Published in final edited form as:
Med Hypotheses. 2014 February ; 82(2): 171–174. doi:10.1016/j.mehy.2013.11.028.

Insulin-Associated Neuroinflammatory Pathways as Therapeutic Targets for Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is characterized by an abrupt blow or exchange of force against the head and can be categorized as mild, moderate, and severe. The secondary cell death after TBI displays ischemic-like patterns including neuroinflammation. The scavenger receptor cluster of differentiation (CD) 36 is a lipid-associated protein capable of transducing intracellular signals to promote inflammatory mechanisms within different cell types. Expression and activation of CD36 is closely related to dyslipidemia secondary to diabetes. Diabetes mellitus (DM) has been documented as a co-morbidity factor in TBI, in that patients with a history of diabetes present with more severe brain damage and slower recovery from TBI than non-diabetic patients. Indeed, a strict regulation of blood serum glucose by the use of insulin promotes a better outcome for TBI patients. Based on these recent findings, we now advance the hypothesis that CD36 via DM insulin-associated pathways is closely involved in TBI chronic pathology.

Societal Impact of Traumatic Brain Injury

Every year in the US, 1.7 million people bear a Traumatic Brain Injury (TBI); from which 275,000 are hospitalized and 52,000 die (1). Overall incidence of TBI in the US is estimated to be 506.4 cases for every 100,000 (2). Of note, armed troops deployed in Afghanistan and Iraq, are exposed to blast-induced TBI. This type of TBI has been commonly said to be a “signature wound” continuously increasing among the military population (3,4). Scarce data about the impact of TBI in low and middle-income countries from the Latin American & Caribbean region suggest high incidence ratios of TBI caused mainly by violence and traffic accidents which may even overcome those in developed countries (5).

CD36-mediated neuroinflammation in TBI

The secondary cell death triggered by TBI displays ischemic-like patterns including neuroinflammation (6). Neuroinflammation is said to be a “double-edged sword”, capable of

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eliciting both damaging and reparative effects (7). The physiologic goal of inflammation is to draft diverse immune cell types into the site of the injury to remove damaged tissue and cellular debris allowing further creation of scar tissue. Microglia is the main immune cell type within the central nervous system (CNS). Activation of microglia varies according to stimuli, promoting three phenotypes: classical activation, alternative activation, and acquired deactivation. While the last two have been identified as promoters of anti-inflammatory mechanisms, the first is related to pro-inflammatory mechanisms (8).

Thirty minutes after a TBI, microglia respond and migrate to the injured area through chemokines and damage-associated molecular patterns, and may remain activated for many years promoting a chronic inflammatory process (9,10). In addition, blood brain barrier disruption following brain injury stimulates the infiltration of inflammatory cells including leukocytes and macrophages to the brain parenchyma, which further contribute to secondary brain injury (11). Several immune receptors are responsible for this pro-inflammatory effect, including toll-like receptors and scavenger receptors (12, 13).

The CD36 is an 88-kDa heavily glycosylated scavenger receptor with a large extracellular domain capable of interacting with several ligands and Src family kinases (SFK) (14,15). In mice, it has been identified as a key sensing protein that regulates chylomicron synthesis when stimulated by luminal long chain fatty acids (16). Action of the CD36 in the peripheral tissue has been linked to that of lipoprotein lipase and contributes to the uptake of free fatty acids (17). Nevertheless functions of the CD36 go further than those of lipid metabolism, as it interacts with toll-like receptors (TLR) 4 and 6 to form a heterotrimeric complex capable of transducing intracellular responses (18). Advanced glycation-end products, Amyloid β (Aβ) and oxidized low-density lipoproteins (OxLDL) are all ligands of the CD36; the last one specifically binds to a domain within amino acids 155-183 of the protein (19). Interestingly, OxLDL has been shown to share molecular similarities with a bacterial pathogen *Streptococcus pneumoniae* (20,21). Parallel to this, Aβ is a pathogenic endogenous peptide that is linked to the pathology of Alzheimer disease by the formation of amyloid plaques with further induction of chronic inflammatory damage in the brain. Indeed the capacity of the CD36 to recognize pathogen associated molecular patterns has been known for some time, for the CD36 promotes phagocytosis of *Plasmodium falciparum* infected erythrocytes and *Staphylococcus aureus*. This evidence suggests that although CD36 is capable of regulating the absorption of lipids within the peripheral tissue, oxidation of low-density lipoproteins (LDL) into OxLDL and Aβ may promote a different pro-inflammatory effect within the same receptor.

Diabetes promotes a cyclic neuroinflammatory process in the brain by OxLDL crosstalk with CD36

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (22). In North American countries, the prevalence for DM has been estimated to be 8.7%, 9.2% and 11.3% of all the Canadians, Mexicans and U.S. Citizens over 20 years of age respectively. The pathology is considered a significant health issue (23–25). “Diabetic dyslipidemia” is a term used to refer to the abnormal levels of lipids and lipoproteins under the pathology of diabetes (17). Diabetic dyslipidemia positively correlates with levels of triglycerides and cholesterol hyperlipidemia, LDL hyperlipoproteinemia and perhaps HDL hypolipoproteinemia (17). The relevance of increased LDL levels relies on the ease with which LDLs may be oxidized, for even minimal oxidation of lipids within LDLs is enough to trigger pro-inflammatory mechanisms that lead to further oxidation of these lipoproteins and deleterious pathways within the organism (26). Diabetes and TBI both increase oxidative pathways of LDL through hyperglycemia and inflammation (6,27–29). Recognition of OxLDL by the CD36 is

known to promote pro-inflammatory mechanisms in atherosclerotic plaques and worsen outcome for cerebral ischemia murine models (30–32).

The metabolic failure present after TBI results in the depletion of ATP levels, which in turn leads to the failure of Na+/K+ ATPase. Subsequently, the loss of membrane potential induces sodium and calcium influx into the cell and release of neurotransmitters (33,34). Production of reactive oxygen species (ROS) in the mitochondria is closely related to calcium levels inside the cell, meaning that higher levels of calcium induce ROS production that in turn stimulate further calcium release creating a feedback loop that can be deleterious in situations where there is a calcium overload in the cell (29). Mitochondrial uncouplers can inhibit mitochondrial production of ROS by promoting H+ leakage; this has been shown to reduce the damage after both stroke and TBI (35,36). Furthermore, cell stress activates the membrane bound enzyme NADPH oxidase (37), which catalyzes the production of ROS, specifically O_2- and peroxynitrite ($ONOO^-$) (38,39). Oxidative stress occurs when the capacity of the cells to detoxify ROS is exceeded by production of ROS, and under oxidative stress the process of lipid peroxidation through which LDLs are oxidized into OxLDL is increased (40). Aβ is produced when the BACE1 and γ–secretase cleave the amyloid precursor protein (APP) within an endosome (41). BACE1 is upregulated by the effects of oxidative stress secondary to hyperglycemia, hypercholesteremia and hypoxia after acute neurological conditions (42).

Interaction of CD36 with OxLDL exacerbates inflammation in atherosclerotic plaques (43). Nevertheless this has been a thoroughly debated subject, in that increasing evidence suggests the lack of CD36 may actually worsen the outcome of atherosclerotic models (44). A pathophysiologic event advances the notion of a frustrated phagocytosis whereby the uptake of OxLDL by macrophages is a normal physiologic process but under western diet such process becomes pathologic (45). The result is the build-up of macrophages that “eat more than they can chew” eventually turning into foam cells and triggering chronic inflammatory mechanisms (46). Phagocytosis of OxLDL may lead to the formation of a secondary lysosome in which the insoluble molecules of cholesterol are capable of forming intracellular cholesterol crystals (30). Inflammatory mechanisms by which cholesterol crystals promote inflammation have been documented (47,49).

The interaction of the CD36 microglia with a prionic protein results in the expression of the pro-inflammatory cytokines, including CD36 mRNA, and SFK phosphorylation (50). The crosstalk between CD36 and Aβ can stimulate the production of ROS in microglia and macrophages, resulting in CNS recruitment of inflammatory cells (51,52). Signaling pathways for these microglial and macrophagic neuroinflammatory effects have been identified (53) involving precipitation of the CD36 with cholesterol crystal formation by Aβ via SFK (30). This evidence suggests that the constant LDL hyperlipoproteinemia within diabetic patients may promote an excessive activation of CD36 mediated inflammatory pathways after oxidation of such lipoproteins, promoting cyclic microglial activation that worsens the long-term outcome after a TBI.

Hypothesis

DM patients diagnosed with TBI have a higher mortality along with a longer hospital stay, lower Glasgow comma scale values, and higher injury severity scores (54). Changes in glucose levels are well known to occur in the CNS following TBI (55) and indeed secondary brain injury management requires aggressive control of the metabolic supply into the brain (56). Although many of these parameters have been related to the progression of TBI, much of the interactions between these values are yet to be described (56). The use of insulin to maintain blood glucose levels less than 110 mg/dl significantly diminished mortality rates

after severe TBI, but the exact mechanism for this protective effect remains to be determined (57). To this end, we advance the hypothesis that hyperlipidemia and hyperglycemia, which are hallmark features of diabetes, may exacerbate TBI in the long-term via the CD36-mediated neuroinflammation.

DM and TBI may be pathologically linked via pro-inflammatory by-products of CD36, which have been implicated as comorbidity factors for chronic neurological conditions including Alzheimer's disease and Parkinson's disease (2,58,59), all of which have been documented as TBI-associated disease symptoms. Accordingly, CD36 can be used as TBI biomarker for the long-term assessment of the pathology. If CD36 is closely associated with neuroinflammation then studying the levels of CD36 will provide an excellent approximation of long-term TBI pathology, as well as a sensitive outcome measure of novel treatments for TBI. The complexity of CD36 mediated neuroinflammatory pathways leads us to believe that even slight elevations in CD36 levels of activity could initiate massive processes of self-propagating neuroinflammation. Determining a threshold of CD36 values, which if exceeded may potentiate such self-propagating neuroinflammation, will definitely help clinicians in the management of glucose and lipid levels of TBI patients in the long-term. The use of adjacent biomarkers for the management of blood glucose levels in diabetic patients is not a novelty. Glycosylated hemoglobin (HbA1c) levels are widely used in the daily clinical practice of many physicians to evaluate the different blood glucose levels throughout the past three months allowing them to adjust the treatment accordingly (60). Hyperlipidemic ApoE−/−, CD36 −/− double KO mice have been used to determine the role played by CD36 in the pathophysiology of stroke (61). Similar studies using both hyperglycemic and hyperlipidemic comparative animal TBI models will definitely help acquire further understanding of the mechanisms and impact CD36 plays on TBI pathology. Management of DM may be indicated for TBI. Both tight and conventional tendencies prevail regarding glycemic control with levels ranging from 80–110 mg/dl and 180–215 mg/dl respectively (62). Given the frailty of the CD36-mediated neuroinflammatory pathways, we believe that glucose management based on CD36 levels will emulate that of tight glycemic control. Additionally, DM drugs may have therapeutic benefits in TBI as recently demonstrated by an improved long-term outcome of TBI murine models following the administration of Exendin-4 (63), a glucagon-like peptide hormone known to stimulate glucose-dependent insulin secretion. Similarly, metformin, another drug used to treat DM, has shown to promote neurogenesis and spatial memory through the activation of signaling pathways that enhance neural stem cell differentiation and recruitment (64), which could similarly abrogate the cell loss associated with TBI. The present hypothesis implicates CD36 pathway DM and TBI, and warrants preclinical studies to reveal the safety and efficacy of DM drugs for long-term management of TBI patients.

Acknowledgments

CVB is supported by NIH NINDS 1R01NS071956-01, Department of Defense W81XWH1110634, James and Esther King Foundation for Biomedical Research Program 1KG01-33966, SanBio Inc., Celgene Cellular Therapeutics, KMPHC and NeuralStem Inc.

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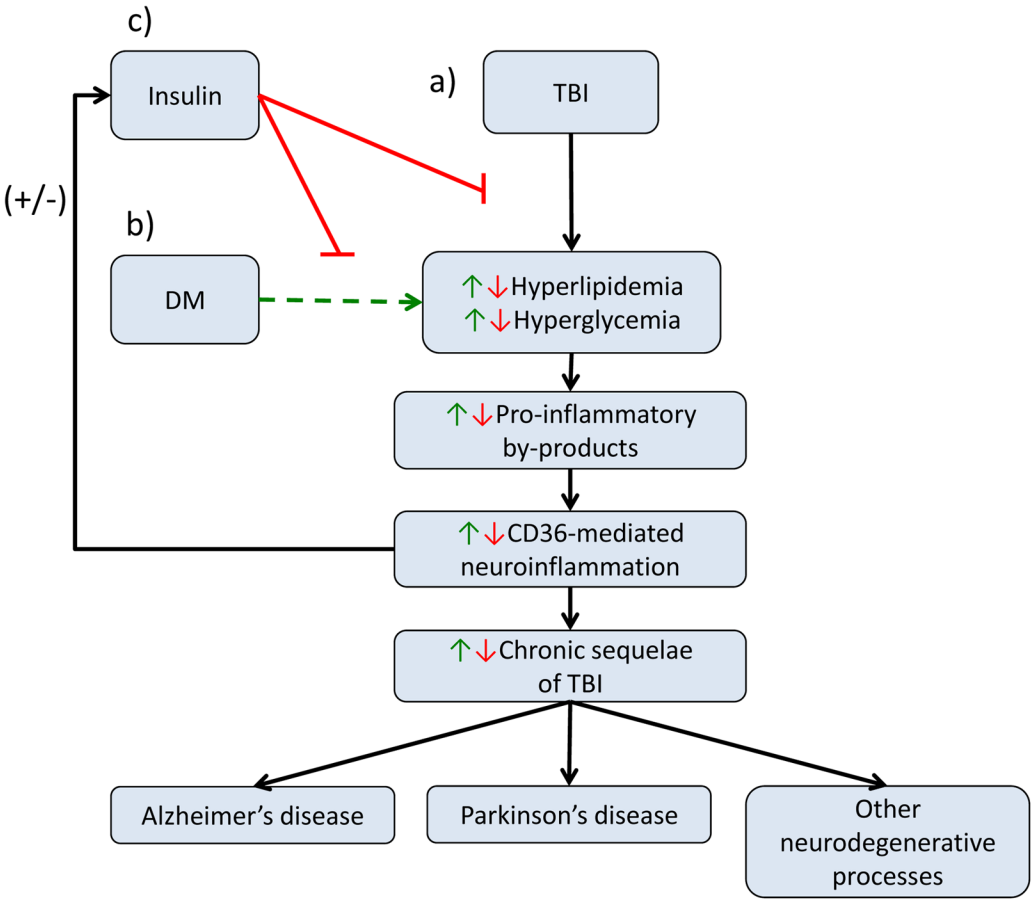

Figure 1.

a) Traumatic brain injury (TBI) pathophysiology involves hyperlipidemia and hyperglycemia, which promotes a cascade of events leading to CD36 mediated neuroinflammation, causing chronic sequelae of TBI including Alzheimer's disease, Parkinson's disease and other neurodegenerative processes. b) Diabetes mellitus (DM) increases the levels of hyperglycemia and hyperlipidemia following TBI, which in turn upregulates the pathological mechanism of TBI. c) Insulin decreases the levels of hyperglycemia and hyperlipidemia following TBI, resulting in a down regulation of the pathological mechanisms of TBI.