RNA was reverse transcribed using random primers, 0.1 mM DTT and 10 mM dNTP in a 20 µL volume, with the cDNA subsequently divided and stored at −20°C until use.

The fidelity of reverse transcription was demonstrated by agarose gel electrophoresis of the cDNA reaction product before continuing with quantitative amplification.

Quantitative RT-qPCR

Primer design and target gene

The transcriptional expression of the SERCA1 (ATP2A1) gene was assesed by RT-qPCR using SYBR® Green chemistry on a StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Gene-specific primers were designed to span exon-exon junctions to prevent amplification of genomic DNA and were used at a final working concentration of 300 nM. The primer sequences employed were as follows:

SERCA1_Forward: 5′-TTGATCATCCACAAGGAGGA-3′

SERCA1_Reverse: 5′-AGCAGCAATCATTGCAGAGG-3′

18S rRNA_Forward: 5′-AACAGATACGGTCGTACTTC-3′

18S rRNA_Reverse: 5′-TACCGTGAATTCCTATAAG-3′

RT-qPCR thermal cycling conditions

Each 20 µL reaction contained 10 µL of Power SYBR® Green PCR Master Mix (Applied Biosystems), 300 nM each of forward and reverse primer, and 2 µL of cDNA template. The thermocycling protocol consisted of an initial denaturation step at 95°C for 10 minutes, followed by 40 cycles of denaturation at 94°C for 30 seconds, primer annealing at 58°C for 30 seconds, and extension at 72°C for 30 seconds. Specificity of amplification was shown by post-run dissociation (melt) curve analysis, and the absence of non-specific products and primer dimers was confirmed by 2% agarose gel electrophoresis of selected amplicons. No-template controls (NTC) and no-reverse-transcriptase controls (−RT) were involved on each plate to detect potential DNA contamination.

All target genes were analyzed in technical triplicates for each biological sample. RRelative gene expression was determined using the 2^−ΔΔCt technique, with 18S ribosomal RNA (18S rRNA) serving as the internal reference gene to normalize inter-sample variance in RNA input and cDNA synthesis efficiency. The amount of the gene of interest in each sample was quantified based on the observed fluorescence derived from the amplification plot, with ΔCq computed as the difference between the target gene and the reference gene.

Agarose gel electrophoresis

The integrity of total RNA, the verification of cDNA synthesis, and the specificity of RT-qPCR products were evaluated using conventional agarose gel electrophoresis. Gels were formulated at a concentration of 2% (w/v) agarose in 1× Tris-acetate-EDTA (TAE) buffer, augmented with 0.5 µg/mL ethidium bromide (EtBr) to facilitate fluorescence visualization of nucleic acids under UV light. Samples were prepared by combining with 6× loading dye at a suitable ratio and subjected to electrophoresis at 100 V for 30–45 minutes. As a size reference a 50 bp or 100 bp DNA ladder (as appropriate) was included in each gel. After electrophoresis, gels were visualized by UV transillumination and digitally recorded. The presence of sharp, well-defined 28S and 18S rRNA bands at an approximate 2:1 intensity ratio was used as the primary criterion for RNA integrity, while a single band of the expected amplicon size was used to verify specificity of PCR products.

Results

RNA isolation and quantification

Total RNA was successfully isolated from six rabbit muscle tissues, namely TA, EDL, soleus, trapezius, GCN, and ventricle using TRIzol reagent. Spectrophotometric analysis exhibits acceptable RNA purity, with A260/A280 ratios ranging between 2.03 and 3.28, indicating minimal protein contamination. The RNA concentration altered among the muscle tissues, starting from 261.26 ng/µl in tibialis anterior to 1011.32 ng/µl in ventricle tissue. The RNA yield achieved was acceptable for downstream molecular analysis (Figure 1, Table 1).

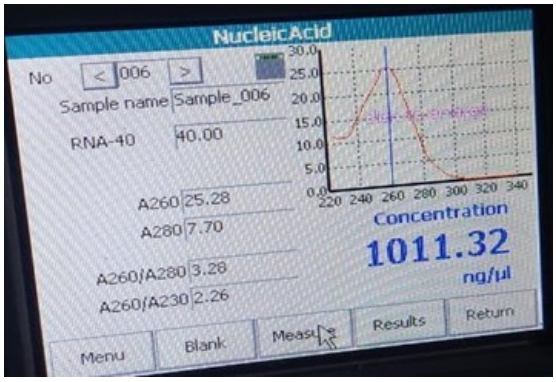

Figure 1. Quantification in nano drop results of ventricle muscle.

Table 1. List of RNAs in studied muscles.

SN.	RNA	260/280	260/230	CONCENTRATION
1	TA	2.15	1.12	261.26
2	EDL	2.23	2.15	830.56
3	Soleus	3.23	2.77	1111.36
4	Trapezius	2.06	1.47	374.47
5	GCN	2.03	1.1	296.44
6	Ventricle	3.28	2.26	1011.32

RNA integrity assessment

The integrity of RNA was verified using 2% agarose gel electrophoresis, revealing clear and intact RNA bands with minimal degradation. The electrophoretic profile demonstrated high-quality RNA appropriate for reverse transcription and gene expression investigation (Figure 2).

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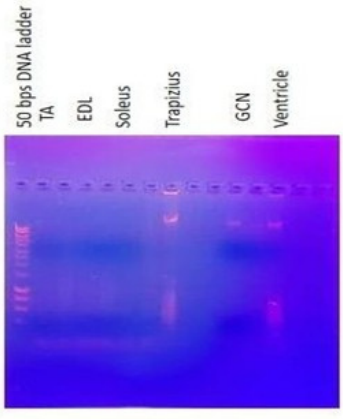

Figure 2. Agarose gel of electrophoresis of RNA.

cDNA synthesis validation

cDNA was synthesized from isolated RNA using reverse transcriptase and random primers. Agarose gel electrophoresis confirmed successful reverse transcription, as indicated by clear band formation corresponding to synthesized cDNA fragments. The cDNA quality was found to be appropriate for PCR amplification (Figure 3).

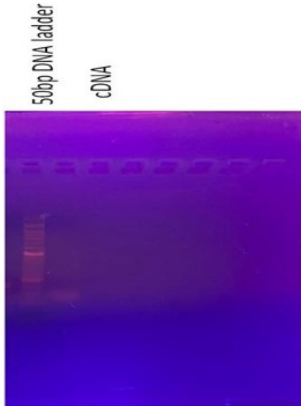

Figure 3. Visualization of cDNA in an agarose gel electrophoresis.

Amplification of SERCA-1 gene by qRT-PCR

Quantitative real-time PCR analysis shows successful amplification of the SERCA-1 gene in all six rabbit muscle tissues. The amplification plots show characteristic sigmoidal curves, confirming efficient amplification kinetics. The housekeeping gene 18S rRNA was consistently expressed across all samples, validating the reliability of normalization and experimental reproducibility (Figure 4, Figure 5).

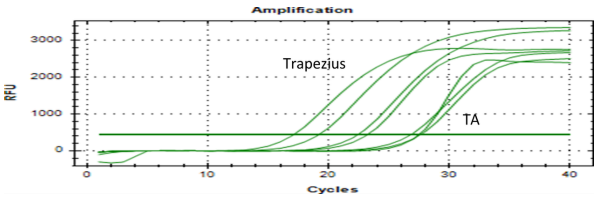

Figure 4. Amplification curve showing expression of SERCA-1.

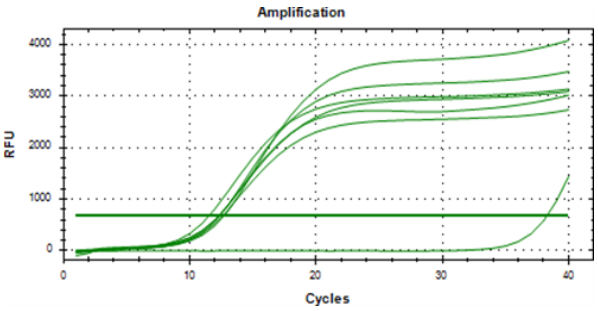

Figure 5. 18S RT-PCR used as internal control.

Melt curve analysis

Melt curve analysis revealed a single sharp peak for SERCA-1 amplicons across all tissues, confirming the specificity of primer binding and absence of non-specific amplification or primer-dimer formation. These findings show that experimental design and primer sequences were suitable for accurate gene expression analysis (Figure 6, Figure 7).

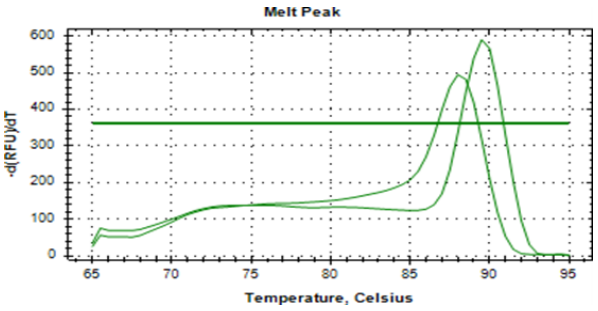

Figure 6. Melt curve of SERCA-1 in TA muscle.

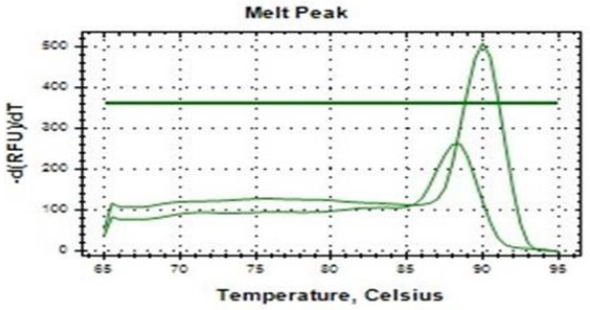

Figure 7. Melt curve of SERCA-1 in EDL muscle.

Comparative expression profile of SERCA-1

Comparative gene expression analysis shows differential transcription levels of SERCA-1 between the studied muscle tissues. The highest expression level was identified in trapezius muscle, showing greater Ca^{2+} transport activity associated with high metabolic demand. The second highest expression was identified in EDL. Moderate expression levels were observed in tibialis anterior and soleus muscles, whereas GCN and ventricle tissues showed comparatively lower SERCA-1 expression. The presence of amplification products of approximately 200 bp further confirmed successful target gene amplification (Figure 8).

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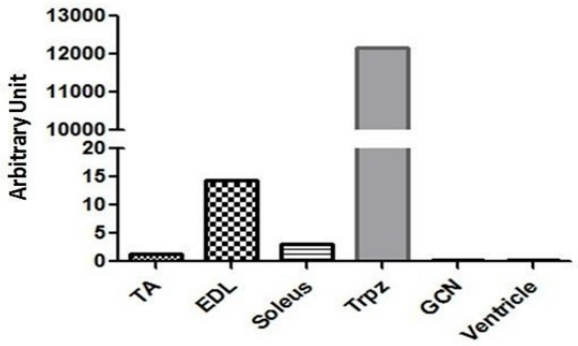

Figure 8. Comparative analysis of muscle cell.

Discussion

The SERCA is a key membrane-bound P-type ATPase that stimulates intracellular calcium homeostasis via ATP-dependent transport of Ca^{2+} ions from cytosol to the sarcoplasmic reticulum (SR). This process plays a vital role in excitation–contraction coupling, muscle relaxation, metabolic regulation, thermogenesis, and signal transduction [10,11]. The current study shows differential expression of SERCA-1 in six rabbit muscle tissues, namely trapezius, EDL, TA, soleus, GCN, and ventricle, indicating tissue-specific regulation of Ca^{2+} transport mechanisms.

The detected expression pattern, with highest SERCA-1 expression in trapezius muscle led by EDL, supports the concept that SERCA-1 is predominantly linked with fast-twitch skeletal muscle fibers. Fast-twitch muscles need rapid Ca^{2+} reuptake to keep repeated contraction–relaxation cycles, results in higher SERCA activity. Structural and mechanistic studies of SERCA confirm that ATP hydrolysis drives conformational changes between E1 and E2 states, regulating proper Ca^{2+} transport beyond the SR membrane [12]. The increased expression observed in trapezius muscle may contribute to its involvement in regular mechanical activity, postural stabilization, and thermogenic processes, which require efficient Ca^{2+} cycling.

The moderate to high expression found in EDL muscle aligns with past biochemical investigations examining that SERCA isolated from fast-twitch muscle shows high ATPase activity and strong dependence on Ca^{2+} for catalytic activation. The study confirms that SERCA keeps structural integrity and catalytic efficiency only in the presence of Ca^{2+} ions, supporting the biological importance of increased SERCA expression in muscles characterized by fast contraction dynamics. These findings promote the hypothesis that SERCA-1 expression correlates with metabolic demand and Ca^{2+} flux needs in skeletal muscle physiology [13].

Certain observations from the study partially contradict existing literature. The relatively low expression of SERCA-1 in GCN muscle differs from past reports showing that GCN contains a significant proportion of rapid glycolytic fibres. Structural analyses of SERCA have shown that catalytic efficiency relay on specific conformational coupling between nucleotide-binding (N), phosphorylation (P), and actuator (A) domains [14]. Variability in expression levels shown in this study may arise from experimental conditions, sample heterogeneity, or differential isoform expression patterns such as coexistence of SERCA-2 isoforms in certain muscle tissues.

Another contrasting observation is associated with the relatively low SERCA-1 expression detected in ventricle tissue. Previous molecular studies have shown that cardiac muscle mostly expresses SERCA-2a isoform, which is suitable for rhythmic contraction and energy-efficient Ca^{2+} cycling. The study shows that structural stability and catalytic efficiency of SERCA isoforms relayed strongly on microenvironmental conditions such as Ca^{2+} availability and protein stabilization mechanisms [15]. The lower expression of SERCA-1 in ventricle tissue describes in this research is consistent with isoform specialization rather than reduced functional importance of Ca^{2+} transport mechanisms.

The present discoveries align with structural studies showing that SERCA undergoes ATP-dependent conformational transitions including phosphoenzyme intermediates, facilitating active Ca^{2+} transport across the SR membrane. These structural changes are vital for the maintenance cytosolic Ca^{2+} concentration within physiological limits (50–100 nM), important for proper muscle contraction and relaxation cycles. The changes shown in gene expression between muscle tissues therefore reflect physiological adaptation to varying mechanical loads and metabolic activity [16].

At the molecular level, SERCA activity is controlled by regulatory proteins such as phospholamban and sarcolipin, which facilitate Ca^{2+} uptake efficiency and thermogenic activity. Variations in SERCA expression observed in trapezius and EDL muscles may also indicate enhanced mitochondrial activity along with sustained contractile function. The hyperbolic ATP-dependence curve observed in purified SERCA further supports the enzymatic kinetics consistent with Michaelis–Menten behaviour [17]. This supports the interpretation that increased SERCA expression results with increased catalytic efficiency for rapid Ca^{2+} cycling in active muscle tissues.

Gene expression analysis was performed using qRT-PCR without complementary protein quantification methods such as Western blotting or proteomic profiling. Structural studies show that post-translational modifications, protein stability, and membrane composition significantly influence SERCA activity. The transcript-level variation may not fully represent functional enzymatic activity. It has been demonstrated that SERCA stability is impacted by environmental variables as pH, temperature, and oxidative stress during the purifying and testing processes [18].

Despite minor contradictions, most of the findings support the hypothesis that SERCA-1 expression corresponds with muscle fibre specialization and physiological workload. The highest expression observed in trapezius muscle shows increased Ca^{2+} cycling requirement linked with high mechanical demand [19,20]. The relatively lower expression observed in cardiac ventricle indicates isoform-specific regulation consistent with established literature on SERCA-2 dominance in cardiac tissues

Conclusion

The current study provides a comparative analysis of SERCA-1 gene expression in six rabbit muscle tissues, namely trapezius, EDL, TA, soleus, GCN, and ventricle. SERCA-1 is a vital P-type ATPase responsible for maintaining intracellular Ca^{2+} homeostasis by actively transporting Ca^{2+} ions from the cytoplasm into the sarcoplasmic reticulum (SR), regulating excitation–contraction coupling and muscle relaxation. The findings of this study confirm that SERCA-1 is expressed in all

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examined muscle tissues, indicating its fundamental physiological importance in skeletal muscle function and cellular signaling pathways.

Comparative gene expression analysis showed significant variation in SERCA-1 transcription levels between different muscle tissues. The highest expression was observed in trapezius muscle, followed by EDL, whereas moderate expression levels were recorded in TA and soleus muscles. GCN and ventricle tissues show comparatively lower expression levels. These differences suggest that SERCA-1 expression is linked with muscle fibre composition, metabolic demand, and contractile activity. Muscles with higher functional workload and rapid contraction–relaxation cycles need efficient Ca^{2+} transport mechanisms, explaining the elevated SERCA-1 expression detected in trapezius and EDL muscles.

The qRT-PCR amplification plots, melt curve analysis, and agarose gel electrophoresis confirmed the specificity and reliability of gene expression results. The presence of amplification across all samples indicates that SERCA-1 plays a universal role in maintaining Ca^{2+} balance in muscle cells. Variability in expression levels further shows physiological adaptation of muscle tissues to their functional needs.

Overall, the study highlights the significance of SERCA-1 in regulating Ca^{2+} dynamics vital for muscle contraction, relaxation, and metabolic activity. The findings provide molecular-level insight into tissue-specific regulation of Ca^{2+} transport and establish a foundation for future investigations on SERCA-mediated mechanisms in muscle physiology, metabolic adaptation, and Ca^{2+}-related pathological disorders.

Disclosure Statement

No potential conflict of interest was reported by the author.

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