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

Tommaso Venneri1, Ester Pagano1, Barbara Romano1, Fabio Arturo Iannotti2, Olga Alessandra Parisi1, Maria D’Armiento3, Lorena Coretti1, Marianna Lucafo4, Gabriele Stocco4, Francesca Lembo1, Raffaele Capasso1, Vincenzo Di Marzo2, Angelo Antonio Izzo1, Francesca Borrelli1

1Dipartimento di Farmacia, Università di Naples Federico II, Naples - Italy, 2Istituto di Chimica Biomolecolare Consiglio Nazionale delle Ricerche, Pozzuoli - Italy, 3Dipartimento di Scienze Biomorfologiche e Funzionali, Università di Naples Federico II, Naples - Italy, 4Dipartimento 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 Anchirin-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, TRPA1 expression 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-6 and 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 TRPA1 antagonist HC030031. Furthermore, CBDV lessened inflammation in colonic biopsies collected from UC paediatric patients, a condition in which we demonstrated the TRPA1 up-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.