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Short communication

Synthesis, biological activities of CBD and its derivatives

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Introduction

Cannabinoids as the hallmark constituents of Cannabis and their analogs have been drawing keen attention from scientists due to their potential medical use. Cannabidiol (CBD), a non-psychotropic cannabinoid, has been approved for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome by FDA in 2018. Cannabidivarin (CBDV) and other natural or synthetic derivatives of cannabidiol especially those with various C4'-side chains in place of the pentyl group, such as KLS-13019, also demonstrated attractive biological activity. However, the bioactivities of many cannabinoids have not been well-studied, such as the antidepressant activity of CBD, partially due to the lack of availability either by natural product separation or chemical synthesis. Herein, we reported an elegant approach to prepare CBD and its analogs with readily available phloroglucinol as the starting material.

With sufficient CBD synthesized from commercially available materials, the antidepressant mechanism of the synthetic CBD after chronic administration was studied in mice. Finally, the antidepressant, anxiolytic and antinociceptive effect of CBD derivatives were also explored.

Materials and methods

Materials

All commercially available chemical reagents and solvents were used directly without further purification. Behavioural experiments were performed using 7-weeks-old male C57BL/6J mice (22-25 g) from Shanghai Sippe-Bk Lab Animal Co., Ltd (Shanghai, China). Experiments were conducted in accordance with guidelines set forth by the national institutes of health and the IACUC protocol.

Methods

Behavioural tests such as forced swim test (FST), open-field test (OFT), western blotting, mRNA expression studies by LightCycler RT-PCR, high-performance liquid chromatography-electrochemical detection (HPLC-ECD) were conducted according to the literature or our previous publications.

Results and discussion

Excess of phloroglucinol (10 eq.) was used for the Friedel-Crafts alkylation of phloroglucinol to avoid bis-alkylation, leading to the desired product CBD-tri-OH in over 80% yield. Regioselective triflation of the C4' phenolic hydroxyl group of CBD-tri-OH was smoothly realized by treatment with Tf_2O in the presence of 2,6-lutidine. Then several protecting groups of phenolic hydroxyl were studied for the Negishi cross-coupling. The large sterically hindered protecting group-"Piv" group was found to be the most suitable in an excellent yield, and the resulted CBD-bis-OPiv-OTf was finally selected as the key intermediate to form the CBD analogues with versatile side chains by the Negishi cross-coupling approach.

Different pharmacologically interesting side chains were successfully coupled in good to high yield, including alkyl, alkenyl, aryl, heteroaryl or alkynyl groups. As CBD is unstable in the presence of acids, the removal of Piv groups was carried out under basic conditions. CH_3MgBr

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was found to be optimal and provided CBD in an excellent 99% yield.

Efficient CBD from synthesis provided material basis for the investigation of its biological activities. Firstly the synthesized CBD was employed to demonstrate the dose level of chronic CBD administration that inducing antidepressant effects in mice, explore the relative changes, and establish the relation of behavioral phenotypes with neurotransmitters and proteins. In our study chronic high dose of CBD (100 mg/kg) treatment significantly decreased IT, while CBD (10 mg/kg, 30 mg/kg) did not alter the IT. Chronic administration of CBD failed to change the locomotor activity of mice, which is in agreement with previous reports. We then investigated expression of some gene and protein (BDNF, mTOR, GluA1, PSD95, eEF-2, NF-κB) levels in HPC but only the expression level of NF-κB protein was changed. NF-κB plays vital role in depressive-like behavior and effects of antidepressants. Inflammation triggers depression and NF-κB could regulate the expression of inflammatory cytokine gene in HPC. Recently it was reported that CBD decreases the production of inflammatory cytokines, hereby lowering TNF-α and IL-6 levels in HPC. In addition, in vitro study demonstrated that CBD prevented the activation and translocation of NF-κB. In our study chronic administration of CBD (30 and 100 mg/kg) significantly decreased NF-κB in mice HPC. Altogether it is possible to suggest that CBD is able to inhibit NF-κB p65 subunit which promoted the production of pro-IL-1β and cleavage by NLRP3 to mature the IL-1β inflammasome pathway and facilitate antidepressant-like effects in HPC. There is a proposed relation between specific symptoms of depression and 5-HT or NA deficiency. In our study, chronic treatment with high dose of CBD increased NA level in HPC without changing its metabolite HVA level, suggesting that chronic administration of CBD elevated NA levels in HPC which may play a vital role in CBD induced antidepressant effect. Chronic administration of CBD 100 mg/kg also significantly increased the 5-HT level in HPC, suggesting that behavioral effects induced by CBD require fully functional serotonin nerve endings in HPC for antidepressant activity. Moreover, CBD significantly decreased the 5-HIAA level, thus further study could reveal new important evidence about effects of CBD on 5-HT metabolism. Finally, the antidepressive, anxiolytic and antinociceptive of CBD analogs were evaluated in different tests such as forced swim test, stress induced hyperthemia and acetic acid induced writhing test. Several CBD derivatives displayed higher potency than CBD in the depression, anxiety or pain models in mice after a single intraperitoneal or subcutaneous administration with the minimum effective doses ranging from 1-10 mg/kg.

Conclusion

A versatile compound of CBD-bis-OPiv-OTf was recognized as a key material for the late-stage introduction of C4'-side chains to efficiently prepare a wide range of CBD analogs under mild conditions by Negishi cross-coupling reaction. Chronic administration of high dose (100 mg/kg) synthetic CBD induces antidepressant effects in behavioral phenotypes in mice. Correlation between behavioral phenotypes with protein and neurotransmitters was established and the possible mechanism was herein postulated. The results showed that a chronic high dose of CBD induced antidepressant effects might be mediated by increasing NA and 5-HT neurotransmitters level and possibly involving the NF-κB signaling pathway. Several CBD derivatives displayed higher potency than that of CBD in the depression, anxiety or pain models in mice after a single administration.

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