ORAL COMMUNICATIONS

B-SITOSTEROL-D-GLUCOSIDE TRIGGERS INTESTINAL INFLAMMATION IN ZEBRAFISH LARVAE POSSIBLY LEADING TO NEURODEGENERATION THROUGH THE GUT-BRAIN AXIS

Francesca Terrin[1], Sofia Faggin[2|3], Chiara Consorti[4], Stefania Marcotti[5], Paolo Bonaldo[4], Maria Cecilia Giron[2], Nicoletta Plotegher[1], Luisa Dalla Valle[1]

[1]Department of Biology, University of Padova, Italy; [2]Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Italy; [3]Institute of Digestive Health Research (IRSD), Toulouse University, France; [4]Department of Molecular Medicine, University of Padova, Italy; [5]Randall Centre for Cell and Molecular Biophysics, King's College London, London; UK

Glucosylated-sterols are lipids that can be synthetized endogenously, derive from bacterial infection or be absorbed through the diet. Since their functions in cellular metabolism are still poorly understood, their clinical relevance is likely underestimated, although imbalances in their levels have been associated with an increased risk of neurodegeneration. We investigated the detrimental effects elicited by the plant-derived β-sitosterol-D-glucoside (BSSG), which has been implicated in the occurrence of a complex neurodegenerative disorder, to clarify its mechanism of action.

Zebrafish larvae were treated with BSSG and, as the intestine emerged as the primary target tissue, we performed an extensive characterization of this organ through morphological, physiological and transcriptional analyses, also exploiting different transgenic lines. Effects on the central nervous system (CNS) were assessed through locomotor behavior assay, evaluation of motor neuron axonal arborization, analysis of neuromuscular junctions (NMJs), and quantification of protein expression.

BSSG exposure induced intestinal inflammation, as evidenced by inflammatory response, gut dysmotility and upregulation of inflammation-related genes. In the CNS, we observed motor impairment, axonal disorganization, defective NMJs, and altered levels of proteins associated with neurodegeneration. Intriguingly, our results suggest that BSSG, likely due to its chemical structure, may interact with the glucocorticoid receptor, potentially impairing its canonical anti-inflammatory activity.

Overall, we found that dietary BSSG initially triggers gut inflammation, possibly promoting neurodegeneration through interference with the well-known gut-brain axis.