

Communication

Blue Light Irradiation Exacerbates STZ-Induced Type 1 Diabetes via the β -Catenin Pathway Initiated by Gp91phox-Derived Reactive Oxygen Species

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Abstract

Background/Objectives: Diabetes is classified into type 1 and type 2 diabetes. Type 1 diabetes is an autoimmune disease that develops in young people. While several factors are known to worsen type 1 diabetes, the effects of blue light remain unclear. This study aimed to explore this literature gap. **Methods:** In this study, we examined the effects of blue light exposure on diabetes using streptozotocin-induced type 1 diabetic mice. Furthermore, we used gp91phox^{-/-} mice to investigate the cause of blue light-induced diabetes exacerbation. **Results:** Blue light exposure exacerbated type 1 diabetes and activated the gp91phox/reactive oxygen species (ROS)/complement component 1/wingless-type MMTV integration site family, member 5A (Wnt5a)/ α -catenin or peroxisome proliferator-activated receptor γ pathway in the liver and the gp91phox/ROS/DKK1/Wnt3a/ α -catenin pathway in the pancreas, resulting in decreased β -catenin expression. These results indicated that blue light exacerbates type 1 diabetes by activating Wnt5a in the liver and decreasing Wnt3a in the pancreas. The use of gp91phox^{-/-} was shown to cancel the worsening of diabetic symptoms caused by blue light. **Conclusions:** These results suggest that type 1 diabetes worsens with blue light and that this is due to the activation of gp91phox by blue light.

Keywords: gp91phox; wingless-type MMTV integration site family; member 5A; wingless-type MMTV integration site family; member 3A; β -catenin

1. Introduction

In recent years, the use of light-emitting diodes (LEDs) has become widespread. LEDs emit more blue light (visible light with wavelengths of 380–495 nm) than fluorescent or incandescent lights. Similarly, the liquid-crystal display screens of computers and smartphones also emit a lot of blue light [1,2]. In modern society, the use of computers and smartphones has increased due to changes in work styles, with most information now being accessed via smartphones. Additionally, the popularity of computer games has dramatically increased our exposure to blue light.

Generally, exposure to the blue light in morning sunlight helps reset the body clock [3–5]. Furthermore, about 12 h later, the body secretes a hormone called melatonin, which promotes sleep and facilitates a restful night. Exposure to blue light at night can disrupt the body clock, leading to various problems such as sleep disorders and obesity [6–10]. Continued exposure to blue light from the smartphone screen at night, even after the



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natural sunset (nighttime), can create a perception of daytime in the brain. This results in the disruption of the body clock, which, in turn, reduces the function of insulin, a hormone that lowers blood sugar levels; this increases the risk of diabetes and obesity [11].

Regarding diabetes, the International Diabetes Federation (IDF) estimated that in 2017, the prevalence of diabetes among the 4.84 billion people aged 20 to 79 out of a world population of 7.5 billion was 8.8% and the number of people with diabetes was 425 million. The prevalence of prediabetes was 7.3%, meaning that approximately 800 million people worldwide are affected by diabetes [12]. Diabetes can lead to complications such as microvascular disease (diabetic neuropathy, retinopathy, diabetic nephropathy) [13], macrovascular disease (cerebrovascular disease, coronary artery disease, peripheral arterial disease) [14], and diabetic foot disease [15]. These diabetic complications are serious and life-threatening diseases, so it is extremely important to prevent and improve diabetes.

In this study, we used the streptozotocin (STZ)-induced type 1 diabetes model as a type 1 diabetes model. STZ is the most common drug, and the STZ-induced type 1 diabetes model shares many similarities with human type 1 diabetes in terms of clinical symptoms, disease process, and morphological changes in pancreatic islets [16]. Furthermore, STZ specifically damages pancreatic islet B cells in animals, making it possible to induce type 1 diabetes in animals [17].

In our previous study, we reported that blue light exposure aggravated type 1 diabetes in STZ-induced type 1 diabetes model mice [18]. It activated insulin-like growth factor-1 and reactive oxygen species (ROS)/caspase 3/apoptosis/endothelial-monocyte activating polypeptide II/neutrophil/neutrophil extracellular trap (NET)-associated cell death (NETosis) system signaling; it also increased the expression of angiopoietin-like protein 2 (Agptl2). These results indicate that blue light worsens type 1 diabetes by increasing NETosis production and the expression of Agptl2.

However, the downstream mechanism by which blue light exacerbates type 1 diabetes mellitus via neutrophils remains unclear. To confirm these results, we administered DNase1, which breaks down NETs, to reduce NETosis. This attenuated the blue light-induced exacerbation of diabetes, but it did not eliminate the effects. Furthermore, previous studies have reported that the formation of NETosis is low in humans and that NETosis is quickly removed by DNase [19,20]. As described above, blue light induces various biological effects by inducing NETosis, but signal transduction from neutrophils is complex. Therefore, in this study, we focused on neutrophil-derived gp91phox to investigate the effects of blue light on neutrophils other than NETosis induction. We investigated the effects of gp91phox upon blue light irradiation and the organs in which it exerts its effects.

2. Materials and Methods

2.1. Animal Experiments

Nine-week-old male C57BL/6j mice (gp91phox^{+/+} mice) (SLC, Hamamatsu, Shizuoka, Japan) and gp91phox^{-/-} mice (Jackson Laboratories, Bar Harbor, ME, USA) were used for the experiments. The mice were maintained on a 12 h light/12 h dark cycle at 23 ± 1 °C under specific-pathogen-free conditions, and all animals were allowed free access to laboratory chow (rodent diet EQ 5L37; SLC, Hamamatsu, Shizuoka, Japan) and water during the experiments. Mice were categorized into six groups of five animals each: gp91phox^{+/+} group, gp91phox^{+/+} + STZ-treated group, gp91phox^{+/+} + STZ-treated + blue light-irradiation group, gp91phox^{-/-} group, gp91phox^{-/-} + STZ-treated group, and gp91phox^{-/-} + STZ-treated + blue light-irradiation group. A fluorescent lamp with blue LED light (wavelength: 380–500 nm, peak emission wavelength: 479 nm, 40 kJ/m², ISLM-150X150-BB, CCS Inc., Kamigyo-ku, Kyoto, Japan) was used as the light source. The LED light energy was measured using a photoanalyzer LA-105 (Nippon Medical and Chemical Instruments Co., Ltd.,

Osaka, Japan). Additionally, the control and STZ-treated mice were exposed to fluorescent light used in normal breeding. For 28 days from STZ administration to the end of the study, the mice's entire bodies were irradiated with blue LED light every day (10 min per day) (Figure 1). Since there was no difference in the effects of STZ between the groups exposed to fluorescent lamps and LED light of wavelengths other than blue light, this study was conducted with exposure to blue light only [18]. In this study, 40 kJ/m² was used as the most effective and minimal energy for blue light exposure to affect living organisms [18]. Our laboratory's irradiation device can irradiate 40 kJ/m² of energy in a 10 min exposure. This energy amount is twice the amount of shade we measured and half the total amount of room lighting (LED), television, fluorescent light, computer, and smartphone. Therefore, it is thought to reflect a typical daily environmental exposure. The exposure was also directed at the entire body, including the skin and eyes. This study was approved by the Suzuka University of Medical Science Animal Experiment Ethics Committee on 25 September 2014, and was conducted in strict accordance with the "Guidelines for the Care and Use of Laboratory Animals at Suzuka University of Medical Science" (approval number: 34). All mouse surgeries were performed under isoflurane anesthesia, and efforts were made to minimize the pain of the animals.

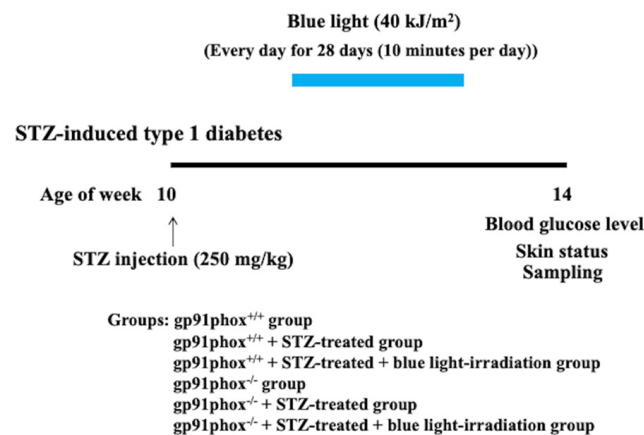


Figure 1. Schematic of the experimental procedure. STZ, streptozotocin.

2.2. Preparation of Pancreas and Liver Samples and Staining

On the final day of the experiment, pancreas and liver samples were harvested under anesthesia. Samples were fixed in 4% phosphate-buffered paraformaldehyde and embedded in Tissue Tek OCT compound (Sakura Finetek, Tokyo, Japan), followed by cryosectioning. Sections were stained with hematoxylin and eosin according to established procedures for histological analysis of skin. Other sections were stained with antibodies for immunohistological analysis as previously described [21]. Pancreatic specimens were incubated with mouse monoclonal anti-lymphocyte antigen 6 complex locus G6D (Ly6G; neutrophil marker) (1:100, BD Biosciences, Franklin Lakes, NJ, USA), rabbit polyclonal anti-Wnt5a (1:100, Abcam, Cambridge, MA, USA), rabbit monoclonal anti-Wnt3a (1:100, Cell Signaling Technology, Denver, MA, USA), rabbit polyclonal anti-pan protein kinase C (PKC) (1:100, Proteintech, Rosemont, IL, USA), rabbit polyclonal anti-activate Ca^{2+} /calmodulin-dependent protein kinase (CaMK) 2 (1:100, Proteintech), rabbit polyclonal anti-peroxisome proliferator-activated receptor (PPAR) γ (1:100, Bioss Inc., Woburn, MA, USA), mouse monoclonal anti-complement component 1q (C1q) (1:100, Abcam), or rabbit polyclonal anti-gp91phox (1:100, Bioss Inc.) primary antibodies. Samples were washed and then incubated with fluorescein isothiocyanate-conjugated anti-mouse or anti-rabbit secondary antibodies (1:30, Dako Cytomation, Glostrup, Denmark). The expression levels of Ly6G, Wnt5a, Wnt3a, pan-PKC, CaMK2, PPAR γ , C1q, and gp91phox were assessed

immunohistochemically using a fluorescent microscope. Additionally, the expression of Ly6G, Wnt5a, Wnt3a, pan-PKC, CaMK2, PPAR γ , C1q, and gp91phox was quantified by visualizing staining in five random fields with a constant area using ImageJ software version 1.53 (National Institutes of Health, Bethesda, MD, USA). Briefly, the original files were converted to monochrome 8-bit files. Then, a luminosity threshold was arbitrarily set. The areas above the threshold were measured for each sample. In this study, these areas were defined as “intensity.”

2.3. Measurement of ROS Levels and Hydrogen Peroxide (H₂O₂) in Plasma and β -Catenin in Pancreas

At the end of the experiment, blood, as well as pancreatic and liver tissue samples, were collected. Blood samples were centrifuged at 3000 $\times$ g for 10 min at 4 °C to separate plasma, which was used for further analysis. ROS and H₂O₂ concentrations were measured using the OxiSelect™ STA-347 in vivo ROS/RNS Assay Kit (Cell Biolabs, Inc., San Diego, CA, USA) according to the manufacturer's instructions. Pancreatic and liver samples were homogenized at 15,000 $\times$ g for 15 min at 4 °C, and the supernatants were collected and used for analysis. Tissue levels of β -catenin were measured using a commercial kit (Cusabio, Houston, TX, USA) according to the manufacturer's instructions. Respective optical densities were measured using a microplate reader (Medical Devices, Sunnyvale, CA, USA).

2.4. Statistical Analysis

All data are presented as mean $\pm$ standard deviation. Statistical significance between groups was determined using two-way analysis of variance followed by Tukey's post hoc test (SPSS version 20, IBM, Armonk, NY, USA). *p*-values < 0.05 (*) and <0.01 (**) were considered statistically significant.

3. Results

3.1. Effect of Blue Light Radiation on Body Weight, Water Intake, Urine Production, and Blood Glucose Levels in Gp91phox^{-/-} Mice with STZ-Induced Type 1 Diabetes

The body weight (Figure 2a,b), water intake (Figure 2c,d), urine production (Figure 2e,f), and blood glucose (Figure 2g,h) levels in gp91phox^{+/+} and gp91phox^{-/-} mice with STZ-induced type 1 diabetes were measured. In both the gp91phox^{-/-} and gp91phox^{-/-} groups, weight loss was observed in the STZ + blue light group compared with the control group. In STZ-induced type 1 diabetic gp91phox^{+/+} mice, water intake, urine volume, and blood glucose levels increased, and blue light exposure further elevated these values, exacerbating diabetes. However, in gp91phox^{-/-} mice, these diabetic indicators were reduced, and the increase due to blue light exposure was cancelled.

3.2. Effect of Blue Light Radiation on Conditions of Pancreas and Liver in Gp91phox^{-/-} Mice with STZ-Induced Type 1 Diabetes

Macroscopic observation of liver and pancreas samples from gp91phox^{+/+} mice revealed scattered tissue degeneration in both the pancreas and liver of STZ-treated mice (Figure 3a,b). In the pancreas, this degeneration included degeneration of the exocrine pancreatic gland, morphological abnormalities of the main pancreatic duct, and local inflammation (yellow arrow), while in the liver, fat accumulation and increased inflammation (yellow arrow) were observed. Furthermore, blue light irradiation was observed to expand the degenerated areas. Contrastingly, in gp91phox^{-/-} mice, there was little tissue degeneration in STZ-treated mice, and no expansion of the degenerated areas was observed with blue light. Aside from a slight tissue degeneration observed in STZ-treated gp91phox^{-/-} mice, there was no difference between them and the control group (Figure 3c,d).

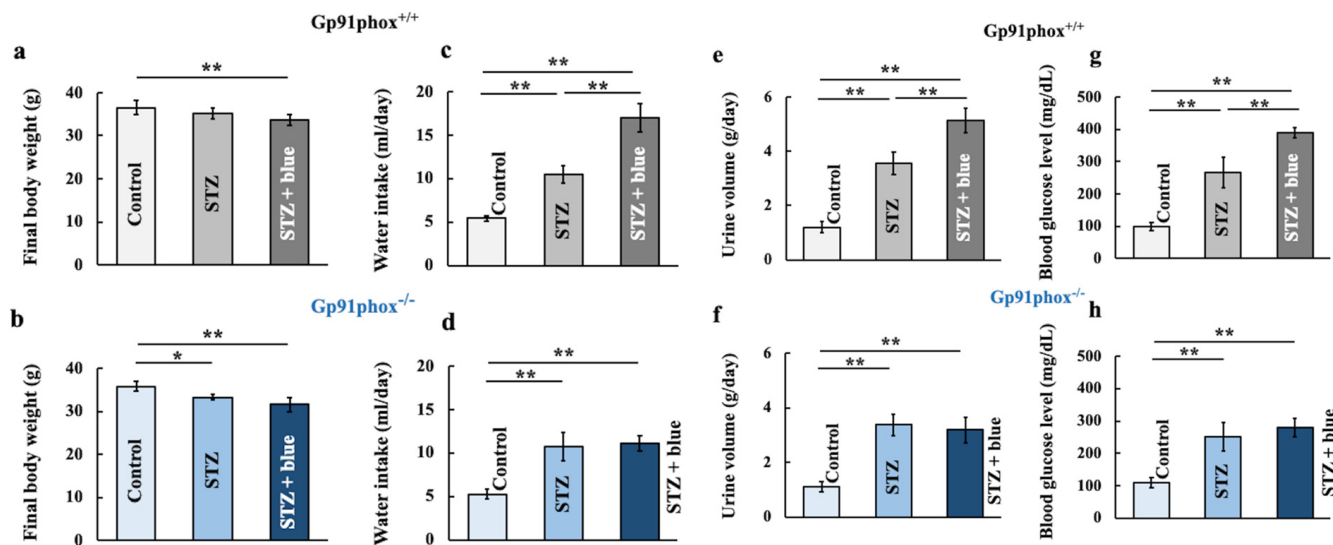


Figure 2. Effect of blue light irradiation on body weight (a,b), water intake (c,d), urine production (e,f), and blood glucose levels (g,h) in *gp91phox*^{+/+} or *gp91phox*^{-/-} mice with streptozotocin (STZ)-induced type 1 diabetes. The values are expressed as means $\pm$ SD for five animals. ** $p < 0.01$. * $p < 0.05$. SD, standard deviation.

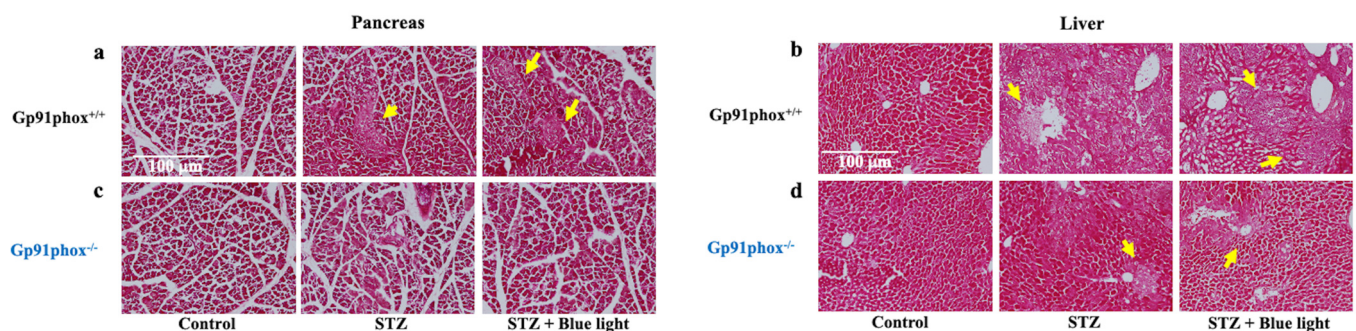


Figure 3. Effect of blue light on the histology of pancreas (a,c) and liver (b,d) from *gp91phox*^{+/+} or *gp91phox*^{-/-} mice with streptozotocin (STZ)-induced type 1 diabetes. Scale bar = 100 μ m. Arrows indicate tissue damage (pancreas: beta cells, liver: hepatocytes).

3.3. Effect of Blue Light Radiation on the Levels of *Gp91phox*, Neutrophil (Ly6G), ROS, H_2O_2 and C1q in *Gp91phox*^{-/-} Mice with STZ-Induced Type 1 Diabetes

The expression of *Gp91phox* was significantly increased in both the liver and pancreas of *gp91phox*^{+/+} mice by blue light irradiation (Figure 4a,c). However, *gp91phox* expression was barely observed in *gp91phox*^{-/-} mice (Figure 4b,d). Neutrophil expression in both the liver and pancreas of *gp91phox*^{+/+} and *gp91phox*^{-/-} mice was increased by STZ administration and further increased by blue light irradiation (Figure 4e–h). Similarly, the expression of ROS, H_2O_2 , and C1q, which are involved in *gp91phox*, was significantly increased in both the liver and pancreas of *gp91phox*^{+/+} mice by blue light irradiation (Figure 4i–l). Although the expression levels of ROS, H_2O_2 , and C1q were low in *gp91phox*^{-/-} mice, they were increased by STZ treatment relative to the control group. The expression levels in the blue light-irradiated group were not different from those in the STZ-treated group (Figure 4m–p).

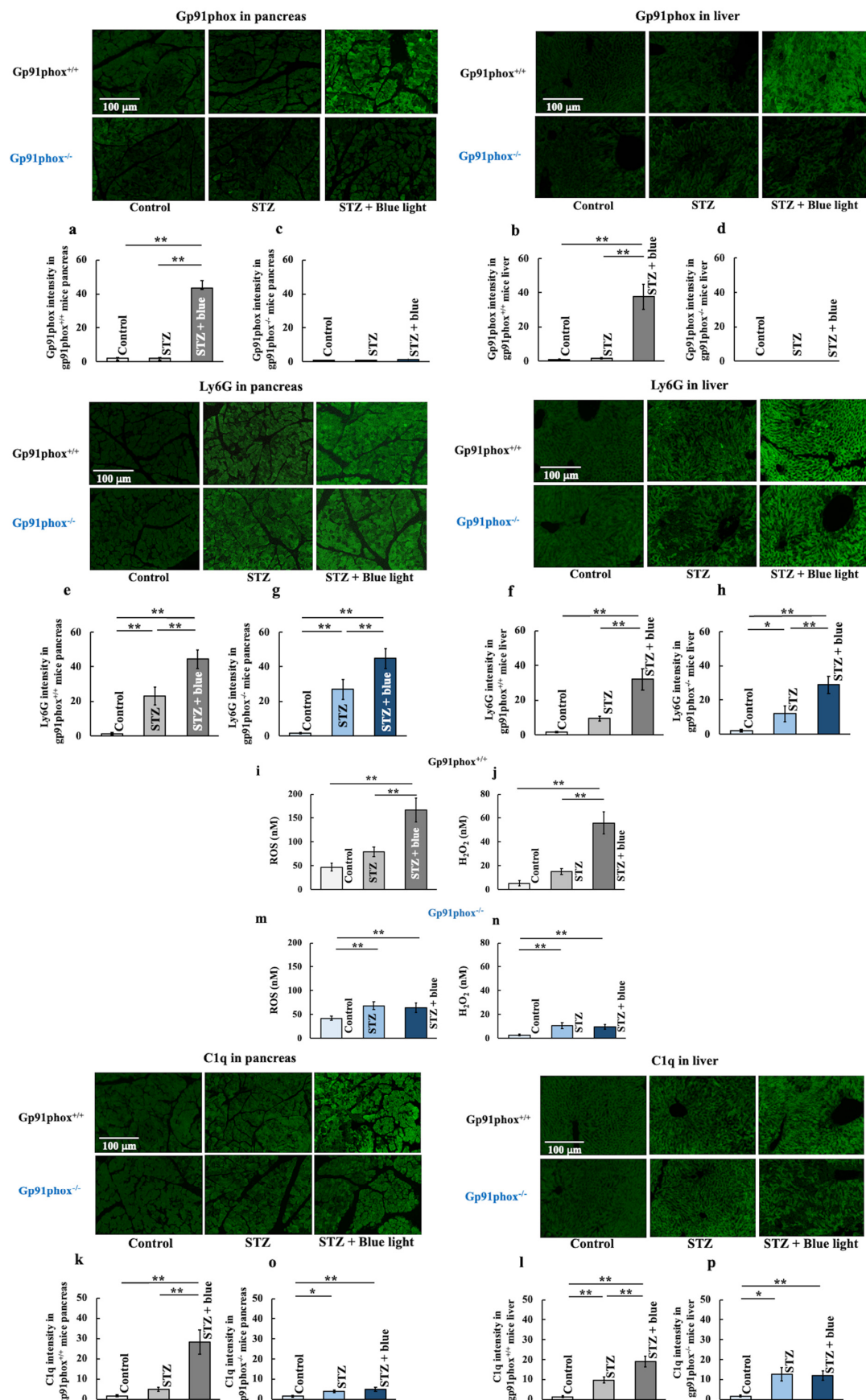


Figure 4. Effect of blue light radiation on the levels of gp91phox (a–d), Neutrophil (Ly6G) (e–h), ROS (i,m), H₂O₂ (j,n), and C1q (k,l,o,p) in gp91phox^{-/-} mice with STZ-induced type 1 diabetes.

Scale bar = 100 μ m. Arrows indicate tissue damage (pancreas: beta cells, liver: hepatocytes). The values are expressed as means $\pm$ SD for five animals. ** $p < 0.01$. * $p < 0.05$. ROS, reactive oxygen species; H_2O_2 , hydrogen peroxide; C1q, Complement component 1q.

3.4. Effect of Blue Light Radiation on the Levels of DKK1 and Wnt3a in the Pancreas and Liver of *Gp91phox*^{-/-} Mice with STZ-Induced Type 1 Diabetes

DKK1 expression in the pancreas of *gp91phox*^{+/+} mice was increased by STZ treatment and further increased in blue light + STZ-treated mice (Figure 5a,c). In *gp91phox*^{-/-} mice, pancreatic DKK1 expression remained unchanged in all groups (Figure 5b,d). However, Wnt3a expression in the pancreas of *gp91phox*^{+/+} mice was significantly increased by STZ treatment (Figure 5e,g). Blue light exposure also increased expression in the group compared to the control group, but decreased it compared to the STZ-treated group. In the pancreas of *gp91phox*^{-/-} mice, both STZ-treated and blue light + STZ-treated groups showed increased expression compared to the control group, but no difference was observed between the STZ-treated and blue light + STZ-treated groups (Figure 5f,h). Additionally, in the livers of *gp91phox*^{+/+} and *gp91phox*^{-/-} mice, no changes in DKK1 and Wnt3a expression were observed in any groups.

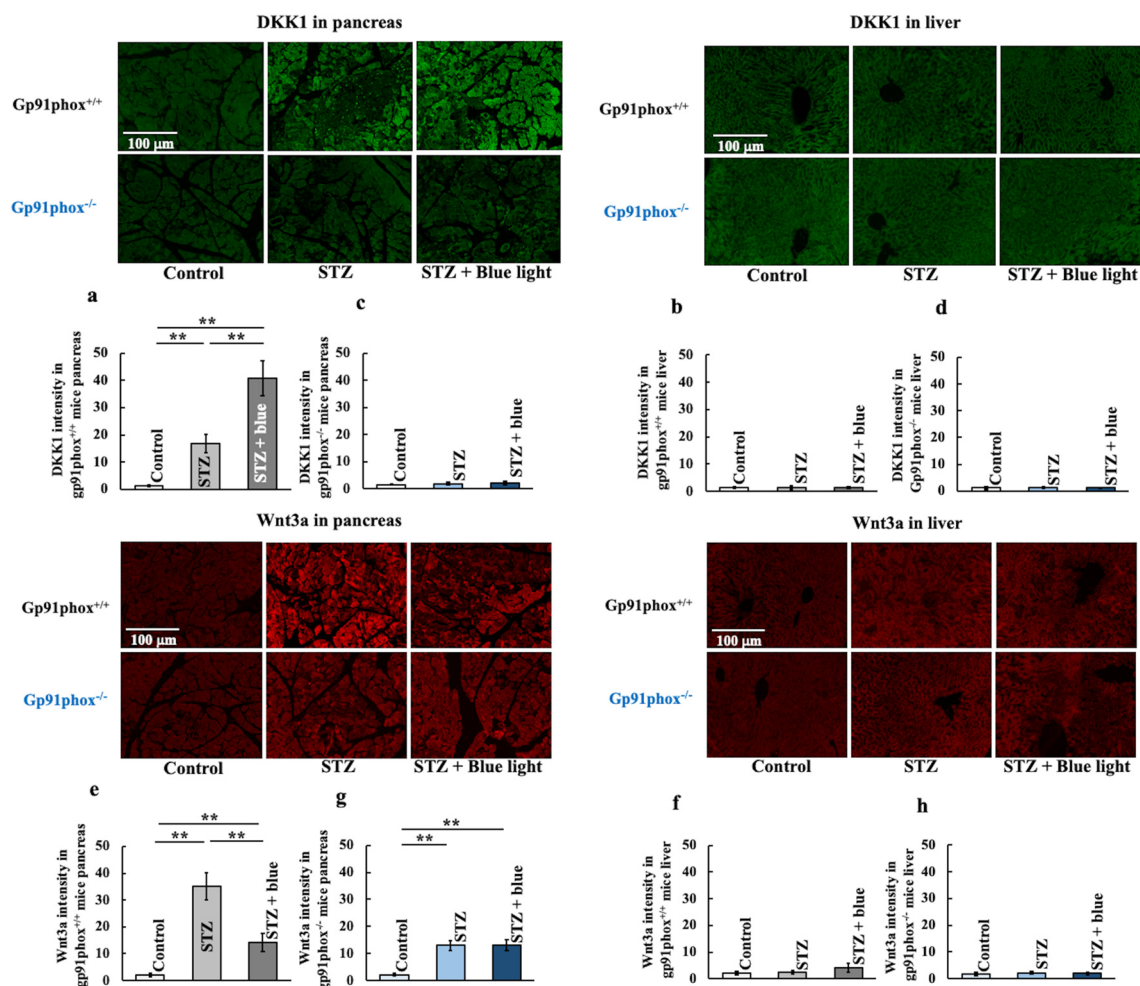


Figure 5. Effect of blue light radiation on the levels of DKK1 (a–d) and Wnt3a (e–h) in the pancreas and liver of *gp91phox*^{-/-} mice with STZ-induced type 1 diabetes. Scale bar = 100 μ m. The values are expressed as means $\pm$ SD for five animals. ** $p < 0.01$.

3.5. Effect of Blue Light Radiation on the Levels of Wnt5a, PKC, CaMK2, and PPAR γ in Liver of Gp91phox $^{-/-}$ Mice with STZ-Induced Type 1 Diabetes

The expression of Wnt5a in the liver was increased by STZ treatment and further increased by blue light irradiation in gp91phox $^{+/+}$ mice (Figure 6a). In gp91phox $^{-/-}$ mice, the expression level was increased by STZ treatment, but no further increase was observed with blue light irradiation (Figure 6e). Like Wnt5a, expressions of PKC (Figure 6b), CaMK2 (Figure 6c), and PPAR γ (Figure 6d) in the liver were also increased by STZ treatment in gp91phox $^{+/+}$ mice and further increased by blue light irradiation. However, no changes were observed across all groups in gp91phox $^{-/-}$ mice (Figure 6f–h). Additionally, in the pancreas of gp91phox $^{+/+}$ and gp91phox $^{-/-}$ mice, no changes in Wnt5a, PKC, CaMK2, and PPAR γ expression were observed in any groups (Figure 6i–p).

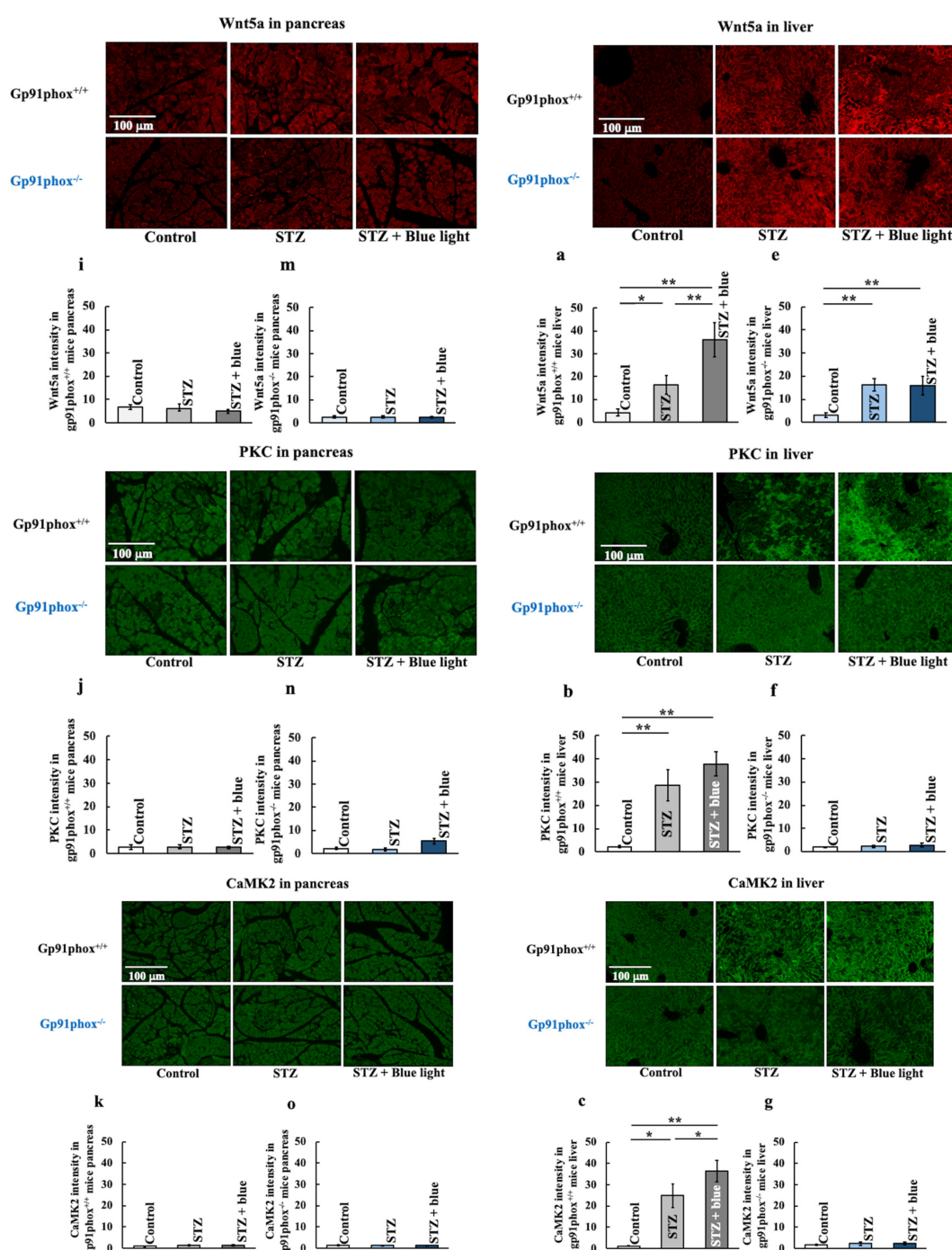


Figure 6. Cont.

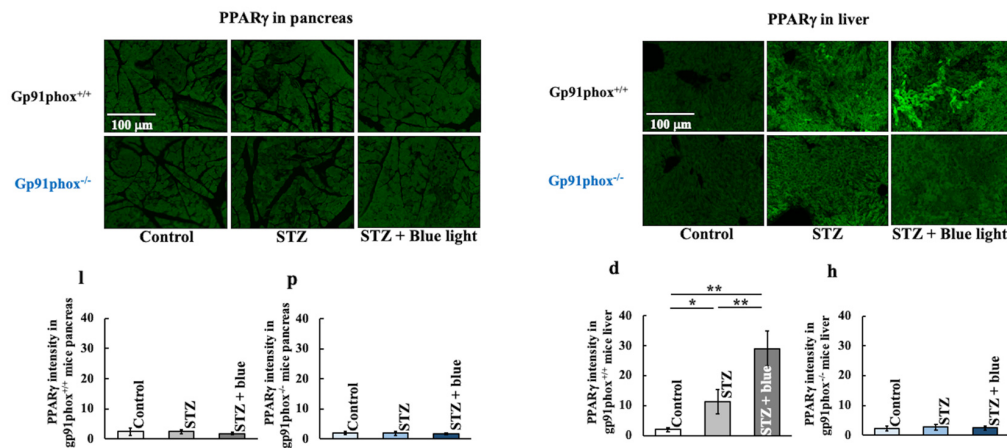


Figure 6. Effect of blue light radiation on the levels of Wnt5a (a,e,i,m), PKC (b,f,j,n), CaMK2 (c,g,k,o), and PPAR γ (d,h,l,p) in pancreas and liver of gp91phox $^{-/-}$ mice with STZ-induced type 1 diabetes. Scale bar = 100 μ m. The values are expressed as means $\pm$ SD for five animals. ** $p < 0.01$. * $p < 0.05$. PKC, protein kinase C; CaMK2, Ca $^{2+}$ /calmodulin-dependent protein kinase 2; PPAR γ , peroxisome proliferator-activated Receptor γ .

3.6. Effect of Blue Light Radiation on the Levels of β -Catenin in the Liver and Pancreas of Gp91phox $^{-/-}$ Mice with STZ-Induced Type 1 Diabetes

Finally, we investigated the β -catenin pathway mediated by Wnts and DKK1. In gp91phox $^{+/+}$ mice, β -catenin levels in both the liver and pancreas were increased by STZ administration, but decreased by STZ administration plus blue light irradiation, showing similar expressions as those observed in controls (Figure 7a,b). However, no changes were observed in the liver or pancreas of gp91phox $^{-/-}$ mice across all groups (Figure 7c,d).

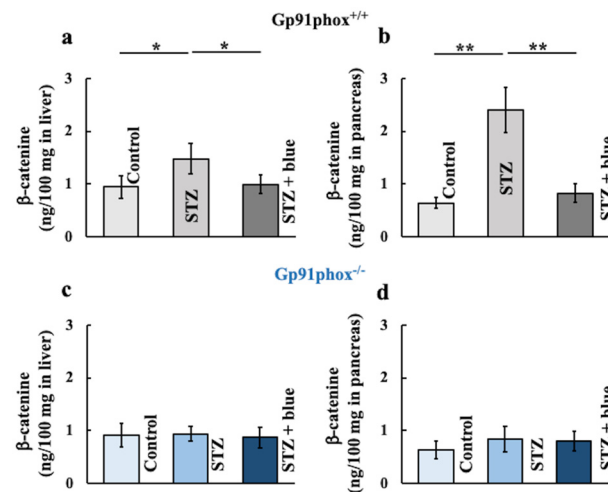


Figure 7. Effect of blue light radiation on the levels of β -catenin (a–d) in the liver and pancreas of gp91phox $^{-/-}$ mice with STZ-induced type 1 diabetes. The values are expressed as means $\pm$ SD for five animals. ** $p < 0.01$. * $p < 0.05$.

4. Discussion

In this study, we found that STZ-induced type 1 diabetes is exacerbated by blue light irradiation. In STZ-treated mice, the expression of gp91phox, ROS, and C1q was increased, and blue light irradiation further increased these expressions. In the pancreas, blue light irradiation increased DKK1 expression, and the levels of Wnt3 and β -catenin were decreased compared to the STZ-treated group. In the liver, blue light irradiation increased the expression of Wnt5a and PPAR γ , and the level of β -catenin was decreased compared to the STZ-treated group.

When cells are exposed to blue light, ROS are produced via mitochondria [22]. Furthermore, blue light increases ROS via NOX₂ (gp91phox; a component of NADPH oxidase) [23]. In this study, blue light irradiation was observed to increase gp91phox and ROS levels. In a high ROS environment, the expression of complement factors increases. C1q is the first protein in the complement system and is an important molecule involved in immune responses, cell removal, and suppression of inflammation. This C1q is closely related to ROS and increases with an increase in ROS [24]. This study showed that C1q carries out unique signaling in the liver and pancreas.

C1q acts as a pattern recognition molecule in the classical pathway of complement activation [25] and is known to activate Wnt signaling [26]. Wnts form a large family of evolutionarily conserved secreted proteins that induce cell signaling and affect diverse cellular responses. They are important in various pathological processes such as self-renewal/differentiation, disease, and oncogenesis [27–29]. The intracellular signaling pathways activated by Wnt include the β -catenin pathway (classical pathway), in which β -catenin controls gene expression; the PCP pathway, which controls planar cell polarity; and the Ca²⁺ pathway, which promotes intracellular Ca²⁺ mobilization [30]. The Ca²⁺ pathway involves Wnt5a mobilizing intracellular Ca²⁺, activating CaMK and PKC [31,32], and acting antagonistically against the β -catenin pathway [31]. In this study, blue light irradiation significantly increased Wnt5a in the liver, and the expression of CaMK2 and PKC was also increased. It is thought that the upregulation of these signaling activities reduced β -catenin and exacerbated diabetes. Furthermore, Wnt5 is known to activate histone methyltransferases via CaMK, which in turn suppresses the transcriptional activity of PPAR γ and inhibits the differentiation of mesenchymal stem cells into adipocytes [33,34]. PPAR γ thus contributes to the development of type 2 diabetes [35], and blue light-induced increase in PPAR γ expression may exacerbate not only type 2 diabetes but also type 1 diabetes, but further investigation is needed.

In the pancreas, no change in Wnt5a was observed with blue light irradiation, but a decrease in Wnt3a was observed. Wnt3a is involved in the β -catenin pathway, and in the absence of Wnt3a stimulation, the amount of β -catenin is maintained at a low level [30]. When Wnt3a binds to its receptor, Frizzled, or its co-receptor, low-density lipoprotein receptor-related protein (LRP) 5/6, dishevelled (Dvl) is recruited to the cell membrane. As a result, the function of the Axin complex is suppressed, and β -catenin is activated [30]. Additionally, blue light irradiation increased DKK1 expression in the pancreas. DKK1 inhibits Wnt signaling by binding to the Wnt co-receptor LRP5/6 and blocking the interaction between Wnt and the Wnt receptor Frizzled [36]. Therefore, the increase in β -catenin levels was suppressed, worsening diabetes. This increase in DKK1 is driven by an increase in ROS [37,38]. Therefore, it was speculated that blue light irradiation affects the gp91phox/neutrophil/ROS/DKK1/Wnt3a/ β -catenin signaling pathway in the pancreas. Furthermore, it has been reported that a decrease in β -catenin inhibits glucagon-like peptide 1-stimulated insulin secretion. Depletion of β -catenin has been shown to disrupt the intracellular actin cytoskeleton, which may also be involved in preventing the movement/release of insulin granules to the juxtamembrane [39].

These findings suggest that blue light affects the ROS/C1q/Wnt5a/ β -catenine pathway in the liver and the ROS/Wnt3a/ β -catenine pathway in the pancreas in type 1 diabetes. We have previously reported that blue light induces NETosis in type 1 diabetes, leading to its worsening [18]. These findings suggest that blue light acts on neutrophils to increase ROS secretion, affecting both the NETosis pathway and the C1q-mediated β -catenine pathway, leading to a worsening of symptoms. ROS play an important role in both pathways. These neutrophil-derived ROS also induce type 1 macrophage proliferation and increased secretion of inflammatory cytokines in various organs, potentially contributing to

organ degeneration [40]. The effects of blue light on type 1 diabetes are diverse, requiring further study.

In this study, we investigated the mechanism by which blue light exposure worsens type 1 diabetes using gp91phox^{-/-} mice. We found that depletion of gp91phox/neutrophil normalized all downstream signaling of gp91phox/neutrophil (to the level observed in diabetic model mice without blue light exposure), thereby canceling the adverse effects of blue light. These findings suggest that blue light exacerbates type 1 diabetes by activating gp91phox/neutrophil levels.

5. Conclusions

This study demonstrated that STZ-induced type 1 diabetes was exacerbated by blue light irradiation and that the exacerbation by blue light irradiation was canceled in gp91phox^{-/-} mice. The mechanism of this phenomenon showed different responses in the liver and pancreas. The gp91phox/ROS/C1q/Wnt5a/b-catenin or PPAR γ pathway is involved in the liver, and the gp91phox/ROS/DKK1/Wnt3a/b-catenin pathway is involved in the pancreas (Figure 8). These results suggest that blue light exposure may worsen type 1 diabetes via gp91phox and emphasize the need for blue light protection in diabetic patients. However, the mechanisms underlying the differences in Wnt responses between the liver and pancreas remain unclear, and further research is needed. Furthermore, this study examined STZ-induced type 1 diabetes in mice, so it is unclear whether the findings are applicable to humans. Therefore, clinical trials are awaited.

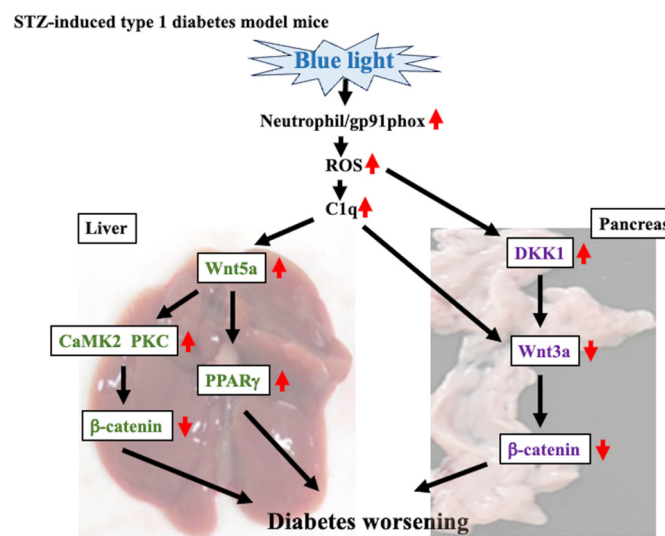


Figure 8. Mechanism by which blue light irradiation aggravates STZ-induced type 1 diabetes. Upward red arrow: increase, Downward red arrow: decrease, ROS: reactive oxygen species, C1q: complement component 1q, Wnt5a: wingless-type MMTV integration site family, member 5A, DKK1: dickkopf-1, CaMK2: activate Ca²⁺/calmodulin-dependent protein kinase 2, PKC: pan protein kinase C, PPAR γ : peroxisome proliferator-activated receptor γ .

Author Contributions: Conceptualization, K.H.; methodology, K.H. and E.F.S.; software, E.F.S.; validation, K.H. and E.F.S.; formal analysis, E.F.S.; investigation, K.H.; resources, K.H.; data curation, E.F.S.; writing—original draft preparation, K.H.; writing—review and editing, K.H.; visualization, K.H.; supervision, K.H.; project administration, K.H.; funding acquisition, K.H. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The animal study protocol was approved by the Institutional Review Board of Laboratory Animals of Suzuka University of Medical Science (approval number: 34/7 October 2017).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author.

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Conflicts of Interest: There are no conflicts of interest to declare.

Abbreviations

The following abbreviations are used in this manuscript:

STZ	Streptozotocin
ROS	Reactive oxygen species
LEDs	Light-emitting diodes
NET	Neutrophil extracellular trap
Agptl2	Angiopoietin-like protein 2
PKC	Protein kinase C
CaMK	Ca ²⁺ /calmodulin-dependent protein kinase
PPAR	Peroxisome proliferator-activated receptor
C1q	Complement component 1q
LRP	Low-density lipoprotein receptor-related protein

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