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Dihydrotestosterone-Damaged Human Dermal Microvascular Endothelial Cells"

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Abstracts

Prostaglandin E2 (PGE2) is known to activate stem cells and promote tissue regeneration. Similarly, Prostaglandin F2α (PGF2α) analogs, such as bimatoprost, have been FDA-approved as eyelash growth enhancers and have shown efficacy in cultured human hair follicles. To enhance PGE2 levels for hair loss treatment, we developed an inhibitor of 15-prostaglandin dehydrogenase (15-PGDH), an enzyme that degrades prostaglandins, using DeepZema®, an AI-based drug discovery platform. This inhibitor, termed 15-PGDHI, was previously shown to improve the viability of human follicle dermal papilla cells (HFDPCs) damaged by dihydrotestosterone (DHT), a key factor in hair loss.

Alopecia is linked to a reduction in the microvasculature surrounding hair follicles. The normal hair follicle cycle includes three stages: anagen, catagen, and telogen. During the anagen phase, blood vessels proliferate and reorganize into a vertical structure extending toward the epidermis. In the catagen phase, the vasculature shifts to form a horizontal plexus beneath the hair germ. Human dermal microvascular endothelial cells (HDMECs) make up the endothelial layer lining the interior of arteries, veins, and capillaries. These capillaries are closely associated with human dermal papilla cells, which play a key role in hair growth. This connection enables hair follicles to grow and regenerate by receiving oxygen and nutrients from the surrounding blood vessels.

Hair growth, as demonstrated by the FDA-approved hair loss treatment minoxidil, is strongly connected to the surrounding blood vessels. Thus, we further investigated the effects of 15-PGDHI on HDMECs damaged by DHT. Our findings revealed that 15-PGDHI increased cell proliferation in cell viability assay and promoted wound healing in DHT-damaged HDMECs. 15-PGDHI significantly reduced DHT-induced reactive oxygen species (ROS) levels in these cells. Additionally, 15-PGDHI restored mitochondrial membrane potential in HDMECs affected by DHT and downregulated the phosphorylation of MAPKs, a critical signaling pathway as its underlying mechanism.

These results indicate that 15-PGDHI has protective and restorative effects on DHT-damaged HDMECs, suggesting its potential as a promising therapeutic agent for hair loss treatment.

1. Introduction

Hair follicle regeneration is intricately regulated by prostaglandins, which are key mediators of tissue homeostasis and repair [1, 2]. Prostaglandin E2 (PGE2) has been recognized for its ability to activate stem cells and promote tissue regeneration [3-7]. Similarly, Prostaglandin F2α (PGF2α) analogs, such as bimatoprost, have received FDA approval for enhancing eyelash growth and have demonstrated positive effects in cultured human hair follicles [8]. These findings suggest that modulation of prostaglandin pathways could represent a promising approach for treating hair loss.

To explore this therapeutic potential, we utilized DeepZema®, an AI-driven drug discovery platform, and identified dihydroisoquinolinone piperidinylcarboxy pyrazolopyridine (DPP), a novel inhibitor of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the key enzyme responsible for prostaglandin degradation. DPP was previously shown to protect human hair follicle dermal papilla cells (HFDPCs) from dihydrotestosterone (DHT)-induced damage, a major contributor to androgenetic alopecia [9].

Hair loss is also associated with the deterioration of the microvascular network surrounding hair follicles [10, 11]. Throughout the hair cycle, which includes the anagen, catagen, and telogen phases, vascular remodeling plays a critical role in sustaining follicular growth [12, 13]. In particular, dermal microvascular endothelial cells (HDMECs) form the capillary networks closely connected to dermal papilla cells, supplying essential oxygen and nutrients necessary for hair regeneration [14, 15].

Given the importance of vascular health in hair growth, as exemplified by the effects of minoxidil (MIX), we extended our investigation to evaluate the effects of DPP on HDMECs damaged by DHT [16, 17]. Our study assessed whether DPP could protect and restore HDMEC function by reducing oxidative stress, improving mitochondrial integrity, and modulating key signaling pathways.

Thus, the primary objective of this study was to explore the therapeutic potential of DPP in alleviating DHT-induced cellular damage in HDMECs, aiming to establish its utility as a novel treatment strategy for hair loss.

2. Materials and Methods

2.1. Cell culture

HDMECs (Promo Cell, Heidelberg, Germany) were cultivated at 37 °C in a 5 % CO_2 incubator using endothelial cell growth medium (Promo Cell, Heidelberg, Germany) supplemented with 1 % penicillin-streptomycin (Welgene Inc., Gyeongsan, Korea).

2.2. Cell viability assay

HDMECs were incubated with DPP at concentrations of 0.1, 1, and 5 μM for 24 hours. After incubation, the culture medium was discarded, and EZ-Cytox reagent (DoGenBio, Seoul, Korea) diluted in fresh medium was added to each well. The cells were further incubated for 1 hour, and absorbance was then measured at 450 nm.

2.3. Wound healing assay

HDMECs were seeded into 6-well plates and incubated for 24 hours at 37 °C in 5 % CO_2. A linear wound was created in the center of each well using a sterile 1 mL pipette tip. The cells were then treated with 1 μM DHT (Sigma-Aldrich, St. Louis, USA), 1 μM MIX (Sigma-Aldrich), or DPP at concentrations of 0.1, 1, and 5 μM. Following treatment, the cells were further incubated for 24 hours under identical conditions. Phase-contrast images were taken at 0 and 24 hours post-treatment using a Nikon light microscope (Tokyo, Japan) to evaluate wound closure.

2.4. DCF-DA ROS assay

Intracellular reactive oxygen species (ROS) levels were evaluated using a Cellular ROS Assay Kit (Abcam, Cambridge, UK). HDMECs were seeded into a confocal dish and incubated for 24 hours at 37 °C in a 5 % CO_2 incubator. The cells were subsequently treated with 1 μM DHT, 1 μM MIX, or 5 μM DPP for 24 hours. Following the 24-hour treatment, cells were stained with 10 μM 2′,7′-dichlorofluorescin diacetate (DCF-DA) and incubated at 37 °C for 20 minutes in light-protected conditions. The staining solution was then removed, and the cells were rinsed with Dulbecco's phosphate-buffered saline (DPBS) (Welgene Inc.,

Gyeongsan, Republic of Korea). Fluorescence intensity was visualized using a Nikon Eclipse Ti2 live-cell fluorescence microscope (Tokyo, Japan).

2.5. Measurement of Mitochondrial Membrane Potential

Mitochondrial membrane potential was assessed using the JC-1 Mitochondrial Membrane Potential Assay Kit (Abcam, Cambridge, UK). HDMECs were seeded into a confocal dish and cultured for 24 hours at 37 °C in a 5 % CO_2 incubator. The cells were subsequently treated with 1 μM DHT, 1 μM MIX, or 5 μM DPP for an additional 24 hours. After removing the culture medium, cells were stained with 2 μM JC-1 dye and incubated at 37 °C for 30 minutes under light-protected conditions. Following staining, the cells were rinsed with DPBS, and fluorescence images were acquired using a Nikon Eclipse Ti2 live-cell fluorescence microscope (Tokyo, Japan).

2.6. ATP assay

Mitochondrial ATP production was evaluated using ATP Red™ and MitoLite™ Green FM dyes (AAT Bioquest, Pleasanton, USA). HDMECs were plated in a confocal dish and maintained for 24 hours at 37 °C in a 5 % CO_2 incubator. The cells were then treated with 1 μM DHT, 1 μM MIX, or 5 μM DPP for 24 hours. After treatment, ATP Red™ working solution was applied, and the cells were incubated for 30 minutes at 37 °C. The cells were then gently rinsed with DPBS and incubated again with MitoLite™ Green FM for another 30 minutes under the same conditions. After final washing, fluorescence signals were captured using a Nikon Eclipse Ti2 live-cell fluorescence microscope (Tokyo, Japan).

2.6. Tube Formation assay

Tube formation was assessed using the Angiogenesis Assay Kit (Cell Biolabs, San Diego, CA, USA). A pre-chilled 96-well plate was coated with 50 μL of Matrigel per well and incubated at 37 °C in a 5 % CO_2 incubator for 30 minutes to allow gelation. HDMECs (2.5×10^4 cells/well) were suspended in 150 μL of culture medium and seeded onto the Matrigel-coated wells. After 6 and 24 hours of incubation, tube formation was visualized using a Nikon light microscope (Tokyo, Japan).

3. Results

3.1. Effect of DPP Treatment on the Viability of HDMECs

To assess the cytotoxic effects of DPP on HDMECs, an MTT assay was performed. The results indicated that DPP at concentrations of 0.1, 1, and 5 μM did not induce significant cytotoxicity. Furthermore, DPP treatment enhanced the viability of HDMECs relative to the untreated control group, suggesting its potential role in promoting HDMEC proliferation (data not shown).

3.2. DPP Enhances the Migration of DHT-Damaged HDMECs

Migration of HDMECs plays a critical role in hair follicle vascularization and regeneration. Impairment of HDMEC migration may contribute to the development of androgenetic alopecia (AGA). DHT binds to the androgen receptor (AR) and inhibits hair growth during the hair cycle [18]. Additionally, AR activation has been shown to suppress endothelial cell migration [19, 20]. To evaluate the impact of DPP on the migration ability of DHT-damaged HDMECs, a wound healing assay was conducted. Cells exposed to DHT alone exhibited markedly slower wound closure compared to the untreated control group, suggesting that DHT negatively affected cell migration. However, treatment with DPP or MIX signific-

antly promoted wound closure after 24 hours compared to DHT treatment alone. These findings indicate that DPP improves the migratory function of HDMECs (Figure 1).

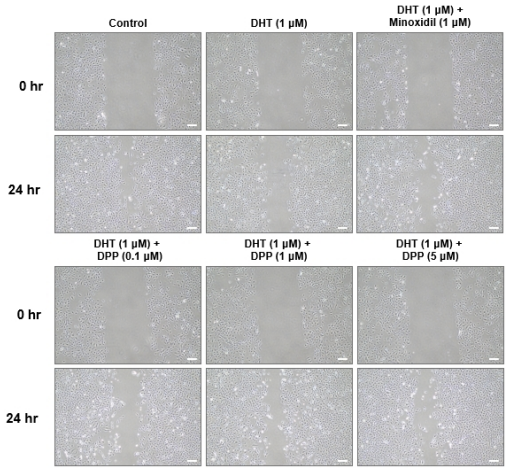

Figure 1. Wound healing effects of DPP on HDMECs stimulated with 1 μM DHT. Cells were treated with DPP (0.1, 1, and 5 μM) or 1 μM MIX for 24 hours. Wound closure was evaluated using phase-contrast microscopy at 24 hours (scale bar 20 μm).

3.3. DPP Reduces ROS Accumulation in DHT-Damaged HDMECs

Elevated levels of ROS are known to impair vascular function by disrupting endothelial cell homeostasis and compromising the structural integrity [21]. To assess the ability of DPP to reduce ROS accumulation, DCF-DA staining was conducted. As expected, DHT-treated HDMECs exhibited markedly higher ROS levels compared to the untreated control group. Treatment with MIX significantly lowered ROS accumulation in DHT-exposed cells. Likewise, DPP treatment effectively suppressed DHT-induced ROS elevation, bringing levels close to those observed in the control group (Figure 2).

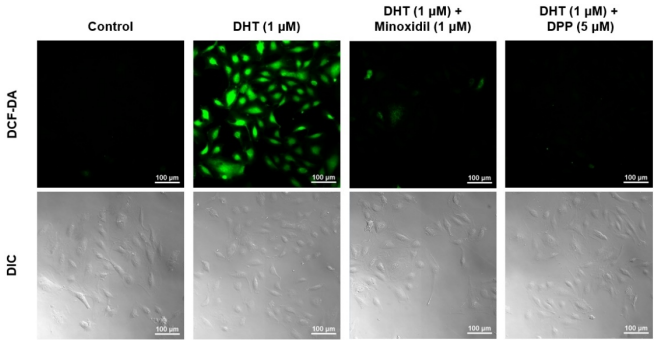

Figure 2. Effects of DPP on ROS levels in HDMECs stimulated with 1 μM DHT. DCF-DA fluorescence images showing green fluorescence as an indicator of intracellular ROS accumulation (scale bar 100 μm).

3.4. DPP Restores Mitochondrial Membrane Potential in DHT-Damaged HDMECs

Mitochondria are essential for sustaining cellular energy demands, particularly during the highly proliferative anagen phase of the hair cycle. Disruption of mitochondrial function impairs energy metabolism, which can hinder follicular regeneration and lead to hair cycle arrest. Recent studies have shown that endothelial cells, including HDMECs, are sensitive to mitochondrial dysfunction, resulting in compromised vascular support essential for hair follicle maintenance.

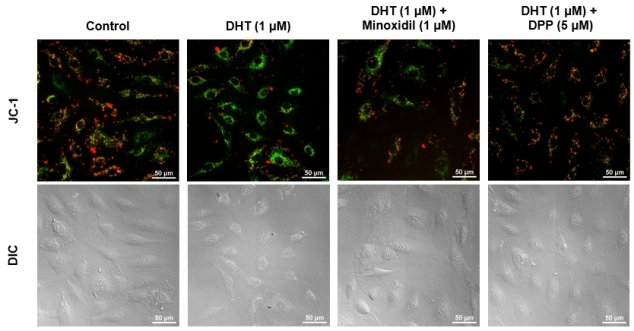

Figure 3. Effects of DPP on mitochondrial membrane potential in HDMECs stimulated with 1 μM DHT. JC-1 staining was performed on HDMECs treated with 1 μM DHT, followed by treatment with 5 μM DPP or 1 μM MIX for 24 hours. JC-1 fluorescence images are shown, where green fluorescence indicates depolarized mitochondria and red fluorescence represents hyperpolarized mitochondria (scale bar 50 μm).

A JC-1 assay was conducted to evaluate the effects of DPP on mitochondrial membrane potential in DHT-damaged HDMECs. In this assay, red fluorescence indicates polarized, functional mitochondria, whereas green fluorescence reflects depolarized, dysfunctional mitochondria. DHT exposure resulted in a marked increase in green fluorescence intensity compared to the control group, suggesting mitochondrial impairment. In contrast, DPP treatment enhanced red fluorescence, indicating that DPP restored mitochondrial membrane potential in DHT-compromised HDMECs (Figure 3).

3.5. DPP Enhances ATP Production in DHT-Damaged HDMECs

Mitochondria play a crucial role in endothelial cells by regulating ATP production and maintaining vascular homeostasis. Proper mitochondrial function is essential for endothelial integrity, and impairment can lead to reduced ATP synthesis and contribute to vascular dysfunction.

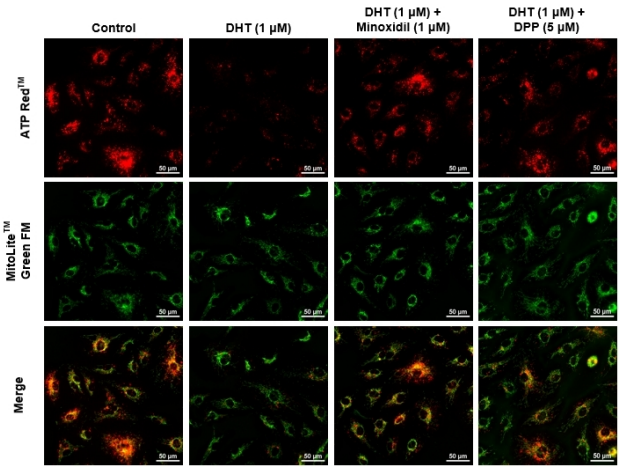

Figure 4. Effects of DPP on ATP levels in HDMECs stimulated with 1 μM DHT. ATP assay was conducted on HDMECs treated with 1 μM DHT, followed by treatment with 5 μM DPP or 1 μM MIX for 24 hours. Red fluorescence indicates ATP levels and green fluorescence marks mitochondria (scale bar 50 μm).

To assess the impact of DPP on ATP production, ATP levels were visualized using fluorescence-based detection. In this analysis, green fluorescence was used to visualize mitochondrial structures, while red fluorescence indicated intracellular ATP levels. DHT-treated HDMECs showed a notable reduction in red fluorescence intensity compared to the control group, suggesting impaired ATP production. In contrast, DPP treatment effectively restored

red fluorescence signals, reflecting the recovery of mitochondrial ATP synthesis. These results demonstrate that DPP significantly enhanced ATP production in DHT-compromised HDMECs (Figure 4).

3.6. DDP Restored Tube Formation in DHT-Damaged HDMECs

Endothelial cells are capable of differentiating and forming capillary-like structures when cultured on Matrigel . The tube formation assay is a widely utilized method for quantitatively assessing angiogenesis by measuring tube length, the number of nodes, meshes, and branches [22-24]. This assay reflects the ability of endothelial cells to respond to angiogenic signals through proliferation and migration, particularly within 2–6 hours of stimulation. In our study, treatment with DHT significantly reduced the total tube length, number of meshes, and branching points compared to the untreated control group. To investigate the protective role of DDP, HDMECs were simultaneously with DHT and DDP. DDP treatment markedly restored tube formation capacity in DHT-damaged HDMECs, as evidenced by improvements in tube length, meshes, and branch numbers relative to the DHT-only group. These results suggest that DDP may promote vascular regeneration by enhancing the angiogenic potential of endothelial cells under DHT-induced stress conditions (Figure 5).

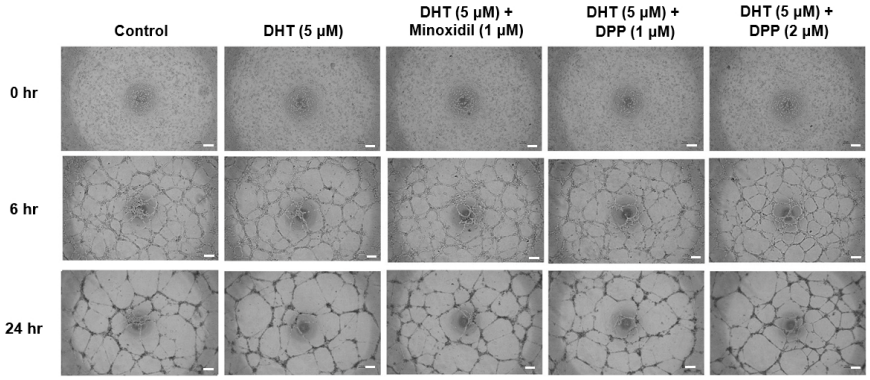

Figure 5. The effects of DDP on tube formation in DHT-damaged HDMECs. Each image was taken at 0, 6, and 24 h, respectively (scale bar 20 μm).

4. Discussion

Prostaglandin pathways have been implicated in tissue regeneration and vascular health, offering promising therapeutic avenues for hair loss treatment [25-28]. In this study, we evaluated the protective effects of DPP, a 15-PGDH inhibitor discovered through DeepZema®, against DHT-induced damage in HDMECs.

DHT is known to induce oxidative stress, leading to endothelial damage and impaired cell migration, both of which are critical for vascular remodeling and follicular regeneration [29]. In this study, DPP treatment effectively counteracted these pathological effects by restoring key cellular functions, including cell migration, oxidative balance, mitochondrial integrity, and angiogenic potential.

Specifically, DPP markedly reduced ROS accumulation and restored mitochondrial membrane potential and ATP production in DHT-damaged HDMECs. Since mitochondrial dysfunction and oxidative stress are major contributors to endothelial impairment, these findings highlight DPP's broader significance in preserving microvascular integrity under pathological conditions.

Furthermore, DPP treatment restored tube formation capacity in DHT-exposed HDMECs, suggesting a recovery of angiogenic potential essential for maintaining follicular cycling and regeneration.

Collectively, these results indicate that 15-PGDH inhibition by DPP may offer a novel therapeutic strategy to counteract DHT-induced endothelial dysfunction through antioxidative and pro-regenerative mechanisms. Future studies should aim to validate these protective effects in in vivo models and assess the long-term efficacy of DPP in promoting hair regeneration.

5. Conclusion

In summary, our study demonstrates that DPP, a novel 15-PGDH inhibitor, effectively protects HDMECs from DHT-induced dysfunction by enhancing cell viability, migration, mitochondrial function, and angiogenic potential. These findings support the therapeutic potential of DPP as a plant-derived agent for mitigating hair loss associated with vascular impairment.

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