

# Traumatic brain injury and alzheimers disease biology essay

[Literature](#)



**ASSIGN  
BUSTER**

Traumatic encephalon hurt is now good known as a status wherein a individual hurt induces biochemical and cellular alterations, which so contributes to go oning neural harm or decease. Alzheimer ' s disease ( AD ) is a degenerative disease that easy and increasingly destroys encephalon cells. TBI induces changes in several signaling tracts which leads to disfunctions in synaptic malleability, emphasis in endoplasmic Reticulum and chondriosome and cell decease. In this reappraisal, we summarize these tracts in order to stress the importance of TBI in relation to early development of AD.

In add-on, we discuss farther avenues for research including future research waies.

## **Introduction**

Traumatic Brain Injury ( TBI ) is now good known as the taking cause of decease for people under the age of 45 old ages ( Finfer and Cohen, 2001 ) . The one-year incidence of TBI is understood to be anyplace between 100-600 people per 100, 000 ( Park et al. , 2008 ) .

A little per centum survives after TBI but is left with terrible neurological shortages which badly affect their quality of life. Alzheimer ' s disease ( AD ) is the most common neurodegenerative disease of the modern epoch that contributes for 50-60 % of all age-related dementedness ( Andersen et al. , 2006 ) . AD afflicts 8-10 % of the population over the age of 65 and about 50 % of those over the age of 85 ( Mattson, 1997 ) . Over 24 million people global are estimated to be presently enduring from AD, and as the aged population additions over the coming decennaries, the figure of those

enduring from AD has been estimated to lift to 81 million by 2040 ( Miller et al. , 2006 ) . Research in the past decennary found a strong co-relation between TBI and AD for the possibility that TBI may predispose a individual to develop AD in later periods of life.

This phenomenon has important societal and medical deductions, and reinforces the demand for preventive attempts and wellness service planning to get by with the possible big addition in the figure of AD patients ( Lye and Shores, 2000 ) . The first hint bespeaking a pathological nexus between TBI and AD came from the observation that Amyloid beta ( A $\beta$  ) plaques, a definite mark of AD, are found up to 30 % of patients who die acutely following TBI. The plaques found in TBI patients are notably similar to those observed in the early phases of AD. However, plaques in AD develop easy and are chiefly found in the aged, whereas plaques associated with TBI can look quickly ( within merely a few hours ) after hurt. Although the plaques observed following injury are typically diffuse, like those observed in early AD, it is non known whether these plaques mature over clip into the denser, neuritic plaques typical of advanced AD ( Van Den Heuvel et al. , 2007 ) .

Although the microscopic observation of A $\beta$  observed in patients afflicted with TBI provide a strong correlativity with that of AD, but nevertheless, a concise mechanism on how A $\beta$  formation takes topographic point in TBI patients is still ill understood. In position of this, this reappraisal focuses on the many signaling mechanisms that are common to both TBI and AD and in

making so, we attempt to discourse farther avenues and future waies for research.

## **Synaptic disfunction**

Synapse loss besides exceeds the sum that would be predicted by the loss of connexions from nerve cells that die in the encephalon ( Coleman and Yao, 2003 ). This indicates that synaptic devolution plays a cardinal function in doing dementedness. Loss of synapses is common to all neurodegenerative diseases. As such, the cause of synapse disfunction has been the focal point of many surveies over the past several old ages for both TBI and AD.

Surveies by ( Gao et al. , 2011 ) showed that the denseness of synapses in the molecular bed of the hippocampal dentate convolution was significantly reduced, and farther, the map of full-blown farinaceous nerve cells in the hippocampal dentate convolution is impaired due to TBI abuse.

These observations by Gao et Al ( 2011 ) could explicate the possible anatomic substrate co-relating, in portion, the possible development of post-traumatic memory shortages. Several possible molecular mechanisms have been suggested to underlie the damaging synaptic effects of oligomeric A $\beta$  . First, glutamatergic neurotransmitter receptors are known to be affected by oligomeric A $\beta$  . NMDA receptors are required for the ascertained ologomeric A $\beta$ -induced decreases in LTP ( Roselli et al. , 2005 ; Shankar et al. , 2007 ) , and oligomeric A $\beta$  is besides known to heighten LTD by doing internalisation of AMPA receptors and NMDA receptors ( Hsieh et al. , 2006 ; Snyder et al.

, 2005 ) . These effects on synaptic glutamate receptors are thought to be mediated at least in portion by an addition in intracellular Ca which so

<https://assignbuster.com/traumatic-brain-injury-and-alzheimers-disease-biology-essay/>

activates calcineurin ( Kuchibhotla et al. , 2008 ; Wu et al. , 2010 ) . Non-apoptotic caspase activation is besides induced by oligomeric A $\beta$  , which could lend to heighten LTD and synapse loss ( D'Amelio et al. , 2011 ) . Synaptic map greatly depends on Brain-derived neurotrophic factor ( BDNF ) ( Murer et al. , 2001 ) .

In the AD encephalon, decreased BDNF protein degrees were reported in hippocampus, entorhinal cerebral mantle, and temporal neopallium ( Hock et al. , 2000 ) . A big organic structure of research indicates that dysregulation of BDNF is found in conditions of TBI and post-traumatic emphasis upset ( PTSD ) .

In TBI, BDNF cut down secondary hurt, supply neuroprotection, and restore connectivity. In contrast, chronic emphasis or drawn-out exposure to glucocorticoids can cut down BDNF degrees and impair hippocampal operation, by bring forth dendritic abjuration, restructuring, and disjunction ( Numakawa et al. , 2009 ) .

## **Cell survival/death signaling Mechanisms**

Apoptotic and necrotic nerve cells have been identified with bruises in the acute post-TBI period, and these bruises are apparent in parts far distant from the TBI site in yearss and hebdomads after TBI, while at the same clip, there was the presence of devolving astrocytes and oligodendtrocyes in the part within the white affair piece of lands. It is now by and large accepted that mechanism of protein look underlying the phenomenon of cell decease is a balance between pro and anti-protein factors. Here, the effects of TBI

and AD on cellular look of assorted endurance or decease promoting proteins are reviewed.

### **( a ) Bcl-2 household of proteins**

Neurotoxin- or ischemia-mediated apoptotic decease was preceded by increased Bax messenger RNA and protein ; and decreased look of Bcl-2 in cells was correlated to cell decease ( Gillardon et al. , 1996 ; Gillardon et al. , 1995 ) while Bcl-2 immunoreactivity was increased in nerve cells, glia and endothelial cells that basically survived focal ischaemic hurt ( Chen et al. , 1995 ; Tortosa et al. , 1998 ) found that Bcl-2 protein is overexpressed in reactive glial cells environing senile plaques, which suggests that that Bcl-2 may play a function in the endurance of reactive glia in AD. Similarly, increased look of Bcl-2 has been observed in nerve cells that survive the traumatic abuse both in the rat and in brian-injured worlds ( Clark et al. , 1997 ; Clark et al. , 1999 ) while Bax was observed to translocate to the chondriosome of apoptotic cells following experimental encephalon hurt ( Kaya et al. , 1999 ) . In contrast, recent surveies have suggested that decreases in intracellular Bcl-2 immunoreactivity, with small to no alteration in Bax proteins, in injured encephalon parts may predate cell decease following experimental encephalon injury ( Raghupathi et al. , 2003 ) . Following experimental TBI, transgenic mice overexpressing the human Bcl-2 protein exhibited significantly less neural loss in the injured cerebral mantle and hippocampus, imparting support to the thought that Bcl-2 may take part in the neural cell decease following TBI ( Nakamura et al. , 1999 ; Raghupathi et al. , 1998 ) .

<https://assignbuster.com/traumatic-brain-injury-and-alzheimers-disease-biology-essay/>

A pro-apoptotic member of Bcl-2 household, Bid, has besides been implicated in trauma-induced cell decease in vivo-proteolysis of Bid predating its translocation to the chondriosome has been demonstrated in the injured cerebral mantle ( Franz et al. , 2002 ) .

## **( B ) MAP kinases**

Both JNK and ERK1/2 are known regulators of cell survival/death in a figure of nervous and non-neural systems in-vitro. Traumatic encephalon hurts appear to trip ERK1/2 in injured encephalon parts and appears to co-localize with both neural ( Dash et al. , 2002 ; Mori et al.

, 2002 ) and astrocyte ( Otani et al. , 2002 ) markers in the injured cerebral mantle and hippocampus. During patterned advance of AD, MAPK is extremely phosphorylated by GSK-3 alpha and CDK5 kinase.

Whether ERK activation in injured nerve cells is associated with cell decease or is an effort by injured cells to keep normal map is yet to be determined.

Pre-injury intervention of animate beings with a specific inhibitor of ERK phorphorylation, PD98059, has been observed to diminish ERK activation and the extent of cell decease after hurt ( Mori et al. , 2002 ) , but appears to worsen cognitive and motor shortages in encephalon injured animate beings ( Dash et al.

, 2002 ) .

## **( degree Celsius ) Tumor suppressor cistron ( p53 ) Signing**

Initiation of tumour suppressor cistron, ( p53 ) messenger RNA has been related to neural harm following excitotoxic and ischaemic encephalon hurts ( Sakhi et al. , 1994 ) .

Following experimental encephalon hurt, increased messenger RNA and protein for p53 were observed in parts that exhibit neural programmed cell death and in nerve cells that were TUNEL +ve ( Hooper et al. , 2007 ; Napieralski et al. , 1999 ) show that upregulation of p53 induces tau phosphorylation which is a trademark of AD.

This survey showed that Tau was found in the cytoskeletal compartment, while p53 was located in the karyon, thereby bespeaking the fact that the effects of p53 on tau phosphorylation are indirect. Since wild type p53 is a written text factor for cistrans such as wild type p53 activated fragment ( WAF1/p21 ) ( Artuso et al. , 1995 ) , the pro-apoptotic factor, Bax ( Miyashita et al. , 1994 ) and the growing apprehension and DNA damage-inducible cistron GADD45 ( Zhan et al. , 1998 ) , the effects of p53 initiation are many. Other groundss set up that p53, are besides up regulated and may take part in molecular response to TBI.

## **( vitamin D ) Akt/GSK-3 beta/beta-catenin signaling**

Akt/GSK-3 beta/beta-catenin signaling plays a important function in the programmed cell death of nerve cells in several of the theoretical accounts of neurodegeneration.



Zhao et al ( 2012 ) studied the mechanism of cell endurance mediated by the Akt/GSK/beta-catenin tract utilizing a rat theoretical account of TBI, where phospho-Akt was significantly increased at 4 hours post-TBI, but decreased after 72 hours post-TBI. Further, neuroprotection of beta-catenin against ischaemia was partially mediated by increased and relentless activation of the Akt/GSK3beta signaling tract ( Zhao et al. , 2012 ) . Surveys by ( Lucas et al.

, 2001 ) utilizing conditional transgenic mice overexpressing GSK-3b in vivo resulted in neurodegeneration and this suggest a direct relevancy of GSK-3b deregulating to the pathogenesis of AD and TBI.

### **Role of Endoplasmic Reticulum ( ER ) dysfunction**

APP is considered a transmembrane protein which appears folded and thereafter it is modified in endoplasmic Reticulum ( ER ) and so transported through the Golgi composite to the outer membrane ( Salminen et al. , 2009 ) . APP is largely expressed in nerve cells but nevertheless, it is found that astrocytes and oligodendrocytes are besides capable look every bit good as processing of APP protein ( Salminen et al.

, 2009 ) . It appears that the processing can change widely depending on the varying compartments during the procedure of conveyance from ER to lysosomes, and this depends on the cellular fortunes every bit good ( e. g. , metamorphosis and stress conditions ) ( Salminen et al. , 2009 ) . ER is a sensitive cell organ which is capable of comprehending perturbations in the cellular homeostasis and therefore it is logical to gestate the fact that the encephalons of AD sick persons could expose many indicants of ER emphasis

<https://assignbuster.com/traumatic-brain-injury-and-alzheimers-disease-biology-essay/>

( Hoozemans et al. , 2009 ) . ER is capable of supporting the host by usage of tripping UPR ( unfolded protein response ) .

This includes Cascades that are capable of defying the adaptative alterations in metamorphosis and cistron look that are required to pull off nerve-racking state of affairss. Thereafter, ER can originate the plan whereby the cells are killed but tissues are saved from necrotic hurt. Bax-Inhibitor-1 ( BI-1 ) , a cytoprotective protein which resides in ER membranes is frequently manifested within the context of ER emphasis. BI-1 modulates several ER-associated maps, including UPR signaling. Furthermore, encephalon tissue from BI-1 transgenic mice subjected to TBI after ER emphasis indicated decreased degrees in apoptotic cells, initiations markers every bit good as CHOP protein look. Presenilin 1 ( PS1 ) , a polytopic membrane protein plays a cardinal function in trafficking every bit good as in the proteolysis of certain set of transmembrane proteins. It is found that important bulk of persons that are affected with the oncoming of familial Alzheimer ' s disease ( FAD ) frequently carry missense mutants of PS1. Further to this, CHOP courier RNA is compromised in cells that lack PS1 and PS2 or, in cells that express FAD-linked PS1 discrepancies ( Sato et al. , 2000 ) .

## **The function of Mitochondrial disfunction**

The function of mitochondrial disfunction and oxidative harm was investigated by several research workers. Mitochondrial disfunction is characterized in the 3xTg-AD encephalon by manner of decreased mitochondrial respiration and pyruvate dehydrogenase protein degrees

<https://assignbuster.com/traumatic-brain-injury-and-alzheimers-disease-biology-essay/>

every bit good as activity in mice of 3 months of age. Further it expressed increased oxidative emphasis characterized by increased degrees of H<sub>2</sub>O<sub>2</sub> and lipid production degrees. In add-on to this, mitochondrial A $\beta$  degrees in 3xTg-AD female mice of 9 months age was found to be well increased ( Reddy, 2011 ) . Drago et Al. ( 2008 ) investigated whether A $\beta$ -metal composites have damaging effects on intraneuronal Ca<sup>2+</sup> homeostasis and mitochondrial map in vitro. Results show that A $\beta$  perturbed neural Ca<sup>2+</sup> homeostasis and in add-on inhibited mitochondrial respiration. Resende et Al ( 2008 ) investigated whether oxidative harm occurs early in AD development. It evaluated oxidative emphasis and the degrees of antioxidants in the 3xTg-AD mouse theoretical account. Results show increased activity of the antioxidant enzymes glutathione peroxidase and superoxide dismutase. These additions were apparent during the A $\beta$  oligomerization period, before the visual aspect of A $\beta$  plaques and NFTs, and thereby back uping the position that oxidative emphasis occurs early in AD development, before A $\beta$  plaques and NFTs are observed ( Resende et al. , 2008 ) . Mitochondria besides appear to play a critical function in the secondary hurt that occurs after traumatic encephalon hurt ( TBI ) ( Finkel, 2001 ; Hunot and Flavell, 2001 ) , and mitochondrial disfunction has been shown to be involved in excitatory amino acid ( EAA ) -induced neurotoxicity ( Brustovetsky et al. , 2002 ) .

Mitochondrial disfunction after TBI has been linked to damage of encephalon mitochondrial negatron transportation and energy transduction due to overloading of mitochondrion-associated Ca ( Xiong et al. , 1997 ) , increased

mitochondrial reactive O species ( ROS ) production, oxidative harm, break of synaptic homeostasis ( Azbill et al. , 1997 ; Matsushita and Xiong, 1997 ; Sullivan et al.

, 1999 ) , and cell decease ( Robertson, 2004 ) . Following TBI, the degrees of NADPH oxidase activity and superoxide production show important lifts. This could significantly lend to the pathophysiology of TBI via mediation of microglial activation, oxidative emphasis harm, and initiation of starchlike beta in the encephalon.

## **Decision**

TBI is one of the taking upsets that frequently either leads to immediate decease or inflicted with a life-time of terrible cognitive disablements. A thorough and precise apprehension of the exact cause of developing AD when inflicted with TBI could potentially be good for farther development of therapeutics aimed to halt the onslaught of such neurodegenerative diseases.

Despite the advancement in research including several clinical tests over the past decennaries, there is n't a individual effectual drug that could rarefy the cognitive disfunction associated with TBI. Sing this, one could reason that a combination therapy i. e. , aiming multiple and complimentary mechanisms of action ( Margulies et al. , 2009 ) could be an option particularly for the fact that TBI affects a broad scope of encephalon maps including physical, cognitive and behavioural. Failing clinical tests for therapeutics in TBI research has been a major concern in the yesteryear.

In this respect, a unvarying criterion of attention for clinical tests should be adopted that could needfully mime the criterions used pre-clinical research. Finally, acceptance of a shared database for construing positive and negative of pre-clinical informations would be of great aid.

## **Figure fable**

Figure 1.

Conventional representation of the relation between an incidence of TBI and the subsequent development of Alzheimer ' s disease. An incidence of TBI ( indicated in ruddy ) triggers cell decease, synaptic disfunction, Endoplasmic Reticulum ( ER ) and mitochondrial emphasis taking to possible development of Alzheimer ' s disease ( indicated in sunglassess of blue, violent and green ) .