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ORIGINAL ARTICLE

Mechanisms of β-adrenergic receptors agonists in mediating pro and anti-apoptotic pathways in hyperglycemic Müller cells

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Abstract

Background The current study aimed to investigate the stimulatory effect of beta-adrenergic receptors (β-ARs) on brain derived neurotropic factor (BDNF) and cAMP response element binding protein (CREB).

Methods Human Müller cells were cultured in low and high glucose conditions. Cells were treated with xamoterol (selective agonist for β1-AR), salmeterol (selective agonist for β2-AR), isoproterenol (β-ARs agonist) and propranolol (β-ARs antagonist), at 20 μM concentration for 24 h. Western Blotting assay was performed for the gene expression analysis. DNA damage was evaluated by TUNEL assay. DCFH-DA assay was used to check the level of reactive oxygen species (ROS). Cytochrome C release was measured by ELISA.

Results Xamoterol, salmeterol and isoproterenol showed no effect on Caspase-8 but it reduced the apoptosis and increased the expression of BDNF in Müller cells. A significant change in the expression of caspase-3 was observed in cells treated with xamoterol and salmeterol as compared to isoproterenol. Xamoterol, salmeterol and isoproterenol significantly decreased the reactive oxygen species (ROS) when treated for 24 hours. Glucose-induced cytochrome c release was disrupted in Müller cells.

Conclusion β-ARs, stimulated by agonist play a protective role in hyperglycemic Müller cells, with the suppression of glucose-induced caspase-3 and cytochrome c release. B-Ars may directly mediate the gene expression of BDNF.

Keywords Müller cells · CREB · Caspase-3 · Caspase 8 · Cytochrome C

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Introduction

Diabetes is a group of metabolic disorders characterized by high blood glucose levels, which leads over time to serious heart, eyes, kidney and nerve complications [1–3]. Müller cells are the key glial cells of the retina. They contribute to retinal homeostasis by regulating blood flow and synaptic activity in the retina. In diabetes, these cells become activated and modulate a number of immune responses by producing proinflammatory cytokines [4]. They maintain the blood retinal barrier and protect the retina against oxidative stress by scavenging free radicals and providing energy metabolites [5–9].

Diabetic retinopathy is considered one of the major causes of vision loss. It also contributes to the development of other sight threatening diseases such as cataract and glaucoma [10, 11]. β1 and β2 ARs are the subtypes of β-ARs, and are present in the Müller cells. Many studies have reported that changes in the expression of downstream genes can change the expression of β-ARs [12–16].

β-ARs agonists are used to treat diseases like bronchospasm and asthma. These agonists can also target metabolic abnormalities involving diabetes and cardiovascular diseases. These roles are attributed to their ability to reduce the level of pro-apoptotic and pro-inflammatory factors such as ROS, IL-1B, TNF-α, iNOS and other cytokines [17]. Diabetic retina responds to a variety of factors including high ROS, oxidative stress, and increased expression of inflammatory markers [18]. A high glucose concentrations in the retina usually lead to changes in the redox regulatory capacity of Nrf2, which is mediated by the NF-kB [19].

In the initial phases of diabetic retinopathy (DR), the expression of glial fibrillary acidic protein (GFAP) is high. Increase in the GFAP levels transforms the Müller cells into a reactive state, which alters the whole cascade of events from normal to dysfunctional regulation of glucose transport, inflammatory markers, cell survival, growth factors and oxidative stress. These reactive changes in Müller cells results in functional death and loss of neurons in diabetic retinopathy [20–23].

Brain-derived neurotrophic factor (BDNF) and cyclic AMP response element-binding protein (CREB) are reported to play a significant role in neuronal survival, oxidative stress, insulin secretion, hyperglycemia and several other diabetic complications [24–26]. Following a prolonged exposure to hyperglycemic conditions, a number of changes occur in the cellular activity of Müller cells. Increased apoptosis is one of those changes in them [27]. Caspase-8 resides in the cytosol in an inactive form. It is activated by proteolytic processing which cleaves it into large and small polypeptides [28, 29]. Extrinsic pathway is activated when trimerization of the death receptors occurs. It leads to the recruitment of the FADD (Fas associated death domain), which then recruits caspase-8, caspase-3 and other downstream caspases [30].

The transcription of BDNF is increased upon binding of phosphorylated CREB (pCREB) to the promotor of PDNF. This transcription results in the activation of CREB-ERK-BDNF pathway which performs key roles in a number of biological processes including synaptic plasticity, cell survival and synaptic structure (32). This study aims to evaluate the effect of xamoterol (selective agonist for β1-AR), salmeterol (selective agonist for β2-AR), isoproterenol (β-ARs agonist) and propranolol (β-ARs antagonist) in mediating pro and anti-apoptotic pathways in hyperglycemic Müller cells.

Materials and methods

Cell culture

Human Müller cells (MIO-M1) were kindly provided by Dr. Astrid Lim (University College London), which were isolated from the neural retina of cadaveric donor eyes at the Moorfields Hospital Eye Bank. Cells were cultured in DMEM (Dulbecco's Modified Eagle Medium, which was supplemented with 10% Fetal Bovine Serum (FBS), 1% Penicillin–Streptomycin and animal-derived growth factors (Thermo Fisher Scientific, US). For shRNA experiment, transfection was performed using SMART vector Lentiviral CREB shRNA following manufacturer's instructions (Dharmacon). Müller cells were transduced with lentiviral vectors and harvested when cultures reached 70–80% confluency. Cells were cultured in 25 ml flask and treated with normal (5 mM) and high (25 mM) glucose concentrations, followed by a 24 h exposure to xamoterol, salmeterol, isoproterenol and propranolol each in 20 µM concentrations. Cells in some flasks were also treated with a 10 ng/ml concentration of TNF-α. Cells were maintained at 37 °C with 5% CO_2. Media was changed every 2–3 days.

Western Blot analysis

Before the extraction of protein, Müller cells were extensively washed with PBS (phosphate buffer saline). Cells were then lysed, using CelLytic M protein extraction kit (Sigma-Aldrich, USA), following manufacturer's instructions. Protein extraction was followed by loading (30 µg in each well) and then separation on a 10% SDS/PAGE (Precast gels, Bio-Rad, cat no 456-1093). The samples were then transferred and blotted with primary antibodies (1:3000) against BDNF, caspase 3 and caspase 8 (Santa Cruz, CA, USA). Sampled loaded membranes were then subjected to HRP-conjugated IgG secondary antibodies (Santa Cruz, CA,

USA). Chemiluminescence was performed using enhanced chemiluminescence (Amersham Life Sciences, UK), and gel imaging system (Biospectrum 410, UVP).

TUNEL assay

The terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) assay was performed to examine the DNA damage, using a colorimetric detection kit, following manufacturer's specifications (Titer TACS; R&D System). Müller cells were cultured at a density of 1×10^5 in a 96-well plate and fixed with 3.7% buffered formaldehyde. Cells were then washed with PBS, which was followed by permeabilization with 100% methanol for 20 min. 0.2 N HCl was used to stop the reaction after labelling and the absorbance was measured using a microplate reader at 450 nm.

DCFH-DA assay

2′7′-dichloro-dihydro-fluorescein diacetate (DCFH-DA) assay was performed to measure Intracellular ROS. Briefly, Müller cells were seeded using a 96-well plates. Cells were then treated with 5 µM DCFH-DA reagent followed by taking readings by a microplate reader at 485 and 530 nm.

Enzyme linked immunosorbent assay (ELISA)

ELISA assay was performed to measure the Cytochrome c release, using ELISA assay kit (Invitrogen, Carlsbad, CA, USA).

Statistical analysis

In this study, all the analyses were performed in triplicates. Data were shown as mean ± SD. One-way ANOVA test was used (SPSS-17.0) and a value of $p < 0.05$ was considered significant while $p < 0.01$ was considered as highly significant.

Results

Caspase-8 and beta-adrenergic receptors stimulation

No effect was observed on caspase-8 in Müller cells treated with 25 mM glucose in combinations with 20 µM concentrations of each xamoterol, salmeterol and isoproterenol for 24 h. Propranolol also showed no stimulatory effect on caspase-8 (Fig. 1A). This led us to the idea to first stimulate caspase-8 with TNF-α, and then probe if there is any effect. Treatment of TNF-α (10 ng/ml) further increased the cleavage of caspase-8 but interestingly no effect was observed by xamoterol, salmeterol and isoproterenol (20 µM; 24 h). Propranolol also showed no effect (Fig. 1B).

Caspase-3 and beta-adrenergic receptors stimulation

Xamoterol, salmeterol and isoproterenol reduced the activation of caspase-3. Xamoterol and salmeterol (20 µM; 24 h) had significant effect on the expression of caspase-3 in Müller cell. Isoproterenol did not exert any effect on the activation of caspase-3. Propranolol (20 µM; 24 h), disrupted the agonists-induced inhibiting effect (Fig. 1C).

Effect of β-ARs on apoptosis

To determine the effect of xamoterol, salmeterol, isoproterenol and propranolol on apoptosis, TUNEL assay was conducted in hyperglycemic Müller cells. Apoptosis was reduced by the treatment of xamoterol, salmeterol and isoproterenol (20 µM; 24 h). Propranolol reversed the agonists-induced cytoprotective effect (Fig. 1D).

Effect of β-ARs on BDNF and CREB

An increase in the expression of BDNF was observed when treated with 20 µM xamoterol, salmeterol and isoproterenol for 24 h (Fig. 2A). Being a transcriptional regulator of BDNF, β-ARs might be mediating BDNF via CREB. To test this idea, we carried out small hairpin RNA (shRNA)-mediated depletion of CREB. The results showed an overall decrease in the BDNF protein but interestingly beta-adrenergic receptors were still able to induce the expression of BDNF in hyperglycemic Müller cells, treated with 20 µM of xamoterol, salmeterol and isoproterenol for 24 h. These data demonstrate that CREB regulates BDNF transcription because after the depletion of CREB, there was also depletion in the expression of BDNF. Concomitantly, these results demonstrate that β-ARs stimulation may directly mediates the expression of BDNF, because β-ARs stimulation increased the expression of BDNF, even when CREB was silenced by shRNA (Fig. 2B).

Effect of β-ARs stimulation on ROS

In view of the association of reactive oxygen species (ROS), hyperglycemia and apoptosis, we wanted to determined the effect of these agonists on the ROS levels in hyperglycemic Müller cells. A decrease in the level of ROS was observed when cells were treated with 20 µM concentration of xamoterol, salmeterol and isoproterenol for 24 h (Fig. 3A).

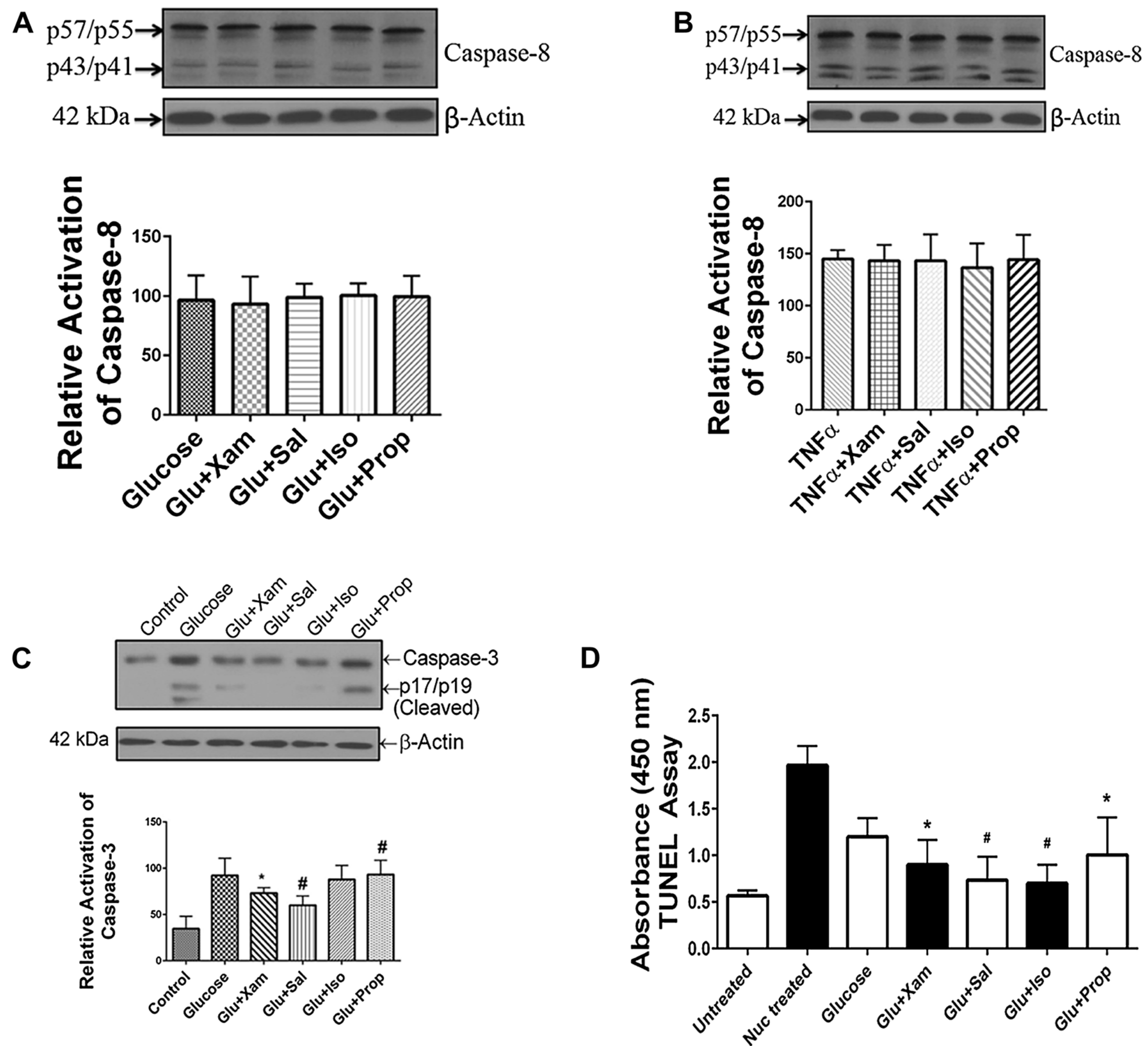

Fig. 1 This figure shows the expression of caspase-8 in Muller cells treated with high glucose, xamoterol, salmeterol, isoproterenol and propranolol (**A**), the expression of caspase-8 in Muller cells treated with TNF-α (10 ng/ml), xamoterol, salmeterol, isoproterenol and propranolol (**B**), the expression of caspase-3 in Muller cells treated with high glucose, xamoterol, salmeterol, isoproterenol and propranolol (**C**) and TUNEL assay (apoptosis) in Muller cells treated with high glucose, xamoterol, salmeterol, isoproterenol and propranolol (**D**)

Effect of β-ARs stimulation on cytochrome c release

When hyperglycemic Müller cells were treated with 20 μM xamoterol, salmeterol and isoproterenol for 24 h, a reduced cytochrome c release was observed. However, propranolol reversed this effect (Fig. 3B).

Discussion

Beta-adrenergic receptors elicit a range of transmembrane signaling in a wide variety of cellular and biochemical events. β1 and β2 ARs are the subtypes of β-ARs which are present in a number of cells including Müller cells. Diabetic retina responds to a number of pro-diabetic, pro-apoptotic and pro-inflammatory factors such as increased oxidative stress and hyper-glycemic conditions [18]. This study aimed to evaluate the stimulatory effect of β-ARs on caspase-3, caspase-8, BDNF and the transcription factor CREB.

Caspase-8, resides in the cytosol as an inactive form and is activated by proteolytic processing when it cleaves into large and small polypeptides [28–31]. Extrinsic pathway is activated upon the trimerization of death receptors, which results binding of FADD (Fas associated death domain), and activation of caspase-8. Activated caspase-8 is known to propagate the apoptotic signal by cleaving and activating caspase-3 and other downstream caspases [30]. In our study hyperglycemia activated caspase-8; however beta-adrenergic receptors stimulation with xamoterol, salmeterol and isoproterenol had no effect on caspase-8. Antagonist proptorenol

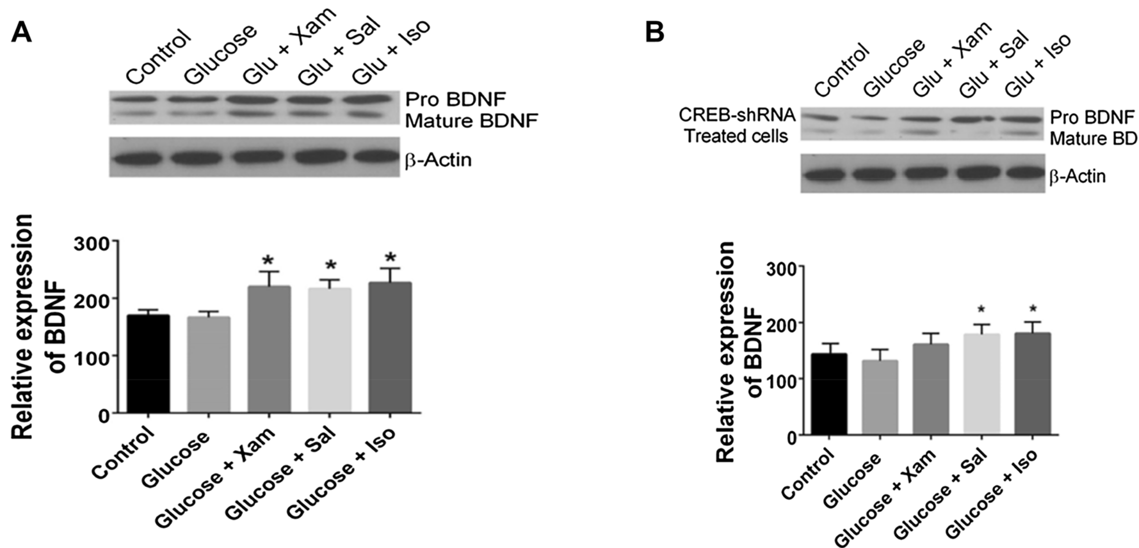

Fig. 2 This figure shows the expression of BDNF in Muller cells treated with high glucose, xamoterol, salmeterol and isoproterenol (**A**), and the expression of BDNF treated with high glucose, xamoterol, salmeterol and isoproterenol after treating with CREB-shRNA (**B**)

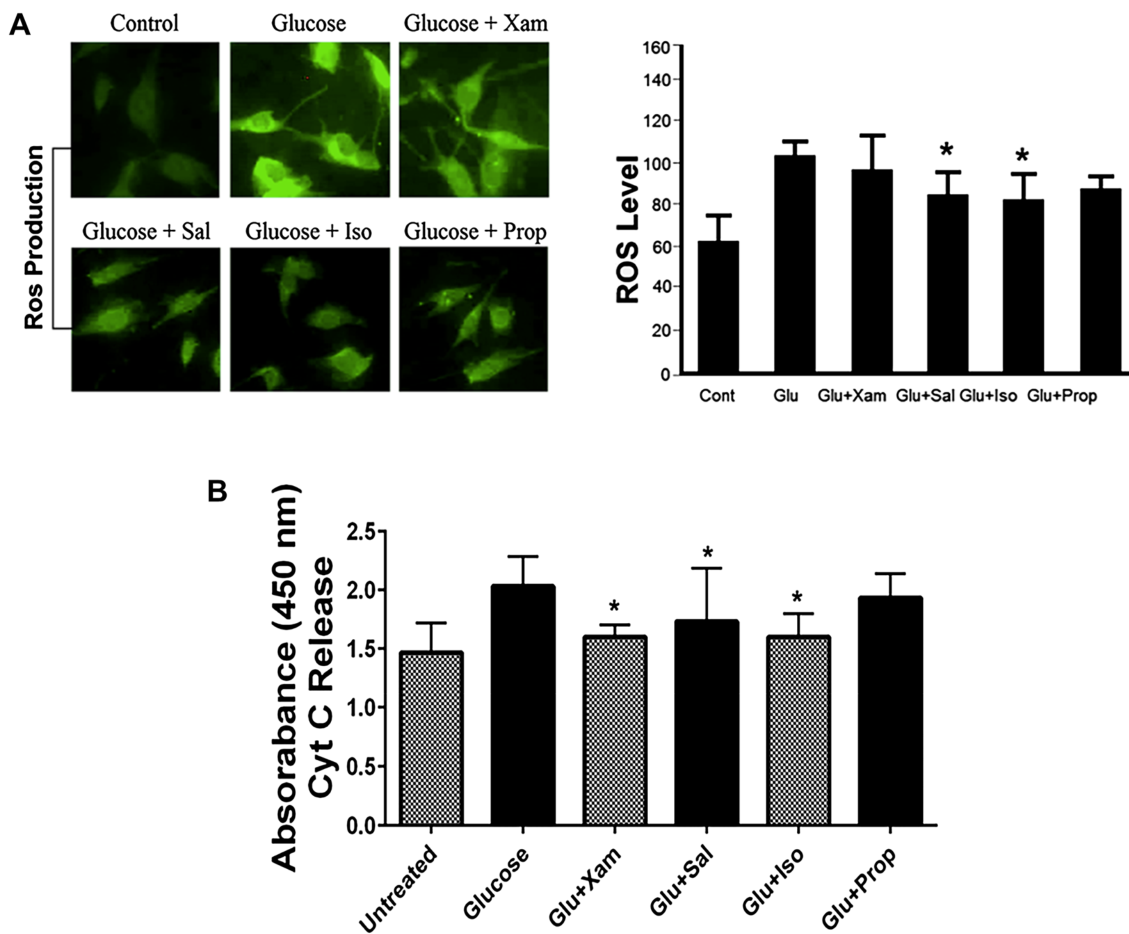

Fig. 3 This figure shows the DCFH-DA assay (generation of reactive oxygen species) in Muller cells in glucose and glucose + beta-adrenergic receptors agonists (**A**) and ELISA assay showing the effect of xamoterol, salmeterol, isoproterenol and propranolol on cytochrome c release in hyperglycemic Muller cells (**B**)

was also unable to induce any effect. Activation of caspase-8 was increased by treating the cells with TNFα, however again no effect of beta-adrenergic receptors stimulation was observed on caspase-8 in Müller cells.

Interestingly, high glucose activated caspase-3, by cleaving it into p17 and p19 components and then xamoterol, a specific agonist for β1-AR, and salmeterol, a specific agonist for β2-AR, significantly reduced the activation of caspase-3. This demonstrated that β-ARs signaling is involved in the regulation of caspase-3, thus having an anti-apoptotic effect on the intrinsic pathway. It is therefore possible that stimulation of these cells with xamoterol, salmeterol and isoproterenol directly suppress the cleavage of caspase-3, independent of caspase-8. A recent study suggests that TNF-α activated several factors, which resulted increased mitophagy and apoptosis in RPE cells in high glucose environment [32].

CREBP regulates the transcription of many genes in neurons, including BDNF, which supports the growth and survival of neurons [33, 34]. In the present study the relative expression of BDNF was significantly increased when treated with agonists xamoterol, salmeterol and isoproterenol for 24 h. Our results demonstrated that CREB was involved in regulating the transcription of BDNF because after the depletion of CREB (by shRNA), a depletion was observed in the expression of BDNF. Concomitantly, β-ARs stimulation mediated the expression of BDNF without involving CREB, because β-ARs stimulation increased the expression of BDNF, even when CREB was silenced by shRNA.

A study reported the N-acetyl serotonin (NAS) induced anti-apoptotic effect by mediating TrkB/CREB/BDNF pathway in cells and animal models. They suggested that NAS was protecting neuronal cells by regulating the key apoptotic factors and activation of CREB and BDNF [35]. β-ARs are possibly using the same way to protect the Müller cells. These data suggest that β-ARs signaling which regulates the intrinsic apoptotic pathway and cytochrome c release, may directly activate caspase-9. Our results also demonstrate that there is an increase in cytochrome c release and apoptosis upon glucose treatment; however both apoptosis and glucose induced cytochrome c release were attenuated by the treatment of xamoterol, salmeterol and isoproterenol. Propranolol, a beta-adrenergic receptors antagonist, disrupted the effect of these agonists.

In hepatocytes and various other cell lines, both intrinsic and extrinsic pathways have to crosstalk to achieve apoptosis [36]. Our results demonstrated that beta-adrenergic receptor reduced the activated caspase-3 and cytochrome c, showing that both the pathways are being involved in the Müller cells. There is a clear link between hyperglycemia, ROS, inflammation; and the development of diabetic complications [37–40]. Our data show that hyperglycemi condition causes several pro-diabetic conditions which are reduced by the β-ARs agonists xamoterol, salmeterol and isoproterenol.

Conclusion

The present study revealed that beta-adrenergic receptors, stimulated by xamoterol, salmeterol and isoproterenol play protective role in hyperglycemic Müller cells. This effect is apparently controlled by the suppression of glucose-induced caspase-3 and cytochrome c release. Moreover, beta-adrenergic receptors are possibly mediating BDNF directly.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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