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The Beehive Theory: Role of microorganisms in late sequelae of traumatic brain injury and chronic traumatic encephalopathy

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A B S T R A C T

Traumatic brain injury and chronic traumatic encephalopathy are both major health problems, well-publicized for the severe delayed effects attributed to them, including cognitive decline, psychiatric disorders, seizures, impaired motor function, and personality changes. For convenience, the two afflictions are considered together under the rubric traumatic brain injury. Despite the need for neuroprotective agents, no substances have shown efficacy in clinical studies. Thus, a deeper understanding of the neuropathological mechanism of such injury is still needed. Proposed here is a theory that microorganisms from within the brain and elsewhere in the body contribute to the long-term neurological deterioration characteristic of traumatic brain injury. The label, "The Beehive Theory", is drawn from the well-known fact that disturbing a tranquil beehive with a blow can cause a swarm of angry bees to exit their dwelling place and attack nearby humans. Similarly, an impact to the head can initiate dislocations and disruptions in the microbiota present in the brain and body. First, since the normal human brain is not sterile, but is host to a variety of microorganisms, blows to the skull may dislodge them from their accustomed local environments, in which they have been living in quiet equilibrium with neighboring brain cells. Deleterious substances may be released by the displaced microbes, including metabolic products and antigens. Second, upon impact commensal microbes already resident on surfaces of the nose, mouth, and eyes, and potentially harmful organisms from the environment, may gain access to the brain through the distal ends of the olfactory and optic nerves or even a disrupted blood-brain barrier. Third, microbes dwelling in more distant parts of the body may be propelled through the walls of local blood vessels into the bloodstream, and then leak out into damaged areas of the brain that have increased blood-brain barrier permeability. Fourth, the impact may cause dysbiosis in the gastrointestinal microbiome, thereby disrupting signaling via the gut-brain axis. Possible preventatives or therapeutics that would address the adverse contributions of microbes to the late sequelae of traumatic brain injury include anti-inflammatories, antibacterials, antivirals, and probiotics.

Background

The early and late sequelae of traumatic brain injury

The late sequelae of non-penetrating traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE) are a leading cause of disability worldwide in those under 50 years of age, and are thought to contribute to many cases of premature death and even suicide. The degenerative brain disease CTE has been highly publicized for its occurrence in boxers, football players, and military personnel exposed to repetitive concussive and sub-concussive trauma. TBI has drawn attention because of blast injuries, such as result from improvised explosive devices, and traffic accidents. The delayed effects of both conditions are reported to include personality changes, cognition problems, psychiatric disorders, seizures, and impaired motor function [1]. Because the terminology and definitions used by researchers are still in flux, for convenience we will use the rubric TBI to embrace both CTE and closed-head TBI, including the qualifiers used by some researchers: minor, mild, and repetitive [2].

For the purposes of this hypothesis, it is important to draw a distinction between early and late effects of TBI, though the first may subtly evolve into the second. The possible early results of the initial blow to the head have been well characterized. First there is direct damage to intracranial neural tissue, followed quickly by effects that include hematoma, focal intracranial hemorrhage, direct axonal damage, and contusion [3,4]. These often lead quickly to a cascade of harmful events: brain swelling, edema formation, changes in cerebral blood flow, increased intracranial pressure, hypoxia, free radical generation (damaging neural cells), excitotoxicity from excess glutamate, and neuroinflammation (due to a systemic as well as local immune response) [4,5].

Knowledge gaps in pathophysiology of late sequelae of TBI

Obviously, there would be no late-onset problems to be dealt with if the initial blow or blows to the head could be prevented in the first place, or effectively cushioned. Unfortunately, that ideal situation must await changes within sports, driving, and military engagements, or progress in creating protective cushioning for the head.

Thus, we are left with the challenge of preventing the delayed sequelae from developing, or ameliorating them. Currently there are no effective therapies to accomplish these goals, as no neuroprotective

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agents have improved mortality or neurological outcomes in clinical studies, or shown efficacy beyond preclinical studies [6–8]. This indicates that we need a better understanding of the pathophysiology of these deleterious changes.

Considerable research has already been done, although there is a general acknowledgment that the neurophysiological characterization of TBI is still in its infancy [9]. Laboratory experiments have used animal models, involving closed and open head injury, as well as blast injury [1,10–12]. However, there is difficulty in defining an appropriate animal model that can recapitulate the diverse types of impact and primary/secondary injury conditions faced by athletes or military personnel who experience a TBI [4]. For example, a real-life TBI usually involves whole body impact, which is substantially different from impacts conducted under lab conditions. These usually involve keeping an animal immobile during, for example, the commonly used weight drop procedure. Also, a well-run laboratory does not expose animals to the same environmental conditions of dirt, bacteria, etc. that are inevitable with real-life TBIs, and which may contribute to the delayed effects. The knowledge gaps in understanding of TBI thus present an opportunity to consider the as yet unrecognized roles that microbes may be playing in its late sequelae.

The Beehive Theory: A microbial mechanism for late sequelae of TBI

Proposed here is a theory that activated microbes participate in causing the long-term neurological damage from closed-skull TBI. I suggest the apt name is “The Beehive Theory”. The central barrier to such considerations has been the decades of belief, and teaching, that the normal human brain is sterile, i.e., there are no microorganisms present. Accordingly, there seemed no need to consider such agents in understanding the mechanisms behind the loss of brain structure and function which can develop as late effects of TBI. However, in recognition of newer evidence, the central idea behind “The Beehive Theory” is that microorganisms both from within the brain itself, and/or from elsewhere in the body, may contribute to the late-onset injury.

There is now abundant evidence that the brain is not sterile, but is home to a variety of microbes, which may be commensals or pathogenic [13–19]. In addition, there are a wide variety of microbiota throughout the body, some of which can circulate in the blood and potentially enter the brain, under the right circumstances [20]. In a healthy individual, all of these microbial communities are generally existing in a harmonious state with their human host, even contributing a wide range of beneficial health effects [21].

This equilibrium in the healthy body and brain is similar to that within a tranquil beehive in which, under normal conditions, there is a hum of activity – with bees producing honey, reproducing, communicating with each other, etc. An external knock into the beehive causes the bees to become agitated, abandon their routine tasks, and go immediately on the attack. They swarm out of the hive, and deposit their venom into whomever they find nearby, punishing that person – guilty or not – for disturbing them. The Beehive Theory postulates, similarly, that the sharp blows to the head initiating the TBI may disturb the microbial equilibrium in the brain and elsewhere, wherein organisms are living in a dormant or possibly commensal form. These disruptions of microorganisms may lead to harmful consequences to brain tissues and their functions.

While numerous animal studies have been carried out to study TBI, they all essentially involve hitting the skull of the animal, or exposing it to a blast, and then testing it on the performance of an activity for which it has been previously trained, e.g. swimming, in order to evaluate its cognitive impairment. Afterwards, the animal is sacrificed, and the brain is studied to see if there are pathological changes that can be correlated with the experimental blow to the head [11,12]. Through animal and human pathologic studies, as well as epidemiological ones, the concept has arisen that the physical blow – single or repetitive over time – is the sole or proximal factor that causes the loss of cognition following a TBI.

The Beehive Theory presents and incorporates an important intermediate step that has not yet been recognized or thoroughly studied. It principally holds that commensal or pathogenic microbes can be important contributors to ultimate cognitive and functional damage in the brain. First, those living in quiet equilibrium, or dormant, within the brain may be dislodged/disrupted by the blow to the head, and incite damage locally. Second, microbes commensally inhabiting the mouth, nose or eyes, or contributed from environmental sources such as dirt, etc., can gain access to the brain, through a disrupted intracranial blood-brain barrier (BBB) or via the nasal or ocular nerves’ distal endings in the nose and eyes. Third, microbes in other parts of the body may be propelled by the impact into the bloodstream, travel into the brain’s blood vessels, and leak out there through increased permeability of the BBB. A fourth possibility is that the impact that causes a TBI may also cause a disruption elsewhere in the body’s normal pattern of healthy microbiota, in abundance and type, especially in the intestinal microbiome, which subsequently hinders or alters signals sent via the gut-brain axis to the brain [22]. Evidence supporting these four possibilities will now be considered.

Microbes are within the brain at time of TBI impact

In both a diseased and a healthy state, the brain is now known to be host to commensal and other co-existing microorganisms and their metabolites. For example, human herpesviruses (HHVs) can persist in the body for an indefinite period in a latent form, and they have unique mechanisms allowing them to invade the central nervous system (CNS), making them the most frequently detected pathogen in the human brain [13]. Specifically, herpes simplex virus type 1 (HSV-1), has been found both in non-diseased brains and the brains of Alzheimer’s disease (AD) patients [23]. In addition, bacteriophage and HHV-4, -5 and -6 have been reported in the autopsied brains of people with HIV/AIDS, AD, and in non-diseased controls [14,24].

Bacteria have also been detected in the brain tissue of patients with HIV/AIDS [14], multiple sclerosis (MS) [15], and AD [16,19,25]. Importantly, studies have reported that bacteria were also detected in the CNS of healthy human subjects [17,18,25].

Additionally, fungi, yeast, parasites, and prions have been detected in the brain tissue of humans not known to be ill with any disease related to these microbes. Fungal genera have been reported in the brains of AD patients [19,26] and their controls [19], with AD patients having a higher prevalence of certain genera. Human brain specimens have also been host to yeast *(C. albicans)* [27], as well as Protozoan parasites (Toxoplasma gondii) [28], the latter of which may persist in the CNS for the lifetime of the patient [29]. The prion protein PRNP has been detected in the brains of patients with transmissible spongiform encephalopathies [30].

There is also evidence of microbes dwelling in axons, glial cells, and dendrites [18]. A TBI impact may create axonal [4], neuronal [10], and glial damage [1,10], which may disrupt any of these microbial habitats.

The variety of microbial types already in the brain also provides suggestive evidence that microorganisms reported near the BBB may cross into the brain tissue under certain conditions [18].

Another source of brain microbes and their products is the oral cavity. Dental procedures and even simple toothbrushing may cause bacteremia [31]. Spirochetes, probably from dental locations, have been found in the post-mortem brains of AD patients [31]. Furthermore, bacteria, bacterial products, and pro-inflammatory molecules that originate in the periodontal area can travel via neural pathways or the bloodstream to be deposited in the brain. This has been shown to increase inflammatory cytokine levels, likely contributing to amyloid deposits and cognitive decline in patients [32].

As we can see from the research cited, the presence of microbes in the human brain is not limited to active infection, or even to disease-causing microbes. Much like an undisturbed beehive, there are a wide

variety of commensal and potentially pathogenic microbes that can dwell in the brain and body, apparently in a state that is not harmful to the host. But impacts to the head may disturb this peace.

TBI and disruption of microflora outside the brain

In contrast to the constrained actions and limited variables in laboratory experiments, in real life the force which creates the head trauma is usually not isolated to the head; the whole body often receives an impact. Thus, a TBI may disrupt the microflora of body areas beyond the brain itself.

Affected areas can include the oropharyngeal region and the gastrointestinal system. Evidence of such is the dramatic changes in the abundance and bacterial composition of gastrointestinal microflora which occur in humans within the first 72 h of an impact from a TBI [22]. Findings from TBI injuries in rats reveal changes in bacterial composition and diversity of gastrointestinal microbiota occur within the first 2 h, persisting for 7 days [22]. There is also evidence of TBI causing acute dysbiosis in the gastrointestinal/fecal microbiome of mice [33].

One mechanism through which TBI disrupts the gut microbiota is by increasing intestinal permeability, which allows bacterial movement into the bloodstream, leading to sepsis [22,34]. It can also allow the flow of antigens and toxins into the bloodstream, causing systemic inflammation and other detrimental effects [35].

TBI may alter microbial signaling and contribute to neuroinflammation

Inflammation occurs after all brain injuries, and several reviews have covered the cell types and molecular pathways involved in this complex process [36,37]. Within 90 min of a TBI, serum cytokine and chemokine levels are significantly elevated [38].

It is well established that commensal bacteria in the gastrointestinal system exert an immunomodulatory effect throughout the body, with a healthy microbiome promoting a healthy immune response, and a dysbiotic microbiome causing detrimental effects, such as chronic inflammation [39]. Alterations in the gut microbiota diversity and abundance have been implicated in cognitive and behavioral changes, as well as in numerous diseases, including neurodegenerative disorders [40,41]. Plus, they are known to cause inflammation within various organs and tissues, including the brain [40].

Following injury from a TBI, alterations in gastrointestinal microbiota lead to a CNS that is driven towards a pro-inflammatory state [4,22]. The body-wide impact from a TBI causes microbial dysbiosis in the gastrointestinal tract, which can lead to disruption of the normal signaling involved in the gut-brain axis, the bi-directional communication system between gut microbiota and the CNS [22]. This can lead to neuroinflammation, an observed phenomenon in late sequelae of TBI [4,5,22].

Further, signaling via the gut-brain axis is known to involve not only immune pathways, but also the nervous system, the endocrine system (through the hypothalamic-pituitary-adrenal axis), and/or the metabolic system (such as bacterial short-chain fatty acid metabolites) [22,42]. Thus, one way in which TBI may impact the nervous system is by prompting signals from a dysbiotic intestinal microbiota in the enteric nervous system to travel to the CNS via glial cells in the intestines [34]. The vagus nerve, spinal cord, and bloodstream can also serve as conduits to the brain for neurotransmitters produced by gut microbes, such as dopamine, γ-aminobutyric acid (GABA), and serotonin [40,42].

As the gut-brain axis is bi-directional, another possibility is that some of the secondary early intracranial injuries stemming from TBI, such as hemorrhage, neuronal damage, ischemia, and BBB damage may disrupt the gut microbiota via a pro-inflammatory cytokine cascade, resulting in further damage [22].

Microbial access to the brain

There are a few pathogens already well known for their ability to traverse the BBB, thus creating recognizable infections. Prominent are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and group B Streptococcus. These invaders may transit paracellularly, transcellularly, or by a Trojan horse mechanism, through infected phagocytes [43].

The normal protective role of the BBB can also be vitiated by a TBI, both on a microstructural level as well as functionally [44]. Whether the bacteria are within the body or external to it, this impaired BBB becomes a potential portal for them to cross over into the brain [45]. HHV-6 has exhibited high levels of tropism for inflammation-activated $CD4^+$ T lymphocytes, and may latch onto them to gain entry to the CNS via a 'Trojan horse' mechanism [13].

Microorganisms activated within the brain, whether they are residents or new arrivals, can do further damage by prompting cytokine or chemokine release, inducing further BBB permeability, which promotes further access by pathogens [43]. This leaves the brain vulnerable to CNS infection and/or cognitive dysfunction [46]. In fact, there is evidence that brain capillary damage and breakdown of the BBB is an early indication of cognitive dysfunction [46].

A TBI's traumatic impact may also cause microorganisms in the brain to be displaced from their normal environment, with impairment of their normal functioning. As a result, the microbes may release their contents or metabolites into the local environment, potentially producing disturbances in nerve conduction and brain function. This response is seen in bacterial meningitis, in which detrimental production of cytokines, chemokines, oxidants and proteolytic enzymes in the brain occurs as an antibacterial response. These substances can cause neuronal or glial damage [47].

TBI impact causes environmental microorganisms to enter the body

In addition to its effects on microbes that are already resident in the victim's brain or body, the real-world impact that causes a TBI usually drives nearby environmental organisms into the body. Football players, boxers, and soldiers are performing in dusty, sweaty, and/or dirty surroundings. Microbial carriers such as dried or wet sweat, dead insects, animal urine or feces, and dead plant detritus are often present. Every tackle, punch, or explosion provides opportunity for such particles to enter the eyes, nose, and mouth.

Once microorganisms arrive in these portals, there are several paths through which they can gain access to the CNS and brain. HHV and other bacteria can directly cross the BBB [13,45] or enter the brain through peripheral nerve endings, making use of transport networks within axons [13]. Cryptococcus neoformans, which causes meningoencephalitis, enters through inhalation, and invades the brain through cerebral capillaries [43].

The interior of the nose is especially noteworthy: located therein is the olfactory bulb, a neural structure of the forebrain, and its associated neurons. These provide a direct route for viruses to enter the limbic and olfactory systems of the CNS [13]. Two herpes viruses, HHV-6 and HSV-1, have been found in the bulb [13,48]. Ocular infection by HSV-1 has led to infection of it [49]. Also, forensic evidence and autopsies reveal that other viruses can enter the brain through the olfactory route: influenza A, rabies, and Borna disease [48].

The Beehive Theory may lead to preventatives or therapies for late sequelae of TBI

The clinical significance of this Beehive Theory is that it suggests little-explored ways to possibly prevent, lessen, or even treat the late complications of TBI. Strategies for efficacious therapeutics may be developed through a focus on counteracting microorganisms, directly or through reducing their adverse effects like inflammation. There is

precedent for treating or forestalling cognitive problems with an antiviral medication. An antiherpetic therapeutic given to young adults with HSV-1 infection has been reported to lower their risk of developing AD in later life by almost 10-fold within 10 years, with greater effectiveness seen with longer treatments [23].

Because TBI is associated with neuroinflammation [4,5], there is potential for treatment with an anti-inflammatory agent. Numerous mouse and rat studies have tested such drugs administered soon after a TBI. The results revealed therapeutics with both a narrow and a broad anti-inflammatory action that provided significant benefits, limiting injury during a TBI. One anti-inflammatory, anatabine, administered 30 min after closed, mild TBI to mice enhanced spatial memory six months post-injury [50]. Unfortunately, these preclinical studies do not translate well into the clinical situation, in which dosing one hour before or after a TBI is not a realistic possibility [10].

The antibiotic minocycline, which can pass through the BBB, has been shown to limit neuroinflammation after TBI in multiple preclinical studies. In those experiments it was administered at levels higher than needed for its anti-microbial function [10]. Whether any of its beneficial effect could have been due to microbial suppression was not examined.

Early studies have examined a variety of neuroprotective agents. Some pharmacological agents have shown promising properties in preclinical and clinical studies, but a systematic review of randomized clinical studies (evaluating nitric oxide synthase inhibitor, N-acetyl cysteine, statins, Cerebrolysin, Enzogenol) revealed no therapeutics with definitive neuroprotective effects and improved functional outcomes [6,7]. As far as can be determined, there have been no systematic laboratory or clinical tests of the many available antibacterial and antiviral drugs to evaluate their possible effects on forestalling or ameliorating late sequelae of TBI.

Another possibility for treatment, albeit a remote one, stems from the evidence that the gut microbiome may be in a state of dysbiosis as a result of TBI, which contributes to neuroinflammation [22]. It is possible that restoration to a non-inflammatory state may be made via a fecal microbiota transplant, which involves transferring strained fecal matter from a healthy donor to a patient. This methodology has successfully treated patients with Clostridium difficile infection, ulcerative colitis, Crohn's disease, and irritable bowel syndrome [51].

Probiotics could also be considered as potential aids, as they increase IL-10 production and reduce pro-inflammatory cytokine levels, thus reducing inflammation [52,53]. They also reduce intestinal permeability via the endocrine system and the hypothalamic-pituitary-adrenal axis [22].

The major late-onset perils faced by TBI survivors continue to be a serious world concern. So far, no preventatives or treatments are available. The Beehive Theory provides a new perspective for examining the mechanisms responsible for TBI sequelae, and will hopefully stimulate investigations of the role of microbes and other unconventional possibilities.

Conflict of interest statement

The author has no conflict of interest to declare.

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