EFFECT OF CANNABIDIVARIN, A NON-EUPHORIC PHYTOCANNABINOID, ON MURINE INTESTINAL INFLAMMATION AND BIOPSIES OF ULCERATIVE COLITIS PAEDIATRIC PATIENTS

Tommaso Venneri[1], Ester Pagano[1], Barbara Romano[1], Fabio Arturo Iannotti[2], Olga Alessandra Parisi[1], Maria D'Armiento[3], Lorena Coretti[1], Marianna Lucafò[4], Gabriele Stocco[4], Francesca Lembo[1], Raffaele Capasso[1], Vincenzo Di Marzo[2], Angelo Antonio Izzo[1], Francesca Borrelli[1]

[1]Dipartimento di Farmacia, Università di Naples Federico II, Naples - Italy, [2]Istituto di Chimica Biomolecolare Consiglio Nazionale delle Ricerche, Pozzuoli - Italy, [3]Dipartimento di Scienze Biomorfologiche e Funzionali, Università di Naples Federico II, Naples - Italy, [4]Dipartimento di Scienze della Vita, Università di Trieste, Trieste - Italy

Introduction: Ulcerative colitis (UC) is one of the most common chronic diseases of the gastrointestinal tract, characterized by mucosal and submucosal inflammation. UC results from a complex interaction between environmental, genetic and epigenetic risk factors that cause an inappropriate immune response leading to intestinal inflammation. Cannabidivarin (CBDV), is a non-psychoactive phytocannabinoid able to bind and activate a number of biological targets, including the transient receptor potential Ankirin-1(TRPA1), a member of the TRP channels family, crucially involved in intestinal inflammation. Here, we have evaluated the effect of CBDV in murine models of colitis as well as in biopsies of UC paediatric patients.

Materials and methods: Colitis was induced in mice by intracolonic administration of 2,4-dinitrobenzenesulfonic acid (DNBS) and by oral administration of dextran sulphate sodium salt (DSS). The effect of CBDV was evaluated after oral and intraperitoneal administration on: i) inflammatory markers/parameters (i.e. colon weight/colon length ratio, myeloperoxidase (MPO) activity, intestinal permeability and cytokines production); ii) tissue damage (by histology and immunohistochemistry) and iii) composition of the gut microbiota. Moreover, TRPA1expression was determined (by RT-PCR) in inflamed colons of mice as well as in mucosal colonic biopsies of children with active UC, whose response to incubation with CBDV was also investigated.

Results: CBDV administration attenuated the inflammation in DNBS-induced colitis by reducing the neutrophil infiltration, intestinal permeability, and cytokines (i.e. IL-1β, IL-6and the chemokine MCP-1) production. CBDV also altered the dysregulation of gut microbiota associated to DNBS-induced colitis. The CBDV anti-inflammatory effect was also confirmed in the DSS model of colitis. The effect of CBDV in the DNBS model of colitis was counteracted by the selective TRPA1antagonist HC030031. Furthermore, CBDV lessened inflammation in colonic biopsies collected from UC paediatric patients, a condition in which we demonstrated the TRPA1up-regulation.

Discussion and conclusions: CBDV administration is able to attenuate, via TRPA1, intestinal inflammation in mice by reducing a set of well-established inflammatory parameters. Also, CBDV partially normalized the dysregulation of gut microbiota, which could have a role in the observed anti-inflammatory effect. In the light of its favourable safety profile in humans, CBDV might be considered for possible clinical trials in patients with UC.