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Pharmacological Modulation of Toll-Like Receptors in Brain Disorders

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Abstract

The knowledge regarding pathological and treatment resistance mechanisms involved in the pathology of complex brain disorders is far from understood. The neuroinflammation hypothesis of psychiatric, neurological, and neurodegenerative diseases is well-acknowledged. However, this hypothesis is far from understood. Toll-like receptors (TLRs) family is an innate immunity molecule implicated in neuroinflammation in complex brain disorders. This chapter reviews considerable evidence indicating that activation of endotoxins such as lipopolysaccharide is a common factor. Additionally, we report clinical and preclinical studies highlighting the link between lipopolysaccharide, TLRs, and different types of brain disorders. Also, we review the current pharmacological modulations of TLRs. Hoping we would help in filling our knowledge gaps and highlight potential links to tackle new angles in managing complex brain disorders. This chapter's primary goal is to encourage scientists and researchers to conduct future studies characterizing the nature of endotoxin activation of TLRs in complex brain disorders, filling our knowledge gaps, and finding new treatment strategies.

Keywords: Brain disorders, Toll-like receptors, TLR4, Endotoxins, lipopolysaccharide

1. Introduction

The complex nature of neurodegenerative and psychiatric diseases stems from pathological interactions, among which inflammation [1]. Neuroinflammation is a crucial mechanism involved in the pathogenesis of psychiatric [2] and neurodegenerative diseases [3]. Accumulating evidence indicating that targeting neuroinflammation is an appealing strategy since that inflammatory-related diseases comorbid with brain disorders [4–7]. In preclinical settings, triggering inflammation by administering of endotoxins and other activators are well-acknowledged animal models [8]. Preclinical studies found that attenuating inflammation reduces phenotypic features associated with psychiatric and neurodegenerative disorders. In line with this, clinical studies suggest that treatment with anti-inflammatory medications affects memory, cognition, and mood [9–11].

Developmental studies have shown that TLRs are essential elements in regulating brain development. Previously, it was reported that both TLR7 and TLR9 are expressed in corticolimbic regions of the developing brain. *In situ* hybridization and PCR studies indicated that TLR7 and TLR9 expression increased significantly in pre and early postnatal stages, whereas the expression reduced as the rodents reached adult developmental stages [12]. Epidemiological reports indicated that exposure to infection at prenatal stages, where the brain and the central nervous system are developing and vulnerable to an unfavorable environment, increases mental illness risk later in life [13, 14]. Inflammatory cytokines involve ubiquitously in modulating different pathways. For instance, it may alter the developing brain epigenetic system, which could be due to excessive glucocorticoids [14]. According to the Danish National Psychiatric Register, prenatal exposure to bacterial infection was linked to schizophrenia. In a set of about 8000 individuals, 1.1% of cases were diagnosed with schizophrenia by their thirties [15]. In line with this, a previous study linked developmental delay and mental retardation to maternal urinary tract infections [16]. On another cohort, the risk of schizophrenia increases in offspring born to mothers diagnosed with reproductive infections during pregnancy [17]. Also, other reports link cytokine-related mechanisms to the pathology of Attention deficit hyperactivity disorder [18, 19]. *In vitro* studies have shown that TLR3, TLR7 and, TLR8 regulate dendritic arborization in an MYD88 dependent signaling. The studies indicated that among these receptors, the TLR8 is the major contributor in regulating dendritic pruning. It further showed that both TLR3 and TLR7 are essential in regulating axonal development. This evidence indicated that the TLR family is vital in modulating proper neuronal development [20].

All these evidences indicate a functional direct link between inflammation and mental illness. This chapter was undertaken to further highlight the association of TLRs, endotoxins, and brain disorders. We also emphasize the diverse role of multiple TLR family members in both nonregenerative and psychiatric diseases. Lastly, we review the pharmacological modulation of TLRs in the context of brain disorders. Aiming this chapter would stimulate future research in characterizing the nature of endotoxin activation of TLRs in complex brain disorders, filling our knowledge gaps, and finding new treatment strategies.

2. The role of endotoxins in mediating brain disorders

In comparison to most bacterial activators of inflammatory cytokines, endotoxins are considered one of the most potent. Mostly, endotoxins are referred to as lipopolysaccharide (LPS) [21]. LPS is a composition of the bacterial cell wall; an elevated level of LPS reaches different biological systems during infections. Administration of LPS to healthy participants induces both the initiation and the transition phases of acute inflammation. Besides, this activation level reaches the transcriptomic level along with the functional and physiological levels [22]. The systemic application of LPS is utilized extensively in pharmacological animal models of brain disorders [23], including Alzheimer's [24], Parkinson's [25], depression [26], and anxiety [27]. This is mainly regarded as the potency in triggering inflammation.

Previous reports indicated that LPS stimulates the aggregations of both amyloid β and tau, a neuropathological feature of Alzheimer's [28]. Treating Tg2576 mice with LPS increases the mRNA level of cytokines in the cortex [29]. In a transgenic animal model of Alzheimer's, the 3xTg-AD mice, administration of LPS trigger pathological changes in microglia populations associated with later on aggregations of hyperphosphorylated tau. Even though the researchers exposed these mice to

LPS at early developmental stages, before the detection of pathological features related to Alzheimer’s disease. Additionally, they reported that the aggregation of phosphorylated tau was mediated mechanistically through the activation of the cyclin-dependent kinase 5 (cdk5) [30]. Cdk5 is a member of the cyclin-dependent kinases family. Specifically, they are proline-directed serine–threonine kinases group. Functionally, Cdk5 modulates the cell cycle [31, 32], synaptic wiring, neuronal transmission [33], and neuronal development and survival [34]. In accordance with this, a previous report demonstrated that following the stereotaxic introduction of Aβ in mice, the pharmacological inhibition of Cdk5 using roscovitine resulted in reducing inflammatory and oxidative stress mediators at the mRNA level. Indicating that, Cdk5 is a crucial modulator of neuroinflammation associated with molecular phenotypic features of Alzheimer’s disease [35]. Lipopolysaccharide alters the blood–brain barrier transport of amyloid beta protein: a mechanism for inflammation in the progression of Alzheimer’s disease [36]. Also, in a transgenic model lacking the NADPH oxidase regulatory gene, the administration of LPS led to molecular and cellular neurodegenerative changes associated with Parkinson’s disease [37]. In line with this, the pre-administration with LPS resulted in accelerated aging and Parkinson -related symptoms in a Parkinson’s animal model [38]. Describes the main mechanisms involved in the LPS animal models **Table 1**.

In a clinical setting, a previous report indicated that depression and marital distress were significantly associated with an increased LPS, LPS binding protein, and soluble CD14, an LPS co-receptor. Indicating that activation and the translocation of bacterial endotoxin are crucial in mediating mood disorders and stress-related diseases [39]. Functional imaging indicated that individuals exposed to endotoxemia had shown elevated levels of alertness [40], and emotional sensitivity toward visual stimuli [41]. Biochemical changes were observed peripherally, such as elevated stress hormones and inflammation [40, 41], and alterations in the sympathetic nerve’s activity [42]. In another clinical study, the cognitive capacity of

Disease model	Phenotypic molecular and behavioral features	Reference
Model of Alzheimer’s disease (Tg2576 mice).	• Treating Tg2576 mice with LPS increases the mRNA level of cytokines in the cortex	[29]
Model of Alzheimer’s disease (3xTg-AD mice)	• Pathological changes in microglia populations. • Aggregations of hyperphosphorylated tau. • Activation of the cyclin-dependent kinase 5 (cdk5).	[30]
LPS administration to a Parkinson’s disease animal model. (NOX2-/-)mice	• A loss in dopaminergic neurons. • Oxidative stress and Parkinson-related features.	[37]
Endotoxin-Induced Neuroinflammation Model of Parkinson’s Disease.	• Resulted in accelerated aging and Parkinson -related symptoms. • Modify reactive microglia. • Alter the peripheral level of inflammatory cytokines (IL-6, IL-2,TNF-alpha,IFN-gamma)	[38]
Model of Alzheimer’s disease.	• The administration of LPS in mice promoted the influx of amyloid beta protein to the brain and reduced their efflux, a unifying feature of Alzheimer’s disease.	[36]

Tg2576: Transgenic Tg2576 mice; LPS: lipopolysaccharide; NOX2: NADPH oxidase 2; IL-2: Interleukin 2; IL-6: Interleukin 6; IFN-gamma: Interferon gamma.

Table 1.
Main mechanisms involved in the lipopolysaccharide animal models.

healthy participants exposed to endotoxin systemically was examined. The results suggested that the endotoxin-exposed group exhibited a reduction in cognitive function and reduced capability in processing emotional information compared to the placebo group [43]. Suggesting that short-term exposure to systemic endotoxin has a profound impact on higher cognitive tasks. Disrupted sociability [44], and impaired cognitive capacity are hallmarks of psychiatric disorders [45], mainly schizophrenia, and autism [46, 47]. In another report, a battery of socio-behavioral factors was examined and reported to be functionally linked to the systemic administration of LPS. Indicating a mechanistic link between LPS-inflammation and major depressive disorder [48]. In line with this, the administration of a citalopram, a selective serotonin reuptake inhibitor antidepressant agent, leads to a reduction in fatigue and multiple inflammatory cytokines associated with endotoxins activation [49]. In another clinical setting, the level of circulating endotoxins correlates with the severity of neurodegenerative disorders, including Alzheimer's, sporadic amyotrophic lateral sclerosis (sALS) [50].

3. TLR and brain disorders

Toll-like receptor (TLR) is a family composed of multiple pattern recognition members, and these receptors play a crucial role in mediating and modulating innate immunity [51]. This family has an essential role in modulating and maintaining the microglia and microglia translocation protein activity. Histological studies indicated that multiple members of this family are expressed in the brain [52, 53], gut and blood mononuclear cells [54]. Additionally, these receptors are functionally involved in modulating excitatory [55], and inhibitory neuronal populations [56–58]. These modulations include orchestrating different signaling pathways [20]. Also, a couple of TLRs (TLR2 and TLR9) regulate the enteric nervous system. A previous report has shown that both receptors were detected using histological studies in multiple markers of the enteric nervous system. Upon activation of innate immunity by administration LPS, both members were upregulated in the enteric nervous system. Indicating selective disease activation mechanism [55]. Correspondingly, LPS activation of TLR4 leads to stimulation of cytokines-related pathological mechanisms such as dysregulation in oligodendrocytes maintenance, microglial toxicity, and alter myelination [59, 60].

Previous reports linked Alzheimer's disease and polymorphisms in both TLR4 and CD14 genetic codes [61, 62]. Multiple forms of aggregated α -synuclein, a pathological feature of neurodegenerative diseases, can trigger and activate different TLRs. This indicates that TLRs contribute to the pathology of psychiatric and neurodegenerative diseases. Behaviorally they are implicated in regulating impulsivity [63]. A previous study linked TLR4 and the Gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain, and the GABAergic inhibitory neurons release it. It was reported that the alpha-2 GABAergic receptor activation of the TLR4 is essential in mediating impulsivity. The co-immunoprecipitation of the alpha-2 GABAergic and TLR4 in the ventral tegmental area leads to Cyclic adenosine monophosphate (cAMP) activation. The cAMP translocation activates the cAMP-response element-binding protein (CREB), subsequently stimulating the tyrosine hydroxylase and the corticotropin-releasing factor. Interestingly, the stereotaxic infusion of alpha-2 GABAergic and TLR4 siRNA in herpes simplex virus vector in the ventral tegmental area prevented alcohol and nicotine seeking. Indicating that TLR4 is involved mechanistically in regulating drug abuse mechanisms [64]. GABAergic synapses are modulated by TLR4 signaling. Stimulation

of TLR4 by the administration of Lipopolysaccharide (LPS) alters both pre and postsynaptic function of the GABAergic system. The study indicated that both the synthesis and the reuptake of GABA are altered. Electrophysiological recordings have shown that Lipopolysaccharide's administration reduces the miniature inhibitory postsynaptic currents in acute slices, and this inhibition is mediated through the microglia [56]. Another study linked the GABAergic system to TLR in their report pharmacological activation of the GABAB receptor (baclofen) reduced TLR3- and TLR4 mediated inflammation in primary glial cell lines. Similar findings were observed in the expression of TLR3 in blood mononuclear cells isolated from multiple sclerosis patients [65]. Indicating the existence of complex interaction between microglia, TLR4, and GABAergic system.

Besides, activation of TLR4 could interfere with addiction and drug abuse through another mechanism. In another report, it was indicated that pharmacological application of opiate antagonists (naloxone and naltrexone) prevented the TLR4 signaling achieved in LPS treated rodents. Both naloxone and naltrexone have been shown to non stereoselectively inhibit TLR4 [66].

On the other hand, studies have linked TLR signaling and neurodevelopmental disorders such as Autism spectrum disorders [67, 68]. An impairment identifies these disorders in sociability, communication, and characteristics of repetitive behaviors [69]. Accumulated evidence has linked Autism to neuroinflammation. The peripheral level of different TLRs, including TLR2–5 and TLR9, was elevated significantly in autistic patients in clinical settings [70]. In a previous report, flow-cytometric analysis of TLR4/TLR5 and neuregulin 1 - ErbB in the monocytes of schizophrenic and healthy subjects revealed that both TLR4 and TLR5 were elevated where the level of ErbB is reduced significantly in drug-naïve schizophrenic patients compared to healthy controls [67]. Neuregulin 1 – ErbB signaling is crucial in modulating brain development [71]. For example, it is involved in axonal growth [72] and maintenance [73], the expression of acetylcholine receptors [74], electrophysiological firing [75], and synaptic wiring [76]. Cytokine-related mechanisms are unified features of schizophrenia and an emerging hypothesis for the pathology of schizophrenia [77].

The link between TLRs and depression has been identified in both preclinical [78] clinical [79], and postmortem studies [80]. It was further reported that both protein, and mRNA level of TLR2–4, TLR6 and TLR10 was significantly reduced in the prefrontal brain region of depressed suicide subjects compared to the controls [52].

Adult neurogenesis is a physiological process essential for cognitive capacity, learning and memory, synaptic plasticity, modulating mood, and other processes [81, 82]. Dysregulation in adult neurogenesis is linked to schizophrenia [83], Alzheimer's [84], Parkinson's [85], and autism [86]. In TLR2-mutant mice, adult hippocampal neurogenesis was altered. Proliferative cells that are BrdU/doublecortin positive cells were significantly reduced in TLR2-mutant mice. *In Vitro* studies showed that activation of TLR2 enhances the differentiation of neural stem/progenitor cells [87].

4. Pharmacological modulation of TLRs

The pharmacological targeting of TLR has emerged as an appealing strategy for many reasons. First, they are an essential part of the innate immune system responsible for the initiation of the immune response [88]. Also, studies indicated that TLRs modulate the homeostasis [89], neuronal morphogenesis [90, 91], and neurogenesis [87]. Additionally, it was reported that TLRs are implicated in the pathology

of multiple brain disorders such as depression [92], Alzheimer [93], Parkinson [94], and ischemia [95]. Molecularly, it is involved in activating one of the key neuronal signaling pathways [96].

Electrophysiological studies have shown that the administration of immunostimulant results in activation of TLR3 alters the expression of AMPAR, decrease the spontaneous firing, and reduce both the frequency and amplitude of mEPSCs [97]. In line with this, the administration of LPS affect the hippocampal neuronal mEPSC both the frequency and amplitude in hippocampal neurons via modulation of TLR4 [98]. Tlr7 knockout mice showed altered hippocampal LTP, an activity-dependent neurophysiological feature, suggesting defects in memory-related functions [99]. Also, Tlr4 mutant mice exhibited an impairment of long-term depression (LTD) in the nucleus accumbens, another activity-dependent neurophysiological feature, suggesting potential alterations in the reward circuitry [100].

Behaviorally, preclinical studies have shown that TLRs' pharmacological modulation is linked to significant phenotypic features of neurological and psychiatric disorders [90]. In a maternal immune activation (MIA) animal model, a valid model for neurodevelopmental psychiatric disorders such as autism and schizophrenia [101], also linked to increased risks for neurodegenerative disorders [102], it was found that the offspring exhibited schizophrenic-like behaviors via modulation of TLR [103]. Clinical and preclinical studies have shown that altered TLR pathway is associated with schizophrenic and autism-related behaviors [90, 101, 103–105].

Mice lacking the TLR3 gene exhibited impairment in amygdala-related behaviors and elevated anxiety while performing cued fear-conditioning and elevated plus maze tests [106]. Anatomically, the amygdala is encompassed by a group of subnuclei, more than ten regions [107]. At circuitry level, this brain region receives input from sensory cortical and thalamic areas, which is responsible for the conditioned (CS) and unconditioned stimulus, prefrontal cortex, and hippocampus that mediate the extinction of fear responses and bed nucleus of the stria terminalis (BNST) that coordinate the stress-related responses. Its output is projected to the brainstem, hypothalamic, and cortical areas responsible for emotional responses [108, 109]. The TLR4 mutant mice exhibited altered higher cognitive tasks such as memory retention, acquisition, and contextual fear-learning [110]. The long-term intraventricular infusion with a TLR9 ligand resulted in memory dysfunction and increased risk of neurodegenerative disorders [111].

Prion diseases are a group of progressive neurodegenerative disorders [112], previously it was reported that TLR9 could be involved in the pathology of the progression of prion diseases. A preclinical study has shown that the administration of a TLR 9 ligand, cytosine phosphate guanosine (CpG-ODN) oligodeoxynucleotides, in mice resulted in a significant increase in the survival rate. Suggesting that the activation of TLRs in neurodegenerative diseases could be attributed to neuroprotective mechanisms that involve eliminating of neurotoxic misfolded proteins, which may prove to be a possible therapeutic strategy to the prion diseases [113]. This immunostimulant has been employed and examined in infectious, allergies and cancer-related studies [114].

Similarly, genetic therapy targeting TLR2 reduces the accumulation of Amyloid β 1–42 in the hippocampus of an animal model of Alzheimer's disease and alters the progression of memory loss [115]. Misfolded α -synuclein is a characteristic feature and a leading cause of neurodegenerative diseases. Employment of immunization has gained a lot of attention as an attractive therapeutic option for neurodegenerative disorders. In a transgenic mice model of Parkinson's, it was found that the immunization with human α -synuclein associated with a marked reduction in the accumulated α -Synuclein and overall reduced neurodegeneration. Indicating

that α -Synuclein vaccination could be efficient in reducing neurodegeneration associated with accumulated α -Synuclein [116].

A recent study has reported that treating Parkinson's mice model with a natural compound, Juglanin, lead to enhanced memory function, reduced amyloid-beta accumulation, reversed α -synuclein accumulation and overall anti-inflammatory, and antioxidant effects through the modulation of TLR4/nuclear factor (NF)- κ B pathway in the hippocampus [117]. In a clinical setting, treatment with vinpocetine, an alkaloid derivative and a phosphodiesterase type 1 inhibitor, compared to traditional treatment with levodopa, resulted in a significant reduction of TLR 2,4 mRNA level along with reduced the level of serum inflammatory mediators. Interestingly these alterations were associated with a marked elevation while performing the Mini-Mental State Examination score [118]. Although this study did not elucidate the link between TLR2,4 and the enhanced cognitive capacity, it was reported previously that in a dementia model, vinpocetine modulates long-term potentiation [119]. Additionally, vinpocetine was found learning and memory while performing Morris maze tasks in fetal alcohol spectrum disorders mice model [120]. Although this study did not elucidate the link between TLR2,4 and the enhanced cognitive capacity, it was reported previously that in a dementia model, vinpocetine modulates long-term potentiation [119]. Additionally, vinpocetine was found learning and memory while performing Morris maze tasks in fetal alcohol spectrum disorders mice model [120]. Interestingly, previously it was found that the inhibition of Cyclic Nucleotide Phosphodiesterase is associated with an alteration of TLRs signaling, apoptotic pathway, and in chronic lymphocytic leukemia cells [121].

Transgenic animal studies have demonstrated that genetic manipulation of TLRs is associated with increased aggravated of A β [122]. Treatment with an anti-TLR2 antibody has found to be an effective strategy in providing significant protection preclinically against sepsis-associated death [123], stroke [124], Alzheimer's [123], and its safety, tolerability, along with pharmacokinetic profiling have been conducted clinically in healthy subjects [125]. A 7-month administration of anti-TLR2 antibody to an Alzheimer mice model, APP/PS1 Mice, resulted in an overall reduction in the activation of both microglial and astroglia. This reduction was detected by quantifying immunoreactive MHCII, CD68 (microglial markers), and GFAP (astroglia marker) positive cells. Along with a marked reduction in Ab plaque burden in the hippocampal brain region. Behaviorally, the chronic treatment with TLR2 antibody has improved their performance in water maze test, and the latency was reduced significantly, and the time spent in the platform zone [126].

Studies have linked vitamin D deficiency and increased risk of neurodegenerative diseases [127, 128]. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-Parkinson's induced mouse model treatment with vitamin D has shown notable attenuated nigrostriatal neurodegeneration. Additionally, it increased the tyrosine hydrolase neuronal cells, altered the expression of Iba1 positive cells (microglial activation marker), and TLR-4 [129]. In another study, the same model has employed and treated with Rosmarinus acid, a phenolic compound with anti-oxidant, anti-apoptotic, and anti-inflammatory effects [130]. In a dose-dependent manner, Rosmarinus acid treatment led to a significant improvement of motor dysfunction, elevated the number of tyrosine hydroxylase-positive cells, and downregulated TLR4 [131].

In a rat model of subarachnoid hemorrhage, pharmacological application of a natural flavonoid (Fisetin) minimizes the brain edema, improved modulate neurological scores, and modulate apoptosis, mainly through the regulation of TLR 4/ NF- κ B signaling [132]. Taken together, the TLR pathway is an attractive candidate for the development of future neurodegenerative therapies.

5. Conclusion

TLRs contribute to modulate physiological and pathological processes. Besides, immunomodulation of TLRs seems to be a promising strategy. More studies are needed to decipher the molecular, cellular, and functional mechanisms involved in modulating proper brain function. Understanding such mechanisms would significantly clarify the complex nature of brain disorders. On broader aspects, mechanistic studies would facilitate finding the best therapeutic intervention for neurodegenerative and psychiatric diseases.

Acknowledgements

The authors extend their appreciation to the Deputyship for Research and Innovation of the Ministry of Education in Saudi Arabia for funding this research work through the project number IFKSURP- 332.

The authors extend their appreciation to the Mentoring Track program.

Conflict of interest

The authors declare no conflict of interest.

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