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Lipopolysaccharide-induced memory impairment in rats: a model of Alzheimer's disease

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Short title

Lipopolysaccharide and Alzheimer's disease

Summary

Alzheimer's disease (AD) is a primary cause of dementia in the middle-aged and elderly worldwide. Animal models for AD are widely used to study the disease mechanisms as well as to test potential therapeutic agents for disease modification. Among the non-genetically manipulated neuroinflammation models for AD, lipopolysaccharide (LPS)-induced animal model is commonly used. This review paper aims to discuss the possible factors that influence rats' response following LPS injection. Factors such as dose of LPS, route of administration, nature and duration of exposure as well as age and gender of animal used should be taken into account when designing a study using LPS-induced memory impairment as model for AD.

Keywords: Alzheimer's disease; lipopolysaccharide; rats; memory impairment

Introduction

Alzheimer's disease (AD) was first described by Alois Alzheimer in 1906. It is a progressive neuropsychiatric disorder characterized by progressive loss of cognitive abilities (Wilkins and Brody 1969, Cavanaugh *et al.* 2014). It is a debilitating, ultimately fatal disease and is the primary cause of dementia in the middle-aged and elderly (Wilkins and Brody 1969, Fitzpatrick *et al.* 2005, Alzheimer's Disease International 2009, Cavanaugh *et al.* 2014).

The common initial symptoms are forgetfulness and difficulties with routine tasks. As the disease progresses, patients develop more severe memory loss, speech impairment, visual and spatial deficits, and loss of coordination and fine motor control (Rossor *et al.* 1996, Alzheimer's Disease International 2009, Obermeyer *et al.* 2012). Besides the cognitive, sensory, and motor deficits caused by the disease progression, there are a number of behavioral and psychological symptoms related to dementia. These symptoms include agitation and aggression, wandering, disturbances in the sleep cycle, depression, anxiety, delusions and hallucinations (Ferri *et al.* 2004, de Vugt *et al.* 2005, Obermeyer *et al.* 2012). AD reduces the life expectancy of those affected, with an average survival time after diagnosis of 5-7 years (Fitzpatrick *et al.* 2005, Ganguli *et al.* 2005).

AD can be categorized into early and late onset. Early-onset AD (EOAD) typically begins between the ages of 30 and 60 years, and accounts for fewer than 5% of AD cases. The more common form, late-onset or sporadic AD (LOAD), presents after the age of 65 (Rossor *et al.* 1996, Irvine *et al.* 2008).

Risk factors for AD

The single greatest risk factor for developing AD is age, with a risk of 10% for persons older than 65 years and nearly 50% for those older than 85 years (Rossor *et al.* 1996, Gatz *et al.* 2006, Chai 2007).

Apart from age, genetic component is another risk factor for AD. Autosomal dominant familial AD (FAD), which is typically an EOAD, has been linked to mutations in genes encoding presenilin1 (*PSEN1*), presenilin2 (*PSEN2*), and beta-amyloid precursor protein (*APP*) (Chartier-Harlin *et al.* 1991, Goate *et al.* 1991, Mullan *et al.* 1992, Schellenberg *et al.* 1992, Levy-Lahad *et al.* 1995, Sherrington *et al.* 1995). Inheritance of the apolipoprotein E type 4 allele (*ApoE4*) may also increase the risk of developing sporadic LOAD, though *ApoE4* alone is neither necessary nor sufficient to cause AD (Corder *et al.* 1993, Strittmatter *et al.* 1993, Rossor *et al.* 1996, Sadigh-Eteghad *et al.* 2012).

Non-genetically manipulated neuroinflammation models for AD

The unique neuropathological hallmarks of AD are extracellular accumulation of beta-amyloid (A β) peptide and intracellular accumulation of hyperphosphorylated tau protein or neurofibrillary tangles (NFTs,) (Hardy and Selkoe 2002, Iqbal and Grundke-Iqbal 2006). A true model that fits the inflammation hypothesis of AD is an aged animal (older than 22 months) that manifests early chronic neuroinflammation lasting more than 7 days prior to hyperphosphorylation of tau and A β plaque deposition (Burton and Johnson 2012).

The intracellular accumulation of A β , especially A β 1-42, has been shown to precede the formation of extracellular amyloid deposits in subjects with AD and trisomy 21 (Gouras *et al.* 2000), in brains of young Tg mice (8-month-old) harboring APP with three FAD-linked mutations (KM670/671NL, E693Q, and V717I) and the PS1 mutation M146L (Wirhns *et al.* 2001), and in the brains of older Tg mice (17-month-old) harboring various FAD-linked PS1 mutations (Chui *et al.* 1999). Based on these findings, Sheng *et al.* (2003) concluded that intracellular accumulation of A β may be an early stage of a process that may eventually lead to extracellular amyloid deposits and the formation of plaques.

However, other potential rodent models of AD that present with early neuroinflammation in the disease process and are not genetically manipulated by mutations related to A β or tau production are also commonly used. These include lipopolysaccharide (LPS)-, polyI C-, streptozotocin-, okadaic acid- and colchicine-induced neuroinflammation. LPS-induced neuroinflammation represents the current standard paradigm to study neuroinflammation both *in vivo* (Hausse-Wegrzyniak *et al.* 1998; Sheng *et al.* 2003; Anaeigoudari *et al.* 2016) and *in vitro* (Candiracci *et al.* 2012). There are several other non-genetically manipulated rat models of AD which are not limited to induced neuroinflammation. For example, the ferrous amyloid buthionine (FAB) rat model (Lecanu and Papadopoulos 2013), the sodium azide model (Szabados *et al.* 2004) and the Samaritan AD rat model (Petrasek *et al.* 2016). This review focuses only on the widely studied LPS-induced cognitive deficit in rats and the possible factors that can influence rats' response to LPS.

Lipopolysaccharide

LPS is used worldwide in experimental *in vitro* and *in vivo* models of neuroinflammation and amyloidosis (Miklossy 2008). LPS-induced systemic inflammation is used in a number of neurodegenerative diseases; AD (Haus-Wegrzyniak *et al.* 1998; Sheng *et al.* 2003; Anaeigoudari *et al.* 2016), Parkinson disease (Gao *et al.* 2002; Whitton 2007), amyotrophic lateral sclerosis (Zhao *et al.* 2004) and multiple sclerosis (Walter *et al.* 2006).

LPS is a component of the outer membrane of gram-negative bacteria. It is a potent endotoxin and is highly resistant to degradation by mammalian enzymes thus providing a persistent inflammatory stimulus (Ohanian and Schwab 1967) that produces proinflammatory cytokines. These proinflammatory cytokines activate both the neuroimmune and neuroendocrine systems (Maitra *et al.* 2012) that result in similar responses as produced by behavioural stress (Oitzl *et al.* 1993).

LPS produces a wide range of non-specific behavioural effects collectively termed ‘sickness behaviours’ (Klein and Nelson 1999). These behaviours include reduction in activity, reduction in exploration, decreased social interaction, fever, reduction in consumption of food and drink, hypersomnia, activation of the hypothalamic–pituitary–adrenal (HPA) axis and causing increased sympathetic activation (Hart 1988, Kebl *et al.* 1992, Pugh *et al.* 1998).

Mechanism of action of LPS in the central nervous system (CNS)

A direct action of LPS within the CNS is an important possibility (Elmqvist *et al.* 1997). It is possible that LPS can access the brain directly via peripheral nerve transduction (Hansen *et al.* 2000), the circumventricular organs (Blatteirs *et al.* 1992), area postrema (Ericsson *et al.* 1994)

or even at the level of the hypothalamus (Yasuda and Greer 1978, Zhang *et al.* 2000). Mechanism of LPS action in CNS is shown in Fig. 1.

LPS binds CD14 on microglia membranes forming the LPS-CD14 complex which then interacts with toll-like receptor (TLR)-4 (Hailman *et al.* 1994, Lehnardt *et al.* 2003). TLR-4, in turn, activates microglia by initiating signal transduction cascades leading to rapid transcription and release of proinflammatory cytokines including interleukin (IL)-1, IL-6, IL-12, IL-17A, IL-18, p40, inducible nitric oxide synthase (iNOS) and tumor necrosis factor- α (TNF- α) (Rivest 2009, Bossu *et al.* 2012, Sun *et al.* 2015); chemokines such as CCL2, CCL5, and CXCL8; complement system proteins such as C3, C3a, and C5a receptors (Rivest 2009); and anti-inflammatory cytokines such as IL-10 (Mizuno *et al.* 1994) and transforming growth factor- β (TGF- β) (Welser-Alves and Milner 2013). It has been shown that the level of expression of TNF- α , IL-1 β , and IL-6 in the hippocampus was increased compared to controls after three days of LPS administration (Daulatzai 2016).

Proinflammatory cytokines are key molecules that modulate immune responses. Their lack of reversibility in chronic inflammation would enhance dyshomeostasis (Ghosh *et al.* 2015). Chronic inflammation is characterized by long-standing activation of microglia that sustains the release of inflammatory mediators, leading to an increase of oxidative and nitrosative stress. This perpetuates the inflammatory cycle (Tansey *et al.* 2007), further prolonging the inflammation (Schmid *et al.* 2009) that is detrimental for several neurodegenerative diseases (Block and Hong 2005).

An excessive inflammatory response is characterized not only by elevated proinflammatory cytokines, but also by increases in mitochondrial dysfunction, reactive oxygen species (ROS), and nitric oxide (NO). Consequently, there may be damage to the systemic vascular endothelium, redox-glutathione depletion, and mitochondrial respiratory dysfunction causing reduction in ATP and O₂ consumption. Hence, inflammation and oxidative stress are intertwined (Exline and Crouser 2008, Bivalacqua *et al.* 2009, Victor *et al.* 2009; Galley 2011, Lowes *et al.* 2013) and have been implicated in the pathophysiology of AD.

It has been shown that inflammatory cytokines such as IL-1 β , IL-6, TNF- α and TGF- β can augment APP expression (Buxbaum *et al.* 1992, Hirose *et al.* 1994) and A β formation (Blasko *et al.* 1999). It has also been reported that cytokines are able to transcriptionally upregulate β -secretase mRNA, and protein and enzymatic activity (Sastre *et al.* 2003). β -secretase is a key rate-limiting enzyme that initiates A β formation (Vassar 2001). Without β -secretase, A β synthesis is either abolished or considerably reduced (Walter *et al.* 2001).

It has been pointed out in the literature that LPS-induced inflammation promotes AD pathology by altering A β transport at the blood brain barrier (BBB) (Jaeger *et al.* 2009) and decreasing the central clearance of A β (Erickson *et al.* 2012). Alteration of BBB effectively increases brain influx of A β but decreases its efflux (Jaeger *et al.* 2009). The level of expression of A β in the hippocampus is shown to increase (compared with controls) after seven days of LPS administration (Daulatzai 2016).

LPS-induced neuronal cell death could be the result of cyclooxygenase-2 (COX-2) and extracellular signal-regulated kinase (ERK) activation (Lee *et al.* 2008). COX-2 is barely detectable under normal physiological conditions, but can be induced rapidly and transiently by proinflammatory mediators and mitogenic stimuli, thereby mediating deleterious effects in the neurodegenerative disorders (Pasinetti *et al.* 2001). In Alzheimer brain, COX-2 is notably up-regulated, which seems to be associated with A β plaque formation (Pasinetti *et al.* 1998, Hoozemans *et al.* 2001, Pasinetti *et al.* 2002). Conversely, deposition of A β in the brain has been reported to trigger an inflammatory response associated with the neuropathophysiology of AD (Paris *et al.* 2002). Jang and Surh (2005) showed that A β -induced apoptosis is associated with COX-2 up-regulation through activation of NF- κ B, which is mediated by upstream kinases including ERK and p38 mitogen-activated protein kinases (MAPK).

LPS may disrupt the consolidation of certain memory processes. Acute administration of LPS prior to training impairs contextual-cue fear conditioning, a hippocampal-dependent learning paradigm (Pugh *et al.* 1998); while chronic infusion of LPS has been found to impair spatial memory (Hauss-Wegrzyniak *et al.* 1998 and 2000) and induce memory and learning deficits analogous to AD cognitive decline (Lee *et al.* 2008). Systemic LPS administration leads to selective hippocampal impairment in context-object discrimination but not spatial memory (Czerniawski *et al.* 2015). Major cognitive findings in LPS-treated rats are summarized in Table 1.

Animal Response Following LPS Administration

There are a number of factors that can influence animal response to LPS injections, including dose, nature of exposure, route of administration, duration of exposure, age and gender of the animals.

Dose of LPS

Houdek, *et al.* (2014) demonstrated that direct LPS infusion into the fourth ventricle of the male rat brain resulted in a dose-dependent response of activated microglia and astrocyte. Very low-dose LPS infusion (0.05 ng/hr) was sufficient to induce neuroglial activation while moderate and high doses (50 ng/hr and above) were required to induce significant loss of choline acetyltransferase (ChAT)-positive cells in the basal forebrain.

Nature of LPS exposure

Pugh *et al.* (1998) demonstrated that 0.125 and 0.25 mg/kg LPS interfered with contextual fear conditioning, while 0.5 mg/kg had no effect. Similarly, LPS differentially affects the hypothalamic–pituitary axis in that a higher dose of LPS stimulates the sustained release of corticosterone (Nguyen *et al.* 1998, Pugh *et al.* 1998). This appears to be only true for acute exposure to LPS; repeated injections of LPS have no such effect on corticosterone levels (Takemura *et al.* 1997).

Later studies by Shaw *et al.* (2001 and 2005) showed that a single injection of LPS impaired escape latency in both the acquisition and retention phases of hippocampal-dependent learning–spatial learning while a daily injection did not. Repeated LPS exposure also resulted in lower IL-1 β activation; this may be due to an alteration in peripheral sympathetic responsiveness (Zhang

et al. 2000). It is possible that repeated exposure to LPS produces a tolerance effect, as suggested by the lower IL-1 β activation, which may account for the observed behavioural changes in the study.

Repeated endotoxin exposure has long been known to result in a tolerance-like phenomenon (Habicht 1981). The acute administration of LPS has been better characterized, and a few studies have examined the effects of repeated LPS injections upon behaviour or how endotoxin tolerance may be observed in terms of an animal's learning. Kobayashi *et al.* (2002) demonstrated at least one of the molecular bases for the tolerance-like phenomenon. They showed that repeated stimulation of the TLR results in the induction of IL-1 receptor associated kinase-M (IRAK-M), negatively regulating the TLR signaling cascade by halting IRAK's interaction with TNF-receptor associated factor-6 (TRAF6). This mechanism of tolerance may be an adaptive event critical in avoiding endotoxic shock.

Route of LPS administration

The most common routes of LPS administration using LPS-induced cognitive impairment rat model are intraperitoneal and intracerebroventricular. However, we found no studies that explicitly compare different routes of LPS administration with the effect of cognitive function in rats.

Duration of LPS exposure

Bordou and colleagues (2014) investigated the role of duration of exposure to LPS on the neuroinflammatory response to LPS. Male rats received continuous infusion of picomolar levels of LPS (or artificial CSF as control) into their fourth ventricle for either 3 or 8 weeks. Longer

duration of exposure to LPS infusion further increased the elevated levels of IL-1- α , IL-2, IL-4, IL-5, IL-6, IL-12, IL-13, and GM-CSF. This study provides evidence of the influence of chronicity of infection on neuroinflammatory responses in certain brain regions, such as locus coeruleus, that undergo significant cell loss in the early stages of AD (Grudzien *et al.* 2007). However, the study did not investigate the role of duration of exposure to LPS on cognitive behaviour.

In a study of Zhu *et al.* (2014), the results demonstrated that 7 days of LPS administration significantly increased the latency to the platform and decreased the proportion of time spent in the target quadrant during Morris water maze test, compared to 3 days of LPS administration. Increased expression of A β in the hippocampus was observed following administration of LPS for 7 days but not for 3 days, indicating that the increased expression of A β may be a major factor in the pathogenesis of cognitive dysfunction.

Age of animal during LPS exposure

Age appears to be an important factor influencing the behavioral responses to LPS. Prenatal (Bakos *et al.* 2004) and early postnatal (Fan *et al.* 2005, Pang *et al.* 2006) LPS exposure has been shown to induce poor neurobehavioural performance and is frequently used to model diseases such as schizophrenia and autism (Powell 2010; Meyer 2014; Waterhouse *et al.* 2016).

Younger animals seem to be affected to a lesser degree, at a slower pace and do not show speed decrement on day one as shown by the year-old mice (Sparkman *et al.* 2005). Bardou and colleagues (2014) investigated the age of exposed rats on the neuroinflammatory response to

LPS. Male rats at three age groups of young (3 months), middle-aged (9 months), and aged (23 months) received continuous infusion of picomolar levels of LPS (or artificial CSF as control) into their fourth ventricle. Among all cytokines, TNF- α increase in response to LPS infusion was similar in the different age groups. However, in contrast to young rats, IL-1 β did not significantly increase after 3 weeks of infusion in middle-aged and aged rats. Instead, aged rats had significantly increased IFN- γ compared to younger rats. In another study, however, LPS administration in aged rats induced prolonged neuroinflammation and astrogliosis in the hippocampus (dentate gyrus) with higher mRNA expression and protein levels of TNF- α and IL-1 β (Fu *et al.* 2014).

Age is also an important factor to develop tolerance-like phenomenon (Habicht 1985). Splenic lymphocytes of 12-month and 24-month-old animals are less likely to develop tolerance following repeated endotoxin exposure when compared to splenic lymphocytes obtained from young animals. Thus, old animals exposed to long-term LPS seem to be an ideal model of AD.

Gender

Almost all rat studies of LPS-induced cognitive impairment model used male rats. Studies in mice, however, demonstrated a heightened HPA response to LPS in females (Frederic *et al.* 1993, Spinedi *et al.* 1997), which may have important behavioural implications.

Conclusion

Extra caution is needed before extrapolating preclinical findings using LPS to clinical situations. Sensitivity to LPS and the consequent production of proinflammatory cytokines is much greater

in humans compared to rodents (Warren *et al.* 2010). Thus, the doses of LPS given in most rodent models are about 10^3 – 10^4 times the dose required to induce severe disease in humans (Sauter *et al.* 1980, Taveira *et al.* 1993). Other factors such as route of administration, nature and duration of exposure as well as age and gender of animal used should be taken into account when designing a study using LPS-induced memory impairment as model for AD.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

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Table 1. Major cognitive findings in LPS-treated rats

Gender and strains	LPS dosage (mode of administration)	LPS injection (duration)	Major cognitive findings (Behaviour test)	Reference
Adult male Sprague Dawley rats (3 months)	0.25 µg/h (i.c.v.)	Single injection daily for 28 days	Chronic infusion significantly impaired alternation performance (T maze)	Hauss-Wegrzyniak <i>et al.</i> 1998
Young male and female Hooded Long Evans rats	0.125, 0.25 and 0.50 mg/kg (i.p.)	Single injection	LPS administration after conditioning selectively impaired contextual fear conditioning in both young and adult rats of two different strains. It had no effect on auditory-cue fear conditioning (Contextual fear conditioning)	Pugh <i>et al.</i> 1998
Adult male Albino Sprague Dawley rats				
Adult male Wistar rats	0.5–5 µg/2 µl (i.c.v.)	Single injection	Significantly impaired spontaneous alternation behavior but no change in the number of arm entries and impaired spatial memory impairments (Y maze and Morris water maze)	Yamada <i>et al.</i> 1999
Adult male Sprague Dawley rats (6 months)	0.25 µg/h (i.c.v.)	Single injection daily for 37 days	Chronic infusion significantly impaired alternation performance but had no effect upon object recognition performance (T maze and object recognition)	Hauss-Wegrzyniak <i>et al.</i> 2000
Adult male Wistar rats	100 µg/kg (i.p.)	Single injection daily for 5 days	LPS impaired escape latency in both the acquisition and retention phases of the Morris water maze test (Morris water maze)	Shaw <i>et al.</i> 2001
Adult male Wistar rats	250 µg/kg (i.p.)	Single injection	LPS impaired hippocampal-dependent spatial learning (Water maze)	Shaw <i>et al.</i> 2005
Sprague Dawley pups of both sexes (Day 5)	1 mg/kg (i.c.v.)	Single injection daily for 3 days	The number of electric foot shocks needed to retain the rat on the safe board was increased	Fan <i>et al.</i> 2005

			significantly in the LPS-injected group at postnatal day 20. LPS also reduced the retention latency to step down from the board the next day as compared to the latency in the control group. (Passive avoidance memory retention test)	
Sprague Dawley pups of both sexes (Day 5)	10 µg (i.c.v.)	Single injection	The number of electric foot shocks required to retain the rat on the safe board was significantly increased in the LPS-injected group at postnatal day 20. In the test trial the next day, the retention latency to step down from the board was remarkably less than control (Passive avoidance memory retention test)	Pang <i>et al.</i> 2006
Adult male Wistar rats	100 µg/kg (i.p.)	Single injection	LPS impaired recognition memory (Object recognition)	Hennigan <i>et al.</i> 2007
Adult male Wistar rats	5 mg/kg (i.p.)	Single injection	The behavioural assessment was done 7 days and 10 months post-LPS injection. Both resulted in discriminative deficits not associated to any spatial memory deficit (Open field with objects and Morris water maze)	Bossù <i>et al.</i> 2012
Adult male Wistar rats	5 µg/5 µl (i.c.v.)	Single injection	LPS impaired working memory and long-term memory (Y maze)	Joshi <i>et al.</i> 2014
Adult male Wistar rats	1 mg/kg (i.v.)	Single injection	LPS impaired cognitive performance (Barnes maze and inhibitory avoidance test)	Vasconcelos <i>et al.</i> 2014
Adult male Wistar rats	250 µg/kg (i.p.)	Single injection	LPS for 7 days caused higher memory	Zhu <i>et al.</i> 2014

		daily for 3 or 7 days	impairment compared to LPS for 3 days (Morris water maze)	
Adult male Sprague Dawley rats	167 µg/kg (i.p.)	Single injection	LPS significantly impaired context-object discrimination but not spatial memory and object recognition (water maze task, context-object discrimination, and novel object recognition)	Czerniawski <i>et al.</i> 2015
Adult male Wistar rats	1 mg/kg (i.p.)	Single injection	LPS impaired passive avoidance memory retention	Anaeigoudari <i>et al.</i> 2015
Aged male Sprague Dawley rats (18 months)	500 µg/kg (i.p.)	Single injection	LPS impaired cognitive performance (Trace fear conditioning and Y maze)	Sun <i>et al.</i> 2015
Adult male Wistar rats	1 mg/kg (i.p.)	Single injection	Time latency and traveled path were higher in LPS group than the control group (Morris water maze)	Anaeigoudari <i>et al.</i> 2016
Adult male Sprague Dawley rats	50 µg/5 µl (i.c.v.)	Single injection	Injection of LPS into lateral ventricle caused learning and memory impairment (Y maze and Morris water maze)	Song <i>et al.</i> 2016

i.c.v., intracerebroventricular; i.p., intraperitoneally; i.v., intravenous.

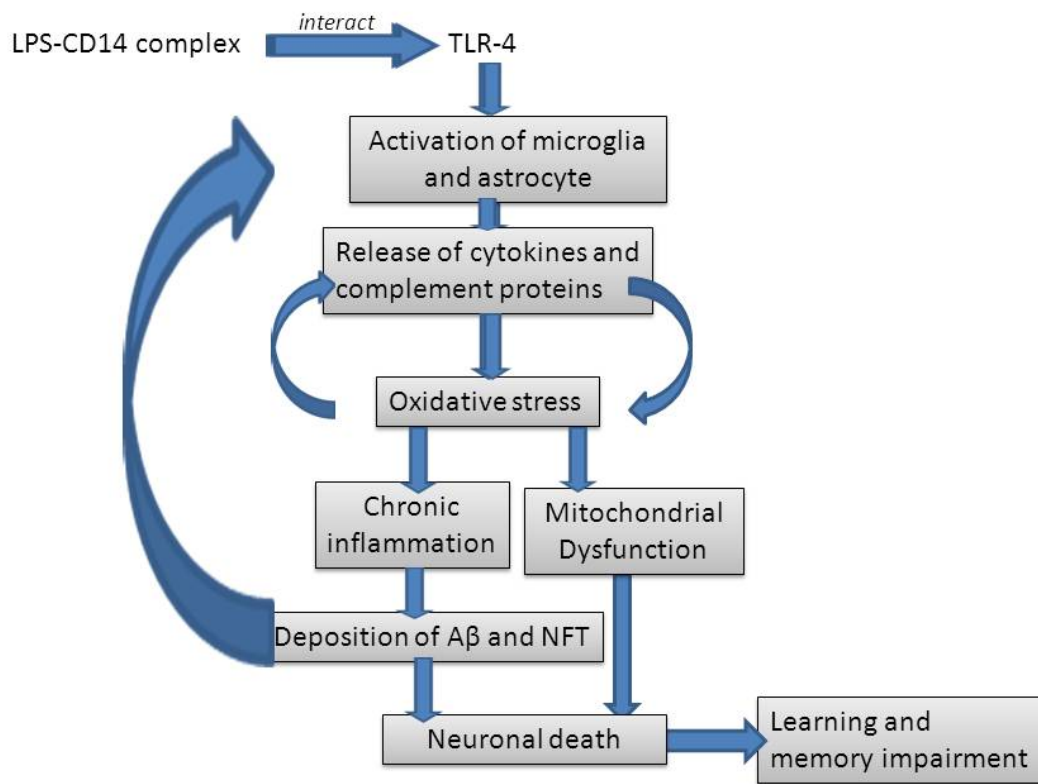


Fig. 1. Mechanism of LPS action in CNS