

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

Maryam Keshavarz, Amir Hossein Norooznejhad, Kamran Mansouri, Ali Mostafaie

Angaben zur Veröffentlichung / Publication details:

Keshavarz, Maryam, Amir Hossein Norooznejhad, Kamran Mansouri, and Ali Mostafaie. 2010. "Cannabinoid (JWH-133) therapy could be effective for treatment of corneal neovascularization." Iranian Journal of Medical Hypotheses and Ideas 4: 3.

Nutzungsbedingungen / Terms of use:

licgercopyright

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under the following conditions:

Deutsches Urheberrecht

Weitere Informationen finden Sie unter: / For more information see:

<https://www.uni-augsburg.de/de/organisation/bibliothek/publizieren-zitieren-archivieren/publizieren>





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

Maryam Keshavarz¹, Amir Hossein Norooznezhad¹, Kamran Mansouri¹ and Ali Mostafaie¹

¹Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, I.R. Iran

Corresponding author:

Ali Mostafaie
Medical Biology Research Center, P.O. Box: 1568, Sorkheh Lige, Kermanshah, Iran.
Tel: 98-831-4276473
Fax: 98-831-4276471
E-mail: amostafaie@kums.ac.ir, amostafaie@mbrc.ac.ir

Received: 30 Aug 2009

Accepted: 16 Jan 2010

Published: 25 Jan 2010

Iran J Med Hypotheses Ideas, 2010, 4:3

© 2010 Maryam Keshavarz et al.; licensee Tehran Univ. Med. Sci.

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 neovascularization. However, further investigations in animal models are needed to place JWH-133 alongside corneal neovascularization therapeutics.

Keywords

Cornea, Neovascularization, JWH-133, Cannabinoids, Angiogenesis



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 antinociceptive 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.

References

1. Benelli U, Ross JR, Nardi M, Klintworth GK. Corneal neovascularization induced by xenografts or chemical cautery. Inhibition by cyclosporin A. *Invest Ophthalmol Vis Sci* 1997;382:274–282.
2. Bellner L, Vitto M, Patil KA, Dunn MW, Regan R, Laniado-Schwartzman M. Exacerbated corneal inflammation and neovascularization in the HO-2 null mice is ameliorated by biliverdin. *Exp Eye Res* 2008;87:268–278.
3. Lee P, Wang CC, Adamis AP. Ocular neovascularization. An epidemiologic review. *Surv Ophthalmol* 1998;433: 245–269.
4. Kim SW, Ha BJ, Kim EK, Tchah H, Kim TI. The Effect of Topical Bevacizumab on Corneal Neovascularization. *American Academy of Ophthalmology*, 2008, Published by Elsevier Inc.
5. Chang JH, Gabison EE, Kato T, Azar DT. Corneal neovascularization. *Curr Opin Ophthalmol* 2001;12:242–249.
6. Azar DT. Corneal angiogenic privilege: angiogenic and antiangiogenic factors in corneal avascularity, vasculogenesis, and wound healing (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2006;104:264–302.
7. Ingber D, Fujita T, Kishimoto S, Sudo K, Kanamaru T, Brem H, Folkman J. Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumors growth. *Nature* 1990;348: 555–557.
8. Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. *Exp Eye Res* 1997;646:971–978
9. Gonzalez RP, D-Soares FS, Farias RF, Pessoa C, Leyva A, De Barros Viana GS et al. Demonstration of inhibitory effect of oral shark cartilage on basic fibroblast growth factor-induced angiogenesis in the rabbit cornea. *Biol Pharm Bull* 2001;24:151–154.
10. Hassan ZM, Feyzi R, Sheikhan A, Bargahi A, Mostafaie A, Mansouri K et al. Low molecular weight fraction of shark cartilage can modulate immune responses and abolish angiogenesis. *Int Immunopharmacol* 2005;5-6:964-970.
11. Pertwee RG. Cannabinoid receptors and pain. *Prog Neurobiol* 2001;63:569–611.
12. Guzman M. Cannabinoids: potential anticancer agents. *Nat Rev Cancer* 2003;3:745-755.
13. Bifulco M, Laezza C, Gazzero P, Pentimalli F. Endocannabinoids as emerging suppressors of angiogenesis and tumor invasion (Review). *Oncol Rep* 2007;17:813-816.
14. Huang AJ, Watson BD, Hernandez E, Tseng SC. Induction of conjunctival transdifferentiation on vascularized corneas by photothrombotic occlusion of corneal neovascularization. *Ophthalmology* 1998;952:228–235.
15. Plank MJ, Sleeman BD. Tumor – induced angiogenesis: A review. *J Theor Med* 2004;5:137-153.
16. Murray JC. *Methods in molecular medicine: Angiogenesis protocols*. Totowa, NJ: Humana press: 2001. pp. 3-20 and 185-203.
17. Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. *Endocrine Reviews* 2004;25:581-611.
18. Haider AS, Grabarek J, Eng B, Pedraza P, Ferreri NR, Balazs EA et al. In vitro model of “Wound Healing” analyzed by laser scanning cytometry: accelerated healing of epithelial cell monolayer in the presence of hyaluronate. *Cytometry Part A* 2003;53A:1–8.
19. Hidalgo M, Eckhardt SG. Development of Matrix Metalloproteinase Inhibitors in Cancer Therapy. *J National Cancer Institute* 2001;93(3).
20. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SL, Holash J. Vascular-specific growth factors and blood vessel formation. *Nature* 2000;407:242-248.
21. Holash J, Wiegand SJ, Yancopoulos GD. New model of tumor angiogenesis: dynamic balance between vessel regression and growth mediated by angiopoietins and VEGF. *Oncogene* 1999;18:5356-5362.
22. Lai CM, Spilisbury K, Brankov M, Zaknich, T, Rakoczy PE. Inhibition of corneal neovascularization by recombinant adenovirus mediated antisense VEGF RNA. *Exp Eye Res* 2002;756:625–634.
23. Gan L, Fagerholm P, Palmblad J. Vascular endothelial growth factor VEGF and its receptor VEGFR-2 in the regulation of corneal neovascularization and wound healing. *Acta Ophthalmol Scand* 2004;825:557–563.
24. Zhou LH, Xing YQ, Chen CL, Wang DW. Antisense vascular endothelial growth factor suppressed corneal neovascularization in rats. *Zhonghua Yan Ke Za Zhi* 2006;425:426–430.
25. Murata M, Takanami T, Shimizu S, Kubota Y, Kubota Y, Horiuchi S, et al. Inhibition of ocular angiogenesis by diced small interfering RNAs siRNAs specific to vascular endothelial growth factor VEGF. *Curr Eye Res* 2006;312:171–180.
26. Amano S, Rohan R, Kuroki M, Tolentino M, Adamis AP. Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization. *Invest Ophthalmol Vis Sci* 1998;391:18–22.
27. Paul Aiello L, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, et al. Suppression of Retinal Neovascularization in vivo by Inhibition of Vascular Endothelial Growth Factor (VEGF) Using Soluble VEGF-Receptor Chimeric Proteins. *Proc Nat Acad Sci USA* 1995;92:10457-10461.
28. Adamis AP, Shima DT. The role of vascular endothelial growth factor in ocular health and disease. *Retina* 2005;252:111–118.
29. Sethi CS, Bailey TA, Luthert PJ, Chong NHV. Matrix metalloproteinase biology applied to vitreoretinal disorders. *Br J Ophthalmol* 2000;84:654-666.
30. Ma DH, Chen JK, Kim WS, Hao YX, Wu HC, Tsai RJF, et al. Expression of matrix metalloproteinases 2 and 9 and tissue inhibitors of metalloproteinase 1 and 2 in inflammation-induced corneal neovascularization. *Ophthalmic Res* 2001;336:353–362.
31. Zhang H, Li C, Baciuc PC. Expression of integrins and MMPs during alkaline-burn-induced corneal angiogenesis. *Invest Ophthalmol Vis Sci* 2002;434:955–962.
32. Fang J, Shing Y, Wiederschain D, Yan L, Butterfield C, Jackson G, et al. Matrix metalloproteinase-2 is required for the switch to the angiogenic phenotype in a tumor model. *PNAS* 2000;97:3884-3889.
33. Samolov B, Steen B, Seregard S, van der Ploeg I, Montan P, Kvanta A. Delayed inflammation-associated corneal neovascularization in MMP-2-deficient mice. *Exp Eye Res* 2005;802:159–166.

34. Ohno-Matsui K, Uetama T, Yoshida T, Hayano M, Itoh T, Morita I, et al. Reduced Retinal Angiogenesis in MMP-2-Deficient Mice. *Invest Ophthalmol Vis Sci* 2003;44: 5370-5375.
35. Berglin L, Sarman S, van der Ploeg I, Steen B, Ming Y, Itohara S, et al. Reduced choroidal neovascular membrane formation in matrix metalloproteinase-2-deficient mice. *Invest Ophthalmol Vis Sci* 2003;44:403-408.
36. Blázquez C, González-Feria L, Álvarez L, Haro A, Casanova ML, Guzmán M. Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas. *Cancer Res* 2004;64:5617-5623.
37. Song ZH, Jiang J, Hemesath A, McCloud C, Zhong L. Anterior Segment CB1 and CB2 Cannabinoid Receptors. *Invest Ophthalmol Vis Sci* 2002;43:E- 4027.
38. Cheng BC, Xu H, Calbay L, Pertwee RG, Coutts A, Forrester JV. Specific CB2 receptor agonist suppresses the murine model of experimental autoimmune uveitis. *Invest Ophthalmol Vis Sci* 2004;45; Abstract 552.
39. Xu H, Cheng CL, Chen M, Manivannan A, Cabay L, Pertwee RG, et al. Anti-inflammatory property of the cannabinoid receptor-2-selective agonist JWH-133 in a rodent model of autoimmune uveoretinitis. *J Leukocyte Biol* 2007;82:532-541.
40. Aguado T, Carracedo A, Julien B, Velasco G, Milman G, Mechoulam R. Cannabinoids Induce Glioma Stem-like Cell Differentiation and Inhibit Gliomagenesis. *J Biological Chem* 2007;282:6854-6862.
41. Carracedo A, Gironella M, Lorente M, Garcia S, Guzmán M, Velasco G, et al. Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress-Related Genes. *Cancer Res* 2006;66:6748-6755.
42. Casanova ML, Blázquez C, Martínez-Palacio J, Villanueva C, Fernandez-Acenero, M. Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. *J Clin Invest* 2003;111:43-50.
43. Blázquez C, Casanova ML, Planas A, Gómez del Pulgar T, Villanueva C, Fernández-Aceñero MJ et al. Inhibition of tumor angiogenesis by cannabinoids. *FASEB J* 2003;17: 529-531.
44. Guzmán M. Cannabinoids: potential anticancer agents. *Nat Rev Cancer* 2003;3:745-755.
45. Bifulco M, Di Marzo V. Targeting the endocannabinoid system in cancer therapy: a call for further research. *Nat Med* 2002;8:547-550.
46. Sánchez C, Ceballos ML, Gómez del Pulgar T, Rueda D, Corbacho C, Velasco G, et al. Inhibition of Glioma Growth in Vivo by Selective Activation of the CB2 Cannabinoid Receptor. *Cancer Res* 2001;61:5784-5789.
47. Portella G, Laezza C, Laccetti P, Petrocellis PL, Marzo VD, Bifulco, M. Inhibitory effects of cannabinoid CB1 receptor stimulation on tumor growth and metastatic spreading: actions on signals involved in angiogenesis and metastasis. *FASEB J* 2003;17: 1771-1773.
48. Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. *Support Care Cancer* 2003;11:137-143.
49. Strieter RM. Masters of angiogenesis. *Nat Med* 2005;11:925-927.
50. Blázquez C, Salazar M, Carracedo A, Lorente M, Egia A, González-Feria L, et al. Cannabinoids Inhibit Glioma Cell Invasion by Down-regulating Matrix Metalloproteinase-2 Expression. *Cancer Res* 2008;68:1945-1952.
51. Shakiba Y, Arshadi D. Inhibition of Corneal Neovascularization with new Tyrosine Kinase Inhibitors Targeting Vascular Endothelial Growth Factor Receptors: Sunitinib malate and Sorafenib. *Im J Med Hypotheses Ideas* 2007; 1:1.
52. Shakiba Y, Mostafaie A. Inhibition of corneal neovascularization with a nutrient mixture containing lysine, proline, ascorbic acid, and green tea extract. *Arch Med Res* 2007;38:789-791.
53. Keshavarz M, Mostafaie A, Mansouri K, Shakiba Y, Mohammadi-Motlagh HR. Inhibition of corneal neovascularization with propolis extract. *Arch Med Res* 2009;40: 59-61.
54. Tomida I, Pertwee RG, Azuara-Blanco A. Cannabinoids and glaucoma. *Br J Ophthalmol* 2004;88:708-713.
55. Ashton JC, Wright JL, Mcpartland JM, Tyndall JD. Cannabinoid CB1 and CB2 receptors ligand specificity and the development of CB2-selective agonists. *Curr Med Chem* 2008;15(4):1428-43.
56. Laine K, Järvinen K, Järvinen T. Topically administered CB2-receptor agonist, JWH-133, does not decrease intraocular pressure (IOP) in normotensive rabbits. *Life Sciences* 2003;72:837-842.