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Cannabinoids: Possible agents for treatment of psoriasis via suppression of angiogenesis and inflammation

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ABSTRACT

Psoriasis is a chronic skin disease also affecting other sites such as joints. This disease highly depends on inflammation and angiogenesis as well as other pathways. At each step of the psoriasis molecular pathway, different inflammatory cytokines and angiogenic growth factors are involved such as hypoxia inducible factor-1 α (HIF-1 α), vascular endothelial growth factor (VEGF), matrix metalo proteinases (MMPs), basic fibroblast growth factor (bFGF), Angiopoitin-2, interleukin-8 (IL-8), IL-17, and IL-2. Beside the mentioned growth factors and cytokines, cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) which play roles in both angiogenesis and inflammation are also involved in the pathogenesis. Cannabinoids are active compounds of *Cannabina Sativa* inducing their effects through cannabinoid receptors (CBs). JWH-133 is a synthetic cannabinoid with strong anti-angiogenic and anti-inflammatory activities. This agent is able to inhibit HIF-1 α, VEGF, MMPs, bFGF, IL-8, IL-17, and other mentioned cytokines and adhesion molecules both in vivo and in vitro. Altogether, authors suggest using this cannabinoid for treatment of psoriasis due to its potential in suppressing the two main steps of psoriatic pathogenesis. Of course complementary animal studies and human trials are still required.

Introduction

Psoriasis (PS) is categorized as a skin and also joint disease which affects 2–4% of Caucasian population [1]. This disease is associated with hyperkeratotic plaques in different regions such as elbow, knee, and scalp. Other demonstrations include psoriatic arthritis (PSA) which is a kind of inflammatory synovitis presenting enthesitis and dactylitis leading to polyarthritis and oligoarthritis [1,2]. Histologically, psoriasis has been found to induce the following events: 1) Infiltration of inflammatory cells into the dermis and epidermis. 2) Epidermal hyperplasia and abnormal differentiation of keratinocytes. 3) Hyper-vascular culture in dermis [3–5]. Putting all together, inflammation and angiogenesis could be the two main targets of treatment for psoriasis.

Angiogenesis, the formation of new blood vessels from pre-existing ones, is the key mechanism in corneal neovascularization, tumor growth, rheumatoid arthritis and psoriasis [6–8]. This process is directed by angiogenic cytokines and growth factors such as hypoxia inducible factor-1 α (HIF-1 α), vascular endothelial growth factor (VEGF), matrix metalo proteinases (MMPs), basic fibroblast growth factor (bFGF), Angiopoitin-2, interleukin 8 (IL-8), IL-2 and IL-17. HIF-1α which is secreted under hypoxic situation triggers angiogenesis by inducing VEGF expression. VEGF is considered as a key role player in proliferation and migration of endothelial cells (ECs) finally leading to angiogenesis. Following VEGF activation MMPs (especially MMP-2 and MMP-9) also express and degrade basement membrane in order to facilitate migration of ECs. The mentioned cytokines such as ILs are involved in inflammatory and even angiogenesis processes [6,9–11].

Cannabinoids are known as active compounds of *Cannabina Sativa* with strong anti-inflammatory and anti-angiogenic activities [8]. These compounds are divided into different categories such as endocannabinoids [12] (physiologically produced in the body) and exocannabinoids (synthetics and plant derived CBNs) [13]. JWH-133, with an affinity to G-protein coupled cannabinoid receptor 2 (CB2) is a synthesized cannabinoid with various activities such as anti-angiogenic potential [8]. The CB2 is presented on the various types of cells such as ECs [14], T cells [15] and dendritic cells [16].

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Hypothesis

Considering the proved role of cannabinoids in inhibition and suppression of inflammation and angiogenesis, authors of this study suggest JWH-133 for the treatment of PS. So far two papers hypothesized on possible role of CBNs in PS treatment, but no hypothesized angiogenic pathway is presented [17,18]. Although Namazi [17] stated anti-inflammatory potential of CBNs as a possible pathway but he just considered the role of TNF- α and IL-2. Derakhshande and Kazemi also presented the anti-inflammatory role of CBNs due to the cholinergic anti-inflammatory pathway [18].

Evaluation of hypothesis

Angiogenesis mainly consists of 3 major steps: proliferation, migration and tube formation of endothelial cells [19,20]. Each of these steps is affected by different cytokines and growth factors. As already mentioned, the hypoxia induced response molecule, HIF-1 α is increased in PS as a result of different conditions. This increase is mostly due to the secondary changes in nutrition and oxygen demand and supply following the cellular hyperproliferation (of mostly keratinocytes) or prolongation of diffusion distance due to the plaque formation in dermis [10,21–23]. There is a positive correlation between HIF-1 α and VEGF levels in psoriatic patients' skin [23]. HIF-1 α is mostly responsible for the induction of VEGF expression [24]; although VEGF could express in other pathways as well [25]. VEGF is a key player of angiogenesis in most angiogenic dependent diseases. This factor causes endothelial cells proliferation and also induces the secretion of other angiogenic factors such as MMPs [26]. It has been showed that VEGF is significantly higher in PS patients' blood samples and psoriatic plaques [27–29]. Also, its plasma level could be directly associated with severity of PS considering the clinical presentations [30]. According to the studies, MMPs, especially MMP-2, are found to be highly elevated (up to two folds) in psoriatic patients. MMP-2 is a gelatinase A able to degrade gelatin types III, IV, V and XIV collagen, elastin and aggrecan which helps proliferated ECs to migrate to the proper site [31]. As Simonetti et al. showed, MMP-2 is significantly increased in PS skin tissue compared with normal controls. Also, this enzyme has a positive correlation with VEGF in these patients [23]. Different studies have shown that bFGF concentration is significantly higher in blood samples of psoriatic patients in comparison with controls [32,33]. One of the approved treatments for PS is Goeckerman's therapy. It has been destablished that both VEGF and bFGF serum levels are decreased following Goeckerman's therapy in 44 evaluated psoriatic patients compared with their pretreatment conditions [32]. Ang-2, the other angiogenic factor accompanying VEGF, is able to destabilize the capillaries for initiation of angiogenesis by acting through its specific receptor Tie-2 [33]. Other than sensitizing ECs to TNF-α [34], Ang-2 could increase the expression of ICAM-1 and VCAM-1, two main intracellular molecules engaged in leukocytes infiltration to the tissues through the capillaries [6]. It has been demonstrated that both Ang-2 and Tie-2 are elevated in psoriatic skin in comparison with healthy situation. This expression was positively affected by over-expression of VEGF and bFGF as stimulators of ECs proliferation [33].

According to the data, infiltrated $CD4^+$ cells into the skin are initiators of cutaneous inflammatory state which is characterized by production of different cytokines such as interferon γ (INF-γ), TNF-α and IL-2 [35,36]. TNF-α is responsible for VEGF, IL-8, bFGF expression through stimulation of ECs. Dendritic cells are able to induce VEGF expression via secretion of TNF-α in psoriasis which leads to angiogenesis [6]. IL-8 is a strong cytokine playing role in angiogenesis and inflammation. This cytokine is produced in dermal or epidermal layers by different cells such as ECs, T cells, fibroblasts and keratinocytes [37]. This cytokine is elevated in epidermis of psoriatic skin. IL-8 help lymphocytes to transmigrate through the capillaries to the tissue, which finally leads to the inflammation [38]. Also, this cytokine is able to induce keratinocytes hyper-proliferation as well as ECs. Besides, it can prevent the apoptosis through Bcl-2 pathway in ECs. More to mention IL-8 could induce production of both MMP-2 and MMP-9 in ECs [39]. Moreover, IL-8 and its receptor (IL-8 R) are significantly elevated in psoriatic patients' epidermis in comparison to healthy controls [40]. The other cytokine involved in PS pathogenesis is IL-17 which produces by T helper 17 cells [41]. This cytokine is able to induce angiogenesis through over-expression of other angiogenic factors such as VEGF [22].

So far, different treatments targeting each of the mentioned cytokines or growth factors are suggested and successfully used for treatment of psoriasis. According to Datta-Mitra's study on a PS patient with renal cancer which was treated by an anti-VEGF monoclonal anti-body (Bevacizumab®), a complete remission of PS and psoriatic arthritis was observed [42]. Additionally, in two cases with psoriasis who received Sunitinib (a tyrosine kinase inhibitor of VEGFR) an acceptable improvement in their condition was observed [43,44]. Monoclonal antibodies against TNF-α such as Infliximab® has been confirmed as a systemic treatment for adults' psoriasis by food and drug administration (FDA) in 2006 [45]. This anti-TNF-α antibody is able to inhibit VEGF, MMP-2, Ang-2 and Tie-2 expression which its anti-VEGF and anti-MMP-2 activities in psoriatic patients are proved [6]. Also Methotroxate another FDA approved (1972) agent for treatment of PS, is able to suppress VEGF in PS patients which is completely expected due to its anti-angiogenic activity [46]. Other treatments such as Cyclosporine (with anti-angiogenic and anti-inflammatory activity) and Neovastat® (an anti-angiogenic agent) are used in clinical trials for treatment of psoriasis successfully [6]. Also Secukinumab, Ixekizumab and Brodalumab, three monoclonal antibodies against IL-17 are introduced for PS treatment [41].

As mentioned earlier, PS close relationship with inflammation and angiogenesis has been proved by strong evidences [22]. It has been noted that vascular hyper-density in patients diagnosed with PS is an important step which precedes other steps such as epidermal hyperplasia [47].

Cannabinoids are known to have a critical role in suppressing and inhibiting angiogenesis and inflammation [48]. JWH-133 is able to inhibit angiogenesis both in vivo and in vitro [43,36] through suppression of ECs migration and proliferation [8]. Expression of HIF-1 α gene is 60% decreased after JWH-133 treatment in comparison to control. One of the known paths through which JWH-133 inhibits ECs proliferation is down-regulating VEGF expression. This inhibition occurs up to 50% and 80% for VEGF-A and VEGF-B genes, respectively. Also, this agent is able to decrease the production of VEGF receptor-2 which is the prominent VEGF receptor. A 50% decrease in Ang-2 expression was also detected as well as 60% suppression in Tie-1 [49]. As mentioned before, MMP-2 is a key factor in ECs migration which is strongly suppressed by JWH-133 [50]. Also, cannabinoids could inhibit TNF-α, INF-γ and IL-2 and IL-8 which are considered as key elements of both angiogenesis and inflammation in PS [51,52]. As Rossi et al. showed, JWH-133 could suppress IL-8, IL-1, TNF-α and INF-γ [53]. Furthermore, JWH-133 caused a 40% decrease in wild-type $CD4^+$ T cell proliferation in comparison to controls [52]. Moreover, data show that JWH-133 is capable of suppressing TNF-α induced VCAM-1 and ICAM-1 expression on the surface of ECs [54]. Also JWH-133 could suppress dendritic cells function and maturation through TLR4 which is a main receptor for their function and maturation [51,52]. Moreover this CB2 selective agonist could down-regulate IL-17 expression in T helper cells [55]. Also CBNs are used