

Identification of a Choroid Plexus Vascular Barrier whose closure upon Intestinal Inflammation leads to Behavioral Impairments.

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Thirty four percent of patients with inflammatory bowel disease (IBD, Crohn's disease and ulcerative colitis) suffers from anxiety/depression¹. This number may be even higher as intracerebral white matter lesions have been described by MRI in 40% of patients with asymptomatic IBD². Depression in IBD patients has often been considered a consequence of the difficulty to cope with the chronicity and self-management of the disorder. However, it is difficult to think that this may be the only cause of depression³. We have recently demonstrated the existence of a gut vascular barrier (GVB) throughout the intestine, which controls the systemic dissemination of molecules and bacteria from the intestine to the liver, and can be considered a gateway between the gut and the liver^{4,5}. We hypothesized here that IBD-related depression may be a pathological condition arising as a consequence of the inflammatory state in the intestine, and may be linked to a deregulated gut-liver-brain vascular axis. We show that during intestinal inflammation the GVB opens up and allows the recruitment of inflammatory cells not only in the gut, but also in the liver and the brain. However, when we analyzed whether intestinal inflammation resulted in blood-brain barrier (BBB) disruption, we observed that the BBB was not affected. By contrast, we found that the principal gateway for the brain parenchyma is the choroid plexus (CP), which after an initial increased permeability, is completely shut-off to protect the brain from further damage. Serum untargeted metabolomics analysis of mice with genetically closed CP, identified four significantly altered metabolites that have been reported to be involved in depression in humans and mouse models. Consistently, genetically-driven closure of the CP, even in the absence of inflammation, resulted in a depression state.

These results indicate the existence of a so far unappreciated additional barrier in the brain: the plexus vascular barrier (PVB), that is functionally connected with the GVB and that responds to systemic inflammation by modulating its permeability to protect the brain from inflammatory-induced damage. This provides a link between IBD and depression indicating that the latter is the consequence of a defense mechanism to protect the brain.

