Microbiota Metabolites Modulate the T Helper 17 to Regulatory T Cell (Th17/Treg) Imbalance Promoting Resilience to Stress-Induced Anxiety- and Depressive-Like Behaviors

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Objectives: Chronic stress disrupts immune homeostasis while gut microbiota-derived metabolites attenuate inflammation, thus promoting resilience to stress-induced immune and behavioral abnormalities. There are both peripheral and brain region-specific maladaptations of the immune response to chronic stress that produce interrelated mechanistic considerations required for the design of novel therapeutic strategies for prevention of stress-induced psychological impairment.

Methods: Pharmacokinetic studies revealed that this effect may be attributed to specific synbiotic-produced metabolites including 4-hydroxyphenylpropionic, 4-hydroxyphenylacetic acid and caffeic acid. Using a model of chronic unpredictable stress, behavioral abnormalities were associated to strong immune cell activation and recruitment in the ileum while inflammasome pathways were implicated in the prefrontal cortex and hippocampus. Chronic stress also upregulated the ratio of activated proinflammatory T helper 17 (Th17) to regulatory T cells (Treg) in the liver and ileum and it was predicted with ingenuity pathway analysis that the aryl hydrocarbon receptor (AHR) could be driving the synbiotic’s effect on the ileum’s inflammatory response to stress. Synbiotic treatment indiscriminately attenuated the stress-induced immune and behavioral aberrations in both the ileum and the brain while in a gut-immune co-culture model, the synbiotic-specific metabolites promoted anti-inflammatory activity through the AHR.

Results: This study shows that a combination of probiotics and polyphenol-rich prebiotics, a synbiotic, attenuates the chronic-stress induced inflammatory responses in the ileum and the prefrontal cortex promoting resilience to the consequent depressive- and anxiety-like behaviors in male mice.

Conclusions: Overall, this study characterizes a novel synbiotic treatment for chronic-stress induced behavioral impairments while defining a putative mechanism of gut-microbiota host interaction for modulating the peripheral and brain immune systems.

Funding Sources: Grant AT008661 from the NIH’s ODS and the NCCIH.