

## Gluten and the Gut-Microbiota-Brain Axis: A Disturbance in the Force

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**Abbreviations:** EGCs: Enteric glial cells; FODMAPs: Fermentable Oligo-Di-Monosaccharides and Polyols; MGB: Gut-Microbiota-Brain axis; CD: Celiac disease; NCGS: Nonceliac gluten sensitivity; TG2: Tissue-transglutaminase 2

The prevalence of gluten-related disorders from a recent studies of 392 self-diagnosed patients after an elimination diet and reintroduction of was found to be 7%, significantly greater than previously published estimates of NCGS of 1% [1,2]. Gluten and gliadin are good at disrupting the microbiome in susceptible individuals [3]. Pathogenic gut microbiota up regulates inflammatory cytokines resulting in reactive enteric gliosis which stimulates a change in gut motility.

Researchers are connecting the dots between the gut, microbiome, and healthy brain function. The Gut-Microbiota-Brain (GMB) axis hypothesis not only proposes a role for enteric glial cells (EGCs) as defenders of the intestinal epithelial barrier, but outlines for us how the shift from gut homeostasis to a state of chronic inflammation likely takes place as has been shown in celiac disease, non-celiac gluten sensitivity, and various neuropsychiatric disorders[4-7]. When the colonization and homeostasis of the “force” (gut microbiota) is disturbed in a gluten sensitive individual, two scenarios occur resulting in intestinal inflammation. The first involves the deamidation of gliadin by enzyme tissue-transglutaminase 2 (TG2) resulting in gliadin peptides being presented to the innate immune system [8,9]. The second are mucosal protective mechanisms such as the release of anti-inflammatory gliomediators by EGCs, and upon activation of IFN-  $\gamma$  in CD and increase in mRNA for IFN-  $\gamma$  and increased CD3+ IELs in NCGS patients [10-14]. A true gut-brain connection presumes that there is bi-directional flow of neuro regulatory molecules between the two systems. The discovery of the “glymphatic system,” which moves cerebral spinal fluid through a system of glial water channels is theorized to facilitate transport into the brain of proteins from peripheral tissues, and the removal of the metabolic solute and proteins to the liver [11].

For nutrition scientists this opens the door to taking a fresh look at the nutritional needs of the human microbiota themselves, as well as the flow of anti-inflammatory nutrients in an out of the brain [15]. Nutrition and health assessments in the future will include an analysis of key fecal macrobiota early in life [16-18]. Diet intervention in gluten-related disorders, such as autism, epilepsy, ataxia, and dementia, should include appropriate prebiotics, probiotics, omega-3 fatty acids, butyrate, and a modified diet low in fermentable sugars (FODMAPs) [19-25].

The phrase *what goes around comes around* is an apt description of the synergy between gastroenterology and neuroscience literatures on gluten-related disorders, as well as the discoveries of how our food choices shape the microbiome - our frontline for the defense of physical and mental health.

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