Prevention of traumatic brain injury-related death using the brain-gut axis

Traumatic brain injuries (TBIs) are often unavoidable injuries that occur acutely and can cause severe disabilities to those involved. They can occur in sports, or unavoidable accidents. The symptoms of TBI range from dizziness and loss of consciousness, to more severe symptoms such as immobility and death. Recovery from these injuries is lengthy and is associated with mortality. Work done by Elise L. Ma *et al.* has uncovered a potential relationship between the brain injuries and the gut integrity. Brain injuries can compromise gut barrier integrity and allow infections to spread easily following a TBI. By using these new associations, further research can be done to investigate the role of the brain-gut axis after an injury, and potentially be used to prevent infections and reduce mortality during recovery.

The work done by Elise L. Ma *et al.* has shined a light on the complex relationship present between the brain and the colon after a TBI. The bidirectional communication after a brain injury, including changes in the mucosa of the colon, offers an exciting avenue for future research focused on combating these changes. Successful follow-up research has the potential to enhance recovery from a TBI.

The researchers focused on mucosal changes in the colon of mice after inflicting a TBI, and then followed up with infection by a bacterium analogous to the human *Escherichia coli* to track the bidirectional communication following moderate level TBI. Their results lead to various findings. The first finding is that, in the colon, mucosal depth had increased, and smooth muscle had thickened after a TBI. The second finding is that 28-day post-TBI, claudin-1, a tight junction protein, messenger RNA expression had decreased, and paracellular permeability had increased. Mucosal enteric glial cell (EGC) activity in the colon was tracked using glial fibrillary acidic protein (GFAP), a protein expressed by EGCs. GFAP levels increased following TBI, signifying that there was increased EGC activity. Bacterial infection leads to increased EGC activity as well, and additionally exacerbated the TBI injury.^[1]

These results offer potential research options. One implication of the study is that claudin-1 expression is decreased, presumably leading to the decreased barrier function of the colon. With a weakened barrier, extrinsic infections have a route to spread systemically, leading to infection secondary to TBI. Upregulating

claudin-1 expression post-TBI is a potential avenue for exploration to prevent secondary infections. Relatedly, there are many other claudin proteins that play a pivotal role in barrier function, which leads to the question if overexpression of these would play a protective role.

Mucosal EGCs are implicated in epithelial barrier integrity, and their upregulation post-TBI may likely be in response to mucosal barrier dysfunction. Research focusing on the specific role of EGCs and potential upregulation may offer a protective role following injury. This is another route to offer protection against exogenous infections that can further exacerbate TBI symptoms, leading to complication in recovery or death. Previous studies have shown that treating mice with an antiviral drug, ganciclovir, resulted in decreased GFAP expression in the intestine as well as increases in inflammatory cytokines.^[2] These results support that EGCs play a role in maintaining a gut barrier. Will upregulating their activity have a prophylactic effect following TBI? Furthermore, an EGC-derived compound, S-Nitrosoglutathione, was shown to induce epithelial resistance.^[2] Further work can be done to understand how the EGCs and their compounds function in barrier maintenance, and if their role is vital in the brain-gut axis to prevent infection.

The link between bacterial infection in the gut and exacerbation of brain injury needs further research as well. Understanding how the brain-gut axis works and finding therapeutic mechanisms to alter the communication post-TBI can lead to a potential decrease in TBI exacerbation due to secondary infection. Some studies have demonstrated that the gut microbiome plays an important role in the regulation of the enteric nervous system and the central nervous system, and without a healthy bacterial population, there can be variations in neurotransmitter expression and gut function.^[3] Can treating with probiotics post-TBI serve a protective measure to prevent further brain damage?

Elise L. Ma *et al.* have highlighted many interesting findings regarding the brain-gut axis and its effects post-TBI. The CDC states that in 2013, there were 2.8 million TBI-related ED visits. In 2010, the rate of TBI-related death was 17.1/100,000.^[4] Insight into how the brain-gut axis works post-TBI as well as exacerbation of TBI after a gut infection is the first step in working to

reduce TBI-related deaths. With more research on the link between TBI and the gut, these numbers have the potential of being reduced further.

TBIs are a still a prevalent injury, especially in areas of athletics, traumatic falls, and unintended accidents. Recovery from a TBI is lengthy and results in weakened motor skills for the patient. These injuries are further complicated by the related mortality during recovery. The research has indicated that a potential cause of TBI-related mortality may be due to infection secondary to the injury, specifically due to a compromised gut barrier following TBIs. The current research suggests that the brain-gut axis is responsible for cellular communication linking the intestinal system with the central nervous system. The work done by Elise L. Ma *et al.* supports the hypothesis that TBI correlates with a weakened intestinal barrier system, with evidence suggesting it may be related to claudin-1 expression and EGC properties. Looking forward, further investigation into the precise mechanisms as well as protective agents has the likelihood of decreasing TBI-related mortality due to secondary infections.

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