Iranian Journal of
Medical Hypotheses and Ideas

Original article

Cannabinoid (JWH-133) therapy could be effective for treatment of corneal neovascularization

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Received: 30 Aug 2009
Accepted: 16 Jan 2010
Published: 25 Jan 2010
Iran J Med Hypotheses Ideas, 2010, 4:3

Abstract

Neovascularization of the normally avascular cornea was associated with a notable increase in the expression of the major proangiogenic factors and proteases. The data supporting a causal role for vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) are extensive. Anti-angiogenic therapy is considered as a possible tool for controlling corneal neovascularization. Endocannabinoids are now considering as suppressors of angiogenesis and tumor spreading since they have been reported to inhibit angiogenesis, cell migration and metastasis in different types of cancers. JWH-133 as a CB2 selective ligand is one of the pharmacological cannabinoid derivatives that could induce apoptosis and reduce secretion of major stimulatory factors involved in cell proliferation and angiogenesis. Several studies have indicated that JWH-133 inhibit tumor angiogenesis in vitro and in vivo through direct inhibition of vascular endothelial cell migration and survival, as well as suppression of proangiogenic factor and MMP-2 expression.

Based on the present information about inducing factors involved in corneal angiogenesis and pharmacological properties of cannabinoids, we hypothesize that topical application of JWH-133 is potentially useful for inhibiting corneal neovascularization and restoration of corneal clarity. The potential use of JWH-133 in other eye related reports is even more appealing considering that it could be a good safety profile for retarding corneal neovascularzation. However, further investigations in animal models are needed to place JWH-133 alongside corneal neovascularization therapeutics.

Keywords
Cornea, Neovascularization, JWH-133, Cannabinoids, Angiogenesis

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Introduction

Corneal neovascularization is seen in many pathological conditions, which include infection, mechanical and chemical injury and corneal transplantation (1, 2). Corneal neovascularization leads to decreased vision, graft rejection and incompetent barrier function, thus presetting a serious clinical problem for which treatment is often lacking (2). Corneal avascularity requires low levels of angiogenic and high levels of anti-angiogenic factors under basal conditions (3). Corneal neovascularization occurs as a result of disequilibrium between angiogenic and antiangiogenic stimuli (4-6).

Several anti-angiogenic agents have been characterized to inhibit neovascularization in recent years in animal models. Fumagillin analogs (7), thalidomide (8), cyclosporine A (1) and shark cartilage extract (9, 10) exhibit antiangiogenic activity. Cannabinoids have anti-inflammatory and anti-nociceptive properties that seem to involve several different pathways including both cannabinoid (CB) receptor dependent and independent mechanisms (11). Pharmacological cannabinoid derivatives have great advantage of being well tolerated, regarding toxicity, and of having such remarkable palliative effects in cancer patients that their use has already been approved for clinical practice (12, 13). They can help regulation of corneal neovascularization and maintain the transparency and immune privilege of the cornea (14).

Mechanisms of neovascularization

Angiogenesis, formation of new blood vessels from preexisting vessels, is associated with several steps including: digestion of basement membrane and extra cellular matrix, migration, proliferation and rearrangement of endothelial cells to form new blood vessels (15). Hence, inhibition of endothelial cell adhesion and migration, and interference with metalloproteinase may constitute a novel therapeutic strategy for the treatment of corneal disorders associated with excessive neovascularization (16-19). VEGF is likely the most important proangiogenic cytokine and its expression has been strongly implicated in the pathogenesis of conditions leading to inappropriate blood vessel growth in the eye. Therefore, VEGF is an attractive target for anti-angiogenic therapies designed to treat neovascular eye diseases (20-27). VEGF over expression in cornea stimulates proteolytic activities, proliferation, migration, and tube formation of endothelial cells and initiates formation of new blood vessels (3). Interestingly, requirement of VEGF for corneal angiogenesis was shown by the inhibition of neovascularization after stromal implantation of an anti-VEGF blocking antibody in a rat model (26, 27). At least two VEGF inhibitors are in advanced clinical development for ophthalmic disease, Lucetis (rhu-Fab V2; Genetech, Inc.) and Macugen (pegaptanib sodium; Eyetech Pharmaceuticals), and more are poised to enter to clinical practice (28).

The matrix metalloproteinases (MMPs) are a family of zinc dependent proteinases involved in the degradation of basement membrane and extra cellular matrix. Several MMPs are believed to be important in angiogenesis, but particular interest has been focused on the MMP-2 and MMP-9 (29). MMP-2 is one of the earliest and its sustained activity required for successful corneal neovascularization (30-41). A shift in the proteolytic balance between MMPs and their inhibitors, in favor of MMPs inhibition, would result in the suppression of the angiogenic phenotype and subsequent neovascularization (32).

Two recent studies investigated corneal neovascularization in MMP-2-deficient mice compared with wild-type mice and showed statistically significant delay of neovascularization in MMP-2-deficient mice (33, 34). Another study reported that MMP-2 is required for optimal experimental choroidal neovascularization in a mouse model (35).

Hypothesis

JWH-133 may be an effective treatment for inhibiting corneal neovascularization due to its anti angiogenic activity. This cannabinoid targets angiogenic steps and some proangiogenic factors that they are very important in angiogenesis cycle.

Evaluation of hypothesis

Corneal neovascularization was associated with angiogenic steps: proliferation, migration and capillary tube formation. Consequently, any mechanism that could strongly depress angiogenesis steps or angiogenic factors may limit the visual loss associated with corneal neovascularization. Therefore, we propose the hypothesis that local administration of JWH-133 may be effective in corneal neovascularization treatment. JWH-133 is one of the pharmacological cannabinoid derivatives, members of this group are active components of Cannabis sativa (marijuana). Marijuana and its derivatives have been used in medicine for many centuries (36). These compounds have anti-inflammatory and antinociceptive properties that seem to be involved in several different pathways including both cannabinoid (CB) receptor dependent and independent mechanisms (11). Song et al. (37) used the specific anti-sense probe to CB2 mRNA and detected positive hybridization signals in cornea, iris and ciliary body. JWH-133, a selective CB2 receptor agonist, is effective in suppressing murine experiment autoimmune uveoretinitis (EAU) and resultant prevention of tissue damage in the retina (38, 39).

Several studies on JWH-133 showed that it is effective in cancer treatment through some pathways like inhibition of vascular endothelial cells migration and survival and decreasing the expression of proangiogenic factors such as VEGF, angiopoietin-2 and MMP2 (40-50).

JWH-133 administration inhibits tumor angiogenesis in vivo and in vitro (36, 43). JWH-133 could down-regulate the expression of several VEGF pathway-related genes, such as VEGF itself and the hypoxia-inducible factor-1 (HIF-1) a master transcription factor for oxygen homeostasis regulation. Accordingly, treatment with JWH-133 resulted in decreased activation of the VEGF receptor VEGFR-2, and this effect could be inhibited by pharmacological blockade of ceramide biosynthesis (13, 36, 49).

Discussion

These data strongly suggest that JWH-133 would treat corneal neovascularization by inhibiting angiogenesis steps such as proliferation, migration and inhibition of involving factors like VEGF, and functionally related proteins to it and also MMP-2, a proteolytic enzyme involved in tissue remodeling during angiogenesis (36, 40-48). Moreover, it was hypothesized that local administration of both sunitinib malate and sorafenib may be effective in corneal angiogenesis treatment (51).

In our previous hypotheses for inhibition of corneal neovascularization we suggested to use nutrient mixture containing Lysine, Proline, Ascorbic Acid, and Green tea extract (52) and Propolis extract (53). In this hypothesis we recommend to use JWH-133 for inhibition of corneal neovascularization in an ophthalmic drop for local using. Studies have also evidenced that JWH-133 as a selective CB2 ligand-does not mediate psychoactivity and cytotoxic effects (54-56), making this derivative as a potential agent for inhibiting corneal neovascularization.

Conclusion

Corneal neovascularization is depended on digestion of basement membrane and extra cellular matrix, migration, proliferation and rearrangement of endothelial cells, thus inhibition of these steps by targeting proangiogenic factors could be effective for treatment of corneal neovascularization. Preparing and using of JWH-133 could be easier than some other antiangiogenic agents such as specific antibodies, also because of the low molecular weight of this cannabinoid it could be use as an eye drop. This cannabinoid could strongly inhibit angiogenesis by inhibition of vascular endothelial cells migration, proliferation and survival and suppression the expression of proangiogenic factors such as VEGF, angiopoietin-2 and MMP2. In addition, JWH-133 could down-regulate the expression of several VEGF pathway-related genes. These data collectively indicate that JWH-133 is a good choice for inhibition of neovascularization due to its strong anti angiogenic activity. However, Before clinical application, JWH-133 should be tested in appropriate animal models of corneal neovascularization.

Overview Box

What do we already know about the subject?
Taken together, JWH-133 could strongly inhibit angiogenesis by inhibition of vascular endothelial cells migration, proliferation and survival, and suppress the expression of proangiogenic factors such as VEGF, angiopoietin-2 and MMP2. Therefore, we propose the hypothesis that local administration of JWH-133 may be effective in corneal neovascularization treatment.

What does your proposed theory add to the current knowledge available, and what benefits does it have?
To test this hypothesis we propose local use of this compound as ophthalmic drop in corneal neovascular states such as infection, mechanical and chemical injury and corneal transplantation to limit the decreased vision and graft rejection associated with corneal neovascularization.

Among numerous available studies, what special further study is proposed for testing the idea?
Before clinical application, JWH-133 should be tested in appropriate animal models of corneal neovascularization.

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