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LETTER TO THE EDITOR

The gut microbiome integrates immune-inflammatory processes in depression

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Dear Editor,

I read with interest the recent article published in Dusunen Adam The Journal of Psychiatry and Neurological Sciences by Usta et al. (1) on the increased levels of inflammatory factors in adolescents with mood disorders. This is an area in which our research group has considerable interest, particularly as to the upstream effects of gut dysbiosis and increased gut permeability and the downstream effects of pro-inflammatory cytokine-induced kynurenine pathway products (2-4).

Alterations in the constitution of the gut microbiome (gut dysbiosis) and associated increases in gut permeability are evident in both major depressive disorder (MDD) and bipolar disorders (BD) (5). The increase in gut permeability allows the transfer of gut bacterial fragments (lipopolysaccharide-LPS) or tiny fragments of partially digested food into the circulation, thereby triggering immune-inflammatory processes. Consequently, there is an increase in innate and adaptive immune cell activation coupled to elevated levels of pro-inflammatory cytokines. Heightened levels of interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor-alpha (TNF-α) and interferon-gamma can increase indoleamine 2,3-dioxygenase, which takes tryptophan away from serotonin and melatonin synthesis by driving tryptophan to the production of kynurenine and kynurenine pathway products. Likewise stress/cortisol can increase tryptophan 2,3-dioxygenase, similarly leading to elevations in the kynurenine pathway activity. A decrease in the tryptophan/kynurenine ratio is common in mood disorders (4).

An increase in the kynurenine pathway product, quinolinic acid, results in excitotoxicity via the glutamatergic N-methyl-d-aspartate (NMDA) receptor, with heightened levels of quinolinic acid in the frontal cortex associated with an elevated suicide risk in mood disorder patients (6). The effects of quinolinic acid may be attenuated by increases in another kynurenine pathway product, kynurenic acid, which is an antagonist at the NMDA receptor. As such, variations in the quinolinic acid/kynurenic acid ratio are an important determinant of the effects of heightened immune-inflammatory processes in MDD and BD patients (6).

The activation of the kynurenine pathway leads to a decrease in tryptophan availability for serotonin synthesis, linking to the classical role of decreased serotonin in mood disorders. The lower levels of serotonin result in a decrease in serotonin as a precursor for the melatonergic pathway, leading to a decreased synthesis of N-acetylserotonin and melatonin. It is now appreciated that this is of some importance, with recent data showing melatonin to be produced within the mitochondria of all cells, where it acts to regulate and optimize mitochondrial function (7). Suboptimal mitochondrial function is common in the cells of many tissues in mood disorder patients (8). As such, immune-inflammatory processes may be directly linked to the alterations in mitochondrial function in MDD and BD patients. It is also of note that variations in mitochondrial function are important to the regulation

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of immune cells, with reactive immune cells shifting from oxidative phosphorylation to a more glycolytic metabolism. Consequently, immune-inflammatory activity may act to drive alterations in immune responses, if not acted upon by the compensatory immune-inflammatory response system (9). It is alterations in immune cell responses that underpin neuroprogression in MDD and BD patients, whereby alterations in the biological underpinnings of a given patients will change with recurrent episodes (10). This is of clinical importance as it results in previously effective medication in a prior episode having no efficacy in a subsequent mood episode, due to such alterations in immune activity and immune-mediated processes.

An increase in gut permeability is also associated with changes in the contents of intestinal epithelial cell exosomes, including the release of high mobility group box (HMGB)1 within such exosomes. Exosomal HMGB1 can activate the microglial toll-like receptor 4, where it can parallel the effects of LPS by reactivating microglia. Alterations in the content of intestinal epithelial cell exosomes may also act to prime the immune system (11), with exosomal content being another aspect of how gut permeability can influence systemic processes.

The other related aspect of the gut's influence on systemic processes is gut dysbiosis. Across a host of medical conditions (12-14), gut dysbiosis is associated with a decrease in the short-chain fatty acid, butyrate. Butyrate not only acts to maintain gut barrier integrity via histone deacetylase (HDAC) inhibition and the induction of the melatonergic pathway (15), but can also transfer across intestinal epithelial cells to reach the general circulation. Butyrate acts to suppress immune cell activity, at least partly via HDAC inhibition and its ability of optimize mitochondrial function, likely mediated by its induction of the melatonergic pathway. Consequently, increasing the production of butyrate, or treating patients with its nutraceutical equivalent, sodium butyrate, prevents gut permeability and therefore gut-derived LPS and HMGB1 effects in immune and brain glial cells.

Many factors can act to induce gut dysbiosis and increase gut permeability, including dietary factors and stress, with stress acting via the induction of hypothalamic and amygdala corticotrophin releasing factor (CRF), which acts in mucosal mast cells to increase TNF-α, leading to a slackening of tight junctions and an increase in gut permeability (16). Incorporating changes in the gut more readily allows stressors to be better integrated into the biological underpinnings of mood disorders. It also explains better how mood disorders and stress are associated with a host of other diverse medical conditions, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, and borderline personality disorder (17). The contrasting impacts of butyrate and LPS on immune and glial mitochondrial function allows modelling of gut-related changes in mood disorders to explain better the often-ubiquitous decrease in mitochondrial function that is evident in MDD and BD, including in muscle cells and platelets (8).

Incorporating the gut into how immune-inflammatory processes form the biological underpinnings of mood disorders also has treatment implications. Recent work shows the efficacy of probiotics in mood disorders, whilst the efficacy of sodium butyrate has only been shown in preclinical models to date (18). Overall, gut dysbiosis and gut permeability would seem a major aspect of the pathoetiology and pathophysiology of MDD and BD, with significant treatment implications.

Conflict of Interest: The author declares that there is no conflict of interest.

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