β-ARRESTIN 2 KNOCKOUT MODULATES INFLAMMATORY RESPONSES IN A MOUSE MODEL OF STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

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Diabetes mellitus (DM) is associated with systemic inflammation and neuroinflammation, but the role of β-arrestin 2 in these processes remains poorly understood. The experimental study aimed to assess the effect of β-arrestin 2 deficiency on the pro-inflammatory state of mice with streptozotocin-induced diabetes. Male C57BL/6J mice and mice with the global β-arrestin 2 gene knockout (*Arrb2-/-*) were divided into four groups: non-diabetic wild type mice (WT, $n = 8$), diabetic wild-type mice (WTd, $n = 8$), non-diabetic knockout mice (KO, $n = 8$) and diabetic knockout mice (KOd, $n = 9$). Arrb2 knockout delayed the development of hyperglycemia: on day 39, blood glucose levels were significantly higher in WTd mice than in KOd mice (22.3 ± 8.09 vs. 14.37 ± 7.65 mmol/L, $p < 0.05$). *Arrb2-/-* mice also showed increased systemic inflammatory markers: the baseline percentage of neutrophils in KO mice was 2.6-fold higher than in WT mice ($p < 0.0001$). Starting from day 18 KOd mice had significantly higher neutrophil counts compared to KO and WTd ($p < 0.05$). β-Arrestin 2 deficiency was associated with increased mRNA expression of the genes encoding pro-inflammatory cytokines and protease-activated receptors. The most pronounced changes included a significant increased *Il6* mRNA expression in the hippocampus of KO compared to WT (2.9-fold, $p < 0.01$), increased *Tnf* expression in the cerebral cortex (4.3-fold for KO/WT and 2.0-fold for KOd/WTd) and the hippocampus (3.2- and 2.3-fold, respectively) of *Arrb2-/-* animals compared to appropriate wild type groups ($p < 0.05$), as well as the increased *Par1* and *Par4* expression in the cerebral cortex and hippocampus of *Arrb2-/-* mice (2.4–7.3-fold, $p < 0.01$). These findings suggest that β-arrestin 2 deficiency is associated with a pro-inflammatory phenotype in the CNS and may contribute to inflammation dysregulation in DM.

Keywords: diabetes, β-arrestin 2, PAR, knockout, inflammation

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ВЛИЯНИЕ НОКАУТА ГЕНА β-АРРЕСТИНА 2 НА ПРОВОСПАЛИТЕЛЬНЫЙ СТАТУС МЫШЕЙ В УСЛОВИЯХ СТРЕПТОЗОТОЦИН-ВЫЗВАННОГО САХАРНОГО ДИАБЕТА

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Сахарный диабет (СД) сопровождается системным воспалением и нейровоспалением, однако роль β-аррестина 2 в этих процессах изучена недостаточно. Цель экспериментального исследования — изучить влияние дефицита β-аррестина 2 на провоспалительный статус мышей в условиях стрептозотоцин-вызванного сахарного диабета. Самцов мышей линии C57BL/6J и мышей с глобальным нокаутом гена β-аррестина 2 (*Arrb2-/-*) разделили на четыре группы: животные дикого типа без диабета (WT, $n = 8$) и с диабетом (WTd, $n = 8$), нокаутные животные без диабета (KO, $n = 8$) и с диабетом (KOd, $n = 9$). Показано, что нокаут гена *Arrb2* замедляет развитие гипергликемии: к 39-му дню эксперимента уровень глюкозы у животных WTd составлял 22,3 ± 8,09 ммоль/л, у KOd — 14,37 ± 7,65 ммоль/л ($p < 0,05$). У мышей *Arrb2-/-* был повышен системный воспалительный фон: базальная доля нейтрофилов в крови у KO животных была в 2,6 раза выше, чем у WT ($p < 0,0001$). С 18-го дня эксперимента у KOd мышей доля нейтрофилов была значимо выше по сравнению с KO и WTd ($p < 0,05$). Дефицит β-аррестина 2 сопровождался усилением экспрессии мРНК генов провоспалительных цитокинов и рецепторов, активируемых протеазами. Наиболее выраженные изменения включали статистически значимое повышение экспрессии мРНК *Il6* в гиппокампе у KO по сравнению с WT в 2,9 раза ($p < 0,01$), повышение экспрессии *Tnf* в коре (4,3 раза для KO/WT и 2,0 раза для KOd/WTd) и гиппокампе (3,2 и 2,3 раза соответственно) у *Arrb2-/-* животных по сравнению с соответствующими группами дикого типа ($p < 0,05$), а также увеличение экспрессии *Par1* и *Par4* в коре и гиппокампе у *Arrb2-/-* мышей от 2,4 до 7,3 раза ($p < 0,01$). Полученные данные указывают на противовоспалительную роль β-аррестина 2 в центральной нервной системе и его участие в регуляции воспаления при СД.

Ключевые слова: диабет, β-аррестин 2, PAR, нокаут, воспаление

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Diabetes mellitus (DM) is one of the leading non-communicable disorders becoming more and more prevalent all over the world [1, 2]. DM is associated with a high risk of cardiovascular complications, including cerebrovascular disorders, as well as the increased likelihood of cognitive impairment and neurodegenerative diseases [3, 4]. The factors linking DM with the development of comorbidities include systemic inflammation and neuroinflammation accompanying the disorder [5, 6].

Non-enzymatic glycation of proteins and other molecules is one of the mechanisms linking chronic hyperglycemia to inflammatory response. With an excess of glucose its carbonyl group reacts with free amino groups leading to the formation of advanced glycation end products (AGEs) [7]. The interaction of AGEs with the receptor for advanced glycation end products (RAGE) activates the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase), TGFβ (transforming growth factor β), JNK (c-Jun N-terminal kinase), and NF-κB (nuclear factor κB) signaling pathways, which is accompanied by the release of pro-inflammatory mediators, including interleukin-1 (IL1), interleukin-6 (IL6), and tumor necrosis factor α (TNFα) [8]. Furthermore, AGE/RAGE signaling and glucose autooxidation enhance the formation of reactive oxygen species (ROS), thereby further supporting the inflammatory response associated with DM [9, 10]. DM-associated metabolic disorder also contributes to endothelial dysfunction. In particular, insulin resistance is accompanied by reduced activity of the PI3K/Akt signaling pathway (phosphoinositide 3-kinase/protein kinase B) and compensatory enhancement of the MAPK/ERK-dependent signaling, which results in the decreased nitric oxide (NO) production and the increased endothelin-1 formation in endothelial cells [11, 12]. The blood-brain barrier (BBB) integrity may be disrupted against the background of endothelial dysfunction, activation of astrocytes and microglia, which contributes to neuroinflammation and neurodegenerative changes [13, 14].

Understanding the molecular mechanisms linking diabetes and inflammation is important for the development of new therapeutic strategies aimed at modulating inflammatory responses in DM and preventing neurological complications. One promising area is the study of β-arrestins, multifunctional adapter proteins involved in the regulation of signaling pathways associated with glucose metabolism and inflammation [15].

β-Arrestin 2 was first described due to its key role in desensitization of G protein-coupled receptors (GPCR) [16]. However, along with regulation of GPCR, β-arrestin 2 has an important adapter function, since it is involved in signal transmission through the cascades both related (activation of ERK, JNK, and p38-kinases) [17] and unrelated to G-proteins (Wnt, Notch, TGFβ, Hedgehog) [18]. β-Arrestin 2 is essential for normal insulin secretion by pancreatic β-cells [19]. Furthermore, it inhibits the glucagon receptor signaling and helps maintain euglycemia [15]. However, according to the literature data, β-arrestin 2 has a multidirectional effect on inflammation, functioning as both pro- and anti-inflammatory factor.In inflammatory models, mice with the global β-arrestin 2 gene (*Arrb2*, arrestin beta 2) knockout showed the increased expression of pro-inflammatory markers (IL6, IL1 β, TNFα) and the inhibitor of NF-κB kinases β (IKKβ) [20]. Conversely, in mouse fibroblasts the β-arrestin 2 expression is essential for NF-κB activation through the lysophosphatidic acid (LPA) receptor [21]. β-Arrestin 2 has also been shown to stimulate proliferation and migration of smooth muscle cells (SMCs) from the media to the intima, increasing the atherosclerotic lesion extent [22].

Thus, the study aimed to assess the pro-inflammatory state of Arrb2-knockout mice in the context of long-term streptozotocin-induced diabetes mellitus.

METHODS

Animals

The experiments involved male C57BL/6J mice and mice with the global knockout of the *Arrb2* gene (*Arrb2-/-*) obtained on the C57BL/6J genetic background (body weight 15–25 g, age 8 weeks). The animals were kept under standard vivarium conditions at the temperature of 22 °C with the 12-h light/dark cycle and *ad libitum* access to food and water. The *Arrb2-/-* lineage used had been earlier verified using PCR and Western blot [23].

Induction of Diabetes Mellitus

Animals were randomly allocated into four groups: two non-diabetic controls — wild-type (WT) and *Arrb2*-knockout (KO) — and two diabetic experimental groups — wild-type with diabetes (WTd) and *Arrb2*-knockout with diabetes (KOd). Diabetes was induced by intraperitoneal (i.p.) injection of streptozotocin (STZ) over five consecutive days. Animals were fasted for 4 h prior to each injection. The WTd and KOd groups received i.p. injections of STZ (Sigma-Aldrich, St. Louis, MO, USA) dissolved in freshly prepared 50 mM sodium citrate buffer (pH 4.5) at a dose of 55 mg/kg. The WT and KO control groups received an equivalent volume of citrate buffer.

Blood glucose levels were measured on days 1, 5, 10, 18, 25, 32, and 39 following the initiation of STZ administration using a Diacont Classic 2598 glucometer (Diacont, Taiwan). Body weight was monitored at the same time points (Fig. 1). Blood samples were collected by lateral tail vein puncture using a 27G needle, following a 4 h fast.

Assessment of Systemic Inflammation

Systemic inflammation was assessed by determining the neutrophil percentage in peripheral blood smears prepared from lateral tail vein blood at the same time points as glucose measurements. Smears were fixed with methanol (FisherChemical, Germany), stained with the Giemsa dye (PanEco, Russia) for 10–15 min and analyzed with the 400× magnification. The slides were coded before microscopy assessment; the researcher, who counted the white blood cell differential, had no information about the sample belonging to the experimental group. The cells were enumerated manually using the WBC Counter software (Kazuyoshi Sasaoka, Japan), until the total white blood cell count reached 100; after that the percentage of neutrophils was calculated. The following values were considered as reference values for adult C57BL/6J mice: segmented neutrophils — 8–20%, lymphocytes — 76–91% [24]. To analyze the dynamic changes in the neutrophil link, the share of neutrophils was further normalized to the individual value obtained for the same animal on day 1 of the experiment.

RNA Extraction and RT-qPCR

mRNA expression levels of pro-inflammatory cytokine genes (*Il6*, *Il1b*, *Tnf*) and protease-activated receptor genes (*Par1*, Par4) were assessed by reverse transcription quantitative polymerase chain reaction (RT-qPCR). Hippocampal and right hemisphere cerebral cortex samples were homogenized in the ExtractRNA reagent (Evrogen, Russia); total RNA was extracted in accordance with the manufacturer's protocol. RNA concentration and purity were assessed using a Nanodrop spectrophotometer (Thermo Fisher Scientific, USA); only

Table. Primers used for RT-PCR

Gene	Forward primer (5'→3')	Reverse primer (5'→3')
Il6	AGGACCAAGACCATCCAATTCA	CGCACTAGGTTTGCCGAGTA
Par1	GTCGCTTCCACGAAAGTCCT	CACAGACAGAACACGGGACA
Par4	CAGCCCTAGACACCCTGATTT	AGACACCCATCATCCTTTGGC
Il1b	GCCTGTGTTTTCCTCCTTGC	GCTGCCTAATGTCCCCTTGA
Tnf	ACCTGGCCTCTCTACCTTGT	GATTACAGTCACGGCTCCCG
Actb	ACTCTGTGTGGATTGGTGGC	GAAAGGGTGTAAAACGCAGCTC

samples with A260/280 = 1.8–2.0 and A260/230 = 1.8–2.2 were used for further analysis. To obtain sufficient RNA amouts, some specimens from the brain cortex and hippocampus were combined into pools.

After treatment with DNAse I (Thermo Fisher Scientific, USA) cDNA was synthesized using the MMLV RT kit (Evrogen, Russia). A Random(dN)10 and Oligo(dT)15 primer mix was used in the reverse transcription reaction.

The real-time PCR was conducted in the CFX Connect Real-Time PCR Detection System thermal cycler (Bio-Rad, USA) using SYBR Green I (5x qPCRmix-HS SYBR mixture; Evrogen, Russia). The amplification specificity was controlled by melting curves; the matrix-free reaction was used as a negative control. The sequences of primers are provided in Table.

The efficiency of all primer pairs was 95–105%. Expression levels were calculated by the ΔΔCq method involving normalization to the reference β-actin gene (*Actb*). All samples were analyzed in triplicate.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 8.0.1 (GraphPad Software Inc., USA). Data normality was assessed using the Shapiro–Wilk test, and outliers were identified using the ROUT method (Q = 1%). Statistical significance was estimated using the unpaired t-test or two-way ANOVA with the post-hoc Tukey's test; for unequal group sizes, the Tukey–Kramer test was applied, which was implemented automatically in GraphPad Prism. When performing the post-hoc analysis, the effect of both diabetes within each genotype (WT/WTd and KO/KOd) and of the genotype under appropriate conditions was assessed: WT/KO in the control and WTd/KOd against the background of diabetes. The differences were considered significant at $p < 0.05$. The figures show significant differences only.

RESULTS

Effect of *Arrb2* gene knockout on hyperglycemia development

Chronic hyperglycemia is the key damaging factor determining the development of diabetic complications in experimental animals. The STZ administration protocol used in this study produced sustained hyperglycemia in wild-type animals by day 10, with blood glucose reaching 17.06 ± 4.41 mmol/L, which corresponded to severe hyperglycemia. In KOd mice, blood glucose concentrations did not differ significantly from those of the KO control group until day 25. On day 25, KOd mice exhibited blood glucose of 12.93 ± 5.93 mmol/L, consistent with mild hyperglycemia, while severe hyperglycemia (17.28 ± 5.75 mmol/L) did not develop until day 32. By day 39, blood glucose in WTd animals (22.3 ± 8.09 mmol/L) was significantly higher than in KOd animals (14.37 ± 7.65 mmol/L) (Fig. 1).

The weight loss represents another symptom typical for type 1 DM, along with hyperglycemia. Therefore, this parameter was assessed regularly, along with changes in blood glucose concentration. In our study, comparison of days 1 and 39 of the experiment revealed the weight gain in all groups of animals. In WT and WTd animals, the increase was 3.23 ± 0.83 g and 0.84 ± 1.54 g; in KO and KOd it was 7.00 ± 0.79 g and 1.72 ± 1.46 g, respectively. Thus, diabetes significantly reduces the weight gain in both wild type and *Arrb2* knockout mice. Notably, weight gain in knockout mice throughout the experiment — with or without diabetes — was more than twice that of wild-type animals (Fig. 2). It should be also noted, that there were significant differences between the wild type and knockout animals was already present at baseline: on day 1, wild-type mice weighed 21.88 ± 1.37 g versus 18.81 ± 3.37 g in *Arrb2*$^{-/-}$ animals.

Effect of *Arrb2* gene knockout on systemic inflammation

Systemic inflammation was assessed by quantifying the neutrophil percentage in peripheral blood smears stained with Romanowsky–Giemsa stain. No significant differences in neutrophil counts between the WT and WTd groups were revealed both throughout the experiment and when comparing initial and final values. In contrast, KOd animals exhibited a significant increase in neutrophil percentage on day 18 compared with day 1 within the same group, and KOd neutrophil levels were significantly elevated relative to the KO control group (Fig. 3A). However, it should be noted that in the beginning of the experiment the baseline value of the percentage of neutrophils in blood of knockout mice was 2.6 times higher compared

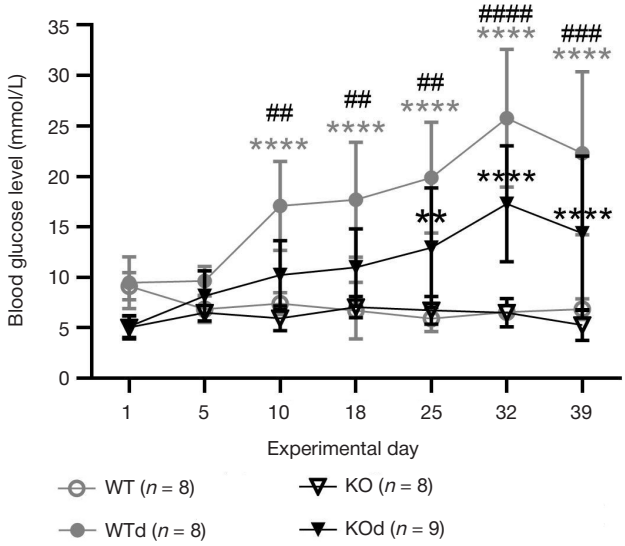

Fig. 1. Changes in blood glucose levels in mice in the control and streptozotocin (STZ)-induced diabetes groups. Two-way ANOVA, Tukey's test. ** — $p < 0.01$; **** — $p < 0.0001$ (WT/WTd and KO/KOd comparison); ## — $p < 0.01$; ### — $p < 0.001$; #### — $p < 0.0001$ (WTd/KOd comparison)

to that of wild type animals: 40.8 ± 10.3% vs. 15.6 ± 5.3%, respectively (Fig. 3B).

mRNa Expression of *Il6*, *Il1b*, and *Tnf* in the cortex and Hippocampus

The real-time PCR was used to assess the expression of the genes encoding pro-inflammatory cytokines IL6, IL1β, and TNFα. No significant differences in the mRNA expression of the test genes in the brain between the WT and WTd groups were observed. At the same time, the KOd mice with diabetes had a significantly increased expression of the *Il6* and *Il1b* mRNA in the cerebral cortex compared to the KO group. Furthermore, *Il6*, *Il1b*, and *Tnf* mRNA expression in the hippocampus and *Tnf* expression in the cerebral cortex was significantly higher in KO mice compared to the WT group and in KOd mice compared to WTd animals (Fig. 4).

mRNA Expression of *Par1* and *Par4* in the cortex and hippocampus

Par1 and *Par4* mRNA expression in both the cerebral cortex and hippocampus was significantly elevated in *Arrb2*-knockout mice compared with wild-type animals, both under baseline conditions and under diabetic conditions. In addition, the KOd group showed a statistically significant increase in *Par4* mRNA expression in the hippocampus compared with the KO control group (Fig. 5).

DISCUSSION

The dynamics of the blood glucose level increase in the wild type animals administered STZ that was reported in our study was consistent with those reported for the standard multiple low-dose STZ protocol [25]. An unexpected and seemingly paradoxical observation was the delayed development of hyperglycemia in *Arrb2* knockout mice. In these animals, severe hyperglycemia developed only by day 32, and final glucose levels were significantly lower than in wild-type animals (Fig. 1). Such a result would seem to contradict the established role

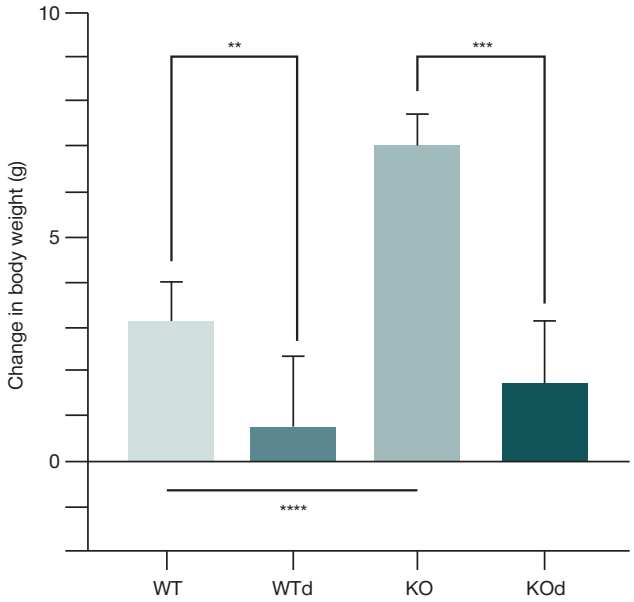

Fig. 2. Changes in body weight of animals in the studied groups (difference between final and initial days of the experiment). Data are presented as the mean ± standard deviation. Two-way ANOVA, Tukey's test. ** — $p < 0.01$; **** — $p < 0.0001$

of β-arrestin 2 as a positive regulator of glucose-dependent insulin secretion: This protein is involved in the activation of calmodulin-dependent protein kinase II (CaMKII) in β-cells and maintaining the normal β-cell function under physiological conditions [19, 26]. However, in the STZ-induced diabetes model the key factor of the hyperglycemia progression is not so much the insulin secretion functional insufficiency, but the damage and death of β-cells. STZ that is selectively taken up by β-cells via the GLUT2 low-affinity glucose transporter induces nitrosative and oxidative stress, activation of MAPK-dependent signaling cascades, and DNA damage [27]. That is why we assume that the *Arrb2* knockout protective effect is associated not with the β-cell functional state improvement, but the increase in their resistance to the STZ cytotoxic effect.

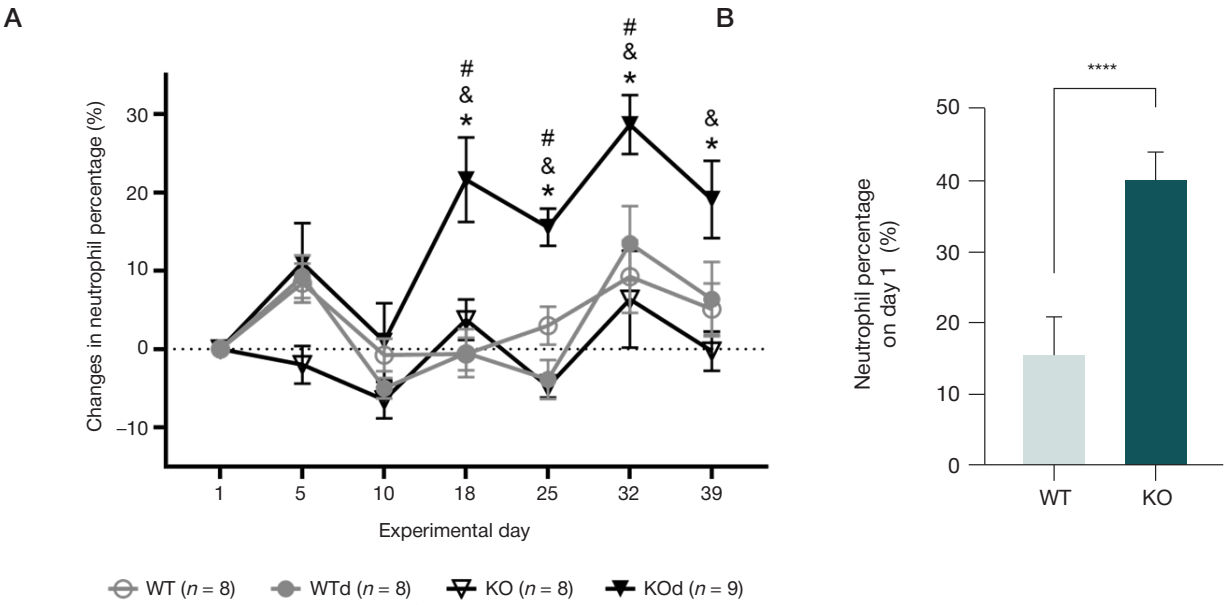

Fig. 3. Assessment of neutrophil levels in mice under diabetic conditions. A.Changes in neutrophil percentage (data normalized to day 1 values within each group) in the blood of control and STZ-induced diabetic mice. B. Neutrophil percentage in the blood of wild-type and Arrb2-knockout mice on day 1 of the experiment. Two-way ANOVA, Tukey's test. * — $p < 0.05$ (KO/KOd comparison); & — $p < 0.05$ (difference within the KOd group relative to day 1); # — $p < 0.05$ (WTd/KOd comparison). Data are presented as the mean ± standard deviation. Unpaired t-test. **** — $p < 0.0001$

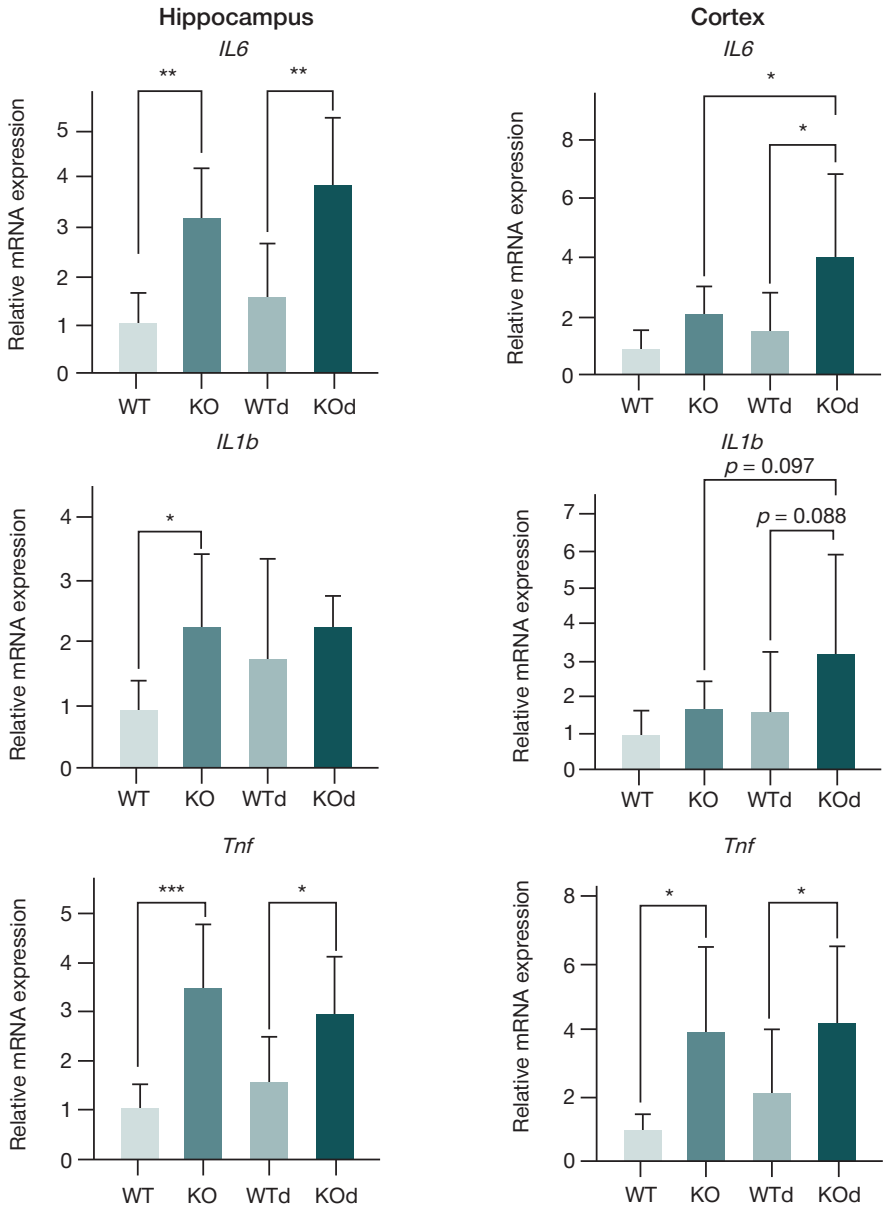

Fig. 4. Relative mRNA expression (fold change) of *Il6*, *Il1b*, and *Tnf* in the hippocampus and cerebral cortex of mice from the studied groups. Data are presented as values normalized to the expression of the reference β-actin gene. WT (n = 5–8); WTd (n = 5–8); KO (n = 5–8); KOd (n = 5–8). Data are presented as the mean ± standard deviation. Two-way ANOVA, Tukey's test. * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$

The oxidative stress modulation can play an important role in the delayed hyperglycemia development in knockout animals. CCl_4-induced hepatic fibrosis in *Arrb2*$^{-/-}$ mice was accompanied by less severe inflammation and cellular damage, attributed to reduced NADPH oxidase 4 (NOX4) levels [28]. NOX4 is one of the sources of ROS in β-cells, and the NOX4 inhibition promotesβ-cell survival in diabetes [29, 30]. Thus, the lack of β-arrestin 2 could reduce the severity of the STZ-induced NOX4-dependent oxidative damage.

Attenuation of proinflammatory signaling in pancreatic islets can be one more mechanism underlying the delayed hyperglycemia development in knockout mice. It is well known that β-arrestin 2 forms a complex with p38 MAPK and potentiates its activation [31]. This signaling cascade is also activated under the exposure to pro-inflammatory cytokines and stimulates β-cell disruption and hyperglycemia development [32]. The Mkk3 (gene of the MKK3 kinase activating p38 MAPK) knockout mice showed the STZ cytotoxic effect reduction due to the decrease in leukocyte infiltration of β-cells and pro-inflammatory cytokine production [33]. Therefore, activation of the p38 MAPK cascade in response to injury can be impaired in the *Arrb2-/-* mice, which contributes to the preservation of functionally active β-cells.

Despite the fact that in our study the knockout mice showed elevated systemic inflammation levels in blood plasma, local effects in the pancreatic islet microenvironment can be different. Perhaps, a decrease in the immune cell capability of infiltration and activation (mediated by p38 MAPK and NOX4 mechanisms) outweighs the systemic proinflammatory. Furthermore, β-arrestin 2 is involved in the neutrophil chemotaxis via internalization of chemokine receptors [34], and the lack of β-arrestin 2 could disturb the immune cell recruitment to the islets.

Thus, the delayed hyperglycemia development in the *Arrb2-/-* mice with the STZ-induced diabetes is likely to result from the combination of factors: oxidative stress reduction (via NOX4), attenuation of the p38 MAPK-dependent inflammation and impairment of the immune cell recruitment to the islets. This suggests that β-arrestin 2 promotes β-cell death under the conditions of toxic stress, and the lack of β-arrestin 2 has a

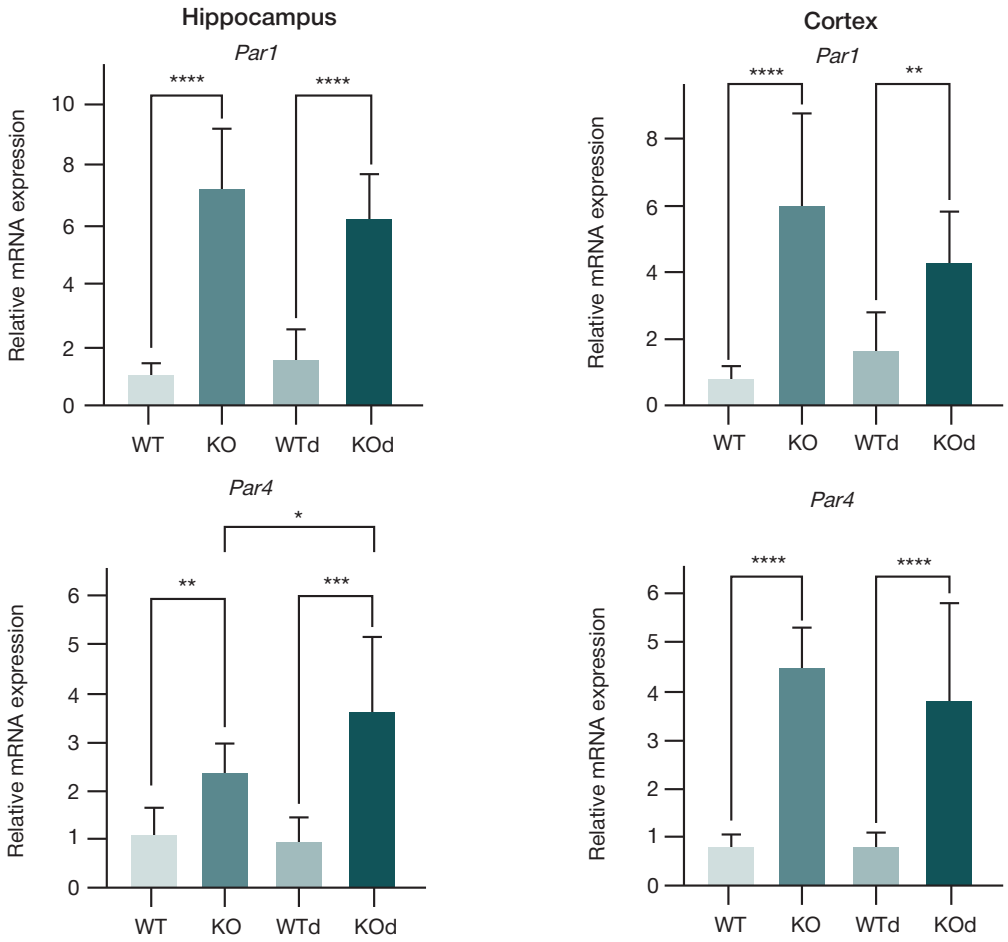

Fig. 5. Relative mRNA expression (fold change) of *Par1* and *Par4* in the hippocampus and cerebral cortex of mice from the studied groups. Data are presented as values normalized to the expression of the reference β-actin gene. WT (n = 5–8); WTd (n = 5–8); KO (n = 5–8); KOd (n = 5–8). Data are presented as the mean ± standard deviation. Two-way ANOVA, Tukey's test. * — $p < 0.05$; ** — $p < 0.01$; **** — $p < 0.0001$

protective effect, regardless of possible basal insulin secretion impairment reported under physiological conditions.

In our study, body weight increased in mice of all groups, which could be due to the fact that the animals continued growing in the 2th–3rd months of life. Diabetes significantly reduced the weight gain in mice with both genotypes compared to appropriate control groups (Fig. 2), which is in line with the classic concepts of metabolic disorder in T1D. It should be noted that the literature reports different variants of dynamic changes in body weight: from no changes to the weight gain or loss [25].

The more pronounced weight gain in knockout mice should be interpreted considering the baseline intergroup differences: in the beginning of the experiment the *Arrb2-/-* animals had significantly lower body weight compared to wild type mice. Furthermore, β-arrestin 2 is a negative regulator of the β3-adrenergic receptor (β3-AR) signaling pathway in adipocytes, the major functions of which are stimulation of lipolysis, thermogenesis and the increase of oxygen consumption by mitochondria. The β-arrestin 2 knockout results in the prolonged β3-AR signaling and stimulation of the brown adipose tissue formation, which, presumably, contributes to the decrease in the adipose tissue weight [35].

The more pronounced weight gain in *Arrb2-/-* mice is likely to result from a combination of factors. First, the knockout animals had a lower baseline weight, which could contribute to the higher relative growth in the active age-related growth phase typical for the C57BL/6J mice aged 5–12 weeks [36, 37]. Second, the development of severe hyperglycemia in *Arrb2-/-* animals was delayed, which was likely to be associated with the less severe catabolic effects of diabetes and contributed to better body weight preservation. Thus, the differences in the body weight dynamics can reflect not the direct effect of the lack of β-arrestin 2 on the growth, but the indirect effect on metabolic processes.

In our study, the STZ-induced diabetes had no significant influence on the neutrophil levels of wild type mice (Fig. 3A). The lack of the pronounced neutrophil response in WTd mice can be due to the fact that the model used is not associated with such a pronounced systemic inflammatory response, as models with the high-fat diet or autoimmune T1D models, despite the development of severe hyperglycemia. Furthermore, the follow-up period (39 days) may be insufficient for the development of chronic systemic inflammation, recorded by changes in the white blood cell differential.

In contrast to the effect of diabetes, the genotype factor had a significant influence on neutrophil levels. The *Arrb2-/-* mice had the significantly higher baseline neutrophil percentage compared to the wild type animals as early as on day 1 of the experiment (Fig. 3B), and against the background of diabetes, the KOd group showed further increase in this indicator compared to KO (Fig. 3A). The data obtained are consistent with the known role of β-arrestin 2 as a negative regulator of systemic inflammatory responses. It has been shown that β-arrestin 2 necessary for the internalization of chemokine receptors CXCR1 and CXCR2. In *Arrb2-/-* mice, disruption of this mechanism leads to the enhanced chemotaxis of neutrophils to the sites of inflammation and the increased IL8,

IL6, and TNFα production [38, 39]. Thus, the lack of β-arrestin 2 creates a pro-inflammatory background, which can be further enhanced under the conditions of diabetes.

To understand our results, it is important to note that the literature describes multidirectional changes of neutrophils in diabetes. In DM, the production of pro-inflammatory cytokines by neutrophils may be increased [40] and the recruitment of leukocytes to the site of inflammation can be enhanced [41]. However, under different conditions, including early-stage T1D [42] or the HbA1c decrease ≥ 1.5% associated with the glucose-lowering drug therapy, the counts of circulating leucocytes and neutrophils may decrease [43]. These data emphasize the the complexity of neutrophil regulation in diabetes and the importance of taking into account both the disease model and genetic factors when interpreting the results.

The analysis of the expression of pro-inflammatory markers in brain tissues revealed a significant increase in the *Il6*, *Il1b*, and *Tnf* gene mRNA levels in the brain cortex and hippocampus of the *Arrb2* knockout mice, both control and diabetic (Fig. 4). In wild type animals, the diabetes induction did not lead to significant changes in the studied cytokine mRNA expression. The data obtained suggest that the genotype represents the key factor determining the pro-inflammatory state in the studied brain regions, and the lack of β-arrestin 2 creates the baseline pro-inflammatory background. A similar pattern was reported for the protease-activated receptors (PAR). The *Par1* and *Par4* gene mRNA expression was significantly increased in the brain cortex and hippocampus of *Arrb2-/-* mice, both control and diabetic, relative to the wild type ones; the *Par4* expression in the hippocampus was further increased in the KOd group compared to the KO one (Fig. 5).

The results obtained are consistent with the well known role of β-arrestin 2 as a negative regulator of inflammatory responses in the CNS. According to the literature data, β-arrestin 2 is an important negative regulator of the TLR4 (toll-like receptor 4)-mediated production of NLRP3 (NOD-like receptor family, pyrin domain containing 3 protein) [44]. Furthermore, β-arrestin 2 can bind directly to TRAF6 and decrease the NF-κB phosphorylation through inhibition of oligomerization and ubiquitination of TRAF6 (tumor necrosis factor receptor-associated factor 6), thereby further inhibiting the NF-κB pathway activation [45]. β-Arrestin 2 also suppresses astroglial activation through the G protein-independent dopamine D2 receptor signaling and disturbs the NLRP3 inflammasome assembly [46]. It has been shown that in *Arrb2-/-* mice, stimulation with LPS (lipopolysaccharides) causes the more pronounced neuronal death and microglial activation, associated with the increase in the levels of pro-inflammatory markers (IL6, IL1β, TNFα, and Nos2) and the decrease in the levels of anti-inflammatory markers (Arg1, Ym-1, and Mrc1) compared to wild type mice [20].

PAR1 and *PAR4* represent the G protein-coupled receptors activated by proteolytic cleavage. Thrombin is one of the major physiological activators of these receptors, and PAR1 shows higher affinity for thrombin, than PAR4 [47]. PARs have been found in both neurons and glial cells. Under pathophysiological conditions, the PAR1 activation in astrocytes stimulates the release of glutamate and production of the TNFα, IL6, IL1β, and iNOS pro-inflammatory cytokines. PAR4 stimulates the TNFα secretion, promotes the NF-κB transcription factor activation, causes the long-term increase in intracellular calcium levels, and increases the ROS production [48].

In aggregate, the data obtained suggest the β-arrestin 2 anti-inflammatory function in the central nervous system (CNS). The lack of β-arrestin 2 is associated with the increase in the baseline expression of mRNA of pro-inflammatory cytokines and PAR receptors in the cerebral cortex and hippocampus, which suggests the persistent pro-inflammatory phenotype formation. This effect is generally preserved against the background of STZ-induced diabetes. However, the *Par4* expression is further increased in the hippocampus of knockout animals, which suggests the receptor possible involvement in the response to diabetic hyperglycemia.

Taken together, the data allow us to come up with a common hypothesis explaining the seemingly conflicting *Arrb2* knockout effects. β-Arrestin 2 functions as a dual regulator having tissue-specific effects: in the pancreas, it contributes to the β-cell death through the NOX4-dependent oxidative stress increase and the p38 MAPK signaling potentiation under the oxidative stress conditions, while in the immune cells and the CNS it functions as a negative regulator of inflammatory responses. The lack of β-arrestin 2 simultaneously increases the β-cell resistance to STZ and removes the inhibitory control over inflammatory cascades, which manifests itself both at the systemic level (in the form of the increased percentage of neutrophils) and locally in the CNS (in the form of the increased expression of mRNA of pro-inflammatory cytokines and PAR receptors). We assume that the systemic inflammatory background resulting from disturbances of the β-arrestin 2-dependent internalization of chemokine receptors [39, 49] sets the stage for the increased glial cell activation and increased *Par1* and *Par4* expression in the cerebral cortex and hippocampus. Thus, the β-arrestin 2 deficiency shifts the tissue-specific balance of its pro- and anti-inflammatory functions depending on the predominant pathological stimulus, which determines both protective metabolic phenotype and stronger pro-inflammatory state in the CNS.

Study limitations

A number of limitations should be acknowledged when interpreting the results. First, we used a global *Arrb2* knockout model, which makes it impossible to delineate the contribution of β-arrestin 2 in distinct cell types, including β-cells of the pancreas, immune cells, neurons, and glial cells. Second, the hypothetic involvement in the NOX4-dependent oxidative stress, p38 MAPK signaling, and immune cell recruitment was not assessed directly; we also did not conduct histological assessment of the pancreas with the evaluation of β-cell mass, apoptosis, and pancreatic islet infiltration. Third, the pro-inflammatory cytokine and PAR expression was assessed at the mRNA level without determining the levels of appropriate proteins. Furthermore, the diabetic phenotype was characterized based on the blood glucose levels and dynamic changes in body weight without any additional metabolic tests. Finally, the study involved male mice only, which makes it impossible to estimate possible sex-related differences.

CONCLUSIONS

In this study, the streptozotocin-induced diabetes model was used to show that global knockout of the β-arrestin 2 gene resulted in the delayed hyperglycemia development. Additionally, β-arrestin 2 deficiency is associated with elevated basal systemic inflammation and formation of a pro-inflammatory transcriptional profile in the CNS, characterized by increased mRNA expression of *Il6*, *Il1b*, *Tnf*, *Par1*, and *Par4*, which may reflect enhanced neuroinflammatory signaling in the cortex and hippocampus. Under diabetic conditions, knockout animals exhibited an additional increase in *Par4* expression in the hippocampus, suggesting a potential role of β-arrestin 2–PAR4-dependent mechanisms in neuroinflammation under hyperglycemic conditions. These findings open avenues for further investigation of the role of β-arrestin 2 in the pathogenesis of diabetic complications.

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