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Review Article

Hypoxia and Cigarette Smoke - A Combined Threat to the Brain: Role of Toll-like Receptor 4 in Neuroinflammatory Changes

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I N F O

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A B S T R A C T

The mammalian brain is composed of 20% of oxygen. The depletion in the level of oxygen may lead to hypoxia, resulting in neurological changes. Recent findings of Toll-like receptors (TLR) such as TLR-2, 3, 4 and 8 in the mammalian nervous system showedneuroinflammation in the brain. The activation of TLR4 by both exogenous and endogenous ligands leads to various inflammatory diseases likeatherosclerosis, Crohn's disease, ulcerative colitis, rheumatoid arthritis and prostate cancer. This study confirms the involvement of NF-κB in TLR4-axis-induced neuroinflammationin the brain. Cigarette Smoke contains many toxic chemicals such as carcinogenic compounds which areinjurious to health, causing death worldwide. The role of TLR4 in activating the Brain during Cigarette Smoke exposure is not yet understood. Hence this study reviewed the use of the cell culture in vitro model as well as in vivo mouse model of TLR4-/- mouse exposed to hypobaric hypoxia to test hypothesis.

Methodology: This review explored articles fromthe past 15 years to study the action of toll-like receptor 4 in neuroinflammatory changes. Those articles which lacked full texts were excluded from the review. A total of 61 articles were enrolled in this review article.

Results: The recent findings of TLR in Neurons, showed the involvement of external stimuli such as Cigarette smoke causing various neurological disorders and brain inflammation. The role of TLR4 in activating the brain during acute and chronic cigarette smoke exposure is not yet investigated and also the neuroimmune mechanisms of cigarette smoke are not yet clearly understood.

Conclusion: Smoking-related neurological disorders requirea proper understanding of the mechanisms of such damage for therapeutic development. Hence research should be carried out to study the TLR4 mechanisms and pathways in various inflammatory diseases.

Keywords: TLR4, NF-Kb, (IFN-β), Janus Associated Kinases/ Signal Transducer and Activator of Transcription (JAK/STAT), Pathogen Associated Molecular Patterns (PAMPS), Cigarette Smoke, Neuroinflammation

Introduction

Hypobaric hypoxia is injurious to health. The brain is highly susceptible to hypoxia; it is only 2% of body weight and consumes 20% of oxygen. Hypoxia causes memory impairment leading to learning deficiencies, anterograde amnesia[1] and cognitive functions in humans. Hypobaric hypoxic effects in the brain arecharacterized by changes in the biochemical components, apoptosis, neurotransmitter release and neuroinflammation.[2]Brain inflammation is a consequence of hypoxia. The causes and mechanisms of brain inflammation following hypoxia are not well understood. Hypoxia stress itself might act as neuroinflammation. Toll-like receptors (TLRs) are archetypal pattern recognition receptors expressed in the immune system and regulatethousands of genes that are involved in innate and adaptive immune responses to fight against microbial infection.[3] TLRs are not only expressed in the immune system, the non-immune cells such as brain cells, endothelial cells and fibroblasts, hepatocytes also express them.[4] Astrocytes express TLR4 and it has been investigated for pro-inflammatory mediators.[5] Microglia expresses all known TLRs and experiments indicate that they can robustly respond to both TLR4 and TLR3 ligands.[6] Recently some studies pointed out that neurons, as well as neural progenitor cells, can also express TLRs.[7] Further reports also reveal that TLR2, 3, 4 and 8 are expressed in neurons.[8] Direct stimulation of TLR4 by LPS has been reported to cause memory impairment.[9] Another study of hypobaric hypoxia indicated memory impairment in rats.[10] However, the cause of this is not clearly understood. The studies[11,12] using single-Ig-IL-1 related receptor (SIGIRR) KO in mice identified that overstimulation by TLR4 by High Mobility Group Box1 (HMGB1) was involved in memory dysfunctions. It is possible that increased HMGB1 levels may be involved in high altitude-induced memory impairment, by stimulating TLR4 signalling. Hence in this review, focus is on usingthe cell culture in vitro model as well as in vivo mouse model of TLR4-/- mouse exposed to hypobaric hypoxia to test our hypothesis.

The actual mechanisms of memory impairment was explored using the cell lines such as BV2 cells, HT22 cell line and IMA 2.1 as potential model systems to study microglial, neuronal and astrocyte functions. Thus, the study aimed to understand the non-additive responses to identify/ delineate the signalling mechanisms.

The Pathways

The pathways are numerous in a cell; especially in CNS, the cells do interact extensively with each other by releasing the neurotransmitters, up taking the neurotransmitters, etc. A study stated that if two separate pathways are triggered by two distinct ligands, then they regulate the transcription of the same gene and the associated stimulation with both ligands must result in an additive response which should correspondent to the sum of the separate responses.[13] Despite, that, if the pathways intersect or modulate each other, then the concomitant addition of ligands will yield a non-additive response which will be either greater or less than the expected additive response. For example, the signalling pathways used by exogenous and endogenous ligands of KDO can be modulated by the presence of interferon-β (IFN-β) and/or 8-bromoadenosine-3',5'-cyclic monophosphate (8-Br). IFN- β signalling occurs via Janus Associated Kinases/ Signal Transducer and Activator of Transcription (JAK/STAT) pathways in neurons during hypoxia[14]and during oxygen glucose deprivation. 8-Br increases cAMP levels in the neurons.[15] IFN-β and 8-Br might modulate the signalling mechanisms of TLR4 ligands in the proposed cell models. With this rationale, this present investigation was used to understand the pathway interactions and modulations among the TLR4 ligand exogenous and endogenous (such as KDO and HMGB1) individually and non-TLR4 ligand stimulation (such as IFN-β and 8-Br in combination with KDO and HMGB1 as a double and triple combination) in neurons, astrocytes and microglia. The investigation also aimed to analyze whetherpathways triggered by these ligands will be different from each other by using systems biological approaches. The present study aimed to understand the memory impairment caused by hypobaric hypoxia using KDO and HMGB1as TLR4 ligands in vitrocell culture models.

Methodology

This review focuses on the studies carried out across the globe. In this search, all the research articles related to toll-like receptor 4 in neuroinflammatory changes and hypoxia were explored from national and international journals. The articles were assimilated from Google scholar and PubMed using keywords such as TLR4, Nuclear Factor Kappa B, Hypoxia, Neuroinflammation, Cigarette Smoke and IFN.

This review explored articles from the past 15 years to study the action of toll-like receptor 4 in neuroinflammatory changes. Those articles which lacked full textwere excluded from the review. A total of 61 articles were enrolled in this review article.

Results

CNS and Immune Functions

Central Nervous System (CNS) is under the monitoring of the immune cells constantly from the layer of meninges itself.[24] The mechanisms of those immune monitoring under various stress and disease conditions of the CNS are very poorly researched. Recently Louveauet al.,(2015)[24] reported the presence of lymphatic vessels in the central nervous system in the dural sinuses of the mouse brain. Such discovery is a break through in the field of neuroimmunology to find new

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therapeutic approaches for immune-related neurological diseases. While discussing about the trafficking of immune cells to the brain various routes of entry are emphasized. T cells and monocytes continuously influx intothe brain via various routes, as the presence of Blood Brain Barrier (BBB) is not a barrier totheir entry because these cells enter viapost-capillary venules[24] thus making the brain highly vulnerable to immunological attack. Understanding such functions of CNS thus becomes a priority as it can lead to inflammation and also neurological disturbances.

Toll-Like Receptors (TLRs)

The TLR family of proteins is highly conserved during evolution and they have the capacity to recognize and bind with both self and non-self-molecules, which elicit both innate and adaptive responses. TLRs are unique in their ligand binding specificity and display distinct sensing and intracellular pathways. Among the TLR family of proteins, TLR4 can bind with a variety of Pathogen Associated Molecular Patterns (PAMPS) and Damage Associated Molecular patterns (DAMPS). The PAMPS of TLR4 includesgram-negative Lipopolysaccharide (LPS),[25] fibronectin,[26] hyaluronan,[27] fibrinogen,[28] heat shock proteins[29] and respiratory syncytial virus (RSV) fusion (F) protein, etc.[30] In humansand micetodate 13 toll-like receptors (TLRs) have been discovered. Nine TLRs are common between humansand mice; TLR10 is not present in miceand is expressed in humans. TLR11, 12 and 13 are expressed in mice and not expressed in human.[30] They are also termed as evolutionarily conserved receptors of the immune system.[3,31]

TLR stimulation is tightly controlled by phosphorylation events, ubiquitylation, physical interactions, conformational changes and proteasome-mediated degradation that are under the control of various regulatory molecules.[3,31] TLR4 gene is located in human chromosome 9 (9q32-q33) with 4 exons and 3 introns and of 19kb in sequence.[15,32] It is observed that single nucleotide polymorphisms in TLR4 gene can lead to the hypo-responsiveness for mounting immune reactions and pose the risk for various diseases which are inflammatory in nature including, atherosclerosis, Crohn'sdisease, ulcerative colitis, rheumatoid arthritis and prostate cancer.[33,34,35]

TLR4 and Neuroinflammation

Neuroinflammation is the phenomenon of coordinated insult to the cells of the nervous system leading to tissue damage. Expression and activation of TLR4 leadto various inflammatory diseases. TLR4 can be activated by both exogenous and endogenous ligands and once activated it leads to robust production of proinflammatory cytokines.[34,35] TLRs are not only involved in the PAMS and DAMPS induced neuroinflammatory changes in the brain, but they actively participate in the development of Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Alzheimer's disease(AD).[36]

Various studies have reported the involvement of TLR4 in brain diseases. The signaling pathway studies showed that treatment of LPS in rat hippocampal neurons caused neuroinflammation through PTEN/PI3K/AKT/NF-κB pathway.[37] This study confirms the involvement of NF-κB in TLR4-LPS axis-induced neuroinflammation in the brain.

Inhibitory studies shed light on the role of TLR4 in neuroinflammation. Blockade of TLR4 signal inhibitor resatorvid during ischemic stress downregulated the phospho-p38, NF-κB, matrix metalloproteinase9(MMP9) levels and also it reduced NOX4 expression thus preventing both nitrative and oxidative stress. This inhibition protected the neurons from apoptosis.[38]Curcumin inhibits the TLR4-MyD88-NF-κB axis and protectsthe brain from acute inflammatory injury during experimental traumatic brain injury.[13]

Some reports suggest that external antitumor agents used to treat cancers can exert their toxic effect on neuronal cells, through TLRs. Recently,it has been shown that, Paclitaxel, achemotherapeutic agent, when administered at high concentrations through TLR4 mediates its damaging effects on axonal growth on DRG (dorsal root ganglion) neurons. The TLRs are expressed in CNS both in Glia and neurons and can bind with both exogenous as well as endogenous ligands.[39]

Specifically, TLRs are targeted as therapeutic agents in CNS inflammation.[39] In the case of CNS, TLR2 and TLR4 are reported to bind with DAMPs and PAMPs.[39]Various brain research studies reported the involvement of TLR4 as an important mediator of neuroinflammation during neuropathic pain[40] and in acute and chronic itch conditions. Moreover, alcohol-induced brain damage and neuroinflammation aremediated by TLR4.[41,42] The role of TLR4 in various neuronal injuries remains completely unknown and less understood.

Cigarette Smoke and Neurological Disturbances

Cigarette smoke increases anxiety disorders and symptoms[22] and causes disturbances in blood-brain barrier BBB.[44] Oxidative stress and inflammation in rat brain havebeen the hallmark of cigarette smoke exposure.[8,28] Cigarette smoke also causes lipid peroxidation and increased the activity of acetylcholinesterase and these were ameliorated by vitamin E supplements.[45] Carbon monoxide in Cigarette smoke disturbs the long-term potentiation in the hippocampus in rats.[45] Human smokers have both disturbed and poor quality of sleep followed by visual memory impairments when compared with non-smokers.[4] Structural abnormality in the brain and also neuropsychological tests have been noted in patients who are smokers as well as alcoholics.[23]

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Nicotine had a profound impact on the attention index in human patients.[27] Grey matter volume and grey matter density was reduced in smokers when compared with non-smokers.[46,47]Such differences are noted in areas of the brain which mediate working memory, attention and drug reinforcement. Pregnant rats infused with Nicotine showed teratogenic effects and synaptic dysfunctions.[48]

Previous studies have shown that nicotine can cause increased release of glutamate, GABA,norepinephrine, dopamine and acetylchoine.[49,50,51] But the precise mechanism of such release is not yet understood. A study by Karamaet al., 2015,[29] showed that in the human brain cortical thinning occurs because of Cigarette smoke. A total of 504 subjects were analyzed by brain magnetic resonance imaging (MRI) revealed this cortex thinning. Way back in 1998 the effects of cigarette smoke on working memory started to be noticed.[29] There are reports which suggest a protective role of nicotine in the brain, but the majority of studies reveal the negative effects of cigarette smoke on brain functions. Cigarette smoke has been associated with numerous health effects but in particular to the brain, as shown by the Centers for Disease Control and Prevention. Cognitive flexibility and memory are very poor in smokers.[52] There are reports which suggestthat dementia and cigarette smoking to the extent of 14 % are associated with the development of Alzheimer's.[53,54]

Selected regions of the cortex of the smoking brain showed atrophy and reduced cortical volume.[55-60] Further, interesting studies report that in the frontal lobe there is a reduction in thickness and also abnormal levels of NAA, a marker for neuronal integrity(N-acetyl aspartate) was abnormal. This area of the brain is involved in addictive brain disorders.[57,59] Cigarette smoke causes cognitive impairment and also redox imbalance.[61] Medial orbito-frontalcortex showed a reduced thickness in smokers. This region is involved in the brain's reward, impulse control and decision-making. Cortical thinning is important because it is one of the markers for cognitive aging. Mojtaba et al., 2012[62] noted that cortical thinning is noted even after the cessation of Cigarette Smoke even after many years.The effects of cigarette smoke include cancer, neurological disorders, silent cerebral infarction, stroke and cerebral aneurysm.[63-65] Cigarettes which contain very low levels of nicotine as well as nicotine-free cigarettes are equally harmful to the blood-brain barrier endothelial cells.[44] Various disorders such as Alzheimer's, multiple sclerosis, small vessel ischemic disease, developmental problems during the pregnancy, all the other problems associated with cigarette smoking.[66] One more possibility that the nicotine present in cigarette smoke can activate the nicotinic receptors. Nicotine decreases the ZO1 expression, a tight junctional protein and leading to disturbances in ion homeostasis. In these disturbances, the released product might activate the glial and neuronal cells for further exacerbation of the situation. The exact mechanism of action of cigarette smoke in brain neuroimmune/neuropathology is not yet understood. Recentstudies point out the link between cigarette smoke and neurologicaldisturbances.[19,67] Animal studies also reveal that exposure to cigarette smoke in general, can increase ROS levels and circulating pro-inflammatory markers and decreased levelsof antioxidant markers.[6,18,28,68-70] In human smokers, urine levelsof oxidation products and also immunosuppression are noted.[18,68,69]

In Lewis rat brain (Khanna et al.,2015)[8] found increased markers of proinflammatory cytokines and oxidative stress markers in the brain. This study explored the entire brain homogenates, but did not examine individual brain regionsof cigarette smoke-exposed rats. The pro-inflammatorycytokines such as Tumor Necrosis Factor (TNF-α), Interleukins-IL-1α, IL-1β, IL-6, IL-23, IL-17, IL-10 and Transforming Growth Factor (TGF-β) observed in this study can only be produced by the activation of TLR4 signalingpathways. This is also not examined yet and probably this is the first study thataddresses this issue. The LPS in cigarette smoke may have activated TLR4 in the brain or the endogenous TLR4 ligands such as HMGB1, HSP60, 70 and 90 could have activated the TLR4 in microglial cells and the activated products from activated microglialcells could have further stimulated the inflammatorychanges in brain regions to further exacerbate the already existing situation. The role of TLR4 in cigarette smoke-induced memory dysfunctions isnot yet understood. The brainis a highly vulnerable organ tooxidative stress as it contains a high concentration of Polyunsaturatedfatty acids (PUFAs). The free radicals present in cigarette smoke can easily damage the BBB and damage the PUFAs of neuronal cells. Cigarette Smoke contains biologically active endotoxin LPS, it can also be absorbed from the lungs and it can be seen in venous blood and in plasma by increasing the expression of TNF., IL-6, sTNFR-I and II.[2,45,71]

In mice treated with alcohol, it showed disturbances in behavioral and cognitive disturbanceswhereas TLR-/- mice wereprotected from these effects during alcohol exposure.[42] LPS treated TLR-/- mice/rat is protected from brain inflammatory changes and cognitive dysfunctions. LPS is a component of tobaccosmoke, dust and pollution, it is represented in various inflammatory diseases.[2,45,71,72] LPS is known to activate the brain neuronal and glial TLR4.[73,74]The pro-inflammatorycytokines such as Tumor Necrosis Factor (TNF-α), Interleukins-IL-1α, IL-1β, IL-6, IL-23, IL-17, IL-10 and Transforming Growth Factor (TGF-β) observed in this study can only be produced by the activation of TLR4 signaling pathways. This is also not examined yet and probably this is the first study that addresses this issue.

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Discussion

Cigarette Smoke is injurious to health because it contains over 4,700 different chemical compounds which include oxidants and carcinogenic substances.[11,16,38] Cigarette smoke is formed of many toxic chemicals such as carcinogenic compounds[41,42] and also the free radicals[18] which can cause potent oxidative damage to tissues.[19] According to a scientific report death by tobacco increased from 5.4 million in 2005 and in 2006 it increased to 6.4 million and in 2030 it will increase to more than 8.3 million.[20] Death by tobacco accounts for 10% globally and it can kill almost 50% more people than the dangerous disease like HIV –AIDS.[20]

Evolution did not allow the cells of the human body to tolerate such toxic chemical compounds to pass on the cells without causing any notifiable injury to the cells. Lungs are very special organs because they do interact with the external environment through the epithelial cells. In particular, tobacco smoke, Cigarette Smoke and airborne pollutants can easily attack the lung epithelial cells, leading to inflammation. The consequences of such stress arethe formation of oxidative stress, apoptosis, senescence and inflammation, increased HDAC activity, aggregation of insoluble polyubiquitinated aggregates and lack of antioxidant production.[43,22] Even though the lungs are special organs for counteracting pollutants and other toxic substances, Central Nervous System (CNS), especially the brain is highly vulnerable to these effects for the following reasons.

Conclusion

The recent findings of TLR in Neurons, showed the involvement of external stimuli such as Cigarette smoke causing various neurological disorders and brain inflammation. The role of TLR4 in activating the brain during acute and chronic cigarette exposure is not yet investigated and also the neuroimmune mechanisms of cigarette smoke are not yet clearly understood. Smoking-related neurological disorders requireproper understanding of the mechanisms of such damage for therapeutic development. Hence research should be carried out to study the TLR4 mechanisms and pathways in various inflammatory diseases.

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