Neurochemical Research (2026) 51:139
https://doi.org/10.1007/s11064-026-04750-6

RESEARCH

Expression and Localization of Branched-Chain Ketoacid Dehydrogenase E1 Subunits and LAT1 Transporter in Rat Retinal and Ocular Tissues

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Received: 10 December 2025 / Revised: 5 March 2026 / Accepted: 1 April 2026

Abstract

Branched-chain amino acids (BCAAs) are essential for various metabolic and physiological functions. The enzymes responsible for breaking down and transporting them are organized in a tissue-specific manner, playing a crucial role in moving metabolites between cells but often being overlooked. This is particularly true for the rate-limiting enzyme, branched-chain keto-acid dehydrogenase (BCKD). To address this gap, our study investigated the expression and distribution of the BCKDE1 subunits and the BCAA transporter LAT1 in normal rat eye tissues, with a focus on the retina, by applying immunohistochemistry (IHC) and immunofluorescence (IF) with specific antibodies. Our findings show that BCKDE1 subunits are highly expressed in retinal neurons, specifically in the ganglion cell layer (GCL), inner and outer nuclear layers (INL/ONL), and the plexiform layers (IPL/OPL), although they are notably absent in Müller cells. Expression was also strong in the epithelial cells of the lens, iris, and ciliary body. Similarly, we observed LAT1 localized in the GCL and INL of the retina, as well as in the iris, ciliary body, and lens epithelium. These results complement our previous work, which indicated that branched-chain aminotransferase (BCAT) isozymes are widely expressed across most ocular tissues. Overall, this evidence strongly indicates that a complete BCAA metabolic pathway exists in the eye. This provides a comprehensive understanding of BCAA metabolism in eye tissues, highlighting its crucial role in maintaining amino acid balance, neurotransmitter production, and energy generation. Furthermore, this study lays a foundation for future studies on how disruptions in these enzymatic pathways might affect neurodegeneration in diabetic retinopathy and contribute to other eye conditions.

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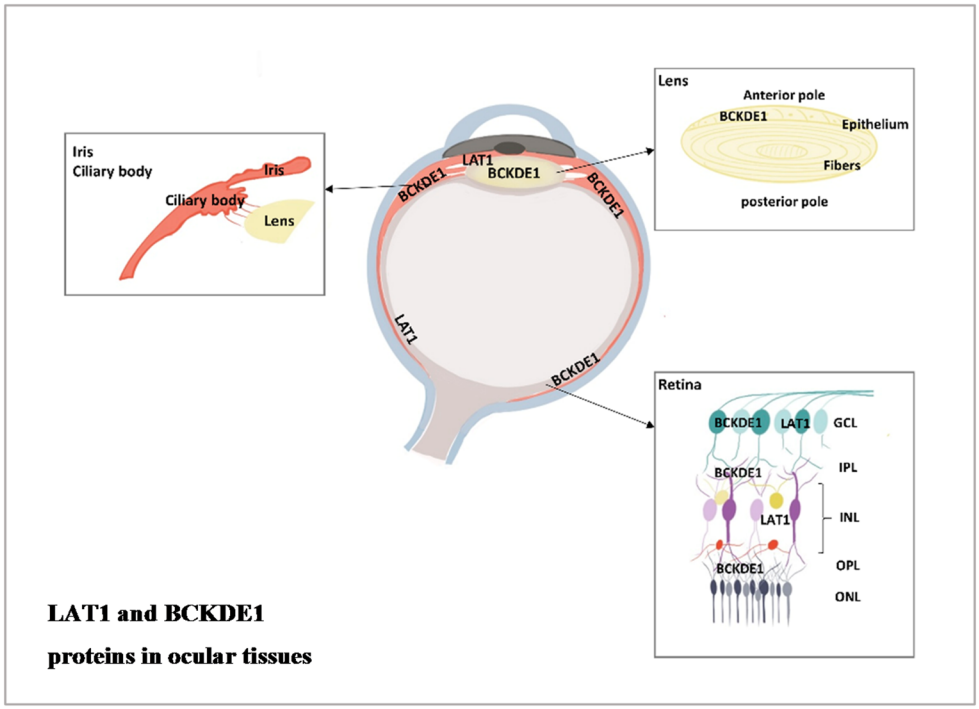
Published online: 17 April 2026

Graphical Abstract



Keywords Retina · Lens · Iris · Ciliary body · Histochemistry · BCAA · BCKD · LAT1

Introduction

Branched-chain amino acids (BCAAs: leucine (Leu), isoleucine (Ile), and valine (Val)) are essential amino acids necessary for various metabolic and physiological functions in the body. These amino acids play a critical role in glucose, lipid, and protein metabolism, helping to maintain energy balance [1, 2]. They also serve as nitrogen donors for the synthesis of the neurotransmitters glutamate and GABA in the brain and retina [1, 3]. Additionally, they exert an anabolic effect partly by activating the mTORC1 pathway, which controls neurogenesis in the eye [4]. Furthermore, 3-hydroxy-3-methylglutaryl-CoA, a byproduct of leucine breakdown, contributes to cholesterol production, which is essential for maintaining membrane integrity, fluidity, and the permeability of the blood-brain barrier [2].

BCAAs cannot rapidly cross lipid membranes and require membrane-spanning proteins to facilitate their transport in and out of the cell, as well as between intracellular membrane compartments [5]. Furthermore, many ocular tissues, such as the retina, cornea, and iris, are protected by barrier properties that restrict direct access of nutrient compounds, including BCAAs, from the blood. The presence of specific membrane transporters is essential [6, 7]. There are three types of amino acid transporters: cationic, anionic, and neutral. Among them, large neutral amino acid transporters, known as system L, are the primary plasma membrane transporters with relatively high transport capacity [8, 9]. System L transports large neutral amino acids in a Na-independent manner. This transporter type includes L-type AAT1 (LAT1), an essential amino acid exchanger that requires coupling between amino acid inflow and outflow. It primarily facilitates the inward transport of BCAAs and bulky amino acids [10]. Previous studies have identified mRNA expression of LAT1 in some ocular tissues, such as the cornea and the inner retinal blood barrier [11, 12]; however, these findings did not confirm whether the protein was expressed or functional at the plasma membrane.

After BCAAs are transported to tissues or cells, they are either incorporated into proteins or broken down into other compounds. Unlike other amino acids, BCAA breakdown mainly starts outside the liver and involves cooperation among multiple tissues to fully oxidize them. This process results in the shuttling of BCAAs and their related metabolites between cells and tissues [1]. The first two steps of BCAA metabolism, transamination and oxidative decarboxylation, are shared among all three BCAAs. Transamination involves reversible reactions catalyzed by branched-chain aminotransferase isozymes, including cytosolic (BCATc) and mitochondrial (BCATm) forms. The mitochondrial

isozyme BCATm is widely expressed in most tissues, with high levels in the kidneys, stomach, brain, and eye [1, 13, 14]. The cytosolic isozyme BCATc is found in the retina, cornea, brain, peripheral nerves, ovaries, and placenta [14–16]. Both enzymes help transfer the amino group from a BCAA to α-ketoglutarate (α-KG), producing glutamate and branched-chain keto acids (BCKAs). The BCKAs are further processed by the branched-chain ketoacid dehydrogenase complex (BCKDc) into NADH and acyl-CoA derivatives. This reaction controls the oxidation rate of the BCAAs' carbon skeletons (irreversible loss) and completes the nitrogen transfer from BCAAs to glutamate [17].

BCKDc is located on the inner mitochondrial membrane and belongs to the keto acid dehydrogenase family, which includes the pyruvate dehydrogenase complex and α-KG dehydrogenase complex [18]. These complexes are essential enzymes involved in the tricarboxylic acid cycle (TCA cycle). BCKDc consists of multiple copies of three enzymes: branched-chain α-keto acid dehydrogenase (E1), dihydrolipoyl transacylase (E2), and dihydrolipoyl dehydrogenase (E3). The E1 part of BCKDc is a heterotetramer composed of 12 copies of two subunits, the 2α-subunit and the 2β-subunit, whereas the other two enzymes are homodimers, comprising 24 copies of E2 and six copies of E3. The activity of BCKDc is tightly controlled by the phosphorylation and dephosphorylation of the E1α subunit. Additionally, BCKDc enzyme activity is highest in the liver, lower in skeletal muscle, adipose tissue, and brain, and moderate in the kidneys and heart [1]. Furthermore, dysregulation of BCKDc enzymes activity has been implicated in various neurodegenerative diseases such as Alzheimer, Parkinson and maple syrup urine disease [19–22]. Therefore, a complete understanding of the widespread presence and activity of BCAA catabolic enzymes, the transamination reaction, and oxidative decarboxylation across ocular tissues and cells might provide valuable insights into the pathophysiology of neurodegeneration in diabetic retinopathy and other eye conditions. Thus, the aims of this study are to investigate the cellular distribution of the BCKDE1 subunit enzymes and the LAT1 transporter in the retina and other ocular tissues, with the goal of enhancing our understanding of their roles in BCAA metabolism and function.

Methods

Experimental Animals

Twelve-week-old male Sprague Dawley rats were obtained from the Experimental Surgery and Animal Laboratory at the College of Medicine, King Saud University in Riyadh, Saudi Arabia. The rats were kept under controlled environmental conditions (25 °C, 12-hour light/dark cycle). They had unlimited access to Purina rat chow (produced by Grain Silos and Flour Mills Organization, Riyadh, Saudi Arabia) and drinking water. The rats were anesthetized with sevoflurane (Tabuk Pharmaceutical, KSA), and the eyeballs from five different rats were carefully removed and prepared for immunohistochemical and immunofluorescent analysis. All experimental procedures and protocols adhered to the guidelines established by the Experimental Animals and Experimental Surgery and Animal (ESAL) Laboratory, College of Medicine, King Saud University, Riyadh, Saudi Arabia. This study was approved by the Animal Ethics Committee at King Saud University (Reference No: KSU-SE-21-04).

Immunofluorescence

Immunohistological methods for eye tissues were performed as described previously [14]. Briefly, 3 µm-thick serial sections were obtained from the whole eyes of rats, mounted on glass slides, and incubated at 60°C overnight. The slides with tissue sections were then deparaffinized using xylene, rehydrated through a series of decreasing ethanol concentrations, washed twice with distilled water, and once with phosphate-buffered saline (PBS). The deparaffinized sections were pretreated with 10 mM sodium citrate buffer containing 0.05% Tween-20. Nonspecific binding sites were blocked with 10% normal goat serum for 1 h. Sections were then incubated overnight at 4°C with the primary antibodies: mouse anti-BCKD-E1A (1:50; SC-271538, Santa Cruz Biotechnology, Dallas, USA) and anti-BCKDHB (1:100; SC-374630, Santa Cruz Biotechnology, Dallas, USA). In another set of experiments, the localization of rabbit anti-BCKDE1 subunits (Antibodies-online, Aachen, Germany), and mouse anti- glutamine synthetase (GS) antibodies within the retina was assessed at a dilution of 1:150 and 1:300, respectively. The eye sections were also incubated with only 10% normal goat serum as a negative control. After primary antibody incubation, the sections were rinsed with PBS and incubated with the corresponding secondary antibodies: goat anti-mouse IgG H&L (Alexa Fluor® 488, 1:500; Abcam, Cambridge, UK) and/ or goat anti-rabbit (Alexa Fluor® 594, 1:500; Abcam, Cambridge, UK) for 45 min at room temperature in the dark. Subsequently, the slides were washed with PBS and incubated in DAPI solution (Abcam, Cambridge, UK) for 3 min, protected from light. Finally, coverslips were applied, and the sections were examined and imaged using a ZEISS spinning disk confocal microscope (Zeiss, Germany).

Immunohistochemistry

The fixed eye sections . (3 µm thick) were mounted on glass slides. The slides with tissue sections were heated to 30°C for 20 min, then deparaffinized with xylene and rehydrated through a series of decreasing ethanol concentrations. They were then washed twice with distilled water and 1× PBS. The deparaffinized sections were immersed in a 10 mM sodium citrate buffer containing 0.05% Tween 20 for antigen retrieval. Next, immunostaining for BCKDE1α and BCKDE1β was performed using a rabbit-specific horseradish peroxidase/diaminobenzidine ABC detection IHC kit (ab64261, Abcam). The tissue sections were treated with hydrogen peroxide (kit) for 10 min to block endogenous peroxidase activity, followed by two washes with PBS. Then, they were incubated with a blocking solution (kit) for 30 min to reduce nonspecific background staining. After a 5-minute wash with PBS, the primary anti-BCKDE1α (1:50) and anti-BCKDE1β (1:100) polyclonal antibodies were applied overnight at 4°C. Negative control sections were prepared by adding only PBS buffer without the primary antibody. Following incubation, all sections were washed with PBS, incubated with an anti-rabbit antibody (kit), and reacted for 30 min at room temperature. The slides were then washed again with PBS, and the streptavidin peroxidase solution (kit) was added for 30 min. After rinsing four times with PBS, the chromogen diaminobenzidine/substrate solution was added until a brown precipitate appeared.

Results

BCKDE1 Subunit Expression in the Retina Layers

Immunohistochemistry was used to examine the localization of BCKDE1α and BCKDE1β in the rat retina. Both subunits exhibited strong expression in neuronal layers, including the ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL). Labeling was especially prominent in neuronal cell bodies and synaptic regions, indicating widespread neuronal distribution (Fig. 1). In contrast, no signal was observed in non-neuronal areas, suggesting that BCKDE1 expression is limited to neuronal elements of the retina. Negative control sections processed without primary antibodies showed no labeling, confirming the specificity of the staining for both α- and β-subunits. These findings demonstrate that BCKDE1 subunits are prominently localized in multiple neuronal compartments of the retina under normal physiological conditions.

We further analyzed the expression of BCKDE1 subunits in the retina and their co-localization with GS, a marker enzyme for retinal Müller cells (Fig. 2). As shown in panels A and B, BCKDE1 subunits are mainly present in neuronal cells. In contrast, Müller cells in the retina do not express this protein. The overlay panel shows little to no overlap in the distribution of these two proteins. Therefore, this suggests that BCKDE1 is primarily expressed in neuronal cells of the intact rat retina.

BCKDE1 Expression in the Lens

The lens of the eye is an avascular, non-innervated structure situated between the pupil and the retina. It consists of three main parts: the capsule, the epithelium, and the fibers. The expression of BCKDE1 subunits was examined in these lens parts using immunostaining. Both α- and β-chains were observed in the anterior region of the lens. Immunoreactivity for both subunits was clearly visible in the epithelial layer of the anterior lens, indicating their presence in the lens epithelium (Panels A & B). No specific staining was evident in the negative control section, confirming the specificity of the immunolabeling (Panel C) (Fig. 3).

We further confirmed the expression of branched-chain keto-acid dehydrogenase (BCKD) E1 subunits in the rat lens

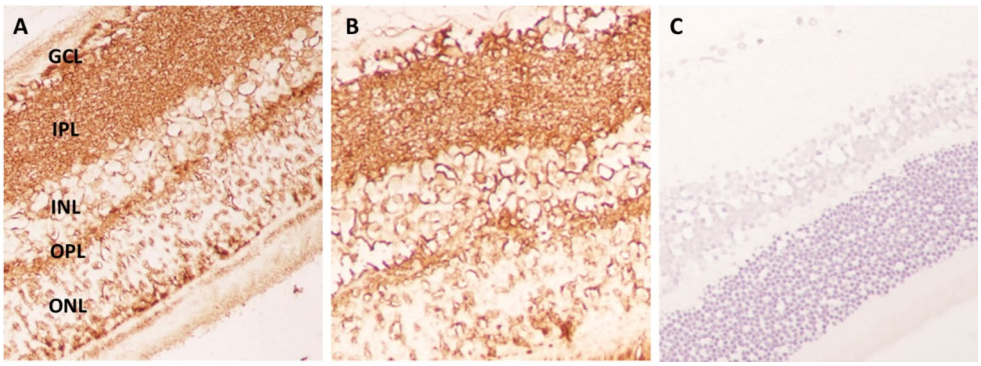


Fig. 1 Expression of branched-chain keto-acid dehydrogenase E1 subunits in the layers of the rat retina under normal conditions. **A** BCKDE1α staining of the retina layer; **B** BCKDE1β staining of the retina layer; **C** Negative control. GCL (ganglion cell layer); IPL (inner plexiform layer); INL (inner nuclear layer); OPL (outer plexiform layer); OLM (outer limiting membrane); ONL (outer nuclear layer). Scale bar: 40 and 20 µm, 20x and 40x magnification

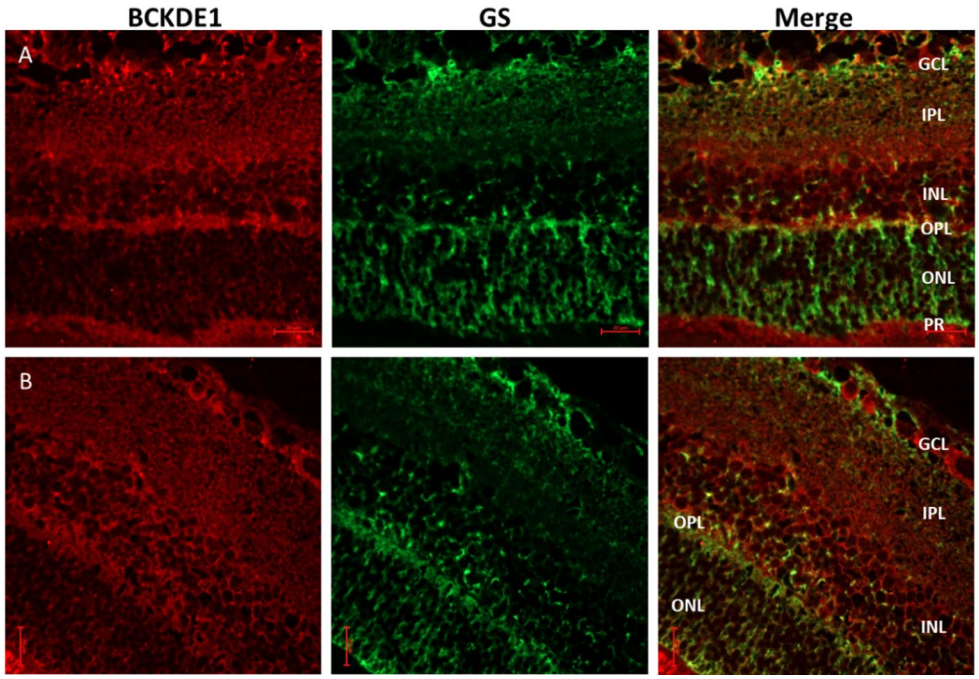


Fig. 2 Expression and immunocolocalization of branched-chain keto-acid dehydrogenase E1 subunits in the layers of the rat retina. **A** Red immunofluorescence stained for BCKDE1α (rabbit polyclonal antibody), green immunofluorescence stained for glutamine synthetase (GS) (a marker of Müller cells), and a merged image showing the overlap of BCKDE1α and GS. **B** Red immunofluorescence stained for BCKDE1β, green immunofluorescence stained for GS, and a merged image illustrating the overlap between BCKDE1β and GS. Abbreviations: GCL (ganglion cell layer); IPL (inner plexiform layer); INL (inner nuclear layer); OPL (outer plexiform layer); ONL (outer nuclear layer); PR (photoreceptors). Scale bar: 20 µm

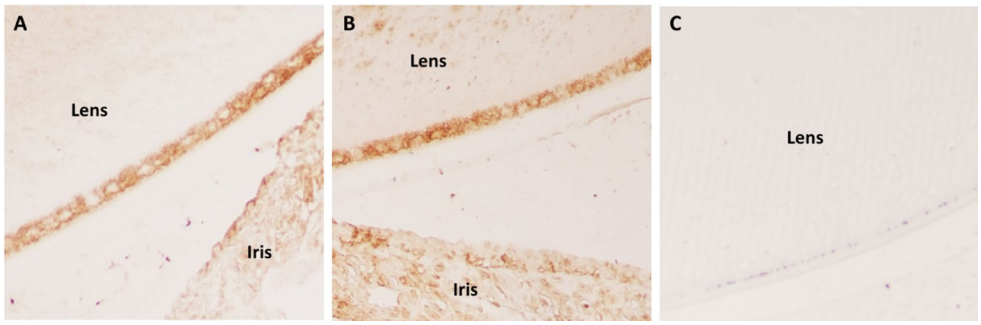


Fig. 3 Expression of branched-chain keto-acid dehydrogenase E1 subunits in normal rat lens sections. **A** BCKDE1α staining in the epithelial layer of the anterior pole of the lens. **B** BCKDE1β staining in the anterior pole of the lens. **C** Negative control. Scale bar 20 µm, 40x magnification

using immunofluorescence techniques, as shown in Fig. 4. Immunofluorescence staining confirmed that BCKDE1α immunoreactivity (Panel A) was clearly localized within the lens tissue, showing distinct staining patterns relative to the nuclear counterstain (DAPI). Similarly, BCKDE1β staining (Panel B) demonstrated strong expression in the lens, with a distribution pattern comparable to that of BCKDE1α. DAPI staining confirmed nuclear localization, serving as a reference for cellular organization.

BCKDE1 Expression in the Iris and Ciliary Body

The iris is a pigmented structure in the eye that regulates the amount of light reaching the retina. In this study, we also examined the expression of BCKDE1α and BCKDE1β subunits in the iris using immunofluorescence. A distinct expression of BCKDE1α subunits was detected in the iris, especially in the epithelial layer, anterior limiting layer, and arterial circle, as shown in Panel A, Fig. 5. Similarly, BCKDE1β staining (Panel B) showed a comparable distribution pattern, with expression evident in the epithelial layer, anterior limiting layer, and arterial circle. Nuclear staining with DAPI clearly delineated cellular organization and confirmed that BCKDE1 subunit expression is associated with multiple structural components of the iris. Furthermore, BCKDE1 was also detected in the ciliary body, as illustrated in Fig. 6. For both subunits, staining appears to be localized within the cytoplasm of cells, surrounding the nuclei, which are stained blue with DAPI.

LAT1 Transporter Expression in the Retina Layers

BCAAs are transported by the branched-chain amino acid transporter (LAT1) in the retinal layers through the blood-retinal barrier (BRB). Here, we examined the expression and distribution of LAT1 in the retina. The LAT1 protein, indicated by green fluorescence, shows distinct localization across different retinal layers. Strong positive staining was observed in the GCL and INL. In contrast, LAT1 expression was largely absent from the photoreceptor cell bodies in the ONL (Fig. 7).

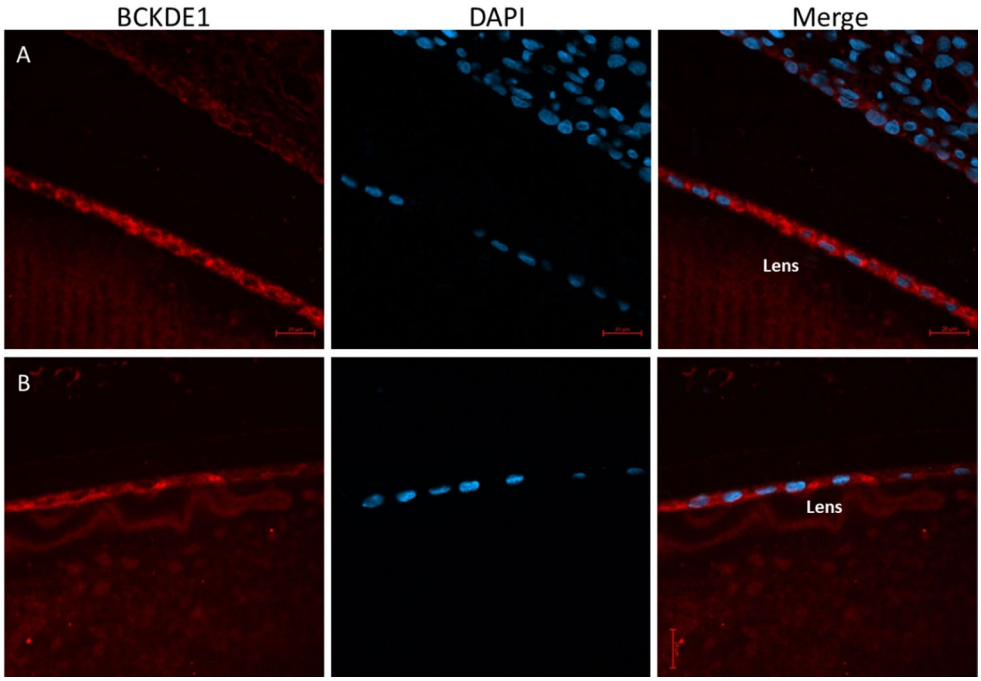


Fig. 4 Immunofluorescence staining of branched-chain keto-acid dehydrogenase E1 subunits in sections of rat lenses. **A** Immunofluorescence staining for BCKDE1α (rabbit polyclonal). **B** Immunofluorescence staining for BCKDE1β (rabbit polyclonal antibody). DAPI served as a nuclear stain.

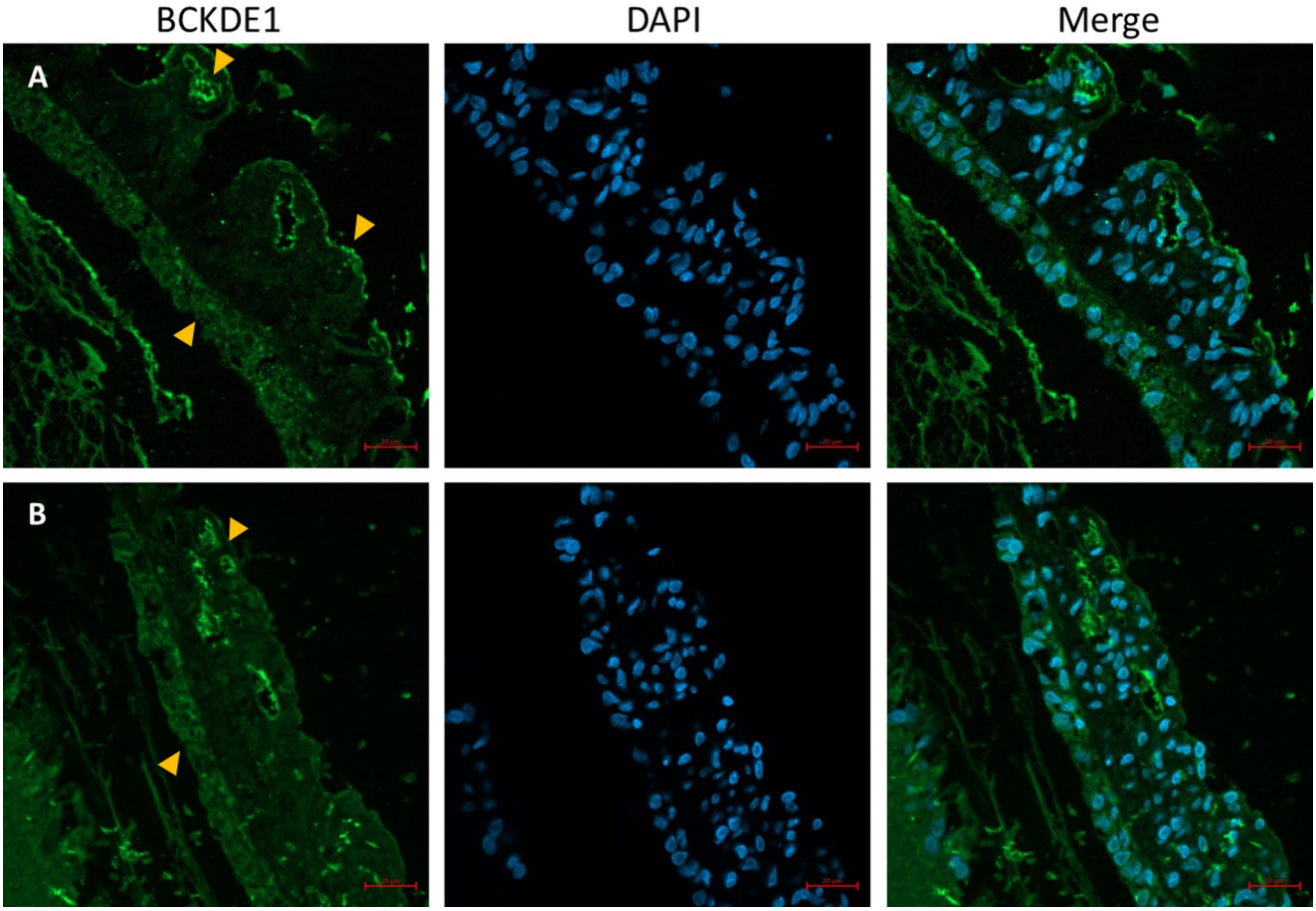


Fig. 5 Immunofluorescence staining of branched-chain keto-acid dehydrogenase E1 subunits in sections of rat iris. **A** Immunofluorescence stained for BCKDE1α. **B** Immunofluorescence stained for BCKDE1β. DAPI was used as a nuclear stain.

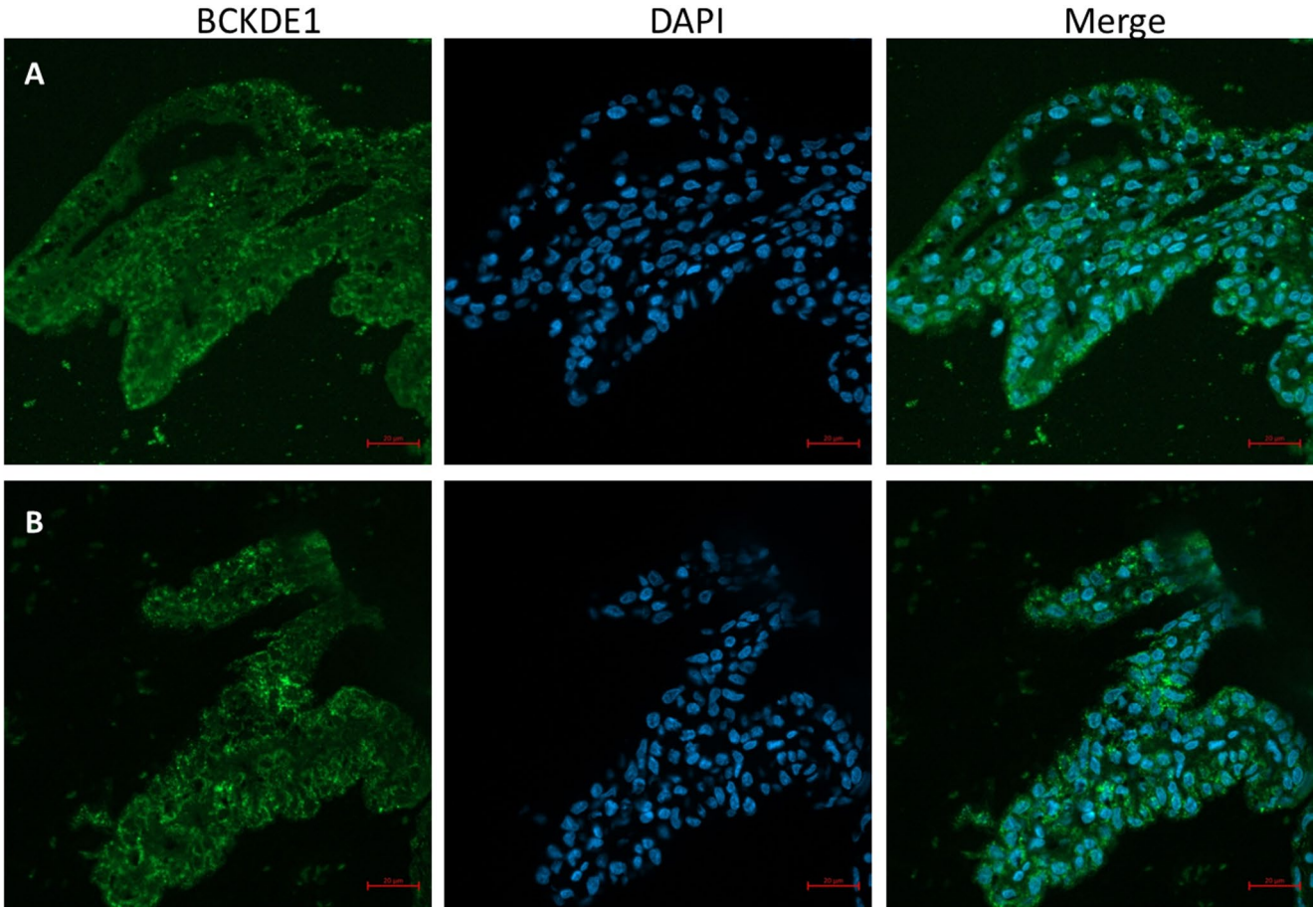


Fig. 6 Immunofluorescence staining of the branched-chain keto-acid dehydrogenase E1 subunits in a section of the rat ciliary body. **A** Immunofluorescence staining for BCKDE1α. **B** Immunofluorescence staining for BCKDE1β. DAPI was utilized as a nuclear stain. Scale bar: 20 µm

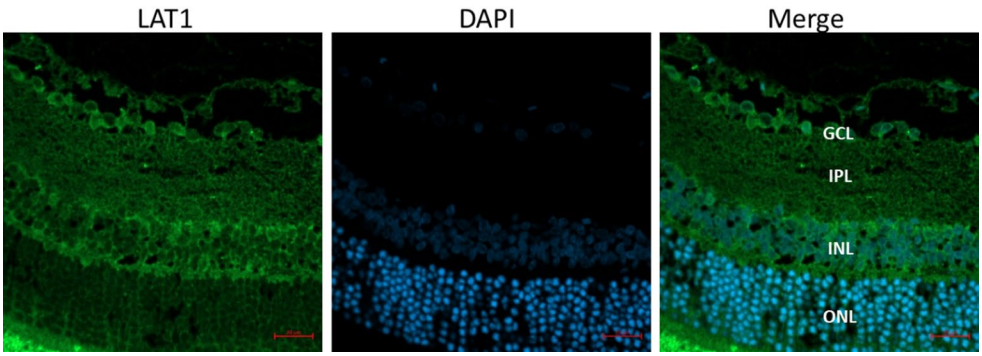


Fig. 7 Immunofluorescence staining of the branched-chain amino acid transporter LAT1 in rat retinal layers. DAPI served as a nuclear stain. Abbreviations: GCL (ganglion cell layer); IPL (inner plexiform layer); INL (inner nuclear layer); ONL (outer nuclear layer). Scale bar: 20 µm

LAT1 Expression in the Iris and Lens

The expression of the LAT1 transporter was also examined in the iris and lens . The results show positive LAT1 staining (green signal) in both tissues. As shown in Fig. 8, a distinct, strong signal for LAT1 was observed in the lens epithelial cell layer. Similarly, widespread and strong LAT1 expression was detected throughout the cells and the anterior limiting layer of the iris.

Discussion

BCAA metabolism plays a key role in maintaining energy homeostasis and regulating metabolite turnover between cells and tissues. To understand the functional roles of BCAAs' metabolic enzymes and transporters, we previously identified the expression and distribution of the initial enzyme involved in BCAA catabolism in ocular tissues [14]. In the present study, we determined the expression and localization of the BCAA transporter, LAT1, and the subsequent enzyme in the BCAA

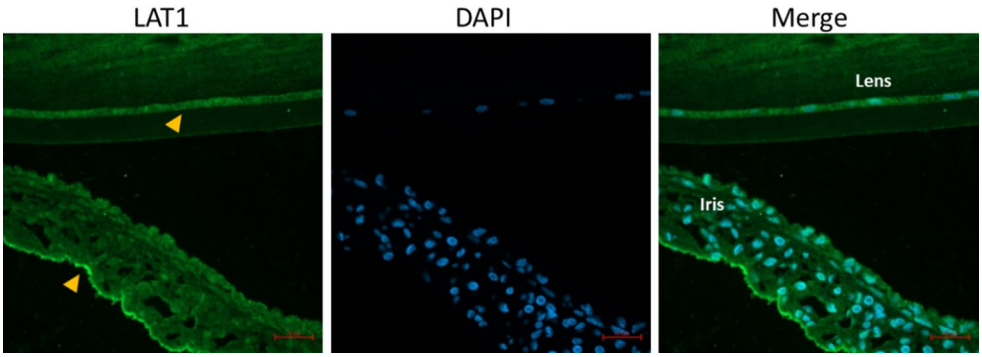


Fig. 8 Immunofluorescence staining of branched-chain amino acid transporter LAT1 in the section of rat iris layers and lens. DAPI was used as a nuclear stain. Scale bar 20 μm

catabolism pathway, specifically the BCKDE1 subunits within ocular tissues.

The retina depends on substantial energy metabolites to sustain energy balance and regulate neurotransmitters for proper vision. Meanwhile, the BRB safeguards the retina from excessive metabolites while regulating the exchange of essential nutrients and metabolites between the bloodstream and retinal cells. BCAAs are transported from the blood to the retina via the LAT1 transporter [11]. This transporter also facilitates the transport of other large neutral amino acids, including histidine, phenylalanine, tryptophan, and tyrosine, which leads to competition among these amino acids [10, 23]. In this study, we found that LAT1 is expressed in the inner nuclear layer (INL) and the ganglion cell layer (GCL) of the retina. This observation is consistent with previous reports demonstrating its localization at the inner blood–retinal barrier (iBRB) [11, 24]. Notably, these retinal layers also contain neuronal and glial cells. A study by Huttunen et al. reported that this transporter is expressed in both neuronal and glial cells of the brain [17]. Together, these findings suggest that LAT1 is not only associated with the blood–retinal barrier but may also be present on cellular membranes, where it could contribute to the intercellular transport of BCAAs and large neutral amino acids, or provide metabolic support. The positive staining of LAT1 was also noted in other ocular tissues, including the lens, iris, and ciliary body. A previous study using chicken eye tissues has similarly reported the presence of this transporter in the iris and ciliary body [25], further supporting our findings. The presence of this transporter across multiple eye sections suggests it may play a significant role in intraocular transport. Moreover, its widespread distribution could provide a potential route for targeted drug delivery and the treatment of ocular diseases.

In our previous work, we identified the differential expression of the BCAT isoform in retina cells and layers [14]. The BCATc was localized to retinal neurons, while BCATm was found in Müller cells. The present study shows that within the rat retina, the strong labeling of the BCKDE1 subunits in the GCL, IPL, INL, and ONL reflects the distribution of BCATc in the neuronal layers of the retina. This finding aligns with a previous study by Cole et al. (2012), which reported the expression of the BCKDE1 subunit in neuronal cells of rat brains [26]. No staining of this subunit was observed in Müller cells, indicating that the BCKAs produced by transamination via BCATm in Müller cells must be exported to neurons for complete oxidation or recycling, supporting neurotransmitter maintenance. This finding is consistent with earlier studies in humans and rodent brains, which have shown that the BCKD enzyme is absent in glial cells [26–28]. This suggests that neurons produce glutamate from BCAAs, prevent retransamination, and fully oxidize BCKAs for energy production.

Like other peripheral tissues, the labeling pattern of BCKDE1 subunits across different parts of the eye closely parallels the reported expression pattern of BCATm enzymes [14], supporting the formation of a functional BCAA metabolon (protein-protein complex). The benefits of a protein-protein complex between BCATm and BCKDE1 include facilitating the transfer of the BCATm transamination product to the E1 subunits of BCKD, which increases the rate of E1-catalyzed decarboxylation and overall BCKD activity [29]. These results strongly support our observations of increased BCKDE1 subunit expression in the anterior part of the lens, which coincides with BCATm expression localized within mitochondria in lens epithelial cells. This is also supported by a previous study using radioactively labeled leucine in the lens, which showed that leucine flux through BCKD produces acetyl-CoA, which enters the tricarboxylic acid cycle and is subsequently incorporated into fatty acids [30]. This suggests the possibility of complete BCAA catabolism and energy production within the lens.

The iris and ciliary body are pigmented tissues containing melanin. Previous research has reported that BCAAs can suppress melanin production in melanoma cells, potentially explaining the elevated levels of BCATm and BCKDE1 enzymes observed in these tissues. Additionally, BCKD plays a crucial role in driving the irreversible step of BCAA catabolism by converting BCKAs into their respective acyl-CoA derivatives. This step is essential to prevent the reverse reaction of BCAT enzymes, which catalyze a reversible reaction between BCAAs and α-ketoglutarate (KG) to produce the reaction catalyzed by BCAT enzymes, which convert BCAAs and α-ketoglutarate (KG) into BCKAs and glutamate. Without BCKD activity, BCKAs could be converted back into BCAAs, resulting in the consumption of glutamate. Therefore, the

expression of BCKDE1 in this tissue ensures the forward progression of BCAA degradation and preserves glutamate within the cell. This may explain the elevated levels of glutamate in the iris and ciliary body [31].

Conclusions

This study along with our recent works provides further insights into the role of BCAAs in ocular tissues [14, 32]. We confirm that the neurons are the primary site of BCAA metabolism in the retina, and the compartmentalization of catabolic enzymes may play a crucial role in BCAA/BCKA shuttling to maintain glutamate homeostasis, similar to the interaction observed between neurons and astrocytes in the brain. In addition, the compartmentalization of BCAAs catabolic enzymes within ocular tissues may also contribute to the movement of metabolites between eye tissues, facilitating energy production, antioxidant activity, and maintaining glutamate balance.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11064-026-04750-6.

Acknowledgements The authors thank the Department of Biochemistry and the Graduate Research Program, College of Science, KSU, for supporting the study. The authors are grateful to the Ongoing Research Funding Program (ORF-2026-710) from King Saud University, Riyadh, Saudi Arabia.

Author Contributions D.I.A and M.S.O. conceived and designed the experiments. D.I.A performed the experiments. M.S.O., W.S.A., N.K.A and A.S.A. contributed reagents/materials tools and techniques. D.I.A wrote the paper, and M.S.O. revised and edited the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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