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Cannabinoids as Treatment for Hemophilic Arthropathy: Hypothesized Molecular Pathways

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Hemophilia is a recessive X linked hereditary disease which causes coagulation problems. In severe cases, one of the most common issues is hemophilic arthropathy (HA) leading to a range of problems such as joint pain, swelling, crippling and decreased range of motion. Regarding pathogenesis of this phenomenon, the main consequence is emerged as repeated episodes of bleeding leading to inflammation, angiogenesis and synovium hypertrophy. These pathways are triggered and directed by some cytokines and growth factors such as IL-1, IL-6, TNF-α, HIF-α, VEGF and MMP-9. Cannabinoids (CBNs) are active compounds of *Cannabis Sativa* known for their highly potent anti-angiogenic and anti-inflammatory activity. In molecular aspects, they are able to suppress all mentioned cytokines, growth factors and even more angiogenic regulators such as Ang-1 and Ang2. Here we suggested that CBNs could be valid candidates for targeting HA due to their anti-inflammatory and anti-angiogenic activity.

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Introduction

Hemophilia is a hereditary X linked recessive disease which exhibits bleeding disorders [1]. Any deficiency in coagulation pathway factors could lead to halting this condition. Based on the absence of any of these factors, two major types of hemophilia have been categorized: hemophilia A or classic (defect in factor VIII) and hemophilia B or Christmas disease (defect in factor IX) [2]. Both types are characterized by three states of severity: mild, moderate and severe which are associated with present of 5-40%, 1-5% and less than 1% of normal factor amount respectively [3]. As a result of coagulopathy, patients with hemophilia experience spontaneous or traumatic bleeding which could be of different intensity due to different levels of normal factors. According to other studies, sever hemophilia (45% of hemophilic patients) exhibit spontaneous bleeding in which 85% occurs in joints known as hemophilic arthropathy (HA). Among all types of joint bleeding, 80% occur in knee, elbow and ankle drastically affecting their functions [4]. Hemarthrosis in HA patients causes pain, swelling and muscular spasm in short term and crippling and range of decreased motion in long term when there is repeated bleeding episodes. This condition of course is related to multiple bleeding statuses in intra articular space. By repeated articular hemorrhages, imported red blood cells (RBCs) would cause an accumulation of hemosiderin with which inhabitant macrophages start to react. Finally this situation leads to synovial hypertrophy and neovessel formation [5].

Cannabinoids (CBs), known as active compounds of *Cannabis Sativa,* have been divided into two major categories: endocannabinoids (produced in human body) and exocannabinoids. The second group consists of synthetic and plant derived CBNs [6]**.** These compounds are distinguished by their potent anti-inflammatory and anti-angiogenic activity both in vivo and in vitro [7]. CBNs operate by binding to their specific receptors named cannabinoid receptor (CBR) 1 and 2 on cell surface. So far, CBNs are studied on glioma, melanoma, prostate cancer, breast cancer and uveoretinitis. Beside anti-cancer activity, they have been studied in some several immune related diseases such as atherosclerosis, multiple sclerosis, allergic asthma and gut disease [8]. Also as a result of their strong anti-angiogenic activity, CBNs are suggested to be used in treating corneal neovascularization and multiple evanesce white dot syndrome due to their anti-angiogenic and anti-inflammatory potential [7, 9].

Hypothesis

Due to the anti-inflammatory and anti-angiogenic activity of cannabinoids, authors of this study hypothesis possible effect of cannabinoids on hemophilic arthropathy. Synthetic cannabinoids such as JWH-133 and WIN-55 212-2 with anti-angiogenic and anti-inflammatory potentials could be considered as possible agents.

Evaluation of hypothesis

In the molecular pathogenesis of HA, inflammation and neovascularization have been quite bold recently. Experimental data show increased vascular tissue and also an elevated number of inflammatory cells recruited to secret inflammatory cytokines and angiogenic growth factors [10]. An evidence regarding the role of inflammation in HA is the increased number of $CD68^{+}$ macrophages and $CD11^{+}$b monocytes in peripheral blood samples and synovium of HA patients which are known as pro-angiogenic cytokine sources [11]. Also high levels of loaded Iron following the articular hemorrhage has been confirmed to up regulate interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) in the synovium and circulation system in comparison to normal controls [12]. As mentioned above, high vascular density is shrewdly observed in hypertrophied synovium of HA patients [5]. Neovascularization is defined as formation of new blood vessels from pre-existing ones as a response to hypoxia or other angiogenic inducers [13]. Other than physiological conditions such as female reproductive cycle, this phenomenon could also be seen in pathologic conditions such as tumor growth, rheumatoid arthritis, wound healing and psoriatic arthritis [14]. When bleeding occurs in HA, an inflammatory situation is inevitable resulting

in expression and releasing of various angiogenic factors. In hypoxic situation, the affected cells starts to secrete hypoxia inducible factor-1α (HIF-1α) which finally activates expression of vascular endothelial growth factor (VEGF) [15-16] responsible for proliferation of endothelial cells in neovascularization process. Not only VEGF acts as an autocrine agent but also it is considered a stimulator for expression of matrix metalloproteinases (MMPs) and some other pro-angiogenic factors [14]. As in hand data indicates, a significant higher level of HIF-1α is detected in HA synovium which supports the idea of neovascularization having a great role in this process. If HIF-1α is increased, there must be an effect seen on VEGF expression which is approved to be up regulated in both synovium and circulation system in clinic. Other than HIF-1α, factor IX, thrombin and heme also induce VEGF expression in the synovium of HA patients. Acharya et al indicated that migration of endothelial cells is also VEGF dependent and could be suppressed using an anti-VEGF agent. Like VEGF, MMP-9 is elevated 4 folds in synovium and peripheral blood [16]. These two angiogenic factors are key elements to two neovascularization phases: proliferation and migration of endothelial cells. The process of neovascularization, due to the imbalance between vessels and connective tissue, promotes further future bleeding episodes [17]. As explained, in synovium the $CD68^{+}$ macrophages are shown to be colocalized with VEGF beside the VEGF receptor-1 (VEGFR-1) positive $CD11^{+}$b monocytes [16].

As mentioned before CBNs exert effects through CBR 1 and 2. Although the CBR1 is mostly presented on nerves system, it has been detected in eye, testis and endothelial cells too. On the other hand, CBR2 is mostly expressed on immune cells [18] and on endothelial cells where CBR1 is also found [19]. By going through a non-CBR dependent mechanism, CBNs have been reported to reduce secretion of IL-1α, IL-1ß, IL-6 and TNF-α. Also in rheumatoid fibroblast-like synoviocytes, IL-6 level has decreased after CBN treatment [20-21]. Also in synovial cells mRNA levels of TNF-α, IL-6 and IL-1 were also decreased using CBNs through CBR2 [22]. Beside the anti-inflammatory activity of CBNs, a great anti-angiogenic activity has been described for these molecules. CBNs are able to induce their angiogenic inhibitory effect through both CBR 1 and 2 expressed on endothelial cells. CBNs exerted anti-angiogenic effect in vitro and in vivo by inhibiting endothelial cells proliferation, migration, VEGF expression, MMP-2 [19] and 9 secretion and TNF-α production as well as suppressing VEGFR-1 [23] and VEGFR-2 [24]. Moreover, they operate through other pathways to inhibit angiogenesis by affecting Angiopoitin-2 (Ang-2) which has been proved to play an important role in angiogenesis [25]. Although these cytokines are not proved to be directly involved in HA, they are of great importance in angiogenesis process which in turn is ascertained to have a critical role in this pathology condition. (Fig 1)

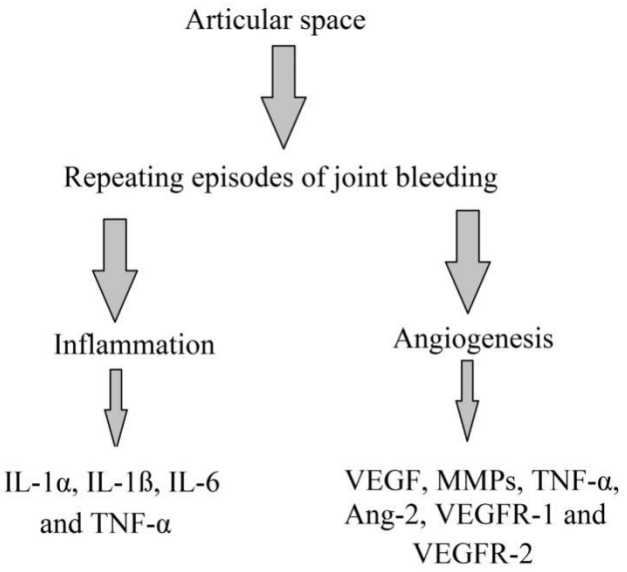

Fig. 1. A summary of both angiogenesis and inflammation roles in hemophilic arthropathy.

Conclusion

As mentioned before, hemophilia with the recurrent joint bleeding causes synovium hypertrophy which finally turns into an articular disorder. The befallen HA is considered the most cause of morbidity in hemophilic patients and burdens a remarkable cost to health system and also society due to its morbidity [4]. In this hypothesis, CBNs potential to combat this issue

was evaluated from a different aspect: targeting inflammation and angiogenesis. According to the data, inflammation and angiogenesis are involved in HA pathogenesis which finally leads to abovementioned problems in the joint [5]. CBNs selection for this aim was due to their highly anti-inflammatory and anti-angiogenic activity [20-26]. On the other hand, as data have illustrated, CBNs could suppress TNF-α secretion, a key cytokine in inflammation and also an intermediate able to conduct angiogenesis in some ways. Thus, this link is no longer permanent by using CBNs. In clinic, CBNs (Δ^9-tetrahydrocannabinol a CBR-1 and 2agonist) have been prescribed to treat recurrent glioblastoma multiform with some side effects of non-repeated, transient to very mild euphoria and transient episode of bulimia, hypothermia and euphoria. Other symptoms were case-specific [27]. Based on the data presented about CBNs and CBRs and their defined mechanism of action leading to suppression of inflammation and angiogenesis, they seem to be beneficial agents for HA therapy or even prophylaxis, although it still demands more animal models such as mice deficient in coagulation factor VIII or IX model of hemophilic arthropathy as well as human studies after [28].

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Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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