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Research Article,

Effect of Different Physiological Mechanisms on Traumatic Brain Injury

Dr Debopriya Ghosh[1], Dr Ekta Verma[2], Dr Stephen Gershman[3], Dr Gregor[4]

[1]Department of Physiology, University College of Medical Sciences. Delhi, India
[2]Department of Paediatrics, All India Institute of medical Sciences, Gorakhpur, India
[3]Department of Neuroscience, University of Alberta, Canada
[4]Department of Chemical and Life Science Engineering, Virginia Commonwealth University, USA

Abstract:

The literature has emphasised the necessity for efficient therapeutic therapies in chronic neurological disorders as TBI and other variations of chronic neurological ailments. Three common themes that cross all of these problem types have been emphasised in recent studies regarding cellular and neurochemical processes: immunological and autoimmune mechanisms, inflammatory pathways, and oxidative phosphorylation or other energy generation damage. The limitations of medical and surgical methods are clear, and they are made more difficult by the physiological interdependence of these channels. Due to the risks of polypharmacy, the prevalence of lifestyle diseases, and rising research pointing to effective treatments and procedures, there is an increasing need for non-drug, non-surgical choices. This paper reviews and links a number of studies that examine the precise, quantifiable effects of brain injury on various bodily systems, and it suggests a new direction for outcome-based, multifactorial functional neurological evaluation and treatment of some of the aftereffects of chronic TBI and mTBI (mild traumatic brain injury).

Keywords: Neuroinflammation, Neurodegeneration, Neuropsychological, Neuroendocrine, Vestibular, TBI

Introduction:

The dogma of permanence tells individuals who are left with chronic issues to accept their destiny since many people recover from common brain injuries during the first year of recovery. This idea has come under investigation as a result of studies on brain plasticity. Numerous and multidisciplinary pathways have been identified by studies on the neurochemistry and sensory effects of chronic brain damage. The comprehension of both pathogenic and dysfunctional symptoms within this class of sickness has improved as a result of these quantifiable phenomena. Therefore, in order to understand and make use of this abundance and to avoid the pitfalls of heuristic decision making and specialist-dumping in a clinical environment, strong generalist thinking is becoming more necessary. To advance, careful investigation of a variety of extensive patient assessments, including reflexive eye movements, hormone panels, sensorimotor alterations, immunological and inflammatory markers, and mental and emotional states, must be incorporated. It will be necessary to broaden historical study to incorporate hitherto unconnected lifestyle elements. It's possible that these communities of people with persistent brain injuries may not only suffer from compartmentalised diagnosis and care as well as indiscriminate medication. The first section of this study will examine the processes that underlie many of the aforementioned chronic neurological diseases, starting with intracellular effects and moving on to endocrine and tissue impacts. This covers the environment that existed before the damage, the fuel, the immunity and inflammation, the obstacles, and the endocrine impacts. The CDC classifies concussions as a subgroup of TBI,

and several sources classify them as a kind of mTBI (mild traumatic brain injury). The reader is advised that each reference may describe mTBI and concussion using somewhat different symptoms since these conditions have a variety of criteria. Part II covers the psychological impacts of trauma, therapeutic neurological rehabilitation applications, and chronic post-concussion syndrome (PPCS). Multiple concussions have known negative consequences due to accumulated neuroinflammation and neurodegeneration. The fact that non-traumatic mechanisms can have pro-inflammatory effects on the brain that affect the same cellular signalling mechanisms as those seen with trauma suggests that both traumatic (injury) and non-traumatic (insult) sources, as well as their interactions, must be taken into account in order to comprehend the total burden of brain pathology in a given patient. Non-traumatic causes of brain injury may cause microglial priming prior to TBI or mTBI, exacerbating the outcome of the injury.

Neurons and microglia:

Gray matter density decreases with time in the adult brain. For instance, Sowell et al. observed that grey matter density decreased by around 32% between the years of 7 and 60 and by 5% between the ages of 40 and 87 [186]. Thus, neurons pass away daily. They must be eliminated or they will trigger immune system activation via the damage associated molecular pattern (DAMP) pathway, leading to a pro-inflammatory response in the brain [3,187]. The majority of immune cells in a healthy brain are called microglia [1]. Ramified microglia are responsible for phagocytizing the dead neurons in the normal, resting state, just way macrophages phagocytize apoptotic cells and tissue debris in peripheral tissues. In both situations, this routine level of phagocytic activity promotes the production of IL-10 and TGF-, two molecules that serve as anti-inflammatory mediators. Through the use of regulatory T cells and anti-inflammatory cytokines, phagocytosis of apoptotic cells controls the immune system [2]. The option of cleaning phagocytized detritus from tissue through the lymph system, as is the case in the periphery, is not accessible in the brain, however, since there is no considerable outflow of lymph from the brain, save for very little at the cribriform plate. Therefore, in order to reuse dead neurons as fuel and building materials, microglia must completely breakdown them. The number of instantaneous events involving microglial cells being activated or inhibited in the decision flow to initiate phagocytosis of a neuron is very high given the billions of neurons and an estimated ten microglia per neuron, as well as a theme of continuous monitoring. Microglial activity is regulated by neurons [3]. While 'On' signals from neurons may be induced, they are 'Off' signals from neurons that retain microglia in their resting state and limit pro-inflammatory activity. glutamate, chemokines, and purines. Thus, it is important to consider neurons as major immunological modulators in the brain [3]. The interaction between neurons and microglia is balanced in a healthy brain. Ample OFF signals are produced by healthy, functional neurons to deter microglial phagocytic interest. Additionally, electrical activity is produced in abundance by healthy neurons. An effective inhibitor of microglial activation is the electrical activity of neurons [4]. Ramified microglia release TGFbeta, which fosters a tolerogenic and anti-inflammatory tissue milieu in the healthy, non-inflamed brain [5]. In addition, microglia and astrocytes in a healthy brain produce FasL, which causes T cells that migrate from the periphery into the brain to commit suicide [6]. Cellular death signals, such as CD95Fas/CD95L, FasL, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), and TNF receptor (TNFR), are expressed by neurons and glia and may cause T lymphocytes and other invading cells to undergo apoptosis [2].

Neuronal-microglial signalling:

Neurons must be able to maintain a high frequency of firing (FOF) in order to produce neurotransmitters and sustain electrical activity, two crucial 'OFF' signals. Presynaptic stimulation, neuronal oxygen, and neuronal glucose are all necessary for the cell to reach its central integrative state (CIS). The neuron-microglial ON/OFF equation may alter as a result of variations in neuronal FOF, which can be attributed to physiological conditions that have the potential to degrade these three parameters. The metabolic health of the neurons themselves affects their ability to sustain a strong FOF. The metabolic integrity of neurons is influenced by several variables. Lack of exercise, excessive buildup of mitochondrial ROS, reduced thyroid hormone signalling, and a CoQ10 shortage are a few factors that might disrupt function and result in reduced FOF (statin-induced or other). The balance between electron buildup from excessive

caloric intake and electron usage during exercise determines the formation of ROS in mitochondria. Lack of activity and an excessive calorie intake result in an oversupply of electrons (general biology). They combine with oxygen to form superoxide. The mitochondria are harmed if this happens in a quantity that is more than what can be eliminated by antioxidant systems in the mitochondria. Patients who have glutathione or SOD single nucleotide polymorphisms (snips) may be more likely to experience mitochondrial damage from ROS. The GSTM-1 gene, which is the main one responsible for producing glutathione s-transferase, is spliced in around half of the population [188]. The neurosensory environment may be changed by sensory stimulation variables including inactivity, the degeneration of joint mechanoreceptors in arthritic circumstances, inadequate muscle tone, reduced rib movement with respiratory problems, and other similar alterations. Diabetes, hypoglycemia, insulin resistance, and other similar disorders that cause glycemic dysregulation may affect systemic glucose levels, which in turn affects CNS glucose levels. Many of these individuals have microcirculatory issues that worsen low blood sugar levels and poor transport of glucose to the brain. Similar to how breathing issues, microcirculation issues, and other similar issues may affect CNS oxygen levels.

Inflamatory Response:

However, when the brain is injured, the ensuing inflammatory chemicals might alter the situation. With inflammation, neurons and microglia both alter in ways that enhance microglial phagocytosis of neurons. Inflammation jeopardises metabolic integrity, just as it does in any cell. This results in decreased neurotransmitter synthesis and electrical activity in neurons. Two strong "Off" signals are therefore lost. Microglia that are inflamed alter their appearance. The relative lack of leukocytes and antibodies in inflammation in the brain sets it apart from inflammation in the periphery. There is only a small amount of traffic that can get through this barrier, and inflammation, which may draw leukocytes into the brain, can increase this flow [1]. Microglia, a specialised kind of macrophage, do, however, develop the ability to deliver antigens in the inflamed brain [4]. Inflamed microglia deliver antigen to invading T lymphocytes instead of causing them to undergo apoptosis. Pathogen pieces that have been treated may serve as antigenic material. This beneficial antibacterial action encourages pathogen elimination. The antigen may also be delivered by microglia as pieces of degraded neural tissue, which might trigger a T cell's self-antigenic response. This T cell self-antigenic activation seems to have reparative effects in a modest and temporary manner. However, persistent or very enthusiastic self-antigenic T cell activation might harm the brain permanently [4]. It is notable that some of the research in this area was conducted before the significance of TH17 polarisation in T cell/microglial interactions was well understood. It is well recognised that inflammation causes mitochondrial uncoupling, which reduces the integrity of the mitochondria in all cells. Therefore, decreased mitochondrial integrity and FOF of neurons are also caused by inflammation. Glial cells, including microglia, develop the ability to deliver antigens via the production of MHC molecules in a number of inflammatory and neurodegenerative disorders. Only in the lesioned CNS regions do the pro-inflammatory cytokines promote microglial MHC expression [4]. In order to prevent the immune system's inflammatory activation in the brain, neuronal transmission acts as a powerful "Off" signal. As a result, induction of brain immunity is substantially counterregulated in intact CNS regions. Neurons' signalling activity also functions as an inhibitory signal. Neuronal activity is a necessary component for controlling MHC expression. The local microenvironment, in particular physiologically active neurons, inhibits immunity in the CNS to avoid unintended immune-mediated neuronal injury [4]. Some scientists, however, hold the opinion that CNS-infiltrating T cells deliver critical anti-inflammatory cytokine signals that are needed for the resolution of neuroinflammation since systemic anti-inflammatory drugs have failed to ameliorate neuroinflammatory illnesses [7]. It is interesting that non-steroidal anti-inflammatory drugs have been labelled "resolution hazardous" in the literature due to their inhibition of signalling pathways involved in the reduction of inflammation [8]. This theory might help explain why anti-inflammatories were not successful as a treatment for persistent neuroinflammation. T cells that invade the CNS when there is systemic inflammation are likely to adopt a pro-inflammatory morphology, just as they do in the periphery, as a result of pro-inflammatory cytokines and other variables. They

are likely to create pro-inflammatory cytokines after being thus impacted, which will help to further the pro-inflammatory CNS environment. Pathogens in tissue produce molecular patterns that are connected with them (PAMPs). Damaged tissue produces cellular patterns that are related to the injury (DAMPs). PHOX, a component of phagocyte NADPH oxidase, is activated by PAMPs and DAMPs that are detected by microglial pattern recognition receptors (PRRs). Molecular oxygen into reactive oxygen species (ROS) (ROS). This conversion depletes the tissue of molecular oxygen, resulting in hypoxia, which activates the transcription factors NF-B, IL-1beta, and TNF-alpha, all of which enhance the expression of NF-B. Inducible nitric oxide synthase (iNOS) expression is regulated by NF-B. Nitric oxide (NO), although cytoprotective, impairs cellular respiration when combined with hypoxia, leading to excitotoxicity. While moderate levels of ROS are necessary for microglial activity, their interaction with NO produces peroxynitrite, which triggers the death of neurons. Microglia are more likely to produce neurotoxic levels of ROS in individuals with antioxidant depletion, whether as a result of glutathione (gsh) snips or other reasons. Neuroinflammation and Non-Traumatic Factors Contributing to Microglial Priming. When microglia are subjected to microglial priming, they transition from the ramified state, where they carry out maintenance tasks and minimise neuro-inflammation, to the expanded and filled-with-pro-inflammatory cytokine state [9,10,11,12]. Aging, stress, illness, and other triggers may all cause priming. Long periods of time may pass when microglia stay in this condition without changing back to their ramified form or releasing their bolus of cytokines. However, more brain injury will result in a surge of pro-inflammatory cytokines that might harm the brain [9,10,11,12]. Increases in pro-inflammatory cytokines in the periphery have been shown to upregulate brain inflammation and facilitate neuronal death [13,14]. It has also been shown that elevating peripheral LPS levels, even when just a small quantity of LPS is utilised for stimulation or when the levels of peripheral inflammatory cytokines are artificially reduced, may cause the activation of central pro-inflammatory pathways. Localized brain inflammation and neuronal death may be made worse by both central and peripheral inflammation [15]. The main concern is whether neuroinflammation will resolve rapidly or result in a continuously active state, which causes more neuronal death. In response to pathophysiological brain insults, microglia change the way they look and become active. The phenotype of microglia is also altered by systemic infection or inflammation. Alzheimer's disease risk factors include chronic systemic inflammation. This suggests that systemic inflammation and microglia in the CNS interact with one another [16]. Inflammatorily activated glia may be triggered by pathogens, protein aggregates, or injured neurons, which can subsequently kill neurons. the IL-1b gene microglia has been shown to be mostly activated during brain disorders. Once it reaches the brain, systemic IL-1b may lead to CNS inflammation, establishing a connection between systemic inflammation and immunological activation [12]. Two pathways exist for the overactivation of microglia. First, by identifying pro-inflammatory stimuli like lipopolysaccharide (LPS), microglia may startle neurons and cause damage. Second, in reaction to neuronal injury, microglia may overactivate [11]. Even at very modest dosages, LPS may directly activate the brain endothelium, eliminating the requirement for systemic cytokine activation [9,10]. Excitotoxicity exhibits several of the pathogenic occurrences mentioned in traumatic brain injury [12]. Nuclear factor-kappaB (NF- B) activity is influenced by neuronal injury or pathogen-induced receptor stimulation. When PHOX (Phagocyte NADPH oxidase) and iNOS (inducible nitric oxide synthase) were both activated simultaneously in microglia, NO disappeared, peroxynitrite appeared, and death occurred. However, the chronic state of activation may advance to the "resolution phase," when microglia are amoeboid, highly phagocytic, and generate anti-inflammatory cytokines (including IL- 10 and TGFb) to clean up the mess and resolve the inflammation [1]. When apoptotic neurons are successfully phagocytosed by non-phlogistic microglia, no further damage-associated molecular patterns (DAMPs) are released into the tissue milieu. Instead, the neuron is absorbed and digested. As a result, the brain parenchyma is more likely to produce anti-inflammatory cytokines and progress toward the resolution of tissue inflammation. As opposed to this, if the neuron dies by necrosis as a result of direct or indirect trauma, necrosis brought on by a pathogen, or necrosis induced by a toxin, its demise releases cell fragments and cytosolic

contents into the tissue environment, causing microglia in the vicinity to become pro-inflammatory. A more aggressive microglial cell phenotype and more enthusiastic phagocytosis of neurons are favoured by neuroinflammation, resulting in a greater loss of neurons than is required to resolve the underlying illness.

Neuroimmunological Disorders:

Acute neuroimmunological disorders such systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), and injury-induced immune deficiency syndrome (SIDS) have been discussed elsewhere [17]. However, whether these disorders have a gradient of severity is not obvious from the research. It is unknown, for instance, whether a patient with mTBI (mild traumatic brain injury) may be predicted to have a moderate form of the TH1 and innate immune cell apoptosis reported in SIDS. If this were the case, the patient may become progressively more vulnerable to long-term infection, encouraging systemic and consequently neuroinflammatory processes. The doctor treating a patient with a TBI or mTBI should be on the lookout for signs of reduced immunological vigilance against infections, whether or not mild variants of these disorders apply. Chronic infection, a recognised trigger of microglial priming and neuroinflammation, might result from such an event.

Neuronal Changes:

The neuron is the focal point of the physiological narrative in the context of traumatic brain damage [18]. Factors such as the preexisting central integrated state of different neuronal pools, the integrity of existing neuronal circuitry, peripheral receptor integrity, level of circulating cytokines, polarisation status of a dynamic immune system, level of glial priming and function, balance and integrity of the endocrine system, various underlying infectious organisms, genetic predisposition, associated comorbidities, the extent of damage. All assess neuronal integrity and the likelihood of recovery after an injury [19]. The patient's nutritional and digestive condition, as well as arterial perfusion and autonomic integrity, are other elements that may have an effect on the neuron. Recovery and maintaining humanism and vitality after a neurological lesion depend heavily on the neuron's potential to live and retain optimal functional capacity and adequate cellular plasticity. When determining the severity of the injury, developing suitable treatment plans, and caring for patients with traumatic brain injury or neurodegeneration, it is crucial to comprehend and assess all converging physiological scenarios that can affect the health of the neuron and how it relates to head injury and damage to the CNS [20]. After a head injury, a complicated intracellular cascade that includes organelle function, metabolic and ionic changes, and surface receptor interaction occurs. Cellular plasticity, immunoexcitotoxicity, intracellular calcium and binding proteins, caspase cascades, apoptosis, cerebral blood flow, glucose metabolism, phospholipase and free radical production, protease and cytoskeleton breakdown, endonuclease and DNA damage, nitric oxide isomers, and superoxide anions are all affected by this gross level interplay [12]. Organelle participation also affects synaptic function, protein replication, secretory vesicle generation, neurofilaments and microtubules, lysosomes, epigenetic activity, and mitochondrial function on a lower intracellular scale. Cellular energy, axonal and myelin integrity, cellular swelling, synaptic transmission, lipid membrane stability, synaptic transmission, and cellular summation capacities will all be affected by the long-term effects of intracellular and organelle changes. Neurons are affected, glial cells are changed, glutamate receptors may become hypersensitive, GABA receptors may get internalised, the immune system may be affected, the vasculature may be compromised, and the blood-brain barrier may be harmed when the CNS is injured. Cellular damage, microglial priming, prolonged inflammation within the CNS, antigen presentation of neural tissues, potential autoimmunity, and disruption in the healing process post-injury are all possible outcomes of this confluence of events [21]. The kinds, densities, and sensitivities of surface receptors can affect metabolism [22]. There are many different receptor types, but the ionotropic receptors including NMDA, AMPA, Kainate, and voltage-gated calcium channels are of special relevance. The intracellular cascades, cellular function, cellular plasticity, and long-term potentiation are all made possible by these receptor types' capacity to control the entrance of calcium into the cell. N-methyl-D-aspartate, a particular kind of ionotropic glutamate receptor, is ultimately promoted by calcium storage within the cell as well as external calcium influx. The correct activation of kinase

dependent signalling cascades results in the activation of cAMP (cyclic adenosine monophosphate) element binding protein. This activation is caused by the rise and proper control of cytosolic calcium. The phosphorylation of SER 133 (serine 133) as a result of the activation of CREB (cAMP Response Element-Binding protein) eventually results in the production of protein synthesis inside the nucleus. In turn, this increases the cell's natural capacity to produce more surface receptors, intracellular structures, cytokines, neurotrophic factors, cellular efficiency, dendritic growth, and repair cycles that are essential for cell survival. Long-term potentiation and synaptic plasticity are the final results of this process. This procedure plays a significant role in learning and memory and serves as a key mechanism for brain circuitry that has been disrupted by a head injury or a neurodegenerative condition to be repaired [23]. However, the imbalance of intracellular calcium might result in excitotoxic and deteriorating processes. When intracellular calcium-buffering proteins become abnormal and cell surface receptors become more permeable to calcium, the intracellular calcium levels become dysregulated. The ability to change NMDA receptor activation and skew AMPA:NMDA receptor ratios, which then permits a greater influx of extracellular calcium into the cell, is mediated by a variety of neurodegenerative conditions, inflammatory scenarios, and disease processes as well as excitotoxin loads and glutamate levels [18]. Pathology is brought on by the resulting intracellular calcium imbalance. Cell membrane damage results from intracellular lipases being activated. Activated nucleases destroy DNA. Prostaglandins, arachidonic acid, and leukotrienes are promoted by calcium-induced phospholipase activation and cause inflammation, vascular dysfunction, white matter pathology, myelin damage, axonal damage, and further free radical production [24]. Protein phosphorylation is made possible by energy uncoupling, which modifies gene expression and ion channel function as well as the central integrated state and firing potential of the neuron. The cytoskeletal framework of the neuron is destroyed by calcium-induced proteolysis, which changes the cell body's supporting structures, transport systems, and axonal projections. This may change anterograde and retrograde function, which may change synaptic vesicle transport and decrease synaptic activity. Reactive oxygen and nitrogen species activation causes mitochondrial damage, NF-B activation, and, if it continues, cellular death. Continued oxidative stress, excitotoxicity, and inflammation may result in altered neurochemical environments, stimulated glial cells, dysfunctional neurons, reduced plasticity, and impaired plasticity. In spite of having no further physical injuries, this ongoing process may result in post concussive syndromes, second impact syndromes, and repeat concussive symptoms. An energetic failure between normal mitochondrial function and the cell's overall energy production occurs in conditions of oxidative stress, inflammation, or neurodegeneration [25]. This may result in an active mitochondrial permeability exchanger, a breakdown in the electron transport chain, and a reduction in the capability of the mitochondria to load calcium. The exchanger permits the deposit of calcium from the mitochondria into the cellular cytoplasm, upsetting the control of intracellular calcium. Respiratory chain uncoupling and the release of intermembrane space proteins as a consequence of MPT (membrane permeability transition) activation causes various cascades to occur [26]. Intracellular caspases, caspase independent cell death effectors, NLRP3 inflammasomes, nuclear factor-kappa B, and interferon regulatory factors are a few of them. When cytochrome C is released from the mitochondria, caspase 3 is activated, programming apoptosis and cell death. Together, these cascades cause the onset of inflammation, a reduction in cellular energy generation, and ongoing mitochondrial and cellular malfunction. Thus, even before the death or life receptors are activated, the cell's environment primes the receptor sensitivity. This process of "setting receptor tone" is conceptually related to how the muscle spindle tone is pre-set before to a disturbance and the tympanum tension is pre-set to sense or defend from sound prior to the occurrence. This has ramifications for cellular apoptosis and clinical prognosis, and there may be some room for improvement in terms of leverage via clinical cell mediator modification. Evoked potentials and the administration of drugs are two possible methods of manipulation.

Conclusion:

There are several physiologic aspects that might affect a patient's treatment after a TBI or mTBI, leading to a broad range of possible outcomes

following head trauma, including PPCS. It takes skillful evaluation and awareness of these factors, their possible linkages, and their influence at the cellular and systemic levels for a doctor to comprehend a specific patient. Therefore, in order to understand and make use of the wealth of modern research as well as to avoid the pitfalls of heuristic decision-making and placing too much focus on specialised niches in both research and clinical settings, strong generalist thinking is becoming more important. Research, preventative measures, and post-injury clinical treatment will take new turns if pathophysiology is understood in relation to prior medical history, family history, genetics, multiple system participation, and systemic peripheral contributions to central nervous system (CNS) function. Research in a number of fields has shown that it is beneficial to combine studies of the underlying neuronal circuitry that connects the visual, vestibular, memory, immunological, and autonomic regulatory nuclei and is evolutionarily conserved and shared. If we are to advance in enhancing the outcomes of chronic brain injury, their expansion and integration are required. Reflexive eye movements, hormone panels, sensorimotor alterations, immunological and inflammatory indicators, mental and emotional states, and other elements essential to recognise each patient's individuality must be carefully examined in both research and therapeutic settings in order to advance. It will be necessary to broaden historical study to incorporate hitherto unconnected lifestyle elements. Any individual's PPCS risk will be significantly influenced by their pre-concussion health state. In order to fully understand the possible non-homogeneity of patient populations involved in a particular study, it is crucial in the research context to take into consideration physiological factors that might affect TBI and mTBI outcomes. The possibility to uncover important clinical objectives that might significantly enhance results or, if neglected, halt development in the clinical situation is made possible by accounting for the same physiological characteristics. Once these clinical targets have been determined, they must be treated using the best-suited methodologies, not all of which will be pharmacological. The key to the emerging strategy for efficient concussion care is to comprehend the post-injury, and ideally the pre-injury status of these patients using outcome-based multifactorial neurological assessment and treatment.

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