Lipopolysaccharide-Induced Memory Impairment in Rats: a Model of Alzheimer’s Disease

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Received September 5, 2016
Accepted January 6, 2017
On-line April 12, 2017

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.

Key words
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 Alzheimer’s Disease

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 neuro-inflammation models for AD

The unique neuropathological hallmarks of AD are extracellular accumulation of beta-amyloid (Aβ) 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 neuro-inflammation lasting more than 7 days prior to hyperphosphorylation of tau and Aβ plaque deposition (Burton and Johnson 2012).

The intracellular accumulation of Aβ, especially Aβ1-42, 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 (Wirths 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 Aβ 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 Aβ 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 (Hauss-Wegrzyniak et al. 1998, Sheng et al. 2003, Anaieigoudari 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 (Hauss-Wegrzyniak et al. 1998, Sheng et al. 2003; Anaieigoudari 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 behavioral stress (Oitzl et al. 1993).

LPS produces a wide range of non-specific behavioral effects collectively termed ‘sickness behaviors’ (Klein and Nelson 1999). These behaviors 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, Kebt 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 (Elmquist 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 Figure 1.

![Fig. 1. Mechanism of LPS action in CNS.](image)

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-1β, 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-1β, IL-6, TNF-α and TGF-β can augment APP expression (Buxbaum et al. 1992, Hirose et al. 1994) and Aβ formation (Blasko et al. 1999). It has also been reported that cytokines are able to transcriptionally upregulate β-secretase mRNA, protein and enzymatic activity (Sastre et al. 2003). β-secretase is a key rate-limiting enzyme that initiates Aβ formation (Vassar 2001). Without β-secretase, Aβ 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 Aβ transport at the blood brain barrier (BBB) (Jaeger et al. 2009) and decreasing the central clearance of Aβ (Erickson et al. 2012). Alteration of BBB effectively increases brain influx of Aβ but decreases its efflux (Jaeger et al. 2009). The level of expression of Aβ 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.
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 Aβ plaque formation (Pasinetti et al. 1998, Hoozemans et al. 2001, Pasinetti et al. 2002). Conversely, deposition of Aβ 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 Aβ-induced apoptosis is associated with COX-2 up-regulation through activation of NF-κB, 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, Hauss-Wegrzyniak et al. 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/h) was sufficient to induce neuroglial activation while moderate and high doses (50 ng/h 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) showed that a single injection of LPS impaired escape latency in both the acquisition and retention phases of the Morris water maze while a daily injection did not. Repeated LPS exposure also resulted in lower IL-1β 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-1β activation, which may account for the observed behavioral 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 behavior or how endotoxin tolerance may be observed in terms of an animal’s learning. Kobayashi et al. (2002) demonstrated that repeated LPS exposure resulted in decreased IL-1β 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-1β activation, which may account for the observed behavioral changes in the study.

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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-1α, 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 behavior.

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 Aβ in the hippocampus was observed following administration of LPS for 7 days, but not for 3 days, indicating that the increased expression of Aβ 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 neurobehavioral 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-1β 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. However, in another study 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-1β (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. However, studies in mice demonstrated a heightened HPA response to LPS in females (Frederic et al. 1993, Spinedi et al. 1997), which may have important behavioral 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 Interest

There is no conflict of interest.

Acknowledgements

The authors wish to acknowledge funding from Fundamental Research Grant Scheme (FRGS) (203/PPSP/6171174).
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</tr>
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i.c.v., intracerebroventricular; i.p., intraperitoneally; i.v., intravenous.
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