Gut–brain axis modulation by rifaximin treatment improves neurological and anatomical outcomes after traumatic brain injury

Francesca Tribuzio[1], Francesca Pischiutta[1], Akash Bera[2], Francesca Sironi[1], Gabriele Cattaneo[2], Costanza Bertani[1], Alessia Boccacci[1], Federico Moro[1], Annamaria Vezzani[2], Teresa Ravizza[2], Elisa R Zanier[1]

[1] Laboratory of Traumatic Brain Injury and Neuroprotection, Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, [2] Laboratory of Epilepsy and Therapeutic Strategies, Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Background: Traumatic brain injury (TBI) disrupts gut homeostasis, leading to inflammation, increased barrier permeability and dysbiosis. However, the contribution of gut dysfunction to neurological deterioration remains unclear. Here we investigate whether a gut-targeted intervention, based on the gastrointestinal-specific antibiotic rifaximin, can affect gut-brain axis and improve neurological outcomes.

Materials and methods: Adult C57BL/6J male and female mice underwent sham (n=8) or severe TBI (by controlled cortical impact, n=20) surgery. Treatment (placebo/rifaximin dosage: ≥115 mg/kg body weight) was delivered per o.s. acutely (1 hour post TBI, then daily up to day 3) and through medicated diet for 2 months (m). Outcome measurements included: sensorimotor (SNAP, at 3 days then every week [w]) and cognitive (Barnes Maze, 4w) functions, anatomical damage (T2-weighted MRI, 6w), longitudinal serum NfL levels as a biomarker of neuronal damage, gut morphometric parameters (histological analyses) and inflammation (Iba1 IHC) at 2m.

Results: TBI induced gut pathology at 2m, as shown by a reduction in duodenal villus height (-12%, $p<0.001$), villus height/crypt depth ratio (VH/CD) (-14%, $p<0.001$), goblet cells/villus (-29%, $p<0.0001$), and increased Iba1+ macrophages in the lamina propria (+36%, $p<0.0001$) compared to sham mice. Rifaximin treatment improved gut morphometric alterations (VH: +16%, VH/CD: +23%, goblet cells/villus: +52%) and inflammation (Iba1+ cells: -26%) compared to TBI placebo (all $p<0.001$). Rifaximin significantly ameliorated sensorimotor deficits (at 3d and 7w, $p<0.05$) and cognitive function (primary latency in 3-days learning period AUC: +32%, $p<0.05$), and reduced contusion volume (-14%, $p<0.01$) but did not affect circulating NfL levels.

Conclusion: Following TBI, gut-targeted intervention with rifaximin reduces intestinal alterations and improves neurological outcome. These findings underscore the contribution of gut dysfunction to post-TBI deterioration and support gut-targeted interventions as a promising avenue for therapeutic development.

Funding: Italian Ministry of Health, Next Generation EU – PNRR-MAD-2022-12375695.